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Approaches for Assessing Health Risks from Complex Mixtures in Indoor Air: A Panel Overview

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Critical to a more definitive human health assessment of the potential health risks from exposure to complex mixtures in indoor air is the need for a more definitive clinical measure and etiology of the helath effects of complex mixtures. This panel overview highlights six of the eight presentations of the conference panel discussion and features a number of the major topical areas of indoor air concern. W. G. Meggs assessed clinical research priorities with primary focus on the role of volatile organic chemicals in human health, recognizing the areas where definitive data are lacking. By recognizing many types of chemical sensitivity, it may be possible to design studies that can illuminate the mechanisms by which chemical exposure may cause disease. The critically important topic of multiple chemical sensitivity was discussed by N. A. Ashford, who identified four high risk groups and defined the demographics of these groups. P. A. Schulte addressed the issue of biological markers of susceptibility with specific considerations of both methodological and societal aspects that may be operative in the ability to detect innate or inborne differences between individuals and populations. Three case studies were reviewed. H. Anderson discussed the past and present priorities from a public health perspective, focusing on those issues dealing with exposures to environmental tobacco smoke and formaldehyde off-gassing from materials used in mobile home construction. J. J. Osborne described several case studies involving wood smoke exposure to children, with emphasis on the significantly greater occurrence of chronic respiratory symptoms and acute chest illness for children from homes heated with woodburning stoves. D. W. Sepkovic focused on the use of a specific nicotine metabolite, cotinine, as a biomarker of environmental tobacco smoke uptake in controlled studies.

Introduction

Reports of illnesses believed to be related to indoor air environments have increased dramatically over the past decade. Indoor air may be polluted by a host of chemical and microbial toxins depending on particle size, air exchange rates, by particles infiltrating from outdoors, as well as poor indoor air quality arising from inadequate design, operation, and maintenance of ventilation and filtration systems.

Both chemical and biological agents in complex mixtures in indoor air have been reported to cause specific illnesses and have raised questions regarding potential acute and chronic health risks. A broad spectrum of complaints in office environments, often referred to as "sick building syndrome," has been characterized by frequency of irritative symptoms of the eyes, throat and lower airways, skin reactions, nonspecific hypersensitivity, mental fatigue, headache, nausea, and dizziness. The term "multiple chemical sensitivity" (MCS) has developed as a controversial term describing a variety of symptoms associated with exposure to indoor air pollution.

There is acknowledged difficulty in distinguishing between sensitivity resulting from indoor air exposure to chemicals and sensitivity that may arise from bacteria, mites, foods, or allergens such as dust. Additionally, the role of "adaptation" in chemical or bacterial sensitivity is currently not well characterized, but may represent developed tolerance under exposure conditions.

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It is broadly acknowledged that a more rigorous characterization of the agents in indoor air complex mixtures as well as a more definitive clinical measure and etiology of their health effects are all critical for human health assessment. This Panel Overview highlights six of the eight presentations of the Workshop Panel Discussion and features a number of the major topical areas of indoor air concern: the role of volatile organic chemicals (VOCs) in human health; multiple chemical sensitivity, biological markers of susceptibility, and three case studies dealing with resolution of indoor air exposures and priorities in Wisconsin, exposure of children to wood smoke, and the use of a specific biomarker to quantitate exposure to environmental tobacco smoke.

Clinical Research Priorities: VOCs in Human Health

For the past 40 years or so, claims have been made that VOCs found in indoor air play a role in disease processes ranging from asthma to schizophrenia. Data are now available on exposure to VOCs (*1–3*), but scientific documentation of the role these compounds play in human health is at this time inadequate. Certainly, the type of definitive data that establishes a consensus is lacking. It is important to extrapolate our current knowledge about the role of chemical exposures in human health to determine research priorities.

Criteria for selecting fruitful areas for investigating a role for VOCs in human health are given in Table 1. Epidemiologic data documenting increasing incidences of certain disorders in recent years, particularly if the increases are in industrialized nations while sparse in primitive cultures, suggest possible environmental factors. Diseases that can be induced by exposure to organic chemicals such as pharmaceuticals and chemicals occurring in foods should be studied with regard to VOCs. If there are animal models of a disease in which chemical exposures induce the disease or if there are case reports and anecdotal data linking a disease to chemical inhalants, then this disease should be investigated for a role for VOCs. If a disease meets several of the criteria given in Table 1, then special emphasis should be given for study. Areas of particular concern are autoimmune diseases, hypersensitivity disorders, and psychiatric illnesses.

Autoimmune diseases are known to be caused by environmental chemicals in some patients (*4,5*). It is known that pharmaceuticals can cause autoimmune hemolytic anemia (*6*), drug-induced lupus (*7*), and other autoimmune diseases. Hydrazine, an organic solvent, similar to hydralazine, which is an antihypertensive associated with lupus, can cause a lupuslike syndrome from occupational exposure via inhalation (*8*). Other environmental chemicals, for example, an amino acid analogue found in alfalfa sprouts (*9*), can induce lupus. If a person develops an autoimmune disease, the first question he or she is asked by a clinician is if they are taking any medications, and if so, these are discontinued as the possible cause of the autoimmune process with in many cases a curative outcome. If no medications are being taken, the autoimmune process is described as "idiopathic" and treated with medications that are usually not curative. We need to determine the extent to which environmental chemicals, in particular the VOCs, may be causative in some cases of autoimmunity. If it can be established that inhaled chemicals in the indoor air play a role in autoimmunity, clinical practice needs to be broadened to include an assessment of nonpharmaceutical exposures to organic chemicals.

Table 1. Criteria for prioritizing clinical research on volatile organic chemicals.

Diseases with increasing incidence in industrial societies
Diseases known to be induced by exposure to organic chemicals such as pharmaceuticals and chemicals occurring in foods
Diseases in animal models in which chemical exposures induce the disease
Diseases with case reports and anecdotal data supporting a role for volatile organic compounds

Table 2. Categories of xenobiotics that induce hypersensitivity diseases.

Sensitizers
Environmental adjuvants
End-organ inducers

Another area of concern is the role VOCs may play in hypersensitivity disorders. There are three ways in which a xenobiotic can play a role in hypersensitivity, as shown in Table 2. Some low molecular weight compounds are sensitizers, in that an immune response develops to the compound, perhaps in conjugated form to endogenous proteins. Well-known examples from the study of occupational asthma include toluene diisocyanate (*10*), platinum salts (*11*), and trimellitic anhydride (*12*). IgE production against the materials have been demonstrated in some cases, but in all cases the clinical response is the same, with an initial exposure followed by sensitivity on reexposure.

Environmental adjuvants are compounds that enhance or potentiate the immune response to a second substance. Concurrent exposure to an environmental adjuvant and a second substance, most commonly a protein aeroallergen, leads to an immune response mounted toward the second substance. Table 3 lists some demonstrated environmental adjuvants and the related allergens from animal models.

To suffer from a hypersensitivity disorder, it is necessary but not sufficient to manufacture IgE against an environmental substance. One must also have a responsive target organ. If a group of people who make IgE against chicken egg protein were fed eggs, some would get hives or gastrointestinal symptoms, and a few might have rhinitis or asthma from the exposure, demonstrating a target organ in the skin, gastrointestinal tract, nose, or lungs, respectively. Another group would remain asymptomatic because they do not have a responsive organ. Our knowledge of the mechanisms by which one acquires a responsive organ to immediate hypersensitivity reactions is scant, but the induction of bronchial hyperactivity in the human lung by exposure to organic chemicals has been reported (*13*).

With the incidence of asthma increasing in industrialized societies (*14*), it is important that the relationship between VOCs and asthma be studied. Depression is also increasing in recent

Table 3. Examples of environmental adjuvants.

Species	Environmental adjuvant	Allergen	Reference
Guinea pig	Sulfur dioxide, ozone, and nitrogen dioxide	Ovalbumin	(*18*)
Guinea pig	Sulfur dioxide	Ovalbumin	(*19*)
Monkey	Ozone	Platinum	(*20*)
Mouse	Diesel exhaust particles	Japanese cedar pollen	(*21*)

Table 4. Chemically sensitive groups.

Group	Nature of exposure	Demographics
Industrial workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20–65 years old
Tight building occupants	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white-collar office workers and professionals; 20–65 years old; school children
Contaminated communities	Toxic waste sites; aerial pesticide spraying; ground water contamination; air contamination by nearby industry; and other community exposures	All ages, male and female; children and infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
Individuals	Heterogeneous; indoor air (domestic); consumer products; drugs; pesticides	70–80% females; 50% 30–50 years old; white; middle to upper-middle class and professionals

times, and dramatically so among the young (*15*), and it is known that pharmaceuticals can induce depression and hallucinations as side effects. Exposure to leaky furnace fumes has been reported in association with depression (*16*). There are reasons to think that other mental illnesses may be related to VOCs, and this area needs clarification with good clinical research.

Clinical research to study the role of VOCs in human diseases will require a special clinical research unit in which indoor air is as pure as technically possible. [For a discussion of Environmental Control Units including historical references, see Ashford and Miller (*17*).] Individuals with known diseases such as rheumatoid arthritis, lupus, asthma, and depression will be housed in this unit and monitored for improvement of their symptoms. If there is improvement, subjects will be reexposed in a double-blinded fashion and monitored for exacerbations. Such a program will be expensive, but if the hypothesis that VOCs induce or exacerbate human diseases is sustained, the savings in health care costs will be enormous. More importantly, the improved quality of life and alleviation of suffering that could result is priceless.

Multiple Chemical Sensitivity

Much of the following discussion is drawn from Ashford and Miller (*22*). The problems that present themselves as chemical sensitivity seem to occur in at least four identifiably different clusters of individuals (Table 4) (*22*). We see these problems not only among tight-building occupants (category two), but also in occupational settings (category one), and in contaminated communities (category three) that are downwind from a chemical plant or in places like Love Canal or Woburn, Massachusetts. There are also a potpourri of individuals with a complex history of exposures who end up going to many physicians with a set of multiple complaints that are yet to be fully understood (category four).

It is worth noting that the demographics of these groups of people are very different. The occupational demographics, from the people who live in contaminated communities and from people who live or work in tight buildings, the age, sex, and social characteristics of affected individuals seem quite different. The similarities and differences among these groups will eventually elucidate this problem.

It is important to distinguish different concepts of sensitivity. In Figure 1 the percent of a population first exhibiting some defined harmful effect versus the dose at which it is observed is plotted. There are at least three different curves that can be constructed. One is curve A, which represents a classical toxic effect—like the exposure to lead. Curve A depicts a rather broad distribution of doses at which different people respond to the classical toxic substance. Some people respond at much lower levels than the norm and are in the tails of the distribution. We tend to define these people as sensitive people. The people who are at the other end and in the other tail we call resilient people. Everybody, sooner or later when they are exposed to lead, exhibits a certain particular neurological end point or toxicological end point. Those who respond at low doses we call "sensitive."

Classical toxic effects are different from allergy or atopy (curve B) where a group of people suffer from pollen allergies or in some cases from immunologically mediated sensitivity to chemicals such as toluene diisocyanate (TDI). But here it is clear that 100% of the people will not be affected at the concentrations of pollen or TDI ever likely to be found in the environment. Thus we call the entire distribution a "sensitive population"; this is a different concept of sensitivity.

Finally, we have an emerging problem that we are struggling to understand, multiple chemical sensitivity, which appears to be a more complex process. What seems to be required is a sensitizing event, very often to a high level of toxic material, followed thereafter by a reaction triggered at flow levels of exposure to chemicals—much lower than that observed in the context of ordinary toxic effects. Curve C is a hypothetical distribution of one such triggering event in a sensitized population. The sensitizing event or process, which may affect the immune system, the limbic or nervous system, or enzyme detoxification, may be in fact some kind of classical toxic effect that we have yet to understand. But once individuals are sensitized, the triggering mechanism is not explained by ordinary toxicology as we know it.

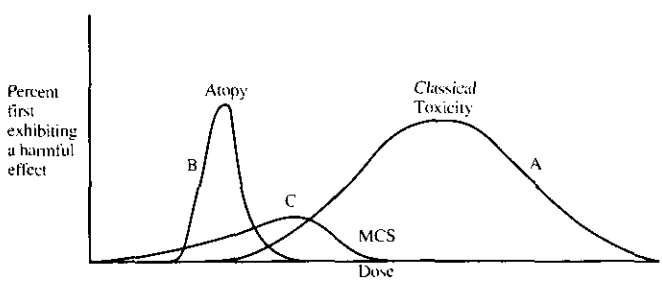

FIGURE 1. Hypothetical distribution of different types of sensitivities as a function of dose. Curve *A* is a sensitivity distribution of classical toxicity, e.g., to lead or solvent. Sensitive individuals are found in the left-hand tail of the distribution. Curve *B* is a sensitivity distribution of atopic or allergic individuals in the population who are sensitive to an allergen, e.g., ragweed or bee venom. Curve *C* is a sensitivity distribution of individuals with multiple chemical sensitivities who, because they are already sensitized, subsequently respond to particular incitants, e.g., formaldehyde or phenol.

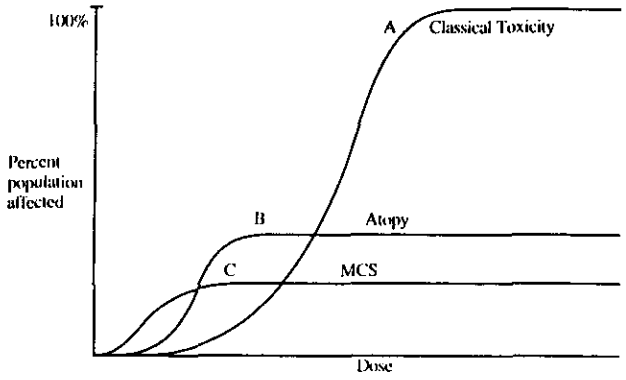

FIGURE 2. Hypothetical population dose-response curves for different effects. Curve *A* is a cumulative dose-response curve for classical toxicity, e.g., to lead or a solvent. Curve *B* is a cumulative dose-response curve for atopic or allergic individuals in the population who are sensitive to an allergen, e.g., ragweed or bee venom. Curve *C* is a cumulative dose-response curve for individuals with multiple chemical sensitivities who because they are already sensitized, subsequently respond to particular irritants, e.g., formaldehyde or phenol.

Table 5. Observations concerning multiple chemical sensitivity.

Symptoms involving virtually any system of the body or several systems simultaneously
Differing symptoms and severity in different individuals, even those with the same exposure
Induction (i.e., sensitization) by a wide range of environmental agents
Subsequent triggering by lower levels of exposure than those involved in initial induction of the illness
Concommitant food intolerances, estimated to occur in a sizable percentage of those with chemical sensitivities
"Spreading" of sensitivity to other, often chemically dissimiliar, substances. Each substance may trigger a different constellation of symptoms.
Adaptation (masking), i.e., acclimatization to environmental incidents, both chemical and food, with continued exposure; loss of this tolerance with removal from the incident(s); and augmented response with re-exposure after an appropriate interval (e.g., 4–7 days)
An apparent threshold effect referred to by some (including certain tradional allergists) as the patient's "total load"

Just as when we began to recognize that cancer is a two-step process (at least), initiation and then promotion, and a full understanding of cancer could not be appreciated with the ordinary toxicological model, here too the processes that are underway must be fully understood to appreciate what chemical sensitivity is. A failure to define the problem of multiple chemical sensitivity has been largely due to the failure to acknowledge the differences in the different concepts of sensitivity.

In Figure 2, if we plot the number of people affected in a cumulative fashion, we have the more familiar dose-response curves, with classical toxicity leveling off at 100% of the population affected, and multiple chemical sensitivity leveling off some place different. Not 100% of the people are sensitive or have been sensitized and not 100% will respond at those low levels.

In Table 5, we have a description of what it is that physicians and observers call the chemically sensitive population. We have to be able to explain all these characteristics some day if we are going to get a handle on the problem. First, the symptoms seem to involve virtually any system in the body or several systems simultaneously. Second, there are a variety of symptoms differing in severity in different individuals, even in those with the same exposure. This is hard to explain with a simple dose-response concept. Third, induction is observed by a wide range of environmental agents most frequently found with pesticides and solvents exposure. Fourth, there is a subsequent triggering of chemical sensitivity by lower levels of exposure than those involved in the initial induction of the disease (the second step of a two-step process).

Fifth, concomitant food intolerance is estimated to occur in a sizable percentage of those with chemical sensitivities. We may be observing a cross-reactivity with food, e.g., as in the case of toluene diisocyanate and radishes. Food sensitivities and chemical sensitivities may not be all that unrelated. Sixth, there seems to be a spreading of sensitivity to other chemically dissimilar substances. Seventh, adaptation or masking is a key concept: some people who are triggered initially do not seem to be triggered after continual exposure. This presents a formidable diagnostic challenge. If a patient is looked at in a kind of saturated, adapted state, a physician may not be able to discover the things that the patient has reported in his own home. Finally, there appears to be an apparent threshold effect having to do with the patient's total load. Eventually all these observations will have to be adequately explained if others are to be convinced that the problem is real.

Adaptation is the key to understanding chemical sensitivity. It is characterized by a tolerance after repeated exposure that results in a masking of symptoms. Adaptation makes it difficult to discover the effects of a particular exposure on the body. Further exposures may have little impact and therefore effects are not observed. This is why you need an environmental unit in which people are housed and de-adapted to discover the range and nature of the response to chemicals or foods. Chemical exposure may adversely affect adaptive mechanisms thus leading to illness. It may be that this whole problem is related to a maladaptation in some individuals; thus adaptation is extremely important to understand and research.

Instead of searching for a narrow case definition for chemical sensitivity by finding a physiological marker or biological marker, for research purposes at this stage, it is better to be empirical and to focus on the notion that the patient with multiple chemical sensitivities can be discovered by removal from the suspected offending agents and by rechallenge after an appropriate interval under strictly controlled environmental conditions (preferably double-blind, placebo controlled). Causality is inferred by the clearing of symptoms with removal from the offending environment and the reoccurrence of symptom with specific challenge. It has to be done very carefully, because de-adapted people may be extremely sensitive.

The mechanisms of damage are just beginning to be understood. It has been suggested that both physiological as well as psychogenic mechanisms may be at play. Some of the physiological mechanisms that have been suggested are the nervous system, particularly involving the limbic system, the immune systems and enzyme detoxification. It is crucial that we not confuse presentation of psychological symptoms with psychogenic causes. Chemicals are known to have psychological sequelae. Because people have central nervous system problems does not mean that there is a psychological or psychogenic origin of that problem. One has to separate the presentation of symptoms from the origin of the condition; pursuing a psychogenicet

iology may be misguided without first eliminating environmental causes. The environment unit is essential for this task.

From the perspective of strategies, for research we need to advance the theory of causation at low levels. We have to understand this two-step process of induction and triggering, and we need to be able to compare the groups that seem to be exhibiting these problems to understand the nature of the problems. Tight buildings are characterized by a unique feature: often there is an event involving a unique exposure after which people seem to be sick. We can follow the development of illnesses and symptoms over time after an initiating event.

We need to advance the analytical techniques for exposure, for susceptibility, and for health effects. There is a need for biomarkers, but we may not be able to get biomarkers for limbic system damage. Those markers are unlikely to be found in the bloodstream.

Finally, we need to advance epidemiology of exposure to chemicals where we have not only multiple exposures, but multiple symptoms that might be unconnected in analysis of disease without an underlying mechanism.

The challenges presented by multiple chemical sensitivity require painstaking approaches. A public health problem of increasing dimensions demands this attention.

Biological Markers of Susceptibility

Molecular biology is beginning to substantiate what biologists have observed since Darwin's time, which has been subsumed under the concept of "population thinking." That is, to think of populations in terms of averages glosses over the extensive heterogeneity and variability within populations. This has implications for the study of contemporary building environments. This heterogeneity and variability needs to be taken into account in these studies. With that prerequisite, biological markers of susceptibility can be potentially useful in these studies.

There are both methodologic and societal aspects that should be considered when thinking about markers of susceptibility. The methodologic aspects are that in developing studies of populations who work in buildings or who live in various kinds of residential configurations. Studies need to include these kinds of indicators of susceptibility. The word "susceptibility" is an emotionally polarizing term, and I prefer to use the epidemiologic concept of "effect modifier." In other words, why do some subsets of a population experience an effect when others do not. This is treated in epidemiologic research as an effect modifier.

To account for this extensive variability (and a lot of it is genetic) we should consider other characteristics of host factors that pertain to the experiences that people have had in their lives. We also need to have designs that account for the other nonhost factors that might result in a potential health effect. These other factors include such things in an environment as light, sound, and the social relations that go on among people who work within these structures. To consider this as just an indoor air quality problem misses some of the kinds of wide, ranging aspects of the problem. Hence, it is important not to just think of this as an indoor air problem, but as a problem of contemporary building environments. To do that, we need multidisciplinary teams. This conference is a good first step. It brings together a partial range of the disciplines involved, but not nearly as many of the disciplines that should be brought to bear on this problem. In terms of the methodologies used, we have to put much more emphasis on the use of multivariate statistical models to try to incorporate the wide range of characteristics that are involved in these kinds of problems. This is not only an epidemiological question, it is also a question that has to bring together epidemiology and toxicology. We have to have a better working relationship between people doing the animal studies and people doing the field studies. We do not have that at this time.

If we are to consider markers of susceptibility as indicators of effect modification in studies of buildings and contemporary environments, we need to set up a societal framework to allow that. Right now we do not have that societal framework. Our society does not have a good track record in dealing with individual differences and we have seen that in terms of how society deals with different races, how it deals with people with handicaps, and even how it deals with talented people. We raise talented people up and discriminate against people with handicaps. We take people who are different and treat them unfairly. We have to start to come to a societal consensus on how we are going to deal with individual differences. We do not have that consensus. We do not even have at this conference the kind of people who can initiate that kind of discussion.

If we are going to start using molecular biological assays to detect subtle differences between people, we have to have some sort of societal understanding of how we are going to respond to those differences. How are we going to treat the people who have those differences? How will we protect their rights? How will we protect them from discrimination? We do not have that kind of societal understanding at this point.

Consequently, it is difficult for the research to be sanctioned to allow us to start to look at the kinds of genetic variability that may well impact on who gets an effect and who does not get an effect in a particular environment. My message is, we have to have a broader group of people brought to bear to address these kinds of problems.

Case Study: Past and Present State Program Priorities

Over the past decade, public health officials have experienced a steady rise in citizen acute heath complaints attributed to residential and commercial indoor environments (*23*). Initially, the combination of increased energy efficiency demands with new construction and consumer products material technology was implicated as a critical factor explaining much of the increase. The early investigations provided us with a better understanding of the fragility of the indoor environment. Often, only a narrow margin existed between typical concentrations of pollutants and the level at which acute irritation occurred among a significant proportion of exposed individuals.

To what extent exposures below irritant/odor thresholds may contribute to chronic disease is the focus of research efforts and risk assessment. Seemingly inconsequential physical changes to the indoor environment can have significant public health impacts.

A second element that surely contributed to the increase in citizen complaints is best described as a lowering of the public's discomfort tolerance. For decades environmental tobacco smoke (ETS) was known as the most common indoor air pollutant. It

was just as irritating in the past as it is today. Instead of masking unpleasant odors with agreeable ones as many air fresheners do, ETS masked other agents with unpleasant odors and effects. For years the public identified the ETS, but appeared prepared to tolerate its aggravation. Today, the majority of people are not prepared to continue tolerating that level of irritation. The identification of serious chronic disease risks associated with ETS has hastened its rejection and led to an increase in clean indoor air legislation.

With ETS removed from more and more work areas, other agents, whose effects had been masked or overpowered by the odor and irritation from ETS, became noticeable. These have now become our second generation targets for evaluation. In addition to the removal of ETS from indoor environments, fewer individuals are smoking cigarettes, with the result that more people have a rejuvenated sense of smell and are noticing indoor pollutants. Indoor air specialists must now address complex volatile chemical mixtures, "sick building syndrome," and multiple chemical sensitivity issues.

In Wisconsin as well as in many health departments, an indoor air program was first instituted to address acute, irritant complaints related to formaldehyde off-gassing from foam insulation and/or particle board used in mobile home construction (*24*). Risk management decisions in the early 1980s significantly reduced exposure to formaldehyde from these sources. Complaints have been significantly reduced since the establishment of an industry-wide product standard.

Most state health programs have been unable to break out of the "reactive epidemiology" mode of only having sufficient resources to selectively conduct complaint investigations. This means that priority is placed on agents causing acute irritant symptoms. Priorities reflect constituency concerns and demands, not the public health or scientific assessment of comparative risk.

Historically, the priority given to complaints has left few resources to implement more "proactive" epidemiologic programs. Priorities have been driven by acute health effects rather than perhaps more serious chronic disease concerns. Few state health programs are able to devote effort to identifying and investigating potential new products/agents as problem exposure sources before consumers begin to complain. Agents that do not result in symptomatic complaints are likely to be given little attention even though they may have important adverse health impacts. Questions such as What are the health consequences of the new high efficiency furnaces which no longer require chimneys? and What are the impacts of the new synthetic carpet materials with their antistain treatments? need to be answered.

Risk assessment has been most useful in evaluating chronic health risks and could be used to order programmatic priority by severity of risk for such agents as environmental tobacco smoke, radon, lead, and asbestos. How to use risk assessment for the acute, irritant effects most commonly reported from indoor environments and compare results to chronic disease risk estimates remains more problematical. Its application to all indoor air pollution issues should help renew attention to the "old standbys" of indoor air pollution: lead, house dust allergens, and humidity.

Assessment of indoor environments and their potential health effects is growing in complexity. It is time to evaluate the existing state and federal program priorities. Risk assessment can be a useful tool in that process.

Case Study: Wood Smoke and Children

An increasing number of families in the United States are electing to heat their homes with wood. Estimates indicate that over 1,000,000 new woodburning stoves (WBS) are sold for domestic use in the United States each year and that usage is increasing in all socioeconomic groups (*25,26*). The three basic types of WBS are free-standing, fireplace insert, and furnace add-on units. Documented hazards associated with their use include accumulation of carbon monoxide as well as an increased number of burn injuries and fires (*27,28*).

Different types of WBS vary in quality and efficiency. However, even the most efficient WBS emit some hazardous pollutants directly into the home when the stove is operating and the door is opened to add wood (*25,29–34*). This issue is especially important when one considers the trend to increase home insulation and overall airtightness in an effort to conserve energy and reduce heat loss (*27*). Therefore, questions arise regarding possible health effects from exposure to byproducts of wood combustion.

Two recent studies have explored the occurrence of respiratory problems in young children from homes heated with WBS in the United States. The first was a prospective study in Michigan of 62 young children (31 from WBS-heated homes and 31 controls from homes heated by conventional means) matched for age, sex, and place of residence (to control for the potentially confounding effects of these variables) from 1980 to 1985. Principal outcomes assessed were chronic respiratory symptoms and acute chest illness; related outcomes were duration of acute illness and hospitalization for severe chest illness before age 2 years (*35–37*).

The second was a case-control study in Arizona in 1988 of 58 pairs of American Indian children matched for age (2 weeks–2 years) and sex. The children were stratified at selection by the presence of lower respiratory tract illness (LRTI) and followed backward in time to determine the distribution of exposures (*38*).

Findings for the Michigan study indicated that the occurrence of chronic respiratory symptoms and acute chest illness were significantly greater for children from homes heated with WBS. In addition, the duration of acute chest illness was two times greater, and the number of hospitalizations for severe chest illness before 2 years of age was 67% greater than for controls.

Findings for the Arizona study indicated that WBS exposure was a significant risk factor for LRTI in young children. The calculated odds ratio was 4.9, with 95% confidence interval boundaries of 1.7 to 12.9.

The Michigan study assessed a number of factors potentially associated with the respiratory outcomes of interest, including socioeconomic status, medical history, frequency of physician visits, use of humidifiers and air filters, and use of other sources of indoor air pollution associated with the occurrence of respiratory problems in young children (i.e., parental smoking, cooking with gas, and ureaformaldehyde foam insulation). The Arizona study assessed medical history, humidifier use, parental smoking, presence of pets in the home, having more than people in the home, having a, one-room home, absence of running water, and having a dirt floor.

None of the potentially confounding variables assessed in the Michigan study were found to significantly affect differences in outcomes between study and control groups. In the Arizona study, the effect of WBS exposure was found to be independent

of other factors, including recent respiratory illness exposure, which was the only other factor significantly associated with LRTI.

One other study has investigated respiratory effects of exposure to WBS. The study subjects were elementary school children up to the sixth grade from Western Massachusetts. Although 64% of children from homes heated with WBS had at least one acute respiratory episode and 22.5% had at least two episodes, occurrence in controls was not found to be significantly different (*39*).

If exposure to WBS is associated with the occurrence of respiratory symptoms and chest illness, as current findings suggest, then it remains to determine which aspects of WBS use may be involved. Indoor heating with WBS can generate a significant amount of air pollution. Documented pollutant emissions of WBS include carbon monoxide, nitrogen dioxide, sulfur dioxide, respirable particulates, aldehydes, polycyclic organic compounds, benzo[*a*]pyrene, elemental carbon, and a variety of priority pollutants and elements found in priority pollutants (such as aluminum, calcium, potassium, sodium, sulfur, and silicon) (*25,29–34*).

Respiration of these compounds could reasonably compromise the ciliated epithelial cells, which are a significant component of the immune system throughout the tracheobronchial tree. The respiratory effects of such exposure would probably be greatest on the smaller, developing airways of young children who are largely confined within the home during winter months.

A number of other factors may also affect indoor air pollution and potential respiratory effects from heating with WBS. These include peak versus average exposure, type of WBS and location within the home, type and amount of wood burned, degree of air tightness and volume of the home, reintroduction of vented emissions, temperature fluctuations in wood-heated homes (as compared to homes with a thermostat keeping indoor temperatures in a fairly narrow range), and low indoor humidity (especially at night when WBS use is greatest for indoor heating).

Data from the Michigan and Arizona studies do not support an association between the occurrence of respiratory problems and the type of WBS, location within the home, or amount of wood burned. It may be that respiratory responses to WBS exposure may best fit a model of threshold response rather than dose response, which would explain the lack of correlation between frequency of outcomes and amount of wood burned in the Michigan study.

Positive findings from two of three independent studies suggest that epidemiologic assessment of risks from indoor heating with WBS should be pursued. The two studies focusing on young children had significant findings, whereas the study focusing on older children did not. No studies have been conducted for adults. This suggests that the most useful information would come from prospective studies that include different age groups and acquire as much information as possible on WBS and home parameters, pollutant levels, and respiratory outcome measurements. Future epidemiologic studies addressing these areas should significantly contribute to our understanding of respiratory risks from indoor heating with wood.

Case Study: Environmental Tobacco Smoke

The major focus of this section is on the use of a specific nicotine metabolite, cotinine, as a biomarker of ETS uptake. More than 4000 compounds are present in tobacco smoke. Table 6 summarizes the predominant compounds that have been identified in the vapor phase. On the right of the table, sidestream to mainstream smoke ratios have been tabulated. Table 7 provides similar data for the main compounds found in the particulate phase of tobacco smoke (*40*).

To quantitate the uptake of ETS in clinical studies, a sensitive and specific biomarker is needed. The most extensively used indicator of exposure is cotinine, which is found in a variety of body fluids. Cotinine has been quantitated successfully using several methods. At present, the two most commonly used methods are gas chromatography and radioimmunoassay. More recently, highly sensitive gas chromatographic/mass spectrometric methods (GC/MS) have been developed that have the potential to accurately quantitate cotinine in the low nanogram range.

Urine cotinine was quantitated by radioimmunoassay in the studies described below. This method has several advantages. It is both highly sensitive and specific for tobacco smoke exposure. Because there is no extraction step, extraction loss is eliminated. The volume of sample required for analysis is quite small (approximately 20 μL of plasma and 10–20 μL of urine or saliva). The method has some disadvantages. The antibody cross reacts to some degree with other nicotine metabolites that may be present in urine, specifically, 3-hydroxycotinine.

I would like to briefly summarize two studies where cotinine measurements were used to quantitate ETS uptake. The first is an experimental chamber study. Six nonsmokers were exposed

Table 6. Distribution of compounds in the gas phase in cigarette mainstream smoke (MS) and sidestream smoke (SS), nonfilter cigarettes.

Gas phase	MS	SS/MS
Carbon monoxide	10–23 mg	2.5–4.7
Carbon dioxide	20–60 mg	8–11
Formaldehyde	70–100 μg	0.1–50 (?)
Acrolein	60–100 μg	8–15
Acetone	100–250 μg	2–5
Pyridine	20–40 μg	10–20
3-Vinylpyridine	15–30 μg	20–40
Hydrogen cyanide	400–500 μg	0.1–0.25
Nitrogen oxides	100–600 μg	4–10
Ammonia	50–130 μg	40–130
N-Nitrosodimethylamine	10–40 μg	20–100
N-Nitrosopyrrolidine	6–30 μg	6–30

Table 7. Distribution of compounds in the particulate phase in cigarette mainstream smoke (MS) and sidestream smoke (SS), nonfilter cigarettes.

Particulate phase	MS	SS/MS
Particulate matter	15–40 mg	1.3–1.9
Nicotine	0–2.3 mg	2.6–3.3
Phenol	60–120 μg	2.0–3.0
Catechol	100–280 μg	0.6–0.9
Aniline	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine	1.7 ng	30
Benz[*a*]anthracene	20–500 ng	2–4
Benzo[*a*]pyrene	20–40 ng	2.5–3.5
N'-Nitrosonornicotine	200–3000 ng	0.5–3
NNK	100–1000 ng	1–4
N-Nitrosodiethanolamine	20–70 ng	1.2
Nickel	20–80 ng	13–30
Polonium-210	0.03–0.5 pCi	

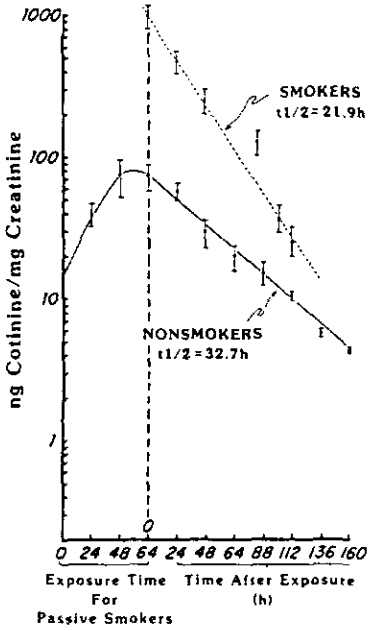

FIGURE 3. Urinary cotinine elimination in smokers and in passively exposed nonsmokers. Urinary cotinine concentrations are normalized by creatinine.

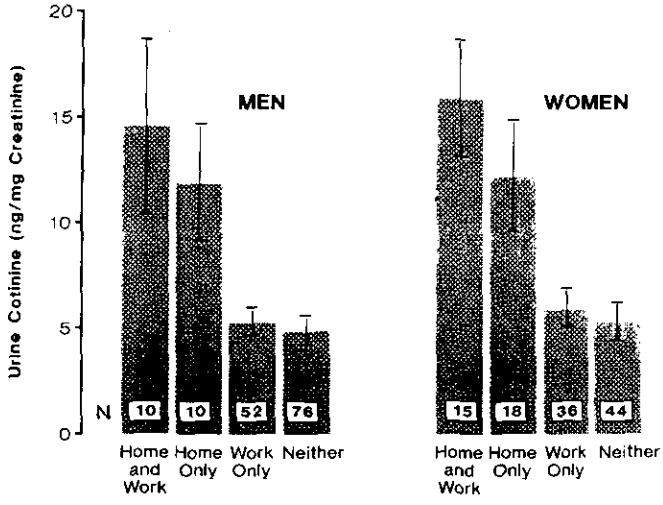

FIGURE 4. Place of exposure. Domestic versus work exposure to ETS in male and female municipal workers. The height of each bar is equal to the mean urinary cotinine (±SEM) for each group. Mean urinary cotinine is plotted versus domestic exposure, work exposure, domestic or work exposure, and no exposure, for both men and women.

to ETS generated by commercial cigarettes. Urine cotinine levels were determined from daily measurements over the following 230 hr. Maximum urinary excretion of cotinine was noted at approximately 24 hr after exposure (Fig. 3). Using these data, we determined the rate of cotinine elimination (t1/2B) in exposed never-smokers. We then compared this approximate cotinine elimination rate with that of a number of active smokers who abstained from smoking for a similar period. We observed a significant decrease in the rate of cotinine elimination in never-smokers when compared to smokers. The prolonged elimination and likely slower metabolism in nonsmokers suggests that passively exposed individuals may also carry a body burden of other toxic tobacco smoke components for longer periods than smokers themselves (*41*).

The second study is from a metabolic epidemiologic perspective. We recruited a population of municipal workers from the city of Dallas, Texas, that consisted of 148 men and 112 women. Both men and women were between 35 and 40 years of age. We asked these individuals to fill out a questionnaire of perceived ETS exposure and obtained a random urine sample from each participant. Significant increases in urine cotinine concentrations were observed in those volunteers who responded affirmatively to the questions of social exposure, exposure in transit, and at home exposure (*42*).

Using a qualitative scale (1 = no exposure and 4 = heavy exposure), we were able to correlate perceived exposure with urine cotinine concentrations and to show that most exposure to ETS occurs in the domestic environment (Fig. 4). These studies and others can yield important data regarding perceived exposure in nonsmokers exposed to tobacco smoke. The use of cotinine as an objective marker strengthens epidemiological studies that rely on subjective or questionnaire data on ETS exposure.

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