

# Multiple Chemical Sensitivities

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## Terms of Reference

The objective is to produce a reference report for the Environmental Risk Management Authority (the Authority) that:

- (1) Outlines and evaluates the state of scientific knowledge with respect to the condition of multiple chemical sensitivities (MCS).
- (2) Considers the recommendations of international agencies about multiple chemical sensitivities.
- (3) Draws conclusions about how multiple chemical sensitivities should be dealt with in the context of applications under Part V of the Hazardous Substances and New Organisms (HSNO) Act 1996.
- (4) Identifies unresolved or uncertain issues in this area which either should be further investigated and/or on which future developments should be monitored.

## Method

A literature search of on-line bibliographic databases was undertaken using DIALOG for publications in English about MCS. Key words used in the search included synonyms and related terms for MCS. The search period focused on publications from January 1995 up until November 2001. Some publications outside this period have been included. Bibliographies of identified papers were also examined. Not all articles that were viewed have been cited.

Members of ERMA New Zealand's NGO Consultative Group were invited to identify any literature that may not be readily identified by a search of scientific databases.

## Summary

This summary identifies key points and draws conclusions from the report that addresses each of the Terms of Reference.

### **The state of scientific knowledge with respect to MCS**

Multiple chemical sensitivities is the term most frequently used to describe a cluster of medically unexplained symptoms. Symptoms involve multiple organ systems and often the central nervous system. This term implies that the condition affects the immune system and that chemical exposure is its *sine qua non*. This is uncertain.

A comprehensive review undertaken by Graveling et al (1999) concluded that there is some evidence to suggest that in some people chemical exposure can initiate a clinical response that recurs with subsequent exposures to very low levels of that chemical and structurally unrelated chemicals. These levels are below those known to cause toxicity in the general population. However there is a lack of objective evidence and no agreed battery of investigations.

Pesticides and solvents are the two major classes of chemicals most frequently reported as having initiated MCS. The list of chemicals that then elicit symptoms is almost limitless and they are usually, although not always, identified by odour. People with MCS may be significantly disabled in terms of their physical, occupational, and social functioning.

The best estimate of prevalence that can be derived from available data in the United States seems to be less than one percent. The prevalence in New Zealand is unknown but unlikely to be higher.

There is considerable debate over what MCS is and whether it is a single distinct entity. There is debate over whether MCS is best characterised as a biological disorder, a psychogenic disorder, or some combination of both. There is no agreement with respect to aetiology other than toxicity in the usual sense does not explain the phenomenon. Since there are no currently known biological mechanisms or anatomical alterations that can explain such effects biological explanations of MCS are often rejected.

The condition is reported only in western industrialised countries particularly the United States. This suggests that given the ubiquitous presence of the implicated chemicals it may be a culturally bound phenomenon whose existence depends on certain social or cultural conditions. It is more common in women and there is an overlap with other medically unexplained conditions such as chronic fatigue syndrome (CFS).

Although there are well-documented associations between MCS and psychological factors it is not possible to clarify whether they are the cause or effect of MCS. Of all the biological explanations proposed current evidence, though limited, is greatest for a mechanism involving sensitisation of the limbic system of the brain. This requires further research. Against this is evidence from double-blind placebo-controlled (DBPC) challenge studies that perception and cognitive processing affect responses to chemical exposure and mediate symptoms.

Many published articles contain opinion, anecdote or rhetoric rather than data. Controlled studies are rare and most studies have methodological limitations raising concerns about conclusions.

## **Recommendations of international agencies about MCS**

A number of medical professional organisations particularly in the United States have issued position statements stating that the aetiology, and diagnostic and treatment practices regarding MCS are at best unproven. Against these are the statements issued by organisations made up of environmental physicians who are proponents of MCS and some concepts that are not accepted by conventional medicine.

A World Health Organisation workshop in 1996 proposed the term “idiopathic environmental intolerances” and concluded that it cannot be recognised as a clinically defined disease but supportive care, and research to determine its aetiology, are needed.

A federal government interagency workgroup on MCS and many workshops and conferences by state governments, federal agencies and other organisations in the United States have recommended further research particularly basic epidemiological research.

In the United States the legal ramifications of MCS are far ahead of the science and MCS has been widely recognised in policy arenas. Some of the regulatory and policy actions provide criteria and terms to define MCS whereas other actions include affected individuals not by a diagnosis of MCS but as a result of their impaired functional ability.

In response to a resolution in 2000 from an independent advisory body to the US Environmental Protection Agency (EPA) calling for increased regulatory action, the EPA stated that current knowledge regarding the definition, causes and treatment of MCS was insufficiently defined to warrant such action.

## **Conclusions about how MCS should be dealt with in the context of applications under Part V of the HSNO Act 1996**

Multiple chemical sensitivities is a complex issue that raises many scientific and policy questions for which there are no simple answers.

However many substances that are implicated in MCS are outside the scope of the HSNO Act and its regulations either because they are not covered by the Act or do not meet any regulatory toxic threshold.

For those substances that fall within the HSNO regime the Authority’s decision making in relation to individual substances is based on risk management including risk assessment. With respect to MCS currently it is not feasible to carry out even the first step in risk assessment, hazard identification, due to lack of agreement about case definition, diagnostic methods, aetiology, or the nature of the adverse health effects. The HSNO risk management regime includes a range of controls to protect public health from substances with toxic properties. For additional or varied controls to be implemented under the Act to protect susceptible people valid reliable data on prevalence, causative substances, human exposures,

aetiology, dose-response relationships, and susceptible population groups are required. These data are unavailable.

Once all existing substances with toxic properties have been transferred to the HSNO regime there is likely to be much greater protection against initiation of MCS in susceptible people than from previous legislation, and some increased protection for those with MCS depending on the implicated substances. Protection for those with MCS is necessarily limited due to the large number of common substances that trigger symptoms which are outside the HSNO regime.

### **Unresolved or uncertain issues which should be further investigated and/or on which future developments should be monitored**

Much basic epidemiological information is unknown and many studies are not strictly comparable due to varying definitions of MCS. Lack of a consistently used case definition impedes needed research to obtain data to clarify incidence and prevalence, natural history, aetiology, diagnosis, and management.

A number of methodological problems limit interpretation of much of the published research. These include over-reliance on surveys and self-reported symptoms, lack of valid reliable exposure data, small sample size, selection bias, recall bias, lack of control groups, lack of blinding, and problems with laboratory tests. Until the quality as well as the quantity of scientific knowledge improves MCS is likely to remain an unexplained phenomenon.

Approaches to clinical management have paralleled aetiological theories and very little is known about the proper treatment of MCS. No treatment has been subjected to controlled clinical trials to confirm its efficacy.

## Definitions

Multiple chemical sensitivities is the term most frequently used to describe a cluster of medically unexplained symptoms. There are many synonyms and related terms for MCS in the literature (Table 1).

Table 1 Terminology

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Synonyms and related terms for MCS
environmental or ecological illness
chemical acquired immune deficiency syndrome (chemical AIDS)
total allergy syndrome
20 <sup>th</sup> century disease
cerebral allergy
chemical sensitivity
chemical intolerance
environmental hypersensitivity
toxic encephalopathy
toxicant-induced loss of tolerance
eco-syndrome <sup>1</sup>

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Although the scientific community uses the term MCS this term implies that the condition affects the immune system and that chemical exposure is its *sine qua non*. This is uncertain.

The condition was first defined and the term MCS coined by Cullen (1987). According to Cullen MCS has seven main features:

- It is acquired in relation to some documentable environmental exposure.
- Symptoms involve more than one organ system.
- Symptoms recur and abate in response to predictable stimuli.
- Symptoms are elicited by exposures to chemicals of diverse structural classes and toxicological modes of action.
- Symptoms are elicited by demonstrable exposures.
- Exposures that elicit symptoms are very low (below those known to cause adverse effects in the general population).
- There is no single widely available test of organ system function that can explain the symptoms.

In 1996 a World Health Organisation (WHO) workshop concluded that use of the term MCS should be discontinued because of its unsupported judgement on causation. The term “idiopathic environmental intolerances” was proposed instead because many people are thought to develop symptoms in response to environmental agents other than chemicals. Idiopathic environmental intolerances was defined as an acquired disorder with multiple recurrent symptoms, associated with diverse environmental factors tolerated by most people, unexplained by any known medical or psychiatric disorder, and without specific tests to diagnose the condition (Anon., 1997).

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<sup>1</sup> The term eco-syndrome coined by Ring et al (1998/99) is specific to Germany.

The most recent definition is broad and describes MCS as a chronic condition with reproducible symptoms involving multiple organ systems whose symptoms are produced by low levels (lower than previously or commonly tolerated) of exposure to multiple unrelated chemicals, and improve or resolve when the chemicals are removed (Bartha et al, 1999). This definition was based on five criteria identified in a 1989 survey of 89 clinicians and researchers who had extensive experience in MCS but held widely different views about its aetiology (Nethercott et al, 1993) with the addition of involvement of multiple organ systems to distinguish it from single organ system disorders e.g. migraine that may also meet the five criteria. These criteria are commonly included in research definitions but there is a lack of standardised use in clinical settings.

Many proponents of the concept of MCS such as environmental physicians (formerly known as clinical ecologists) find the published case definitions restrictive and inappropriate for diagnostic purposes. They also include people with reaction to one chemical only, those in which some measurable change is produced e.g. bronchospasm (Eaton et al, 2000), and all diseases judged by them to be caused or aggravated by chemical exposure. This includes many chronic diseases. The journal *Clinical Ecology* defines MCS as “a chronic multi-system disorder, usually polysymptomatic, caused by adverse reactions to environmental incitants, modified by individual susceptibility and specific adaptation”. There are some concepts that are not accepted by conventional medicine such as total load<sup>2</sup> and adaptation<sup>3</sup> that many environmental physicians consider essential to the understanding of MCS.

Some e.g. British Society for Allergy, Environmental and Nutritional Medicine (BSAENM) favour the criteria proposed by Miller (2000) for the concept of toxicant-induced loss of tolerance (TILT) for diagnosis (Eaton et al, 2000). In conventional medicine the condition mainly depends on diagnosis by exclusion.

Cullen’s case definition, though primarily developed for research purposes, is now the most widely used clinical definition. Another definition by Simon et al (1990) focuses on lifestyle changes attributable to chemicals. There is a reasonably high level of agreement between individuals who meet either of these sets of criteria. Other definitions and other names for MCS have been published but none has been validated, substantially reviewed or widely acknowledged (Kipen and Fiedler, 2000).

Lack of a consistently used case definition has impeded the epidemiological and clinical research needed to obtain the data to clarify prevalence, natural history, aetiology, diagnosis and management.

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<sup>2</sup> Total load is the total physical or psychological stress load a person is experiencing at any time. Stress factors can be physical, chemical, biological, or psychosocial. As load increases that person is believed to be more susceptible to illness. A person whose load has passed a critical limit is more likely to react negatively to additional, though low level, exposure.

<sup>3</sup> Adaptation is the development of tolerance for stressors after repeated exposure. This masks acute deterioration and as a result of repeated exposure the total load continues to increase and chronic illness or physical damage may develop.

## History

The first descriptions of MCS have been attributed by Donnay (1999) to Edgar Allen Poe in 1839 in the *The Fall of House of Usher* and in *The Tell Tale Heart* in 1843. In the latter Poe states “And have I not told you that what you mistake for madness is but overacuteness of the senses?”

The condition Poe described was not defined in medicine until 1869 when an American neurologist Beard and an American insane asylum director Van Deusen separately published papers suggesting that it should be called “neurasthenia”. Although the diagnosis had become one of the most common in urban America by 1900 reference to neurasthenia in the medical literature disappeared rapidly after the turn of the century (Donnay, 1999).

The condition re-emerged in the 1950s by an American doctor Randolph who proposed that exposure to common environmental chemicals could cause a wide variety of symptoms and initiate a pathological process that could lead to what is now referred to as MCS. Randolph went on to cofound the Society for Clinical Ecology (now the American Academy of Environmental Medicine).

Clinical ecology (now known as environmental medicine), the diagnosis and treatment of individuals believed to be suffering from disease or injury secondary to exposure to a component of the physical environment developed from these ideas. The concept is based on the idea that practically all man-made chemical substances in the environment can produce symptoms and immune reactions (Labarge and McCaffrey, 2000). In addition to the American Academy of Environmental Medicine environmental physicians also play a significant role in the American Academy of Otolaryngic Allergy (Barrett, 2000a). This group of doctors has mainly used the diagnostic label of MCS. There are similar professional organisations in Australia and New Zealand (Australasian College of Nutritional and Environmental Medicine and New Zealand College of Nutritional and Environmental Medicine).

Most of the MCS literature has been published in the last ten years including complete issues of journals on the topic.

## The Clinical Picture

Sufferers of MCS often report that they had no symptoms before one large chemical exposure which is then followed by exacerbation of symptoms in response to previously tolerated low level exposures. They often describe an inability to tolerate a wide variety of foods and medicines as well as chemicals. Intolerance is subjective and contrasts markedly to food or drug allergy in which immunologically specific sensitivity can be demonstrated and exposure to the allergen causes objective evidence of target organ inflammation (Fishbein, 1996).

There is no symptom constellation that constitutes MCS (Miller, 1996). Although almost any symptom has been attributed to MCS the symptoms generally fall into three groups: central nervous system, respiratory system or gastrointestinal system. A literature review by Labarge and McCaffrey (1997) (cited in Labarge and McCaffrey, 2000) identified 151 symptoms associated with MCS. Table 2 lists commonly reported symptoms.

Table 2 Common symptoms of MCS

Symptoms	
Headache	shortness of breath
confusion	chest pain
depression	muscle pain
inability to concentrate	joint pain
memory loss	gastrointestinal problems
dizziness	nausea
fatigue	skin problems
malaise	eye, ear, nose, throat irritation

There are no accurate data on the prevalence of such non-specific symptoms as those subsumed as being MCS among the general population (Wolf, 1996).

MCS should be differentiated from several other disorders with potentially similar symptoms or presumed aetiologies e.g. neurotoxic syndromes such as those arising from exposure to heavy metals or solvents, sick building syndrome<sup>4</sup>, or mass psychogenic illness<sup>5</sup>. MCS is generally differentiated from neurotoxic syndromes by the lack of consistent and specific effects from exposure to specific chemicals in those with MCS. Some argue that MCS is a neurotoxic syndrome but one in which the dose-response relationship and disease mechanism is not understood.

Many abnormal signs and diagnostic tests have been reported in the literature to be associated with MCS (Donnay, 1999). Waickman and Vojdani (1998) list the immunological and neurological tests that may be useful in the evaluation of MCS. However no single sign or diagnostic test is consistently abnormal in all MCS cases.

The relationship to health of immunological tests such as serum antibodies, and concentrations of most nutrients and antioxidant enzymes are unknown and as most chemicals

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<sup>4</sup> Sick building syndrome is a site-specific building related illness that includes upper airway and mucous membrane irritation and central nervous system complaints.

<sup>5</sup> Mass psychogenic illness is the collective occurrence of symptoms and related beliefs in the absence of an identifiable pathogen that spreads within specific social networks.

of interest e.g. solvents, heavy metals, organochlorines are widespread their demonstration in affected people is of limited value. Such tests may be used as biomarkers of MCS only when a difference is shown between affected and unaffected people (Cullen and Redlich, 1995). Many investigations have relied on case series of affected individuals without reference to a larger normative population or appropriate controls.

Many people with MCS report cognitive impairment such as memory loss and difficulty concentrating. Few studies involve neuropsychological evaluation and those that do suggest there is little difference from controls (Fiedler et al, 1996). Where MCS patients perform more poorly than controls or normative samples data do not indicate a consistent or specific pattern of neuropsychological deficits (Labarge and McCaffrey, 2000).

Function neuroimaging (e.g. positron emission tomography, single photon emission computed tomography) shows non-specific alterations and no consistent pathological findings (Bornschein et al, 2001).

The heterogeneity of symptoms and the lack of unique identifying physical findings in published investigations have increased scepticism about the existence of MCS.

## Epidemiology

The area of MCS is dominated by clinical case reports (e.g. Eaton et al, 2000; Kipen and Fiedler, 2000). These focus on symptoms in patients with health problems that might be elicited by a range of different initiating exposures or events which has added to the difficulty in understanding its aetiology (Ashford, 1999).

There is a lack of information, even in the United States where MCS has been most widely studied, on the population prevalence of people who report sensitivity to a chemical or many chemicals, or who report a doctor's diagnosis of MCS, and the demographic or other variables associated with these reports.

Some studies relate to the symptom of chemical sensitivity or intolerance<sup>6</sup> rather than specifically MCS. It is not known how many, if any, of these people may develop MCS. Miller (1996) argues that chemical sensitivity may also be insensitive as an indicator of illness associated with low level chemical exposure as affected individuals may not be aware they are chemically sensitive e.g. migraine sufferers.

Cases have been identified in studies on the basis of questions regarding feeling unwell from specific chemical odours, certain symptoms attributable to chemicals, lifestyle changes in response to perceived chemical sensitivity, and receiving a doctor's diagnosis of MCS. Mild MCS-like conditions, which may not represent alterations from background are common in the general population. However the sensitivity described seems distinct from that reported in MCS with few symptoms, involvement of the upper respiratory system, and resolution within one hour (Davidoff and Keyl, 1996).

Validated questionnaires have been developed (Kipen et al, 1995; Miller and Prihoda, 1999a; McKeown-Eyssen et al, 2000). McKeown-Eyssen et al (2000) evaluated the reproducibility of a self-administered questionnaire (the University of Toronto Health Survey) with respect to seven published case definitions including the 1999 consensus definition. Good reproducibility was achieved for all the definitions including 90 percent for the 1999 consensus definition.

Miller and Prihoda (1999a) found that the Environmental Exposure and Sensitivity Inventory that includes five dimensions relevant to chemical sensitivity discriminated between chemically sensitive individuals and controls (92 percent sensitivity and 95 percent specificity).

The questionnaire developed by Kipen et al (1995) was used among MCS cases and controls to develop a brief questionnaire for screening for MCS e.g. in large population samples that have multiple study objectives. Seven items to which exposure most differentiated cases from controls were identified. Further studies are needed to confirm this in case there are subgroups of people with MCS who have different patterns with respect to the exposures to which they react (Hu et al, 1999).

Prevalence estimates are generally not strictly comparable across studies as not all studies have used case definitions and those that have have not all used the same definition. Some

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<sup>6</sup> Chemical intolerance (cacostmia) involves feeling unwell (e.g. headache, nausea) from chemical odours that have no adverse effects on normal individuals.

case definitions have not been specifically tested for reliability or for evidence of validity in other settings. Odour of chemicals is poorly correlated with toxicity and hence estimates based only on reports of illness due to odours have little validity.

There is a discrepancy between an individual's self-report of suffering from MCS and meeting research operational criteria. For example only 30 percent of those who self-reported MCS met study criteria for MCS (Reid et al, 2001). Operational definitions and self-reported diagnoses are two almost completely different entities which has implications for epidemiological studies in which the diagnosis is made by self-report. The best estimate that can be derived from available data in the United States seems to be less than one percent.

MCS has been reported only in western industrialised countries despite the ubiquitous presence of implicated chemicals. The diagnosis of MCS is common in the United States, Canada, and Germany in contrast to the United Kingdom (Reid et al, 2001). It has been suggested that this reflects a lack of awareness of MCS in the United Kingdom but it is also possible that the prevalence in the two countries is different.

There have been no community-based studies of prevalence in the United Kingdom (Eaton et al, 2000) although MCS has been reported in British military personnel including Gulf War veterans (Reid et al, 2001). Estimates of population prevalence are also unknown for other European populations (Graveling et al, 1999) and other countries including New Zealand. Within Europe there also seem to be regional differences in prevalence e.g. higher in Germany than France (Bornschein et al, 2001).

In New Zealand "poisoning arising from chemical contamination of the environment" is a notifiable disease under the Health Act 1956. Such notifications to the Medical Officer of Health are rare probably reflecting a lack of acceptance by doctors that diagnostic criteria for this condition have been met as well as under-reporting.

Some of the implicated chemicals such as solvents and pesticides are reported from both Europe and North America although within Europe there are differences that may relate to use patterns. For example, pesticides are not frequently cited in Sweden, Finland and the Netherlands and pentachlorophenol is cited in Germany (Ashford, 1999). In both Europe and North America patients report spreading of their sensitivities to a variety of common exposures including fragrances, cleaning agents, engine exhaust, alcohol, and foods and medicines they formerly tolerated without problems.

Cultural practices such as time spent indoors, and differences in building construction materials and furnishings, ventilation practices and use of chemicals may affect prevalence (Ashford, 1999).

Susceptible risk groups are not yet clearly defined. MCS seems to be less common among populations who might be presumed to be more at risk e.g. those working with chemicals. The question of whether MCS is becoming more or less common is also unanswered as is the question of whether it is preventable.

No studies have been identified that prospectively examined the onset of MCS (Aaron and Buchwald, 2001) and there are few longitudinal data.

The most rigorous published epidemiological survey to date was that of Kreutzer et al (1999). Questions about chemical sensitivity were included in the California Department of Health

Services' 1995 Behavioural Risk Factor Survey, an annual telephone survey of randomly selected adults which collects information on a variety of health-related behaviours. Six percent of respondents reported doctor-diagnosed MCS and 15.9 percent stated they were unusually sensitive to everyday chemicals. Which of these symptoms are disease and which are part of general living is unclear (Kipen and Fiedler, 1999). Less than one percent (n=25) of the sample was identified as approximating patients described as MCS sufferers in medical clinic settings. These individuals reported perceived unusual sensitivity to chemicals, a doctor's diagnosis of chemical sensitivity, and a health problem that restricted their daily activities (Kreutzer et al, 1999).

The average annual incidence over the past five years (a time interval presumed to have less recall bias) was 3.6 per 1000. More females reported doctor-diagnosed MCS (7.7 percent compared to 4.5 percent) and perceived chemical sensitivities (16 percent compared to 6.9 percent). Most respondents (76.7 percent) reported age at onset at 30 years or less. Reports of doctor-diagnosed MCS and self-assessed chemical sensitivities were distributed homogeneously across ethnic, geographical location, education, marital status, income, and employment status categories (Kreutzer et al, 1999).

Thirty-three percent (n=336) of a randomly selected rural North Carolina population self-reported chemical sensitivity. Four percent reported daily occurrence of symptoms of chemical sensitivity and 18.2 percent reported chemical sensitivity without allergy (Meggs et al, 1996).

Twenty-eight percent of College students enrolled in an introductory psychology course considered themselves to be particularly sensitive to certain chemicals and 0.2 percent (n=2) reported a doctor's diagnosis of MCS (Bell et al, 1996).

Only 1.8 percent of patients treated in a five year period at an occupational and environmental clinic that is a referral centre for MCS met the Cullen definition of MCS. The rate in the general population is likely to be much lower (Mooser, 1987).

Kutsogiannis and Davidoff (2001) carried out a cross-sectional survey of patients visiting eight traditional medical and three clinical ecological practices (11 outpatient occupational, otolaryngology, allergy, and clinical ecological clinics) in the United States and Canada to evaluate two sets of criteria for defining MCS – one based on six domains representing widely considered characteristic features including relatively severe manifestations and a less stringent four-domain definition.

Patients visiting traditional doctors and ecologists had similar health status. Seven percent met criteria for the six-domain definition and 23.3 percent met criteria for the four-domain definition. Prevalence was highest among patients seen by clinical ecologists followed by occupational physicians then allergists and lowest among patients seen by otolaryngologists. The high prevalence is likely to have been affected by study exclusion criteria, inclusion of clinical ecological practices and above average interest in MCS of the participating doctors who therefore may have attracted a large proportion of such patients.

Irrespective of the criteria used doctors' diagnoses had low sensitivities (range 6-50 percent) and high specificities (range 82-99 percent). Prevalences based on doctors' diagnostic criteria for MCS were lower than the prevalences based on the patient questionnaire data. Traditional doctors were more specific than ecologists irrespective of whether six- or four-domain

questionnaire based criteria were used suggesting that ecologists are more likely to falsely diagnose MCS (Kutsogiannis and Davidoff, 2001).

In 1997-1998 the prevalence of MCS in British military personnel who served in the Gulf and Bosnia, and during the Gulf War but were not deployed there was 1.3 percent (95% CI 1.0-1.7), 0.3 percent, and 0.2 percent respectively. In Gulf veterans, MCS was strongly associated with exposure to pesticides (adjusted odds ratio =12.3, CI 5.1- 30.0). Theories about MCS would suggest that other chemical exposures e.g. solvents should be similarly associated with symptoms, but media coverage in the United Kingdom has been largely confined to pesticide exposure suggesting recall bias may be relevant (Reid et al, 2001).

Thirty percent of a small sample of randomly selected Department of Veterans' Affairs outpatients who were Gulf War and Gulf War era veterans reported chemical sensitivity. The ill Gulf War subgroup had the highest prevalence of current self-perceived chemical sensitivity and significantly higher ratings for both pre-service and current frequency of chemical odour intolerances compared with the healthy Gulf War subgroup (Bell et al, 1998).

Thirty-six percent of a randomly selected sample of Gulf War veterans on the Veteran Affairs' Gulf War registry considered themselves unusually sensitive to certain chemicals and 13.1 percent (n=131) met a conservative case definition for MCS reporting at least three of four possible lifestyle changes. Demographic and military characteristics of the Gulf War veterans who met criteria for MCS were generally not significantly different from those of all respondents apart from significantly increased risk of MCS in women and in African American veterans (Kipen et al, 1999).

Three percent of a randomly selected sample from Iowa Gulf War era military personnel met study criteria for MCS. Two percent reported having received a doctor's diagnosis of MCS. Deployed military personnel were nearly twice as likely as non-deployed military personnel to report symptoms suggestive of MCS (Black et al, 2000).

Davidoff et al (1998) followed up a small random sample of a cohort of male primarily low socioeconomic status workers who had been exposed to gasoline fumes for up to two months whilst excavating a tunnel. None identified their symptoms as MCS at the time of contact. Ten to 13 months after the tunnel was shut down 33 percent (n=10) reported three or more heightened or new sensitivities since the exposure but no sensitivities preceding the exposure. Eight of the 10 (26.7 percent) met the Cullen criteria for MCS.

Four groups of MCS subjects who reported different sensitising exposures (onset from industrial organic solvents, organophosphate pesticides, sick building syndrome, and chlorine dioxide) had very similar general and specific indices of illness and sensitivity to chemicals despite considerable diversity in socioeconomic status, education, gender, and reporting of sensitising exposure. Collectively the MCS groups were significantly different from the general population on all symptom categories, except diagnosed autoimmune disorders, and significantly different from the general population with respect to all general health and illness status variables (Davidoff and Keyl, 1996).

The typical patient profile in MCS studies is a middle-aged well-educated female. Although frequency peaks in middle age young as well as older people report symptoms consistent with MCS. There are few case reports of children in the scientific literature (Woolf, 2000).

Clinic-based studies tend to report high socioeconomic status as a characteristic. The socioeconomic distribution of MCS in specialist clinics, which is the reverse of that expected if MCS is an occupational disease, may be a result of referral and/or selection bias. This is supported by the lack of association found in community-based studies (Kreutzer et al, 1999).

Joffres et al (2001) found higher severity scores in women, participants who were separated or divorced, and in low income groups. Although this study's response rate was only 47 percent similar findings in relation to low income were found by Kreutzer et al (1999). This may reflect loss of employment due to severity or stressors that predispose to the development of MCS.

Miller and Mitzel (1995) found that pesticide exposed (organophosphate or carbamate pesticide) and building renovation exposed MCS groups reported similar symptom patterns and identified similar symptom triggers. The pesticide exposed group reported significantly greater symptom severity. The authors concluded that a possible biological basis and distinct pathophysiology appeared to be common to both groups and features were inconsistent with a somatoform disorder. However this study had a number of significant methodological limitations including a self-selected sample, a 54 percent response rate, and no verification of exposure.

Pesticide exposure is widely considered to be a precipitant of MCS although there is no conclusive evidence for this. The list of chemicals that subsequently trigger symptoms is almost limitless. They are usually, although not always, identified by odour. The most common chemicals cited are perfume and scented products, pesticides, solvents, new carpet and furnishings, vehicle exhaust, and tobacco smoke.

Lax and Henneberger (1995) identified 35 new patients seen at an occupational health clinic from 1989-1991 that met a case definition similar to that of Cullen. They were predominantly female (80 percent) and in the 36-50 years age category. Nervous system symptoms were the most frequently reported and the most common exposures were occupational exposures to solvents (31 percent), poor indoor air quality and building renovation. Forty percent of MCS patients worked in service industries (compared to 20 percent of non-MCS patients).

In a small case control study by Hu et al (1999) 84 percent of cases reported that MCS was initiated by occupationally based exposures. Exposure to unspecified indoor air contaminants (59 percent) was the most common initiating exposure followed by solvents (27 percent) and pesticides (4.5 percent). Controls were more likely to be employed but there were no significant differences with respect to occupational attainment and educational status. Miller and Prihoda (1999b) found the most frequently reported initiating events involved exposures to solvents and cleaners (54 percent), indoor air contaminants (45 percent), and pesticides (24 percent).

The gender difference could reflect a biological difference (e.g. diseases such as multiple sclerosis and systemic lupus erythematosus are more common in women), cultural differences where men under-report, or more severe responses in women than men. Relatively little attention has been paid to the extent to which chemical sensitivity is a function of other medical or psychiatric conditions. Rates of self-reported sensitivity among patients with chronic fatigue syndrome, Addison's disease and seasonal affective disorder have been reported to be higher than healthy controls (Nawab et al, 2000).

There is marked overlap between MCS and other medically unexplained conditions such as CFS, fibromyalgia (FM) and sick building syndrome (Aaron and Buchwald, 2001; Bornschein et al, 2001). Sick building syndrome is considered by some to constitute a less fully expressed pattern of MCS.

Jason et al (2000) found that 14.4 percent of those they diagnosed with MCS also met criteria for CFS and 8.9 percent also met criteria for FM. Seventy-six percent had MCS alone indicating that MCS is more likely to exist without any other co-existing condition. Higher percentages of co-existing diagnoses have been found in other studies but these may be influenced by sample selection from a medical clinic whereas this study was community-based. The findings may also have been influenced by the study's selection criteria that focused on identifying people in the general population who had chronic fatigue and at least four other minor symptoms associated with CFS. This group and a control group then received medical and psychiatric examinations, and a proportion was then diagnosed with CFS, FM, and/or MCS. However a similar proportion (15.2 percent) of cases defined as MCS among British military personnel met the criteria for CFS (Reid et al, 2001).

## Follow Up

There is a relative lack of longitudinal data on MCS. Multiple chemical sensitivities is not known to be progressive in terms of measurable physical dysfunction or development of medical complications. Symptomatic reactions to chemicals tend to persist although some patients learn to cope and reach relatively normal levels of functioning (Kipen and Fiedler, 2000).

Black et al (2001) carried out a nine year follow up study comprising structured interviews and self-report questionnaires of 18 MCS patients. Most had improved since the original evaluation but many remained symptomatic and reported ongoing lifestyle changes particularly avoidance. All still believed that they had MCS though most acknowledged that the diagnosis was controversial.

The frequency of psychiatric diagnoses at follow up was higher – 83 percent met DSM-IV<sup>7</sup> criteria for a lifetime mood disorder, 56 percent for a lifetime anxiety disorder and 56 percent for a lifetime somatoform disorder. None met current or lifetime criteria for a substance use disorder (Black et al, 2001).

Among 35 people with work-related MCS almost half reported that their MCS had improved from the time of the original evaluation to a follow up telephone interview on average 1.4 years later. This was despite an average of 7.4 more symptoms at follow up than at presentation. Most had made lifestyle changes (Lax and Henneberger, 1995).

Ring et al (1998/99) report two-thirds of 23 patients followed up for two to four years reported improvement or disappearance of their symptoms. Eaton et al (2000) reported that most patients improved during a three week admission to the United Kingdom's environmental unit<sup>8</sup> and remained improved when followed up at least six months later, but provided no details as to the number of patients, their characteristics, and how improvement was measured.

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<sup>7</sup> DSM-IV, the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders 4th edition is the current psychiatric diagnostic classification.

<sup>8</sup> The United Kingdom's only environmental unit, the Airedale Allergy Centre, opened in 1985 as a private venture and closed in 1999 due to a change in NHS funding arrangements.

## **Aetiology**

Many theories have been proposed to explain MCS with the debate focussing on whether its aetiology is biological, psychogenic, or a combination of both. Twenty-four possible mechanisms were identified in a recent review (Winder, 2002).

The medical profession tends to reject a biological mechanism for MCS because it conflicts with current knowledge about the causes of diseases. Similar debates have existed regarding the status of disorders that were once not fully understood, were difficult to diagnose, and often accompanied by psychological symptoms e.g. systemic lupus erythematosus.

Debate over its aetiology dates back to the first descriptions of MCS. In 1869 both Beard and Van Deusen interpreted neurasthenia as an organic brain disorder which they attributed to the technological and social stresses of the time such as the steam engine, telegraph, printing press and the higher education of women. Its biological aetiology was debated as no brain or other lesion could be found and it was gradually reinterpreted by conventional medicine as psychogenic. The rapid disappearance of reference to neurasthenia in the medical literature after the turn of the century has been linked to the phasing out of the use of illuminating gas (Donnay, 1999) but this is unproven.

On the basis of published data including case reports there is some evidence to suggest that in some people chemical exposure can result in a clinical response to very low levels of that chemical or structurally unrelated chemicals. Graveling et al (1999) state that whether this evidence is convincing or not depends on the diagnostic criteria used. If existence depends on consistent results from validated objective tests then no such data are available for MCS. In psychological and some physical diseases, particularly those affecting the central nervous system, a diagnosis is often made on the basis of consistent symptoms and observed changes in a person's functioning. Using these criteria then there is evidence that some people report consistent symptoms that recur on exposure to the same or structurally unrelated chemicals. Graveling et al (1999) comments that the evidence is more convincing in those cases where the illness has resulted in disability with no apparent benefit. On the other hand use of MCS as an umbrella term that results in misdiagnosis of other conditions diminishes the evidence (Graveling et al, 1999).

The various aetiological mechanisms commonly proposed to account for MCS are reviewed briefly in the following sections.

### ***Psychogenic theories***

There is a tendency by some to regard a psychogenic origin as the default explanation because MCS does not fit current knowledge regarding disease mechanisms. This is presumptuous when other plausible mechanisms still require investigation. The tendency to classify disease as either biological or psychogenic is also a simplification when in fact the boundaries are less well defined and often there is an interplay of psychological and biological factors in pathogenesis and the emergence of symptoms.

Gots and Pirages (1999) conclude that current evidence suggests psychogenic explanations predominate for MCS and a pure biological theory requires a major paradigm shift. Another proponent of psychogenic explanations states: "The argument for a paradigm shift at the

beginning of this millennium would have us displace objective science with belief and perception and reverse the Renaissance” (Staudenmayer, 2001).

Critics of biological theories argue that psychosocial and psychophysiological factors are necessary and sufficient to explain MCS. Some claim that the studies that did not find a premorbid psychiatric history had flawed diagnostic methods and were possibly biased but do not corroborate their claims.

Psychogenic theories receive negative comment in much of the literature on MCS. However such explanations do not exclude the possibility of biological factors. Some authors such as Bell who support a biological explanation do also acknowledge the involvement of psychological factors.

## **Psychiatric disorder**

Proponents of the psychiatric disorder theory take the relatively high incidence of anxiety or depression as evidence that the symptoms of MCS are psychogenic. Proponents of biological theories argue that psychiatric disorders are the result of the disorder and not a risk factor, or represent misclassification. They note that chronic, debilitating illness can lead to depression, anxiety, or unexplained physical complaints and that these same symptoms could be induced by the biological mechanisms underlying MCS. They do not explain why those with MCS often have psychiatric morbidity that precedes the presumed initiating chemical exposure and the subsequent development of MCS. Although a premorbid psychiatric history can be used to counter the argument that the symptoms are an effect of MCS rather than causal this could indicate a higher sensitivity to MCS among those susceptible to psychiatric disorders.

Specific psychiatric diagnoses that have been proposed to account for MCS include somatoform disorder<sup>9</sup>, depressive disorder, post-traumatic stress disorder and panic disorder.

Bornsche in et al (2001) reviewed studies examining psychiatric disorders in MCS. In the eight studies psychiatric disorders were found in 36-100 percent of patients. The number of study subjects and diagnostic methods varied among the studies.

The biological basis of reactions to chemicals appears similar to those occurring in panic disorder (Binkley and Kutcher, 1997). Similar to patients with panic disorder those with MCS in a blinded study experienced heightened anxiety and panic attacks compared to healthy controls in response to inhaled carbon dioxide (Poonai et al, 2000).

A study comparing the results of self-report psychological questionnaires measuring anxiety, depression, stress, and agoraphobia in cases and controls with no pre-existing psychiatric history found that cases had significantly higher morbidity than controls but less than what would be expected for a clinical psychiatric population with panic disorder, depression and agoraphobia. The authors concluded that MCS may represent a group whose psychiatric morbidity is intermediate between a clinical psychiatric population and a non-clinical population (Poonai et al, 2001).

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<sup>9</sup> The essential features of somatoform disorder include a history of physical complaints involving one or more organ systems that cannot be fully explained by known general medical conditions.

Tonori et al (2001) found no difference on anxiety and depressive scores between MCS patients and controls at the time of the initial examination among those visiting an ophthalmologist but significantly higher mean anxiety and depressive scores in MCS patients at the follow up examination. In contrast scores in controls had decreased to a normal level at follow up.

Labarge and McCaffrey (2000) conclude from a review of studies investigating psychological factors that MCS comprises a heterogeneous group of people exhibiting a range of psychological disorders in which the manifestation of symptoms is mediated by actual or perceived chemical exposure. The review suggests that many with MCS have a history of physical or psychological problems that existed prior to the alleged initiating chemical exposure and often these pre-existing problems can account for the symptoms attributed to MCS. However the authors also acknowledge that there appears to be a subgroup with a diagnosis of MCS whose history does not account for current symptoms.

There were no significant differences in psychiatric history and status between four MCS groups with different reported sensitising exposures and between the groups collectively and the general population. Compared to the general population the MCS subjects had higher negative affect scores. The authors concluded that differences were more related to the presence of illness than psychiatric history (Davidoff and Keyl, 1996).

Among Gulf War era veterans those with symptoms suggestive of MCS had a higher prevalence of current psychiatric symptoms and disorders and a high prevalence of anxiety disorders, particularly panic disorder. After adjusting for age, sex, and training preparedness, previous professional psychiatric treatment and previous psychotropic medication use showed a strong association with symptoms suggestive of MCS (Black et al, 2000). MCS among British military personnel was also found to be associated with high levels of psychological morbidity (Reid et al, 2001).

Clauw (2001) argues that the type of study sample used e.g. general population versus tertiary care, or the case definition may predict the relative importance of psychological factors. Most investigators use a variation of the Cullen definition which requires lifestyle change. This may lead to an increased rate of psychiatric comorbidity in the study population than if the illness was defined on the basis of symptoms alone.

Joffres et al (2001) argue that the type and consistency of symptoms experienced after exposure particularly symptoms commonly associated with irritation may not fit a solely psychogenic origin as more random symptom distribution would be expected. Davidoff and Keyl (1996) also concluded that if MCS were primarily psychogenic more diverse symptoms would be expected as would consistent signs of illness at a younger age.

## Conditioning

Classic Pavlovian conditioning<sup>10</sup> offers a mechanism whereby somatic responses can be produced in response to apparently inappropriate stimuli. Many case reports support the

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<sup>10</sup> Pavlovian conditioning is a process by which a neutral conditioned stimulus (CS) is paired with a biologically significant unconditioned stimulus (UCS). At the start of conditioning the unconditioned stimulus elicits some response. As a result of CS-UCS pairings the CS becomes associated with the UCS and a response emerges to the previously neutral CS.

theory of a conditioned response leading to MCS. Olfactory cues like taste are effective conditioned stimuli. Individuals with a conditioned response to a stimulus can have neurophysiological correlates of that response e.g. EEG changes.

Siegel (1999) argues that it is likely that some MCS patients have acquired a conditioned response at the time of a chemical exposure. Conditioned responses can generalise and be induced by stimuli that have never been paired with the conditioned stimulus. Typically the greater the similarity between a new stimulus and the conditioned stimulus, the stronger the generalised conditioned response.

Van den Bergh et al (2001) found that after a few breathing trials containing CO<sub>2</sub> enriched air as an unconditioned stimulus in a compound with harmless smelling substances as conditioned stimuli, subjective symptoms were elicited and respiratory behaviour was altered by the odours only. The learned symptoms generalised to new odours. In other experiments the authors have shown that learned symptoms were easily reduced in a procedure involving a series of unreinforced conditioned stimuli exposures.

Conditioning may account for some cases but the response pattern for conditioning in terms of the type and pattern of response is not fully consistent with that reported by many patients with MCS.

## **Belief systems**

By analogy with the placebo effect Bock has termed the belief of being adversely affected by chemicals as the nocebo or negative placebo effect. Expectancy and reinforcement of the nocebo effect play an important role in generation of nocebo reactions and strong negative expectations cause endocrine and behavioural changes (Bock and Birbaumer, 1997).

Some also suggest symptoms are fostered by an iatrogenic belief system established by those providing treatment particularly environmental physicians.

Davidoff and Keyl (1996) examined data on interviewed MCS subjects from four different exposure groups who had and who had not been in contact with a clinical ecologist. Those treated by ecologists had more changes in tolerance and more musculoskeletal complaints. The two groups were not differentiated by indicators of general health, illness, and chemical sensitivity, or by average number of symptoms attributed to chemical exposures. The congruence found in self-reports of the chlorine dioxide onset MCS group (none of whom had been seen by a clinical ecologist, labelled their condition as MCS or appeared to be aware of media coverage of MCS) and ecologist untreated subjects from other groups and among ecologist treated and untreated subjects contradicts the view of some that MCS is an “invention” of clinical ecologists (Davidoff and Keyl, 1996).

Negative information about the consequences of exposure has been shown in a study by Dalton and co-workers (cited in Dalton and Hummel, 2000) of healthy people to increase symptom reporting. Positive information about benefits of exposure has been shown to reduce symptom reports and perceived irritation below the baseline response when no information is provided. The authors suggest efforts to provide education and communication addressing the

relationship between odour, irritation, perceived toxicity and actual health risk may be of value for those with MCS.

## ***Biological theories***

Any biological theory has to explain why MCS is not more prevalent among groups with higher chemical exposures and account for the apparent lack of a direct dose-response relationship.

## **Immunological disorder**

Immune dysfunction is one of the most commonly held theories among those who maintain a biological explanation.

If a substance acts as an allergen a specific cell or antibody mediated response develops so the body recognises the antigen or one with the same structure. It is difficult to explain how structurally different chemicals could result in such diverse symptoms and organ involvement due to an adverse effect on the immune system (Gad, 1999). Proponents of hypotheses proposing a role for immune system involvement maintain that MCS is distinct from allergy or propose an alternative type of allergic mechanism (e.g. Eaton et al, 2000). There is no agreement on mechanisms of immune system effect (Thomas, 1998) but it cannot be excluded that some patients suffer from hypersensitivity reactions elicited by not yet detected mechanisms (independent of IgE) or unknown or not measurable triggers (Ring et al, 1998/99).

Most of the papers in this area present collations of clinical immunological test results e.g. white blood cell, lymphocyte and T cell counts rather than results from experimental studies. A review of studies involving immunological testing of individuals with MCS found no consistent evidence that supports immunological involvement in the aetiology or maintenance of MCS or of immunological abnormality as a consistent finding (Labarge and McCaffrey, 2000).

Problems with these studies included lack of standardisation of protocols, wide variation in test results within and between patients, lack of control for variables that influence the immune system (e.g. stress, smoking) and lack of concordance in reports of immune function response (Gad, 1999). Some proponents argue that the variable pattern found is due to factors such as total body burden, adaptation and biochemical individuality. The lack of consistency in response both between and within individual MCS patients limits the plausibility of this theory.

Where immunological abnormalities are found it is important to show reproducibility of the results in studies using appropriately matched controls and to take into account normal variability in cellular immunological profiles.

Eaton et al (2000) propose that some chemicals may be acting as immunological adjuvants that increase and modify the response of the immune system to any allergens present. No evidence other than circumstantial is provided.

## Respiratory disorder or neurogenic inflammation

The theory of neurogenic inflammation suggests MCS may be initiated by interaction of chemical irritants with sensory nerves. Inhaled chemicals bind to receptors on sensory nerve C-fibres which triggers the release of inflammatory mediators from nerve endings leading to altered function of the central nervous and respiratory systems. There is some evidence in animals for this theory though similar studies in humans do not generally support it (Gad, 1999).

Meggs (1999) believes that the central nervous system mediates switching of the site of inflammation from the site of the stimulus. It is proposed that if a person has an irritant reaction to a chemical it may be that they become conditioned to also react to the odour which can have a threshold orders of magnitude lower than the irritancy threshold.

MCS patients report a greater than normal sensitivity to odours. This has led to the hypothesis that intranasal chemoreceptive senses are involved in the pathophysiology. It has been proposed that those with MCS may have a lower olfactory threshold and higher awareness of chemical air contaminants. Measurement of their chemosensory function did not detect abnormalities in terms of olfactory hypersensitivity (Doty, 1994).

The most rigorous study to date that does not support a biological explanation involved 20 doctor referred MCS patients who were exposed to a single chemical exposure in an environmental unit using a DBPC challenge test. Based on symptom reporting participants were unable to reliably differentiate active agents from the placebo (clean air). Sensitivity, specificity and efficiency ratings for each participant did not show a reliable response pattern across the series of challenge tests (Staudenmayer et al, 1993). The study's main limitation was the lack of a period in the environmental unit before the challenge testing.

Hummel et al (1996) carried out DBPC provocation studies with the solvent 2-propanol and room air at sub-threshold levels on 23 cases and a group of healthy controls. Olfactory thresholds of the cases were not significantly different from controls. Nasal volume did not change significantly in relation to the 2-propanol challenge for either group, challenges with 2-propanol did not produce effects on chemosensory function that differed from challenges with room air, and there were no differences between cases and controls following exposure in either condition.

Dalton and Hummel (2000) found that differences between cases and controls regarding reactions to intranasal challenge appear to reflect changes in cognitive processing rather than differences in sensitivity or chemical sensory processing. When olfactory function was assessed objectively cases appeared to show normal sensitivity to threshold concentrations and decreased responses to supra-threshold stimuli. When sensitivity to odours was assessed subjectively they appeared to be more responsive and experience more adverse effects than healthy controls. They propose several mechanisms that may account for the adverse responses of MCS patients to odour and which can result in changes in autonomic responses such as respiration, heart rate, and blood pressure.

Doty et al (1988) found no significant differences between cases and controls for odour thresholds for phenyl ethyl alcohol and methyl ethyl ketone. There was significantly higher total nasal resistance and higher respiratory rate in cases than controls. Increased nasal resistance was also reported by Meggs and Cleveland (1993) as well as altered nasal mucosa.

Evidence of nasal or upper airways involvement in some groups of MCS patients cannot alone account for the multiple organ system involvement and theories have been proposed to explain transmission of effects to other organ systems.

Bolt and Kiesswetter (2002) suggest that olfactory and cognitive processing models together explain why multiple and structurally unrelated chemicals trigger similar symptoms.

### **Limbic kindling and neural sensitisation**

Connections between the olfactory nerve, limbic system and hypothalamus may be important when chemicals trigger a response involving multiple systems. Chemicals enter the central nervous system via olfactory and limbic pathways. Absence of a blood-brain barrier in the olfactory system could allow direct access of chemicals through the nasal mucosa to the olfactory nerve. Olfactory and limbic systems are anatomically linked and directly and indirectly are involved in regulation of cognitive, endocrine and immune functions. In this hypothesis chemical exposure could elicit permanent changes in limbic and neuronal activity and alter a range of behavioural and physiological functions.

It has been suggested that neural sensitisation can occur by kindling and non-kindling (time dependent sensitisation) mechanisms. Animal studies show olfactory and limbic pathways are susceptible to kindling and that acute administration of a high dose or intermittent repeated low dose chemical exposure cause limbic kindling. Kindling is the ability of a stimulus previously unable to induce a seizure to later induce one and this response is amplified depending on the time between stimuli. Kindling without a seizure has been shown to cause affective behaviour changes in animals. It is proposed that it could amplify reactivity and lower the threshold response to low levels of chemicals.

In these studies animals repeatedly exposed to seizure-inducing chemicals or electrical stimulation have been found to develop lower thresholds for seizure induction than thresholds observed before exposure. With other stimuli, animals have been found to have an amplification of the response to the stimulus over time.

On the basis of these animal studies it is assumed that chemicals might be able to produce features of MCS. However there are also too few animal sensitisation studies with adequate exposure substances and adequate exposure levels (Kiesswetter, 1998/99). Kindling has not been reported in animals at the low doses alleged to cause MCS. If kindling is part of the aetiology of MCS a higher prevalence of MCS than currently exists in people with higher levels of chemical exposure might be expected (Magill and Suruda, 1998).

Neural sensitisation has been contrasted with conditioning as a potential model. The sensitisation model requires reactivity to an initial exposure whereas a conditioning model does not (It requires a new response is learned to the chemical exposure).

Bell et al (1997) outline a research plan involving human case control and longitudinal studies and animal studies which would test the neural sensitisation hypothesis and also differentiate between sensitisation and conditioning.

This theory is plausible and there is indirect supportive evidence from animal studies and studies on humans with chemical odour intolerance (cacosmia). Cacosmia is seen as a human

model for studying MCS that offers the opportunity to avoid the sampling biases common to earlier MCS studies.

Arnetz (1999) suggests that different environmental stressors, including psychosocial stress, act as initiators and after initiation the limbic system and other parts of the brain become sensitised and hyperactive to triggers e.g. odour. According to this model elicitation occurs at lower levels if other environmental exposures such as noise or stress co-exist with the chemical exposure.

Among the theories suggesting a biological explanation limbic kindling and its associated processes cannot as yet be excluded. This theory gives an explanation for a sensitisation process and allows for the effects of co-existing or pre-existing psychological factors. To confirm or refute this theory more research is required into the role of the human limbic system (Graveling et al, 1999). No papers were identified attempting to refute this explanation.

## **Biochemical explanations**

Biochemical mechanisms have also been proposed. For example, individuals who have genetically or nutritionally defective enzyme detoxification systems might be more susceptible to low level chemical exposure (Gad, 1999).

Environmental physicians claim that increasing quantities of essential nutrients are used as the load on detoxification from chemicals increases. If the amount of nutrients is insufficient excretion of chemicals is impaired and growth, repair and immune system function may be impaired which increases the health risk from even low exposures (Eaton et al, 2000).

Chemical exposure can cause or trigger disorders in haem synthesis (porphyria) which has led to some attributing MCS to this. There is no convincing evidence that there is or is not increased prevalence of abnormal measures of haem synthesis associated with MCS.

## **Toxicant-induced loss of tolerance**

Miller (1996) argues that chemical sensitivity may be more accurately described as a class of diseases like infectious diseases which share a common general mechanism but the members of which may involve different symptoms, agents and pathophysiological pathways. Between classes symptoms are quite similar e.g. rashes, headache, diarrhoea but the specific diseases within classes have recognisable symptom constellations that facilitate diagnosis.

Miller (1997) proposes a new theory of disease, TILT, to explain MCS in toxicological terms. An initial loss of tolerance caused by chemical exposure is followed by apparently disproportionate responses to exposure to other substances. No mechanism is proposed to account for the initial loss of tolerance or the apparent spread of sensitivity to other unrelated chemicals. It is suggested a specific response to a specific toxicant may be masked by responses to other exposures still affecting the person and hence false responses may occur if the person is exposed to test substances in an environmental unit before cleared of those masking responses. Masking helps explain why symptoms vary between people and from one

day to the next in the same person. Much of the supportive material is drawn from studies on other populations such as those with addictions or is anecdotal (Miller, 2000).

### ***Psychogenic or biological?***

The relationship of MCS symptoms to chemical exposure does not meet accepted toxicological principles. Current evidence and biological theories do not meet the criteria used by epidemiologists to establish a causal relationship such as strength, consistency and specificity of association; temporality; biological gradient; plausibility; coherence; experimental evidence; and analogy. Miller (1996) argues that the criteria are met or that the required research has yet to be done.

The literature reflects a lack of certainty in the area and no recognition or acceptance of any single disease entity or mechanism. Conventional doctors tend to presume that MCS is not an entity, that the suggestion of an environmental cause for the symptoms needs critical evaluation in each case and that there may be different subgroups of patients for which there are different explanations (Lessof, 1997). It is likely that there are some with MCS who have a biological disorder and some that have some other biological disorder or a psychogenic disorder. As MCS has been reported only in western industrialised countries despite the ubiquitous presence of the implicated chemicals it may be a culturally bound phenomenon whose existence depends on certain social or cultural conditions.

Some suggest identifying the cause is irrelevant as patients require compassion and treatment. Others argue that there is need to identify the primary cause if MCS patients are to receive correct treatment. It is important not to conclude that because a biological cause has yet to be determined then MCS should be considered a psychological disorder (Labarge and McCaffrey, 2000). Whatever the aetiology it is an important public health problem with potential for significant morbidity and economic loss as those with MCS are often disabled and some become totally disabled in terms of employment.

## Clinical Management

Approaches to treatment have paralleled aetiological theories and very little is known about the proper treatment of MCS. No therapy has been subjected to controlled clinical trials to confirm short or long term efficacy (Kipen and Fiedler, 2000).

Many recommend a multi-disciplinary approach to treatment as this avoids labelling of patients by referral to other services such as psychiatric. While some view aetiology as important in determining appropriate management others argue the focus should be on the presenting symptoms.

Many advocates for a biological explanation for MCS argue for avoidance of chemicals and often exclude treatment that addresses psychological responses such as behavioural therapy (Gots and Pirages, 1999). Avoidance of chemicals identified by diverse testing procedures has a central role in management by environmental physicians. Avoidance strategies can involve extensive lifestyle changes and range from special diets, change of occupation, restriction of social activities, to use of respirators, construction of special housing, or to moving to an “intact” environment. The basis for avoidance is the assumption that there is an upper limit for a tolerable amount of chemicals in the body and if exceeded the body’s detoxification system is overloaded. It is assumed to recover by a reduction in uptake of chemicals. Other environmental medicine approaches to treatment include intradermal or sublingual symptom neutralisation<sup>11</sup>, vitamin and mineral supplements, saunas, chelation, antiviral and antifungal drugs.

Rational drug treatments do not exist since causal factors have not been identified. Often patients resist drugs on the grounds of their sensitivity. Methods that have proven useful include relaxation, biofeedback and psychotherapeutic techniques (Wolf, 1996). These forms of treatment focus on reducing disability rather than focusing on specific symptoms.

Heinzow (1998/99) argues for early intervention to prevent chronicity, and implementing coping strategies that avoid focus on presumed aetiology and rigorous avoidance that reinforces social withdrawal and disability. In contrast some suggest treatment contributes to chronicity (Bornschein et al, 2001). Since MCS is similar to somatoform disorder which responds to behaviour therapy similar management has been advocated (Bornschein et al, 2001). Those with MCS clearly suffer from this disabling condition and clinical management should aim at improving their health and wellbeing.

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<sup>11</sup> Symptom neutralisation involves the administration of a lower dose of the implicated substance.

## Methodological Limitations of Available Research

Besides the lack of a single case definition a number of methodological problems limit interpretation of the published research. These include over-reliance on surveys and self-reported symptoms, selection bias, lack of blinding, and inconsistent quality assurance of laboratory determinations.

Self-report measures predominate and are often used without corroboration from prior medical records or physical examinations and laboratory testing to rule out other disorders.

Sample sizes are frequently small and have specific exposures. Selection criteria are often vague or unspecified making across study comparisons difficult. Study samples are sometimes self-selected e.g. recruited via advertisements in MCS patient newsletters (e.g. Miller and Mitzel, 1995), associated with compensation cases, or selected from referrals from interested doctors or support groups. This may have influenced participants' notions of the condition. Some findings however dispute this (Davidoff and Keyl, 1996). Study participants have been typically recruited from specialist medical clinics. Studies of prevalence in these clinics vary widely according to selection criteria. Results are likely to not be generalisable to the general population or to patients in primary care settings. Descriptions in primary care settings have also not been reported (Magill and Suruda, 1998).

Many studies do not make comparisons to control groups. When control groups are used researchers are often (or cannot be) blind to the participants' group membership introducing potential researcher bias.

Recall bias is a poorly understood but well-recognised problem in retrospective studies and can substantially alter the frequency of symptom reports. Media reports and health care professionals may have sometimes unwittingly led some people e.g. Gulf War veterans to become overly concerned about the possibility of developing chemical sensitivity or other unexplained illnesses and to report more symptoms.

There are many problems with the use of immunological tests. These include wide natural variation in test results over time and between people, few reference standards to determine what statistically "normal" is, and lack of reproducibility (Magill and Suruda, 1998).

Study designs are generally inadequate to justify conclusions regarding cause and effect relationships yet such conclusions are often inferred (Labarge and McCaffrey, 2000).

The validity of exposure information is a fundamental problem in MCS research. When exposure has been well documented it tends not to have been well characterised e.g. Davidoff et al (1998). Since data on the dose of specific chemicals required to provoke symptoms are not available it is not feasible to construct dose-response relationships. However such relationships are often inferred and accepted (Graveling et al, 1999).

The Cullen case definition is the most frequently cited and includes proof that symptoms depend on exposure. However most studies are clinical and based mainly on self-reports with no verification of actual or lifetime exposure. Most of the studies that include exposure information deal with occupational exposure e.g. Lax and Henneberger (1995); Miller and Mitzel (1995); Davidoff and Keyl (1996). These studies are not randomly selected samples of workers exposed to the implicated chemicals and the exposure is not well characterised.

There are few studies with valid information on chemical exposure. A study by Kiesswetter and coworkers (cited in Kiesswetter, 1998/99) found that cumulative exposure and lifetime weighted average exposure to the solvent toluene were not related to prevalence of self-reported MCS in a randomly selected group with homogeneous occupational lifetime exposure to toluene.

## Views of Professional Organisations to MCS

Many medical professional organisations have issued position statements outlining the limitations of the MCS diagnosis (Table 3). These state that aetiological theories, diagnostic and treatment practices are at best unproven. Labarge and McCaffrey (2000) comment that they can be viewed as methods to limit the growth of alternative or unsupported medical practice or as self-serving to protect specialists' scope of practice.

Table 3 Medical professional organisations with MCS position statements

Organisation	Year of most recent statement
California Medical Association	1986
American College of Physicians	1989
American Medical Association	1992
Royal College of Physicians and Royal College of Pathologists	1995
American Academy of Allergy and Immunology	1999
American College of Occupational and Environmental Medicine	1999

The two most recent position statements are from the American Academy of Allergy and Immunology (AAAI) and the American College of Occupational and Environmental Medicine (ACOEM).

The AAAI first issued a position statement in 1986 which was most recently updated in 1999. Conclusions included:

- There is no scientific evidence to establish any aetiological mechanisms as definitive.
- Rigorously controlled studies to verify individuals' reported subjective sensitivity to specific chemicals have yet to be done.
- There is no evidence that these patients have immunological or neurological abnormalities.
- No form of treatment has yet been shown to be effective (AAAI, 1999).

The ACOEM first issued a position statement in 1991 which was updated in 1993 and 1999. It states that although evidence does not yet exist to define MCS as a distinct entity, and methodological problems and the lack of a single case definition limit interpretation of the published research, data have accumulated that support some tentative conclusions. These are:

- There is evidence against an immunological basis.
- There is overlap with other non-specific conditions e.g. FM, CFS.
- Survey data suggest odour related symptoms are common in the general population but the extent and prevalence of associated disability is unclear.
- The prevalence of pre-existing and concurrent psychiatric disease is still controversial.
- The relationship of MCS to environmental contaminants remains unproven.

The ACOEM recognises that measurable indoor air quality problems can exist that cause human illness and discomfort and support regulatory efforts to provide indoor air and

environmental regulations to minimise risk of harm to public health. However it concludes that:

“No scientific basis currently exists for investigating, regulating or managing the environment with the goal of minimizing the incidence or severity of MCS” (ACOEM, 1999).

The statements of the American Academy of Environmental Medicine (AAEM) (1992) and the British Society for Allergy, Environmental and Nutritional Medicine (BSAENM) (Eaton et al, 2000) differ from those of other medical organisations.

The AAEM states that a wide variety of symptoms arising from many different organs may be the result of biological system dysfunctions triggered by environmental stressors in susceptible people. It uses a number of terms that are specific to the environmental medicine approach to MCS and its theories of causation and mechanisms such as total load and adaptation (Interagency Workgroup, 1998).

The BSAENM argue for change in regulatory policy. Although MCS is largely unacknowledged in the United Kingdom the BSAENM believes this is likely to change. Its conclusions include:

- There should be efforts to reduce chemical exposures of the general population so that fewer individuals become sensitised as preventing symptom provocation in sensitised individuals requires much greater control of exposure.
- In the current state of knowledge about MCS the only practical solution appears to be to keep environmental exposures for everyone below levels that have been shown to initiate sensitivity in susceptible individuals. Initiation would be less likely if exposures were reduced and levels for ambient volatile organic compounds kept below about 5 ppb<sup>12</sup>.
- Since it is impossible to prove that chemicals are entirely safe the precautionary principle should be invoked and actions taken to reduce exposure to chemicals to which the general population is most exposed if there is any evidence of possible long term adverse effects. Particular attention should be paid to reducing exposure to pesticides and volatile organic compounds including artificial fragrances.
- Assessments of interaction, immunological adjuvant activity and hormone mimicry should be included in safety assessments of chemicals for use in household products.
- There is circumstantial evidence that chemical exposure may have contributed to the increasing prevalence of allergic disease. The BSAENM propose that some chemicals may be acting as immunological adjuvants which increase and modify the response of the immune system to allergens.
- Failure to recognise that some form of allergy probably contributes to chronic conditions is delaying progress in understanding them and in establishing the mechanisms responsible.
- Uncertainties about mechanisms should not influence judgement as to whether the evidence of efficacy of avoidance as a treatment is convincing or not (Eaton et al, 2000).

Other organisations which have issued statements on MCS include the American Council on Science and Health (1994) and the American Health Foundation (1999).

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<sup>12</sup> The level of 5 ppb to provoke sensitisation is derived from unpublished data of 5-15 ppb from a sick building syndrome incident following refurbishment of a US EPA building in 1987-8.

A review of the mechanisms of MCS by the Environmental Health and Safety Council of the American Health Foundation concluded:

- There was no convincing evidence that any olfactory mechanism underlies induction of a sensitised state or triggering of symptoms.
- The hypothesis that MCS involves limbic kindling or time dependent sensitisation (TDS) cannot explain its mechanism because limbic kindling itself is not understood as a mechanism and TDS describes a pattern not a mechanism (Ross et al, 1999).

Misrepresentation of professional organisations was detected in the literature. Donnay (1999) presented a statement that complaints of MCS should not be dismissed as psychogenic and a thorough workup was necessary to be a position statement by the American Lung Association, American Medical Association, US Environmental Protection Agency and US Consumer Product Safety Commission. This statement was made in a publication on indoor air quality co-sponsored by the four organisations and is not a position statement (Colome et al, 1994).

## World Health Organisation and MCS

In 1996 an international workshop was organised in collaboration with WHO's International Programme on Chemical Safety, and the German Ministries of Health, Health Protection, and the Environment.

As well as proposing the term "idiopathic environmental intolerances" instead of MCS, it concluded that:

- IEI cannot be recognised as a clinically defined disease.
- Clinical assessment should be designed to exclude conditions requiring specific treatment.
- There are no specific tests to diagnose the condition.
- Effective treatment has not been validated in controlled clinical trials.
- Approaches to care based on supportive care and understanding is necessary.
- Human research is urgently needed to determine its nature.
- Interdisciplinary approaches should be sought for diagnosis and treatment (Anon, 1997).

## The Approach to MCS in the United States

The issue of MCS has become politicised in the United States resulting in debate that has polarised medical, research and regulatory communities. Claims of scientific misconduct and inquiry proceedings in response to some research findings have occurred (Labarge and McCaffrey, 2000).

Federal and state government interest in MCS has a relatively long history dating from 1979 but particularly during the 1990s. The issue has been discussed and examined through workshops and conferences by state governments, federal agencies, the National Academy of Sciences (1992), and professional organisations e.g. International Society of Regulatory Toxicology and Pharmacology (1993). The need for more basic epidemiological research has been a common theme.

A 1995 conference of researchers recommended research protocols to address various aspects of the problem (Bell et al, 1997; Miller et al, 1997; Weiss, 1997).

Despite this interest federal government research agencies are considered not to regard MCS, except perhaps more recently Gulf War illnesses, as high priorities for funding (Kipen and Fiedler, 1999). Few of the many research as well as policy recommendations from the almost annual conferences sponsored by federal agencies in the 1990s have been adopted (Donnay, 1999).

A list of research projects in progress sponsored by government agencies or philanthropic foundations with a protocol review process is published on the internet by the Environmental Sensitivities Research Institute (<http://www.esri.org/research.htm>).

In 1996 the US EPA stated that there was no medical consensus regarding the definition or nature of MCS (US EPA, 1996). Research activities related to MCS are part of the EPA's programme on indoor air pollutants (Interagency Workgroup, 1998).

The EPA initiated a federal government interagency workgroup on MCS that was co-chaired by the Agency for Toxic Substances and Disease Registry and National Center for Environmental Health of the Centers for Disease Control and Prevention. Other agencies involved were the Departments of Defense, Energy, and Veterans' Affairs, the National Institute for Occupational Health and Safety, and the National Institute for Environmental Health Sciences.

After four years a draft report intended to be a guide to public health policy-making and research planning was released for public consultation in August 1998. The draft report provides a public health evaluation of the extent and nature of MCS and recommends future actions for federal agencies to consider.

The report comments that it appears that environmental agents can trigger a variety of disorders in susceptible people. Some respond to very low levels of chemicals in the environment by expressing a variety of symptoms in one or more organ systems frequently involving the central nervous system. Symptoms appear to be associated with community exposures, indoor air pollution and industrial activities. Pesticides and solvents are the two major classes of chemicals most frequently reported as having initiated MCS (Interagency Workgroup, 1998).

The report lists research recommendations and some policy recommendations concerning research, health care, and interagency coordination. The workgroup concluded that the major recommendations (a need for a case definition, basic epidemiology, and case-comparison and challenge studies) from several expert workshops held since 1990 were still appropriate. If addressed, they should advance the public health response to the public's concerns about MCS (Interagency Workgroup, 1998).

Advocates of MCS criticised the workgroup for a number of process issues and the draft report for not including a review of all the published literature, the funding or results of all federally funded research, or the policies of all federal government authorities. Critics of MCS argued the workgroup was too willing to listen to advocates (Anon, 2000b).

In May 2000 the National Environmental Justice Advisory Council (NEJAC)<sup>13</sup> proposed a number of actions to the EPA including making MCS a notifiable disease, review of existing environmental laws to assure protection from chemicals that initiate and trigger MCS, and inclusion of MCS as a factor when setting standards and establishing regulations. In October 2000 the EPA stated that the state of knowledge regarding the definition, causes and treatment of MCS was insufficiently defined to warrant the type of regulatory action called for in the NEJAC resolution.

The Occupational Safety and Health Administration (OSHA) of the Department of Labor statement says that MCS is not occupationally related, and control methods could only be based on unproven theories because the cause is not currently known (OSHA, 2001).

In the United States the legal ramifications of MCS are far ahead of the science (Gots, 1995). Despite equivocal scientific evidence courts and workers' compensation boards in eight states have recognised MCS as a physical disorder (Labarge and McCaffrey, 2000). However an opponent of MCS claims that some courts have excluded testimony by MCS proponents on the grounds that MCS lacks scientific corroboration (Barrett, 2000b). This was unable to be corroborated.

MCS has been widely recognised in policy arenas. Some of the regulations that have been implemented and policy statements that have been made provide criteria and terms to define MCS. Other regulatory and policy actions include affected individuals not by a diagnosis of MCS but as a result of the fact that their ability to function has been impaired e.g. the Social Security Administration and Department of Housing and Urban Development grant affected individuals protection under the Social Security Act and Fair Housing Act. In 1991 the Department of Housing and Urban Development stated that people with MCS can seek protection under federal housing discrimination laws. As an example this allows establishment of a pesticide-free zone around a person's home.

The main federal laws that facilitate recognition of MCS are the Department of Labor Americans with Disabilities (AD) Act and the Department of Veterans' Affairs Compensation Acts. Since 1991 MCS can be considered a disability under the AD Act. Claims of disability are decided on a case-by-case basis. Under the Act employers are required to provide reasonable accommodation to a disabled employee. MCS advocates have argued for prohibition of perfumes and fragrant products in the workplace. There has been no ruling as to

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<sup>13</sup> The National Environmental Justice Advisory Council was set up in 1993 to provide independent advice to the EPA Administrator on issues related to environmental justice.

whether such prohibition is reasonable and difficulties associated with enforcement have not been addressed (Gots, 1995).

Some states e.g. Florida have passed legislation creating a pesticide notification registry for persons with MCS. Typically these registries require that pesticide application to adjacent property is notified in advance to those on the registry. Medical certification of chemical sensitivity is usually required before residents can enrol on the register (Interagency Workgroup, 1998).

## Approaches to MCS in Other Countries including New Zealand

The Canadian government first examined the problem in 1985 (Ministry of Health, Ontario) and has since sponsored several workshops to help define a research agenda.

In the United Kingdom there have been position statements issued by medical proponents (Eaton et al, 2000) and opponents of MCS (Royal College of Physicians and Royal College of Pathologists, 1995). The Health and Safety Executive commissioned a review of the literature on MCS from the Institute of Occupational Medicine, Edinburgh. The report is less dismissive of a biological explanation than many published statements and reviews. It concluded that the available, though limited, evidence suggests a biological mechanism involving sensitisation of the limbic system of the brain and recommended further research (Graveling et al, 1999).

Advice on this review was sought by the Health and Safety Executive from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment which undertakes independent scientific and medical reviews of chemicals and advises the Department of Health's Chief Medical Officer. The Committee agreed that on the basis of current knowledge there was insufficient evidence to make comments on potential mechanisms of MCS or to recommend further research in this area (Anon, 2000a).

In Australia cases of medical retirement and compensation for MCS have occurred (Winder, 2002).

No position or policy statements were identified for New Zealand organisations in this review. However submissions relating to MCS have been received in response to a number of government discussion documents (e.g. MacIntyre et al, 1989). The issue was also raised in the ICI chemical fire inquiry (Elias et al, 1990) and most recently by the Agrichemical Trespass Ministerial Advisory Committee set up by the Minister for the Environment and in a discussion document on pesticides risk reduction policy (Ministry for the Environment, 2002).

Successful claims have been made to the Accident Rehabilitation and Compensation Insurance Corporation (formerly the Accident Compensation Corporation). The number is unknown. Some recent cases that had gone to the Accident Compensation Appeal Authority were identified during this review.

In 1998 the Accident Compensation Appeal Authority granted cover to Burston for chemical poisoning from exposure to various chemicals arising from his employment, Wardle for chemical poisoning from exposure to chemical sprays on his family property, and McPherson for chemical poisoning from exposure to herbicides. The McPherson case dated back to 1987. In this case dismissal of an appeal to the Accident Compensation Appeal Authority was appealed to the High Court in 1996 as a result of special leave granted by the Appeal Authority on the grounds there was a question of general or public importance that ought to be submitted to the High Court for decision. Judge Anderson allowed the appeal to the extent that it was remitted to the Appeal Authority for reconsideration without reference to the technique electroacupuncture according to Voll (EAV) practised by a medical practitioner, Dr M Tizard, in the evaluation of the appellant's case. This technique was discredited by a task

force set up by the Department of Health to investigate notifications of chronic pesticide poisoning diagnosed using EAV by Dr Tizard (Task force on chronic agricultural chemical poisoning notifications, 1986).

In 2000 the appeal of Prichard for chemical poisoning arising from exposure to fumes from the factory floor below her office was unsuccessful. In this case it was submitted that the decisions in Burston, McPherson and Wardle should be disregarded as they pertained to the Accident Compensation Act 1982 in which personal injury was defined to include the mental as well as physical consequences of the injury unlike the Accident Rehabilitation and Compensation Insurance Act 1992. Judge Middleton commented: “The whole area appears to be clouded by indecision as to exactly what MCS is and the reasons for it, and both the specialists and the authors of the review article [published in the *Journal of Occupational and Environmental Medicine* in 1999] indicate that a wide variety of psychological factors may well be linked with the problem.” It was also stated that there was no evidence as to which if any of the chemicals used in the factory could be incriminated in the problems claimed, doubt as to the extent of any exposure, and indications that the appellant’s non-occupational environment may be a contributor to her symptoms.

## Research Needs

Recommendations for basic epidemiology, case-comparison studies, development of a case definition, and challenge studies from expert workshops held since 1990 are still appropriate and yet to be fully addressed (Interagency Workgroup, 1998). An interdisciplinary approach including toxicology, psychology, psychophysiology and medicine is needed for progress (Bolt and Kiesswetter, 2002).

Neutra (1994) maintains that since the principal debate is whether MCS exists or not the current research goal is to identify the group of people who are most likely to show a clear response when challenged in an environmental unit<sup>14</sup> and then carry out descriptive epidemiological studies of this population.

The main research needs are:

- To identify the classes of chemicals that initiate and trigger MCS
- To define clinical presentation and natural history
- To determine prevalence and incidence
- To evaluate potential biomarkers of MCS once the susceptible group has been clearly identified
- To carry out cross-country comparisons
- Animal studies to explore possible underlying mechanisms
- The role of MCS patients' health beliefs and their attribution of symptoms to the environment (Neutra, 1994).

Prospective studies could be undertaken within industries where exposure to specific classes of chemicals might be expected to produce MCS in a small group of susceptible people, and of populations unintentionally exposed to chemicals as a result of incidents.

Future studies need to include DBPC challenge tests in a controlled environment. The DBPC challenge test is the most effective method for objectively determining the validity of an adverse reaction to a chemical. It involves exposing participants to either the substance to which they are expected to react or a placebo. If they are sensitive to the substance they will react to it but not to the placebo. Ability to discriminate also suggests a biological rather than a psychogenic mechanism for MCS. To control for bias neither the participant nor the person administering the samples should be aware of whether a sample is the test substance or placebo. The DBPC challenge test can reveal large differences in self-perception of illness and its objective measurement.

There are difficulties in carrying out this type of study for MCS. It is often difficult to mask differences between the test substance and placebo because of the test substance's odour. It is therefore difficult to separate reactions to odour from physiological effects. Since those with MCS react to a wide variety of common chemicals it is necessary to carry out testing in an environmental unit. Some researchers suggest that the person spends several days in the unit before challenge testing occurs because it is hypothesised that those with MCS may react for several days after exposure. This means there should be periods between each exposure. Adequate numbers of patients and controls must be involved to facilitate valid comparisons.

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<sup>14</sup> An environmental unit is a room in which there is control over ventilation and limited off-gassing of chemicals to which the participant may be sensitive.

Dyer and Sexton (1996) identify research priorities to elucidate the aetiology of MCS with the highest priority being for research based on highly plausible and readily testable hypotheses which will generate results that are valuable for risk-related decision making and significantly advance current scientific knowledge and understanding (Table 4).

Table 4 Priorities for research into MCS aetiology

Level of priority	Hypothesis for aetiology
High	learning/conditioning, neurogenic inflammation, mucous membrane irritation, chronic sinusitis
Medium (based on research being more plausible but less readily testable)	mood disorder, anxiety, obsessive personality, prolonged stress, somatoform disorder, psychosomatic illness, atypical post-traumatic stress disorder
Medium (based on research being less plausible but more readily testable)	pollutant injury to the lungs, bioaccumulation, antioxidant deficiency, nutritional depletion, immune hypersensitivity and other immune responses
Low	sensitisation of peripheral organs, time-dependent sensitisation, partial kindling, tissue adaptation, failed detoxification

(Dyer and Sexton, 1996)

Arnetz (1999) argues that research that does not involve a comprehensive picture of the chemical, physical and psychosocial environments of MCS patients does not add to existing knowledge and should be discouraged. Future research should assess biological, environmental and psychosocial data and involve patient groups with similar symptoms but different diagnoses. Similarities and differences of patients with different diagnoses need to be understood before the clinical entities can be understood, diagnosed, treated and prevented. In particular Arnetz (1999) states that future research should address concurrent environmental stressors that trigger the limbic system of the brain.

Application of diagnostic and research methods used to evaluate drug-induced allergic reactions and chemicals that cause occupational asthma may provide insights into the pathogenesis of MCS (Bernstein, 1996).

Miller et al (1997) have described appropriate methods for controlled scientific study of MCS including development of a case definition, appropriate sample selection, randomisation and use of DBPC challenge tests in an environmental unit with documentation of subjective and objective responses. Weiss (1997) has suggested a single case time-series design may be the best research approach for investigating MCS.

There is a significant need for a standardised clinical definition and a clinical protocol that can be used to evaluate MCS. A consensus statement issued by 34 MCS researchers and clinicians recommended that protocols include validated questionnaires for screening and characterising chemical sensitivity, a list of overlapping disorders to consider in the differential diagnosis, and a list of signs and abnormalities associated with MCS in the peer-reviewed literature (Bartha et al, 1999).

## Regulation and MCS

In this report regulatory decision making refers to the decisions made by the Authority to protect public health from the adverse effects of substances with toxic properties. The HSNO Act defines toxic as “capable of causing ill-health in, or injury to human beings”. Regulations for substances with toxic properties are included in the Hazardous Substances Regulations 2001. However many substances that are implicated in MCS are outside the scope of the HSNO Act and its regulations either because they are not covered by the Act or do not meet any regulatory toxic threshold.

Components of regulatory decision making undertaken by the Authority are identification and evaluation of risks, costs and benefits; risk assessment<sup>15</sup> to estimate the likelihood and magnitude of the risks; determination of what, if any, regulatory controls are required; and risk communication about risks and risk-related decisions.

From the regulatory perspective the lack of scientific information about MCS is most marked in the context of risk assessment. Although many advocates argue for immediate action (or inaction) it is not feasible currently to carry out even the first step in risk assessment, hazard identification, due to lack of agreement about case definition, diagnostic methods, aetiology, or the nature of adverse health effects (Dyer and Sexton, 1996).

Primary prevention is the highest goal in public health and involves anticipating and avoiding adverse health effects before they occur. This is followed by secondary prevention (intervention) to prevent or limit adverse effects, and tertiary prevention (treatment) of impairment and disability in affected individuals. Intervention is aimed at those population groups that are considered to be at most risk because they are either more exposed and/or more susceptible (Dyer and Sexton, 1996).

Valid reliable information about MCS such as data on causative agents, human exposures, aetiology, dose-response relationships, and susceptible population groups are needed to put these public health principles into effect. Reliable information on incidence and prevalence is also required before determining the extent of the controls that would be required to reduce the risk of this condition among susceptible people. These data are unavailable. This means it is not possible for regulatory decision making to be fully informed or for the effectiveness of regulatory measures in protecting public health with respect to MCS to be fully evaluated (Dyer and Sexton, 1996).

Since susceptible population groups are not clearly defined it is not possible to regulate to prevent MCS developing in those groups without imposing very conservative and likely impractical requirements on industry and domestic chemical use.

The Authority is able to decline an application to import or manufacture a substance that triggers a toxic effect threshold if:

“ after taking into account-

- (i) Any controls which may be imposed on the substance; and
- (ii) All effects of the substance during the lifecycle of that substance; and
- (iii) The likely effects of the substance being unavailable,-

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<sup>15</sup> The components of risk assessment are hazard identification, exposure assessment, assessment of the dose-response relationship and risk characterisation.

the adverse effects of the substance outweigh the positive effects; or  
.... insufficient information is available to enable the Authority to determine the adverse effects of the substance” (section 29(b) and (c) HSNO Act 1996).

The Authority is also able to add, substitute or delete any default HSNO controls for a substance with toxic properties in certain prescribed circumstances (section 77 HSNO Act 1996). Without an understanding of aetiology and the nature of the illness action should not result in restricting or prohibiting implicated chemicals.

When a substance triggers any toxic effect threshold the Authority may set an exposure limit to protect public health called a Tolerable Exposure Limit (TEL) for the substance or its components. A person must not use the substance such that the TEL is exceeded. This does not apply to a workplace unless there is public access. Workplace exposure standards apply to workplaces without public access.

Tolerable Exposure Limits are set under the Hazardous Substances (Classes 6, 8 and 9) Regulations 2001, regulations 11-30. A TEL is the maximum concentration of a hazardous substance in an environmental medium that will present a low risk of adverse human health effects from an identified exposure route. For the purposes of setting a TEL an environmental medium is defined in the regulations as “air, water, and soil, or a surface that a hazardous substance may be deposited onto”.

Current best scientific knowledge is the basis for defining exposure limits. The approach to deriving the TEL is based on calculating acceptable and potential daily exposure values. Setting of the Acceptable Daily Exposure (ADE) value uses an uncertainty factor approach that takes a no or lowest observable adverse effect level in animals, or human epidemiological data if it exists, and sets a value on the basis of factors and professional judgement. Up to a factor of ten is allocated for uncertainties in variation in response of human subpopulations. Children, including unborn children, are usually the most sensitive population group that is recognised. The product of the uncertainty factors is up to 10,000. The ADE is defined as “exposure to an amount of a substance for each unit of body weight per day that would not result in an appreciable toxic effect on a person over a lifetime of daily exposure to the substance”. A Potential Daily Exposure (PDE) value is a proportion of the ADE that is expected to occur from one particular exposure route. Setting an exposure limit produces levels that are generally regarded as safe for the general population. Some argue for a quantitative risk approach in setting exposure limits that uses available data to estimate the quantitative level of risk presented at different levels of exposure. These levels are then compared to levels of acceptable or tolerable risk and exposure limits are set below these (Lewis, 2000).

Some advocates maintain that the precautionary principle should be implemented to prevent MCS and regulatory action needs to be focused on reducing or eliminating exposure to chemicals that have already been frequently identified as precipitating onset. Suggested strategies for protecting susceptible people from becoming chemically sensitive include prevention of chemical incidents, prohibition of building occupancy prior to completion, and notification of pesticide applications (Ashford, 1999).

HSNO controls for substances with toxic properties are designed to limit involuntary exposure and exposure during use. In its decision making the Authority also has to “take into

account the need for caution in managing adverse effects where there is scientific and technical uncertainty about those effects” (section 7 HSNO Act 1996).

The HSNO regime includes a range of controls to protect public health. Once all existing substances with toxic properties have been transferred to the regime there is likely to be much greater protection against initiation of MCS in susceptible people than from previous legislation, and some increased protection for those with MCS depending on the implicated substances. Protection for those with MCS is necessarily limited due to the large number of common substances that trigger symptoms which are outside the HSNO regime.

The public’s response to risk is multi-dimensional and varied. Gaps in public and scientific perceptions of risk are common. Slovic (1999) argues for a new approach to risk that introduces increased public participation into risk assessment and decision making to improve the quality and relevance of scientific analysis and the legitimacy and public acceptance of decisions. The HSNO process for hazardous substances applications (with the exception of those for substances in containment and substances eligible for rapid assessment) and reassessments enables public participation which has the potential to contribute to reducing perception gaps. In this regard risk communication about substances with toxic properties is likely to benefit from taking more account of the influence of social factors on public risk perception of toxicity than has historically occurred.

People may attribute similar symptoms to different causes depending on specific personal, social and environmental situations (Arnetz, 1999). It is therefore possible that effective risk communication about substances with toxic properties may have a mitigating effect on MCS. This is suggested by a study by Dalton and coworkers (cited in Dalton and Hummel, 2000) referred to in the Aetiology section of this report.

## References

- Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001; 134: 868-881.
- American Academy of Allergy and Immunology. Position statement 35. Idiopathic environmental intolerances. *J Allergy Clin Immunol* 1999; 103: 173-176.
- American College of Occupational and Environmental Medicine. Position statement. Multiple chemical sensitivities: idiopathic environmental intolerance. 1999 (<http://www.acoem.org>).
- Anon. Report of Multiple Chemical Sensitivities (MCS) Workshop: International Programme on Chemical Safety (IPCS)/ German Workshop on Multiple Chemical Sensitivities. *Int Arch Occup Environ Health* 1997; 69: 224-226.
- Anon. 1999 Annual report of the Committees on Toxicity, Mutagenicity, Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. London: Department of Health, 2000a.
- Anon. Summary of public comments received for the multiple chemical sensitivity report. Prepared for the National Center for Environmental Health. September 29 2000b (<http://www.health.gov/environment/mcs/>).
- Arnetz BB. Model development and research vision for the future of multiple chemical sensitivity. *Scand J Work Environ Health* 1999; 25: 569-573.
- Ashford N. Low-level chemical sensitivity: implications for research and social policy. *Toxicol Ind Health* 1999; 15: 421-427.
- Barrett S. Multiple chemical sensitivity: a spurious diagnosis. September 8 2000a (<http://www.quackwatch.com>).
- Barrett S. An analysis of the National Environmental Justice Advisory Council Enforcement Subcommittee's Resolution #21 on multiple chemical sensitivity. October 16 2000b (<http://www.quackwatch.com>).
- Bartha L, Baumzweiger W, Buscher DS, Callender T, et al. Multiple chemical sensitivity: a 1999 consensus. *Arch Environ Health* 1999; 54: 147-149.
- Bell IR, Miller CS, Schwartz GE, Peterson JM, et al. Neuropsychiatric and somatic characteristics of young adults with and without self-reported chemical odour intolerance and chemical sensitivity. *Arch Environ Health* 1996; 51: 9-21.
- Bell IR, Schwartz GE, Baldwin CM, Hardin EE, et al. Individual differences in neural sensitization and the role of context in illness from low-level environmental chemical exposures. *Environ Health Perspect* 1997; 102 (Suppl 2): 457-466.
- Bell IR, Warg-Damiani L, Baldwin CM, Walsh ME, et al. Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings. *Military Med* 1998; 163: 725-732.

Bernstein DI. Multiple chemical sensitivity: state of the art symposium. The role of chemical allergens. *Regul Toxicol Pharmacol* 1996; 24: S28-S31.

Binkley KE, Kutcher S. Panic response to sodium lactate infusion in patients with multiple chemical sensitivity syndrome. *J Allergy Clin Immunol* 1997; 99: 570-574.

Black DW; Doebbeling BN, Voelker MD, Clarke WR, et al. Multiple chemical sensitivity syndrome. Symptom prevalence and risk factors in a military population. *Arch Intern Med* 2000; 160: 1169-1176 .

Black DW, Okiishi C, Schlosser S. The Iowa follow-up of chemically sensitive persons. *Annals NY Acad Sci* 2001; 933: 48-56.

Bock KW, Birbaumer N. MCS (multiple chemical sensitivity): cooperation between toxicology and psychology may facilitate solutions of the problems: commentary. *Hum Experimental Toxicol* 1997; 16: 481-484.

Bolt HM, Kiesswetter E. Is multiple chemical sensitivity a clinically defined entity? *Toxicol Lett* 2002; 128: 99-106.

Bornschein S, Forstl H, Zilker T. Idiopathic environmental intolerances (formerly multiple chemical sensitivity) psychiatric perspectives. *J Int Med* 2001; 250: 309-321.

Clauw DJ. Potential mechanisms in chemical intolerance and related conditions. *Ann NY Acad Sci* 2001; 933: 235-253.

Colome S, McCunney RJ, Samet JM, Swankin D. Indoor air pollution: an introduction for health professionals. Washington: U.S. Government Printing Office, 1994.

Cullen MR. Workers with multiple chemical sensitivities. *Occup Med: State of the Art Reviews*. 1987; 2: 655-661.

Cullen MR, Redlich CA. Significance of individual sensitivity to chemicals: elucidation of host susceptibility by use of biomarkers in environmental health research. *Clin Chem* 1995; 41: 1809-1813.

Dalton P, Hummel T. Chemosensory function and response in idiopathic environmental intolerance. *Occup Med: State of the Art Reviews* 2000; 15: 539-556.

Davidoff AL, Keyl PM. Symptoms and health status in individuals with multiple chemical sensitivities syndrome from four reported sensitising exposures and a general population comparison group. *Arch Env Health* 1996; 51: 201-213.

Davidoff AL, Keyl PM, Meggs W. Development of multiple chemical sensitivities in labourers after acute gasoline fume exposure in an underground tunnelling operation. *Arch Environ Health* 1998; 53: 183-189.

Donnay AH. On the recognition of multiple chemical sensitivity in medical literature and government policy. *Int J Toxicol* 1999; 18: 383-392.

Doty RL, Deems DA, Frye RE, Pelberg R, et al. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. *Arch Otolaryngol Head Neck Surg* 1988; 114: 1422-1427.

Doty RL. Olfaction and multiple chemical sensitivity. *Toxicol Ind Health* 1994; 10: 359-368.

Dyer RS, Sexton K. What can research contribute to regulatory decisions about the health risks of multiple chemical sensitivity? *Reg Toxicol Pharmacol* 1996; 24: S139-S151.

Elias S, Bandaranayake DR, Edwards IR, Glass WI. The health consequences of the ICI fire. Report to the Minister of Health on the health of firefighters in the fire at the ICI Riverview store, Mount Wellington, Auckland, 21 December 1984. Wellington: Department of Health, 1990.

Eaton KK, Anthony HM, Birtwistle S, Downing D, et al. Multiple chemical sensitivity: recognition and management. A document on the health effects of everyday chemical exposures and their implications. *J Nutr Environ Med* 2000; 10: 39-84.

Fishbein L. Multiple chemical sensitivities: an overview. *Environ Toxicol Pharmacol* 1996; 2: 193-195.

Fiedler N, Kipen HM, De Luca J, Kelly-McNeil, et al. A controlled comparison of multiple chemical sensitivities and chronic fatigue syndrome. *Psychosom Med* 1996; 58: 38-49.

Gad SC. Multiple chemical sensitivity: a moderator's viewpoint. *Int J Toxicol* 1999; 18: 379-381.

Gots RE. Multiple chemical sensitivities – public policy. *Clin Toxicol* 1995; 33: 111-113.

Gots RE, Pirages SW. Multiple chemical sensitivities: psychogenic or toxicodynamic origins. *Int J Toxicol* 1999; 18: 393-400.

Graveling RA, Pilkington A, George JPK, Butler MP, et al. A review of multiple chemical sensitivity. *Occup Environ Med* 1999; 56: 73-85.

Heinzow B. Psychosocial factors in the occurrence of environmental intolerances. *Zbl Hyg Umweltmed* 1998/99; 202: 153-164.

Hu H, Stern A, Rotnitzky A, Schlesinger L, et al. Development of a brief questionnaire for screening for multiple chemical sensitivity syndrome. *Toxicol Ind Health* 1999; 15: 582-588.

Hummel T, Roscher S, Jaumann JP, Kobal G. Intranasal chemoreception in patients with multiple chemical sensitivities: a double-blind investigation. *Regul Toxicol Pharmacol* 1996; 24: S79-S86.

Interagency Workgroup on Multiple Chemical Sensitivity. A report on multiple chemical sensitivity (MCS). Atlanta: Agency for Toxic Substances and Disease Registry and National Center for Environmental Health, Centers for Disease Control and Prevention, August 1998. Predecisional draft.

- Jason L, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. *Psychosomatic Medicine* 2000; 62: 655-663.
- Joffres MR, Williams T, Sabo B, Fox RA. Environmental sensitivities: prevalence of major symptoms in a referral center: the Nova Scotia Environmental Sensitivities Research Center study. *Environ Health Perspect* 2001; 109: 161-165.
- Kiesswetter E. "Multiple chemical sensitivity", the relevance of toxic, neurobiological and psychic effect mechanisms. *Zbl Hyg Umweltmed* 1998/99; 202: 191-205.
- Kipen HM, Hallman W, Kelly-McNeil K, Fiedler N. Measuring chemical sensitivity prevalence: a questionnaire for population studies. *Am J Public Health* 1995; 85: 574-577.
- Kipen HM, Fiedler N. Invited commentary: sensitivities to chemicals – context and implications. *Am J Epidemiol* 1999; 150: 13-16.
- Kipen HM, Hallman W, Kang H, Fiedler N, et al. Prevalence of chronic fatigue and chemical sensitivities in Gulf registry veterans. *Arch Environ Health* 1999; 54: 313-318.
- Kipen HM, Fiedler N. A 37-year-old mechanic with multiple chemical sensitivities. *Environ Health Perspect* 2000; 108: 377-381.
- Kreutzer R, Neutra RR, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population. *Am J Epidemiol* 1999; 150: 1-12.
- Kutsogiannis DJ, Davidoff AL. A multiple center study of multiple chemical sensitivity syndrome. *Arch Environ Health* 2001; 56: 196-207.
- Labarge AS, McCaffrey RJ. Multiple chemical sensitivity: a review of the theoretical and research literature. *Neuropsychology Review* 2000; 10: 183-211.
- Lax MB, Henneberger PK. Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. *Arch Environ Health* 1995; 50: 425-431.
- Lessof M. Report of Multiple Chemical Sensitivities (MCS) Workshop, Berlin, Germany, 21-23 February 1996. PCS/96.29 IPCS, Geneva, Switzerland. *Human Experimental Toxicol* 1997; 16: 233-234.
- Lewis PG. Occupational and environmental medicine: moving the factory fence or hedging our bets? *Occup Med* 2000; 50: 217-220.
- Magill MK, Suruda A. Multiple chemical sensitivity syndrome. *Am Fam Physician* 1998; 58: 721-728.
- MacIntyre A, Allison N, Penman D. Pesticides: issues and options for New Zealand. Wellington: Ministry for the Environment, 1989.

McKeown-Eyssen GE, Sokoloff ER, Jazmaji V, Marshall LM, et al. Reproducibility of the University of Toronto self-administered questionnaire used to assess environmental sensitivity. *Am J Epidemiol* 2000; 151: 1216-1222.

Meggs W, Cleveland JRC. Rhinolaryngoscopic examination of patients with multiple chemical sensitivity syndrome. *Arch Environ Health* 1993; 48: 14-18.

Meggs WJ, Dunn KA, Bloch RM, Goodman PE, et al. Prevalence and nature of allergy and chemical sensitivity in a general population. *Arch Environ Health* 1996; 51: 275-282.

Meggs WJ. Mechanisms of allergy and chemical sensitivity. *Toxicol Ind Health* 1999; 15: 331-338.

Miller CS. Chemical sensitivity: symptom, syndrome or mechanism for disease? *Toxicol* 1996; 111: 69-86.

Miller CS. Toxicant-induced loss of tolerance – an emerging theory of disease. *Environ Health Perspect* 1997; 102 (Suppl 2): 445-453.

Miller CS. Toxicant-induced loss of tolerance. *Addiction* 2000; 96: 115-139.

Miller C, Ashford N, Doty R, Lamielle M, et al. Empirical approaches for the investigation of toxicant-induced loss of tolerance. *Environ Health Perspect* 1997; 102 (Suppl 2): 515-519.

Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. *Arch Environ Health* 1995; 50: 119-129.

Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicol Ind Health* 1999a; 15: 370-385.

Miller CS, Prihoda TJ. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. *Toxicol Ind Health* 1999b; 15: 386-397.

Ministry for the Environment. Towards a pesticides risk reduction policy for New Zealand. Public discussion paper. Wellington: Ministry for the Environment, April 2002.

Mooser SB. The epidemiology of multiple chemical sensitivities. *Occup Med: State of the Art Reviews* 1987; 2: 663-668.

Nawab SS, Miller CS, Dale JK, Greenberg BD, et al. Self-reported sensitivity to chemical exposures in five clinical populations and healthy controls. *Psychiatry Research* 2000; 95: 67-74.

Nethercott JR, Davidoff LL, Curbow B, Abbey H. Multiple chemical sensitivities syndrome: toward a working case definition. *Arch Environ Health* 1993; 48: 19-26.

Neutra RR. Some preliminary thoughts on the potential contribution of epidemiology to the question of multiple chemical sensitivity. *Public Health Rev* 1994; 22: 271-278.

Occupational Safety and Health Administration US Department of Labour. Multiple chemical sensitivities. 2001 (<http://www.osha-slc.gov>).

Poonai N, Antony MM, Binkley KE, Stenn P, et al. Carbon dioxide inhalation challenges in idiopathic environmental intolerance. *J Allergy Clin Immunol* 2000; 105: 358-363.

Poonai NP, Antony MM, Binkley KE, Stenn P, et al. Psychological features of subjects with idiopathic environmental intolerance. *J Psychosom Res* 2001; 51: 537-541.

Reid S, Hotopf M, Hull L, Ismail K, et al. Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans. *Am J Epidemiol* 2001; 153: 604-609.

Ring J, Eberlein-Konig B, Behrendt H. "Eco-Syndrome" ("Multiple chemical sensitivity" – MCS). *Zbl Hyg Umweltmed* 1998/99; 202: 207-218.

Ross PM, Whysner J, Covello VT, Kuschner M, et al. Olfaction and symptoms in multiple chemical sensitivities syndrome. *Prevent Med* 1999; 28: 467-480.

Royal College of Physicians and Royal College of Pathologists. Good allergy practice - standards of care for providers and purchasers of allergy services within the National Health service. *Clin Exp Allergy* 1995; 25: 586-595.

Siegel S. Multiple chemical sensitivity as a conditional response. *Toxicol Ind Health* 1999; 15: 323-330.

Simon GE, Katon WJ, Sparks PJ. Allergic to life: psychological factors in environmental illness. *Am J Psych* 1990; 147: 901-906.

Slovic P. Trust, emotion, sex, politics, and science: surveying the risk-assessment battlefield. *Risk Anal* 1999; 19: 689-701.

Staudenmayer H, Selner JC, Buhr MP. Double-blind provocation chamber challenges in 20 patients presenting with "multiple chemical sensitivity." *Regul Toxicol Pharmacol* 1993; 18: 44-53.

Staudenmayer H. Idiopathic environmental intolerances (IEI): myth and reality. *Toxicol Lett* 2001; 120: 333-342.

Task force on chronic agricultural chemical poisoning notifications. Report to the Director-General of Health. Wellington: Department of Health, June 1986.

Thomas JG. A critical analysis of multiple chemical sensitivity. *Med Hypotheses* 1998; 50: 303-311.

Tonori H, Aizawa Y, Ojima M, Miyata M, et al. Anxiety and depressive states in multiple chemical sensitivity. *Tohoku J Exp Med* 2001; 193: 115-126.

US Environmental Protection Agency. Hazardous air pollutant list. *Federal Register* 1996; 61: 30816-30823.

Van den Bergh O, Devriese S, Winters W, Veulemans H, et al. Acquiring symptoms in response to odors: a learning perspective on multiple chemical sensitivity. *Ann NY Acad Sci* 2001; 933: 278-290.

Waickman FJ, Vojdani A. Putting chemical and environmental sensitivities in perspective. *Otolaryn Clinics N Am* 1998; 31: 55-67.

Weiss B. Experimental strategies for research on multiple chemical sensitivity. *Environ Health Perspect* 1997; 102 (Suppl 2): 487-494.

Winder C. Mechanisms of multiple chemical sensitivity. *Toxicol Lett* 2002; 128: 85-97.

Wolf C. Multiple chemical sensitivity (MCS). Idiopathic environmental intolerances (IEI). *Environ Sci Pollut Res* 1996; 3: 139-143.

Woolf A. A 4-year-old girl with manifestations of multiple chemical sensitivities. *Environ Health Perspect* 2000; 108: 1219-1223.