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A toxicologic approach for evaluating cases of sick building syndrome or multiple chemical sensitivity

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Abstract

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The nonspecificity of symptoms and exposures commonly reported as “sick building syndrome” is very similar to that reported for the condition termed “multiple chemical sensitivity (MCS).” In many instances health care practitioners are divided on the reality of the latter. As in all scientific cases of possible cause-and-effect relationships, an organized, dispassionate approach should be used to evaluate each claim of MCS. Most obviously, known medical conditions must be ruled out before chemical “sensitivity” is proposed. Also, several questions on the toxicology of the chemical exposure must be addressed. Although temporality may be apparent (toxicity followed exposure), the time frame for the appearance of symptoms must be appropriate to the exposure conditions and chemical(s) involved. The chemical(s) must have known or reasonably inferred properties to cause the claimed effect. The dose(s) received must be adequate to effect a response (dose-response characteristics). Alternate causation must be evaluated thoroughly, that is, are there other more logical explanations for the symptoms? In contrast to single-chemical exposures, exposure to mixtures of chemicals, as commonly found in sick buildings, is very difficult to evaluate. However, a rational, scientific approach to cause-and-effect questions will help avoid erroneous and subjective

decision making. (J ALLERGY CLIN IMMUNOL 1994;94:371-5.)

MCS Multiple chemical sensitivity

(Click on a term to search this journal for other articles containing that term.)

Key words: [Sick building syndrome](#), [multiple chemical sensitivity](#), [toxicology](#)

During the past 10 to 20 years, health problems have been reported by employees working in buildings that most commonly have been designed and operated for energy efficiency. The symptoms reported are traced frequently to inadequate ventilation, faulty humidity control, the presence of biologic contaminants (molds, spores, fungi, etc.), or the presence of specific chemical contaminants. However, in many instances the cause(s) of the symptoms are undetermined. When the setting for these problems is restricted to the interior of a building, the term “sick building syndrome” has been applied.¹

Typically, the symptoms associated with the sick building syndrome are nonspecific and involve several organ systems. The term “multiple chemical sensitivity” (MCS) has been coined² to describe a condition that has symptoms similar to those reported by persons in sick buildings (■Table I).³ Common features of MCS include symptoms that involve more than one organ, recur and abate in response to predictable stimuli, and are elicited by exposures to chemicals of diverse structural classes and toxicologic modes of action. The appearance of these symptoms is in response to exposures that are usually below those levels known to cause adverse human responses⁴ or may not even be demonstrable.

TABLE I. Symptoms associated with both sick building syndrome and MCS

Arthritis	Genitourinary problems
Asthma	Gynecologic problems
Behavioral disorders	Headache
Cardiac problems	Immunologic problems
Chronic fatigue	Learning disabilities
Depression	Musculoskeletal problems
Dermatologic problems	Respiratory problems
Eye problems	Schizophrenia
Gastrointestinal problems	Vascular problems

Increasing attention is being paid by lay and professional audiences to the possible occurrence of MCS in several circumstances, including the sick building. As reported recently in the lay press, sick buildings may be caused not only by “a potpourri of pollens, spores, and other allergens,” but also “a mix of sewer gases, a whiff of chlorine, and an overdose of carbon dioxide.”⁵

Although MCS is the term most commonly used to describe the conditions listed previously, synonyms as varied as “environmentally induced disease,” “chemical hypersensitivity syndrome,” “ecologic illness,” “twentieth century disease,” and “cerebral allergy” have been adopted by various groups.⁶ An additional twist on this theme is found in the lay nutrition/health food literature where the term, “food and chemical sensitivity,” is used frequently. It has been asserted that “natural” foods are safe, whereas foods containing artificial components are hazardous. In this situation, avoidance of perfumes, cosmetics, plastics, paper, chlorine, alcohol, detergents, pesticides, smoke, moth balls, fuels, carpets, new clothing, vehicle exhaust, restaurants, laser printers, particle board, plywood, and “synthetics” is recommended.⁷

The validity of MCS as a clinical condition is highly controversial and consequently poses a significant diagnostic challenge to the medical practitioner. Reported symptoms (■Table I) encompass most medical specialties, or alternatively, the individual may claim exposure to chemicals and yet have no symptoms. On the other hand, documented medical conditions (■Table II) may be diagnosed as MCS.⁸

TABLE II. Medical conditions commonly diagnosed as MCS

Infections
Chronic/acute sinusitis
Mononucleosis
Pharyngitis/bronchopneumonitis
Allergic/inflammatory states
Allergic rhinoconjunctivitis
Atopic dermatitis/contact dermatitis
Chronic eustachian tube dysfunction
Chronic serous otitis media
Hypersensitivity pneumonitis
Nasal polyps/tumors
Nonallergic upper airway conditions
Reactive airways disease
Rhinitis medicamentosa

Vasomotor rhinitis

Vocal cord polyps/tumors

Metabolic/toxic conditions

Diabetes mellitus

Drug use

Hypothyroidism/hyperthyroidism

As in any other scientific question of causation, a dispassionate, objective approach should be taken to address the validity of a proposed relationship between chemical exposures and clinical complaints. This report presents guidelines for conducting toxicologic investigations that are applicable to the MCS/sick building syndrome controversy as well as other circumstances of reported chemical exposure/resultant injury.

Although it is true that each case may have multiple unique features (type of chemicals involved, the concentration of chemicals, duration of exposure, susceptibility of the individual, etc.), certain common elements must be considered. Among these, the most commonly encountered is temporality. Frequently this aspect of a situation is accepted erroneously as adequate proof for causality; that is, condition “B” followed exposure “A” and therefore “A” caused “B.” Although temporality is certainly an important consideration, it is necessary to establish whether the injury follows the exposure within a proper time frame. An injury that is claimed long after realistically expected is unlikely to be causally related. For example, exposure of building occupants to an exhaust source of low level carbon monoxide (“A”) would be consistent with appearance of acute symptoms (“B”) including headaches, fatigue, disruption of attention, dizziness, and other symptoms characteristic of reduced oxygen delivery to tissues. These symptoms would appear within a few hours of the onset of exposure. The initial appearance of these same symptoms several months after the exposure has been terminated would have the same temporal relationship (B follows A), but causation would not be supported. Defining the realistic limits of temporality seems apparent but is frequently overlooked.

When temporality is appropriate, the dose received must be carefully evaluated. Was it realistically high enough to produce the injury? The erroneous opinion that exposure to “toxic chemicals” at any dose produces deleterious effects abounds in the lay public and is prevalent in the medical profession. The fact that dose defines toxicity for all chemicals has been recognized for centuries. In our chemophobic society many persons believe that even if only the odor of a chemical is detected, then permanent injury can result. Odor detection does not ordain toxicity; our sense of smell can detect many chemicals at levels far below their toxic thresholds. In addition, individual responses to odor have many subjective influences. For example, “pleasant” odors (e.g., amyl acetate is the fragrance of banana oil) are normally perceived as “safe”; “unpleasant” odors such as sulfides (rotten eggs) or indoles (fecal odor) are popularly associated with “toxicity.” Neither documented exposure nor odor detection necessarily dictates adverse responses to any chemical. To repeat an overused but often ignored truism: the dose of a chemical determines whether that chemical is toxic or nontoxic. Appreciation and application of this basic tenet of toxicology, the dose-response relationship, are necessary when objectively evaluating chemically mediated effects.

It is imperative to compare the toxicologic properties of the chemicals in question with the reported symptoms or injuries. For many chemicals the types of symptoms, injury, or disease that may occur

after exposure can be predicted on the basis of available toxicologic data or known biologic activity of the chemicals. If the complaints do not fit into this known profile, a causal relationship should be questioned further. For example, exposure to formaldehyde vapor can cause headache, dizziness, and ocular irritation. A claim that exposure to formaldehyde caused diabetes could not be supported because the chemical and the disease have never been linked and formaldehyde does not have properties that would be expected to cause this disorder. If toxicologic data are not available for the chemical in question, information may usually be found on structurally similar compounds that may provide directions for inquiry.

In a situation in which a preexisting condition is identical or very similar to the claimed injury, establishment of causation from a subsequent chemical exposure is virtually precluded. For example, if an individual has a history of preexisting asthma that is aggravated by physical, psychological, or chemical stimuli, then a claim that asthma has been caused by exposure to chemicals in the indoor environment or elsewhere is untenable.

Finally, the possibility of alternate causes for the alleged injury must be investigated carefully. Individuals are exposed daily to chemicals and pathogenic organisms, may be taking prescription and nonprescription drugs, may suffer from physiologic and psychological stress, or may have preexisting medical problems. Many of these agents or situations can cause symptoms similar to those reported in sick buildings and MCS. Therefore it is imperative that alternate causes be considered thoroughly in evaluating causal relationships. For example, one of the authors (M.R.M.) has evaluated several cases diagnosed as MCS by local physicians. In one typical case, a patient reported that insomnia, anorexia, irritability, confusion, shaky extremities, anxiety, and depression developed several months after a single exposure to organophosphate insecticide. No acute symptoms from the exposure are claimed. A thorough review of medical and occupational records revealed that this person was taking seven neuroactive prescription medications for other problems concurrently with the diagnosis of MCS. ■ Table III presents those drugs and their commonly encountered side effects. A comparison of clinical complaints and drug side effects supports the conclusion that the most likely cause of the complaints was drug toxicity and not MCS.

TABLE III. Case example: Comparison of reported complaints and medication toxicities

Drug	Side effects
Prozac	Anxiety, nervousness, insomnia, anorexia, dizziness, tremors, nausea, light-headedness
Xanax	Drowsiness, light-headedness, anorexia, muscle spasticity
Elavil	Tremors, peripheral neuropathy (numbness, tingling), anxiety, insomnia, drowsiness, dizziness, depression
Procardia	Dizziness, light-headedness, nausea, muscle cramps
BuSpar	Dizziness, anorexia, muscle spasms
Depakote	Nausea, anorexia, sedation, tremors, emotional upset, depression
Dalmane	Dizziness, light-headedness, drowsiness, nausea, chest pains, blurred vision

Patients' complaints: insomnia, anorexia, irritability, confusion, shaky extremities, anxiety, and depression.

Alternate causation is evaluated ideally by a thorough and frequently tedious review of the complete medical, occupational, and social records of the patient. This is seldom accomplished adequately because of time constraints and frequent lack of availability of such records.

Several toxicologic problems are approached differently than those discussed previously. Allergic (or sensitization) reactions may occur with exposure to very small quantities of chemicals that would be nontoxic to an unsensitized individual. In addition, the allergic response may be unrelated to the toxicologic profile expected from the chemical. Allergic reactions may also have a degree of cross-reactivity among structurally related chemicals; for example, an individual who is allergic to toluene diisocyanate may have an allergic response to the structurally similar diphenylmethane isocyanate. Appropriate evaluation of claimed allergic responses (to chemicals or otherwise) should be based on accepted testing methodologies and objective diagnostic criteria.

Adverse reactions caused by genetic determinants are called idiosyncratic reactions and may occur with exposure to otherwise nontoxic quantities of chemicals. Prediction of these idiosyncratic reactions ranges from easy to difficult to impossible. Little information is available on idiosyncratic reactions in nonclinical situations. Examples drawn from clinical pharmacology show that the frequency may be as common as one in three (slow acetylation of isoniazid) or as rare as one in three thousand (succinylcholine toxicity caused by deficiency of cholinesterase). Other situations can be envisioned where the idiosyncratic reaction to a chemical is so extremely rare that it would be totally unpredictable. Such a very rare reaction could be postulated from exposure to any of the myriad of chemicals in the daily environment; however, an argument proposing an extremely rare idiosyncratic reaction will be without foundation in the absence of patient-specific data derived from molecular genetic investigations.

Injury alleged from exposure to chemical mixtures rather than from individual chemicals is perhaps the most difficult to evaluate and unfortunately may be the most commonly encountered in environments such as building interiors. Toxicologic investigation of mixtures requires a thorough understanding of the various physical, chemical, biochemical, metabolic, and physiologic forces that will be interacting simultaneously. Sound judgment and knowledge of the relative strength and contribution of each influence are imperative. There is no uniformly accepted toxicologic approach to addressing chemical mixtures. Knowing nothing of the interactions among the components of a mixture, the potential toxicities of the individual chemicals may not simply be summed or assumed to be potentiative or synergistically toxic. Even the simplest situation a mixture of two chemicals, each of which has only one potential toxicity provides at least 10 possible outcomes (■ Table IV). If each of the two chemicals has multiple toxicities or if additional chemicals are added to the mixture, the possible interactions increase dramatically. It must be emphasized that complex mixtures may contain various chemicals that are individually toxic at high doses. However, the actual mixture, with much lower individual concentrations of components, may not only be nontoxic but may even be beneficial (e.g., foods). The validity of the final opinion for or against causality from mixtures will depend on the extent of the factual knowledge of the individual components and their potential interactions. The strength of the final opinion should not be greater than the weakest element of that knowledge.

TABLE IV. Some possible toxicologic responses to a mixture of two chemical, “X” and “Y”

Possibility	Response*
1	No response to either chemical
2	Response to X only
3	Response to Y only
4	Unrelated responses† to both X and Y
5	Related‡ additive§ responses to X and Y
6	Potentiative¶ interaction of X on Y
7	Potentiative interaction of Y on X
8	Synergistic interaction of X and Y
9	Antagonistic** interaction of X on Y
10	Antagonistic interaction of Y on X

*Assumes only one toxicity each for X and Y.

†Unrelated means toxicity of each chemical to different organ systems with no interactions causing the toxicities.

‡Related means toxicity of both chemical to the same organ system.

§Additivity means the resultant response is the sum of the individual responses.

¶Potentiation means that although one chemical alone has no toxic effect, when added to another chemical it makes the latter more toxic.

||Synergism means that although each chemical has an individual toxicity, the combined effect is greater than the sum of the two individual effects.

**Antagonism means that the response to one chemical is reduced by the action of the other chemical.

Once all the toxicologic factors have been considered in an individual case, a decision must be made on the probability of a causal association between a chemical exposure and the adverse health condition that is claimed. The medical community must become aware that the ramifications of that decision now extend well beyond the clinical setting. In our increasingly litigious society, diagnoses containing phrases such as “may be due to,” “need to rule out” and “probably caused by” may become the foundation for expensive and frequently unfounded legal actions and may involve the practitioner in an undesired, adverse manner. Medicolegal terms such as “more probable than not,” “within medical/scientific probability,” and so forth have little or no practical meaning beyond legal context. A suggested alternative to such vague and frequently misinterpreted phrases as those listed would be, “based on the following evidence, the most likely cause of (symptom/disease/injury) is . . .” Such an objective statement requires that the conscientious practitioner provide the factual basis and considerations for the decision. More important, diagnostic opinions based on exclusion should be avoided, that is, “I don’t know how ‘A’ could have caused ‘B’ but I have no other explanation for ‘B.’ Since ‘A’ did occur, ‘A’ must have caused ‘B’.” This type of unsupported statement may be “safe” for the practitioner and will avoid the professional embarrassment of simply stating “I don’t know,” but it surely does disservice to the objectivity of scientifically based medicine.

In many instances the final clinical opinion may be a weighted judgment of the relative pros and cons for the causal relationship in question. Although perhaps unsatisfying in a diagnostic context, this apparent equivocation is not a condemnation of the clinician's skills but rather is an affirmation that the scientific process of critical evaluation and objective decision making is being used. The scientific tenet of the null hypothesis (i.e., unproved until evidence shows otherwise) is not inappropriate in clinical medicine as it relates to toxicologic issues.

References

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1. Samet JM, Marbury MC, Spengler JD. Respiratory effects of indoor air pollution. *J ALLERGY CLIN IMMUNOL* 1987;79:685-700.

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2. Cullen M. The worker with multiple chemical sensitivities: an overview. *State Art Rev Occup Med* 1987;2:655-66.

3. Rest KM, ed. Advancing the understanding of multiple chemical sensitivity. *Toxicol Indust Health* 1992;8:1-13.

4. Cullen MR, Pace PE, Redlich CA. The experience of the Yale occupational and environmental medicine clinics with multiple chemical sensitivities, 1986-1991. *Toxicol Indust Health* 1992;8:15-9.

5. Safran C. Schools that make kids sick. *Good Housekeeping* 1992;214:176-ff.

6. American College of Physicians. Clinical ecology. *Ann Intern Med* 1989;111:168-78.

[MEDLINE](#)

7. Hileman B. Multiple chemical sensitivity. *Chem Eng News* 1991;July 22:26-42.

8. Bardana EJ, Montanaro A. Chemically sensitive patients: avoiding the pitfalls. *J Respir Dis* 1989;10:32-45.

Publishing and Reprint Information

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