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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

REPORT OF MULTIPLE CHEMICAL SENSITIVITIES (MCS) WORKSHOP

Berlin, Germany, 21-23 February 1996

Organized in collaboration with the
German Federal Ministry of Health,
Federal Institute for Health Protection of
Consumers and Veterinary Medicine (BGVV)
and the Federal Environmental Agency (UBA)

United Nations Environment Programme

International Labour Organization

World Health Organization

REPORT OF THE WORKSHOP ON MULTIPLE CHEMICAL SENSITIVITIES (MCS)

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This report contains the views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization, or the World Health Organization.

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

IPCS

This Workshop was organized by the International Programme on Chemical Safety (IPCS) in collaboration with the German Federal Ministry of Health, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), and the Federal Environmental Agency (UBA). The Federal Environmental Agency coordinated the Workshop arrangements in Berlin. IPCS wishes to express its gratitude to these German Governmental Agencies for their active support of IPCS activities.

The Workshop outline programme appears as Annex A, the invited participants are listed in Annex B, and representatives and observers in Annex C.

The report was prepared by the Joint Rapporteurs, Professor H. Altenkirch and Dr L. Fishbein, in consultation with their fellow invited experts.

REPORT OF "MCS" WORKSHOP

Berlin, 21-23 February 1996

I. INTRODUCTION

A workshop of invited experts from a number of scientific disciplines was held on 21-23 February, 1996 in Berlin, Germany to discuss "Multiple Chemical Sensitivities" ("MCS"). The workshop was organized by the International Programme on Chemical Safety (IPCS), a cooperative programme of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO) and the World Health Organization (WHO), in collaboration with the German Ministry of Health (BMG), the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), and the Federal Environmental Agency (UBA).

The workshop consisted of 18 introductory presentations by invited experts covering the expanse of European, US and Canadian perceptions of "MCS", various definitions of "MCS", toxicology, immunology, environmental illness, neurology, behavioral sensory irritation, clinical investigation and toxicodynamic, behavioral and psychological characteristics of "MCS". These presentations served as a stimulus for discussion of the major objectives of the workshop which were:

. to review information on "multiple chemical sensitivities" ("MCS")
. to determine whether or not "MCS" constitutes a syndrome
. to examine relationships with other "environmental illnesses" ("EI")
. to identify possible aetiological factors
. to discuss diagnosis, diagnostic testing, differential diagnosis and lines of treatment

During the workshop "ad hoc" panels were convened to review issues and report back to plenary sessions. The panels addressed diagnosis, epidemiology, and the applicability and appropriateness of the term "Multiple Chemical Sensitivities", and also indicated possible research priorities for general consideration in plenary session.

II. SUMMARY

HISTORY OF "MCS"

"Multiple Chemical Sensitivities" ("MCS"), a puzzling, poorly understood and contentious clinical entity emerging in the 1940's, with increased discussion in the 1980's, is often defined by reactivity to common environmental exposures at significantly lower exposure levels than those which would cause noticable illness in the general population and at levels which the preponderance of individuals tolerate quite well (Cullen, 1987; National Research Council, 1992; Terr, 1994; Sikorski et al., 1995).

The concept that "MCS" is a distinct entity caused by exposure to foods and chemicals originated in the work of Randolph in the 1940's and expanded in the 1960's (Randolph, 1956, 1962). In the disease model proposed by Randolph, "MCS" consists of multiple symptoms involving multiple organ systems due to an inability to adapt to chemicals with resulting responsiveness to extremely low concentrations after sensitization. According to this theory, symptoms can occur on exposure to chemicals or on withdrawal from exposure after an adaptive response has taken place (Randolph, 1956, 1962).

The term "Multiple Chemical Sensitivities" was introduced by Cullen (1987) and has also been referred to by many synonyms (introduced by physicians, clinical ecologists as well as the news media) (table 1). A wide range of individual symptoms (typically multiple and at various and multiple sites) are displayed by "MCS" patients (Sparks et al., 1994a,b). The main clinical features include the self-reported complaints of ill-defined symptoms. The lack of reproducible immunological or other laboratory findings have thwarted diagnostic testing. Despite numerous symptoms such as concentration and memory difficulties, respiratory tract irritation, abdominal, joint and muscle pain, nausea, dizziness, headache, fatigue, depression and irritability, physical examination and laboratory tests are generally normal. The illness tends to be a chronic disorder in which the patient may become increasingly disabled (Randolph, 1956, 1962, Doty et al., 1988, Ashford & Miller, 1991; Nethercott et al., 1993).

Clinically many "MCS" patients also report multiple food sensitivities and they may attempt to avoid various chemical substances and foods, as well as caffeine, alcohol and medications as a primary treatment modality (Randolph, 1956, 1962; Ashford & Miller, 1991, 1992).

Diagnostic criteria for "MCS" are lacking and there are no reliable data on the prevalence of individuals with chemical sensitivities. Definition of the phenomenon of "MCS" has been elusive (NRC, 1992).

Well-established descriptive diagnoses such as somatoform disorder, depression, asthma, migraine and post-traumatic stress disorder are believed by many practioners to account for symptoms in the majority of "MCS" cases. However, waxing and waning of symptoms with perceived or real chemical exposure is not an established component of any of these disorders except perhaps asthma and migraine. "MCS" has often been confused with the "sick-building syndrome" ("SBS") due to the sometimes similar constellation of exposures and symptoms and the fact that a subset of "SBS" patients appear to develop "MCS" (Ashford and Miller, 1991; Miller, 1994). "Chronic fatigue syndrome" ("CFS2) is a systemic disease that is accompanied by pronounced fatigue associated with fever, pharyngitis, myalgia, headache, cognitive impairment, insomnia and depression (Buchwald & Garrity, 1991; Buchwald et al., 1992), symptoms that are similar to those seen in "MCS". Thirty to 60% of those with "CFS" report some symptoms of chemical sensitivity.

Many opponents of "MCS" as an organic disease and a singular entity do not question the symptomatology of the patients but question whether these symptoms represent a direct toxic effect of chemicals. They hypothesize that "MCS" may not be a single entity but a manifestation of one or more physical or psychological illnesses that have been improperly diagnosed (Terr, 1993, 1994; Black, 1993; Staudenmayer et al., 1993; Sikorski et al., 1995, Gots, 1993, 1995; Wolf, 1994). Other physicians known as clinical ecologists diagnose patients with unexplained illnesses characterized by multiple, subjective symptoms that are attributed to chemical exposure (Randolph and Moss, 1980; Bell, 1982). However, some other some physicians including occupational medicine practioners, neurologists and others are also using the diagnostic label of "MCS" to describe patients of this type.

While the aetiology of "MCS" is unknown, the illness may be multifactorial. Proposed aetiologies for "MCS" include: toxicological; physiological; neurological; immunoloc; respiratory; olfactory-limbic sensitization; psychiatric or psychological; childhood abuse and porphyria (Bell et al., 1992; Sparks et al.,1994a,b; Harrison, 1995;Sikorski et al., 1995).

Suggested trigger agents of "MCS" have included a broad spectrum of chemicals. These include odorous and non-odorous volatile organic compounds (VOCs), solvents, pesticides, industrial chemicals, metals, consumer products (cosmetics, deodorants, perfumes, soaps, disinfectants, cleaning agents), new carpeting, and combustion products. Alleged sources include: construction materials, office equipment, supplies or furnishings (plastics, synthetic textiles),

tobacco smoke; indoor air (domestic), as well as contaminated community exposure to aerial pesticide sprays, air contamination from nearby industry, toxic waste dumps, ground-water contamination, ozone and miscellaneous community exposures (Randolph, 1956, 1962; Ashford & Miller, 1989, 1991). The list of trigger agents has been constantly expanding, and is not restricted to chemical agents. Physical entities such as electromagnetic fields (EMF) have also been recently reported to be linked to "MCS"-like symptoms (Gothe et al., 1995).

A large number of cases of "MCS" have been reported in the United States (Ashford & Miller, 1989, 1992; Rest, 1992; Miller, 1994; Sparks et al., 1994 a,b). However a survey conducted in 1994 has shown that "MCS" is of increasing public concern in many countries in the European Union (Ashford et al. 1995). As in North America, chemical sensitivity in Europe is an elusive and baffling condition. Compelling scientific evidence of a relationship between exposure to triggering agents and health effects is lacking (Ashford et al., 1995).

In the US, the phenomenon of "Multiple Chemical Sensitivities" has been the subject of numerous symposia, workshops (ISRPT, 1993,1995) and round table discussions (Sikorski et al., 1995); state governments (Ashford & Miller, 1989); federal agencies (Agency for Toxic Substances & Disease Registry) (ATSDR, 1994); the National Academy of Sciences (NRC, 1992) and a number of professional organizations via workshops and position papers (Association of Occupational and Environmental Clinics) (AOEC, 1992); (American College of Physicians) (ACP, 1989); and the American Medical Association (AMA, 1992). Acrimonious debate on "MCS" has been ongoing for nearly a decade in professional meetings and medical journals and in courtrooms (Miller, 1994).

III. REPORT OF OPENING REMARKS AND PRESENTATIONS

A. OPENING ADDRESSES

The workshop was opened with an address of welcome by Prof. A. Somogyi of the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV). He stressed that "MCS" is an international problem, one that warrants study by this group of international experts in Berlin meeting to discuss the phenomenon, to determine whether it could be defined, and form a framework for discussion and further scientific work. The importance of "MCS" to a broad spectrum of individuals (e.g., consumers) is recognized. It is unclear whether "MCS" is a psychogenic or toxicogenic phenomenon and it has been difficult to resolve this distinction by existing methods. The Workshop should try to shed light on the basic mechanisms

and genesis of the phenomenon known as "MCS" and perhaps address what the consumer should be protected against?

Mr. F.J. Bindert of the Federal Ministry of Health (BMG) then welcomed the participants on behalf of Mr. Seehofer, the Federal Minister of Health. Mr. Bindert raised the question of whether there is a connection between "MCS" and other illnesses linked to various agents and physical environments, e.g., sick-building syndrome and wood preservative syndrome. Like "MCS", these syndromes involve subjective complaints and patients lack clear signs of organ dysfunction. There is not a clear picture of the phenomenon as to whether psychomatic factors play a part. Subjects with "MCS" exhibit a lot of suffering. They join support groups and associations, do not want to be known to be suffering from a psychological disorder and some demand official acceptance of their condition and sick compensation. In terms of compensation, it is important to these individuals that the aetiology be physiologically induced. "MCS" symptoms affect a large number of people. Most individuals who are suffering are interested in prevention. For a relatively smaller number of people, individual therapy and prophylaxis may be possible if the causative agents could be identified. In this case the State would have to insist that these substances be identified and therefore removed. It is important to exchange international knowledge of experiences on the subject of "MCS" which will be useful in Germany and in public discussion. "MCS" is a relatively recent phenomenon and public discussion must be well-reasoned as the consequences of discussion of "MCS" can be far reaching.

Prof. Dr. H. Lange-Asschenfeldt, Federal Environmental Agency (UBA), next addressed the Workshop. He stated that "MCS" was not a general problem but affected a small number of individuals. In public discussion in the past, only environmental causes were noted. In Germany, the diagnosis of "MCS" is now being made more often. Afflicted patients can undergo serious economic change. Practioners are in a dilemma since there are no diagnostic criteria. The growing pressure from patients adds to the dilemma. Dr. Lange-Asschenfeldt stressed that the aims of the Workshop should be: 1) definition of terms; 2) education of the public should be encouraged and 3) diverse medical strategies should be outlined to the extent feasible.

Dr. E. Smith/WHO made the last opening presentation, welcoming participants on behalf of IPCS, and the executive heads of its cooperating organisations. IPCS had been established as a joint venture of UNEP, ILO, and WHO with the overall objective of establishing a scientific basis for evaluating human illness associated with exposure to chemicals in order to achieve sound management of chemicals and protect human health and the environment. The outputs of IPCS is available to all countries. The 1992 United Nations Conference in Rio de Janeiro on Environment and Development had emphasized the extreme importance of sound management of chemicals with

the active involvement of international agencies, national governments, and non-governmental organizations (NGOs). WHO has a large number of NGOs in official and working relations and two of these were represented by observers at the Workshop. Dr. Smith stressed the objectives of the Workshop and the need to reach structured conclusions and recommendations. The Workshop had been convened for a full exchange of views and opinions and was intended to result in a report by the invited experts reviewing the field of "MCS", and touching on environmental illnesses, with conclusions and recommendations.

B. PRESENTATIONS

The opening adddresses were followed by 4 sessions comprising 18 short presentations by invited experts.

Prof. H. Altenkirch (Spandau Hospital, Berlin), presenting "MCS" from a European perspective, reviewed the main features of "MCS". Reported in the US for almost 2 decades (under a large number of synonyms), "MCS" is being increasingly diagnosed in a number of European countries. Exposure to a wide range of chemicals of varying structures have been reported to result in patients exhibiting "MCS" (with over 500 papers on the subject published in the US alone). There are no diagnostic criteria set in European countries, and no specific epidemiological or other studies of this condition are in progress.

Prof. Altenkirch discussed purported causes in Germany of "MCS disease" involving wood preservatives (lindane and pentachlorophenol) where no scientific line of reasoning nor any standard for clinical assessment were found. Another current problem in Germany concerns disability claims submitted by employees of large department stores who had allegedly been exposed to low levels of pyrethroids in routine pest control procedures and consequently claimed to suffer from "MCS" symptoms. Individuals exposed to carpets containing pyrethroids (and/or treated with pyrethroids) are expected to be involved in further litigation in Germany.

Prof. Altenkirch discussed clinical investigations involving 23 persons on an in-patient basis who had been reported to BGA in 1993/1994 as cases of pyrethroid intoxication. Eight patients presented with "MCS" symptoms and showed no abnormalities in either laboratory findings nor in their physical examination. Available data did not indicate evidence of PNS or CNS impairment (Altenkirch et al., 1996).

He discussed various diagnostic criteria for "MCS" comparing this with established neurotoxicological disorders such as the Spanish oil neurotoxicity episodes of 1981-1982. "MCS syndrome" is not a neurotoxic disease but is a result of some sort of an initial chemical trauma. In

Prof. Altenkirch's experience, "MCS" is frequently a misdiagnosis, and exposure to chemicals is not the actual cause of the disease. "MCS" cases can actually be somatic and psychiatric illnesses and, in addition, overlap the symptomatology observed with "sick-building syndrome" ("SBS") and "chronic fatigue syndrome" ("CFS") cases.

Prof. Altenkirch discussed various hypotheses on the aetiology of "MCS" such as the olfactory and limbic system involvement (Bell et al., 1993). He listed ten research strategies suggested by the problems raised by "MCS". Foremost among these were: establishment of diagnostic criteria (possibly based on the criteria established by Cullen (1987)); consensus on psychological tests as well as clinical investigative methods including dermatological, allergic, immunological and neurological procedures; prospective and randomized double blind studies on "MCS" patients and a survey and critical evaluation of the different approaches to therapy that have been utilized to date.

Dr. R. Gots (Environmental Sensitivities Research Institute, US) discussed "MCS"from a US perspective and stressed that the fundamental issue is not whether or not the phenomenon of "MCS" really exists; rather it is whether it is primarily a psychogenic (an emotional response to a perceived chemical toxicity) or a toxicodynamic disorder (pathological interaction between chemical agents and organ systems). The causal question (e.g., whether "MCS" is a perceived toxicity or a physical disorder) is critical, first because it determines proper patient care, but also because it determines the nature of legal, societal and occupational response (e.g., possible compensation, litigation potential, workplace hygiene controls, rights under ADA (American Disabilities Act). It was stressed that how patients are treated depends on the underlying aetiology of the symptoms, e.g., a behavioral origin leads to behavioral therapy while a toxicodynamic aetiology may recommend avoidance, and exposure control methodologies.

Dr. Gots cited recognized examples of physical and psychogenic (emotional) causes of identical symptoms (e.g., headache, palpitations, fatigue, dizziness, nausea, etc) and stressed that determining whether the symptoms arise from dysfunctional organs or from mind-body relationships is neither trivial nor unnecessary. He contrasted the notion of an individually determined response (IDR) (somatic manifestation of an emotional response to an external or internal stimulus) with that which is organic or which are a combination of both. For example, for an external cause such as low-level non-allergenic chemicals, the IDR (behavioral) response could be fatigue, loss of memory, weakness, shortness of breath, etc. The organic response could be a mild irritant response. Individually determined responses may lead to a patient exhibiting symptoms or to the worsening of existing symptoms.

Dr. Gots noted that somatization, which is an endpoint (a set of symptoms arising from a wide variety of emotional factors, rather than a specific disorder) can mimic serious disorders such as asthma. Somatization appears to be increasing.

In a discussion of the toxicodynamic process versus psychogenic process and "MCS", Dr. Gots noted that there is no currently known mechanism whereby low levels of chemicals or chemicals of widely varied chemical structure could interact adversely with numerous organ systems. Neither immune dysfunction nor "toxic porphyria" (a recently advanced theory) would explain the multiple and varied symptomatology experienced by "MCS" patients. He stressed that behavioral mechanisms must serve as the intermediary between the sensory awareness and the sympomatology experienced. He further stressed the potential dangers of the misattribution of "poisoning" in the diagnosis of "MCS" which can yield to disability, wrong treatment approaches, contribution to societal chemophobia and the requirements to industry to make unreasonable and unattainable accomodations. Additionally, he expressed concern that such a misdiagnosis could set a precedent of a patient defined disorder unsupported by scientific facts. There are no consistent findings in the various "MCS" studies reported. Dr. Gots recommended that until the aetiology is determined, a more descriptive and less categorical title for "MCS" and one which is less implicative of causation might be "Environmentally Associated Symptoms" ("EAS").

Dr. F.C. Li (Laboratory Centre for Disease Control, Canada) discussing "MCS" from a Canadian perspective, indicated that there is no "single" or "commonly shared" perspective on "MCS" in Canada because of the relative lack of scientific information . Questions regarding the causation and effective management of "MCS" patients have stirred a great deal of controversy and debate. Nevertheless, "MCS" has been having important impacts in Canada. These include adverse physical, psychological, social and economic effects on "MCS" sufferers, and implications on the health care system, social services and the workplace.

Dr. Li highlighted some of the recommendations of the 1990 Environmental Sensitivities Workshop (Health & Welfare, Canada, 1990) and the 1992 "Multiple Chemical Sensitivities and the Relevance to Psychiatric Disorders" Workshop (Health Canada, 1993). The 1990 Canadian Workshop recommended that "disabilities should be rated functionally rather than diagnostically in considering eligibility for pensions/social assistance" and that "with those having subjective symptoms, it would be necessary to do double blind placebo controlled challenges"

To aid practitioners in their management of "MCS" the 1992 Canadian Workshop suggested a set of clinical diagnostic criteria for "possible", "more probable" and "most probable" MCS cases. Under the rubric of a "possible" "MCS" case, the National Research Council (1992) definition should be satisfied, (see p. 28). The diagnostic criteria for a "probable" "MCS" case are

: possible case plus improvement after reduction or elimination of suspected exposure and symptoms recur on re-exposure. The diagnostic criteria for "most probable" "MCS" case include: diagnosed by double-blind challenge(s) in a controlled environment (e.g., Environmental Control Unit) after appropriate de-adaptation.

Dr. Li stressed that there is no doubt that "MCS" patients are suffering from their symptoms, and that they should be treated with understanding and compassion. However, due to the many uncertainties surrounding "MCS" causation and treatment, it is necessary to be careful (e.g., health practioners, governments) and rational in formulating strategies for "MCS", and the temptation of substituting empathy and conjecture for evidence-based decision making must be resisted.

The key question that urgently needs to be addressed is that of "MCS" causation, and specifically, whether "MCS" is of toxicogenic (due to exposure to chemicals and other substances) or psychogenic (due to psychiatric or psychological factors) aetiology. This differentiation is important as each of these two causal mechanisms will lead along entirely different and divergent paths in the quest for knowledge on "MCS" aetiology and treatment.

Although some research studies have been conducted on "MCS" causation, they are however, still relatively sparse and have not been able to provide conclusive evidence. Dr. Li believed that the most direct and appropriate approach to resolving this toxicologic versus psychogenic causation question is to conduct well-controlled double-blind placebo challenge studies on "MCS" patients. The conduct of such challenge studies should be a top resarch priority . To enhance the eventual acceptance of study results, such challenge studies should be designed and implimented collaboratively by researchers with differing views on "MCS" aetiology. Government agencies may also be well-suited for coordinating these studies.

Dr. C. J. Gothe (AB Ekiatrika, Sweden) highlighted the similarities of "MCS" with examples of the "Environmental Somatization Syndrome"("ESS") (Gothe et al., 1995). He asked if "MCS" is a special type of poisoning or a psychogenic reaction of the persons presenting symptoms. According to his opinion, the pathogenesis is psychodynamic. "MCS" demonstrates such similarities with illnesses such as oral galvanism and electric hypersensitivity that they seem to be variants of the same disorder for which the designation "ESS" ("Environmental Somatization Syndrome") has been proposed. Patients with "ESS" (including "MCS") connect their complaints with exposure to tangible components of the external environment, reject alternative explanations of their symptoms, and tend to establish aggressive lobby groups asserting that the problems depend on environmental exposures. "ESS" is distinguished by mental contagiousness and a tendency to cluster. It has a poly-symptomatic touch dominated by fatigue, dizziness, and pains in

different parts of the body. Problems with sleep, concentration and memory are common, and the picture is often coloured by the alleged disease-inducing agent. The illness often starts distinctly in connection with serious life-strains which will be unnoticed without careful case histories.

Dr. L. Fishbein, (US) presented an overview of some definitions, causative agents, exposures and dilemmas associated with "MCS". The description and effects of chemical sensitivity disease (Randolph, 1962), case definition of "MCS" syndrome (Cullen, 1987), operational definition of "MCS" (Ashford and Miller, 1991), clinical ecologist's definition of environmental illness and the many names and synonyms associated with "MCS" (table 1) were all illustrated. A number of major tenets of clinical ecology were outlined including: a) responses occur to multiple, chemically unrelated substances, b) a toxic response to one chemical can lead to a "sensitivity" to all other chemicals, c) a chemical may induce widespread symptoms associated with all organ systems, d) in addition to the chemicals involved in the original exposure event, over time, more and more chemically unrelated substances may trigger symptoms ("spreading" phenomenon) and e) "petrochemicals" or synthetic organic chemicals somehow differ in their toxicological potential from "natural" chemicals.

Dr. Fishbein noted the tremendous spectrum of attributed chemicals and exposures including pesticides, solvents, metals, literally every class of odorous and non-odorous product encountered in outdoor and indoor contaminants; contaminated communities (e.g., from exposure to aerial pesticide spraying, air contamination from nearby industry, toxic waste dumps, ground water contamination, ozone and miscellaneous community exposures. Exposures are not limited to chemicals as electromagnetic fields (EMF) have also been recently implicated (Gothe et al., 1995).

The accepted bedrock toxicological principles such as : there is consistent or specific symptomatology for a given chemical; the degree of reaction must be proportionate to the exposure; symptoms can be elicited only by chemically related substances and there are objective measurable endpoints and reproducible results were noted. These principles were then contrasted with the major dilemmas surrounding "MCS" which included: many different environmental chemicals, foods and medications evoke multiple symptoms in "MCS" that do not correspond to either recognized allergic responses or known toxicities of the particular agent (s); and the provoking chemicals, exposures and symptoms in "MCS" are apparently limitless in number and type. The controversy surrounding "MCS" is heightened by confusion about the relationship of "MCS" to the "sick-building syndrome" ("SBS"), "chronic fatigue syndrome" ("CFS"), occupational illness, hypersensitivity diseases and toxicity from environmental pollution.

Dr. D.E. Ray (Medical Research Council Toxicology Unit, UK) discussed "MCS" from a mechanistic toxicological perspective stressing the initial need to identify preliminary factors

including: definition of the nature of the effects; susceptibility of the population; the definition of the causal agent(s) and its dose-response relationship. It is then often important to identify the mechanism of action of the agent.

In the case of "MCS" there is a lack of criteria for case definition and misdiagnosis is common. A clear distinction between organic and psychological causes is required. Individuals may be chemically poisoned and physicians may overlook chemical causation since putative causal agents are common in the working and domestic environment. Alternatively, a purely psychological condition might be precipitated by organic causes. Two types of exposure were stressed: causal exposures and subsequent exposures. Mechanistic explanations for "MCS" may arise if a subpopulation(s) could be identified where deficiencies in detoxification may exist. However it is important to realize that any such sub-population must be defined by something other than post-hoc diagnosis of "MCS", if this identification is to be of any value.

Because of the many problems involved in investigations of the "MCS" phenomenon, many toxicologists have been somewhat reluctant to become involved. It was noted that since unexpected forms of toxicity do occasionally appear, toxicologists must always examine such phenomenon in an open-minded manner. Clinicians, in contrast, aggressively searching for a cause of their patient's problems are more likely to need to employ "MCS" as an explanation since it is often impossible to determine causation in individual cases.

Dr. B. Heinzow, (Landesamt für Natur und Umwelt, LANU, Germany) described a 1994 survey of the presentation of "MCS" in a number of European countries which found that there were differences between countries perhaps based on cultural background and other factors. For Germany and other European Union countries, no clear definition of "MCS" has been established by the medical communities. The attitude towards "MCS" and its diagnosis differred markedly among countries. In general, the diagnosis of "MCS" did not follow stringent criteria as evidenced by the diagnosis of "MCS" frequently possessing an overlap with "chronic fatigue syndrome" (CFS), "fibromyalgia" and "sick-building syndrome" ("SBS").

Dr. Heinzow stressed the lack of definitive diagnostic criteria for "MCS" patients in Germany. For example, unvalidated diagnostic criteria and unconventional treatment applied by doctors coupled with patients desperately seeking any possible hint of a remedy for their illness were noted.

The most affected groups (and peculiar exposures) were found for the following EU countries and US: 1) Germany: wood preservatives/PCP, dental amalgam; Netherlands: PCP; 3) Denmark: hairdressers; and US: Gulf veterans, insecticides, carpets, mattresses, anesthetics. Other

significant chemical exposures suggested to be implicated with "MCS" in Germany include: dental materials, metals, solvents, formaldehyde and various insecticides.

Dr. Heinzow noted the psychodynamics of "MCS" citing this sequence following exposure : 1) symptoms-anxiety; 2) search for causality: media alert; 3) hypothesis: iatrogenic stigmatization; 4) therapeutic attempts : a) therapeutic failure: increased struggle, loss of trust, social withdrawal-isolation, depression, total avoidance-destruction.

It was stressed that most "MCS" cases in Europe are not sufficiently documented. In practice there is a discrepancy between the refusal of "classical physicians" and the medical acceptance of the "MCS Syndrome". A case definition of "MCS" is urgently needed and a questionnaire should be developed for diagnostic and research purposes.

Dr. C.S. Miller (University of Texas Health Science Center, US), presented the theme that medical understanding of chemicalsensitivity today is only beginning to develop. Biological plausability is dependent upon the scientific knowledge of the time. The illnesses of "MCS" patients and Gulf veterans could have an organic basis since so much is shared in common; the demographic diversity of groups reporting similar and subjective symptoms and intolerances following an exposure event; the temporal cohesiveness between onset of multiple intolerances and an exposure event; the internal consistency in these patients reporting intolerances to common airborne chemicals, various foods, drugs, caffeine and alcoholic beverages and the observations that many "MCS" patients who have avoided problem chemicals and foods report marked improvement or resolution of their symptoms.

Neither "MCS" nShe stated that neither "MCS" nor the "Gulf veterans' illnesses" fullfill criteria for being syndromes. Further, they are not explainable by any currently known mechanism for disease. Dr. Miller proposed that the similar phenomenologies of both conditions suggest that a new general mechanism or theory of disease involving chemically-induced loss of natural tolerance could be operative which could be described as "toxicant-induced loss of tolerance" ("TILT") (Miller, 1996).

Many cases of chemical sensitivity appear to involve a two-step process. A susceptible person initially exhibits loss of tolerance or sensitization (also referred to as initiation, "priming" or "induction") often following acute or chronic exposure to any of a wide range of environmental chemicals. Following this loss of tolerance, these now sensitive persons report that extremely low levels of common chemicals tolerated by the majority of the population trigger severe symptoms. Because of masking (e.g. acclimatization, addiction and apposition (overlapping symptoms resulting from temporally overlapping exposures) both physicians and patients may fail to

recognize that everyday low-level exposures may be triggering symptoms (Miller, 1994; Miller and Ashford, 1995).

Dr. Miller stressed that physicians urgently need a clinical approach for determining whether chemical intolerances are at the root of these patients' (e.g., "MCS", "Gulf veterans' illnesses") problems. Dr. Miller advocated that a controlled testing environment or Environmental Medical Unit (EMU) be employed as a research tool to address questions concerning causality. The EMU is a proposed hospital environment in which chemical exposures have been reduced to the lowest levels practicable via specialized air filtration and the use of construction materials and furnishings that do not emit chemicals into the air. The EMU would serve as a tool for ruling in or ruling out environnmental sensitivities in the most direct and definitive manner possible. It was stressed that confirmation or refutation of illnesses of "MCS" patients and Gulf War veterans which are hypothesized as "toxicant-induced loss of tolerance" rests upon double-blind, placebo-controlled challenges conducted in an Environmental Medical Unit.

Dr. W.A. Nix (University Clinics, Mainz, Germany), stressed the similarity between features of "MCS" with "chronic fatigue syndrome" ("CFS") and that research strategies should be the same for both syndromes. He described the prevalence of psychosomatic symptoms in patients examined in an interdisciplinary "CFS"-clinic. Evaluation with an SCL-90-K questionnaire showed scores outside the normal range for somatization, obsessive compulsive disorders , depression and anxiety in patients who presented as their main complaint severe fatigue and in some cases, self-reported adverse reactions to environmental substances. The nessessity to screen for psychosomatic disorders in patients with a complaint of severe fatigue was stressed as well as the necessity to define subgroups for further evaluation of disease etiology under a bio-psycho-social disease concept.

It was further noted that "MCS" is not only a medical disease but a societal disease. It is difficult to differentiate the scientific and the pragmatic approach to assist the patient. All patients with "CFS" or "MCS" are evaluated at his Clinic with history, physical and mental status examinations. The goal is to determine the extent to which psychological problems are associated with these diseases and to find psychological parameters that disclose a predisposition to develop these symptoms and to see if laboratory parameters are of diagnostic value for these diseases.

Dr. P.S. Spencer (Oregon Health Sciences University, US), focused on recent research studies on unexplained illnesses of veterans associated with service during the Persian Gulf War (PGW). Unexplained illnesses refers to a constellation of symptoms designated as "PGW Unexplained Illness(es)" or "PGWUI". The long-term research goal is to develop a solid understanding of the nature of these conditions, their risk factors and their treatment and

prevention. The research focus concerns environmental factors encountered in military service that pose a threat principally to the neurological and musculoskeletal systems (fatigue, muscle and joint pain and cognitive complaints) of "PGWUI".

The overall research strategy outlined by Dr. Spencer is epidemiologically based involving: (a) case-control design, (b) clinical verification and (c) risk factor identification (exogenous and endogenous) (psychological, physical, chemical and biological). A major goal is thus to determine why some of the 700,000 veterans who were in the Persian Gulf for Desert Shield, Desert Storm and/or desert clean-up phases of the operation are now healthy (e.g., controls) while others (cases) have symptoms of "PGWUI". The primary research question is framed: are there differences between cases and controls in relation to individual subject factors and environmental exposures encountered in the Persian Gulf theater of war. Environmental exposures will be deduced by (a) stratifying subjects by their deployment period (e.g., Desert Shield only, Desert Storm only, desert clean-up only and combinations thereof), each of which is associated with a unique set of exogenous factors, (b) examining their geographical location in the Persian Gulf within the specified deployment periods and (c) assessing their duties and self-reported data on exposures in the Persian Gulf.

The difficulty of assessing and collecting unbiased data in the case of Persian Gulf veterans with unexplained illnesses (phase 1) was described. A major problem centered on different groups of veterans (different deployments as noted above) exhibiting differential exposures for different times. Phase 2 consisted of the deployment of a working case definition for "PGWUI" based in part on an analysis of 388 records of subjects in the Portland, Oregon component of the Veterans Administration (VA) Gulf Veterans Registry. This medical review provided valuable information on the leading symptoms from which a broad initial case-definition has been developed:

- symptom onset: during or after Persian Gulf war
- duration: 1 month or greater
- presence: within past 3 months
- symptoms: any of the following most frequently noted Registry symptoms (> 10%) : (a) muscle-joint pain; (b) cognitive changes; (c) abdominal pain/diarrhea; (d) skin and/or mucous membrane lesions and (e) unexplained fatigue.

Dr. Spencer concluded that the association between exposures and unexplained illness whether it is "MCS" or "Persian Gulf War Syndrome" is difficult to assess because of sources of subject bias and the complexity of physical, psychological, chemical and biological exposures that occur. Studies seeking causal associations must take great care to identify and verify subject bias and to assess the plethora of environmental exposures that may have etiological significance.

Dr. G. Kobal (Institut fur Experimentelle und Klinische Pharmakologie und Toxicologie, Friedrich-Alexander Universitat, Erlangen-Nurnberg, Germany), discussed his studies of olfactory systems with patients with "MCS" and identified areas of the brain affected by olfactory agents. He further focused on intranasal chemoreceptors in patients with "MCS", subjective olfactory tests and acoustic rhinometry.

It is widely believed that intranasal chemoreceptive senses are involved in the pathophysiology of "MCS" since the characteristic symptoms of "MCS" are reprtedly triggered by very low concentrations of chemicals in the range of olfactory thresholds (Doty et al., 1988; Simon et al., 1990; Davidoff and Fogarty, 1994). Dr. Kobal described studies which highlighted changes of both the olfactory and trigeminal systems in "MCS" patients assessed by means of electrophysical correlates of chemoreceptors. Specifically, the focus of the studies were to determine whether patients with "MCS" exhibit differences in responses after they have been challenged to either room air or stimuli such as 2-propanol (Hummel et al., 1998). This question was addressed utilizing chemosensory-event-related potentials (CSERP) and subjective measures of olfactory function (e.g., odor discrimination and phenyl ethyl alcohol odor thresholds). CSERP were recorded in response to olfactory (H_2S) and trigeminal (CO_2) stimuli. CSERP (Kobal et al., 1992; Murphy et al., 1994) have also been demonstrated to be of potential use in the diagnosis of olfactory or neurological disorders (Hummel et al., 1995). Compared to the intergrative nature of psychological responses, CSERP appears to be less prone to influences such as response bias or changes in the subjects mood. CSERP encodes the intensity of a given stimulus but also permits the discrimination between trigeminal and olfactory characteristics of an odorant (Hummel and Kobal, 1992; Kobal et al., 1992).

Out of a total of 23 patients studied (mean age 47 years, 13 female, 10 male) diagnosed with "MCS" according to Cullen's criteria for "MCS" (Cullen, 1987), 20 % of patients presented symptoms regardless of the type of challenge suggesting the susceptibility of these patients to non-specific experimental manipulations. Changes in CSERP latencies indicated a change in the processing of both olfactory and trigeminal stimuli. While odor thresholds remained unchanged, the patients ability to discriminate odors decreased after exposure to room air, in contrast this decrease was less pronounced after exposure to 2-propanol. "MCS" patients responded to a

challenge with 2-propanol at concentrations around threshold values with changes of chemosensory perception which might increase their susceptibility to environmental volatile chemicals. Changes in the pattern of event related potentials were interpreted as the possible changes of the orientation of cortical generators, e.g., neuronal populations that were involved in the processing of chemosensory information (Hummel et al., 1996). Dr. Kobal concluded by stressing that future studies will have to demonstrate how these responses in "MCS" patients compare to those of healthy age and sex-matched controls.

Dr. A.C. Ludolph (Universitats Klinikum und Charite Poliklinik fur Neurologie, Berlin, Germany) addressed whether "MCS" is a neurotoxic disorder by considering the diagnostic criteria for clinical neurotoxicity. These are: 1) suspected compound must indeed be in the environment; 2) a dose-response relationship should be established; 3) after cessation of exposure, clinical progression stops and improvement is considered likely and 4) neurotoxic compounds induce a specific response which is characterized by a uniform pattern of vulnerability and thus a uniform clinical pattern.

Dr. Ludolph concluded that these criteria which are based on currently understood and accepted biological features of the nervous system presently do not support the hypothesis that "MCS" is a neurotoxic disorder. Dr. Ludolph stressed that to increase our knowledge of "MCS", the approach must be more systematic: 1) there must be agreement on diagnostic criteria for this "syndrome"; 2) more intensive efforts to identify compounds consistently associated with "MCS" should be made and 3) dose-response relationships, patterns of vulnerability and the natural course of the disease should be elaborated. Once these goals are at least partially achieved, controlled therapeutic attempts must be organized. He suggested that a priority might be to elucidate whether treatment of a depression or a behavioral therapy influences the symptomatology in "MCS".

Dr. H. Staudenmayer (Allergy Respiration Institute, US) described some of his experiences in working with "MCS" patients. He basically developed an algorithmic approach to discriminate individuals with verifiable chemical reactivity from patients with psychological or psychophysiological disorders (Staudenmayer et al., 1993). For example, double-blind provocation challenges with an olfactory marker were performed in an environmental chamber on each of 20 patients who believed that that they were reactive or hypersensitive to low-level exposure to multiple chemicals: (some patients had been previously evaluated and managed by the tenets of "clinical ecology" and diagnosed as having "MCS"). A variety of chemicals (e.g., formaldehyde, natural gas, cleaners, combusted kerosene, fuel oil, trichloroethane, trichloroethylene, freon, denatured alcohol, printer's ink, oil paint, and insecticides) were employed one or more per subject dependent on an individual's clinical history. Clean air challenges with an olfactory marker

were used as placebo or sham controls. As a group probability analyses of patient symptom reports from 145 chemical and clean air challenges failed to show sensitivity (33.3%), specificity (64.7%), or efficiency (52.4%). Individually none of these patients demonstrated a reliable response pattern across a series of challenges.

Dr. Staudenmayer reported a series of patients presenting with "MCS" who suffered major childhood trauma such as physical or sexual abuse. These highly significant life stressors were difficult to elicit, requiring months of intensive psychotherapeutic interaction. In these patients, the prevalence of physical and sexual childhood abuse was significantly higher ($p < 0.05$) among the cohort of women who attributed their symptoms to environmental or chemically related illness. The data suggested to him that somatization may reflect sequelae of childhood abuse and may play an important role in the illness experienced by women who believe that they are sensitive to environmental chemicals (Staudenmayer et al., 1993).

Dr. Staudenmayer described neuropsychologic measures (EEG, scalp EMG) that were employed during relaxation in individuals who attribute medical and psychologic symptoms to chemical exposures ("universal reactors") compared to subjects with primary psychologic disorders and with a control group (Staudenmayer and Selner, 1990). High levels of EMG scalp activity were observed in a greater number of "universal reactors" than with subjects in the other groups ($p < 0.001$).

Dr. M. Huppe (Universitat Wurzburg, Germany) raised the question of whether environmental stress research can contribute to understanding psychological processes in "MCS". Stress is considered to be a somatic and a psychic reaction related to environmental conditions. How is behavior influenced by environmental factors ("stressors")? In the case of "MCS" such stressors could be chemical or environmental agents. Dr. Huppe described some characteristics of stress. Stress is a temporally protracted longer reaction to environmental conditions and is usually associated with negative mood states such as fear and anxiety. Stress is a process (not a state) which initiates coping as illustrated by two well known nuclear power accidents in Three Mile Island and in Chernobyl. Depending on individual coping strategies, psychic reactions in individuals exposed in the accidents differed greatly. Coping is directed to the environmental factor or to psychic processes of the person. Coping may be positive and reduce stress reactions or it may be negative and increase stress reactions. Currently stress coping strategies are most frequently addressed by questionnaires. Important individual characteristics that modify coping with stress include: psychophysiological state, perception of controlability, personal traits such as neuroticism, annoyance or coping strategies and demographic variables such as age and sex.

The main characteristics of environmental agents that cause "MCS" were illustrated: a) they are external and perceptible, b) the intensity is low, c) they are not new to the patients, d) they are often not contollable and they elicit negative emotional responses.

Dr. Huppe suggested that from the viewpoint of a psychologist, research is needed in the development and use of challenge tests or tests of reactivity. The psychological evaluation of experimental challenge tests should include assessments of mood state, including emotions and somatic feelings and coping with stress. There is a need for sensitive psychological methods for the assessment of symptoms or psychic states since the described manifestations of "MCS" are predominantly subjective. There is an obvious need for control subjects who do not suffer from the symptoms described by "MCS" patients.

Dr. S. Dewey (Forschungszentrum Borstel, Germany) described a number of cases studies and operating procedures of the Environmental Health Consultation Center (Umweltmedizinische Beratunsstelle/UMB) in Hamburg) and the Medical Clinic of the Forschungszentrum Borstel. The procedures of the UMB are based on the approach that there should be some effort at medical and environmental research and consideration between first contact and final counselling of the patient. The predominant environmental problem encountered at the UMB was that of indoor pollution (wood preservatives, pesticides, formaldehyde and solvents). The symptoms generally involved the upper respiratory tract and the skin as well as complaints of fatigue. The "likely" or "very likely" relationship between the environmental exposure and health problems was considered to be only 15% in 254 reported cases with a ratio of 2:1 women to men, while 16% were judged "possible: and 53% were considered unlikely.

Of 31 patients who submitted to the medical clinic of the Forschungszentrum Borstel with diagnosis of food allergy/intolerance, 3/31 had proven food allergy; 3/31 had an intolerance to aspirin and food preservatives and in nearly half of the patients, psychiatric/psychosomatic disorders were the main diagnosis.

Dr. Dewey stressed that in regard to "MCS", existing case definitions and diagnostic criteria are insufficient. Thus he felt that "MCS" should not be applied as a diagnosis in medical practice. A significant portion of "MCS" cases are misdiagnosed with the majority of these patients apparantly having common psychiatric/psychosomatic disorders. It was emphasized however that the experienced complaints are real whatever the etiology may be and hence there is an urgent need for sufficient therapeutic strategies.

Dr. V.M. Weaver (Johns Hopkins University School of Public Health, US) discussed the evaluation and treatment of an "MCS" patient and stressed that the clinical goals were to rule out specific disorders, reduce symptoms and increase function in a patient. Patient evaluation includes

a comprehensive history with a review of past medical records, and a physical examination with specific focus to the affected organ system(s). Laboratory evaluation should be individualized, dependent on past testing and patient symptoms and, although standard baseline tests are helpful, exhaustive testing is not. The evaluation is principally designed to exclude disease requiring other specific medical therapy.

A post evaluation discussion with the patient is important. If "MCS" is an issue, its characteristics should be discussed frankly stressing that the cause is unknown but treatment options are available. According to Dr. Weaver the focus should be on symptoms rather than aetiologic considerations. Although treatment modalities can vary greatly, the most important is the supportive care approach and should be utilized in all "MCS" patients. Since many "MCS" patients do not trust the medical community, entrenched patient beliefs should not be aggressively challenged initially. Dr. Weaver emphasized that a great deal of patience is required by both physician and patient to develop a working relationship and establish trust in the face of a chronic condition surrounded by uncertainty and controversy.

Dr. Weaver noted that a number of therapies are being utilized in "MCS" patients including: supportive care; behavioral techniques including desensitization and psychotherapy; chemical avoidance and clinical ecology regimens such as provocation-neutralization protocols. The extent to which avoidance (particularly long-term avoidance) should be used is an extremely contoversial issue. In general there is great concern regarding the severe isolation that results when patients attempt total chemical avoidance, particularly since evidence of organ damage is lacking. It was stressed that the supportive approach is a primary treatment modality that should be employed for all "MCS" patients. The clinical ecology regimens have no role in the treatment of "MCS" patients since many of these regimens have known serious side effects and have not been studied for efficacy in contolled clinical trials.

Dr. H. Kipen (Environmental and Occupational Health Sciences Institute; University of Medicine & Dentistry of N.J-Robert Wood Johnson Medical School, US) briefly synopsized the issues which surround "MCS". The following points were stressed: 1) while clinical ecology offered a relatively easy target, it is noted that most "MCS" patients have not seen a clinical ecologist who may give patients understanding or misunderstanding; 2) we simply do not know what causes "MCS", the underlying mechanisms, toxicology, etc; 3) while we attempt to understand suspected causes of "MCS" we should investigate it as prevalent phenomenon independent of causation, and 4) it should be stressed that "MCS" overlaps with other syndromes particularly "chronic fatigue syndrome" ("CFS"), the symptoms of which are seen in a high percentage of "MCS" patients. (Fiedler et al., 1996).

Dr. Kipen suggested that the key question with regard to "MCS" is : are we studying causes (which are not easily verifiable) or a clinical phenomenon? He noted that "MCS" is best seen as a syndrome which may have a number of underlying causes or one underlying CNS biological cause which can keep much different company in terms of the accompanying major symptoms. In many ways research and conceptions of CFS can serve as useful models for how one might approach "MCS". Dr. Kipen emphasized that research in "MCS" is greatly hindered by the lack of a working or accepted definition which can be relatively uniformly applied by either experts or non-experts. Contentious issues to resolve in developing a definition(s) include: the role of psychiatric and medical co-morbidity (especially the methods for seeking and scope of the former); the importance of chemical initiation of the syndrome as opposed to subsequent triggering of symptoms (listing the key symptoms which could probably be accomplished as it was for "CFS") and the role of severity/disability as a qualification. Such a definition would facilitate varied clinical research and could be based on a combination of clinical and questionnaire instrument information. Scores on multiple scales of "MCS-ness" as proposed by Neutra et al., (1995) may be more useful for identification of patients/subjects than an unidimensional list of criteria.

Prof. H. Altenkirch (Spandau Hospital, Berlin) presented a video of 3 cases in which patients described "multiple chemical sensitivity syndrome" in their own words. In clinical neurology, videos are often used to present case histories and stimulate discussions on differential diagnosis. These 3 case histories presented, underscored the significance of differential diagnosis and the correct aetiological allocation of symptoms.

For all 3 patients, the presenting complaints were "MCS" symptoms and diagnostic criteria described by Cullen (1987) which were met. There were no abnormalities found in the physical neurological examination. Nonetheless, all three had different diseases that could be distinguished by differential diagnosis. These were: case 1: paranoid development and substance abuse (opiates); case 2: cerebral seizures with focal epilepsy and sleep -associated secondary generalized grand mal seizures and case 3: bipolar affective disorder with uniform symptoms. In all 3 cases the individual disease urgently required treatment, however adequate therapy did not take place.

In one illustrative case, a 30-year-old man reported that since 1989 he had been exposed to pesticides (organophosphates and permethrin) which were sprayed onto his clothes and bed linen in his bedroom. His symptoms consisted of fatigue, feeling of weakness, abdominal pain, light headedness, strong headaches, difficulty concentrating and memory loss. He observed

oversensitivity to fresh paint, solvents, pesticides and sprays which made him tired and restless and forced him to leave the room as quickly as possible.

The clinical neurological examination as well as all additional investigations including neurophysiological findings and neuroimaging showed no abnormalities. Cholinesterase and pyrethroid levels in serum and urine were normal. A sample of a wooden picture frame of a painting that the patient brought from his bedroom showed no indication of pesticides. Further inquiries revealed that his mother wanted to poison him to deny his inheritance. Additional investigations revealed that the patient had demanded prescriptions for opiates from different physicians. Final diagnosis: suspicion of paranoid development; suspicion of substance abuse (opiates).

IV. DESCRIPTION AND DEFINITIONS OF "MCS"

There is an apparent ever increasing demand by various social, political and economic forces in a number of countries that "MCS" be defined medically, even though scientific studies to date have not identified pathogenic mechanisms for the condition or any consistent objective diagnostic criteria (Sparks et al., 1994 a,b). Regulatory, legislative and occupational control responses are also dependent upon the critical distinction between psychogenic and organic aetiologies that might underpin a definition of "MCS" (Miller, 1994; Gots, 1995). The growing polarization of scientists, physicians and medical associations regarding the scientific basis of "MCS" (e.g., whether the syndrome or phenomenon is a psychogenic or a toxicodynamic disorder) coupled by the profusion and escalating number of synonyms attached to "MCS" (table 1), as well as the increasing public and media confusion concerning "MCS" has been frequently noted in many countries.

A number of definitions of "MCS" have been previously proposed. Cullen (1987) proposed the following definition of "MCS": 1) the initial symptoms acquired in relation to an identifiable environmental exposure (s), 2) symptoms involve more than one organ system, 3) symptoms recur and abate in response to predictable stimuli, 4) symptoms are elicited by low-level exposures to chemicals of diverse classes and 5) no standard test of organ system function can explain symptoms. Cullen's definition of "MCS" (primarily for research purposes) is currently the most widely used clinical definition for this condition.

Ashford and Miller (1992) proposed the following operational definition of "MCS" for diagnostic purposes, a definition that is based upon challenge testing: " The patient with "MCS" can be discovered by removal from the suspected offending agents and by rechallenge, after an

appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge". For research purposes, such testing shoulf be conducted using double-blind, placebo-controlled challenges.

The National Research Council definition is as follows: " 1) Sensitivity to chemicals. By sensitivity we mean symptoms or signs related to chemical exposures at levels tolerated by the population at large that is distinct from such well recognized hypersensitivity phenomena as I_gE-mediated immediate hypersensitivity reactions, contact dermatitis, and hypersensitivity pneumonitis. 2) Sensitivity may be expressed as symptoms and signs in one or more organ systems. 3. Symptoms and signs wax and wane with exposures. It is not necessary to identify a chemical exposure associated with the onset of the condition. Pre-existent or concurrent conditions, e.g., asthma, arthritis, somatization disorder or depression should not exclude patients from consideration" (National Research Council,1992).

The Ontario Ministry of Health Committee (1985) definition is as follows : Environmental hypersensitivity is a chronic (i.e., continuing for more than three months) multisystem disorder, usually involving symptoms of the central nervous system and at least one other system. Affected persons are frequently intolerant to some foods and they react adversely to some chemicals and to some environmental agents, singly or in combination, at levels generally tolerated by the majority. Affected persons have varying degrees of morbidity, from mild discomfort to total disability. Upon physical examination, the patient is normally free from any objective findings. Although abnormalities of complement and lymphocytes have been recorded, no single laboratory test, including serum I_gE is consistently altered. Improvement is associated with avoidance of suspected agents and symptoms recur with re-exposure".

Nethercott et al., (1993) proposed the following case definition for "MCS": 1) the symptoms are reproducible with exposure, 2) the condition is chronic, 3) low-level exposure results in manifestations of syndrome, 4) symptoms improve or resolve when incitants are removed and 5) responses occur to multiple, chemically unrelated substances.

In discussion, a number of participants proposed the consideration of different terminology to replace "MCS". For example, Dr. Gothe (Sweden) proposed the term "ESS" ("Environmental Somatization Syndrome") be employed to emphasize the uniform character of the syndrome which he outlined was related to chemical and physical components of the environment as well as ergonomic stress. The pathologic picture was consistent in that almost any symptoms might occur in "ESS"; different combinations of symptoms exhibited by "MCS"patients are common in "ESS" and the symptomatology was influenced by the alleged disease inducing agent. An additional

reason for consideration of a change in the definition for "MCS" was to address the fact that non-chemical triggers, e.g., electromagnetic fields (EMF) have been suggested as the cause of an "MCS" type of illness in Scandinavia (Gothe et al., 1995).

Dr Gots (US) recommended that until the aetiology is determined, a more descriptive and less categorical title for "MCS" and one which is less suggestive of causation would be "Environmentally Associated Symptoms" ("EAS").

Dr. Miller (US) offered the term "Multiple Chemical Intolerances" ("MCI") to circumvent the causation debate, and proposed that this term would still capture the most distinctive clinical feature of the phenomenon.

Following discussion of these proposals the term "Idiopathic Environmental Intolerances" ("IEI") was suggested to be employed in place of "MCS" for salient reasons delineated below and this was endorsed by the majority of participants of the Workshop. It should be noted that the term idiopathic is defined to mean that the condition is unclear or of unknown causation (pathogenesis).

DEFINITION

The majority of invited experts* supported the suggestion for the term "Idiopathic Environmental Intolerances" ("IEI") which would cover a number of disorders sharing similar symptomatologies including what is described as "MCS". A working definition was formulated as follows:

- acquired disorder with multiple recurrent symptoms
- associated with diverse environmental factors tolerated by the majority of people
- cannot be explained by any known medical or psychiatric disorders.

Diverse environmental factors includes: chemical (e.g., volatile organic compounds (VOCs)), biological (e.g., molds), physical (EMR) and psychological (e.g., stress).

There are no specific tests to establish the presence of "IEI". Certain tests are considered to be of no confirmatory value in clinical assessment, including the following: immunological testing, porphyria testing, neuroimaging, biological monitoring and alternative medicine methodologies.

V. AETIOLOGIES

It is well recognized that the lack of a uniform case definition for individuals with "MCS" has greatly hampered the investigation of aetiology. The criteria for study eligibility have varied depending on the target population (Terr, 1993; Sparks et al., 1994 a,b; Harrison, 1995; Sikorski et al., 1995). Aetiologic hypotheses have focused generally on either a primary physiologic or psychiatric aetiology to explain how chemicals produce the many polysymptomatic responses frequently noted in "MCS" patients. The aetiologies that have been suggested for "MCS" are:

. toxicological/physiological
. immunological
. neurological
. psychological/psychiatric
. respiratory
. olfactory-limbic
. violence in childhood
. porphyria

A. Immunologic hypothesis

It has been established in both animals and human beings that a number of environmental and occupational chemical exposures may affect the immune system with a variety of cellular and cell-mediated immunological effects (Gleichman et al., 1989; Sullivan, 1989; Bellant, 1991). For many years, proponents of "MCS" have focused on immunological mechanisms to explain the aetiology and pathogenesis of "MCS" (Rea, 1977; Rea et al., 1979; Levin and Byers, 1987). However published articles on investigations of the immunological status of "MCS" patients have found no consistent abnormalities in immunoglobulins, complement, lymphocytes, or B-cell or T-cell subsets; no evidence of increased autoantibodies, lymphocyte count, helper or suppressor cells, B or T cells and TAI$^+$ or interleukin-2+ cells when compared to control subjects (Terr, 1986, 1993). Taken in sum, there is no currently compelling evidence that "MCS" is an immunological disorder (Terr, 1986; Albright and Goldstein, 1992; Simon et al., 1993; Sikorski et al., 1995). Further, patients with "MCS" have not been shown to have an unusual propensity to make autoantibodies, and their clinical symptoms and absence of any organ or tissue pathology provide no support for the autoimmune theory (Terr, 1993). However it has been noted that

immunological testing of "MCS" has been confined to a limited set of markers; future studies using other markers may be revealing.

B. Neurogenic Inflammation Hypothesis

"MCS" have been hypothesized to represent an amplification of the non-specific immune response to low-level irritants, since many individuals with "MCS" report a heightened sense of smell or develop symptoms at low levels of environmental exposure. Altered function of c-fibers, respiratory epithelium, or neuroepithelial interaction has been postulated to result in increased symptom reporting correlated with physiological abnormalities (Bascom, 1992; Meggs, 1993). A group of subjects with "MCS" have been reported to have significantly higher nasal resistance and respiratory rates (Doty et al., 1988). The neurogenic inflammation hypothesis remains principally untested and its relevance to the etiology of "MCS" remains to be determined (Harrison, 1995; Sikorski et al., 1995).

C. Olfactory-limbic hypothesis (model)

The olfactory nerves with their receptors in the nose, link the external chemical environment to the amygdala, hippocampus, hypothalmus and other parts of the limbic system. The limbic system ("primitive smell brain") is a phylogenetically ancient part of the brain present in all mammals. Since there is no blood-brain barrier at olfactory receptors, it is postulated that various substances can enter the olfactory bulbs via retrograde transport within the olfactory neurons. The olfactory bulbs lie in close proximity to the limbic area and supply much of the neural imput. Lesions in the limbic region have been suggested to be associated with many symptoms in patients reported with "MCS", e.g., irrational fears, feelings of strangeness or unreality, sadness, a sensation of being out of touch with or out of control of one's feelings and thoughts. Sensitization or kindling of olfactory-limbic pathways by acute or chronic exposure has been proposed as a putative mechanism for chemical sensitivity (Bell et al., 1992; Miller, 1992, 1994; Miller and Ashford, 1992; Ashford and Miller, 1995). In this hypothesized model for "MCS", sensitization to chemicals or foods parallels the phenomenon of time-dependent sensitization from drugs or non-drug stressors with heightened sensitivity to stimuli, gradual improvement following withdrawal , and reactivation of symptoms following reexposure (Bell, 1994; Harrison, 1995). The olfactory-limbic model remains to be further tested (Sikorski et al., 1995).

D. Psychiatric hypothesis

A large number of investigators in North America and Europe have concluded that many, if not most "MCS" patients, do not differ significantly from psychiatric patients who do not perceive their symptoms to have environmental triggers. Available studies to date suggest that "MCS" is not a distinctive diagnosis or syndrome. Some feel that the diagnosis of "MCS" has been incorrectly applied to too many patients. Individuals with "MCS" may be a heterogenous group of patients with various psychiatric disorders, either the cause of related or secondary to "MCS", such as depression, anxiety and a variety of somatoform disorders (e.g., phobias, hypochondrias, conversion disorder), somatization disorders and other common psychiatric disorders (Brodsky, 1984, 1987; Stewart and Ruskin, 1985; Schottenfeld, 1987; Staudenmayer and Selner, 1987; Terr, 1986, 1989; Black, 1993; Sparks et al., 1994 a,b; Harrison, 1995; Sikorski et al., 1995). It may also be the expression of a subconscious troubled by early life events such as childhood abuse (Staudenmayer, 1993). On the other hand, one cohort of rigorously defined "MCS" cases, assessed by standardized instruments, showed only a 26% prevalence of diagnosable psychiatric disorders (Fiedler et al., 1996).

Other investigators have argued that psychiatric and psychologic disorders may be a consequence, rather than a cause of "MCS" (Davidoff, 1992). The explanation that primary or misdiagnosed psychiatric disease may be the actual cause of "MCS" has been largely predicated on clinical experience lacking standardized case definitions, examiner blinding and appropriate comparison groups. However it should be also noted that some studies have demonstrated the role of psychologic mechanisms in the manifestation if not the etiology of "MCS" in individuals with the syndrome (Sparks et al., 1994 a,b; Harrison, 1995). It is generally acknowledged that considerable controversy continues to surround the aetiology, case definition, diagnosis and treatment of individuals with "MCS".

VI. DISCUSSION OF IDENTIFICATION AND DIAGNOSIS

There are neither widely accepted theories of underlying mechanisms nor validated clinical criteria for the diagnosis of "MCS", nor for "IEI". Clinical assessment should be designed primarily to rule out conditions requiring specific therapy. This involves a comprehensive history, physical examination, psychological/psychiatric assessment and laboratory testing designed to identify explanatory conditions which are deemed essential to uncover alternative diagnoses that require specific treatments. These clinical assessment procedures should be sufficiently

comprehensive to establish or rule out all other occupational and non-occupational disease conditions in the differential diagnosis.

There are no specific tests to establish the presence of "IEI". Certain tests are considered to be of no current confirmatory value in clinical assessment, including the following: immunological testing, porphyria testing, neuroimaging, biological monitoring and alternative medicine methodologies. The descriptor "IEI" should be used only after a thorough examination of patients and careful consideration of alternative explanations. Focused, interdisciplinary approaches for the diagnosis and treatment should be sought (including good quality toxicological, psychological/psychiatric and analytical advice) in order to provide more effective treatment of the patient.

VII. RESEARCH - PAST, PRESENT -

A. Human Research Priorities

"Idiopathic Environmental Intolerances" ("IEI"), as the name implies, describes an illness with an unknown aetiology but which nevertheless may be associated with, and often attributed by the patient or physician to, exposure to environmental factors. In this context, environmental factors is a broad term that includes external physical (e.g., electromagnetic radiation) and psychological (e.g., stressors) agents as well as a plethora of exogenous chemicals in air, water and food that are perhaps most often considered in relation to this malady. The aetiology of the disorder presumably may be exogenous, endogenous, or some combination of the two. Discriminating between these possibilities is a top research priority since the result will indicate whether "IEI" is psychological or organic (toxicological) in nature. Settlement of this cardinal issue will serve to identify the future direction of "IEI" research.

The key experiment is to determine in a double-blind challenge study whether subjects with "IEI" successfully discriminate between exposures to environmental factors (including those to which illness is attributed) and placebos. Chemicals (e.g., VOCs) might usefully serve as experimental agents given their frequency of association with "IEI", the possibility of administering substances of known purity, dosage and treatment duration, and the convenience of experimental design. If the subjective response (appearance of symptoms) of test subjects is able to discriminate between exposure to test chemicals and placebos, in a blinded design this would suggest the operation of a toxicological mechanism in which culpable agents interact with tissue targets to trigger a receptor-mediated pathophysiological reponse. Confidence in the existence of

this mechanism would increase greatly if the severity of the response was shown in individuals to be related to the dosage and if the response could be blocked by a competing substance (none currently known). If, on the other hand subjects were unable to distinguish between exposure to test chemical and placebos, this would suggest the operation of psychophysiological factors which did not require exogenous chemical activation of a tissue receptor site.

The selection and handling of test subjects is an important consideration. In general, cooperative patients reporting a constellation of robust symptoms should be selected as cases for study. While the proposed experiments can be conducted using individual cases with subjects serving as their own control, comparison of responses between subjects requires a population with uniform characteristics. For example, given that women between the ages of 30 and 40 years appear at high risk for "IEI", this is a convenient population from which cases might be drawn. Factors such as ethnicity and socioeconomic status might also be controlled. Matched subjects would serve as controls in the event these were incorporated into the study (vide infra). Ideally, cases should have a recent (e.g., up to 5 years) onset of "IEI" but be asymptomatic prior to chemical challenge. Cases may be justifiably studied after environmental factors believed to obscure the alleged trigger have been removed if the effects of the ("unmasking") procedure itself are understood. In some instances, it may be possible for the test procedures to take place in a familiar setting (e.g., general atmosphere) rather than in a booth or specially constructed environmental chamber/room, especially if the effects of these environments in the absence of the test articles are unknown. Procedures should be carried out with standardized protocols and with repeated challenges. Detailed methodologies have been proposed (US NIEHS "MCS" Workshop, to be published).

Strength might be added to the experimental design with the introduction of control groups: (a) one serving as a negative control would consist of matching, healthy subjects with no complaints of environmental chemical intolerance, (b) the other serving as a positive control group in which expected responses could be demonstrated. Positive controls, which might include subjects with known intolerance for caffeine or alcohol (disulfuram), serve to demonstrate to others that the observer is able to demonstrate a predictable response to a test agent.

Measures of responses to environmental challenges should include objective physiological changes in test subjects and controls. Examples include: EEG, EKG, blood pressure, skin galvanic responses and psychological measures. More elaborate methods, such as SPECT or functional MRI are not needed at this phase of investigation but may be useful as research tools to evaluate mechanisms underlying subject responses. Unvalidated measures, such as certain immunological and toxicological screens should be avoided.

1. Subjects Able To Distinguish Between Test Agents & Placebos

Subjects who are able successfully to distinguish between chemical triggers of symptomatology and non-provoking placebos provide evidence of the possible existence of an interaction between exogenous triggers and target tissue sites. Attempts to strengthen this association should be sought by demonstrating that the time to onset and/or severity of symptomatology correlates with dose, again using negative and positive control groups, the latter showing the expected presence of dose-dependent phenomenology. Demonstration that cases exhibit symptomatology in proportion to the concentration of test articles used in the challenge would provide compelling evidence that physiological changes are in part mediated by interaction of the offending substances with tissue targets.

Further research might focus on the characterization of organ changes underlying prominent symptoms. For example, complaints of cognitive dysfunction (spaciness, concentration and memory difficulties) would merit studies using brain imaging methods. Muscle and joint complaints might call for investigational studies of circadian cortisol patterns.

For mechanistic investigations, cases with "IEI" might usefully be studied alongside non-IEI subjects with chemical intolerances who display physiological (e.g., pregnant women) or pathophysiological changes (subjects dosed with disulfuram or serotonin-reuptake inhibitors).

Any objective demonstration of a human response to a wide range of chemicals below the threshold for either conventional toxicological effects or subjective detection would pose difficult challenges for toxicologists, which would then need to be addressed. Questions that might be posed include: (1) Is there a generalized reduction of xenobiotic metabolism in "IEI" cases because of genetic polymorphism (e.g., P450 subtypes, A-esterases, multi-drug-resistance genes). If so, why are effects not compound-specific (mirroring those seen in normal subjects at higher doses? (2) Are there novel toxic target sites/mechanisms in "IEI"? If so, how might they be responsive to a wide range of disparate chemicals?

2. Subjects Unable To Distinguish Between Test Agents & Placebos

Cases who are unable to discriminate by symptomatology on repeated challenge between test agents and placebos provide putative evidence that "IEI" is a psychological disorder which, while potentially stimulated by the presence of chemicals, employs no toxicological mechanism to effect the perceived pathophysiological response.

In this event, the overarching concern would be the mechanism by which environmental factors, or the perception thereof, induces a pathophysiological response. High on the list of possibilities are conditioned or other learned responses: of these, the possible existence of a specific event in the past which initiated susceptibility to the subsequent presentation of environmental triggers would merit priority consideration. For example, an environmentally intolerant subject may have been exposed to an agent (e.g., pesticide, combat stress, hyperthermia) that resulted in the unequivocal induction of adverse health effects which, after recovery, are subsequently recapitulated by diverse environmental stimuli normally tolerated by the populace. This type of conditioned response might initially be sought by an epidemiological approach in which either prospectively or retrospectively selected subjects are studied in a population-based approach Populations suitable for such studies should be cooperative and homogenous for retrospective study (e.g., sick-building occupants) or prospective study (e.g., personnel hired into the chemical industry or as pesticide applicators). A key question is the presence or absence of a putative conditioning event; a priori, this might be a distressing transient reaction to a chemical poisoning or a transient psychological stress situation that was temporally associated with an innocuous chemical exposure.

Subjects with a psychological basis for "IEI" might be usefully studied alongside individuals with other distinct psychological disorders, which can be triggered on demand by environmental cues (e.g., carbon dioxide, spiders) other than the factors (e.g., other chemicals) under study in "IEI". For example, comparative physiological monitoring of brain and somatic functions in subjects with "IEI" and arachnophobia might serve to reveal commonalities in these endogenously generated disorders. Research on basic personality dynamics may also help to identify individual susceptibility factors.

3. Other Research Priorities

Once the nature of "IEI" has been elucidated, appropriate models should be developed in suitable laboratory species. An animal model of "IEI" would be a valuable tool (1) to research the relationship between biochemical and behavioral changes, (2) to use as a test-bed for the development of effective therapeutic intervention. Approaches to the development of animal models have been discussed elsewhere (US EPA, 1994).

3. Recommendations on Epidemiology

For research studies, the broad definition of "IEI" has to be further refined. Subdefinitions have to be formed according to specific research interests and needs and situations in different countries. Epidemiologic studies reflect health and disease in populations as opposed to individual cases. Epidemiology includes careful observation,counts of well-defined cases and the demonstration of relationships between cases and risk factors.

Epidemiologic studies are needed:

1) to find out the prevalence and incidence of "IEI" and define those individuals who meet the case definition of "IEI" with respect to demographic factors such as gender, age and sex.

2) to address the question whether the prevalence of the phenomenon in a particular group is increased or decreased and what is the baseline for such statements. If there is a change, to what is it attributable? For example: a) prevalence is influenced by a high interest towards this phenomenon in medicine or only locally due to local reasons; b) the medical community is not well informed and neglects the problem; c) the medical community is hesitant about the diagnosis as it does not believe this phenomenon to be a medical problem; d) the prevalence is influenced by media effects.

3) to assess the need for further research based on the "burden of illness" (e.g., prevalence and severity of illness) documented in these studies.

4) to identify cases for further critical scientific workup. From this patient-grou, persons could be selected who fullfill criteria for studies as outlined in the research recommendations.

5) to test hypothesized causal relationships between "IEI" and various proposed causative risk factors (mechanisms). Experimental, case-control, cohort and/or cross-sectional designs could be employed.

6) to study the natural history and prognosis of "IEI" and evaluate the efficacy and effectiveness of advocated therapeutic interventions.

7) to define the relationship between subcategories of "IEI" and between "IEI" and other idiopathic conditions such as "CFS".

VIII. PRACTICAL IMPLICATIONS AND PRIORITIES

Part (c) of the "IEI" case definition excludes any known medical or psychiatric disorder as an explanation for the symptoms. A number of Workshop participants expressed a wide range of interpretations as to what constitutes a known medical or psychiatric disorder. Known disorders could be interpreted broadly to include asthma, depression, or even somatoform disorder. On the other hand, known disorders may be restricted to those with a well defined primary aetiology, e.g., hypothyroidism, allergic asthma, or simple phobia. The broader the exclusion criteria, the greater the risk of defining away conditions that might have an exogenous chemical aetiology. In order to be useful, any exclusion criteria should be tightly defined.

Dr. Ray (UK) suggested that if "IEI" is found to be a valid entity, then the presence of a minority ("IEI") population with very markedly greater susceptibility to environmental chemicals then the normal population (for whom current safety margins are calculated) would have far reaching practical and financial consequences. In such a situation, possible strategies would involve either specific therapeutic measures based on toxicological mechanisms or avoidance of exposure to "IEI" sufferers or, alternatively, the setting of new low safety limits so as to protect all individuals. If, however, "IEI" is found not to be a valid entity, the action can be restricted to appropriate psychological treatment for individual sufferers.

In addition to the direct health implications of "IEI", there are two important implications for conventional chemical toxicology:

1. Where "IEI" is prevalent in a population, then it becomes difficult to carry out conventional toxicological investigations of the health effects in such a population. It is generally possible to detect adverse effects across a population because the lowest exposure quartile will show minimal changes. The presence of a significant subpopulation with "IEI" (objective or subjective) would lead to positive effects even in the lowest quartile, thereby diluting the power of any analysis. Any survey of such a population would therefore have to carry a selection of questions designed to seggregate "IEI"-like responders from the normal population.

2. Overenthusiastic diagnosis of "IEI" without paying sufficient attention to the elimination of conventional diagnoses would lead to underestimation of conventional, specific, toxic effects and also to inappropriate therapy.

Dr. Miller (US) suggested that because of the possibility that "Idiopathic Chemical Intolerances" could have an organic basis in some individuals, it is important that, in the interim, while research to settle these questions is underway, patients be provided adequate access to sympathetic caregivers and those social support services and accomodations needed to prevent personal hardship.

It should be noted that Dr. Kipen, following the Workshop Meeting, expressed his dissent to the conclusions as follows: "While there was widespread support of the invited participants for most of the components of the report and conclusions, the central idea of whether or not a name change should occur was not unanimously agreed upon. Those opposed to the name change, included Dr. Kipen, the chair of the workshop, among others. It is further understood that the term "idiopathic" has a number of meanings, and that the definition used for purposes of this workshop is that the condition is of unclear or unknown pathogenesis".

Following the Workshop Meeting, Dr. Miller suggested "that the conclusions and recommendations would have been far stronger (no name change, no attempt to exclude psychological diagnoses from consideration as possible manifestations of MCS) had the participation been more balanced".

IX. CONCLUSIONS AND RECOMMENDATIONS

The following Conclusions and Recommendations were endorsed by the majority of invited participants.

A. Conclusions

It is recognized that there are patients who report a variety of unexplained environmental intolerances. It is acknowledged that these patients do suffer and that they need compassion and professional help.

The term "Multiple Chemical Sensitivities" ("MCS") should be discontinued because it makes an unsupported judgement on causation. Although there exist several definitions of what has been called "MCS", it cannot be regarded as a clinically defined disease. There are neither

accepted theories of underlying mechanisms nor validated clinical criteria for diagnosis. A relationship between exposures and symptoms is unproven.

A more appropriate descriptor is "Idiopathic Environmental Intolerances" ("IEI"). This term incorporates a number of disorders sharing similar symptomatologies, including what is described as "MCS". The descriptor may be qualified by the putative origin of the disorder, e.g., "IEI (chemical)".

A working definition of this disorder is that it is:

- an acquired disorder with multiple recurrent symptoms
- associated with diverse environmental factors tolerated by the majority of people
- not explained by any known medical or psychiatric/psychologic disorder

Clinical assessment should be designed to rule out conditions requiring specific therapy. Appropriate evaluation should be based on a biopsychosocial understanding of the patient. This involves history, physical examination, psychological/psychiatric assessment, and laboratory testing designed to identify explanatory conditions. This is essential to avoid misdiagnosing conditions that require specific treatments.

There are no specific tests to establish the presence of "IEI". Certain tests are considered to be of no confirmatory value in clinical assessment, including the following: immunological testing, porphyria testing, neuroimaging, biological monitoring and alternative medicine methodologies.

Effective treatment has not been validated in controlled clinical trials. It will probably evolve from an understanding of the nature (e.g., psychogenic, toxicogenic) of "IEI". For example a demonstratable psychogenic origin would demand psychological/psychiatric intervention; a toxicogenic origin would call for exposure minimization. There is no justification for aggressive and potentially harmful methodologies (e.g., chelation therapy) or other purported detoxification procedures (e.g., vitamins, mineral supplementation, herbal therapy or sauna detoxification).

In the present state of uncertainty concerning "IEI" causation, and therefore appropriate treatment, approaches based on understanding and supportive care are necessary. In addition there are two common approaches, exposure avoidance and psychological/psychiatric therapy. In some instances the implementation of methods to avoid or minimize exposure to possible environmental triggers may be appropriate; however, isolation of patients from the general environment may have adverse consequences. Psychological/psychiatric approaches currently include self-regulation

(relaxation, biofeedback), behavioural therapy (desensitization), psychopharmalogical treatment, cognitive therapy and insight-oriented therapy, tailored to the individual's condition.

Human research is urgently needed to determine the nature (e.g., psychogenic, toxicogenic) of "IEI" since the outcome will influence public policy and clinical practice for IEI prevention and treatment respectively. The key question is whether subjects with "IEI" are able to discriminate in double-blind placebo-controlled challenge studies between reported environmental (e.g., chemical) triggers and placebos. Ability to discriminate suggests a toxicological (i.e., chemical-receptor) mechanism. Inability to discriminate would suggest a psychogenic (e.g., conditioned or other learned) mechanism.

B. Recommendations

1. Diagnosis

- The descriptor "IEI" should be used only after a thorough examination of patients and careful consideration of alternative explanations.

- Focused, interdisciplinary approaches for the diagnosis and treatment of these patients should be sought in order to provide more efficient and effective treatment. These include good quality toxicological and analytical advice.

2. Research

Research on IEI should be given high priority.

- Challenge studies to distinguish psychogenic from toxicogenic or other responses are deemed essential and urgent. These are necessary to define the nature and origins of environmental intolerances so that effective treatment, public health protection and policies can be developed and implemented. Such studies are research prerequisites which must precede further mechanistic studies.

- Epidemiological research should be directed at the prevalance of relevant symptoms and correlates such as demographics, time trends and the concurrent presence or absence of

known and unexplained conditions (e.g., Chronic Fatigue Syndrome (CFS), "Gulf War Veterans' Illnesses"). Risk factors could be sought in case control studies.

3. Communication and Cooperation

- Scientific research on IEI will lead to an improved understanding of environmental hazards that should lead to improved risk communication. Public information should be based on established facts and not on speculation.

- Cooperation should be established between all responsible health care systems, institutions and insurers, in order to coordinate approaches to patients with IEI.

- WHO should promote continuous exchange of knowledge and international cooperation on research into "IEI".

TABLE 1 NAMES ASSOCIATED WITH "MULTIPLE CHEMICAL SENSITIVITIES"

- ALLERGY TOXEMIA
- AUTOINTOXICATION
- CEREBRAL ALLERGY
- CHEMICAL AIDS
- CHEMICAL HYPERSENSITIVITY SYNDROME
- CHEMICALLY INDUCED IMMUNE DYSREGULATION
- CHEMICAL SENSITIVITY
- CLINICAL ECOLOGY SYNDROME
- ECOLOGICAL ILLNESS/DISEASE
- ECO-SYNDROME
- ENVIRONMENTAL ILLNESS
- ENVIRONMENTAL HYPERSENSITIVITY
- ENVIRONMENTAL MALADAPTATION
- ENVIRONMENTAL SOMATIZATION SYNDROME
- ENVIRONMENTAL STRESS SYNDROME
- HYPERSUSCEPTIBILITY
- IMMUNE DYSFUNCTION SYNDROME
- NON-SPECIFIC HYPER-RESPONSIVENESS
- ORGANIC BRAIN SYNDROME
- ORGANIC SOLVENT SYNDROME
- PETROCHEMICAL PROBLEM
- PERSIAN GULF WAR SYNDROME
- PSEUDO-ALLERGY
- TOTAL ALLERGY SYNDROME
- TWENTIETH CENTURY DISEASE
- UNIVERSAL ALLERGY

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ANNEX A

MCS Workshop[1]
21-23 February 1996, Berlin

Organised in collaboration by the International Programme on Chemical Safety (UNEP-ILO-WHO), the Federal Ministry of Health (BMG), the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), and the Federal Environmental Agency (UBA).

OUTLINE PROGRAMME

Wednesday, 21 February

Registration
Opening Session - Official Speakers
Mr F.J. Bindert, Federal Ministry of Health (BMG)
Prof. A. Somogyi, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV)
Prof. H. Lange-Asschenfeld, Federal Environmental Agency (UBA)
Dr E. Smith, IPCS - Objectives of the Workshop -
Administrative announcements
Appointment of Chairman, Vice-Chairman and Rapporteurs

SHORT PRESENTATIONS BY INVITED EXPERTS
Introductory

Prof. H. Altenkirch - "*MCS; a European perspective*"
Dr R.Gots - "*MCS; a US perspective*"
Dr F.Li - "*MCS; a Canadian perspective*"

Toxicology, immunology, environmental illnesses

Dr C-J. Göthe
Dr L. Fishbein
Dr E. Ray
Dr B.Heinzow
Dr C. Miller

Neurology, behavioral, sensory irritation

Prof. W.A. Nix
Dr P.S. Spencer
Prof. G.Kobal
Dr A.C. Ludolph
Dr H. Staudenmayer
Dr M. Hüppe

[1]A WHO Workshop is a meeting for the exchange of technical and scientific information. The emphasis is on free discussion, exchange of ideas, and practical application of skills and principles.

Clinical investigation and diagnosis

Dr S.Dewey
Dr V.M. Weaver
Prof. H.M. Kipen
Prof. H. Altenkirch

General discussion: identification of issues

Thursday, 22 February

Discussion in plenary session and in *ad hoc* panels

Friday, 23 February

Discussion
Outline of report
Conclusions and recommendations
End of Workshop

ANNEX B

MCS WORKSHOP - 21-23 February 1996

Invited experts

Prof. H. Altenkirch, Spandau Hospital, Department of Neurology, Humboldt University, Berlin, Germany (**Joint Rapporteur**)
Dr S. Dewey, Medizinische Klinik, Forschungsinstitut, Borstel, Germany
Dr L. Fishbein, Fairfax, Virginia, United States (**Joint Rapporteur**)
Dr C.-J.B. Göthe, AB Ekiatrika, Stockholm, Sweden
Dr R.E. Gots, Environmental Sensitivities Research Institute, Rockville, Maryland, United States
Dr B. Heinzow, Landesamt für Natur und Umwelt, Kiel, Germany
Dr M. Hüppe, Lehrstuhl für Psychologie der Universität, Würzburg, Germany
Prof. H. Kipen, Environmental & Occupational Health Sciences Institute, State University of New York, Piscataway, New Jersey, United States (**Chairman**)
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ANNEX C

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