Indoor Environmental Exposures and Symptoms

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The label "sick building syndrome" is often used to imply the absence of a physiologic basis for symptoms in the built environment. Although building-related illness is widely recognized but considered rare, several well-studied mechanisms may be responsible for many symptoms in buildings. These mechanisms do not explain why some individuals perceive disability. Until researchers distinguish physiologic mechanisms from other aspects of disease and study them systematically, poorly defined symptoms will remain poorly understood. The disability associated with such symptoms and syndromes, not the physiology, is the primary interest and generates controversy. *Key words:* **complex mixtures, indoor environments, mucosal irritation, occupational health, unexplained symptoms.** *Environ Health Perspect* **110(suppl 4):663–667 (2002).**
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Over the last several years it has become popular to attribute nonspecific symptoms in the indoor environment to the complex mixture of volatile organic compounds and particulate matter, often called a "primordial soup," in indoor air in offices and to individuals' states of mind, implying that there are neither scientific explanations for such symptoms nor solutions. In the context of the medically unexplained symptoms discussed in this monograph, such statements reflect widespread attitudes about patients and workplaces. The term "sick building syndrome" has been used for 20 years without an operational definition. The term represents primarily a starting point for conceptual analysis (*1*). Attempts to provide alternative names, for example, problem buildings, building-related occupant complaint syndrome, abused building syndrome, and many others, have not met with success, and the term remains in common use. Attempts at defining alternatives reveal two major confusions:

- Is the issue one of feeling sick or appearing to be dysfunctional or are problems objectively measurable?
- What can we explain when symptoms are not objectively measurable?

In addition, in the context of other syndromes such as chronic fatigue, fibromyalgia, and multiple chemical sensitivity, how can we understand similarities in presentation, mechanisms of illness, and long-term outcomes, including disability?

What do we do about disability related to such symptoms?

This review is a summary of what we know of physiology and exposures in indoor environments and concludes with unanswered questions. The central tenet is that we can explain many symptoms but that such explanations will not satisfy the question driving the investigations, that is, the degree of disability that patients experience. A potential nosology of disease for all the syndrome categories is presented at the end.

Is There a Basis for Feeling Sick in the Built Environment?

Well-Defined Disease

Data from around the world suggest that complaints in buildings are ubiquitous, occurring on all continents where they have been gathered. Some of these represent diseases related to exposures in the indoor environment, which have been documented in the peer-reviewed literature, with defined diagnostic criteria. Standard textbooks present lists of the diseases and of diagnostic and linkage criteria. We recognize broad groups of chemical toxicity, such as from carbon monoxide, organophosphates, and thallium; infections, such as tuberculosis, Legionnaire's disease, and viral illness; and a range of allergic and immunologic diseases, from allergic rhinitis to hypersensitivity pneumonitis. Although the diseases are straightforward, often physicians fail to consider them. Recent data suggest, for example, that hypersensitivity pneumonitis is frequently misdiagnosed. More recent outbreaks (*2–4*) suggest that occupants with few symptoms and only strong complaints of fatigue and nausea with minimal chest complaints may have evidence of granulomatous pulmonary disease on biopsy.

Although characterization of those symptoms and diagnosis of disease are often straightforward, linkage to an exposure requires far deeper considerations. For some, such as asthma or acute hypersensitivity pneumonitis, linkage strategies using physiologic measures are fairly straightforward. Tests are well defined, widely available, and persuasive by themselves as a measure of disease. On the other hand, immunologic testing, although a valid and widely used approach, is not so straightforward. Antibodies serve as reasonable markers of exposure but not of disease (*5*), and in many recent outbreaks they have not even supported linkage with any particular microorganism. Conversely, since initial building investigations, evidence shows an association of symptoms with moisture. In the course of searching for moisture and humidifier fever (*6*) in buildings, Finnegan et al. (*7*) found that symptoms were associated with humidification and ventilation. Subsequently, cross-sectional studies have supported an association of higher rates of symptoms with endotoxin exposure (*8*) and with the presence of unwanted moisture in ventilation systems (*9*).

The presence of major deficiencies in building systems, such as unwanted moisture with bioaerosol growth, in parallel with plausibly related disease usually serves as adequate evidence to warrant remediation. Similarly, the development of pesticide poisoning or headaches in the setting of a plausible exposure (entrainment of organophosphates or carbon monoxide) with reasonable biological markers (elevated carboxyhemoglobin or depressed but subsequently normalizing cholinesterase levels) represents adequate evidence of disease. Some infectious diseases rely on relatively straightforward, although sometimes expensive, linkage strategies. Identical *Legionella* strains identified from patient fluids and environmental sources with a probable route, or polymerase chain reaction characterization of tuberculosis, relatively rare events, are simple. Upper respiratory infections, on the other hand, a very common problem, occurring at 1.5- to 2-fold rates in commercial office buildings with mechanical ventilation, are currently essentially impossible to link to the workplace.

Some diseases clearly recognized as building related may cause disability and represent obviously compensable adverse health effects.

Unexplained Symptoms with Potentially Explained Mechanisms

The symptoms frequently labeled "sick building syndrome" result from several different mechanisms, some better understood than

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others, none of which result in disability from our current understanding of physiology. In fact, Jaakola (*1*) has argued that the lack of an operational definition reflects the widespread recognition that the syndrome represents a theoretical construct for discussion purposes only. Still, mechanisms to explain these symptoms have been identified, although attribution of individual symptoms to individual exposures still remains a problem.

Several sets of data identify multiple deficiencies in virtually all buildings in which complaints have been identified (*10–12*). Few data suggest that such widespread failure of buildings to meet professional expectations is associated with symptoms, primarily because few studies have been designed to examine this hypothesis, although reviews on this topic (*13*) do suggest associations with building factors in general. In addition, individual studies suggest the ability to change symptoms based on systematic interventions on moisture content (*14,15*), particulates (*16,17*), or known sources (*18*). This suggests that many of these symptoms may in fact have remediable causes.

Volatile Organic Compounds

Molhave and colleagues in Denmark have pursued the hypothesis since the early 1980s that complex mixtures of volatile organic compounds (VOCs) might be the primary cause of mucosal irritation, a prominent symptom, and that these agents might in some way also contribute to headaches, fatigue, and dizziness (*19,20*). Chamber studies have confirmed in Denmark and the United States that symptoms increase in humans and animals after controlled exposures. In addition, individuals with atopy respond with more symptoms at lower levels of exposure (*21*). Field studies support such relationships. Sundell and colleagues (*22,23*) found that symptoms appeared to be related not only to ventilation rates but also to "lost" VOCs. The concentration of VOCs entering the room was higher than that leaving the room, the difference being termed "lost VOCs." As the VOC concentration difference increased from air intake to exhaust, symptoms increased. This decrease likely reflects chemical reactions with reactive agents like ozone that create more irritating, smaller molecules (see indoor chemistry discussion, later). Hodgson et al. (*24*) suggested that symptoms were associated with increasing concentrations of VOCs as measured with a screening device that responds to more reactive VOCs (photoionization detector). Ten Brinke et al. (*25*) identified relationships between symptoms and clusters of VOCs by likely emission sources, suggesting that individual building components, such as carpeting or latex paint emissions, contributed to symptoms.

Mucosal Irritation

More important, such symptoms, commonly attributed to the common chemical sense, appear to follow predictable dose–response relationships with increasing concentrations of complex mixtures of VOCs. Abraham (*26*) used the irritation thresholds derived in these investigations to develop a quantitative structure–activity relationship that allows the prediction of irritation based on the physical characteristics of the molecules. The equation is based on the equations developed by Meyer and colleagues in the early part of this century for anesthetic agents, and more recent systematic attempts using complex statistical modeling to understand physicochemical properties. These characteristics explained 98% of the variance in models to explain irritation. Subsequently, Alarie et al. (*27*) demonstrated that some "reactive" species trigger symptoms that do not follow this predictable pattern and therefore that irritation from reactive species must be caused by a different mechanism. Weschler and Shields (*28*) and Wilkins et al. (*29*) have examined the relationships of reactive species with such relatively nonreactive agents and shown that "indoor chemistry" produces far more irritating substances at a ratio of 2:1 compared with the initial nonirritating agent. Indoor chemistry in this context refers to the reactions of compounds such as ozone and nitrogen oxides with relatively inert VOCs in a fashion that oxidizes them and produces two more irritating for each single previously inert molecule. This effect has been demonstrated for carpet emissions, latex paint offgassing, and other common office pollutants.

Finally, markers of exposure have been identified. Symptomatic individuals appear to have tear film breakup time, conjunctival staining with fluorescein dye, and erythema on photography that appear different from asymptomatic building occupants (*30–32*). Tsubota (*33*) has reviewed the physiology of tear film production and suggests two mechanisms by which underlying susceptibility might increase eye complaints. First, both decreased basal and reflex stimulation lead to dry eye complaints. In addition, decreased Meibomian gland lipid secretion will allow more rapid evaporation of tear fluid in the presence of enlarged exposed ocular surface during computer screen work (*34*). The overlaps of the two groups are large enough to preclude use of these tests in the clinical discrimination of symptom causation.

The recognition of excess symptoms in the late 1970s led to chamber studies identifying mechanisms in people and animals, dose–response relationships in controlled exposure studies, markers in humans supporting some "real effect," and field studies identifying the relationship in unselected populations. VOCs clearly represent at least one cause of mucosal irritation in indoor environments.

Headaches

Headaches represent the single most common symptom in almost all indoor environmental studies (*35,36*). Although rare outbreaks of carbon monoxide poisoning occur, most headaches represent events without clear characterization in the office environment. These have generally not been classified into standard categories (*37*) by the most widely accepted and used nosology. Such standard categories reflect the current state of knowledge on mechanisms for some forms of headache, such as migraine, and allow identification of other forms without as yet explained physiology, such as tension-type headache. Such headaches are no less important given the productivity implications (*38*) and the potential for effective intervention and disability reduction in the office environment (*39*). Although higher symptom rates appear associated with specific exposures, such as VOCs, and with building factors, this may explain triggering of symptoms but not necessarily initial induction of conditions such as the tendency toward migraines.

Thermal Discomfort

Since the early part of this century, engineers have recognized that thermal discomfort is a major contributor to indoor environmental complaints. Flugge [reviewed in Jansen (*40*)] demonstrated that odor perception and heat sensation were the main reasons for ventilating occupied space. Subsequent empiric work has confirmed that the thermal comfort envelope does not provide an adequate margin of comfort when other modalities of exposure approach their own acceptability boundaries. Exceedance beyond the thermal comfort envelope is associated with increases in symptoms not commonly attributed to that domain, such as headaches, mucosal irritation, and fatigue.

Complaints of being too hot or too cold are often associated with headaches, fatigue, and mucosal irritation. The thermal comfort envelope in offices is controlled by the Standard 55 Thermal Conditions for Human Occupancy from the American Society of Heating, Refrigerating and Air Conditioning Engineers (*41*). Maintaining thermal parameters within the confines of the comfort envelope under ideal conditions satisfied approximately 80% of the population, although in practice usually far greater proportions are uncomfortable. The reasons are manifold. Clothing often provides more or less thermal "protection" than assumed under ideal conditions. Office furniture has

changed, with newer chairs often providing more thermal resistance and creating a hotter environment than calculated in the standard. Increasing numbers of electronic devices provide greater heat loads in the office than those for which many buildings were designed. Finally, current mathematical models of thermal comfort, on which current standards are based, fail to include dynamic aspects of work (recent exercise and heat loading), aging, and other critical issues. In any case measurement of temperature and relative humidity often shows poor control, suggesting additional environmental contributions to symptoms of headaches, fatigue, and mucosal irritation.

Symptoms without Explained Physiology but with Objective Markers

Increasingly, outbreaks present with multiple forms of disease, where various combinations of asthma, hypersensitivity pneumonitis, and interstitial pneumonitis appear together (*3,42,43*). In parallel, excess chest symptoms such as wheezing, chest tightness, and coughing (*9*) suggest that symptoms consistent with asthma are not infrequent, associated with moisture. Well-documented cases of disease appear to be accompanied by less clearly defined excess rates of upper airways symptoms, without clearly defined mechanisms (*42,44*).

Still, these symptoms cannot be easily explained based on current physiologic or immunologic knowledge. If they represent "real symptoms," that is, have a cause in the external environment, they too must have some objective markers and eventually show some relationship with external exposures. So, are they accompanied by markers that indicate something we do not yet know how to explain is going on?

There is, meanwhile, clear evidence from nasal lavage studies that bioaerosol exposure is associated with some immunologic markers that are not present in individuals without exposure or symptoms (*45,46*). As in the past, the lack of an explanation for symptoms in individuals may reflect our lack of research rather than the absence of some cause and effect.

Similarly, despite the fundamental validity of dose–response relationships, clear evidence of markers for individual susceptibility separate normal from more sensitive groups. For example, chamber data identify higher levels of symptoms in atopic individuals exposed to the same levels of complex mixtures of VOCs (*16,47,48*). Atopic individuals respond with a larger decrease in nasal resistance to a defined irritant challenge than do nonatopics (*49*). Higher-than-average symptoms after application of dilute lactic acid to the skin are associated with more dermal complaints in the office (*50*). Additional markers that differentiate groups of individuals with more from those with fewer symptoms include nasal hyperreactivity (*51,52*) and more rapid tear film breakup time (*30,31*). Still, the underlying assumption remains that these markers reflect either underlying mechanisms or susceptibility and simply shift the dose–response curve in some predictable fashion.

Odors

Similarly, odors feature prominently in anhedonic responses in the indoor environment and are sometimes considered an integral part of the sick building syndrome construct. Nevertheless, models to explain odorant properties are substantially less well developed. Boswell et al. (*12*) systematically examined the problem of potential indoor odor sources using a well-defined protocol in only one study and found that almost 80% of transient odor complaints had identifiable and remediable causes. Odors associated with moisture and bioaerosol exposure are common and best considered in the context of disease with physiologic indicators. Some VOCs have distinct odor recognition characteristics, but those are then best considered part of the mucosal irritant syndromes. Odor recognition thresholds are usually several orders of magnitude below the irritant thresholds (*53*).

The mechanism for odor recognition is well studied. Although there are attempts at developing structure–activity relationship models analogous to that of Abraham (*26*), such models show much poorer fit. In addition, "odors" do not present a clinical outcome suggesting a well-defined syndrome.

Symptoms, Exposures, and Disability

There is evidence to document and even explain many symptoms at the levels commonly encountered in indoor spaces. Because these symptoms represent well-defined physiologic mechanisms, the label "sick building syndrome" should not be considered synonymous with "unexplained." Most symptoms in the built environment, however, do not represent disease as recognized by clinicians. For some exposures such as bioaerosols, conditions may be evaluated using very traditional tests for well-defined conditions such as asthma or hypersensitivity pneumonitis. There, at least, objective evidence of disease makes subjective perceptions of illness understandable. Although low levels of VOCs may cause symptoms, including mucosal irritation and headaches, no data explain how such symptoms may generate disability at such low levels. The degree of subjective symptom intensity often correlates only poorly with the degree of impairment as defined by organ dysfunction, a well-known problem in disability evaluations.

Some authors have argued that sick building syndrome has similarities to chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. Strikingly, although epidemiologic and clinical case definitions have been developed for these three conditions, it remains unclear whether all subjects meeting those definitions experience the same illness. For example, multiple chemical sensitivity reflects, in the minds of some investigators, respectively, irritation in underlying chronic sinusitis, conditioned psychological responses to external stimuli, misinterpretation of a normal sensation, and an obsessive-compulsive personality disorder. Case definitions do not imply cause (*54,55*). No case definitions even exist for sick building syndrome. Questionnaire-based studies of buildings always include some aspect of prompt symptom resolution with leaving the work environment, implying resolution of the syndrome. This distinguishes the syndrome quite dramatically from common descriptions of multiple chemical sensitivity, where patients often describe longer-term symptoms with "dis-ability" lasting days and weeks after an exposure.

It is difficult to consider occupant discomfort and symptoms in the built environment without acknowledging that all discomfort and disease have a psychologic component. It is clear that symptoms are strongly associated with psychological factors [reviewed in (*13,56*)]. Specific signs such as facial erythema are associated with traditional biologic markers of stress (*57*). As important, work stress appears consistently associated with symptoms (*13*). This may simply reflect our much more robust ability to characterize work stress and our lack of knowledge about specific exposure assessment techniques than a true stronger relationship. Although work stress is associated with symptoms, it is a theoretical construct that reflects beliefs and interpretations of the discussant. It does not imply a specific psychiatric diagnosis nor does it really address the causes of discomfort, exaggeration of symptoms, and distortion of the dose–response relationships.

Pain represents a predictable subjective response to stimuli and has its own body of scientific literature. Elsewhere in this monograph, authors discuss the relationships between the objective stimuli and two kinds of subjective responses, the physiologic sensation and the experience of the associated pain and discomfort. These may diverge in a predictable fashion, as has been shown for multiple chemical sensitivity and fibromyalgia.

In the absence of understanding, we must first attempt to define what we see, classify phenomena into some set of recognizable conditions that allow us to formulate treatment plans, and establish criteria that let us postulate hypotheses for further testing. One example of such nosologic attempts and where they led is the New York Heart Association classification of heart disease (*58*). Such an approach worked well from the 1950s through the 1970s in the attempt to communicate about heart disease, to agree on standards of treatment, and to guide research questions. Based on the descriptions above, and elsewhere in this monograph, questions about each of the syndromes may be classified by a specific set of tools. Such systematic data gathering about the various syndromes may complement the research efforts of individual groups and provide understanding of the shared characteristics of these syndromes. International comparisons suggest that "disability" can only be understood in a social context, that is, when considering not just subjective experience but also the social and legislative infrastructure in which individuals live. An international study of disability has attempted to describe the social and legislative infrastructure surrounding the concept of disability across countries (*59*). Recently, the World Health Organization has released its updated classification on functioning, disability, and health (*60*). The grouping now considers four major classifications (body functions, body structures, activity and participation, and environmental factors). Such systematic attempts at classification have not been undertaken for the understanding of unexplained symptoms or, more broadly of disability, symptoms, medical health, and the physiologic implications.

How can researchers then look beyond physiology to understand?

One possible set of classification criteria to be used for the next years might include those presented in Table 1. For obvious reasons, the presenting case definition, as agreed upon elsewhere, should be the starting point.

Table 1. Potential classification criteria for poorly explained syndromes.

Syndrome	Multiple chemical sensitivity, fibromyalgia, etc.
Additional symptoms	Checklists, questionnaires
Inciting event	History
Physiology	Challenge tests (chamber tests for airborne exposures, thumbscrew tests for fibromyalgias, etc.)
Psychiatric status	Diagnostic interview schedule
Personality style	Personality inventories
Psychosocial issues	Description of family and work dynamics
Functional status	Performance scales (Karnofsky scales, etc.)

This requires agreement on case definitions for multiple chemical sensitivities, fibromyalgia, and so on. Still, additional symptoms of interest not typically associated with that syndrome must be queried in a systematic fashion, best using questionnaires. Otherwise, overlaps cannot be determined. Because of the differences in physiologic responses to defined stimuli, such as pressure (thumbscrews) in fibromyalgia or mucosal irritants (chamber studies) in multiple chemical sensitivity, physiologic characteristics must be included. Finally, among the most dramatic unexplained characteristics are the differences in disability. Traditional approaches to measurement, such as performance or disability scales, appear essential. As important, personality style and disability perceptions remain controversial topics. The subjective experience of "disability" can only be understood by examining that experience. Nevertheless, the scientific literature on this topic appears to be sparse based on literature searches.

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