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**LOW-LEVEL CHEMICAL SENSITIVITY:
IMPLICATIONS FOR RESEARCH AND SOCIAL POLICY¹**

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Abstract

There is increasingly evidence that human exposure to levels of chemicals once thought to be safe -- or presenting insignificant risk -- are, in fact, harmful. So-called low-level exposures are now known to be associated with adverse biological effects including cancer, endocrine disruption, and chemical sensitivity. This requires that we change both (1) the way we design research linking chemicals and health, and (2) the solutions we devise to address chemically-caused injury. The new and emerging science of low-level exposure to chemicals requires appropriate social policy responses which include regulation of toxic substances, notification of those exposed, and compensation and reasonable accommodation to those affected. Research and social policy needs to be focused towards two distinct groups: (1) those individuals who could become chemically intolerant as a result of an initiating exposure and (2) those individuals who have already become chemically intolerant and are now sensitive to chemicals at low levels.

1. INTRODUCTION

While sensitivity to low levels of chemical exposures is not a new problem, it has been approached with renewed interest, and controversy, in the last decade, first in North America and more recently in Europe. The Canadian government first examined the problem of chemical hyper-reactivity in 1985 in its Thomson Report [27] and has since sponsored several workshops to help define a research agenda in this area. In the United States, the issue has been discussed and examined by state governments [5, 9], federal agencies, [8], the National Academy of Sciences [21], and a number of professional organizations through workshops, conferences, and position papers [3,1,2]. A recent workshop recommended research protocols to address various aspects of the problem [20].

Chemical hyper-reactivity continues to engender scientific debate and controversy around issues relating to etiology, diagnosis, and treatment. While an increasing number of patients voice their concern and dissatisfaction with the response of the medical community and government to their illnesses which they believe are caused by exposure to low levels of chemicals in their environments, the scientific debate rages on; and the medical community continues to engage in sometimes acrimonious discussions about the nature of the problem.

As a result of an overview of the problem in North America [7], it is increasingly clear that low-level chemical sensitivity, rather than a clearly-defined disease entity, might be more correctly described as a class of disorders -- like infectious disease -- the members of which may present with similar symptoms, but which have a myriad of precipitating agents and pathophysiological pathways. Chemical sensitivity may be viewed as the *consequence* of a variety of disease processes resulting from "Toxicant-Induced Loss of Tolerance" (TILT). TILT is a new theory of disease providing a phenomenological description of those disease processes [7,18].

In both the lay and scientific literature, a certain illogic attends the many observations made and approaches taken to unraveling this problem. Errors in logic confuse information relevant to cause, presentation and the evaluation of interventions related to the condition. Drawing upon recent work and observations, this paper attempts to (1) contribute to a clearer way of thinking about chemical sensitivity and (2) to underscore the value of narrowing the focus of future enquiry to observations of event-driven studies, rather than concentrate on characterizing collections of patients who present with chemical sensitivity which they identify as having originated with a myriad of different exposure events and at varying times in the past. In addition, the need to regulate chemicals suspected of initiating the condition, to compensate those affected, and to provide reasonable accommodation in housing and employment is emphasized.

2. DISTINGUISHING DIFFERENT TYPES OF SENSITIVITY

The different meanings of the term *sensitivity* are at least partially responsible for the confusion surrounding chemical sensitivity. Chemical sensitivity encompasses three relatively distinct categories [6]:

1) The response of *normal* subjects to known exposures in a traditional dose-response fashion. This category includes responses of persons at the lower end of a population distribution of classical responses to toxic substances, as well as classical allergy or other immunologically-mediated sensitivity.

2) The response of *normal* subjects to known or unknown exposures, unexplained by classical or known mechanisms. This category includes:

a) Sick building syndrome (SBS) in which individuals respond to known or unknown exposures but whose symptoms resolve when they are not exposed to the building, and

b) Sensitivity, such as that induced by toluene di-isocyanate (TDI), which begins as specific hypersensitivity to a single agent (or class of substances) but which may evolve into non-specific hyper-responsiveness described in category 3) below.

3) The heightened, extraordinary, or unusual response of individuals to known or unknown exposures whose symptoms do not completely resolve upon removal from the exposures and/or whose "sensitivities" seem to spread to other agents. These individuals may experience :

a) a heightened response to agents at the same exposure levels as other individuals;

b) a response at lower levels than those that affect other individuals; and/or

c) a response at an earlier time than that experienced by other individuals.

Patients suffering from what North Americans call multiple chemical sensitivity (MCS) [12] exhibit the third type of sensitivity. Their health problems often (but not always) appear to involve a two-step process. The first step originates with some acute or traumatic exposure, after which the triggering of symptoms and observed sensitivities occur at very low levels of chemical exposure (the second step). The inducing chemical or substance may or may not be the same as the substances that thereafter provoke or "trigger" responses. (Sometimes the inducing substance is described as "sensitizing" the individual, and the affected person is termed a "sensitized" person.) Acute or traumatic exposures are not always necessary. Repeated or continuous lower-level exposures may also lead to sensitization.

These "sensitized individuals" are not those on the tails of a *normal* distribution. They are thought to make up a distinct subset of the population. The fact that normal persons do not experience even at higher levels of exposure those symptoms that chemically-sensitive patients describe at much lower levels of exposure probably helps explain the reluctance of some physicians to believe that the problems are physical in nature. To compound the problem of physician acceptance of this illness, multiple organ systems may be affected, and multiple substances may trigger the effects. Over time, sensitivities seem to spread, in terms of both the types of triggering substances and the systems affected [7, 22].

Avoidance of the offending substances is reported to be effective but much more difficult to achieve for these patients than for classically sensitive patients because symptoms may occur at extremely low levels and the exposures are ubiquitous. *Adaptation* to chronic low-level exposure with consequent "masking" of symptoms is alleged to make it exceedingly difficult to discover these sensitivities and unravel the multifactorial triggering of symptoms [7].

Mechanisms to explain this third type of chemical sensitivity range from psychological (psychogenic) to physiological -- including neurological, immunological, and biochemical (or endocrinological) pathways [7]. Odor conditioning, perhaps involving both psychological and physiological mechanisms, has also been suggested [14].

This paper focuses for the most part on type 3 sensitivity, although hypersensitive sub-cohorts of individuals affected in tight buildings from traditional sick building syndrome (type 2a) -- that is, those individuals who might not have recovered, but who experienced subsequent sensitivities -- might constitute a potentially useful group who could provide important information on low-level chemical sensitivity and overlap with other conditions such as chronic fatigue syndrome [11].

3. SEPARATING CAUSE AND EFFECT: DISTINGUISHING CAUSES, EFFECTS AND THE RESULTS OF INTERVENTIONS

In thinking about a research agenda and the presentation and characterization of low-level chemical sensitivity, it is important to distinguish contrasting ways in which observations of affected persons might be recorded. First, physician reports of individual patients can be examined. Since chemical sensitivity was first "discovered" by observant physicians, this might seem like a useful place to start, but there are difficulties with this approach. While physician reports contain much information about the patient's symptoms and complaints, they usually contain inadequate information about possible *initiating exposures or events* and *outcomes* of various interventions -- both clinical and non-clinical. Moreover, information differentiating initiating events/exposures from subsequent sensitivities is often lacking or conceptually muddled. Since the precise nature of and mechanisms for chemical sensitivity remain

ill-defined, information on possible initiating factors and effective interventions is crucial to improving our understanding of this somewhat bewildering condition. Also, each of the more prevalent effects can be caused by a multitude of biological mechanisms and environmental exposures. Therefore, the symptoms do not indicate the nature of the causality, which may be multifactorial.

Most physicians do not usually obtain occupational or environmental histories on their patients, and the patients themselves may not be fully aware of possible precipitating events or exposures. Moreover, physicians approach patients with their own disciplinary orientations and biases, making it difficult to compare reports on individual patients from different physicians. (Of course, different patients with their own convictions about the cause of their condition may also influence their physician's diagnosis.) For example, pulmonary physicians will tend to focus on respiratory symptoms and airborne contaminants, perhaps overlooking or discounting the more subjective (and possibly equally bothersome) central nervous system (CNS) complaints. Indeed, chemically-sensitive patients often go from physician to physician, acquiring different diagnoses and labels -- from organic brain syndrome to chronic fatigue syndrome to psychosomatic disease. Since there seems to be few proven effective medical interventions for these patients, the eventual outcome of the condition and possible success of various interventions (such as avoidance, food rotation, or simply just letting time pass) may not be known to the diagnosing physician or clinic.

Finally, isolated case reports suffer from being symptom/syndrome-focused in patients with health problems that might be induced by a wide variety of different initiating exposures or events. This has compounded the difficulty in understanding the origins of chemical sensitivity. It was suggested earlier that low-level chemical sensitivity might be more correctly described as a class of disorders, like infectious diseases, the members of which may present with similar symptoms, but whose different causes and pathways need to be particularized to successfully address them. Theoretically, the different forms of chemical sensitivity may be differentially precipitated by psychosocial events or stress, or by different physical or chemical exposures. The presenting symptoms -- whether objective or subjective -- are not necessarily indicative of etiology. As already mentioned, chemical sensitivity brought on by chemical exposures has been described as Toxicant-induced Loss of Tolerance [7, 18].

Causes, symptoms, and interventions can each be characterized as physiological (**P**) or psychological (**Ψ**). Both physiological and psychological stressors can precipitate either physiological or psychological symptoms, or both. Psychological interventions (such as biofeedback and social support) can alleviate some aspects of physical disease. Neither the nature of symptoms, nor the successes of interventions, are dispositive of the origins of a condition. Schematically, the three factors -- causes, symptoms, and interventions -- can be represented as separate "dimensions" of illness (Figure 1). Physicians and researchers may operate in different "quadrants." For example, a physician may believe that the cause of a particular patient's chemical sensitivity is physiological, observe CNS (psychological) symptoms, and treat with biofeedback or

other coping (i.e., psychological/behavioral) interventions. In contrast, a researcher may assume stress as the "cause," observe asthma as a consequence, and investigate the use of new drugs to alleviate the symptoms.

Insert figure 1 here

What is disappointing in much of the literature is the continuing failure to distinguish causes and symptoms of the condition and the unjustified drawing of conclusions from successes or failures of possible interventions. Although lip service is given to making these distinctions, the failure to find consistent objective markers of disease [24] or the finding of a history of childhood abuse in some patient groups [26] lead the authors to lean very heavily in the direction of psychogenic causes and the recommendation of psychological interventions, rather than physiologic causes and the avoidance of future exposures as a treatment modality. Even a recent review of some of the literature on low-level chemical sensitivity [25], while acknowledging the multifactorial origins of this condition, ends up recommending psychological interventions as the only acceptable treatment modality. Inasmuch as great uncertainty continues to characterize this condition, these views are premature and perhaps even harmful to patients [17].

4. EMPIRICAL APPROACHES TO UNRAVELING THE MYSTERIES OF LOW-LEVEL CHEMICAL SENSITIVITY

The need to distinguish information that might elucidate causes, presentation and the success of interventions having been discussed above, physicians' observations may be more helpful when: 1) the physician sees a large number of chemically-sensitive patients, takes a complete exposure history; and recognizes subgroups that give clues to different origins and successful interventions of each; 2) the physician happens to see a group of patients who have experienced the same or similar events or exposures, such as living in the same neighborhood or apartment building or using the same type of product, such as new carpets; 3) the physician specializes in occupational or environmental medicine and sees patients with similar exposures, occupations, or environmental histories; or 4) the physicians are specialists -- for example, pulmonary or ear, nose and throat physicians -- who concentrate on specific organ systems and are more likely to recognize subsets of patients who present with problems uncharacteristic of the majority of patients with the same illness. For example, patients whose asthma is precipitated by perfumes, detergents, and clothing stores may constitute a chemically-sensitive subgroup of special interest. In order for these types of fortuitous observations to provide clarification of chemical sensitivity, the occurrence of some of the different presentations of chemical sensitivity would have to be reasonably large.

Perhaps more informative would be observations on the natural history of chemical sensitivity associated with particular *incidents* or *exposure events* rather than isolated case reports. Event-driven information includes both 1) disease or symptom outbreaks in particular communities, buildings, workplaces, or occupational groups and 2)

events/scenarios reported as related to chemical exposures commonly found in certain occupations and those from particular building materials, consumer products, anesthetics, and ethical drugs. Studies of collected case reports or multiple case reports linked to specific incidents or exposure events might be particularly useful. Identification of events or exposures that could be followed over time may be more likely to be reported by public, environmental, or occupational health authorities, compensation or disability agencies, affected individuals, trade unions, and patient associations rather than by physicians. While retrospective investigations may be helpful, prospective studies (for example of greenhouse workers or occupants of newly-renovated office buildings) might yield useful perspectives, especially if the cohort is followed for a sufficiently long period of time.

Already mentioned is the necessity of accounting for adaptation or the masking of symptoms in observing the symptoms of patients with alleged low-level chemically sensitivity, the possible confounding of observations resulting from the use of therapeutic drugs, and the failure to investigate food intolerances in patients with possible low-level chemical sensitivities [7]. Researchers and clinicians who ignore these concerns, and then find no consistent markers, symptoms, or success in chemical avoidance can not rightfully claim to have tested or investigated the many hypotheses suggested for this condition [13].

5. COMPARISON OF EUROPEAN AND NORTH AMERICAN EXPERIENCES WITH LOW-LEVEL CHEMICAL SENSITIVITY AND IMPLICATIONS FOR RESEARCH

The limited data available at this time from North America and Europe suggest that low-level chemical sensitivity is *not* a single, distinct clinical entity. Clinical presentations are extraordinarily diverse, a major reason why consensus on a case definition for the illness has been so difficult to achieve despite numerous attempts [7, 15]. Symptoms appear to involve any and every organ system or several systems simultaneously, although central nervous system symptoms such as fatigue, mood changes (irritability, depression), and memory and concentration difficulties predominate. Even among persons who have shared the same initiating exposure, symptoms and severity differ markedly. Ultimately, chemical sensitivity may be more accurately characterized as a *class* of disorders, like infectious diseases, which share a common general mechanism, yet within the class, particular members may involve different symptoms, agents, and specific mechanisms.

From European [6] and North American observations [7], a wide range of environmental exposures appear able to initiate the problem. While implicated chemicals are structurally diverse, certain ones appear again and again on both continents:

1. Pesticides are frequently cited in North America and Europe, with the exception of Sweden, Finland, and the Netherlands, where indoor use of

pesticides may be less frequent as a consequence of cooler temperatures and reduced insect populations. Organophosphate and carbamate pesticides are those most often reported as causing illness in the United States, but this may simply reflect the fact that these are among the agents most commonly applied. The greater symptom severity reported by chemical sensitivity patients exposed to organophosphates versus remodeling [19] suggests that some compounds in this class might be especially potent sensitizers, at least for a subset of the population.

2. Organic solvent exposure was cited in every European country surveyed and is commonly cited in North America. Such exposures frequently occur in the workplace and are more often chronic than acute in nature.

While there are consistent observations regarding causes of chemical sensitivity between continents, there are also notable differences, for example, the so-called "wood preservative syndrome" associated with pentachlorophenol use in Germany [23].

Although Sick Building Syndrome (SBS) is widely recognized in the Scandinavian countries where a number of internationally-known researchers are engaged in its study, instances of SBS *per se* did not generally reveal chemically sensitive subgroups. Conceivably, preoccupation with immediate effects may have obscured their discovery. Certainly, there was no indication of a large problem in those instances. Initiating experiences with carpets were noted, however. If future inquiry were to reveal that chemical sensitivity does not occur in even a subset of individuals in European SBS episodes, this finding might suggest the importance of other factors, for example, the use of wall-to-wall carpeting (common in the United States and relatively infrequent in Europe), or use of certain fragrances, air fresheners, cleaners, and/or extermination practices.

In both Europe and North America, patients report spreading of their sensitivities to an array of common exposures, including fragrances, cleaning agents, engine exhaust, alcoholic beverages, foods, and medications they formerly tolerated without difficulty. The fact that many of these individuals voluntarily forego pizza, chocolate, beer, or other favorite foods because they make them feel so ill warrants consideration -- there is little secondary gain to be garnered from such forbearance. Many participants in North America reported that drugs, ingestants containing chemical additives (monosodium glutamate, chlorinated tap water), and food-drug combinations (alcoholic beverages or xanthine-containing foods) made them ill, a finding consistent with a hypothesis that these individuals exhibit amplified responses to pharmacologic doses of a variety of substances [10].

Generally speaking, awareness of chemical sensitivity may be greater in countries with more environmental activism, but illnesses resembling chemical sensitivity were described in every European country that was studied [6]. The practice of clinical ecology, a homeopathic, naturalistic, and holistic medical approach to chemical

exposures, had its origin in the United States. The fact that it has spread to other English-speaking nations, including Canada and the United Kingdom, no doubt have influenced the numbers of patients receiving a diagnosis of chemical sensitivity in those countries. Discord among physicians as to what constitutes appropriate diagnostic and therapeutic approaches in these countries permeates professional meetings, medical journals, and court proceedings. Where patients must "prove" a particular exposure caused their illness in order to receive workers= compensation or reimbursement for medical expenses (as in the United States where there is no national health care system), disputes between medical practitioners (who may testify on opposing sides) are most contentious.

Cultural practices may affect the prevalence of chemical sensitivity. In some European countries, people typically spend several hours each day out-of-doors, for example, walking to work or shopping, and windows in homes and offices may be left open part or most of the day. In contrast, on average, Americans spend 90% or more of the day indoors, often in tightly-sealed structures, where levels of certain volatile organic air contaminants can be orders of magnitude higher than out-of-doors.

Choices of building construction materials and furnishings also vary greatly between countries, including use of wall-to-wall carpeting versus washable throw rugs or no floor coverings at all; solid hardwood furnishings versus particle board or pressed wood; paint, wallpaper, and adhesive constituents; office equipment, including photocopiers and computers, etc.

Ventilation practices may be similarly diverse. Tightly-constructed buildings with little fresh make-up air built in North America since the oil embargo of the mid 1970's could be a factor that explains the apparent increase in chemical sensitivity cases over the past two decades in the United States and Canada. The experience with SBS, but not chemical sensitivity, in Scandinavia merits closer examination to determine whether the latter condition has thus far escaped attention or whether environmental or perhaps genetic or cultural differences may prevent development of the condition.

Use of chemicals also varies from country to country, in particular, pesticides, cleaners, and personal care products, including fragrances. Comparing differing rates of consumption of these products, as well as pharmaceuticals, and the incidence of chemical sensitivity among countries, could provide further clues.

6. IMPLICATIONS FOR RESEARCH AND SOCIAL POLICY

Complex questions concerning the origins and mechanisms of chemical sensitivity will probably not be resolved by study of affected persons who come to the condition via a variety of different initiating pathways. Perhaps more informative would be prospective observations on the natural history of chemical sensitivity associated with particular *incidents* or *exposure events* rather than isolated case reports. (See especially a recent comparison of persons identifying the onset of their chemical sensitivities from

organophosphate pesticides with persons identifying newly-remodeled building environments as the origin of the onset of their sensitivities [19]). In addition, enlightening similarities and instructive differences can be gleaned from future, more directed cross-country comparisons of experiences with chemical sensitivity.

In the past ten years in the United States, controversies surrounding chemical sensitivity have exploded far beyond the narrow confines of a medical debate into a national debate with far-reaching policy and regulatory implications. Most recently, a number of U.S. Persian Gulf veterans have reported multi-system health problems and new-onset intolerances to chemicals, foods, and other substances since returning from the war [7, 16]. Some have received a diagnosis of chemical sensitivity from private physicians and now seek medical care and compensation for the condition. Such trends in North America could be mirrored in European countries over the next few decades.

Understanding chemical sensitivity is pivotal to establishing sound environmental policy. If there is a subset of the population that is (or can become) especially sensitive to low-level chemical exposures, strategies for protecting this subset must be implemented. Over the last decade, there is increasing evidence that certain chemical and pesticide exposures can lead to sensitization or loss of tolerance to low levels of chemicals. Regulatory attention needs to be focused on reducing or eliminating exposure to these substances. In particular, the Precautionary Principle should be implemented to prevent chemical injury leading to devastating and slow-to-reverse health effects [4]. Until regulatory intervention seriously addresses these problems, exposures should be avoided wherever possible. Perhaps by preventing chemical accidents, prohibiting occupancy of buildings prior to finish-out or completion, avoiding use of certain cholinesterase-inhibiting pesticides indoors, notifying building residents of pesticide applications, etc., society could protect more vulnerable individuals from becoming chemically intolerant in the first place. It would be far better to keep people from becoming chemically intolerant, than to be forced to regulate chemicals at the parts per billion level or lower. Indeed, by understanding the true nature of chemical sensitivity and who is at risk, we may prevent unnecessary and costly overregulation of environmental exposures in the years to come.

In the meanwhile, compassionate public policy needs to be adopted for those already affected. Reasonable accommodation should be provided in both housing and employment [7]. In addition, compensation and financial support of chemically-intolerant individuals should not await agreement on a case definition which is likely to take years to develop [7].

Chemical sensitivity could be the result of a new mechanism/paradigm of disease -- Toxicant-Induced Loss of Tolerance--that has the potential to explain many chronic and costly illnesses, including fatigue, depression, headaches, and asthma, or it could continue to elude definition. By not understanding chemical sensitivity, we take an immense gamble. Research needs a steady commitment of adequate funding and

institutional support. Future studies on chemical sensitivity need to include double-blinded, placebo-controlled challenges in a controlled environment [an environmental medical unit] and utilize brain imaging, state-of-the-art immunological testing and other sophisticated tests. Adequate numbers of patients and controls must be involved to facilitate valid comparisons. Funding agencies will need to invest adequate sums to acquire answers in this area as they have for other diseases, such as breast cancer and AIDS. Until sufficient research funds become available, chemical sensitivity no doubt will continue to pit physician against physician, perplex both scientists and policy makers, and frustrate patients and corporations alike.

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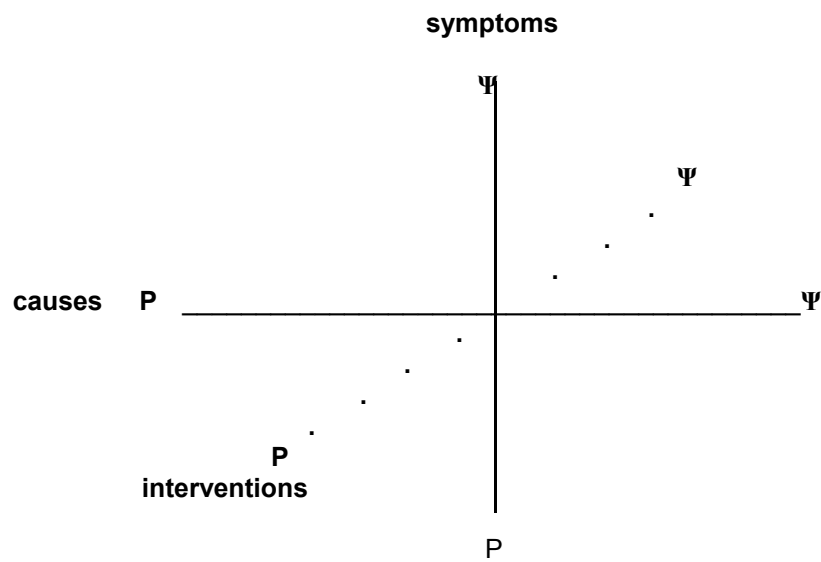


Figure 1. Schematic representation of the three dimensions of illness