CHEMICAL SENSITIVITY IN SELECTED EUROPEAN COUNTRIES: AN EXPLORATORY STUDY

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CHEMICAL SENSITIVITY IN SELECTED EUROPEAN COUNTRIES: AN EXPLORATORY STUDY [1]

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ABSTRACT

Exposure to low levels of chemicals in industrial workplaces, in indoor environments, in contaminated communities, and through the use of consumer products and pharmaceuticals has given rise to a new public health concern of chemical sensitivity, first in North America and now in Europe. Descriptions of the observations and nature of this controversial syndrome within the European context are discussed. Both clinical observations and other scientific evidence for alternative physiologic and psychogenic explanations are explored. Recommendations are made for further study.

EXECUTIVE SUMMARY

As in North America, chemical sensitivity in Europe continues to remain an elusive and baffling condition, devoid of compelling scientific evidence as to the relationship between exposure to precipitating agents and health effects, and without confirmed mechanisms as to its origin. This is due partially to the nature of the condition--which may involve an initiating exposure, followed by subsequent sensitivity to a variety of substances which continues many months after the initiating event--and partially due to the lack of adequate research activity, appropriate observation, and careful study of anecdotal evidence. In the last analysis, chemical sensitivity 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. Below, we describe the focus of the investigation, discuss gaps in knowledge, and highlight the areas where data are lacking. Finally, we summarize recommendations for future clarification of the nature of the condition.

Focus of the Investigation

The purpose of this investigation was to explore the existence and nature of the problem of low-level chemical sensitivity in several European countries. No study or survey has yet been conducted in the European countries on the occurrence or magnitude of the problem, and no clear definition or agreement on the diagnosis of chemical sensitivity is available. The specific aims of the investigation were:

1) to characterize the presentation and estimated occurrence of what may possibly be chemical sensitivity in several countries;

2) to identify exposures or events *possibly* associated with initiating chemical sensitivity;

3) to identify knowledgeable researchers and others in the fields of medicine, epidemiology, toxicology, environmental and occupational health sciences, and industrial hygiene with an interest in this subject;

4) to recommend possible avenues for prevention and follow-up.

Based on the information collected, the literature reviewed, and the persons interviewed, we attempted to critique the experience uncovered in terms of the possible origin and mechanisms for chemical sensitivity. An exploration of the interventions used to "treat" persons purported to have chemical sensitivity was beyond the scope of the investigation, although any reported outcomes of interventions were noted insofar as they helped to elucidate possible mechanisms. The study did not test any particular hypothesis. Rather, we sought to collect and compare information from several countries that might suggest hypotheses for further investigation.

The study has several limitations. It obviously suffers from physician/observer reporting bias and disease-selection bias in the data collection activities in each of the countries studied. In some instances, the reported clinical observations are based on small numbers and some of the information presented comes from the non-peer reviewed "gray" literature. Nonetheless, the countries themselves, as well as the perspectives of the country investigators, were sufficiently diverse to provide more confidence in the results of

the study than might otherwise be expected. Moreover, the clinical observations and gray literature provided additional insight and revealed opportunities for further study. However, the study did not permit us to reach definitive conclusions about the nature of and mechanisms for chemical sensitivity, nor was this the purpose of the investigation.

The project team formulated the following taxonomy to guide its data collection activities and analysis. Chemical sensitivity encompasses three relatively distinct categories:

1) The response of *normal* subjects to known exposures in a traditional dose-response fashion. This category includes 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 in which individuals respond to known or unknown exposures but whose symptoms resolve when they are not exposed to the building.

b) Sensitivity, such as that induced by toluene diisocyanate (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.

The investigation focused primarily on categories 2(b) and 3) above and uses the term "chemical sensitivity" in this report to refer to these categories. This focus essentially excludes traditional sick building syndrome, although hypersensitive sub-cohorts of individuals affected by SBS (that is, those individuals who do not recover, but who experience subsequent sensitivities) might provide useful information on chemical sensitivity.

The Existence of Chemical Sensitivity

Much of the evidence collected during the course of the investigation relates to poorly defined individuals or groups of individuals with symptoms and complaints which are unexplained or poorly understood in the context in which they are found. Certainly, some of the observations may be interpreted as chemical sensitivity. However, without a clearly

defined case definition for chemical sensitivity, a well-defined exposure history, and documentation of long-term consequences, it is difficult to assert with any degree of certainty that a particular incident or set of symptoms is in fact chemical sensitivity. While there are a small number of environmental control units in several countries, no published studies were found that test the hypothesis, in a double-blind fashion, that chemicals at low doses provoke the various symptoms discussed in connection with the condition.

The absence of an identifiable precipitating event does not prove the absence of chemical sensitivity; but the presence of a precipitating event or repeated or continuing exposure, the existence of symptoms at levels where most people do not exhibit symptoms, complaints triggered by more than one substance at low levels, multi-system effects, and the long-term continuance and possible spreading of symptoms all point to chemical sensitivity as many have defined it. None of the experiences we were able to uncover in this investigation provide clear and convincing evidence on the existence or nature of chemical sensitivity as a distinct clinical entity, although some physicians are convinced that the condition has an environmental basis. In the discussion of mechanisms below, our interpretations are tentative, at best, and should be taken advisedly because the available information gleaned from particular examples may not point to a definitive explanation of chemical sensitivity. Of course, where there are more well-established facts about a precipitating event or exposure, triggering exposures, unexplained symptoms, and objective physiological or psychological measures of dysfunction, the experience should be viewed more seriously.

Initiating Exposures/Events, Triggers, and Symptoms

Relatively few substances were specifically associated with the *onset* of chemical sensitivity in our investigation. The substances most often mentioned as initiators included pesticides, solvents, paints and lacquers, and formaldehyde. Repeated or continuous low-level exposure, rather than a single event, characterized most of the experience. Psychosocial stressors were also mentioned as initiating chemical sensitivity.

The predominant loci of the alleged initiating exposures/events in our investigation were in industrial, office, and domestic environments. Agricultural exposures resulting in chemical sensitivity were mentioned in several countries. Hairdressers comprised an occupational group that appeared to be affected in several countries. Instances of sick building syndrome (SBS) *per se* did not generally reveal chemically sensitive subgroups, although the preoccupation with immediate effects may have obscured their discovery. Certainly, we got no indication of a large problem in those instances. Relatively few community-based contamination episodes were uncovered which could have been initiating events. Initiating experiences with carpets and anesthesia were noted.

A much larger number of chemically-diverse substances were reported to trigger symptoms in persons who were already alleged to be chemically sensitive. These parallel the "triggers" frequently reported in the U.S. and include perfumes, detergents and cleaners, smoke, cooking odours, car exhaust, new clothing, nail polish, newspaper print, etc

.

Physicians and patients reported a wide variety of symptoms associated with chemical sensitivity. These included rhinitis, respiratory and gastrointestinal problems, musculoskeletal symptoms, and ear, eye, nose, throat, and skin irritation, as well as headache, fatigue, and a plethora of other CNS complaints. Sensitivity to odours is a

frequent symptom, and food intolerance is also mentioned. These symptoms also parallel those reported in the U.S.

Possible Underlying Mechanisms

Four general classes of mechanisms have been suggested to explain chemical sensitivity: 1) neurological, 2) immunological, 3) biochemical (and endocrinological), and 4) psychological. For the most part, chemical sensitivity is poorly characterized in the studies examined during this investigation, although medical practitioners, scientists and governmental authorities seemed poised to undertake some serious examination of the condition. Many physicians who have seen a few patients and those who have looked at large numbers of patients have *opinions* as to underlying mechanisms based on their (sometimes limited) observations. In addition, some human and animal research has been uncovered which throws light on the possible mechanisms. However, the reader is reminded that chemical sensitivity may be more a collection of diseases/syndromes that have a common response feature -- heightened reactivity to low levels of chemicals--than a single entity. Different mechanisms can be at play and different pathways can lead to what appears to be a common symptomatology.

The investigation found some supporting, though not compelling, evidence for neurological and biochemical (endocrinological) mechanisms. Interestingly, unlike the situation in the United States where immunologic mechanisms were the among the first mechanisms suggested for chemical sensitivity, in Europe, we uncovered less speculation that the underlying mechanism was immunologic. However, little research was uncovered on this pathway. In addition, there was a general absence of reported immunologic abnormalities among the patients of physicians interviewed for this study.

Work in the United States has attempted to evaluate patients with alleged chemically sensitivity by comparing them with other groups of patients using neurobehavioural tests. In contrast, European publications tend to *interpret* the work of others, who report psychological *problems* in chemically-exposed persons as evidence for a psychological *origin* of their complaints. No properly-designed investigations of possible psychogenic *origins* for chemical sensitivity, or comparative neurobehavioural studies, were uncovered in the European literature in the course of this investigation.

The confusion attending the origin of chemical sensitivity underscores the importance of investigating co-precipitating factors, both physiologic and psychologic, and not pursuing one to the exclusion of the other in the course of diagnosis or in research.

Recommendations

The investigation has revealed substantial interest in the subject of low-level chemical sensitivity in Europe. As in North America, there is considerable confusion and skepticism about the disorder. Yet, the medical and scientific communities express interest in furthering their understanding of the problem.

Perhaps the most immediate need is for the convening of a workshop in early 1996 of a small number (30-50) of invited participants from Europe and North America to discuss the experience and evidence related to chemical sensitivity to date, and to make recommendations for further research. Invited participants should include knowledgeable researchers, practitioners, governmental authorities, and policy makers. Both proponents and critics of the condition should be included. The workshop format should allow for presentations, discussion, dialogue, and challenge of views in a structured, focused, and constructive way. To the extent possible, the workshop should help participants resolve differences and agree on research priorities.

A second priority is the development of protocols for taking a complete occupational and environmental exposure history in patients who report sensitivity to low levels of chemicals. The protocol itself should be developed by consensus of knowledgeable researchers, physicians, and patients and should give special attention to uncovering and documenting exposure to: 1) known sensitisers and neurotoxic agents; 2) substances often associated with the onset of chemical sensitivity, such as solvents, pesticides, new or renovated buildings, anesthetic agents, and wood preservatives; and 3) stressful or traumatic life events. In addition, protocols for follow-up in terms of changes in signs, symptoms, and disease over appropriate time periods need to be established.

Obvious opportunities for future study include: 1) the follow-up of *previously-exposed* cohorts of persons most likely to present with or develop chemical sensitivity; 2) the *prospective follow-up* of populations and persons involved in "natural experiments" that might result in chemical sensitivity, such as chemical spills or relocation to a new or renovated building; 3) the work-up of selected persons in an environmental control unit (ECU) in which double-blind placebo controlled studies are conducted to explore the nature and existence of chemical sensitivity in individual persons; and 4) the exploration of possible models that may elucidate mechanisms for chemical sensitivity.

In investigating options (1) and (2), it is important that both an occupational and environmental exposure history be taken and that outcomes (signs, symptoms, and disease) be tracked over a sufficiently long period of time to allow the discovery of chemical-sensitivity if it in fact exists in a particular context. "Initiating" exposures or events should be distinguished from subsequent triggering agents or excitants. Option (3) is important for investigating whether symptoms resulting from low-level exposures are reproducible on an individual basis. Note that an environmental control unit *is not an exposure chamber.* It is a specially-designed hospital unit where patients can be housed, removed from possible excitants (in food, water, air, etc.), and re-challenged under carefully controlled conditions. Option (4) is regarded as essential for clarifying the nature of chemical sensitivity. Both human and animals observations have provided important insight as to possible mechanisms for chemical sensitivity. Neurotoxic pathways in particular need to be examined. Analysis of use patterns in different countries for pesticides, anesthetic agents, and other possible sensitisers may reveal useful information.

Until the nature of the condition is better understood, reasonable preventive and accommodative action should be taken. These may include: 1) serious efforts (public health interventions) to reduce exposures to possible "initiators" of chemical sensitivity (suggested in part by the experience collected to date) and 2) avoidance (as much as possible) in public places of substances known to trigger symptoms in persons who already report chemically-sensitivity. *Reasonable* accommodation should be made in housing and employment, such as limiting and warning occupants about pesticide application in buildings and providing less-contaminated places to work.

CHEMICAL SENSITIVITY IN SELECTED EUROPEAN COUNTRIES: AN EXPLORATORY STUDY

I. INTRODUCTION

The issue of chemical hyper-reactivity, an unexplained heightened response to chemicals at levels far lower than those at which most persons respond, has received substantial attention and generated considerable debate in the U.S. and Canada over the past decade. The Canadian government first examined the problem of chemical hyper-reactivity in 1985 in its Thomson Report **(Thomson, 1985)** 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 **(Ashford and Miller, 1989; Bascom, 1989)**, federal agencies, **(ATSDR, 1994),** the National Academy of Sciences **(NRC, 1992)**, and a number of professional organizations through workshops, conferences, and position papers **(AOEC, 1992; and ACP, 1989; AMA, 1992)**. 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 the 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 discussed in Section III below, there is ample scientific evidence that some chemicals are confirmed sensitisers that can induce sensitivity in exposed persons. More recently, however, the term "chemical sensitivity" has been used to describe an intolerance or hyper-responsiveness to *low levels* of chemicals. In this context, persons with "chemical sensitivity" report a variety of symptoms when exposed to a number of chemicals encountered on their jobs, in their homes, or in the course of their life activities. Persons with this type of heightened response to chemicals in their environments often refer to their condition as "chemical sensitivity," although the condition is not recognized as a discrete or even a "real" clinical entity by the mainstream medical and scientific communities at this time. Some researchers and physicians, however, use the term "chemical sensitivity" as a working definition and even as a diagnosis as they investigate possible mechanisms to explain this perplexing disorder and as they encounter patients in need of assistance. Investigations of causality range from a focus on neurological, immunological, and biochemical mechanisms to study of the purely psychological.

A variety of terms have been used to describe this condition (See Table 1 and Appendix A), often reflecting physicians' and/or patients' views regarding origins or possible mechanisms. Among others, these include "ecological illness," "non-specific hyper-responsiveness," and "pseudo-allergy." Patients with the condition sometimes report that their problems began after a single identifiable event, such as moving into a new or renovated building, or sometimes after sustained exposure to certain substances at work or at home, such as to chemically-treated fabrics or printed materials. Their symptoms are often subjective and may include respiratory effects (such as broncho-constriction, asthma, and rhinitis), gastrointestinal effects, myalgia, central nervous system (CNS) effects (such as headache, memory loss, confusion, difficulty concentrating, and intolerance to odours), and fatigue. Patients report that these symptoms occur in response to certain odours or upon exposure to certain substances, such as perfumes, smoke, car exhaust, nail polish, newsprint, and many others. In addition, food sensitivities are reported by many persons

claiming to be chemically sensitive. For a review of chemical sensitivity in North America, see **Ashford and Miller (1991)**.

Many, if not most, of these patients report that the physicians they consult are unable to help them and often consider their problems to be psychological in nature. Indeed, the origins, natural history, prognosis, and treatment of the condition are far from clear. However, in the U.S. and Canada, and to an increasing degree in Europe, the medical and scientific communities are engaged in both clinical and basic research to help elucidate the condition.

The purpose of this investigation was to explore the existence and nature of the problem of low-level chemical sensitivity in several European countries. No study or survey has yet been conducted in the European countries on the occurrence or magnitude of the problem, and no clear definition or agreement on the diagnosis of chemical sensitivity is available. Cross-country investigations can yield insights into problems that, to some, appear to have significant social and cultural dimensions. In the United States, where the problem has received more recent attention than elsewhere, these social and cultural dimensions have made it difficult to advance the understanding of the problem. These include: physicians with strong and differing opinions about the origins and relevance of chemical sensitivity; arguments about who pays for diagnosis and treatment, fear of liability on the part of chemical and product manufacturers, different professional orientations of those involved, an activated patient community, and a citizenry generally conscious of and concerned with environmental issues, especially at the local level. Some of these factors are absent or of less importance in other countries. A cross-country investigation in Europe provides an opportunity to take a fresh look at the issue, as well as a chance to compare inter-country differences in patterns and use of chemicals and materials, variation in the existence and nature of "tight buildings," and different traditions of occupational and environmental medicine.

The specific aims of this investigation were:

1) to characterize the presentation and estimated occurrence of what may possibly be chemical sensitivity in several countries;

2) to identify exposures or events *possibly* associated with initiating chemical sensitivity;

3) to identify knowledgeable researchers and others in the fields of medicine, epidemiology, toxicology, environmental and occupational health sciences, and industrial hygiene with an interest in this subject;

4) to recommend possible avenues for prevention and follow-up.

Based on the information collected, the literature reviewed, and the persons interviewed, we attempted to critique the experience uncovered in terms of the possible origin and mechanisms for chemical sensitivity. An exploration of the interventions used to "treat" persons purported to have chemical sensitivity was beyond the scope of the investigation, although any reported outcomes of interventions were noted insofar as they helped to elucidate possible mechanisms. The study did not test any particular hypothesis. Rather, we sought to collect and compare information from several countries that might suggest hypotheses for further investigation. Thus, we do not argue that the weight of the

evidence from this study leads us to definitive conclusions about the nature of and mechanisms for chemical sensitivity.

II. APPROACH AND METHODS

Three teams, each using a similar protocol for data collection and reporting, were responsible for investigating the topic of chemical sensitivity in the following countries: Denmark, Finland, Norway, Sweden, and the United Kingdom (Team A); Belgium, Germany, and the Netherlands (Team B); and Greece (Team C), which was also responsible for synthesizing the information from each team and preparing the final report.

Data Sources: A computerized literature search was undertaken, using a broad array of search terms (see Appendix B). Relevant literature was retrieved and reviewed. Following this, each team assembled lists of persons and groups for further and more in-depth contact. Data collection efforts were targeted towards those sources that might be expected to provide the maximum amount of information about the condition. These lists included *group 1*: persons already known to the investigators personally or by reputation who might have an interest in or knowledge about chemical sensitivity; *group 2*: persons identified through the literature review: *group 3*: persons identified through discussion with those in group 1 or in group 4; and *group 4*: organizations or groups likely to have some knowledge of and/or experience with chemical sensitivity, such as Ministries of the Environment or Public Health, active environmental non-governmental organizations (NGOs), labour unions, professional medical associations, etc. Thus, not all interviewed persons were trained scientists or medical practitioners.

Data collection methods: Interview guidelines and a data abstraction sheet (see Appendices C and D) were developed for use by the research teams, who, through personal, telephone, and mail-based interviews, as well as literature reviews attempted to collect data and information on: 1) the definitions and/or conceptualizations of chemical sensitivity and related disorders in each country; 2) events and exposures associated with the onset of chemical sensitivity; 3) subsequent sensitivities and symptomatology; 4) interventions; 5) possible mechanisms; 6) ongoing or planned research in areas relevant to the problem of chemical sensitivity; and 7) other possible sources of information on chemical sensitivity, e.g., unpublished government or organization reports (the so-called "gray" literature). The teams had flexibility in the manner in which they attempted to collect this information. Thus, some relied primarily on telephone interviews, while others relied on questionnaires sent through the mail.

To help the reader distinguish between the data sources while reading this report, we have used curved parentheses **( )** to cite references from the literature or from other written reports, and we have used square brackets **[ ]** to cite anecdotal information obtained from personal interviews.

Reporting of country experiences: Each team prepared a country profile documenting the experience in their subject countries. These comprise background material for this investigation. The information from these profiles was analyzed, synthesized, and used for the development of this report.

Limitations: Our study has several limitations. It obviously suffers from physician/observer reporting bias and disease-selection bias in the data collection activities

in each of the countries studied. In some instances, the reported clinical observations are based on small numbers and some of the information presented comes from the non-peer reviewed "gray" literature. Nonetheless, the countries themselves, as well as the perspectives of the country investigators, were sufficiently diverse to provide more confidence in the results of the study than might otherwise be expected. Moreover, the clinical observations and gray literature provided additional insight and revealed opportunities for further study. However, the study does not permit us to reach definitive conclusions about the nature of and mechanisms for chemical sensitivity.

Contents of the report: After a brief discussion of the North American experience with and perspectives on chemical sensitivity, the report provides sections on 1) the nomenclature and definitions of chemical sensitivity used in European countries and the taxonomy formulated and used in this investigation, 2) a synthesis and comparison of information on events and/or exposures associated with the onset of chemical sensitivity; subsequent "triggering excitants" and symptomatology; and observations/opinions about possible mechanisms, 3) planned studies or activities of potential importance, and 4) recommendations for future work.

III. THE NORTH AMERICAN CONCEPTUALIZATION OF CHEMICAL SENSITIVITY

Groups sensitive to low-level chemical exposures

A recent review of the mainly North American literature **(Ashford and Miller, 1991)** on exposure to low levels of chemicals suggested four groups or clusters of people with heightened reactivity: 1) industrial workers, 2) occupants of "tight buildings," including office workers and school children, 3) residents of communities whose air or water is contaminated by chemicals, and (4) individuals who have had personal and unique exposures to various chemicals in domestic indoor air, pesticides, drugs and consumer products. These four groups differ in professional and educational attainment, age and sex, and the mix and levels of chemicals to which they are exposed, but all have multiple symptoms involving multiple organ systems with marked variability in the type and degree of those systems. Their symptoms are often "subjective." For example, central nervous system (CNS) symptoms, such as difficulty concentrating or irritability, are common, and physical examinations are frequently unremarkable for individuals in each category. Recently, an additional cluster of possibly affected individuals has emerged--the returning Gulf War veterans **(Ember, 1994).**

Problems experienced by people in tight buildings, by industrial workers in a particular workplace, or by the residents of a contaminated community often developed within a relatively short time period--perhaps weeks or a few months. These problems sometimes occurred after a recognized event such as the installation of new carpeting, relocation to a new workplace, or changes in workplace or community exposures. The temporal cohesiveness between exposures and illness has been cited as support for the view that the problem is "real", as has the fact that individuals in demographically divergent groups, including industrial workers, office workers, housewives, children and most recently the Gulf War veterans, report similar poly-symptomatic complaints triggered by chemical exposures. In some chemically-sensitive patients, no single, identifiable, "high-level" exposure seems to have been associated with the onset of their difficulties. Some observers suggest that repetitive or cumulative lower-level exposure events may lead to the development of sensitivities. Still others implicate genetic predisposition, pregnancy, major

surgery with anesthesia, pharmaceuticals, physical trauma, or major psychological stress as contributors to the illness. (For a review, see **Ashford and Miller, 1991**.) However, no consensus on cause or mechanism has emerged in the scientific community.

Types of Sensitivity

The different meanings of the term *sensitivity* are at least partially responsible for the confusion surrounding chemical sensitivity. Individuals differ in their responses to increasing doses of a toxic substance. The underlying causes of inter-individual variability include age, sex, and genetic makeup; lifestyle and behavioral factors, including nutritional and dietary factors, alcohol, tobacco and drug use; environmental factors; and preexisting disease (Ashford et al., 1990). In the *classical, toxicological* use of the word sensitivity, those individuals who require relatively lower doses to induce a particular response are said to be more sensitive than those who would require relatively higher doses before experiencing the same response **(Hattis, et al., 1987)**. A hypothetical distribution of sensitivities, that is, the minimum doses necessary to cause individuals in a population to exhibit a harmful effect, is shown in curve A in Figure 1. This distribution illustrates the traditional toxicological concept of sensitivity. Health effects associated with classical diseases are seen in a significant portion of the normal population as a result of exposure to a relatively narrow range of doses; the sensitive and resilient populations are found in the tails of the distribution. (Of course, not all toxic substances have small variances or significant tails.) For the classically sensitive person, avoidance of low-level exposures generally leads to improvement, or at least to the arrest of the development of the disease.

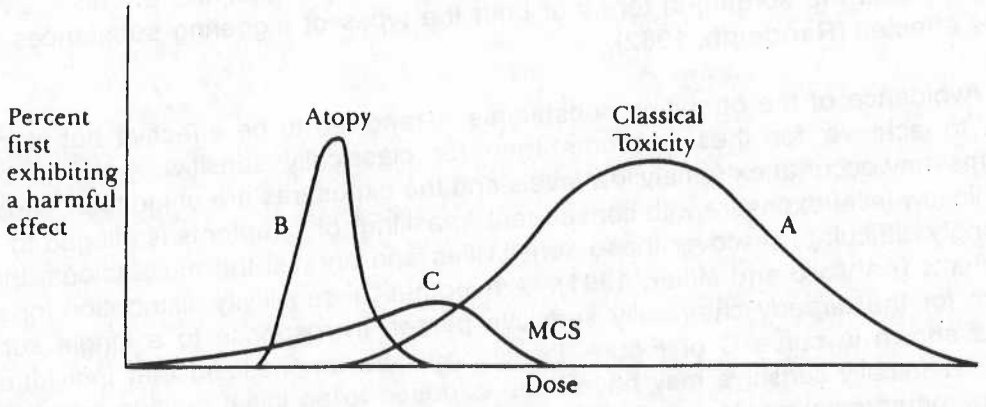

FIGURE 1 Hypothetical distribution of different types of sensitivities as a function of dose. Curve A *is a sensitivity distribution for classical toxicity, e.g., to lead or a solvent. Sensitive individuals are found in the left-hand tail of the distribution. Curve* B *is a sensitivity distribution of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

A second meaning of the word sensitivity appears in the context of classical IgE-mediated *allergy (atopy)*. The atopic individual exhibits a reaction, whereas non-allergic persons do not, even at the highest doses normally found in the environment. A hypothetical sensitivity distribution for an atopic effect is shown in curve B of Figure 1. Allergists include in the term *allergy* well-characterized immune responses that result from industrial exposure to certain chemicals, such as nickel or toluene diisocyanate (TDI). Most allergists refer to such responses as *chemical sensitivity*, but reserve this term for responses that have or appear to have a distinct immunological basis. They prefer to use a different term such as *chemical intolerance* for non-immunological responses to chemicals.

Patients suffering from what North Americans call multiple chemical sensitivity (MCS) **(Cullen, 1987)** may exhibit a third and entirely different 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 "sensitising" the individual, and the affected person is termed a "sensitised" person.) Acute or traumatic exposures are not always necessary. Repeated or continuous lower-level exposures may also lead to sensitisation. To date, there is no clear consensus on this staging process in the scientific community.

These "sensitised 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 **(Randolph, 1962)**.

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 **(Ashford and Miller, 1991)**. A hypothetical sensitivity distribution for a single symptom for the *already* chemically sensitive person in response to a single substance trigger is shown in curve C of Figure 1. It should be emphasized that individuals who become chemically sensitive may have been exposed to an initial *priming* event that was toxic (e.g., neurotoxic) as classically defined. Conceivably, exposure to certain substances, such as formaldehyde, might elicit all three types of sensitivities.

Mechanisms to explain this third type of chemical sensitivity range from psychological to physiological--including neurological, immunological, and biochemical (or endocrinological) pathways **(Ashford and Miller, 1991)**. Odour conditioning, perhaps involving both psychological and physiological mechanisms, has also been suggested **(Doty et al., 1988)**. For reviews in the North American literature on proposed mechanisms, see **Ashford and Miller, 1991** and **Sparks et al., 1994**.

IV. NOMENCLATURE AND DEFINITIONS OF CHEMICAL SENSITIVITY USED IN THIS INVESTIGATION

A wide variety of terms and definitions are commonly used in European countries to refer to chemical sensitivity or to disorders that are alleged to have some relationship to chemical sensitivity, sometimes called "overlap" syndromes. Table 1 shows the numerous terms and concepts used in the EU countries under study. Definitions commonly used for many of these terms are presented in Appendix A.

Table 1. Terms Related To Chemical Sensitivity Commonly Used In Selected European Countries

- Allergy
- Building-related illness (BRI)
- Chronic fatigue syndrome
- Ecological illness/disease; Clinical ecology syndrome; Eco-syndrome
- Environmental somatization syndrome
- Environmental stress syndrome
- Fibromyalgia
- Hyper-reactivity
- Hypersensitivity
- Hypersusceptibility
- Intolerance reaction/syndrome
- Multiple chemical sensitivity (MCS)
- Non-specific hyper-responsiveness
- Organic brain syndrome
- Organic solvent syndrome
- Painters' Syndrome
- Pseudo-allergy
- Psycho-organic syndrome/Organic brain syndrome
- Sensitivity
- Sick building syndrome (SBS)
- Solvent intolerance
- Specific chemical hypersensitivity
- Tight building syndrome
- Triggering compounds
- Toxicopy
- Wood preservative syndrome/Pentachlorophenol syndrome

The project team formulated the following taxonomy to guide its data collection activities and analysis. Chemical sensitivity encompasses three relatively distinct categories:

1) The response of *normal* subjects to known exposures in a traditional dose-response fashion. This category includes 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 in which individuals respond to known or unknown exposures but whose symptoms resolve when they are not exposed to the building.

b) Sensitivity, such as that induced by toluene diisocyanate (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.

This investigation focused primarily on categories 2(b) and 3) above and uses the term "chemical sensitivity" in this report to refer to these categories. This focus essentially excludes traditional sick building syndrome, although hypersensitive sub-cohorts of individuals affected by SBS (that is, those individuals who do not recover, but who experience subsequent sensitivities) might provide useful information on chemical sensitivity **(Chester and Levine, 1994).**

V. PRESENTATION AND CHARACTERIZATION OF CHEMICAL SENSITIVITY IN SELECTED EUROPEAN COUNTRIES

In researching the presentation and characterization of chemical sensitivity, it is useful to distinguish contrasting ways in which observations 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. In the last analysis, *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.* 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.

Causes, symptoms, and interventions can each be characterised 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 2). 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/behavioural) 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.

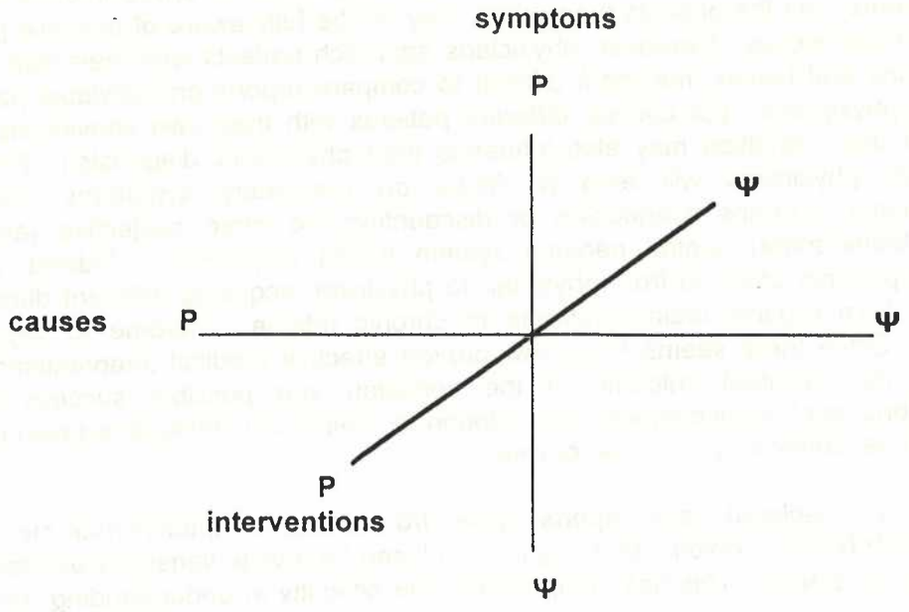

Figure 2. Schematic representation of the three dimensions of illness

The above having been said, 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 in any given country. For this reason alone, the observations from the different countries included in this study might be expected to be differentially useful and revealing.

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. For the purposes of this study, "event-driven" information was defined to include 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.

In characterizing incidents and exposure events, this report will describe, wherever possible, the nature of the purported initiating exposure or event (e.g., an acute exposure, such as a spill, or longer-term exposure to a chemical or product, such as to solvents or new carpets); the type of complaints, symptoms, or signs that are reported by exposed persons; and the nature of any attempted intervention (e.g., removal of carpeting or change of residence or workplace) and their outcomes.

A. Exposure or Event-Driven Information

Despite the potential usefulness of exposure or event-driven information, the research teams were unable to discover many situations or incidents that could provide useful data relevant to chemical sensitivity as defined in this report. There are no paucity of events or exposures; there is simply little information available about the *outcomes* in terms of the development of chemical sensitivity. Information on the temporal features of the development and disappearance/waning of problems would be very important, but was very difficult to obtain. A variety of factors may explain this relative lack of information. For example, the research tended to focus on physicians and the medical literature as sources of data. In general, physicians interact with individual patients and have little reason (and perhaps interest) to recognize that their patient may be part of a larger group of individuals who have experienced a common exposure or event. Second, physicians, researchers, and health authorities who *are* involved in events or exposure situations (e.g., a "sick building" or exposures at a particular workplace/occupation) do not likely have a focus on chemical sensitivity and thus have little reason to: 1) follow the affected individuals for long periods of time; 2) identify subsequent sensitivities; or 3) distinguish between initiating and subsequent triggering exposures. Despite this, the research teams did identify some exposure or event-driven information that may be suggestive of low-level chemical sensitivity.

Industrial, occupational and indoor (residential/office) environments

Denmark

In Denmark, a number of physician reports and published studies suggest that the following exposures, events, and occupations have been associated with cases of chemical sensitivity: dressmakers exposed to formaldehyde-impregnated material **[Dankert, 1994]**; postal workers exposed to printed advertising pamphlets which contain toluene **[Haaning, 1994]**; industrial degreasers exposed to halogenated hydrocarbons **(Rasmussen et al., 1988, 1993a, 1993b)**; garage workers exposed to diesel **[Kirkeskov, 1994]**; hairdressers exposed to low levels of organic solvents at work **[Mørck, 1994]**; men exposed to organic

solvents at work **(Hein et al., 1990 and 1991)**; and gardeners exposed to pesticides **(Lander et al., 1987).**

Many workers involved in these events/exposures (some of which involved only small numbers of workers) experienced symptoms frequently associated with chemical sensitivity, e.g., headache, fatigue, and problems with memory and concentration. At least three groups included workers who were given diagnoses that may overlap with chemical sensitivity. These included psycho-organic syndrome (the degreasers), organic brain syndrome (the garage workers), and brain damage (the hairdressers). In most of these reports and studies, information on subsequent sensitivities or "triggering excitants" was lacking, making it difficult to say anything about chemical sensitivity with any certainty. All of these groups, however, would be interesting subjects of future investigation.

Sweden

Not unexpectedly, many of the events uncovered and described by the project investigators related to sick buildings and sick building syndrome (SBS). Although the project did not focus on SBS, it was difficult to avoid, because physicians and other interviewees often mentioned these types of events when questioned about their experience with chemical sensitivity. The information on SBS provided in the published literature and anecdotally by physicians does not, however, shed much new light on the problem of chemical sensitivity, primarily because there has been little, if any, effort to identify especially-sensitive subgroups among those affected and to obtain information about sensitivities that may evolve or continue after subjects are absent from the problem buildings. The SBS events may, however, suggest cohorts for follow-up or future study. These could include, for example, primary school personnel in Sweden who experienced SBS associated with volatile hydrocarbons and carpeting, among other factors **(Norbäck et al., 1990b)**; occupants of newly constructed homes and office buildings where symptoms such as headache, tiredness, and eye/throat irritation have been associated with mortar containing casein **(Lundholm et al., 1990);** and occupants of rooms painted with water-soluble paints **(Hansen, 1987; Norbäck et al., 1991).**

A recent article by a Swedish group described what they call "Environmental Somatization Syndrome" (ESS) **(Nilsson et al., 1994)** in which patients believe their symptoms to be caused by exposure to chemical or physical components in the external environment or by ergonomic factors at work. They describe ESS epidemics associated with arsenic, carbon monoxide, amalgam, carbonless paper, electromagnetic fields, and repetitive movement. Symptoms include fatigue, headache, joint pain, problems with concentration, and palpitations. Information about subsequent sensitivities is not described.

Finland

Occupational exposure to solvents is also under study in Finland. **Juntunen (1993)** has described the difficulty in detecting and documenting effects caused by chronic, long-term, low-level occupational exposure to solvents, but reports clinical experience with some 2000 cases of suspected occupational solvent intoxication. The most frequent symptoms include headache, fatigue, dizziness, and neurasthenic signs. Information on subsequent sensitivities among these cases is not known.

Germany

A unique situation was reported in Germany, where exposure to emissions from treated wood has been associated with its own clinical entity -- wood preservative syndrome (or pentachlorophenol syndrome) **(Schimmelpfennig, 1994).** Some individuals exposed to wood (or rooms with wood) treated with pentachlorophenol (PCP) and lindane (contaminated with dioxins and furans, and dissolved in solvents at a concentration of about 5%) have experienced the multitude of symptoms commonly associated with chemical sensitivity. These include immunologic, dermatologic, neurologic, psychiatric, endocrinologic, and ophthalmologic symptoms **(Huber et al., 1992).**

In response to our inquiry, many physicians in Germany report that pentachlorophenol and wood preservatives have initiated illness and subsequent sensitivities (e.g., to odours, solvents, and, sometimes, foods) in their patients. The problem is prominent enough in Germany to have spawned an organized interest group of "Persons Harmed by Wood Preservatives," which reports nearly 10,000 cases of acute and chronic "intoxication" by the active substances in wood preservatives. At least 100 cases of chronic intoxication are reported to occur in kindergartens and schools. Despite the large number of reports and significant amount of public concern, there has been little systematic investigation, such as a case control study of persons exposed in their homes, that has clarified the problem. The Federal Health Agency conducted an investigation but found no significant clinical health effects related to PCP exposure; however, the investigators acknowledged credibility of the complaints of the exposed persons **(Krause et al., 1989).** One physician **(Fabig, 1988)** performed SPECT (Single Photon Emission Computed Tomography) scans on 74 wood preservative-exposed persons and 41 unexposed persons, all complaining of CNS symptoms such as headaches, dizziness, inability to concentrate, and depression. The results indicated a decrease in cerebral blood circulation in the forebrain of persons exposed to wood preservatives which corresponded to the duration of their exposure. The results are considered controversial because of the non-specificity of SPECT scans **(Düsseldorf, 1990).** Since the original investigation, additional persons were scanned, bringing the totals to 139 wood preservative-exposed persons and 214 unexposed persons, with similar findings **[Fabig, 1994].**

The Authority of Work, Health, and Social Affairs in Hamburg studied 625 kindergarten children for health effects associated with exposure to wood preservatives. **(BAGS, 1990).** Children were examined clinically and no clinical effects and symptoms associated with wood preservatives were found. Laboratory analyses were all within the normal range. However, the study did show an association between 15 of 47 parameters analysed and exposure to wood preservative, as estimated from one indoor air measurement. No association of health effects with exposure was found, but no measurements of internal exposure to wood preservatives or to dioxins were made.

The question of whether low level exposure to wood preservatives can cause serious health effects remains unresolved in Germany. However, a recent German Court decision **(Landgericht Frankfurt, 1993)** ruled against the manufacturer and found that wood preservatives are most likely responsible for adverse health effects in some patients. However, the ruling was appealed by the manufacturer and is awaiting final disposition.

A second exposure event of interest involved pyrethroids. Some reported cases of pyrethroid intoxication may fall under the classification of chemical sensitivity. Over 70

cases have been registered at the Federal health agency in Berlin; some of the patients claim to react with particular sensitivity upon contact with pyrethroids. After application of pyrethroids, symptoms like headache, daze, irritation of mucous membranes (eyes, nose, respiratory tract), and paresthesia were reported. A clear dose-effect relation could not be established. It seems possible that sensitive individuals react to low concentrations in dust or when in contact with contaminated objects **(Lingk, 1994).** A study of some of the pyrethroid cases will be completed in 1995 **[Altenkirch 1995]**. Twenty three patients underwent intensive and invasive neurological, neuropsychological and neurotoxicological testing. A misdiagnosis of pesticide-related illness was made in nine patients and MCS-syndrome was diagnosed in eight patients. The possiblity of effects due to pyrethroids could not be ruled out in the remaining six patients.

The Netherlands

Concern about wood preservatives also surfaced in the Netherlands. The improper indoor use of such chemicals was investigated in three cities: 's-Gravenhage [the Hague] (pentachlorophenol), Nieuw Amsterdam (pentachlorophenol and lindane) and Amsterdam (moisture-repellant agents dissolved in aliphatic and aromatic hydrocarbons). A survey conducted in 's-Gravenhage revealed no exceptionally high blood levels of PCP in any individual, but the distribution of levels in the residents as a whole was higher than the control group **[Stumpel, 1994]**. Medical examinations of the residents of 's-Gravenhage and Nieuw Amsterdam revealed no abnormalities that could be correlated with blood levels of PCP. These residents complained about exposures to solvents, but these effects were reported to be reversible.

In the twenty houses investigated in the Hague, the residents complained about odours and CNS symptoms of headache. fatigue, and nausea **(Stumpel, 1991)**. High concentrations of PCP were established in the houses. Although it was not possible to conduct a health risk assessment, effects could not be ruled out and the residents obviously felt unwell. Indications of systemic PCP intoxication were not found. None of the residents wanted to return to their homes. In none of these "incidents" were follow-up studies undertaken.

The Dutch National Intoxication Information Centre (NVIC=Nationaal Vergiftigingen Informatie Centrum) has dealt with 30 cases of localised problems of environmental pollution **(Stumpel, 1991)**. These cases included soil or underground water contamination due to waste dumps, industrial sites, solvent and fungicide use indoors and ambient industrial activities. Because most cases involved well-defined problems with clearly defined toxicity, e.g., contamination with cadmium or lead, there was no attempt by the centre to uncover subsequent symptomotology that might be relevant to chemical sensitivity. These cases could well benefit from follow-up, since they involve substances others report to be implicated in chemical sensitivity.

Belgium

A typical case history of the "PCP-syndroom" **(Anonymous, 1991)** in a family in Belgium is identical to several cases described in Germany as "Holzschutzmittel-Syndrom" (wood-preservative syndrome). Prof. P. Schepens from Antwerp, who is also a member of the scientific advisory board of the Dutch Health and Environmental Network (Gezondheid en Milieu), reports chemical sensitivity in several cases related to pentachlorophenol exposure. In his publications **(Jorens and Schepens, 1993; Jorens et al, 1991; and**

Janssens and Schepens, 1985), he discusses the problem more in terms of classical toxicity than in terms of chemical sensitivity. However, patient exposure levels are usually lower than the current exposure standards, as indicated by biomonitoring results in the range of 1/10 to 1/5 of the occupational Biological Exposure Index (BEI). Intolerance, rather then classical toxicity, could be considered a strong alternative diagnosis, since in many homes with similar toxic exposures no complaints were registered. In persons chronically exposed to wood preservatives, Schepens found and described non-specific symptoms congruent with features of chemical intolerance: depression, general fatigue, dizziness, sleep disturbances, aggressive behaviour, loss of appetite, headache, nausea, diarrhoea, anorexia, upper and lower respiratory complaints, fear, and dermatological symptoms like urticaria.

The most frequent symptoms presented by 40 adult patients only moderately exposed to pentachlorophenol were as follows:

Tiredness, dizziness, vertigo	37
Headache	23
Respiratory problems	22
Psychosomatic problems	18
Urticaria, skin problems	17
Diarrhoea, abdominal pain	17

Greece

Perhaps the country with the least *a priori* knowledge about chemical sensitivity was Greece. The Greek team had considerable difficulty eliciting any information about the existence of this problem from the scientific and medical establishment. Through discussions -- primarily with representatives of different environmental NGOs in Greece, i.e., mainly the World Wildlife Fund, the Centre for Ecological Information, and Greenpeace -- some relevant exposure events were identified. Details of the events, their nature and consequences were available for only four events, two in occupational settings, one involving both occupational and community exposures, and one in a community setting.

One event involved the spraying of pesticides in greenhouses at the village of Tymbaki in Crete. An epidemiologic study compared chronic health effects in greenhouse workers who used pesticides carelessly, in concentrations higher than suggested, and with no or inadequate protection **(Kafatos et al., 1989)**. The study found noticeable chronic health effects among the greenhouse workers compared to controls, particularly in the central nervous system. Because the study was not designed to track the possible emergence of chemical sensitivity, the greenhouse workers were not followed up, and there is no information on subsequent sensitivities. The paper does not discuss mechanisms for the observed health effects.

A second event involved a study of landfill workers in the Athens area. Landfill workers are exposed to a complex mixture of chemical substances. In the study, the author evaluated psychosocial factors and health symptoms in 70 landfill workers compared with 240 workers transporting or handling wastes **(Velonakis, 1994; Zannaki et al., 1994)**. A questionnaire was used to assess the degree of job satisfaction, social recognition of work, social relationships within the work environment, work-related fatigue, motivation, and job-related stress. It also asked about common symptoms, such as headache, backache,

persistent cough, loss of smell (anosmia), itching, and skin symptoms, with or without itching. The prevalence of reported headache, skin symptoms and anosmia were statistically higher in landfill workers. No statistical differences were found for social and psychological data. The investigator observes that the symptoms experienced by landfill workers may be related to chemical sensitivity because: 1) they are not recognised in the context of known clinical entities, 2) the exposure to chemicals is below the toxic levels, and 3) related symptoms were observed among resident population close to landfills.

A third event involved a tank explosion at a fertiliser factory at Drapetsona, Attica. In January 1992, at a firm that manufactures fertilisers, three containers of dimethoate (an organophosphate pesticide) exploded, releasing this neurotoxin, (as well as its pyrolysis products, mercaptans) into the atmosphere. Foul odours were experienced in the neighbouring communities for several days. The concentration levels of dimethoate were not considered sufficient to cause acute effects, even in the workplace. Residents of the neighbouring communities reported headache, dizziness, eye and upper respiratory tract irritation, stomach disorders, sweating, and loss of appetite. None of them exhibited clinical or biological indications of pesticide intoxication. The Greek team wondered if these adverse reactions might have been experienced by chemically sensitive individual residents of the communities. Medical and governmental authorities believed that the complaints of the population were due to bad odours of the mercaptans. No systematic study of the health effects associated with this event has been undertaken, and thus no definite conclusions can be reached. The cholinesterase activity levels of the workers were within normal levels and unaffected when compared to their pre-exposure values, even in the workers directly exposed to the pesticide during the accident.

In the same factory, however, the occupational physician noticed that two workers, victims of acute poisoning from organophosphate pesticides in the past, could not stay in the workplace after they returned to work, although the concentrations were very low. These workers could be followed for information about other subsequent sensitivities.

For the above and similar events, generally little or nothing has been written in the scientific or the "gray" literature in Greece, with the exception of the greenhouse workers in Crete. These incidents could provide interesting cohorts for future study.

Community and consumer product-based experience

Of particular interest is the relative lack of reported incidents involving events or exposures outside the industrial/office workplace or residence. In the U.S. context, patients from "contaminated communities" drive a fair amount of the interest in chemical sensitivity. Oftentimes, these communities have been involved in an acute event (like an explosion, chemical fire, or pesticide application) or find themselves proximate to sources of chronic chemical exposure, e.g., hazardous waste sites or industrial emissions. Such events or circumstances are clearly found in the European context, but did they are not sufficiently characterized or followed up to allow definitive conclusions on the subject of chemical sensitivity as described in this report.

For example, in Lekkerkerk, the Netherlands, a study was done to assess health effects in residents of a community built on a former industrial dump site with soil heavily contaminated with toluene, xylene, and benzene. An association of (unspecified) health effects with residence in that community could not be ruled out. **(Stumpel, 1991)**. In Germany (Dortmund-Dorstfeld), there was also a report of a community contamination

episode **(Matthies et al., 1994)**. Prior medical screening of community residents had not shown a significant correlation between the degree of ground contamination and health effects. Using a non-contaminated area as a control group, **Matthies et al.** focused on psychological effects and satisfaction with life, rather than on health effects, and concluded that the many health complaints found were caused by uncertainty and perceptions of threat to health from the contamination. Both of these events could benefit from follow-up investigation.

In Greece, two events involved community exposure -- one discussed above (the explosion of di-methoate-containing tanks) and a second described bellow.

In the city of Ioannina, the water system has been polluted with pentachlorophenol (PCP) released by a wood-treating company located in the area. Studies carried out by scientists at the University of Ioannina have documented the presence of PCP in the drinking water of the city. In spite of the potential risk to the city's residents, no studies were found that explored the possible health effects of this contamination on the population of Ioannina. Nor could the Greek team locate any reliable verbal, anecdotal accounts on the subject, even though it constituted a heated debate in the city. Thus, we can draw no conclusions related to chemical sensitivity on the basis of the available data and information. Further research could provide useful information and would be important given the observations concerning PCP and possible chemical sensitivity in Germany, Holland, and Belgium.

In Norway, research on health effects associated with ambient air pollution is ongoing **[Clench-Aas, 1994]**. Through diary studies, generalized symptoms are correlated with exposure to air pollution. Investigators found some evidence of symptoms at very low exposure levels. These persons may constitute an interesting sub-cohort for future study of chemical sensitivity.

In England, **David and Wessely (1994)** discuss the health effects of an environmental contamination episode in Camelford, a small town in the Southwest of England, whose water supply was contaminated by the inadvertent deposition of 20 tonnes of aluminium sulphate. Immediate symptoms included nausea and vomiting, skin rashes, mouth ulcers, and blue or brown stains on people's hair, skin or finger nails. According to the article, one fourth of the exposed group exhibited the bulk of the reported symptoms, most of which predated the accident. Although they acknowledge that in some subjects, exposure resulted in excess absorption of aluminium, the authors suggest that psychiatric factors explain these phenomena. They conclude that the psychological distress the community suffered and psychiatric disorders heightened Camelford's inhabitants' (and professionals') perception of normal and benign somatic symptoms (physical or mental). Thus, they explain the observed symptoms in terms of somatization. While abnormal evoked potentials were recorded on some of the symptomatic consumers of the contaminated water, the authors dismiss the findings as influenced by anxiety and other emotional disorders and criticize the technique as being unspecific and without proper establishment of baseline in the population under observation.

In the United States, in addition to problems in contaminated communities, health complaints associated with consumer products, such as new carpeting and mattresses, have been reported to and collected by the Consumer Product Safety Commission and the Environmental Protection Agency. In Germany, the federal health agency (BGA) in Berlin registers side effects of chemicals. Physicians are obliged to report cases (and suspected

cases) of chemical exposure or products causing health effects. In 1992, 753 different substances or products were reported, including wood preservatives, lindane, solvents, dioxin, formaldehyde, pyrethroids, other pesticides, lamp oil, aniline, and tobacco **(Heinemeier, 1993)**. While such occurs in some of the other European countries studied, information about these "exposures or events" are not systematically collected or analyzed in these countries.

Summary Comments

Despite the potential usefulness of exposure or event-driven information, the research teams were unable to discover many situations or incidents that could provide useful data relevant to chemical sensitivity as defined in this report. There are no paucity of events or exposures; there is simply little information available about the *outcomes* in terms of the development of chemical sensitivity. This is true for exposure events in industrial, occupational and indoor (residential/office) environments and also for community-based exposures and exposures to consumer products. Follow-up investigations could reveal useful information.

Even though there were few community-based events uncovered by the teams as event-driven information, data obtained from physicians and others do reveal concern with a number of exposures/conditions found in homes and communities as well as in workplaces. These are described below.

B. Patient-driven Information

Aside from event or exposure-driven information, isolated individual experience provides some perspective on the nature of chemical sensitivity. Physicians are a primary resource for individual patients who experience symptoms and "sensitivities" they believe are related to chemicals or products they encounter in their homes, workplaces, and communities or through their personal activities. Thus, the project teams devoted a significant amount of time collecting information, data, and impressions from physicians. Occasionally, their research led them to non-physician researchers, government workers, and to patients themselves. However, most of the information reported in this section reflects the experience of clinics and physicians, and, thus, is anecdotal in nature. This experience can, however, stimulate discussion and suggest hypotheses for future scientific work.

Recognizing the limited purview of any particular medical discipline, project investigators cast a broad net in their search for physicians with experience in chemical sensitivity. Table 2 shows the types of physicians interviewed for this project.

Table 2. Types of Health Professionals/Clinics Providing Information for This Study

SPECIALTY*	Denmark	Norway	Sweden	Finland	U.K.	Greece	Germany	Holland	Belgium
Allergy or Immunology	2	1			1	4	1	1	1
Pulmonary						8	2		
Occupational Med.	9	1	5		1	4	2	1	1
ENT	1		1			1	1		
Dermatology			1			1	1		
Neurology/Psychiatry			1				4		
Psychology			1		1				
General Medicine or Internal Medicine	1	1	1		1	1	24	3	3
Public Health or Environmental Medicine						1	17	17	2
Toxicology							3	6	4
Clinical Ecology or Homeopathy					1	2	2		
Pediatrician							3		
Dentist							1		
Other/Unspecified	*3*		*2*				4	3	

* Primary focus of health professional or clinic

The physicians reported a variety of clinical experiences and impressions that, in many cases, show an interesting degree of consistency regarding possible "initiating" exposures, types of symptoms, and subsequent sensitivities, although information about the latter is often lacking and the distinction between "initiators" and subsequent "triggers" is frequently unclear. The physicians have little to say about the efficacy of their therapeutic and non-therapeutic interventions with these patients. Nonetheless, these physician observations suggest that there is unexplained hyper-responsiveness (with no or little follow-up) which could be classified as chemical sensitivity and that affected patients frequently exhibit characteristics similar to those seen in the U.S. and Canada. It is, however, impossible to speculate about the incidence and prevalence of the disorder in the countries studies, given the lack of a common understanding of the illness and the nature of our investigation. However, our study does reveal pockets of possible occurrence and areas for future study.

Germany

Physicians in Germany were contacted by means of a self-administered questionnaire (number of respondents = 93; 67 physicians and 26 patients) and by telephone for personal interviews (N=98). There is overlap between these two groups because the second group included physicians who returned questionnaires indicating personal experience with postulated chemical sensitivity (63 or 89%). The group

interviewed by telephone (N=98) also included persons identified through the literature review and those known by the team or others to be interested in or have experience with chemical sensitivity. Responses from both these groups were tabulated and, while statistical analysis was inappropriate, there were interesting similarities in their responses.

Alleged Initiating Exposures or Events

The respondents did not always clearly separate initiating from subsequent triggering agents. This could be because the agents were not recognized as distinct or, perhaps, because there was, in fact, no initiating agent. However, pesticides (especially pentachlorophenol, lindane, PCB, and pyrethroids), solvents (unspecified), formaldehyde, and heavy metals (often mercury from amalgams) were cited many times as "causing" chemical sensitivity. Respondents also often mentioned new and renovated buildings as precipitating events. These "initiating" exposures most often were thought to be long-term in nature; one-time, acute exposures were seldom mentioned. Of interest was the virtual lack of reference to any particular occupation by the responding physicians. The physicians in the survey expressed different views on the "origins" of chemical sensitivity: 54% believed the origin was chemicals, 4% believed the origin was psychological, and others were uncertain as to the origin being chemical/unknown/other (13%), chemical/psychological/unknown (14%), chemical/psychological (1%), and psychological/unknown (1%). These statistics reflect respondents' reported *beliefs*; the basis of or justification for these views could not be determined from the survey.

One physician **(Sobetzko, 1994)** implicated pyrethroids as causing chronic fatigue syndrome (CFS), which is argued to be an overlap syndrome with chemical sensitivity **(Finck, 1992; Schönfeld 1993; Kilburn, 1993a; 1993b; Buchwald and Garrity, 1994)**. He observes that victims claiming pyrethroid intoxication resemble those with a diagnosis of CFS and that the increase of CFS in the 1980's is coincident with the increased and widespread use of pyrethroids in the indoor environment.

Subsequent sensitivity, symptoms, and interventions

The patients seen by the German physicians in our survey reported a wide variety of symptomatology. The most common included eye, nose, and throat irritation, itching of the skin, headache, fatigue, problems with memory and concentration, increased sensitivity to odours, and, in some cases, food intolerances. Less often mentioned were gastrointestinal symptoms, joint and muscle pain, and asthma. The physicians indicate that their patients report subsequent "sensitivity" to such things as fragrances, cigarette smoke, car exhaust, solvents, cleaning agents, clothing shops, and alcohol. However, in some cases, the physicians had no information about subsequent "sensitivities."

Ring et al. (1991) from the Dermatological Clinic of the Ludwig-Maximilians-University. Munich, provided a clinical case-based report:

> Thirty patients (20 female, 10 male; age between 16-56 years) with a subjective feeling of allergy to environmental noxious agents were examined. They received intensive allergic investigations, including placebo-controlled oral challenge tests with food additives together with careful interdisciplinary investigations (internal medicine, otolaryngology, gynecology, dental medicine as well as psychosomatic medicine). Most of the patients complained of various subjective symptoms (average seven) involving several organ systems (average three). Some 60% of the

patients showed positive skin prick tests against common food and airborne allergens. In oral provocation procedure, 13% were clearly positive to certain foods, 10% to food additives, and 13% to drugs (mostly mild analgesics). In 7%, focal infections of clinical relevance for the given complaints were detected and treated successfully. In 60% of the patients, psychiatric or psychosomatic disturbances were obvious. When, among the numerous diagnoses, a list of the major pathophysiological conditions relevant to the given complaints was established, "psychogenic condition" and "allergy" were represented with 60% and 40% respectively. It was found that 47% of the patients suffered mainly from severe psychosomatic disorder, 10% from manifest endogenous psychoses, 33% from allergic or pseudo-allergic reactions, one patient from pension neurosis (3%), and 7% from focal infectious disease. Therefore, it is possible that in some of these patients, even [those] with strong psychosomatic overlap, true hypersensitivity reactions against hitherto unidentified substances are hidden. The most frequently suspected noxious agents were: car exhaust, pesticides, formaldehyde, [wood] preservatives, organic solvents, detergents, and electromagnetic radiation.

An evaluation of 100 patients referred to the environmental outpatient clinic of the Institute for Hygiene and Environmental Medicine, University of Heidelberg revealed a psychosomatic background or underlying psychiatric diagnosis in 50% of patients with an environmental illness **(Eis and Sonntag, 1994)**. A large proportion of environmental illness is regarded by the clinic physicians as causal attributing and externalisation of other problems (e.g., functional disorders). The cases are classified as:

a) environmental scare, neurotic toxicophobia, MCS (5%)

b) psychosomatic, somatisation disorder, depression (30%)

c) hypochondria

d) abnormal personality disorder, hysteria, querulants, simulate

e) burn-out syndrome

f) chronic fatigue (post viral)

g) otherwise defined diseases (e.g. Crohn`s disease) with cofactors (urticaria)

As a general rule, the authors recommend the careful psychiatric and psychosomatic exploration of patients presenting with an environmental illness.

German physicians who see chemically-sensitive patients generally recommend avoidance of exposures and substances that seem to trigger symptoms and the establishment of a healthy lifestyle. Other therapeutic interventions included vitamin and antioxidant therapy and diet rotation. Mentioned infrequently were biofeedback, relaxation, and homeopathic remedies. The effectiveness of these therapeutic interventions was not revealed, although several physicians suggested an absence of effective therapies.

Denmark

The team investigating the situation in the Scandinavian countries relied primarily on telephone interviews, in addition to their literature review. In Denmark, data collection centered on occupational medicine clinics, which reported many cases of individuals with non-specific hypersensitivity caused by low-level exposure to chemicals in the environment.

Alleged Initiating Exposures or Events

Because these physicians practice occupational medicine, it is not surprising that they refer to categories of workers or specific occupations when describing potential "initiating" exposures. For example, several clinics report seeing hairdressers exposed to chemicals **[Mørck, 1994; Rasmussen, 1994; Franck, 1994]**, teachers exposed to bad indoor air quality **[Rasmussen, 1994]**, photo laboratory technicians exposed to chemicals **[Mortensen, 1994]**, and painters exposed to solvents and lacquers **[Mortensen, 1994]** among their patients with environmental hypersensitivities. One clinic reported an epidemic of throat irritation and memory loss among house-helps and nurses for the elderly, who blamed their problems on the catalytic convertors in their official cars **[Franck, 1994]**. Although some persons recovered, others remained sick and left their jobs. In all of these cases, workplace exposure to solvents, other chemicals, and poor indoor air quality appears to be important in precipitating hypersensitivity among some patients. Again, the precipitating exposures often appear to be more long-term or repeated in nature than a one-time event. One centre **[DTI, 1994]** reported information about a family exposed to a "cold asphalt" product used on their home which contained several solvents. The mistress of the house became sick and complained of solvent smell inside the home, even months after an intervention to evaporate the solvents. The woman continued to be bothered by the smell although others could smell nothing.

Psychosocial factors are thought by many physicians to be important; one physician **[Weeke, 1994]** reported that many of his hypersensitivity patients are experiencing a personal crisis and stress at work in addition to bad indoor air quality.

Subsequent Sensitivity, Symptoms, and Interventions

Patients from the occupational medicine clinics noted above report a variety of symptoms, similar to those reported in Germany and elsewhere. These include headache, dizziness, irritation of eyes, nose, and throat, rhinitis, fatigue, memory loss, odour sensitivity, and, less often, gastrointestinal complaints. Affected patients report responding to such substances as solvents, paints, nail polish, gasoline and white spirits, tobacco smoke, perfumes, and cooking odours. Reported interventions include removal or avoidance of exposures as well as psychological counseling and referral. There is no information on the efficacy of these interventions, since physicians do not normally follow these patients.

Sweden

Alleged Initiating Exposures or Events

Physicians in Sweden also avoid chemical sensitivity as a diagnosis, expressing confusion and skepticism about the disorder. They do, however, report seeing patients

who react to very low levels of chemicals, and there are several plans to establish clinical centers for patients with alleged environmental hypersensitivities **[Ahlborg, 1994]**. Again, workplace solvents, paints, printed material, and poor indoor climate have been associated with the onset of hypersensitivity in Sweden, as have dental amalgams.

Subsequent Sensitivity, Symptoms, and Interventions

Symptoms include fatigue, dizziness, mood changes, respiratory complaints, and ear, nose and throat irritation. Subsequent sensitivities include buildings recently painted with water-based paints; nail varnish; perfumes and other odours; smoke; dry-cleaned clothes; and solvents, such as gasoline and oils. Although physicians interviewed reported little in the way of intervention with their hypersensitive patients, avoidance and removal of offending agents (in one case, carpeting) have been recommended. One physician **[Wilhelmsson, 1994]** reports seeing 200-400 patients with hypersensitivities per year. Many are hairdressers, dental assistants, and computer workers. Dr. Wilhelmsson tries different intervention strategies with these patients, including nutrition, homeopathy, and detoxification.

Norway

Alleged Initiating Exposures and Events

Physicians interviewed in Norway report a similar picture. An occupational and environmental medicine clinic at Ulleval University Hospital **[Levy, 1994]** sees patients who work in chemical laboratories whose problems ostensibly began with workplace exposure to solvents, including formaldehyde, xylene, and methyl methacrylate. Dental technicians seen in the clinic report "allergy" when exposed to methyl methacrylate and also subsequent symptoms of solvent intoxification. Two patients report chemical sensitivity after exposure to indoor application of insecticides. Some also ascribe their hypersensitivity to amalgams and electricity. A clinical ecologist practicing in Oslo **[Ljøgodt, 1994]** reports that her patients often become chemically sensitive after exposure to antibiotica, solvents, and new buildings.

Subsequent Sensitivity, Symptoms, and Interventions

Patients with occupational solvent exposure and encephalopathy report subsequent sensitivities triggered by solvents, such as acetone and nail polish used at home, paints, and certain foods. Dr. Ljøgdt reports that her patients react to low levels of perfume, hairsprays, solvents, petrol exhaust, formaldehyde, and some food additives. Her patients report various symptoms. They are treated nutritionally and are told to avoid unnecessary chemical exposure. Data on treatment efficacy were not reported.

The Netherlands

In the Netherlands, a society called Health and Environment (Gezondheid en Milieu) has, since 1987, collected some 60 documented, but as yet unpublished, cases of patients who, according to the society's vice-president, believes suffer from "multiple chemical sensitivity" **[Peereboom, 1994]**. He speculates that the authorities do not accept the diagnosis because of financial and political reasons. He reports that most of the patients have had bad experience with the traditional medical system, having been advised by their physicians to see a psychiatrist, much to their embarrassment.

Using a 14 page questionnaire, the Society has found sensitivities after both low-level, long-term exposure and after a one-time single exposure. They uncovered only a few patients exhibiting SBS symptoms and distinguished those from other chemically sensitive patients, the former being much less severely affected. The alleged initiating/triggering agents included a wide variety of chemicals and products: carpets, solvents (like toluene), plastic components, styrene, and heavy metals like mercury. It is thought that many toxic chemicals even with low toxicity may evoke hypersensitivities. Symptoms are varied, from rheumatic pain to heart arrhythmias. Chronic fatigue (myalgia encephalopathy/encephalomyelitis)) is a common complaint. Therapies have included changes in lifestyle, housing, medications, diet, and alcohol use. Acupuncture, sublingual testing of allergens, orthomolecular supplements, and homeopathy are sometimes advised. While not advocates of alternative medicine approaches, the society acknowledges some success with these approaches **[Peereboom, 1994]**.

The board of directors of the Society for Health and the Environment is composed of professionals from many medical and scientific disciplines. The society is planning a nationwide search for sensitive patients with financial support from the Dutch Department of Environmental Affairs (VROM). At present, an information network in six Dutch provinces has been established to collect first-hand reports of health problems related to environmental causes. **[Hoeppener-Helmich, 1994]**. A group to study the problem of low-level sensitivity to chemicals has been formed in the Health Council of the Netherlands, but they consider the evidence insufficient to justify a statement about the condition at this time **[van de Wiel, 1994]**.

Belgium

A physician from Liege **[Bartsch, 1994]**, Department of Internal Medicine and Pulmonology reported two cases fitting the MCS-criteria. These cases are of interest because they resemble case histories uncovered during our inquiries with German colleagues. In his first case, a young man was exposed to insecticides (of unknown composition) sprayed in his sleeping room during a vacation to the Ivory Coast. The next morning he felt dizzy and disoriented and upon return to Belgium he developed sensitivity to chemical exposures at home and at his workplace. He was especially sensitive to odours. He lost his job because he felt unable to concentrate and work when exposed to solvents and odours. Laboratory testing revealed no abnormal results and no immunological allergy; a methacholine challenge test was normal. However, the patient, complained strongly of side-effects of the methacholine exposure with central nervous sensations (like an explosion in the brain). This case is similar to a description of a German case report, in which a tourist was exposed to insecticides in a hotel in Turkey.

The second case involves a medical doctor who developed chemical sensitivity due to unknown causes and who reacted to chemical/odour exposure (especially perfumes) with fatigue, dizziness, and inability to work.

The physician is very cautious in his interpretation of these cases, but speculates that the effects are mediated through the olfactory-limbic-system. He is aware of psychological problems in these patients. He plans to publish the histories as case reports and to do follow-up studies and research on the problem. He emphasized the need for a stringent definition and classification for MCS.

The United Kingdom

Alleged Initiating Exposures or Events

In some ways, the United Kingdom resembles the United States in its contrasting attitudes towards chemical sensitivity. The problem is well known in the U.K., where physicians--including practicing clinical ecologists--report seeing patients with a wide variety of problems allegedly related to chemicals. Some physicians generally regard the problem as likely to have a significant physiological basis. In contrast, some members of the occupational medicine establishment who, while they take patients' complaints quite seriously, incline to a psychosomatic or psychiatric diagnosis. However, unlike in the U.S., there appears to be a genuine interest among at least some allergists and environmental medicine physicians in bridging the gap between classical allergy and chemical sensitivity **(BSAEM, 1994)**.

At the Breakspear Hospital, Hertfordshire, over 12,000 patients who report abnormal responses to chemical exposure have been seen; over 1000 per year are currently being treated. Dr. Jean Monro works with "environmentally-induced" illness and allergy. Patients are reported to have been "over-exposed" to chemicals, solvents, pesticides, etc. The primary symptom is fatigue, followed by headache and achy muscles. Sometimes patients develop food sensitivities and asthma **[Monro, 1994]**. (See later discussion on food sensitivity research.) Patients come from a variety of occupational backgrounds including industry, offices and agriculture. The initiating exposures are sometimes said to be a single large exposure and sometimes a longer term, low-level exposure.

The Institute of Occupational Health at Birmingham reports that their patients who report chemical sensitivity often may not know the precipitating agent or event, but that some have been exposed to pesticides, solvents, and dry cleaning fluids (trichlorethylene) **[L. Levy, 1994]**.

Subsequent sensitivity, symptoms, and interventions

At Breakspear Hospital, patients are reported to have become sensitive to a large number of excitants. At the clinic in Birmingham, patients' symptoms are reported to be triggered by exposure to chemicals, but psychosocial stresses are also reported to trigger symptoms. Symptoms are often neurologic and non-specific and include increased sensitivity to odours and other environmental agents, such as recently painted rooms and psychosocial problems. The only available intervention is to remove the actual or suspected causes. When they receive the diagnosis of chemical sensitivity, many patients go on to consult clinical ecologists.

These two clinics operate under contrasting assumptions about the origin of the chemical sensitivity they see. The Breakspear Hospital assumes an environmental cause, while the clinic in Birmingham assumes a psychogenic one.

Dr. Honor Anthony has been working for over eight years with Dr. Jonathan Maberly at the Airedale Allergy Centre, West Yorkshire, where they treat patients and conduct research on objective evidence of changes in patients with alleged chemical sensitivity **[Anthony, 1994]**. Dr. Maberly built the first environmentally-controlled hospital unit in Europe which opened in 1985. Over 500 patients with "environmental sensitivities" have been treated, most of whom had multiple symptoms. Over half present with alleged

sensitivity to chemicals. Results are reported to be very good, with the median number of severe and frequent/constant symptoms decreasing from 5 per patient on admission to 1 per patient when followed up by questionnaire 6-30 months later **[Anthony, 1994]**.

Drs. Anthony and Maberly treat less severely affected patients as outpatients, as do over 100 colleagues, and they find that reducing exposure to chemicals is an essential part of their management **[Anthony, 1994]**. Most patients are reported to improve, many substantially, unless they have no control over their environment or they live in highly polluted surroundings. These physicians, and those who are members of the British Society for Allergy and Environmental Medicine, state that they could supply hundreds, perhaps thousands, of case histories for study of patients whose symptoms are prevented by avoiding chemical exposure and/or by other specific prophylaxis.

A contrasting experience from that of the Airedale Allergy Centre discussed above is provided by the Allergy Section of the Department of Medicine, University Hospital, South Manchester, which has investigated several hundred patients suffering from alleged chemical sensitivity **[Pearson, 1994]**. They distinguish non-specific bronchial reactivity in asthma from putative multiple chemical sensitivity with symptoms referable to multiple organ symptoms (including mental or psychiatric symptoms). Blinded testing of the latter group is reported to demonstrate that chemical sensitivity is not founded on an organic basis; such individuals are usually found to be suffering from recognized psychiatric disorders.

Greece

Because of the general lack of awareness of any problem labeled "chemical sensitivity" in Greece, the team avoided use of the term and instead asked key physicians about cases in which the patients had problems associated with chemical exposure that could not be classified as classical allergy or toxic reactions. In this manner, they uncovered numerous cases of hyper-reactivity and problems possibly related to chemical sensitivity.

Alleged Initiating Exposures

A variety of chemicals were reported to cause (i.e., to initiate) hypersensitivity in several cases. The pulmonologists interviewed mentioned pesticides, lacquers, and chemicals used at beauty parlours, general anaesthesia, household chemicals (especially those containing chlorine), industrial chemicals, pharmaceuticals (in somebody who was loading already-packaged pharmaceuticals for transport) and paints as initiators of hyper-reactivity in patients they have treated. General anesthesia was also mentioned by allergists and other physicians. Pesticides were cited as initiators/sensitisers not only by pulmonologists but also by allergists (referring to farmers who used them in the fields), other physicians, and alternative medicine practitioners, who mentioned pesticide and fertiliser residues in food and water. The homeopathic practitioner mentioned pharmaceuticals as a very common sensitiser in Greece. The occupational physicians reported cases of hypersensitivity caused by exposure to formaldehyde, toluene, and solvents in the workplace, as well as a case of hypersensitivity caused by stress. The alternative medicine practitioners reported hypersensitivity to substances such as food additives, canned sauces, evaporated cow's milk and environmental pollution.

The most often cited initiating exposures were: pesticides, detergents and household chemicals (containing chlorine), chemicals at the workplace (especially organic solvents), general anesthesia and pharmaceuticals. The initiating exposure(s), as well as subsequent exposure to irritants, usually occurred at the workplace and the home.

Despite careful attempts to distinguish between initiating and subsequent exposures, some physicians did not separate them. Some could not identify the initial exposure since they did not take careful histories of their patients.

Subsequent sensitivity, symptoms, and interventions

Affected patients in Greece report that their ongoing symptoms are triggered by such agents as detergents and cleaning agents, perfumes, paints, kitchen odours, tobacco smoke, solvents, pesticides, and pharmaceuticals.

Bronchial hyper-reactivity, other respiratory symptoms, and rhinitis were predominant symptoms among these patients. As noted earlier, this could reflect a [disease] selection bias in the physicians interviewed for the study. However, skin sensitivity and CNS symptoms, such as headache, anxiety, fatigue, and cacosmia were also reported frequently. Skin sensitivity to many chemicals and bronchial hyper-reactivity related to exposure to different chemicals were, in almost all cases, accompanied by CNS symptoms. Most physicians considered it reasonable that all of these symptoms be viewed as a clinical entity, but they had no name for the condition.

In Greece, as elsewhere, physicians recommend that their patients remove or avoid offending agents, and several, but not all, physicians, report good results with this intervention. At least one physician also recommends avoidance of smoking, alcohol, fats, and "industrial" foods, with good results. Several physicians have also treated their patients' symptoms with steroids (which are temporarily effective) and homeopathic remedies (which one homeopath reports to be effective), but independent assessment of these results are not documented.

Summary Comments

Table 3 summarizes the reports and observations of physicians, scientists, and a few others in the countries studied regarding the agents and exposures associated with the onset ("initiation") of alleged chemical sensitivity in individual persons. The reader is cautioned that: 1) the reporting of a substance does not indicate confirmation of the occurrence of an initiating event; 2) the absence of reports for a specific substance in a particular country does not necessarily mean that patients have not reported the substance as associated with the onset of chemical sensitivity in that country; rather, it likely reflects the limitations of our interviewing (for example, sensitivity to dental amalgams has been reported in Denmark, although none of the persons we interviewed there mentioned that problem); and 3) because a particular substance is not mentioned in many countries does not necessarily mean that it is of little significance in the countries in which it is reported (for example, PCP was regarded as a widespread problem by physicians in the Netherlands and Germany, and was observed in Belgium, although it was not mentioned elsewhere).

Our investigations were neither exhaustive nor comprehensive. Nonetheless, some interesting observations can be made. Pesticides, organic solvents, formaldehyde, and stress are mentioned in many countries, while anesthetic agents is repeatedly mentioned

only in Greece. Problems with hairdressing chemicals are mentioned in Denmark, Sweden, and Greece. Of course, the categories "organic solvents" and "pesticides" are overly-broad. Identification of more specific substances in these categories would be more informative. However, in many cases, those observing or reporting alleged sensitivity did not have more definitive information. This investigation suggests that more careful documentation is needed in order to draw conclusions with confidence. With the exception of pentachlorophenol, these are the same substances associated with the onset of chemical sensitivity in North America **(Ashford and Miller, 1991)**.

Table 3. Some Exposures Reported as Associated with the *Onset* of Chemical Sensitivity in Europe

EXPOSURE	Denmark	Sweden	Norway	Finland	Germany	Holland	Belgium	U.K.	Greece
Amalgam/mercury		✓	✓		✓	✓			
Anesthetic agents									✓
Carpets and glue		✓				✓			
Diesel exhaust	✓								
Formaldehyde	✓		✓		✓				✓
Hairdressing chemicals	✓	✓							✓
Indoor climate	✓	✓		✓					
Industrial degreasers	✓								
Methyl methacrylate		✓	✓						
New/renovated buildings		✓	✓		✓				
Organic solvents	✓	✓	✓	✓	✓	✓	✓	✓	✓
Paints/lacquers	✓	✓			✓				✓
Pentachlorophenol/ wood preservative					✓	✓	✓		
Pesticides	✓		✓		✓		✓	✓	✓
Pharmaceuticals			✓						✓
Printed material	✓	✓							
Stress/psychosocial factors	✓	✓			✓			✓	

Table 4 presents some of the most common substances/agents reported by patients to trigger symptoms associated with chemical sensitivity. Reactions to these substances are reported in each country and parallel the North American experience. Symptoms frequently include: mucous membrane irritation, gastrointestinal complaints, joint pain, respiratory complaints, such as chest tightness and rhinitis, fatigue, and central nervous system problems, such as headache, dizziness, memory loss, difficulty with concentration. Physicians reported a higher occurrence of symptoms we associate with chemical sensitivity among women in the age group 30-50 in Scandinavia, Germany, and Greece.

Table 4. Some Substances Reported to Trigger Symptoms in Patients With Purported Chemical Sensitivity in Europe

- Air fresheners
- Alcohol
- Automobile exhaust
- Carpets
- Cleaners/detergents
- Clothing stores
- Cooking odours
- Cosmetics
- Diesel
- Drugs/pharmaceuticals
- Foods
- Gasoline
- Nail polish
- New cars
- Newly painted rooms
- Newspapers/printed material
- Perfumes/fragrances
- Solvents
- Stress
- Tobacco smoke
- White spirits

C. Other Studies Potentially Relevant To Chemical Sensitivity

Research that may help inform investigations about chemical sensitivity is ongoing in many countries included in this study. These include both human studies and animal research on 1) specific substances, such areas as organic solvents, paints, and pesticides; 2) consumer products, such as perfumes and cosmetics; 3) specific diseases, such as asthma, psycho-organic syndrome, allergy, and atopy; 4) certain environments, most notably building and indoor climate; and 5) certain mechanisms and processes, such as neurotoxicity and olfaction. This section is not intended to be comprehensive, but merely illustrative of the ongoing European research that may held clarify the area of chemical sensitivity.

Research on Specific Substances/Exposures

There is considerable research on the human response to exposure to environmental agents. These may be especially relevant if they relate to agents implicated in chemical sensitivity in some way. For example, several researchers conduct chamber studies exposing human subjects to *volatile organic compounds* (VOCs) and other environmental agents **(Mølhave et al., 1986, 1991a, 1991b, 1993; Kjærgaard et al., 1991; Zweers et al., 1990); [Wolkoff, 1994]**. These studies have found variations in individual sensitivity to environmental chemicals but have not identified hypersensitive subjects. **Sundell et al. (1993)** have also investigated total volatile organic compounds and general symptoms in 29 office buildings. The study found that "loss" of total volatile organic compounds (TVOCs) from supply to room air was associated with raised concentrations of formaldehyde and especially correlated with general symptoms, such as fatigue and feeling heavy-headed.

Researchers at the Department of Toxicology and Toxicokinetic Group, National Institute of Occupational Health, Solna, Sweden study the fate of environmental chemicals through experimental exposure in chambers and via computer models at this Institute are conducting research on water-based paints and sick buildings **[Löf, 1994]**. **K. Aas [1994]** has conducted a double blind and controlled exposure study of five individuals who reported hypersensitivity to water-based paints. Two of these individuals reported symptoms of nasal irritation, headache, malaise, and fatigue after exposure to the water-based paint in a controlled experiment.

In Denmark, a consulting engineering company (COWI-consult) has several projects concerned with the indoor and outdoor environments. For example, the firm evaluates pesticides, chemicals, and building materials on request of various ministries **[T. Hansen, 1994]**.

Several investigators in Sweden are interested in patients who are sensitive to amalgam **[Gunnarsson, 1994; Norbäck, 1994; Kolmurdin-Hedman, 1994]**.

Svensson et al. in Sweden (1992a; 1992b) have studied the effect of *toluene* exposure on hormone status in rotogravure printers and found an effect of low-level toluene exposure (well below the Swedish exposure limit of 80 ppm for printers) on the hypothalamus-pituitary axis. In Denmark, investigators have studied neurological manifestations after long-term exposure to *degreasing solvents* **(Rasmussen et al., 1993a, 1993b)** and have found a highly significant dose-response relationship between exposure and motor dysfunction and a significant effect on the olfactory nerve. Less clear was a trend of cranial nerve disturbance. **Aas (1994)** in Norway has conducted double-blind and controlled exposure experiments in which subjects were exposed to *paints* containing a compound known to cause hypersensitivity and to paints without this compound. Five of 30 subjects showed a special reaction pattern and reported symptoms when exposed to the paint with the compound causing hypersensitivity, and two of them reported symptoms of headache, fatigue, bronchial hyper-reactivity, and nasal symptoms on the following day. In the UK, Levy is investigating symptoms in persons who work with or have been exposed to *pesticides* **[L. Levy, 1994]**. Stollery, also in the UK investigates the relationship between neurotoxicology, cognitive function, and exposure to organic compounds, pesticides, lead, electromagnetic fields, and anesthetics **[Stollery, 1994]**.

Along with colleagues, Professor Buchter, Head of the Institute for Occupational Medicine at the University of the Saarland, Germany, studied the neurotoxic effects of solvents **(Lorenz et al., 1990 and 1991)**. His investigations include detailed occupational medicine, internal medicine, neurological-psychiatric, psychological, and radiological studies. In his multifactorial study of employees of a shoe factory, eight male patients and one female patient were given exhaustive clinical examinations following one- to fourteen-year-long exposure to the solvents dichloromethane, trichlorofluormethane and diphenylmethane-4, 4-diisocyanate, 1,1,1, trichloroethane and; in smaller doses, organic tin compounds and polydimethyl siloxane particles. The patients complained almost without exception of disturbances of concentration, memory, and emotion. In more than half of the cases, there were also symptoms of gastrointestinal disorders, headaches or head congestion, dizziness, hyperhidrosis, sleep disturbances, loss of interest, lack of drive, tendency toward social withdrawal, alcohol intolerance, tremors, and hearing loss.

The clinical examination disclosed high blood pressure and an increase in radiological patterns in the lower parts of the lungs in six patients. Laboratory chemical tests showed increased plasma viscosity values in over 50% of the cases. Neurologically, two-thirds of the patients evidenced, at times, a laterally accentuated tremor, primarily of the proximal extremities. In one case, an acute secondary Parkinson's syndrome was present. Impaired coordination was present in over 50% of the cases, and perception disorders were noted in nearly 50% of the cases. The electroencephalogram merely indicated non-specific general changes in a few cases. The NMR scan (computerised tomography) showed unmistakable signs of brain atrophy in eight of the nine patients.

Psychopathological peculiarities were present in all patients with regard to emotional disturbances. Memory and drive disturbances, as well as a slowing of thought processes were present in over 50% of the cases. Psychometric testing revealed positive results with regard to acquired cerebral-organic decreases in functional capacity and personality changes. The results of EEGs, pulmonary function tests, EMG, nerve conduction velocity, VEP, and SEP were without significant pathological findings.

Kelly et al. (1994) in the UK examined the electrophysiological and biochemical effects of organophosphate exposure in mice. In their study, single doses of a neurotoxic and non-neurotoxic organophosphate (mipafox and ecothiopate, respectively) were given subcutaneously to mice. The authors indicate that the neurotoxic organophosphate alone "produced measurable changes in nerve function"--although the doses used were below the threshold level assumed from the clinical science. These long-term changes are thought to represent a new phenomenon, unrelated to the classical organophosphate-induced delayed neuropathy.

In Germany, a physician **(Schwinger, 1992)** expressed the view that:

> Many chemical biocidal substances (e.g. pentachlorphenol, dioxins and furans, polychlorinated biphenyl's (PCBs) and other hydrocarbons) reveal completely different toxicokinetics when inhaled as for oral intoxications. Intoxication via inhalation exhibit something totally different and in no way comparable with oral intoxications, with respect to concentration in the body and distribution with the organism and furthermore with totally different intoxication symptoms. The mechanism associated with chronic poisoning via minute chemical traces inhaled into the lungs is largely unknown, but cannot be disregarded. Possible causes are leaky "tight junctions" or damaged "surfactants" in the alveoli of the lungs.

Molecules of toxic substances can in this manner creep into the nervous system and immediately induce complaints and neurotoxic symptoms, which confirms that the immune system has failed to react. The defensive system fails to react owing to the minute quantities involved; it was not triggered. At a later date, it may come about that these leaky junctions exhibit a tendency towards paralysis, so that the persons afflicted will always and overall react to increasingly smaller chemical traces. It seems also be the case, that a chronic intoxication via inhalation of the above mentioned environmental substances, gradually brings about an irreversible paralysis of the defensive system, so that a new toxic source - years later - can give rise to serious reactions.

In addition to the above, governmental organizations conduct research which yield information that may be of interest to those involved in studies of chemical sensitivity. For example, the National Occupational Institute in Denmark has done a chemical consumer investigation which found that 4350 of the chemical products used in 1000 Danish workplaces contain one or more compounds with long-term health effects. This is about one third of the chemicals used in Danish factories. The investigation found that 27% of the chemicals are neurotoxic chemicals and 21% might cause allergy. The trades that have significant risk of exposure to these neurotoxic and allergenic chemicals are the iron and metal trades, followed by cleaning, washing, and hairdressing workplaces. The greatest use of neurotoxic chemicals occur in color and lacquer factories and factories that produce oil products. The greatest use of allergenic chemicals occurs in the iron and metal industry **(Flyvholm et al., 1994)**.

Other researchers evaluate the toxicology and health effects associated with workplace chemicals **[Thomsen, 1994]** and very low levels of organic compounds **[Wolkoff, 1994]**. Thomsen has compiled a list of chemicals in the work environment which have neurotoxic effects **(Thomsen, 1990)**. A number of pesticides, as well as industrial chemicals identified in this investigation as "initiating" chemical sensitivity, are included in the list.

Research on Consumer Products

Research on specific chemicals in *consumer products* also exists and should be followed by those interested in chemical sensitivity. For example, The Danish Environmental Research Institute investigates chemicals in consumer products that may cause allergy, e.g., formaldehyde in cosmetics and contact allergens in perfumes **[DERI, 1994]**. A study of particular interest in the context of the European experience with chemical sensitivity is a study of volatile components of water-based paints and sick buildings **[Löf, 1994]**.

Research on Specific Environments

Scandinavian scientists have taken the lead in research relating to *sick buildings and indoor climate*. For example, in Denmark, **Skov et al. (1987)** studied the indoor climate and work-related health complaints of 4369 workers in 14 town halls in Greater Copenhagen. The lowest symptom prevalence was found in the oldest buildings. Preliminary analyses showed that gender, job category, photoprinting, VDT use, and handling of carbonless paper correlated significantly with symptoms. These town halls and town hall workers also have been investigated by **Valbjørn et al. (1987) and Franck et al.**

(1993). **Thestrup-Pedersen et al. (1990)** has investigated the occurrence of allergy in patients with sick building syndrome. Lundin in Sweden is investigating psychological parameters in relation to SBS **[Lundin, 1994]**. **Andersson [1994]** in Sweden has constructed a cohort of more than 6000 office workers for investigating health complaints relating to indoor climate problems and has developed a "standardized" questionnaire which has been translated into may European languages. **Baird et al. (1994)** has conducted a longitudinal study and investigated eye and upper airway symptoms among library staff at a university. Also in Sweden, **Norbäck et al. (1990a; 1990b; 1991; 1993)** have conducted several studies of SBS symptoms, indoor concentrations of hydrocarbons, indoor climate factors, and personal factors, including reported hyper-reactivity and sick leave due to airway disease. **Stenberg et al. (1990)** studied SBS skin symptoms in a cohort of 6000 office workers and found symptoms more prevalent among workers with a history of atopy and among VDT users. The SBS cases were more prevalent among females (11.9%) than males (3.9%). In a later study, Stenberg **(1993)** investigated the prevalence of perceived SBS symptoms and their association with personal and exposure factors. They found that gender, occurrence of asthma/rhinitis, paper, and VDT work were related to an increased prevalence of SBS symptoms. Research on indoor air and sensitivity effects is also ongoing in Finland **[Saarela, 1994]**. Although most of the research on SBS has not specifically focused on chemical sensitivity, these or similar future studies could provide useful information if the cohorts were followed-up to investigate the development or continuation of low-level sensitivities in some patients after the resolution of the sick building or indoor climate problem.

Research on Specific Diseases or Clinical Syndromes

Research into particular *diseases or clinical syndromes* that are alleged to have some relationship to chemical sensitivity could help clarify aspects of the condition. Of particular interest may be diseases, like asthma and allergy, which are relatively common and for which environmental agents are important. This type of research is ongoing in most of the countries studied.

In Denmark, **Johnsen [1994]** and the Danish University of Technology have conducted chamber studies in which *asthmatics* are exposed to vapours from building materials. He observed eye changes at lower exposure levels than observed earlier. **Harving et al. (1990)** has measured the effect of formaldehyde exposure on bronchial hyper-responsiveness in asthmatics and found that residential levels of formaldehyde are of minor importance in the emergence of pulmonary symptoms. **Beck et al. (1989)** studied atopic dermatitis patients moving into houses with excellent indoor climate (per WHO guidelines). The study found improvement in patients' subjective symptoms and clinical status of atopic dermatitis after moving into this "mini-risk" houses. The investigators concluded that indoor climate may be one of many factors affecting their skin condition.

Holmelund, et al. in Denmark has performed advanced vestibular testing on 75 patients with acquired intolerance to solvents **[Holmelund, 1994]**.

Behrendt in Germany **(1991)** conducted a pilot study of children living in polluted and high traffic regions and found that they have experience a significant amount of pollen *allergy*, suggesting that pollutants "prepare the way for allergies." Other experimental research in Germany **(Rohr et al., 1985a, 1985b; Haury et al., 1991a, 1991b; Koller and**

Haury, 1994) has shown that pesticides and heavy metals can release mediators from rat mast cells *in vitro* and human basophiles which imitate the symptoms of allergy.

In the U.K., **Green (1994)**, in a conference report about chemically-induced lung sensitisation, indicates that environmental factors have contributed to the increased incidence of asthma in the industrialised world. He cites a twenty-fold increase of asthma in military conscripts in Finland between 1960 and 1980. In the UK, there are now 1100 new cases of occupational asthma each year; this is the major cause of occupationally-related ill health. He notes that "the list of chemicals used in industry, quite short only a few years ago, is continually extending" and that "there are no well validated tests for predicting respiratory sensitisers." In the report, he notes that research has showed that in some patients with diethylamine-induced asthma, the disease progressed after occupational exposure ceased.

A recent report from Scandinavia **(Bakke et al., 1993)** documents significant increases (a tripling over 30-40 years) in asthma and allergic rhinitis which is attributed to indoor air contamination.

Snashall, Gillett and Chung (1988) in the UK, in a review of the literature on bronchial hyper-responsiveness in asthma, discuss the factors which contribute to asthma and its mechanisms. In this discussion, they acknowledge an "impenetrable 'black box' of great complexity" between the stimuli and the reaction of the human organism, and that there are probably several causes in each individual.

In the U.K., a consecutive series of 19 asthmatics improved after admission to a "clean" environment. Ten developed bronchospasm with very low doses of some chemicals. Symptoms showed a highly-significant reduction on follow-up, and over half the patients were using no medication, regularly or occasionally **(Maberly and Anthony, 1992)]**

Seaton, Godden, and Brown (1994) in the U.K. explore the possible explanation for the increase in asthma. They advocate that increased genetic susceptibility and/or exposure to *outdoor* environmental factors do not seem to provide adequate explanations. Instead, they propose the hypothesis that the increase in asthma may be explained by a lowered host resistance caused by the "westernisation" of diets. Their paper has little discussion of indoor air which now is recognized as constituting the heaviest source of exposure to VOCs in industrialized countries.

In an editorial of the Journal of Neurology, Neurosurgery and Psychiatry (UK), **Williams (1993)** hypothesizes that hypersusceptibility to chemical factors resulting from poor metabolism of xenobiotics may be a risk factor for neurological disease . He writes: "The interaction between chemical exposure and genetically determined hypersusceptibility may be crucial to understanding a number of poorly understood neurological diseases and is worthy of further consideration." In this discussion, he also proposes that foreign chemicals (xenobiotics) may damage the olfactory system along with the brain.

In Finland, **Hyypä et al. (1993)** investigated the possible relationship between cortisol secretion and perceived fatigue. Although hypersecretion of cortisol was not present in fatigue subjects drawn from the general population, the results may not be relevant to selected clinical samples of chronic fatigue patients.

Another disease entity of interest may be *psycho-organic syndrome* because it frequently involves solvents (a class of chemical frequently mentioned by both physicians and patients in relation to chemical sensitivity) and can be associated with specific occupational groups, e.g., painters. In Sweden, **Ödkvist et al. (1987; 1992) and Wennegren et al. (1988)** have focused on this clinical entity and the use of auditory and vestibular test batteries for early diagnosis of psycho-organic syndrome and evaluation of patients with exposure to environmental neurotoxins. **Ledin et al. (1989)** have used static posturography and vestibulo-oculomotor and auditory testing to evaluate postural control in patients with psycho-organic syndrome and in workers exposed to industrial solvents (as well as controls) and found that both methods are of value in assessing CNS lesions in solvent-exposed workers.

In the U.K., Stollery, a researcher in the Department of Psychology, University of Bristol, while not specializing professionally in chemical sensitivity, is investigating neurotoxicity and changes in cognitive function as a result of exposure to volatile organic compounds, pesticides (especially organophosphates), lead, anesthetic agents, and electro-magnetic fields **[Stollery, 1990a, 1990b, 1992);[1994]**. In his research involving subjects from the general population, he encounters patients with increased sensitivity; he does not know the reason for this sensitivity.

Some UK researchers **(Wessely 1992; Howard and Wessely, 1993 and 1994)** have reviewed selected literature and have attempted to explain phenomena such as "multiple unexplained somatic symptoms," multiple or total allergy, chronic fatigue syndrome, non-allergic symptoms, and other related syndromes. Their interpretations of others' work has lead them to reject the existence of chemical sensitivity or new allergic diseases, as they have some times called them, and suggest that there is an overlap between psychiatric disorders or "mass psychogenic illness" and environmental illnesses. Psychosomatisation is the mechanism they propose as an explanation for these cases. Nevertheless, in his earlier article on chronic fatigue syndrome (CFS) **(Wessely, 1992)**, Wessely acknowledges the literature which indicates that patients with CFS may have altered neuroendocrine function **(Demitrack et al., 1991)** and differences in "event-related potentials" **(Prasher et al., 1990)**.

Because some patients report subsequent *food intolerance* associated with chemical sensitivity, research in this area may be particularly informative. Such research may help clarify the role of food and diets in patients with chemical sensitivity and identify interesting subgroups for follow-up. In an exchange of letters in the Lancet **(Anthony et al., 1994)** concerning a recent report on food intolerance **(Young et al., 1994)**, earlier British work on bronchospasm from foods was discussed **(Pelikan and Pelican-Filipek, 1987; Maberly and Anthony, 1992)**. **Sloper et al. (1991)** report a non-immunological food intolerance manifesting as eczema in children. In Denmark, the research of **Fuglsang et. al. (1993 and 1994)** of the National Food Agency of Denmark, Institute of Toxicology, Søborg, on food intolerance and atopy in children has reported asthma, rhinitis, urticaria, gastrointestinal symptoms and atopic dermatitis associated with preservatives, colouring agents and citric acid in carbonated lemonade or soft drinks.

In Germany, **Thiel and Fuchs (1983)** have also studied food intolerance in predisposed people caused by chemicals (additives) due to assumed disturbances of the metabolism of arachidonic acid, especially of prostaglandin and leukotriene synthesis. They suggest this intolerance belongs to a class of pseudo-allergic reactions. The products

of the arachidonic acid metabolism seems to play a key role as mediators of cellular processes. Mediators like histamine and especially SRS-A are also seen as likely to be involved with pseudo-allergic reactions.

Another UK researcher **(Pearson, 1991)** discusses food hypersensitivity and its mechanisms. He attributes food hypersensitivity to psychological origins. He advocates that food hypersensitivity that is not allergic in nature is often not a real reaction to food (he calls it "pseudo-food allergy"). He explains this by referring to food's "enormous psychological, emotional and even ritualistic importance in virtually all cultures". In this article, Pearson openly rejects "unorthodox medical approaches" (his terminology), such as clinical ecology. While he advocates double-blind controlled food challenges, he fails to cite the studies, either British **(Jones and Hunter, 1987)** or American **(King, 1988)** that have been done in this fashion which indicate non-allergic sensitivities to foods.

Research on mechanisms and biochemical/neurological/immunological processes

Studies of odour, olfaction, sensory perception, and nasal hyper-reactivity are of clear relevance to chemical sensitivity because so many patients report increased sensitivity to numerous odours. In Sweden, **Berglund et al. (1993)** have studied self- and cross-adaptation of experimental subjects exposed to chemicals and mixtures of chemicals. Results indicate that olfactory adaptation is specific and that the sense of smell is more robust than generally assumed. No hypersensitive group was identified among the 15 subjects. **Hallén et al. (1993)** developed an objective method to diagnosis nasal hyper-reactivity. Study results confirm that hyper-reactive patients have a higher reactivity to non-specific stimuli compared to rhinologically healthy individuals. Using rhinostereometry, **Falk [1994]** also found that persons with SBS showed more nasal swelling that a control group. **Ohm et al. (1993)** have also used rhinostereometry to investigate nasal mucosa reactivity. One study (1993) attempted to identify non-allergic persons with nasal hyper-reactivity among healthy individuals with a histamine standardization test. Results showed a significant difference between non-allergic persons with hyper-reactivity and the control group of health volunteers.

Mølhave (1991b) has suggested that sensory perceptions of multifactorial exposures, including VOC and thermal factors, may be the cause of SBS. **Berglund et al. (1989)** have suggested that chemical stimulation of the trigeminal or olfactory nerves may explain the SBS. In Sweden, **Berglund et al. (1992)** have studied changes in sensory sensitivities with psychophysical methods. Two studies, involving active and passive smokers, found olfactory and auditory effects, indicating that tobacco smoke is associated with poor odour deductibility and attenuated perception of odour intensities. The 1989 report reviewed how sensory reactions may be useful guidelines for nonindustrial indoor air quality. In this article, the authors conclude that SBS is a physical and environmental problem that may result, in part, from: a) a changed sensitivity in the population exposed; b) a summation of numerous subthreshold sensory stimuli or interaction between stimuli and c) a learned adverse reaction to a chemical (-physical) pattern which instantly is recognized perceptually by the occupant. **Stenberg et al. (1993)** have also studied perception of SBS symptoms and the relationship between their occurrence and psychosocial and exposure factors in the indoor climate at work and at home. They found that gender, occurrence of asthma/rhinitis, paper, and VDT work were related to an increase is SBS symptoms.

German researchers are also involved in studies of olfaction and odour. **Ferstl [1994]** and **Kobal [1994]** are investigating olfactory evoked potential using EEG among patients with chemical sensitivity and control subjects. Others are examining the psychological response **(Winneke and Neuf, 1992)** and the exposure-response **(Steinheider and Winneke, 1994)** to industrial odours and traffic noise.

Several German or Austrian researchers are investigating the role of information in the perception or, response to, and tolerance of odours **(Kofler, 1993a,b; Hazard, 1993; Wagner, 1993)**. For example, Kofler from Austria **(1993a,b)** found information given to individuals could change the dose-effect curve and tolerance level of air pollutants. This may be relevant when trying to clarify odour sensitivities in chemically sensitive patients.

Summary Comments

Research that may help inform investigations about chemical sensitivity is ongoing in many countries included in this study. These include both human studies and animal research on 1) specific substances, such as organic solvents, paints, and pesticides; 2) consumer products containing formaldehyde; 3) specific diseases or disorders, such as asthma, psycho-organic syndrome, allergy, food intolerance, and psychological disorders; 4) certain environments, most notably building and indoor climate; and 5) certain mechanisms and processes, such as neurotoxicity and olfaction. However, the various research activities are undertaken with little cognizance of their possible relevance to chemical sensitivity. Connecting various researchers, for example those investigating neurotoxicity and those researching behavioral changes in populations exposed to chemicals, might be fruitful.

VI. DISCUSSION

A. The Existence of Chemical Sensitivity

Much of the evidence collected during the course of this project relates to poorly defined individuals or groups of individuals with symptoms and complaints which are unexplained or poorly understood in the context in which they are found. Certainly, some of the observations may be interpreted as chemical sensitivity. (See especially the evidence discussed earlier in Sections VA and VB.) However, without a clearly defined case definition for chemical sensitivity, a well-defined exposure history, and documentation of long-term consequences, it is difficult to assert with any degree of certainty that a particular incident or set of symptoms is in fact chemical sensitivity. While there are a small number of environmental control units in several countries, no published studies were found that test the hypothesis, in a double-blind fashion, that chemicals at low doses provoke the various symptoms discussed in connection with the condition. In the United States, the importance of pursuing this kind of validation has been urged by researchers and clinicians from all perspectives **(AOEC, 1992; Ashford and Miller 1991; NRC, 1992)**

The absence of an identifiable precipitating event does not prove the absence of chemical sensitivity; but the presence of a precipitating event or repeated or continuing exposure, the existence of symptoms at levels where most people do not exhibit symptoms, complaints triggered by more than one substance at low levels, multi-system effects, and the long-term continuance and possible spreading of symptoms all point to chemical

sensitivity as many have defined it. None of the experiences we were able to uncover in this investigation provide clear and convincing evidence on the existence or nature of chemical sensitivity as a distinct clinical entity, although some physicians are convinced that the condition has an environmental basis. In the discussion of mechanisms below, our interpretations are tentative, at best, and should be taken advisedly because the available information gleaned from particular examples may not point to a definitive explanation of chemical sensitivity. Of course, where there are more well-established facts about a precipitating event or exposure, triggering exposures, unexplained symptoms, and objective physiological or psychological measures of dysfunction, the experience should be viewed more seriously.

The existence of overlap syndromes with chemical sensitivity has hampered and obscured the understanding of chemical sensitivity. There are two distinctly different types of "overlap." First, there are syndromes, such as chronic fatigue syndrome or fibromyalgia, which could be the same or similar conditions masquerading under different names. However, these syndromes also engender controversy as to their nature and cause, so that overlap of one controversial condition with another often adds little to acceptability by physicians or scientists. In the Netherlands, inquiries about chemical sensitivity were answered by describing the condition as fibromyalgia encephalomyelitis **[Peereboom, 1994]** See also the research of **Ödkvist et al., (1987, 1992)** and **Wennegren (1988)** on psycho-organic syndrome.

The second type of "overlap" may occur in the context of other well-recognized conditions, such as asthma or rhinitis, where there may be persons whose symptoms may result from a non-classical sensitisation, but who are excluded from the definition of chemical sensitivity by some. **Cullen (1987)**, in fact, advocates excluding from the case definition of multiple chemical sensitivity any disease which has a well-defined classical diagnosis. Following this suggestion, the only symptoms that would remain to fulfill that definition would be those that are ill-defined symptoms and of an uncertain origin. Work uncovered during the course of this investigation suggests that asthma and other classical diseases may partly have their origins in a non-classical sensitisation mechanism (**Green, 1994; Snashall et al, 1988; Williams, 1993**).

In the United States, some have confused multiple chemical sensitivity with sick building syndrome (SBS), the latter being distinguished by the absence of symptoms when affected persons are away from the problem building. New work in the United States may help clarify the distinction between SBS and other possibly related conditions. In three apparent outbreaks of SBS, a subset of affected persons with chronic fatigue syndrome were found in percentages that ranged from 10% to 90% of the population **(Chester and Levine, 1994)**. The authors observed that "the agent(s) responsible for the traditional symptoms of SBS may also trigger CFS" and that "CFS can occur in the setting of SBS." **Buchwald and Garrity (1994)** compared thirty patients, each with diagnoses of chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivities (MCS), and concluded that they appear to have a large number of symptoms in common. They suggest that "these three conditions may represent overlapping clinical syndromes." There were, however, important statistically significant differences among the three groups. Post-exertional fatigue was significantly more common among individuals with CFS and FM than among those with MCS ($p<.01$), and patients with MCS more frequently reported sensitivities to pollution, gas, paint and solvent fumes than those with either CFS ($p<.01$) or FM ($p<.001$). The authors mused that "the diagnosis assigned to patients may depend

more on their chief complaint and the type of physician making the diagnosis than on the actual illness process." While the patients in the study did not undergo formal psychiatric evaluation, there were a "high frequency of self-reported neuropsychological symptoms."

B. Initiating Exposures/Events, Triggers, and Symptoms

Relatively few substances were specifically associated with the *onset* of chemical sensitivity in our investigation (see Table 3). The substances most often mentioned as initiators included pesticides, solvents, paints and lacquers, and formaldehyde. Repeated or continuous low-level exposure, rather than a single event, characterized most of the experience. Psychosocial stressors were also mentioned as initiating chemical sensitivity.

The predominant loci of the alleged initiating exposures/events in our investigation were in industrial, office, and domestic environments. Agricultural exposures resulting in chemical sensitivity were mentioned in several countries. Hairdressers comprised an occupational group that appeared to be affected in several countries. Instances of sick building syndrome (SBS) *per se* did not generally reveal chemically sensitive subgroups, although the preoccupation with immediate effects may have obscured their discovery. Certainly, we got no indication of a large problem in those instances. Relatively few community-based contamination episodes were uncovered which could have been initiating events. Initiating experiences with carpets and anesthesia were noted.

A much larger number of chemically-diverse substances were reported to trigger symptoms in persons who were already alleged to be chemically sensitive (see Table 4). These parallel the "triggers" frequently reported in the U.S. and include perfumes, detergents and cleaners, smoke, cooking odours, car exhaust, new clothing, nail polish, newspaper print, etc.

Physicians and patients reported a wide variety of symptoms associated with chemical sensitivity. These included rhinitis, respiratory and gastrointestinal problems, musculoskeletal symptoms, and ear, eye, nose, throat, and skin irritation, as well as headache, fatigue, and a plethora of other CNS complaints. Sensitivity to odours is a frequent symptom, and food intolerance is also mentioned. These symptoms also parallel those reported in the U.S.

C. Possible Underlying Mechanisms

Four general classes of mechanisms have been suggested **(Ashford and Miller, 1991)** to explain chemical sensitivity: 1) neurological, 2) immunological, 3) biochemical (and endocrinological), and 4) psychological. For the most part, chemical sensitivity is poorly characterized in the studies examined during this investigation, although medical practitioners, scientists and governmental authorities seemed poised to undertake some serious examination of the condition. Many physicians who have seen a few patients and those who have looked at large numbers of patients have *opinions* as to underlying mechanisms based on their (sometimes limited) observations. In addition, some human and animal research has been uncovered which throws light on the possible mechanisms. However, the reader is reminded that chemical sensitivity may be more a collection of diseases/syndromes that have a common response feature -- heightened reactivity to low levels of chemicals--than a single entity. Different mechanisms can be at play and different pathways can lead to what appears to be a common symptomatology.

Neurological Mechanisms

A Danish study **[Mørck, 1994]** of hairdressers diagnosed with "brain damage" with symptoms of dizziness, loss of memory etc. and exposed at less than 1% of the occupational exposure limits to chemicals not known to involve the risk of brain damage suggests chemical sensitivity involving the neurological system. Additional suggestive evidence for this mechanism comes from the experience of the Slagelse Clinic in Denmark **[Franck, 1994]** that reports hairdressers who continue to have headaches and dizziness on exposure to gasoline or white spirits subsequent to their organic solvent exposure at work at levels unlikely to result in classical intoxication.

The Occupational Medicine Clinic in Aalborg, Denmark **[Mortensen, 1994]** reports unusual and persistent low-level sensitivity (irritation) to occupational and non-occupational sources of paint, varnish and cleaners in some workers who have had previous occupational exposure to paints and lacquers. This subset of workers react differently than the classically brain-damaged painters.

Mauri Johansson [1994] in Denmark has seen a series of patients who are intolerant to organic solvents and have indoor climate complaints relating to solvents. Originally exposed at work, these patients continue to experience cacosmia, headaches, dizziness, or fatigue months *after* leaving work. Patients with indoor air climate problems experience irritation of the eyes and mucosa but later develop intolerance to perfumes and cleaners. Some have problems with cooking odours and freshly-printed newspapers. The investigator reports that all patients have been healthy without any neurotic signs. At one clinic of occupational medicine **(Gyntelberg, 1986)**, 10% of the patients have an acquired intolerance to organic solvents that often interferes with ability to work. Dizziness complaints have been confirmed by vestibular tests.

Work in Germany **(Lorenz et al., 1990, 1991)** discussed above on the neurotoxicity of a variety of substances lends support to the importance of neurotoxic mechanisms for chemical sensitivity. In addition, the findings of abnormal blood flow to the forebrains of wood preservative-exposed persons compared to controls, though not peer reviewed, are suggestive of significant effects on the brain **(Fabig, 1988); [Fabig, 1994]**. The use of the brain itself as a marker for toxic effects needs further research and confirmation.

The discovery of nerve function changes in mice exposed to organophosphate pesticides below classically toxic thresholds **(Kelly et al., 1994)** suggesting a new type of neurotoxicity is particularly interesting.

Indirect evidence for a neurological mechanism comes from the opportunity for exposure to neurotoxic chemicals for persons possibly exhibiting chemical sensitivity. As mentioned earlier, the National Institute for Occupational Health in Denmark found that approximately one-third (N=4350) of the chemicals used in 1000 Danish workplaces contained one or more compounds with long-term health effects; 27% of the chemicals were found to be neurotoxic and 21% allergenic. The most heavily exposed workers were found in the iron and metal industry and the cleaning, washing and hairdressing industries, in decreasing rank order. Neurotoxic chemicals predominate in the colour, lacquer and oil products factories, while allergenic substances dominate in the iron and metal industries [**Flyvholm et al., 1994**]. See also Thomsen, 1990 for a compilation of neurotoxic chemicals found in the working environment.

Immunological Mechanisms

Interestingly, unlike the situation in the United States where immunologic mechanisms were the among the first mechanisms suggested for chemical sensitivity, in Europe, we uncovered less speculation that the underlying mechanism was immunologic. Little research was done on this pathway. There was a general absence of reported immunologic abnormalities among the patients of physicians interviewed for this study. When physicians did offer an opinion about possible mechanisms for chemical sensitivity, it was most often in support of a neurological or psychological pathway.

In Germany, one physician postulates that immunological factors are not observed in this condition **[Schwenck, 1994]**. A German psychologist, however, argued that the hypothalmus, over-responsive to odours, can lead to disturbance of the immune system resulting in inflammation, through the interplay of the nervous and hormonal system (**Maschewsky, 1994**). Thus while not a classical immune response, it is suggested that the immune system is nonetheless affected through dysregulation. However, neither of these views are presented as the result of scientific studies designed to investigate mechanisms for sensitivity to chemicals.

The work of **Daniel et al. (1994); Schepens (Jorens and Schepens, 1993; Jorens et al., 1991); and Janssens and Schepens (1985)** suggest an immunological mechanism for PCP toxicity.

Biochemical Mechanisms

In Sweden **(Svensson 1992a)**, toluene was found to cause effects on hormone status in rotogravure printers, suggesting effects on the hypothalamus-pituitary axis at exposure levels well below 80 ppm, the Swedish occupational exposure limit.

In the UK, **Williams (1993)** speculates that damaged xenobiotic enzyme systems, ordinarily active in olfactory tissue can be destroyed or made dysfunctional in susceptible individuals. This may contribute in cascade fashion to neurodegenerative diseases as feedback mechanisms that would ordinarily signal the need for avoidance are compromised. This is another example of the possible importance of the interplay between the nervous, endocrine and immune systems.

Psychological Mechanisms

In Denmark **[Johnsen, 1994]**, 15% of asthmatics have been found to exhibit intolerance to perfume; this asthma is not always correlated with a decrease in lung function. The investigator suspects a psychological reaction or hysteria because the asthmatic attack occurs so quickly. (Of course this could also support a neurological mechanism involving the olfactory nerve.)

In the United Kingdom, the work of **David and Wessely (1994)** discussed earlier suggests psychogenic origins of chemical sensitivity resulting from a chemical spill by demonstrating that affected patients have psychiatric disorders. These findings, like other work that focuses on symptoms, suffer from confusing psychological *symptoms* with psychological *origins or causes* of the condition. Nonetheless, many physicians observe

psychological disturbances in their chemically-sensitive patients and conclude their responses are either psychogenic or the result of a conditioned reflex.

Similarly, findings of psychological disturbances and difficulties coping in a contaminated community in Germany are offered as indications of psychogenic mechanisms for poly-symptomatic complaints **(Matthies et al. 1994).**

Work in the United States has attempted to evaluate patients with alleged chemically sensitivity by comparing them with other groups of patients using neurobehavioural tests (see the reviews of **Ashford and Miller, 1991 and Sparks et al., 1994**). In contrast, European publications tend to *interpret* the work of others, who report psychological problems in chemically-exposed persons as evidence for a psychological origin of their complaints (see for example, **Wessely (1992)** and **Howard and Wessely (1993)**. No properly-designed investigations of possible psychogenic *origins* for chemical sensitivity, or comparative neurobehavioural studies, were uncovered in the European literature in the course of this investigation.

The confusion attending the origin of chemical sensitivity underscores the importance of investigating co-precipitating factors, both physiologic and psychologic, and not pursuing one to the exclusion of the other in the course of diagnosis or in research.

D. Biomarkers for Chemical Sensitivity

Acceptance of chemical sensitivity as a *bona fide* medical illness has been hampered by, among other things, the lack of an identified biomarker for the condition. Other illnesses, such as fibromyalgia and chronic fatigue syndrome, share the same difficulty. In the U.S., up to now, most clinical studies of MCS patients have focused on markers of immunological, neurological, inflammatory, and psychological responses. Clinical ecologists, a few other physicians in the private sector, and some commercial laboratories have reported alterations in a number of parameters in these patients, including T- and B-lymphocyte counts; helper/suppressor T-cell ratios; immunoglobulin levels; autoimmune antibodies (including anti-nuclear, anti-smooth muscle, anti-thyroid, anti-parietal cell and other auto antibodies); activated T-lymphocytes (Ta1 or CD-26); quantitative EEGs; evoked potentials; SPECT and other brain scans; levels of various vitamins, minerals, amino acids, and detoxification enzymes; and blood or tissue levels of pesticides, solvents and other "pollutants." **(Miller, 1994)**. Flaws in these studies are many and varied including: failure to define the study population (no case definition used); failure to compare cases with age- and sex-matched controls; failure to blind specimens; and failure to assess the accuracy and reproducibility of the test method. Studies performed by ecologists or commercial laboratories have been viewed with considerable skepticism by regulatory agencies and academic researchers. Some MCS investigators claim that different immunological abnormalities occur in different patients (for a review of the evidence, see **Ashford and Miller, 1991**; **Miller, 1994**).

With regard to claims of immunological dysfunction, no consistently abnormal immunological parameter has been demonstrated in these patients to date. There are, however, a number of reasons why a biomarker for chemical sensitivity may be elusive:

1. If chemical sensitivity in fact involves alterations in brain or limbic function, then salient markers might not be accessible with current technology. For example,

biochemical alterations in the central nervous system may not be reflected in blood chemistry determinations. Conceivably, advances in functional brain imaging (including SPECT and PET) in the future may provide insight into blood flow or metabolic changes that correlate with symptoms;

2. Biomarkers of interest may be in normal ranges during normal non-exposure conditions. Provocative chemical challenges with pre- and post-exposure measurement of markers may be necessary to distinguish between patients and normal controls. Just as methacholine challenges are needed to diagnose certain patients with reactive airway disease, it may be necessary to perform low-level chemical challenges with chemically sensitive patients in order to elicit their symptoms and observe a change in a biomarker; and

3. Patients may need to be "de-adapted" prior to challenge in order to see the most robust symptoms and changes in biomarkers.

The fact that no consistently abnormal immunological marker has been found in these individuals does not necessarily mean that the immune system is unaffected. It is conceivable that chemically-induced limbic/hypothalamic disturbances could alter immune function secondarily but in unpredictable directions. By analogy, if one were to throw a magnet into a computer, dysfunction no doubt would occur, but the direction and degree of dysfunction might vary depending upon where the magnet happened to land.

Alternatively, specific immune cell subsets or immunocytokines not yet explored in these patients may prove significant in the future. In the U.S., we found only one provocative challenge test performed on chemically sensitive patients **(Doty et al., 1988)**. In this study, patients manifested decreased nasal patency relative to controls, both before and after challenge. In Scandinavia, researchers have also studied nasal swelling and reactivity among hyper-reactive patients and found positive results **(Hallén et al., 1992; Ohm et al., 1993)**; **[Falk, 1994].** Similar low-level exposure provocative challenge studies that examine other parameters of interest are needed, e.g., immunological, neurological, and endocrinological markers.

VII. PLANNED EUROPEAN RESEARCH AND OTHER ACTIVITIES OF POTENTIAL RELEVANCE TO CHEMICAL SENSITIVITY

Netherlands

Although chemical sensitivity has not received much attention in the Netherlands or Belgium from either the medical community or the media, interest is beginning to increase. The Dutch Environmental Network Foundation (Stichting Steunpunt Milieunetwerken) has received a grant from the Department of Environmental Affairs (VROM) to establish a complaint registry for suspected environmental effects in the 12 Dutch provinces **[Hoeppener-Helmich, 1994]**. These are intended to include the kinds of complaints associated with reports of chemical sensitivity. The project will be overseen by the scientific advisory board of the Foundation for Health and Environment (Gesondheid en Milieu). This multidisciplinary board is composed of 14 traditional and established members of the scientific and medical community representing, among others, the areas of chemical toxicology, immunology, reproductive toxicology, and epidemiology. The Health Council of

the Netherlands is also considering undertaking a "background study" of low-level sensitivity to chemicals **[van de Wiel, 1994]**.

Germany

There is enormous public interest in chemical sensitivity on the part of the public and the media in Germany and strong interest on the part of the professional community in developing a better understanding of the condition. In August 1993, an expert group was convened by the German Ministry for Health and suggestions for diagnostic classifications for use in diagnosis of chronic fatigue syndrome were made **(Fock and Krüger, 1994).**

Prof. Dr. Holger **Altenkirch [1994]**, Director of the neurology clinic at Spandau Hospital, Berlin is performing a study of "neurotoxicity" related to pyrethroids. To be investigated is whether some patients show a specific sensitivity to low-level exposure to pyrethroids (e.g., from pest control and treated wool mark carpets). Publication of results is expected in 1995 **[Altenkirch 1995]**. Related avenues for useful research that could be pursued include the investigation of symptoms in farmers and pesticide applicators in fruit growing and tree nurseries in Germany, because these groups exhibit exposure characteristics most likely to be associated with chemical sensitivity.

Further epidemiological research is likely to be done. We identified several key researchers and research institutes: 1) Prof. Dr. H. E. **Wichmann** (GSF München, Institut für Umweltmedizin und Epidemiologie, 2) Frau Priv. Doz. Dr. M. **Bullinger** (Psychologisches Institut der Universität München), and 3) Prof. Dr. R. **Frentzel-Beyme** (Bremer Institut für Präventiv- und Sozialmedizin). Dr. Frentzel-Beyme is especially interested in research on chemical sensitivity. His research group is examining the influences of solvent exposures, while Dr. Bullinger is experienced in the evaluation of SBS.

A section of environmental medicine has been established at the special clinic in Bredstedt (Northern-Germany) **[Schwarz, 1994]**. Dr. Eberhard Schwarz worked in the Environmental Health Centre in Dallas and at the Breakspear clinic in the UK and uses clinical ecology methods like the modified Miller-technique. Since 1992, patient registration, diagnosis and a small amount of treatment of disorders with alleged environmental causes have been conducted. Dr. Schwarz is convinced that many patients presenting with psychiatric diagnoses are in fact environmentally sick. Neurotoxic problems have particularly been diagnosed and treated. In 1993, 153 patients were treated (supposed diagnosis: environmental disease). A therapeutic outcome evaluation of a recently established environmental control unit will be now carried out to evaluate the effect (success)of diagnostic and therapeutic interventions. The criteria are diagnosis, prognosis, and therapeutic effects. The study will be carried out under the supervision of Prof. H. Raspe (Institute of Social Medicine and Epidemiology). The patients will be followed up and questioned about their health 6 and 12 months after the treatment.

A second initiative was taken by the regional doctors' association to establish a 'Mobile Environmental Ambulance' in Schleswig-Holstein. Patients who suffer from environmental diseases according to their doctors diagnosis can request an inspection of their home and, if necessary, further analytical steps are taken (indoor analysis etc.). The main objectives are: 1) evaluation of disease and its development, 2) collection and analysis of laboratory findings, 3) search for indoor pollutants and measurement of critical

substances, if indicated, and 4) development of industrial hygiene interventions. According to the operator of the ambulance, about 70% of the patients seen by ambulance showed effects believed to be related to environmental causes. The following pollutants were found: formaldehyde, wood preservatives, pesticides, organic solvents, PCB, and mould, particularly spores. Patients served by this new ambulance could be further evaluated for chemical sensitivity and followed for appropriate time periods.

Denmark

There is considerable interest in conducting future research in the area of chemical sensitivity in Denmark. Several investigators intend to use psychological tests with hypersensitive patients (Dr. **B. Weeke** of Rigshospitalet in Copenhagen and Dr. **C. Franck** at the Occupational Medicine Clinic in Slagelse). Drs. Frank and **Elmo** of the clinic in Slagelse have also planned a controlled experiment in which sensitive and non-sensitive persons are randomly assigned to low dose exposures of acetone. They will then collect data on symptoms and information on how subjects are affected by exposure to items in their daily lives. **M. Holmelund** at the otoneurological laboratory in Copenhagen, together with the Clinic of Occupational Medicine in Gyntelberg, plans a controlled study of persons who have had an acute reaction to solvents. M. Johansson (AT-Århus) is interested in advancing understanding of the olfactorius and in systematically describing the phenomenon. **J. Jelnæs [1994]** of the Danish Institute of Toxicology (DIT) is planning a study in which the residual content of toluene in photogravure printed advertising pamphlets will be measured and compared with subjective symptoms of patients.

Working with physicians and psychologists, **K. Graa Thomsen** plans to look at the occurrence of chemical sensitivity in the general population and try to identify causes and triggers. Dr. Graa Thomsen is in contact with the patient "Union for Odour Hypersensitive Persons" whose chairman, **Edith Moe**, hopes investigators will look at prognosis and treatment. According to **J. Vestbro** of the Hovedstadens Center for Prospective Population Studies, Institute for Prevention of Diseases, the center conducts three large population studies. Although questions about odour sensitivity have not been included in these population surveys, he is interested in this issue. The Danish Environmental Protection Agency is interested in a project that looks at possible legislative action in this area.

Sweden

A number of individuals interviewed for this study indicated an interest in conducting future research on chemical sensitivity. The Department of Occupational and Environmental Medicine at Örebro Medical Center Hospital is planning a clinical center for patients with alleged hypersensitivity to environmental factors. The center will involve collaboration among several specialty clinics at the Hospital; its aim is to help patients improve their well-being and coping ability and to advance knowledge of the development and treatment of hypersensitivity.

B. Karlsson of Yrkes- och Miljømedincinska enheten, Malmö is planning a research project to characterize MCS patients, persons with severe acute reactions from neurotoxic exposures, and persons with toxic encephalopathy with respect to their symptoms, cognitive function, and personality. The study will also include an experimental component; results will be available in 2-3 years.

V. Stejskal of Astra AB hopes to initiate cooperative efforts among laboratories in Europe in the area of chemical sensitivity. Her immunotoxicology laboratory group studies allergy to chemicals such as pharmaceuticals, formaldehyde, and metals using an optimized lymphocyte proliferation test. The group participates in an EU- initiated biotechnology program on "in vitro immunotoxicology."

Norway

Although this study did not uncover a significant amount of research in the area of chemical sensitivity in Norway, there is interest in future work. **K. Aas [1994]** believes that the issue of hypersensitivity will increase in importance and that interdisciplinary research is needed -- especially to distinguish among SBS, chemical hypersensitivity, environmental disease as defined by clinical ecologists, mass psychogenic illness, and other illnesses.

Finland

Finland does not conduct the same amount of medical and scientific research as the other Scandinavian countries, but at least one group, the Technical Research Centre, is trying to identify the levels of indoor air pollution that begin to cause discomfort or to change sensitivity of exposed persons **[Saarela, 1994].**

United Kingdom

H. Anthony and **J. Maberly** of the Airedale Allergy Centre, West Yorkshire, treat patients and do research on objective evidence of changes in chemically-sensitive patients **[Anthony, 1994]**. These physicians, and those who are members of the British Society for Allergy and Environmental Medicine, state that they could supply hundreds, perhaps thousands, of case histories for study of patients whose symptoms are prevented by avoiding chemical exposure and/or by other specific prophylaxis.

L. Levy at the Institute of Occupational Health, Birmingham is investigating symptoms in persons who have been or are working with organophosphate pesticides **[Levy, 1994]**.

B. Stollery, a well-published researcher at the Department of Psychology, University of Bristol, while not specializing professionally in chemical sensitivity, is investigating neurotoxicity and changes in cognitive function as a result of exposure to volatile organic compounds, pesticides (especially organophosphates), lead, anesthetics agents, and electro-magnetic fields **[Stollery, 1994]**.

Summary Comments

Chemical sensitivity is receiving increased interest on the part of both the medical and scientific communities. Understanding of the syndrome is in its infancy in both Europe and in North America, but there is more activity at present in North America. This could change rapidly, as governments undertake systematic studies or establish registries of persons claiming chemical sensitivity (like the Netherlands). Basic research in neurotoxicology, behavioural science, and olfaction; careful epidemiological investigations with appropriate follow-up; and properly-designed challenge studies could advance our understanding quickly.

VIII. RECOMMENDATIONS

The investigation has revealed substantial interest in the subject of low-level chemical sensitivity in Europe. As in North America, there is considerable confusion and skepticism about the disorder. Yet, the medical and scientific communities express interest in furthering their understanding of the problem.

Perhaps the most immediate need is for the convening of a workshop in early 1996 of a small number (30-50) of invited participants from Europe and North America to discuss the experience and evidence related to chemical sensitivity to date, and to make recommendations for further research. Invited participants should include knowledgeable researchers, practitioners, governmental authorities, and policy makers. Both proponents and critics of the condition should be included. The workshop format should allow for presentations, discussion, dialogue, and challenge of views in a structured, focused, and constructive way. To the extent possible, the workshop should help participants resolve differences and agree on research priorities.

A second priority is the development of protocols for taking a complete occupational and environmental exposure history in patients who report sensitivity to low levels of chemicals. The protocol itself should be developed by consensus of knowledgeable researchers, physicians, and patients and should give special attention to uncovering and documenting exposure to: 1) known sensitisers and neurotoxic agents; 2) substances often associated with the onset of chemical sensitivity, such as solvents, pesticides, new or renovated buildings, anesthetic agents, and wood preservatives; and 3) stressful or traumatic life events. In addition, protocols for follow-up in terms of changes in signs, symptoms, and disease over appropriate time periods need to be established.

Obvious opportunities for future study include: 1) the follow-up of *previously-exposed* cohorts of persons most likely to present with or develop chemical sensitivity; 2) the *prospective follow-up* of populations and persons involved in "natural experiments" that might result in chemical sensitivity, such as chemical spills or relocation to a new or renovated building; 3) the work-up of selected persons in an environmental control unit (ECU) in which double-blind placebo controlled studies are conducted to explore the nature and existence of chemical sensitivity in individual persons; and 4) the exploration of possible models that may elucidate mechanisms for chemical sensitivity.

In investigating options (1) and (2), it is important that both an occupational and environmental exposure history be taken and that outcomes (signs, symptoms, and disease) be tracked over a sufficiently long period of time to allow the discovery of chemical-sensitivity if it in fact exists in a particular context. "Initiating" exposures or events should be distinguished from subsequent triggering agents or excitants. Option (3) is important for investigating whether symptoms resulting from low-level exposures are reproducible on an individual basis. Note that an environmental control unit *is not an exposure chamber.* It is a specially-designed hospital unit where patients can be housed, removed from possible excitants (in food, water, air, etc.), and re-challenged under carefully controlled conditions. Option (4) is regarded as essential for clarifying the nature of chemical sensitivity. Both human and animals observations have provided important insight as to possible mechanisms for chemical sensitivity. Neurotoxic pathways in particular need to be examined. Analysis of use patterns in different countries for pesticides, anesthetic agents, and other possible sensitisers may reveal useful information.

Until the nature of the condition is better understood, reasonable preventive and accommodative action should be taken. These may include: 1) serious efforts (public health interventions) to reduce exposures to possible "initiators" of chemical sensitivity (suggested in part by the experience collected to date) and 2) avoidance (as much as possible) in public places of substances known to trigger symptoms in persons who already report chemically-sensitivity. *Reasonable* accommodation should be made in housing and employment, such as limiting and warning occupants about pesticide application in buildings and providing less-contaminated places to work.

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APPENDIX A
Definitions of Terms Commonly Used in European Countries Relating to Chemical Sensitivity

Project investigators assembled lists of terms and definitions commonly used in selected European countries to refer to chemical sensitivity or to disorders that are alleged to have some relationship to chemical sensitivity, some of which may be regarded as "overlap" syndromes. The following pages illustrate the variety of different terms, definitions, constructs, and conceptions used in these countries -- some of which derive from those used in the U.S. There are variations both among and within the countries. Although the list is lengthy, we do not claim that it is exhaustive.

The terms found here are of mixed origin. Some are well-defined in the literature and are widely accepted; others were encountered during interviews conducted as part of this study. Our research uncovered several new terms not commonly found in the North American literature on the subject. The sheer number of terms and the shades of difference in the meaning ascribed to each illustrate the complexity of the issue.

Allergy

1. Specific immunologic hypersensitivity.

Bakke JV and Knudsen BB (1993), Allergy, Hypersensitivity and Chemical Substances: Evaluation of the Ability of Chemical Substances to Cause Allergy and Other Hypersensitivity in the Skin and Airways, NKB Committee and Work Reports 1993:01 E, Nordic Committee on Building Regulations, NKB Indoor Air Climate Committee, Nordic Council of Ministers.

2. Exaggerated or pathological reaction marked by sneezing, respiratory embarrassment, itching, and skin rashes, or other symptoms to substances, situations, or physical states that are without comparable effect on the average individual.

Webster's Third International Dictionary, (1966), Springfield, MA.

Asthma

A chronic inflammatory disease of the airways in which many different cell types participate, including mast cells and eosinophils. In susceptible individuals, this produces symptoms which are usually associated with extensive but variable blockage of the airways which is often reversible, either spontaneously or through treatment, and leads to increased reactivity of the airways to a number of different stimuli.

International Consensus Report on Diagnosis and Management of Asthma (1992). U.S. Department of Health and Human Services. National Institutes of Health. Bethesda, Maryland, June 1992.

Building-Related Illness

1. A specific clinical syndrome associated with stay in a building which may last for several days after leaving the building. In general, the cause can be substantiated.

Examples include humidifier fever and legionellosis. One author suggests that SBS can appear without BRI, but it is unlikely that BRI can be observed without SBS. (Used in Germany)

Seifert B (1990). Das "sick building" Syndrom, *Oeff. Gesundh.-Wes.*, 53.

2. BRI is characterized by a generally uniform clinical picture for which a specific cause has been identified. In outbreaks of BRI, a wide spectrum of causative factors has been implicated: immunologic sensitising agents, infectious agents, specific air contaminants, and environmental conditions, such as temperature and humidity. Outbreaks without an identifiable cause have frequently occurred in new, sealed office buildings and have for that reason also been called the "tight building syndrome" (TBS) (similar to BRI and different from SBS).

Berglund B, Brunekreff B, Knöppel H, Lindvall T, Maroni M, Mølhave L, and Skov, P (1991), Effects of Indoor Air Pollution on Human Health. Commission of the European Communities, Luxembourg. Report No. 10, pp. 1-43.

Chronic Fatigue Syndrome

A disorder defined by the following two main criteria and 8 of the 14 secondary criteria:

Main criteria:

1. Strong weariness combined with a reduction in usual activity, about 50% for a duration of least 6 months;

2. Exclusion of all illnesses that lead to Number One above, e.g., disturbance of metabolism, anaemia, deficiency of vitamins and minerals, chronic intoxication, low blood pressure, alcoholism, addiction to tranquilizers, tumour, etc.

Secondary criteria:

1. Moderate fever or chill
2. Inflammation of the pharynx
3. (Little) pain of the lymph nodes
4. General muscle weakness
5. Muscle pain
6. Exhaustion after efforts that did not previously bother the patient
7. Pain in the whole. This type of headache is different in frequency, type, and seriousness from headaches before the disease
8. Arthralgia without reddening and swelling of the joints
9. Neuropsychiatric complaints
10. Somnolence and/or increased need for sleep

Findings:

1. Temperature between 37.8 and 38.8 degrees C
2. Swelling of the lymph nodes
3. Pharyngitis

Case definition used by the U.S. Centers for Disease Control. In Germany, see also:

Schönfeld U (1993a). "Das Chronische Müdigkeitssyndrom (Chronic Fatigue Syndrome) - Analyse des Forschungsstandes: Diagnostik, Klinik, Aetiopathogenese und Therapie," *Bundesgesundhbl.* 36(12):499-505.

Schönfeld U (1993b). "Das Chronische Müdigkeitssyndrom (Chronic Fatigue Syndrom) - Historische und epidemiologische Aspekte," *Bundesgesundhbl.* 36(12):505-510.

Chemical Sensitivity

1. For purposes of this report, the term "chemical sensitivity" is meant to include:

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

b) 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:

i) a heightened response to agents at the same exposure levels as other individuals;
ii) a response at lower levels than those that affect other individuals;
iii) a response at an earlier time than that experienced by other individuals.

Chemical (hyper-)sensitivity

1. Describes the adverse health effects manifested by certain individuals when they are exposed to low levels of chemicals. (Used in Greece; source unknown).

2. A condition in which certain individuals manifest adverse health effects when they are exposed to a number of chemicals, in concentrations at which most individuals do not manifest any disorder. For chemical sensitivity to be manifested, a previous sensitisation of the individual, by a chemical or other factor, is required. After the onset of chemical sensitivity, the individual can show an altered (excessive/exaggerated) reaction to the sensitiser or other chemicals and conditions. "Chemical sensitivity" is manifested with

various symptoms, mainly from the respiratory system, CNS, and the skin. (Used by the Greek team)

Ecological Illness/Disease; Clinical Ecology Syndrome; Eco-Syndrome

A polysymptomatic, multisystemic, chronic disturbance of health which is caused by undesirable reactions to irritating environmental agents and is modified by individual

sensitivities with specific adaptations. The irritating agents are present in air, water, drugs, and apartments. (Used in Germany)

Schwenck M (1995) "Multiple chemische Sensibilität," in Beyer A and Eis D, Umweltmedizin, Berlin, Springer Verlag, in press.

Ring J, Gabriel G, Vieluf D, and Przybilla B (1991), "Klinisches Ökologie-Syndrom (Öko-Syndrom)," *Münch Med Wschr* 133:50-55.

Environmental Stress

Human reactions due to stress caused by environmental exposures. Environmental stress is described by terms such as:

- Cognitive function effects: Impaired consciousness or awareness, lethargy, drowsiness, sluggishness,; sleepiness (fatigue).

- Impaired memory function

- Mood changes: Emotional lability, irritability, annoyance, tiredness, boredom, confusion; dizziness, unsteadiness, distraction;

- Systemic stress reactions: Stomach/digestion, nausea

- Cardiovascular: Headache, blood pressure

Fatigue

1. A state following a period of mental or body activity characterized by a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness, sleepiness, or irritability; it may also supervene from any cause. Energy expenditure outstrips restorative process, e.g., lack of sleep or food.

2. Sensation of boredom and lassitude due to absence of stimulation, monotony, or lack of interest in one's surroundings. Fatigue may be purely physical and confined to a single organ, e.g., of muscles or glands after a period of prolonged activity.

Stedman's Medical Dictionary. 22nd ed., (1972). Baltimore, MD: Williams and Wilkins.

Hypersensitivity

1. A state of altered reactivity in which the body (organs, cell systems) reacts with exaggerated response to a foreign agent which does not at normal low levels of exposure cause changes or symptoms among persons lacking this hypersensitivity.

Miller BF and Keane CB. (1983) Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health. 3rd. ed. Philadelphia, PA: WB Saunders, Co.

NBK (1993). Allergi, Oeverkanslighet og Kemiske Aemnen, Sammefatning og Konklusioner. Nordiska Kommitten før Byggbestaemmelser, Sverige.

2. A collective term for abnormally elevated sensitivity in one or more of the organs of cell systems of the body to normal or specially low stimuli which do not elicit morbid changes or symptoms in persons without the same hypersensitivity.

Bakke JV and Knudsen BB (1993), Allergy, Hypersensitivity and Chemical Substances: Evaluation of the ability of chemical Substances to Cause Allergy and Other Hypersensitivity in the Skin and airways, NKB Committee and Work Reports 1993:01 E, Nordic Committee on Building Regulations, NKB Indoor Air Climate Committee, Nordic Council of Ministers.

3. A state of increased reactivity of the host to a foreign agent (antigen or chemical substance) and implies that the reaction is damaging to the host. (Used in Greece; source unknown).

4. Abnormal or exaggerated reaction to a foreign agent affected by the immune response or chemical mediators. (Used in Germany)

Lafontaine A. (1983) "Problems and Perspective" in Allergic Responses and Hypersensitivities Induced by Chemicals. Proceedings of a joint WHO/CEC workshop, Frankfurt am Main, 12-15 October 1982, WHO Copenhagen, CEC Health and Safety Directorate, Luxembourg, 1983.

Hyperreactivity

A non-immunologic disorder characterized by hyper-irritability and poor control of one or more organ systems.

Aas K. (1990) "Kemisk overømfintlighet," *Tidssler Nor Laergetoren*, 110:1929-1931.

Hypersusceptibility

Inordinate (extreme, irrational) response to an infective, chemical, or other agent.

Stedman's Medical Dictionary, 22nd ed., 1972, Baltimore, MD: Williams and Wilkins.

Indoor Air Climate

The synthesis of day to day values of physical variables in a building (e.g., temperature, humidity, air movement, air quality, electric and radiation environment, etc.) which affect health and/or comfort of the occupants.

AIC (1981). AIRGLOSS: Air infiltration glossary. Technical Note AIC#5, International Energy Agency, Air Infiltration Centre, Brachnell, England.

Indoor Air Quality (IAQ)

1(a). The extent to which objective IAQ guidelines are met (q.v. measured air quality)

(b). The subjective rating of an indoor atmospheric environment (q.v. perceived air quality.

2. Acceptable IAQ is described as air in which there are no known contaminants at harmful concentrations and in which a substantial majority (e.g., 80% or more) of the people exposed do not express dissatisfaction. (Used in Greece)

Berglund B, Brunekreff B, Knöppel H, Lindvall T, Maroni M, Mølhave L, and Skov, P (1991), Effects of Indoor Air Pollution on Human Health. Commission of the European Communities, Luxembourg. Report No. 10, pp. 1-43.

Initiators

Chemicals that have a particularly great ability to initiate hypersensitivity and asthma through specific chemical hypersensitivity. Initiation of specific chemical hypersensitivity is often followed by (or provokes) non-specific hyper-responsiveness.

Bakke JV and Knudsen BB (1993), Allergy, Hypersensitivity and Chemical Substances: Evaluation of the Ability of Chemical Substances to Cause Allergy and Other Hypersensitivity in the Skin and Airways, NKB Committee and Work Reports 1993:01 E, Nordic Committee on Building Regulations, NKB Indoor Air Climate Committee, Nordic Council of Ministers.

Intolerance Reaction

A non-immunologic disorder often caused by the absence of or functional defects in special enzymes. The agent and the type of enzymatic defects which provoke reactions can be specified. (Used in Scandinavia)

Aas K. (1990) "Kemisk overømfintlighet", *Tidsskr Nor Largeforen*, 110:1929-1931.

Non-immunologically determined abnormal clinical response to a foreign substance. (Used in Germany)

Lafontaine A. (1983) "Problems and Perspective" in Allergic Responses and Hypersensitivities Induced by Chemicals. Proceedings of a joint WHO/CEC workshop, Frankfurt am Main, 12-15 October 1982, WHO Copenhagen, CEC Health and Safety Directorate, Luxembourg, 1983.

Multiple Chemical Sensitivity (MCS)

1. MCS is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general

population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms. Diagnosis relies completely on symptoms. (Definition commonly used in Scandinavia and Germany)

Cullen M (1987), "The worker with multiple chemical sensitivities: An overview," In: M Cullen (Ed.) Workers with Multiple Chemical Sensitivities, Occupational Medicine: State of the Art Reviews, Philadelphia: Hanley & Belfus, 2(4):655-662.

2. An acquired hypersensitivity against chemicals; the sensitivity occurs at concentrations far below the doses which are harmful to the general population. This results in a situation in which even at lowest exposure - primarily to food, water, air, and articles for daily use - causes a lot of discomfort and clinical symptoms in nearly all organ systems. (Used in Germany)

Schwenck M (1995) "Multiple chemische Sensibilität," in Beyer A and Eis D, Umweltmedizin, Berlin, Springer Verlag, in press.

Schimmelfennig W (1994), "Zur Problematik der Begutachtung Umweltbedingter Toxischer Gesundheitsschäden, Bundesgesundheitsblatt," Manuscript in preparation.

3. A widening of the explanation for a manifold of neurological, neuropsychologic, neuropsychiatric, and other disturbances of the state of health. (Used in Germany)

Schwarz M. (1993). Versorgung umweltkranker Patienten am Beispiel der Neurotoxischen Ambulanz des Fachkrankenhauses. Nordfriesland, Vortrag.

4. MCS is characterised by an enhanced hypersensitivity to low concentrations of different chemicals in the environment which do not cause any impairment in normal persons. MCS can cause symptoms in several organ systems. There is a broad range of symptoms which are most often subjective in nature. Some of the people afflicted believe themselves to suffer from an allergy against environmental chemicals, although this cannot be substantiated (so far) by classical test methods. The exact cause/mode of action is unknown at this time. (Used by German team).

Non-specific Hyper-responsiveness

A state of cellular imbalance with over-irritability; represents a change in the function of the cells or organs of the body, with excessive reaction to different stimuli.

Bakke JV and Knudsen BB (1993), Allergy, Hypersensitivity and Chemical Substances: Evaluation of the Ability of Chemical Substances to Cause Allergy and Other Hypersensitivity in the Skin and Airways, NKB Committee and Work Reports 1993:01 E, Nordic Committee on Building Regulations, NKB Indoor Air Climate Committee, Nordic Council of Ministers.

Pseudo-allergy, Idiosyncrasy, Syndrome of Intolerance

Syndromes which closely resemble allergic reactions in their clinical manifestations and cover the range from dramatic anaphylactic reactions to chronic clinical pictures. Allergic cause is unlikely. The reaction is unexpected and depends on the

pharmacological and toxicological side effects of a substance. The reaction is not specific for the causing substance, and it may be evoked at the first contact. There is a genetic predisposition. (Used in Germany)

Gross R. (1986). "Allergien und Pseudo-Allergien" *Deutsches Ärzteblatt* 33:2240-2242.

Idiosyncracy/pseudo-allergic reaction: Abnormal but non-immune reaction to a foreign substance, which is determined by a particular characteristic of certain individuals (e.g., enzyme deficiency). A special form of hypersensitivity with intolerance reactions manifesting themselves as urticaria, edema, asthma, and rhiniti. (Used in Germany)

Lafontaine A. (1983) "Problems and Perspective" in Allergic Responses and Hypersensitivities Induced by Chemicals. Proceedings of a joint WHO/CEC workshop, Frankfurt am Main, 12-15 October 1982, WHO Copenhagen, CEC Health and Safety Directorate, Luxembourg, 1983.

Psychoorganic Syndrome

In modern terminology, this is called chronic toxic encephalopathy (CTE). Occupational exposure to solvents and petroleum products can induce disturbances in the central as well as peripheral nervous system, causing neurasthenia, personality changes, and reduction of intellectual faculties. (Used in Sweden)

Ödkvist LM, Möller C, Thuomas KA (1992), "Otoneurologic disturbances caused by solvent pollution," *Otolaryngol Head Neck Surg*, 106:687-692.

Sensitive

(1) Capable of perceiving sensations; (2) responding to a stimulus; (3) acute perception of interpersonal situations; (4) one who is readily hypnotizable; (5) one supposed to receive communication from spirits; a psychic; (6) readily undergoing a chemical change, with but slight change in environmental conditions, as a reagent; (7) rendered amenable by antibody to the destructive action of a complement.

Stedman's Medical Dictionary, 22nd ed. (1972) Baltimore, MD: William and Wilkins.

Sensitivity

1. The state of quality of being sensitive.

Miller BF and Keane CB. (1983) Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health. 3rd ed., Philadelphia, PA, WB Saunders Company.

2. In sensory analysis, the ability to perceive, identify, and/or differentiate, qualitatively and/or quantitatively, one or more stimuli by means of the sense organs.

Sick Building Syndrome

1. "Sick Building" syndrome is used to describe a building in which a significant number (more than 20 percent) of building occupants report illness perceived as being building-related. The complaints are characterized by a range of symptoms including, but not limited to eye, nose, and throat irritation, dryness of mucous membranes and skin, nosebleeds, skin rash, mental fatigue, headache, cough, hoarseness, wheezing, nausea, and dizziness. The introduction of new building materials, decreased ventilation and decreased air leakage have all contributed to the problem.

Porteous A. (1992) Dictionary of Environmental Science and Technology. New York: J. Wiley & Sons.

2. Is characteristic for a fraction of the occupants in a typical so-called sick building. The SBS involves a specific pattern of symptoms that may be divided into two main classes: 1) general symptoms and perceptions, such as headache, mental fatigue, and weak but persistent odours; and 2) specific symptoms of sensory irritation, such as irritation of the eyes, nose, and throat, sensation of dryness in the mucosa and skin, and erythema of the skin. (Used in Sweden)

Baird JC, Berglund B, Esfandabad HS.(1994) "Longitudinal assessment of sensory reactions in eyes and upper airways of staff in a sick building." *Environment International* 20(2):141-160.

3. An indoor air disease in which non-specific symptoms are dominant. These include: increase of non-specific symptoms in more than 20% of room or building users; irritation of the eyes, mucous membranes, nose, and pharynx; lethargy, lack of drive, and fatigue; and headaches. Commonly, there is a decrease in complaints after leaving the building. Measurements show no exposure to certain specific factors and chemicals. (Used in Germany).

Seeber (1993). "Psychologische Bewertungsansätze zur Innenraumluftqualität, Tagung 'Innen-raumluft'" im Berufsgenossenschaftlichen Institut für Arbeitssicherheit, Sankt Augustin.

4. SBS is identified by the occurrence of general or non-specific symptoms in connection with specific indoor climate. A considerable proportion of the users is affected. Upon leaving the room or the building, the symptoms disappear. There is no clear cause of the disease. (Definition used by the German team)

5. A reaction to the indoor environment among a majority of the occupants whose reactions can not be related to obvious causes such as excessive exposure to a known contaminant or a defective ventilation system. The syndrome is assumed to be caused by a multifactorial interaction of several exposure factors involving different reaction mechanisms. SBS is a term used to describe the reduced comfort and health status of occupants in a particular building or part of it where the occupants complain about indoor air quality and manifest symptoms which they assign to that reduced quality. In SBS, affected workers report non-specific symptoms occurring only when they are at work. Symptoms reported in SBS include mucous membrane and eye irritation, cough, chest tightness, fatigue, headache, and malaise. (Used in Greece)

Berglund B, Brunekreff B, Knöppel H, Lindvall T, Maroni M, Mølhave L, and Skov, P (1991), Effects of Indoor Air Pollution on Human Health. Commission of the European Communities, Luxembourg. Report No. 10, pp. 1-43.

Specific Chemical Hypersensitivity

Specific allergic or non-allergic hypersensitivity to specific chemical substances -- initiators -- and may be manifested by a change in the function of the enzymes and/or the metabolism of the body.

Bakke J V and Knudsen, B B (1993), Allergy, Hypersensitivity and Chemical Substances: Evaluation of the ability of chemical substances to cause allergy and other hypersensitivity in the skin and airways, NKB Committee and Work Reports 1993:01 E, Nordic Committee on Building Regulations, NKB Indoor Air Climate Committee, Nordic Council of Ministers.

Solvent Syndrome/Solvent Poisoning/Painter's Disease/Organic Brain Syndrome

Because of uncertainty of what dose, concentration, or duration produce an increased risk and because of uncertainty about precise diagnostic criteria, the confirmation of solvent poisoning depends partly on clinical experience and partly on a total interpretation of the literature.

The foundation for a decision regarding injury by the Danish Administration of Labour is:

Confirmation of brain damage if the total exposure exceeds 5-6 years work at a concentration which corresponds to the limit value.

The final decision on whether the exposure has been sufficient to cause brain damage is based on an estimate of the total information about type of work, duration of exposure, and the condition under which the work has been done.

The diagnostic criteria include an evaluation of the degree of dementia using neuropsychological investigation and examination is done by specialized physicians at occupational clinics, and by physicians in neuromedicine and psychiatry.

Criteria for exposure:

The use of solvents is considered a risk for developing organic brain injury if the solvent:

a) easily evaporates
b) is used as solvent

This does not include glycols, glycol ethers, various oxygenated solvents (such as epichlorohydrin, phenol, propylenoxide), nitrogen-containing solvents (such as acetonitriles, ethyl amines, ethanol amines, pyridine, etc.)

Vejledning om Oproesningsmiddelforgiftning, Arbejdsskadestyrlsem vejledende retningsliaier før anerkendelse i sager om hjmeskader, eftel arbejde med oplosningsmidler (1992) Arbejdsskadestyrrsem, København, Mytting Bogtrykkeri Aps.

Toxicopy

A term used to describe the occurrence of symptoms of poisoning in the absence of a relevant poison. It is described as a survival mechanism (like the stress mechanism) developed during evolution to mimimise effects from non-physiological events. It is suggested that mass psychogenic illness is a secondary form of toxicopy. (Used in Germany)

Kofler, W (1993a). "Umweltängste, Toxikopie-Mechanismus, komplexes evolutionäres Coping-Modell und die Notwendigkeit neuartiger Anlagen für genehmigungspflichtige Anlagen" in Aurand K, et al. Umweltbelastungen und Ängste, Westdeutscher Verlag GmbH, Opladen, 225-267.

Kofler W. (1993b). "Toxikopie: Die Gesundheitsrelevanz von Umweltinformationen" in Forbildungszentrum Gesundheits- und Umweltschutz Berlin e.V. (Hrsg) Akzeptanzprobleme bei Massnahmen zur Abfallensorgung, Utech Berlin '93, Seminar 28, 35-74.

Wood Preservative Syndrome

Generally, a chronic poisoning caused by long term exposure to wood preservatives, such as pentachlorophenol or lindane (as well as dioxins and furane). Affected patients exhibit a multitude of symptoms, including immunological, dermatological, neurological, psychiatric, endocrinological, and ophthalmological symptoms. (Used in Germany)

Schimmelfennig W (1994), "Zur Problematik der Begutachtung Umweltbedingter Toxischer Gesundheitsschäden, Bundesgesundheitsblatt," Manuscript in preparation.

Huber W, Maletz J, Fonfara J, and Daniel W (1992), "Zur Pathogenität des CKW- (chlorierte Kohlenwasserstoffe) Syndroms am Beispiel des Pentachlorphenol (PCP)," *Klin Lab* 38:456-461.

APPENDIX B
LITERATURE SEARCH STRATEGY [From 1987 onward]

Terms possibly related to chemical sensitivity

multiple chemical sensitivity (MCS)
chemical sensitivity (CS)

building related illness (BRI)
sick building syndrome (SBS)
tight building syndrome (TBS)
indoor air quality + chemicals

chronic fatigue syndrome (CFS)
pseudo-allergy
chemical allergy
chemical illness
environmental illness
ecological illness
eco-syndrome
universal allergy
total allergy syndrome

food sensitivity (narrow search by joining with given key ref. articles, e.g. David King, Brostoff)
allergy + chemicals

hyper-reactivity
hyper-responsiveness
hypersensitivity
hypersusceptibility
responsiveness + chemicals

panic disorder + chemicals
mass hysteria
mass psychogenic illness
psycho-organic syndrome

Additional Key Words

immunotoxicology, immunotoxic + animal
auto-immune antibodies + chemicals

neurotoxicology, neurotoxic + animal
neurogenic inflammation
neurogenic kindling
limbic kindling
neurophysiology + animal
neuropsychology
neuro-immunology
neuro-endocrinology

endocrine + chemical (+ animal)
endocrine disruption + chemicals

sensitisation
behavioral sensitisation
sensitiser (+ animal)
initiators (+ animal)
triggers
mucous membrane irritant (focusing on cases of severe and/or persistent symptoms at exposure levels tolerated by the majority of people)
sensory effects

cacosmia; parosmia; hyposmia
odour and odour conditioning
olfactory

reverse tolerance
time dependent sensitisation
time dependent sensitivity

solvent syndrome
solvent encephalopathy
toxic encephalopathy
pentachlorophenol syndrome
SPECT Scans + chemicals
PET scans + chemicals
EEG + chemicals
evoked potentials + chemicals

Incidents/Exposure Events

indoor air events
schools
contaminated communities
consumer product exposures/complaints
anesthetics/ethical drugs

adverse reactions to pesticides
adverse reactions to remodeling
chemical spills, releases, accidents
toxic waste sites
occupational exposures

Target populations

children
elderly
consumers
others tied to incidents (see above) and sensitisers (see below)

Sensitisers

pesticides
pentachlorophenol
solvents
carpets
anesthetics/ethical drugs
formaldehyde
urea formaldehyde foam (UFI)

Library Systems

TOXLINE
MEDLINE
RIS
DIMDI
RTECS

Psychological Abstracts

APPENDIX C
QUESTIONNAIRE TO
UNCOVER INFORMATION ON CHEMICAL SENSITIVITY

Possible Introductory Remarks:

We are working on a project to assess the possible presence and prevalence of low level chemical sensitivity in selected European countries. In the United States, there is growing concern about a health disorder characterized as intolerance to low levels of chemicals. This disorder is variously called chemical sensitivity, multiple chemical sensitivity (MCS), chemical hypersensitivity, and universal allergy (among other things). Our project will begin to compile information about the possible occurrence of this and related disorders in Europe. It is not a scientific research study, but rather a compilation of information about the subject. We need your help in identifying: 1) individuals who are doing research or have an interest in this subject; 2) ongoing research in areas potentially related to chemical sensitivity, such as sick building syndrome and building-related illness; neurotoxicology or neuroimmunology of low level chemical exposure; limbic kindling and time-dependent sensitisation; odour conditioning; etc.; 3) incidents or exposure events associated with the onset of this problem; 4) case reports, publications, and other reports on this subject; and 5) conferences or workshops on this topic. Please help us by answering the following questions.

1. Do you know individuals who are doing research in this area? Please indicate their area of research and your assessment of their knowledge and work in this area.

2. Are you aware of any specific incidents or exposure events that have been associated or alleged to be associated with the onset of chemical sensitivity? These may include: tight buildings (offices, schools, public buildings); spills or accidental chemical or pesticide exposures; chemical contamination of homes, communities or neighborhoods (via air, ground or well-water, etc); or exposure to consumer or medical products.

   Please describe each one of these events/incidents/reports.

   a) How do you know or did you learn about the event? E.g., your own research; information from colleagues; published research; reports in the media; government investigations or reports, etc.

   b) How would you characterize the nature of the incident/exposure event? E.g., a one-time chemical or pesticide exposure; repeated exposure to pesticides, solvents, new building materials, carpets, medications; a community contamination episode, etc.

   c) Approximately how many people were involved in the incident/exposure event? Who were they (e.g., children, community residents, residents of a building, consumers, office workers, etc)?

d) What was/were the alleged causative agent(s) of the initial exposure/sensitisation? E.g., pesticides; consumer products, such as carpet; treated wood products; cleaners or solvents; anesthetics or pharmaceuticals; etc.

e) What types of symptoms or complaints were reported by those involved in the incident?

f) After the initial exposure/sensitisation, what, if anything, continued to cause symptoms or complaints among those involved in the event?

g) Did the affected individuals report any of the following:

1) Feeling ill when exposed to items/products/foods/or activities that previously never caused a problem?

2) Increased "sensitivity" to smells, sounds, light?

3) Changes in mood, energy, concentration, memory?

h) Did the affected individuals have a medical evaluation? If so, by whom?

i) Was the incident investigated by any public or private authority? If so, by whom?

j) Describe any interventions that were attempted, e.g., removal of the suspected offending agent, other modifications/changes in the environment; etc.

k) Were the interventions successful? To what extent did the problem(s) disappear?

l) Was the incident and/or its investigation written up or published?

3. Can you give us the names of any physicians who see individuals with these types of problems (especially if they have written up case reports) or who have been involved in investigating these types of incidents?

4. Do you know of any unpublished reports on this subject, such as conference proceedings, government reports, abstracts, etc. If yes, can you tell us how to get a copy?

APPENDIX D
DATA ABSTRACTION SHEET

Title of paper/written report/oral presentation _____

_____

Author(s)/Name and Affiliation of Person Interviewed:_____

_____

Citation: _____

Type of Study/Investigation/Report (briefly describe):

Epidemiologic, exposure or event-driven, _____

Epidemiologic, patient-driven,_____

Clinical case report/case series, _____

Basic science research/animal study, _____

Personal Interview/Anecdotal Account,_____

Other, _____

INFORMATION ABOUT ALLEGED INITIATING EVENT/EXPOSURE, I.E., THOSE ASSOCIATED WITH THE ONSET OF THE PROBLEM

1) Alleged Initiating Exposures or Events:

- ♦ tight buildings ____
- ♦ carpets, ____
- ♦ pentachlorophenol ____
- ♦ other consumer products, specify _____
- ♦ anesthetics, ____
- ♦ pesticides ____
- ♦ mattresses, ____
- ♦ ethical drugs, ____
- ♦ community contamination, specify _____
- ♦ other, specify _____

2) Locus of Initiating Event:

- ♦ industrial workplace ___
- ♦ office ___
- ♦ home ___
- ♦ other, specify _____

3) Number and percent of persons involved/exposed _____

INFORMATION ABOUT SUBSEQUENT SENSITIVITY/SYMPTOMATOLOGY

1) Reported triggers/excitants

- ♦ Solvents ____
- ♦ Diesel/automobile exhaust ___
- ♦ Detergents and cleaning agents ___
- ♦ Formaldehyde ____
- ♦ Pesticides ____
- ♦ Remodeling ____
- ♦ Perfumes and other fragrances ____
- ♦ Kitchen odours ____
- ♦ Dry cleaning ____
- ♦ Newsprint ____
- ♦ Carpets ____
- ♦ Other, specify _____

1) Reported symptoms:

- ♦ Eye irritation ___
- ♦ Nose irritation ___
- ♦ Rhinitis ___
- ♦ Cacosmia ___
- ♦ Skin problems ___
- ♦ CNS symptoms ___
- ♦ Respiratory symptoms ___
- ♦ Gastrointestinal symptoms ___
- ♦ Musculoskeletal symptoms ___
- ♦ Other, specify _____

2) Locus of subsequent sensitivity:

- ♦ industrial workplace ___
- ♦ office ___
- ♦ home ___
- ♦ commercial establishments, e.g, stores, restaurants, banks, dry cleaners ___
- ♦ other, specify _____

3) Number and percent of persons affected _____

4) Description of symptoms occurrence over time, with and without intervention

_____

_____

INFORMATION ABOUT INTERVENTIONS UNDERTAKEN

1) Describe interventions undertaken, if any _____

_____

2) Describe outcome of intervention, if known _____

_____

_____

INFORMATION ABOUT POSSIBLE MECHANISMS

1) Were conclusions made about possible mechanisms? Yes ___ No ___

2) If yes, describe _____

_____

YOUR ASSESSMENT

Your comments/assessment of study/report/account

Poor Quality ____ Medium Quality ____ High Quality ____

Comment: _____

_____