Australian Government
Department of Health and Ageing
NICNAS

Australian Government
Department of Health and Ageing
Office of Chemical Safety

A SCIENTIFIC REVIEW OF MULTIPLE CHEMICAL SENSITIVITY: IDENTIFYING KEY RESEARCH NEEDS

Working Draft Report prepared by the
National Industrial Chemicals Notification and Assessment Scheme
(NICNAS) and the Office of Chemical Safety (OCS)

November 2008

GUIDANCE FOR INPUT

This draft report on Multiple Chemical Sensitivity (MCS) represents a snapshot of current understandings with regards to aetiology, diagnosis, modes of action and current treatment and management.

A strong message from this report is that although MCS has been studied and subject to review over the past 25 years, there is need for further focused fundamental research on MCS.

The main aim for seeking reader input to the draft report at this stage is to ensure the report has broad coverage of all available scientific literature and technical information so as to better identify the priority areas for research on MCS. There may be further studies and available scientific papers for a number of areas covered by the review. For example, reports of additional research into proposed underlying causes of MCS such as studies detailing genetic predispositions and other biochemical models are important to fully identify.

So as not to further delay the public release of the report, we advise that we now seek input to this working draft, particularly on the areas of modes of action, clinical aspects of MCS and related technical/scientific information.

To facilitate input, the report poses questions at various points in the report to assist with required information and comment.

It is important for the finalization of this report that factual comment and additional scientific information on Multiple Chemical Sensitivity is now provided to NICNAS/OCS.

Comments and additional information can be sent via email to MCS@nicnas.gov.au

or by mail to:

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PREFACE

What this study is about

Multiple Chemical Sensitivity (MCS) is one of the terms used to describe a complex array of symptoms where the underlying aetiology and cause(s) remain uncertain and ill defined. There is uncertainty about the underlying biological events that lead to MCS symptoms. This has hampered the development of a clinical basis for the diagnosis and treatment of individuals with MCS.

This means that those with MCS face a situation where their symptoms may be poorly understood or mis-diagnosed, are often under treated or have treatment options that are less than optimal. Limited understanding of MCS has seen no consensus for its treatment other than avoidance of chemicals and other triggers that may cause symptoms.

This uncertainty and gaps in our understanding of MCS, together with community concerns over the presence of chemicals in the environment has led the Australian Department of Health and Ageing (DoHA), through the Office of Chemical Safety and the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), to prepare a scientific review of MCS.

Scope of the Study

The aim of this review is to examine current understanding and scientific research on MCS and to identify priority areas for further study and research to inform and engage the clinical and scientific research community.

The report therefore examines evidence about:

- the mode of action for chemical interactions within MCS
- approaches to clinical diagnosis and treatment of MCS, and
- clinical management strategies;

and highlights research efforts and further activities that would enhance diagnosis, treatment and better clinical management practices of MCS in Australia. The study considers practical measures to improve the management of individuals with MCS.

Conduct of the Study

The study has two key areas of focus. Firstly the study reviews the scientific literature and available information to identify biologically plausible hypotheses put forward to explain the underlying cause of MCS. The elucidation of the biological basis for MCS will provide direction for clinical diagnosis and improve treatments options for MCS. If the underlying biological mechanism(s) can be determined for MCS, there is potential to not only better treat symptoms but to effect a significant alleviation of the condition. Secondly, a clinical consultancy has been undertaken to identify current diagnosis and treatment practices and gaps in clinical research and medical education, the addressing of which will better support the diagnosis and management of individuals with MCS.

The study findings point to specific priorities for further scientific and clinical research on MCS.

The cooperation of a number of MCS interest groups and individuals in providing copies of scientific bibliographies, individual studies, national and international reports and information on experiences of MCS suffers is gratefully acknowledged.

ABBREVIATIONS

AAAAI	American Academy of Allergy, Asthma and Immunology
AAAI	American Academy of Allergy and Immunology
AAEM	American Academy of Environmental Medicine
ACP	American College of Physicians
ACTA	Australian Chemical Trauma Alliance Inc.
ADI	Acceptable Daily Intake
AESSRA	Allergy and Environmental Sensitivity Support and Research Association Inc
AIHW	Australian Institute of Health and Welfare
AIRA	Allergies and Intolerant Reactions Association
AMA	American Medical Association
ASCEPT	Australian Society of Clinical and Experimental Pharmacology and Toxicology
ASCIA	Australasian Society of Clinical Immunology and Allergy
ASEHA	Allergy, Sensitivity & Environmental Health Association Qld Inc
ATSDR	Agency for Toxic Substances and Disease Registry, Atlanta, Georgia
BSAENM	British Society for Allergy and Environmental Medicine
CFMCS SG	Circle of Friends MCS Support Group WA
CMA	Californian Medical Association
CTMCS	Community Taskforce on Multiple Chemical Sensitivities- WA
DBPC	Double-blind placebo control
DOD	Department of Defence, USA
DOE	Department of Energy, Washington, D.C. USA
DoHA	Australian Government Department of Health and Ageing
DPMBUS	Department of Preventive Medicine & Biometrics Uniformed Services University of the Health Sciences Bethesda, Maryland, USA
FCSSG	Fragrance and Chemical Sensitivity Support Group
GRCMCS&CI	Global Recognition Campaign for Multiple Chemical Sensitivity and Chemical Injury
IEI	Idiopathic environmental intolerance
IPCS	International Programme on Chemical Safety
MCS Australia	Multiple Chemical Sensitivity Australia
MCS	Multiple chemical sensitivity
ME/CFS	ME/CFS Society (SA) Inc.;
NCEH	National Centre for Environmental Health, Atlanta, Georgia, USA
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIEHS	National Institute for Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health, Cincinnati, Ohio
NTN	National Toxics Network
OCS	Office of Chemical Safety, DoHA, Australian Government
OGTR	Office of the Gene Technology Regulator
PHD	Population Health Division, DoHA, Australian Government
RACP	Royal Australasian College of Physicians
RPAH	Royal Prince Alfred Hospital
SATFMCS	South Australian Task Force on Multiple Chemical Sensitivity
TGA	Therapeutic Goods Administration, Australian Government
TILT	Toxicant-induced loss of tolerance
USEPA	U.S. Environmental Protection Agency Cincinnati, Ohio
WHO	World Health Organization

1 EXECUTIVE SUMMARY

1.1 OVERVIEW

Multiple Chemical Sensitivity (MCS) is one of the terms used to describe a complex array of symptoms where the underlying aeitology/cause(s) remains uncertain and ill defined.

There are reports linking MCS to a wide range of environmental agents (including chemicals) and other factors. A common theme reported by individuals is the experience of heightened responsiveness to very low levels of chemicals. The range of agents linked with MCS symptoms in susceptible individuals is markedly extensive and diverse. Similarly, the symptoms experienced by individuals are equally diverse and reported symptoms can in some cases be quite debilitating.

Available reports suggest that MCS individuals do not show a typical dose-response reaction following exposure to triggering agents. Some challenge tests suggest that it is the smell or odour of a triggering agent, rather any of its pharmacological or toxicological properties *per se* that elicit MCS symptoms.

MCS is difficult to define, and hence treat, clinically and several attempts have been made to establish diagnostic criteria for this disorder. The 'Consensus Criteria' developed in 1999 describe MCS as a chronic condition involving multiple organ systems with reproducible symptoms following low-level exposure to multiple unrelated chemicals. These criteria have been used to a limited extent for research purposes and for surveys of MCS prevalence in the community, including in Australian State health surveys.

However, there are no standardised criteria for identifying cases of MCS in clinical settings. The diagnosis of MCS is currently based on self-reported symptoms. No laboratory tests currently exist for diagnosing MCS. This lack of an accepted case definition and objective laboratory markers for MCS has significantly impeded treatment for patients and offers challenges to further research into MCS.

While numerous attempts have been made to define MCS, there is no unequivocal epidemiological evidence or quantitative or qualitative exposure data to distinguish individuals with MCS from others experiencing symptoms such as fatigue, headache, dizziness, lack of concentration or memory loss and labeled with diagnoses such as Chronic Fatigue Syndrome.

There is currently no standardised treatment for MCS. Current treatments include chemical avoidance, dietary changes, nutritional supplements, detoxification techniques, holistic or body therapies, as well as prescription medicines and behavioural therapies.

Lack of agreement on the underlying cause(s) and pathogenesis of MCS and subsequent lack of agreement on an operational definition of MCS impacts on the clinical management of MCS patients and is a hindrance to scientific analysis/investigation and clinical research efforts regarding MCS.

Both clinical and experimental research into MCS are required. The need for objective clinical criteria to identify MCS subjects and overcome the shortcomings of self-diagnosis is critical. This would allow prevalence data to be collected and also enable discrimination

between individuals with MCS and those with common aversions to smells and odours. Further work is also needed through reproducible and appropriately controlled challenge studies to better investigate causative factors. Longitudinal clinical studies are also required to examine the natural history of MCS and identify eliciting agents/events, to evaluate diagnostic experiences, clinical courses and the impacts of treatment/management strategies.

1.2 FINDINGS

Overall, the following primary research needs are evident:

- identifying the underlying cause and triggers of MCS;
- establishing agreed diagnostic criteria that are acceptable to clinical and scientific groups;
- determining the prevalence of MCS, for both self-reported cases and those that are medically diagnosed;
- determining the basis of the relative contributions of toxicodynamic and psychogenic mechanisms, if any, in the process of the disorder through the use of appropriately blinded challenge tests;
- determining effective treatment/management protocols for MCS based on positive therapeutic alliances and individual self-management.

Specific findings for research into each of these areas are presented below.

1.2.1 Research into the cause(s) of MCS

There is considerable debate as to what causes MCS. The literature describes numerous potential causative modes of action, many of which are amenable to further testing. Analysis of the scientific literature has identified that the most credible physiological mechanism for MCS is limbic kindling/neural sensitisation which proposes that sensitisation of the olfactory, limbic, mesolimbic and related pathways of the central nervous system occurs as a result of, or in the context of, chemical exposure.

The scientific weight-of-evidence currently suggests that while physiological mechanisms may play a part in MCS, there may also be a psychological or psychogenic component in its pathogenesis. Medical/scientific opinion suggests that MCS has a multifactorial origin, involving physiological, psychological and social predispositions.

Finding 1: Targeted research into Proposed Mode (s) of Action

While there are a number of proposed mechanism(s) that warrant further research consideration, based on biological plausibility, testability and known research gaps, the following scientific theories of the cause of MCS are recommended for further scientific research and investigation as priorities:

- Immunological variables
- Respiratory disorder/neurogenic inflammation
- Limbic kindling/neural sensitisation and psychological cofactors
- Elevated nitric oxide, peroxynitrite and NMDA receptor activity.

1.2.2 Clinical research needs

The clinical review has highlighted difficulties with agreed criteria for the diagnosis of MCS, identifying an underlying pathological process and treating or managing MCS.

Available reports suggest that MCS individuals do not show a typical dose-response reaction following exposure to triggering agents. Some challenge tests suggest that it is the smell or odour of a triggering agent, rather any of its pharmacological or toxicological properties *per se* that elicit MCS symptoms.

Overall, a number of primary clinical research needs are evident:

- Establishing agreed diagnostic criteria that are acceptable to clinical and scientific groups;
- Determining the prevalence of MCS, for both self-reported cases and those that are medically diagnosed;
- Determining the relative contributions of toxicodynamic and psychogenic mechanisms in the process of the disorder through the use of appropriately blinded challenge tests;
- Determining effective treatment/management protocols for MCS based on positive therapeutic alliances and individual self-management.

Finding 2. Longitudinal Study
To get a better understanding of the clinical picture of MCS in Australia there is a need to look more closely at the natural history of people with MCS. A longitudinal clinical and sociological study (ie how MCS develops over time) should assist in identifying elements of MCS as well as areas that may have been overlooked to date.

Such a study should examine eliciting agents/events, diagnostic experiences, clinical course and impacts of treatment/management strategies. To undertake such a longitudinal study it would be necessary to identify people with MCS who would be prepared to be involved. Appendix 1 findings provides some suggested practical steps in addressing this issue.

Finding 3: **Education/Training**
The development of a clinical education program be investigated. Such a program should be based on evidence currently available, utilise any findings from clinical research in Australia (such as a longitudinal investigation) and consider the practical guidance on approaches to MCS clinical management agreed by participants in the recent clinical review of MCS.

Finally there is a need for better public information in order to address concerns regarding MCS and to assist those who may be affected to seek appropriate help and treatment. Input should be sought from MCS support and advocacy groups, including the SA Government MCS Reference Group, with the aim of informing clinicians, workplaces and communities about what is currently understood by the term MCS and practical ways to assist people who are affected by MCS.

2 UNDERSTANDING MULTIPLE CHEMICAL SENSITIVITY

2.1 WHAT IS MULTIPLE CHEMICAL SENSITIVITY?

Multiple chemical sensitivity (MCS) is the term most commonly used to describe a disorder which is characterised by a broad array of physical, psychological and emotional symptoms, the cause of which is attributed to exposure to extremely low levels of a wide variety of environmental chemicals.

The initial concepts underlying MCS were developed by allergist Theron G. Randolph who, in the 1950's, asserted that patients had become ill from exposures to a wide variety of environmental, occupational and domestic substances at levels far below those that affect the majority of the population. Randolph and colleagues developed a conceptual framework of allergic reactions, masking and maladaptation, to explain the symptoms that resemble what is referred to most frequently today as MCS. From these ideas evolved the controversial discipline of *clinical ecology*, which is based on a putative diagnosis of 'environmental illness' applied to individuals with multiple symptoms attributed to environmental factors.

Although MCS is the most common term used to describe this disorder, there are many other terms that are used to describe the range of symptoms that contribute to the disorder described as MCS. Some of these terms are as follows:

- Idiopathic Environmental Intolerance (IEI)
- Environmental illness
- Chemical acquired immune deficiency syndrome (Chemical AIDS)
- 20th Century disease
- Cerebral Allergy
- Chemical sensitivity or intolerance
- Environmental hypersensitivity
- Toxic encephalopathy
- Toxicant-induced loss of tolerance (TILT)

In some cases, these terms reflect the particular views of individuals or groups regarding the underlying cause and mode of action of MCS. For this reason, the descriptor Idiopathic Environmental Intolerance or IEI is favoured by many, including the World Health Organization (WHO), because it does not make inferences with regards to causative agents. This reflects the lack of an agreed biological basis for MCS symptoms.

As well as being known by different names, some see MCS not as a single disease entity, but as a collective term describing a range of symptoms associated with environmental exposures (Alterkirch, 2000). This is an important concept as the search for single causative mechanisms and single treatment regimes will not be fruitful if there are a number of conditions existing under the general label of MCS.

Unfortunately, this lack of agreement on the underlying cause and pathogenesis of MCS, and subsequent lack of agreement on an operational definition of MCS has been a serious hindrance to scientific analysis/ investigation and clinical recognition of the condition.

2.2 WHAT ARE THE SYMPTOMS OF MCS?

The range of symptoms expressed by MCS subjects is very broad. A literature review by Labarge & McCaffrey (2000) identified 151 symptoms associated with MCS. The most frequently reported symptoms are listed in Table 1 and generally fall into 3 groups, namely, those affecting the central nervous system, the respiratory system and the gastrointestinal system.

Table 1. Percentage Prevalence of Symptoms Reported for MCS

Symptom	Prevalence[#] (per cent)
Headache	55
Fatigue	51
Confusion	31
Depression	30
Shortness of breath	29
Arthralgia	26
Myalgia	25
Nausea	20
Dizziness	18
Memory problems	14
Gastrointestinal symptoms	14
Respiratory symptoms	14

The percentage of MCS patients exhibiting a particular symptom

A recent review by Lacour et al (2005) noted also the preponderance of nonspecific CNS symptoms, such as headaches, fatigue and cognitive deficits in self-reported MCS subjects.

The Report of the Inquiry into MCS from the Parliament of South Australia noted a 2004 South Australian Department of Health survey in which the principal symptoms reported by MCS subjects were headaches, asthma or other breathing problems as well as burning eyes, nose or throat. Other symptoms reported were concentration or memory problems, nausea/stomach complaints, muscle pain, dizziness, fever, fatigue, depression and eczema. Other testimonies provided at the Inquiry also attested to the wide variability in symptoms. A similar wide range of symptoms was reported in oral and written submissions to a 2004 West Australian Parliamentary enquiry into health complaints allegedly caused by emissions from the Alcoa refinery at Wagerup (West Australian Legislative Council, 2004).

2.3 IS MCS RELATED TO OTHER SYNDROMES OR DISORDERS?

The symptoms associated with MCS have similarities with chronic fatigue syndrome (CFS), fibromyalgia (FM) and post-traumatic stress disorder (PTSD) (Aaron et al. 2001; Bornschein et al. 2001). One study investigating the medical conditions of navy personnel deployed in the Gulf War reported a higher prevalence of CFS, PTSD, MCS and irritable bowel syndrome compared to other navy personnel (Gray et al. 2002). It has been suggested by others that many cases of these disorders seem to be triggered by short-term stressors, most commonly infection for CFS, physical trauma for FM, severe psychological stress in PTSD and exposure to some environmental agents in MCS (Pall, 2003). This overlap in symptoms has led some researchers to suggest that these illnesses share the same aetiology, or elements of aetiology.

Other syndromes and disorders have been reported to either cause MCS or predispose patients to MCS (see Table 2 below; Staudenmayer et al. 2000; 2003b).

Table 2. Syndromes that may be associated with MCS

Syndrome	Possible Triggers
Sick building syndrome (SBS)	Poor building ventilation and volatile organic compounds
Dental amalgam-induced mercury toxicity	Mercury exposure
Electromagnetic fields sensitivity	Electric or magnetic fields
Gulf War syndrome	Anthrax vaccine, biological or chemical weapons
Reactive (upper) airways dysfunction syndrome (RADS/RUDS)	Respiratory irritants
Chronic toxic encephalopathy	Infectious agent, metabolic or mitochondrial dysfunction, brain tumour, chronic exposure to toxic agents
Chronic Fatigue syndrome (CFS)	Major infection
Fibromyalgia (FM)	Physical trauma
Post traumatic stress syndrome	Severe psychological stress
Irritable bowel syndrome	Food intolerances and allergies, stress

The sick building syndrome (SBS) is a syndrome related to working in a particular building (Burge, 2004). Persons with SBS experience symptoms that include eye, nose and throat irritation, headaches, cough, difficult breathing, fatigue, dizziness and difficulty in concentrating. The cause of SBS is unknown, but it is often thought to result from poor building ventilation causing a build-up of vapours from sources that include building materials, furnishings and office equipment. Occasionally, some people with SBS report that they later develop MCS (Hodgson, 2000).

In the case of individuals who report having increased sensitivity to mercury (dental amalgam-induced mercury toxicity) or electromagnetic fields, their apparent heightened sensitivity to these specific triggers may extend to include other environmental triggers commonly associated with MCS.

In contrast, there is little evidence that other syndromes, such as chronic toxic encephalopathy, CFS, RADS, FM, irritable bowel syndrome or Gulf War syndrome are induced or exacerbated by ambient chemical triggers (Staudenmayer et al. 2003b). However, there are overlaps in symptoms between these conditions and MCS. Buchwald and Garrity (1994) compared 30 adults from the USA with CFS, 30 with FM, and 30 with MCS to evaluate the similarities between these three conditions. Approximately 80% of individuals in both the FM and MCS groups met the Centres for Disease Control and Prevention's (CDC) major criteria for CFS (Holmes et al. 1988), and both groups also frequently reported the symptoms of CFS that are classified as minor criteria for this disorder (Interagency Workgroup, 1998).

Jason et al. (2000) found that out of 90 individuals diagnosed with MCS, 13 (14.4%) met the criteria for CFS and 8 (8.9%) met the criteria for FM. In another study, a similar proportion (15.2%) of cases defined as MCS among British military personnel met the criteria for CFS

(Reid et al. 2001). Deployments to war zones has been associated with increased prevalence of MCS and multi-symptom conditions (Gray et al 2002; Thomas et al., 2006; Österberg et al., 2007).

2.4 WHAT TRIGGERS THE SYMPTOMS OF MCS?

The range of agents described in the literature that are linked with MCS symptoms in susceptible individuals is remarkably extensive and diverse and include synthetic chemicals and physical, non-chemical elicitants such as electromagnetic radiation. Some of these chemicals are listed below (Waddell, 1993).

- Coal, oil, gas and combustion products;
- Mineral oil, Vaseline, waxes;
- Asphalts, tars, resins, dyes and adhesives;
- Disinfectants, deodorants and detergents;
- Rubber, plastics, synthetic textiles and finishes;
- Alcohols, glycols, aldehydes, esters and derivatives.

South Australian Department of Health records show that there is a range of chemicals that people with MCS in that State commonly identifies as problematic, with pesticides such as glyphosate frequently cited.

In addition to the chemicals and agents listed above, the Australian Chemical Trauma Alliance (ACTA), in a written submission to the Parliament of South Australia Inquiry into MCS (SA Inquiry, Social Development Committee, 2005), listed the following as common triggers for MCS:

- Pesticides;
- Fragranced products such as perfumes, aftershave and deodorants;
- Virtually all volatile organic compounds, including paint;
- Cigarette smoke;
- Cleaning products;
- Carpeting, printing ink, soft plastics, synthetic fabrics;
- Chlorinated and fluorinated water;
- Pharmaceutical drugs and anaesthetics;
- Electromagnetic radiation emitted from computers, televisions, mobile and landline phones, appliances with motors, photocopiers and microwave transmitters and high tension power lines.

The SA Inquiry also received submissions from workers who identified particular chemicals as triggers of their MCS. Glutaraldehyde was identified as a chemical of concern for health care workers and hydraulic fluids and lubricants were chemicals of concern for aircraft pilots and cabin staff (Social Development Committee, 2005).

In Australia, health issues linked to MCS have also been related to particular industrial environmental emissions, for example, from the Alcoa refinery at Wagerup (West Australian Legislative Council, 2004).

Ashford and Miller (1998) highlighted the need to distinguish between chemical agents that induce MCS and those that subsequently trigger symptoms once the condition is established.

Studies suggest that "inducing" chemicals may not necessarily be the same as those that thereafter "trigger" symptoms in susceptible individuals. This distinction may explain the difficulty in linking the known toxicity of a chemical to the understanding of symptoms and importantly, establishing effective treatment regimes.

Reported chemical triggering agents for MCS are diverse and often chemically unrelated. Research reports suggest that there is likely to be a psychogenic component in the aetiology of MCS.

QUESTION: are there additional triggers identified in MCS?

2.5 CAN MCS BE CLINCALLY DEFINED?

MCS has proved difficult to define clinically and several attempts have been made to establish diagnostic criteria (Kreutzer, 2000). The term "Multiple Chemical Sensitivities" was first coined by Cullen in 1987 who proposed a case definition. The following description (Cullen 1987) is now the most commonly cited case definition within MCS literature:

> "*The disorder is acquired in relation to some documentable environmental exposure. Symptoms involve more than one organ system and are elicited by chemically unrelated compounds at doses far below that known to cause adverse effects in the general population. No single available test of organ system function can explain symptoms."*

Numerous objections were made subsequently to Cullen's case definition. Ashford and Miller (1991) argued that Cullen's criteria are too narrow to be used in clinical settings. They proposed a definition based on one used by the journal *Clinical Ecology*, with an additional statement that can be used for diagnostic purposes. Their definition stated that: "MCS is a chronic multisystem disorder, usually polysymptomatic, caused by adverse reactions to environmental incitants, modified by individual susceptibility and specific adaptation".

For diagnosis, Ashford and Miller (1991) additionally proposed that a patient could be shown to have MCS under carefully controlled double-blinded conditions when, upon removal of the offending agents, their symptoms cleared and returned when rechallenged by the specific agents.

Definitions proposed by the American National Research Council and Association of Environmental and Occupational Clinics in 1992 incorporated all elements of Cullen's criteria, with the exception of the prerequisite for documentable exposure. On the other hand, Sparks et al. (1994) argued that a major practical limitation of Cullen's criteria is that the exposure-symptom relationship is subjective and non-specific, and would be better established using double-blind, placebo controlled (DBPC) challenge testing.

Other researchers rejected these case definitions on the grounds that objective measures or physical findings do not exist to permit confirmation of any organic dysfunction and that the disorder is patient defined, ie. the physician relies on the patient's reports of symptoms and exposure when making a diagnosis (Gots et al. 1993; Waddell, 1993; American Academy of Allergy and Immunology, 1999).

A World Health Organisation workshop on MCS held in 1996 described the condition as an acquired disorder with multiple recurrent symptoms, associated with diverse environmental

factors that are tolerated by the majority of people and that is not explained by any known medical or psychiatric/psychological disorder. The workshop also concluded that use of the term MCS should be discontinued because it makes an unsupported judgement on causation noting the existence of several definitions of what has been caused MCS. The workshop favoured the descriptor "Idiopathic Environmental Intolerances" (IPCS, 1996).

From a 1989 survey of 89 clinicians and researchers with extensive experience of MCS but with disparate views on its aetiology, five diagnostic criteria were established, defining MCS as follows: "MCS is a chronic condition: (1) with symptoms that recur reproducibly; (2) in response to low levels of exposure ;(3) to multiple unrelated chemicals ;(4) which improve or resolve when incitants are removed" (Nethercott et al. 1993). An additional criterion was included subsequently by Bartha et al. (1999), namely, (5) that "symptoms be displayed in multiple organ systems" to distinguish it from single organ system disorders eg. migraine that may also meet these five criteria.

These six criteria of Bartha et al. (1999) are referred to as the '1999 Consensus Criteria' and are commonly included in research definitions.

The 1999 Consensus Criteria for MCS (Bartha et al 1999)
▪ a chronic condition
▪ symptoms are reproducible with repeated chemical exposure
▪ in response to low-level exposure
▪ involves multiple unrelated chemicals
▪ symptoms improve when triggers are removed
▪ involves multiple organ systems

These Consensus criteria were used in the New South Wales (NSW) Department of Health Adult Health Survey in 2002 where questions on chemical sensitivity were included (NSW Department of Health 2002).

Importantly, as well as identifying these six defining criteria for MCS, Bartha et al. (1999) also noted that a diagnosis of MCS can be excluded if another single multi-organ disorder can be attributable to the entire spectrum of signs and symptoms resulting from a chemical exposure.

In many MCS reviews, this additional seventh criterion requiring a lack of attribution to any other single identified disease process is included as part of the 1999 Consensus Criteria (eg. Read 2002; Social Development Committee 2005).

In a subsequent study of the discriminant validity of different MCS definitions, McKeown-Eyssen et al. (2001) surveyed 4126 Canadians who attended general, allergy, occupational and environmental health practices. The case definitions of Nethercott et al. (1993) and the '1999 Consensus' displayed the greatest discriminant validity for distinguishing patients with the greatest likelihood of having MCS from general practice patients.

Unfortunately, in clinical settings, there still appears to be a lack of standardised criteria for diagnosing MCS. Many environmental physicians find the published case definitions restrictive for diagnostic purposes and also include within the MCS diagnosis people with reactions to one chemical only or people in which some measurable change is produced eg. bronchospasm (Eaton et al. 2000).

Other case definitions have been proposed but not substantially tested or widely acknowledged (Simon et al. 1990; Kipen & Fiedler, 2000). The British Society for Allergy, Environmental and Nutritional Medicine (BSAENM) favoured the criteria proposed by Miller (2000) for so-called toxicant-induced loss of tolerance (TILT) for a diagnosis which relies on the elimination of all other potential causes (Eaton et al. 2000; Miller, 2000). A recent review by Lacour et al. (2005) noted a predominance of non-specific central nervous system (CNS) complaints in self-reported MCS subjects, suggesting that the presence of such CNS symptoms, as well as significant lifestyle or functional impairments for at least 6 months, should be obligatory diagnostic criteria.

While a case definition for MCS has not been universally agreed, the 1999 Consensus Criteria are commonly used in research definitions of MCS and these criteria have been used in Australian surveys.

2.6 DOES MCS HAVE A DISEASE CLASSIFICATION?

MCS is not recognised as a classified disease identity in any country in the world.

In Germany, MCS is included in the alphabetical index of the German version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-SGB-V) first published in November 2000 by the German Institute of Medical Documentation and Information (DIMDI). However, this index is a collection of phrases or diagnoses used by some German clinicians and is not a list of diseases "officially recognised" by Germany (M. Schopen, DIMDI, Personal Communication, 2004).

In Australia, MCS was the subject of public submissions for the inclusion of MCS in the Australian version of the International Classification of Diseases (ICD-10-AM [Australian modification]) in 2003. The classification of diseases is a system of categories to which morbid entities are assigned according to established criteria. Health classifications consist of hierarchical systems of codes for diseases, injuries and interventions as documented in health care services. Currently in Australia, diagnoses and procedures are assigned a series of numerical and/or alphanumerical codes using the ICD-10-AM. This allows the comparison, analysis and interpretation of collected morbidity data.

Despite submissions for the inclusion of MCS, Australia has yet to define MCS as a distinct clinical disease and assign a unique disease code.

Public submissions are reviewed by the National Centre for Classification in Health (NCCH), and then researched and discussed with relevant clinical specialists through NCCH expert advisory groups. In the case of MCS, the Immunology Clinical Classification and Coding Group, the Royal Australian College of Physicians, the Casemix Clinical Committee of Australia and the Australasian Society of Clinical Immunology and Allergy were all consulted.

While the experts involved in considering this proposal in 2003 agreed that there is a set of symptoms that represents an important clinical problem, the proposal for a unique code in ICD-10-AM for MCS was rejected on the following basis (J Rust, NCCH, Personal Communication, 2004):

- There is no clinical or laboratory evidence of an underlying pathological process in patients who have acquired this descriptive label, despite many attempts to identify one over the past 20 years;
- There is a wide spectrum of intolerance/irritation from smells and fumes in the general population and it is not possible to draw any clear dividing line to delineate patients who might fall into the category of the proposed classification;
- There are no internationally accepted diagnostic criteria, nor validated diagnostic tests;
- There are a number of syndromes (i.e. symptom complexes) that appear to overlap with the clinical features proposed for the category of MCS such as CFS and FM. The relationship between these entities and MCS syndrome is unclear at present and this creates difficulty with diagnostic categorisation.

The lack of recognition of MCS as a clinical entity and subsequent classification within the health systems significantly limits the collection and analysis of morbidity data.

2.7 DO INDIVIDUALS WITH MCS SHARE COMMON CHEMICAL EXPOSURES?

Currently, there are no epidemiological data that link MCS subjects or those who may be susceptible to MCS with particular chemical exposures or lifestyles. In the published literature, MCS subjects generally are described as female, between the ages of 30-50 years, and with an above-average socioeconomic status (Black et al. 1990; Asford & Miller, 1991; Cullen et al. 1992; Sparks et al. 1994; Lax and Henneberger, 1995; Miller & Mitzel, 1995; Fielder & Kipen, 1997; Levy, 1997).

Ashford and Miller (1998) claimed the following groups of people in the USA have a heightened reactivity to low level exposure to chemicals:

- Industrial workers exposed occupationally to chemicals as part of their daily activities;
- Office workers working in airtight buildings;
- Individuals who may be located in areas of contamination (such as contaminated sites or close to known sources of pollution);
- Individuals who receive an unexpectedly debilitating exposure to a chemical.

A more recent Canadian survey reported a female bias among MCS subjects, and also reported that MCS (together with other medically unexplained physical symptoms) were more common in low income households (Park and Knudson 2007).

With regards to the role of occupational chemical exposure and MCS, a study in the USA reported that only approximately 27% of MCS subjects were occupationally exposed to chemicals, such as in the construction and manufacturing industries (Cullen et al. 1992). Lax and Henneberger (1995) identified 35 of 605 new patients at an occupational health clinic from 1989-1991 who met a case definition similar to that proposed by Cullen (1987). In this study, 54% of the non-MCS patients worked in industries considered to have a greater potential for hazardous chemical exposures than other occupational settings. In contrast, only 26% of the MCS patients were employed in the more hazardous industries.

Little information is available to determine whether occupational susceptibilities exist in Australia. The 2005 SA Inquiry into MCS received several submissions from health care workers who identified chemicals such as cleaning agents, glutaraldehyde and formaldehyde

as triggers of their MCS. The Glutaraldehyde Affected Support Persons injured nurses group (GASPing) identified glutaraldehyde as a chemical of particular concern for health care workers. Similarly, pilots and other aircrew identified lubricants and hydraulic fluids as responsible for their diagnoses of MCS. In general, the inquiry heard that a wide range of people in different occupational groups such as in the health care industry, aviation industry, farmers, mechanics and aluminium workers at Alcoa in Wagerup displayed symptoms of MCS (Social Development Committee, 2005). Although submissions to this parliamentary inquiry suggested a strong link between occupational exposures to chemicals and MCS in Australia, supportive studies providing epidemiological data are lacking.

Overall, available data are currently inadequate to identify individuals who are at risk of developing MCS on the basis of the type or extent of their chemical exposures. The new Australian National Occupational Disease System developed in 2007 is noted. The Australian Safety and Compensation Council (ASCC) has developed the Australian Hazard Assessment database (AHEAD) which contains data arising from surveys of workers self reported exposures and measures of actual exposure. The data base will also cover chemical exposures. It is anticipated that the top line findings from the initial survey data are expected to be published by ASCC in mid 2008.

3 WHAT CAUSES MULTIPLE CHEMICAL SENSITIVITY

The literature relating to causes of MCS invariably highlights differences in views regarding the primary underlying cause of MCS- ie. psychogenic or toxicodynamic. There is much debate as to whether MCS symptoms are due to psychosomatic response to perceived chemical toxicity or to a physiological/pathological interaction between chemical agents and organ systems. While some physicians believe MCS is purely a psychological disorder, others consider it to be an overt, albeit poorly understood, physiological response to chemical exposure. It is also possible that both physiological and psychological factors play a part in the pathogenesis of MCS (Bock and Birbaumer 1997; Österberg et al 2005; Das-Munshi et al., 2007; Haustener et al., 2007).

Despite, or perhaps because of this debate, the underlying biological basis for MCS and its range of variable symptoms remains unresolved. Indeed, a review by Winder (2002) identified no less than 24 possible causative mechanisms.

Mode of Action
A useful framework when considering the biological basis for an adverse health outcome is the concept of a *mode of action - mechanism of action continuum***.** This facilitates understanding of the different evidential needs in establishing a cause for an observed effect. This concept is used in chemical risk assessment and assists in determining the level of evidence needed in making a regulatory decision in relation to adverse effects observed in animal models or symptoms observed in humans.

Mode of action is defined as a series of key biological events leading to an observed toxicological effect (for example, metabolism to a toxic entity, cell death, regenerative repair and tumours). While a hypothesized mode of action is supported by experimental observations and related mechanistic data, it contrasts with mechanism of action, which generally involves a sufficient understanding of the molecular basis for an effect.

The concept of mode of action is becoming increasingly important in interpreting toxicological data in the context of risk assessment and in recommending additional relevant research. It is possible that more than one mode of action may be involved in producing the range of symptoms associated with MCS.

3.1 OVERVIEW OF POSSIBLE MCS MODE (S) OF ACTION

Using the mode of action level of proof as the benchmark appropriate to trigger regulatory, clinical or other action on the causative agent(s) of MCS, a review of the available literature was undertaken to identify which scientific reports of the cause(s) of MCS are most discussed as reflecting biologically plausible and scientifically testable hypotheses. This analysis identifies those theories that warrant further research/testing including in the clinic.

The identified hypotheses for the causes of MCS are presented below (in no specific order).

NOTE: Given difficulties in characterising MCS, this discussion of hypotheses is not exhaustive and may be regarded by some as incomplete. Additionally, there may be views that the weight of evidence for particular hypotheses is stronger than summarised here.

Additional scientific information on these or for other testable hypotheses for modes of action to explain the aetiology and pathogenesis of MCS is required.

3.1.1 Immunological dysregulation

Hypothesis: Immune dysregulation proposes that MCS is caused by a chemically induced disturbance of the immune system (Levin & Byers, 1987; 1992; Meggs, 1992, 1993). Within this theory, a distinction is made between immune mechanisms inducing heightened chemical sensitivity in MCS and those involved in classical allergic reactions.

A classical allergic reaction involves a specific cell or antibody-mediated response that alerts the body to the allergen and results in changes to some immunological parameters (such as increased serum IgE, IgG, complement levels or lymphocyte counts) that can be measured biochemically. It has been noted that a common marker of allergic disease (ie. increases in serum IgE) are not found in MCS subjects (Labarge & McCaffrey, 2000; Bailer et al. 2005). However, details of pathogenetic mechanisms supporting immune dysregulation as a cause of MCS have not been provided.

Although some individual MCS patients do show alterations of certain immunological variables such as changes in peripheral blood lymphocyte subsets, increases in the proportion of circulating activated T-cells or abnormal serum antibodies to tissue antigens and chemical-protein conjugates (Rea et al. 1992; Thrasher et al. 1990; Heuser et al. 1992; Levin & Byers, 1992), no consistent pattern of abnormality indicative of a specific immunological deficit has been found (Simon et al. 1993; Graveling et al. 1999).

Overall, although some researchers acknowledge that allergic or immunotoxicologic reactions could be contributing factors in at least a subset of MCS patients (Selner & Staudenmayer, 1992; Albright & Goldstein 1992; Meggs, 1992; Interagency Workgroup, 1998), the role of the immune system in MCS is difficult to assess from the published reports because of the lack of standardised protocols, wide variations in patient test results and the lack of controls for variables that influence the immune system (eg. stress, smoking) (Gad, 1999).

Research challenge: Further work is needed to examine whether immunological dysregulation is associated with MCS. Such work should include validated immune measurements with appropriate quality controls, well-defined clinical groups and specific chemical challenges (Mitchell et al. 2000).

3.1.2 Respiratory disorder/neurogenic inflammation

Hypothesis: Respiratory disorder/neurogenic inflammation suggests that MCS may be initiated by interaction of chemical irritants with sensory nerves. In essence, the theory suggests that inhaled chemicals bind to receptors on sensory nerve C-fibres in the nasal mucosa which trigger the local release of inflammatory mediators from nerve endings, leading to altered function of the respiratory system.

In addition to respiratory effects at the site of chemical stimulus, multiorgan effects seen in MCS are thought to occur via a neurogenic inflammatory switching mechanism whereby antidromic sensory nerve impulses conducted through the central nervous system release inflammatory mediators at distant tissue sites. Parallels are drawn with a reputed neurogenic mechanism in disorders such as rheumatoid arthritis, migraine headache and FM (Bascom, 1992; Meggs, 1995, 1999; Meggs et al., 1996; Read, 2002).

Meggs and Cleveland (1993) conducted rhinolaryngoscopic examinations of the nose and throat in 10 MCS sufferers and reported chronic inflammatory changes in all subjects. One research group suggests that patients who develop rhinitis after a single high-dose exposure to a chemical may go on to develop a chronic intolerance to low levels of chemicals and/or their associated odours (Meggs, 1995, 1999). Bascom (1992) suggested that neurogenic inflammation resulting from chronic irritation of the nasal mucosa could explain the lower sensitivity thresholds of some MCS patients.

The sensitivity and specificity of chemosensory reactions have been tested in controlled challenge studies in MCS patients. In a double-blind placebo-controlled (DBPC) challenge study by Staudenmayer et al. (1993) using an olfactory masking agent, MCS patients (n=20) were unable to reliably differentiate active agents from the placebo (clean air containing olfactory masker). 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).

In another DBPC challenge study, no significant changes were seen in the olfactory thresholds for phenylethyl alcohol or methylethyl ketone in 18 MCS sufferers compared to an age and gender matched control group. This study did, however, note significantly higher total nasal resistances and higher respiratory rates in MCS sufferers compared to controls (Doty, 1994). Hummel and colleagues found that olfactory thresholds remained unchanged in a DBPC study involving 23 MCS patients (diagnosed according to Cullen's criteria), exposed to either room air or a low concentration of 2-propanol. However, challenges with 2-propanol did produce increases in odour discriminatory performance in these individuals compared to that with room air suggesting an increased susceptibility to volatile chemicals. Also, around 20% of the MCS patients presented symptoms regardless of the type of challenge, suggesting the susceptibility of MCS patients to unspecific experimental manipulations (Hummel et al. 1996).

In a review that included an extension of the above work, Dalton and Hummel (2000) found that olfactory thresholds of the 23 MCS patients were not significantly different from separately tested age and gender matched controls. Also in this study, twice as many MCS patients compared to controls reported symptoms regardless of the type of challenge, suggesting higher susceptibility of MCS patients to non-specific experimental conditions. These authors concluded that differences between MCS patients and controls regarding reactions to intranasal challenge with environmental odours appear to reflect changes in cognitive perceptual processing ie. how odours are perceived, rather than differences in sensitivity or chemical sensory processing (see Section 2.2.4 Odour Perception).

Research challenge: The available data suggest that there may be some effects on nasal or upper airways in at least some MCS patients. However, altered nasal mucosa and other respiratory changes such as increased nasal resistance alone cannot account for the multiple organ system pathology reported in MCS. Further, the involvement of a neurogenic switching mechanism to explain multiple organ pathology (Meggs & Cleveland 1993; Meggs 1995; 1999) has not yet been demonstrated in MCS sufferers (Graveling et al., 1999).

3.1.3 Limbic kindling/neural sensitisation

Hypothesis: The limbic system is a group of interconnected brain structures involved in olfaction, emotions, learning and memory. The limbic system participates in the regulation of

many cognitive, endocrine and immune functions and is particularly vulnerable to sensitisation processes, with repeated exposures to a given stimulus over time leading to increased responsiveness (Gravelling et al. 1999; Sparks, 2000b). Bell and colleagues postulated that olfactory-limbic system dysfunction could lead to polysymptomatic conditions involving multiple organs, such as those experienced by MCS sufferers (Bell et al. 1992; 1997; 1998).

Sensitisation in the context of behavioural studies commonly refers to a progressive increase in behavioural or neurochemical responses after repeated exposures to stress or drugs of abuse. Kindling is a form of sensitisation and is defined as the ability of a repeated, intermittent electrical or chemical stimulus that was previously unable to induce a response, to induce seizure activity in later applications (Sparks, 2000b). Animal studies have demonstrated a variety of acute and chronic changes in brain physiology and behaviour in response to electrical or chemical stimuli (Antelman, 1994; Gilbert, 1995; Sorg et al. 1998; Sorg, 1999; Labarage & McCaffrey, 2000).

In the context of MCS, several researchers have proposed that limbic kindling is a form of time dependent sensitisation, whereby mild chemical stressors (pharmacological or environmental) are able to induce physiological effects that then are amplified with the passage of time (Antelman, 1994) and that limbic kindling may play a role in the aetiology of MCS (Bell et al. 1992; Miller, 1992).

The olfactory-limbic neural sensitisation model of MCS proposes that individual differences in reactivity to environmental substances derive from neurobiologically based differences in susceptibilities of the olfactory, limbic, mesolimbic and related pathways of the CNS to sensitisation (Bell et al. 1992; 1997; 1998). This model notes this point of interaction between nervous, immune and endocrine systems within the central nervous system as an explanation of the wide variety of symptoms expressed in MCS. The neural sensitisation model claims that increases in limbic neuronal network excitability may augment reactivity to low-level chemical exposures.

Early studies attempted to map the electrical activity in the brains of MCS subjects. Unfortunately, these were not able to demonstrate conclusive evidence of electrical abnormalities in these subjects, due to poor experimental techniques and lack of appropriate control groups (Mayberg, 1994). A later neuropsychological study by Brown-DeGagne & McGlone (1999) examined the cognitive profile of MCS subjects within the framework of Bell's olfactory-limbic model. Matched group comparisons found that MCS subjects performed as well as control subjects on all cognitive tasks. However, confounding factors such as the use of medications or chronic illness were not considered when determining the effect on cognitive responses. Thus, no definitive conclusions could be drawn regarding the validity of the olfactory-limbic model from this study.

Positron emission tomography (PET) was used by Bornschein et al (2002b) to determine whether neurotoxic or neuroimmunological damage could be detected in the brains of 12 MCS patients. Mild glucose hypometabolism was present in one patient, however, compared to normal control subjects, MCS patients did not show neurotoxic or neuroimmunological brain changes of functional significance.

In a study of odour thresholds and perceptions, Caccappolo et al. (2000) assessed odour detection thresholds to phenylethyl alcohol and an unpleasant-smelling pyridine. No

differences were found between MCS subjects (n=33), CFS subjects (n=13), controls (n=27), and asthma patients (n=16). When exposed to suprathreshold concentrations of phenylethyl alcohol, MCS subjects reported significantly more trigeminal symptoms and lower aesthetic ratings of phenylethyl alcohol, but did not demonstrate lower olfactory threshold sensitivity or enhanced ability to identify odours (Caccappolo et al. 2000). This study reinforces the notion that MCS subjects do not have increased odour sensitivities compared to healthy individuals and that cognitive, non-sensory factors play a role odour perception (Dalton and Hummel, 2000).

A more recent study of odour processing in MCS subjects was conducted by Hillert et al. (2007) using PET. Following odour challenges, MCS subjects showed *less* activation of normal odour processing brain regions compared to control subjects (measured by changes in regional cerebral blood flow), despite discomfort reported and physiologically confirmed by decreased electrocardiogram waveform intervals. Moreover, MCS subjects showed an odour-related increase in activation of the anterior cingulate cortex and cuneus-precuneus, effects not seen in controls. The authors reported no evidence of general neuronal supersensitivity in olfactory circuitry and concluded that MCS subjects process odours differently than normal individuals, without signs of neural sensitisation. A "top-down" modulation of odour responses through brain regions involved in anticipation, attention, conditioning, harm avoidance and perceptual selection was suggested.

Research challenge It has also been proposed that sensitisation of the limbic system can be induced or augmented by psychosocial stress or "life trauma" events. Once sensitised, the limbic system reacts to a greater number of triggering events that include chemicals, noise and electromagnetic radiation (Arnetz, 1999). Support for the Arnetz model of limbic sensitisation in MCS may be drawn from an animal study by Friedman et al. (1996) demonstrating that in mice, stress significantly increased blood brain barrier permeability to peripherally administered Evan's blue–albumin, plasmid DNA and the acetylcholinesterase inhibitor pyridostigmine. These findings suggest that peripherally acting chemicals administered under stress can reach the brain and affect centrally controlled functions (Friedman et al. 1996). Indeed, some researchers have reported that one of the strongest predictors of MCS is psychiatric morbidity prior to the onset of MCS symptoms (Simon et al. 1990; Reid et al. 2001).

Since both animal and human studies have demonstrated direct olfactory neurological pathways from the olfactory region of nasal cavity to the brain, the model also postulates that in humans the nose offers a direct pathway into the limbic system for many molecules via the nasal mucosa and olfactory nerves bypassing the blood brain barrier. However, although nose to brain transport via olfactory nerves has been demonstrated in animals, the evidence of such a transport mechanism in humans is much less complete and still the subject of debate (Illum, 2004).

With regard to levels of exposure necessary for kindling to occur, chemical kindling or time-dependent sensitisation in animals typically occurs in response to pharmacologically effective doses of chemicals rather than at the low doses alleged to cause MCS in humans. This suggests that if limbic kindling was part of the aetiology of MCS, a higher prevalence of MCS would be expected in individuals with higher levels of chemical exposure, such as those exposed to chemicals in industrial settings, which is not the case (Labrage & McCaffrey, 2000).

3.1.4 Elevated nitric oxide, peroxynitrite and NMDA receptor activity

Hypothesis: Pall (2002; 2003) hypothesised that the hypersensitivity reportedly experienced by MCS sufferers can be explained by interconnected, synergistically operating biochemical mechanisms involving stress-related increases in nitric oxide, the oxidative product peroxynitrite and increases in the sensitivity of N-methyl-D-aspartate (NMDA) receptors in the limbic system of the CNS.

This theory suggests that hypersensitivity arises through a limbic kindling/neural sensitisation process involving short-term stressors such as viral or bacterial infections, chemical exposure or psychological stress that stimulate NMDA receptors producing elevated levels of nitric oxide and peroxynitrite. This is followed by cycles of interconnected reactions such as a) nitric oxide acting as a retrograde messenger and stimulating neurotransmitter (glutamate) release, leading to increased NMDA receptor activity, b) nitric oxide inhibiting cytochrome P450 leading to decreased degradation of environmental chemicals, c) nitric oxide reacting with superoxide to form peroxynitrite which induces increased sensitivity of NMDA receptors and d) peroxynitrite-mediated increased in blood brain permeability, leading to increased access of chemicals to the central nervous system.

The chronic nature of MCS is postulated to occur from continued propagation of these mechanisms. More recent developments of this theory also implicate increased activity of vanilloid receptors (Pall, 2004; 2007). Differences in symptoms in MCS are explained by variations in the tissue distribution of these reactions. In putting forward this mode of action for MCS, the author suggests that MCS would be best treated by agents that down-regulate nitric oxide-peroxynitrite biochemistry.

Research challenge While this theory has not been refuted, there is no *de novo* scientific evidence to support it. For example, given the central role of nitric oxide, peroxynitrite and NMDA receptors in this theory, the effect of agents that disrupt this biochemistry, such as nitric oxide scavengers, synthesis inhibitors or NMDA antagonists, has not been investigated in MCS.

Additionally, this theory implicates hydrophobic organic solvents and organophosphate- or carbamate-based pesticides as the triggering agents (stressors), but the triggers of MCS symptoms are diverse and often include hydrophilic solvents such as alcohol (ie. perfumes) or other pesticides, such as malathion. Indeed, some researchers have shown that alcohols actually inhibit NMDA receptors (Peoples & Ren, 2002), rather than stimulate. Furthermore, given that this hypothesis utilises the limbic kindling/neural sensitisation theory to explain the multiple organ symptoms, this hypothesis draws the same criticisms as the limbic kindling/neural sensitisation model presented above.

3.1.5 Toxicant-induced loss of tolerance (TILT)

Hypothesis: Miller (1997) proposed another disease theory, TILT, to explain MCS pathogenesis. This theory suggests that acute or chronic chemical exposures can cause susceptible persons to lose their tolerance to previously tolerated chemicals, drugs and foods. Once sensitised, low-level exposure to a plethora of substances may trigger symptoms. Miller argues that TILT may prove to be a new theory of disease causation parallel to the germ, immune and cancer theories.

No mechanism is proposed to account for the initial loss of tolerance or the apparent spread of sensitivity to other unrelated chemicals. The diverse symptoms associated with MCS is explained with use of a masking concept, with the specific response to a particular toxicant being masked by responses to other exposures still affecting the person (Miller 1996, 1997; 2000; Miller et al. 1997; 1999a, b). According to this theory, the diagnosis of sensitivity depends on optimising experimental conditions using an environmental medical unit to "unmask" patients and remove the influence of background trigger substances.

Research challenge: According to Miller et al, studies generally have failed to unmask patients before challenge.

3.1.6 Behavioural conditioning

Hypothesis: Some researchers have proposed a behavioural conditioned response to chemical odours in MCS, in which a strong-smelling, chemical irritant causes a direct and unconditioned physical or psychophysiological response (Bolla-Wilson et al. 1988; Shusterman et al. 1988; Siegel 1999). Subsequent exposure to the same irritant at much lower concentrations elicits a conditioned response of the same symptoms. Examples of documented conditioning-related phenomena include pharmacological sensitisation, conditioned immunomodulation and odour/taste aversion (Siegel and Kreutzer, 1997; Giardino and Lehrer, 2000).

Adverse conditioning stimuli may be psychological as well as physiological. Pennebaker (1994) reported that MCS subjects are often people who have suffered traumatic experiences before reporting their symptoms. Deployments to war zones are associated with increased prevalence of MCS and multi-symptom conditions (Thomas et al., 2006; Österberg et al., 2007; also see Section 2.3).

In experimental trials of conditioned reactions in healthy subjects, Van den Bergh et al (1999) demonstrated that subjects can acquire and then lose somatic symptoms and altered respiratory behaviours in response to harmless, but odorous chemical substances, if these odours were associated with an unrelated symptom-inducing physiological challenge (hyperventilation from exposure to CO_2 enriched air). The conditioned responses were modest but reproducible and support the view of MCS at least in part as a behavioural conditioning. Subsequently, through stimulus generalisation, other odorous agents may begin to elicit the conditioned response or even the perception of exposure (Bolla-Wilson et al., 1988; Devriese et al, 2000; Lehrer, 2000).

Research challenge: Behavioural conditioning, however, does not explain directly the diverse range of symptoms reported by MCS sufferers. Additionally, in many cases, there appears to be no substantial initial exposure event that would constitute the unconditional stimulus (Sparks, 2000b).

3.1.7 Psychiatric disorders

Hypothesis: Psychiatric factors have variously been seen as the *cause* of MCS, an *effect* of having MCS, a *predisposing factor* in the development of MCS, and a *co-morbid* occurrence with MCS.

Various investigators claim MCS is a somatoform reaction (i.e. physical symptoms not explained by objective clinical findings), a depressive disorder, post-traumatic stress disorder or a panic disorder (Fiedler & Kipen, 1997; Interagency workgroup, 1998; Labrage &

McCaffrey, 2000). The importance of interactions between biological, psychological and social factors in the aetiology of psychological disorders has also been noted (Barlow, 1993) and the use of neuropsychological testing in MCS has been reviewed (Bolla, 2000).

Some researchers also suggest that MCS is an iatrogenic disorder where those providing treatment may inadvertently provide support to their symptoms and concepts of illness (Black, 1995; Labrage & McCaffrey, 2000; Sparks 2000a).

The prevalence of psychiatric morbidity in MCS has been studied. Black (2000) reported that depending on the assessment procedure used, the prevalence of psychiatric disorders in MCS subjects is 42-100%. In 1990, Black et al. studied 26 subjects diagnosed with MCS and noted that psychiatric assessment revealed the majority (87%) exhibited a major mental or personality disorder not appropriately diagnosed or treated. A follow up study in this group some 9 years later showed a persistence of psychopathology (Black et al. 2000b). In a review of 8 psychological studies reporting varying diagnostic methods, Bornschein et al. (2001) found that psychiatric disorders were found in 36-100% of MCS subjects. Bornschein et al. (2002a) also reported that psychiatric morbidity was high (75%) amongst 264 patients presenting to specialised centres for environmental medicine in Germany. Somatoform disorders (35%), followed by depressive (19%) and anxiety (21%) disorders were the leading diagnostic categories, with < 2% diagnosed with 'chemical sensitivity'. Similarly, of 65 individuals attributing hypersensitivity to indoor air pollutants, 38 (58%) were reported by Eberlein-Konig et al. (2002) to show a psychosomatic or psychotic disorder.

Associations between particular psychological dispositions and MCS have also been drawn from experimental studies. In challenge studies using known triggers of panic attacks (intravenous sodium lactate or carbon dioxide), between 71-100% of MCS patients were reported to experience panic attacks compared to 26% of controls (Simon et al. 1993; Binkley & Kurcher, 1997). Also from challenge studies, signs and symptoms of MCS were reported to be consistent with an anxiety reaction and hyperventilation (Leznoff 1997; Leznoff & Binkley, 2000). As a result of these studies, Leznoff and coworkers suggest that MCS manifests as an anxiety syndrome triggered by the perception of an environmental insult, with at least some symptoms (brain fog or hypocarbia) induced by hyperventilation.

Similar findings were noted in a study by Tarlo et al. where 11 of 15 MCS subjects exposed to their purported chemical trigger experienced hypocarbia driven by hyperventilation that resulted in MCS symptoms (Tarlo et al. 2002). Further support for the association between panic disorder and MCS comes from genotypic analysis of MCS subjects, which show the presence of panic disorder-associated cholecytokinin B receptor alleles in 41% of MCS subjects compared to controls (9%) (Binkley et al., 2001).

Other researchers have reported that the strongest predictors of MCS are, firstly, histories of somatisation ie. converting mental experiences or psychological states to bodily symptoms, and, secondly, psychiatric morbidity prior to the onset of MCS symptoms (Simon et al. 1990; Reid et al. 2001). Bailer et al. (2005) in a study comparing one group of individuals reported to have MCS and another group reported to have somatoform disorders found similarities in symptoms and psychological features between the two groups. A more recent longitudinal study showed both disorders were present in over 90% of respective subjects at 1 year follow-up (Bailer et al., 2007). Both MCS and somatoform groups scored significantly higher than a control group on all measures of somatic symptoms and psychological predictors for somatization. The authors concluded that trait negativity and symptom perception,

interpretation and attribution contribute substantially to the persistence of typical somatoform symptoms in both groups and that treatments for both disorders should address these psychological factors.

In a study to identify early psychological determinants for the development of MCS, Österberg et al. (2006) found that otherwise normal, occupationally engaged individuals who claimed to be annoyed by both chemicals/smells and electrical equipment, or by electrical equipment alone, showed strongly elevated trait anxiety/neuroticism personality traits, mental distress and subjective health complaints. Similar, but much less marked, anxiety dispositions were observed in individuals claiming to be annoyed by chemicals/smells alone. The authors claim that although it cannot be discounted that measured emotional characteristics were the result of, and not a predisposing factor in sensitivities to chemicals/smells and/or electrical equipment, these findings in otherwise normal non-patient participants indicate that anxiety might be an important baseline factor for the acquisition of MCS.

Research challenge: Despite evidence of psychiatric comorbidity in MCS, an important question is the extent to which this is the *cause* or an *effect* of an individual's MCS condition. Davidoff et al. (2000) documented similarities between the psychopathological profiles of MCS sufferers and psychopathological profile changes, predicted by professionals that would likely occur in normal individuals as a result of MCS or a similar chronic condition. They concluded that inferences of mental ill health in chronically sick people may be inevitable and inappropriate with "one shot" psychological profiling and that distinguishing preexisting psychopathology and psychopathology secondary to organic disease in MCS with such profiling may be misleading.

3.1.8 MCS as a 'belief system'

Hypothesis: Sparks (2000b) suggests that MCS is a phenomenon best described as a 'belief system' characterised by an overvalued idea of environmental hazards and their debilitating effects, pointing to evidence illustrating that individual belief systems can be manipulated or conditioned to respond to innocuous, yet odorous triggers that can cause pathophysiology associated with MCS. Behavioural approaches to MCS therefore should aim towards symptom desensitisation and the prevention of reinforcement of illness behaviour (Sparks, 2000b).

A recent review of behavioural and social factors in MCS concluded that MCS can be conceptualised using a multi-factorial model, incorporating physiological, social and psychological factors. Physiological processes such as exposures to odours under distressing circumstances may interact with beliefs, perhaps engendered by media reporting, reinforcing the interpretation of somatic sensations as pathological. Protracted courses of avoidance may lead to chronic disability, in part perpetuated by iatrogenic influences from unproven therapies sought from perceived experts (Mayou et al. 2005; Das-Munshi et al., 2007). A similar conditioning model of MCS is also proposed by Österberg et al (2007) who identify the need for cognitive-behavioural therapy via a large scale treatment study to validate this model and establish effective treatment regimes.

Hausteiner et al. (2007) recommends treating MCS as a somatoform disorder also with special emphasis on the role of threat beliefs. To these authors, an integrative psychiatric approach to MCS is advantageous in that it acknowledges the patients beliefs, perceptions and complaints as real, without necessarily supporting, or requiring, a toxicological explanation, and which can provide a basis for a therapeutic relationship focussing on patient

history and environment, coping strategies and improved quality of life. Lastly, they hold MCS as an illustrative example towards a more integrated and dynamic understanding of illness in general, beyond the restrictive body-mind dichotomy.

3.1.9 Odour perception

Hypothesis: A review of chemosensory function by Dalton and Hummel (2000) concluded that differences between MCS subjects and controls in reactions to intranasal challenge to environmental odours appear to reflect changes in cognitive peceptions rather than differences in sensitivity or chemical sensory processing. Also in FM patients in which olfactory function was assessed objectively, individuals appeared to show normal sensitivity to threshold concentrations and decreased responses to supra-threshold stimuli. However, when assessed subjectively ie. via self-report, these patients rated themselves as more sensitive than the controls. This was despite odour identification task scores for these patients being significantly lower than the controls (Dalton & Hummel, 2000).

MCS subjects have been reported to identify odours equally as well as healthy subjects, but experience more unpleasant reactions to common odours compared to controls (Ojima et al. 2002). Georgellis et al. (2003) reported no differences in the sensations of smell between male painters reporting MCS and matched controls, suggesting that olfactory-sensory function does not differ between painters with and without MCS. However, subjective ratings of irritation of the nose, eyes and airways were significantly higher in the MCS group compared to controls. Increased subjective irritation has been noted also in other investigations (Doty et al., 1998; Fernandez et al, 1999; Dalton and Hummel, 2000; Österberg et al., 2003).

Healthy individuals can acquire somatic symptoms and altered respiration in response to harmless, but odorous chemical substances, especially if an odour has been previously perceived to be the cause of symptoms (Van den Berg et al. 1999) (see Section 3.1.6). Healthy subjects can also experience either ‘adaptation’ or ‘sensitisation’ to odours, depending on whether subjects are led to believe the odour was natural and healthy, or potentially hazardous (Dalton & Hummel, 2000). Also, frequencies and intensities of self-reported irritation and “cued” symptoms have been shown to be significantly higher for subjects exposed to negative information regarding an odour compared to those exposed to neutral or positive information (Dalton and Hummel 2000; Van den Berg et al. 2001). A recent challenge study on healthy volunteers showed that worrying information that a specific harmless odour cue was associated with a symptomatic episode was more powerful than an actual symptomatic exposure (harmless odour plus CO_2 enriched air) in provoking self-reported respiratory symptoms (Devriese et al. 2004).

A systematic review of provocation studies in MCS by Das-Munshi et al. (2006) revealed thirty-seven studies in which a total of 784 MCS subjects were compared to 547 control subjects and 180 subjects amongst whom a subset were chemically sensitive. The review concluded that blinding was inadequate in most studies. In 7 studies in which chemicals were used at or below odour thresholds, 6 studies failed to show consistent responses amongst sensitive individuals after active provocation. In 21 studies in which chemical odours were likely to be above the odour threshold, 19 reported positive responses to provocations amongst chemically sensitive individuals. The authors concluded that MCS subjects do react to chemical challenges, but that these responses occur when discernment is possible between active and sham substances, suggesting that the mechanism of action is not chemical-specific, but related to expectations.

In a recent study in Australia, a review of air emissions from an alumina refinery (Wagerup) and community health complaints some of which were linked to MCS concluded a discontinuity between technical findings on health risks and the perceptions of these risks associated with industrial emissions. The authors concluded that some individuals attributed incidental health symptoms to the detection of refinery odours rather than to exposure to emissions likely to result in health effects. They noted the importance of effectively addressing both technical and perceptions-of-risk issues for organisations responding to community concerns (Donoghue and Cullen, 2007).

3.1.10 Other proposed mechanisms

3.1.10.1 Altered metabolism

Altered metabolism of toxic chemicals is another postulated mechanism for MCS. One case control study of MCS genotypes reported that individuals with higher hepatic cytochrome P450 isozyme CYP2D6 gene activity and NAT2 rapid acetylator gene activity are at greater risk of developing MCS (McKeown-Eyssen et al. 2004). However, a more recent cross-sectional study of gene variants in MCS revealed that self-reported chemical sensitivity cases were significantly more frequently of the NAT2 slow acetylator genotype (Schnakenberg et al., 2007). These contrasting results were explained by differences in case inclusion criteria (Schnakenberg et al., 2007).

NOTE: Although the results from these studies appear to be contradictory, they may stem simply from differences in chemical exposures, as MCS is regarded as a disorder linked to exposures to multiple unrelated chemicals. The hypothesis of metabolic predispositions as an explanation for MCS would benefit from additional information on genetic or biochemical profiling of MCS individuals and reported triggers.

3.1.10.2 Disrupted haem synthesis

Some researchers have suggested that MCS may represent a disturbance in haem synthesis (porphyria), since the clinical manifestation of porphyria can be triggered by chemical exposure and its symptoms have similarities to MCS (Donnay & Ziem, 1995; Ziem & McTammey, 1997). Others question whether there is convincing evidence of an increased prevalence of abnormal haem synthesis associated with MCS. Further, porphyrias triggered by chemical exposure are linked to exposure magnitudes above those purported to be related to MCS (Labrage & McCaffrey, 2000).

3.1.10.3 Serum and intra-erythrocyte biochemical changes

Some clinicians have suggested that altered serum biochemistry and haematology may reflect organ dysfunction in MCS. In a case control study, Baines et al. (2004) conducted routine biochemical analyses and assays of levels of volatile organic compounds in serum samples from 223 females with MCS and 194 normal individuals. The biochemical analyses revealed clinically unimportant case-control differences in means. MCS was negatively associated with lymphocyte counts and total plasma homocysteine, and positively associated with mean cell haemoglobin, alanine aminotransferase and serum vitamin B6. In MCS cases, serum chloroform levels were higher and ethylbenzene, xylene, 3-methylpentane and hexane levels were lower. The findings were regarded as inconsistent with proposals that MCS is associated with vitamin deficiency or thyroid dysfunction, but lower lymphocyte levels in MCS individuals may indicate immune dysfunction.

Symptoms associated with specific mineral deficiencies are held by some to be consistent with symptoms displayed in cases of MCS. Baines et al. (2007) recently evaluated intra-erythrocyte mineral (IEM) levels in a total of 216 women with MCS and 192 case-controls. No statistically significant differences in mineral levels between the two groups of women were observed. However, mean levels for copper, chromium, magnesium, molybdenum, sulphur and zinc were all lower in the MCS group. The authors concluded that IEM measurements do not appear to be a useful diagnostic marker for MCS.

3.2 COMMENTARY ON THE PROPOSED MODELS OF MODES OF ACTION

Whether MCS is a disorder with an underlying toxicodynamic cause or a psychogenic cause, or is particularly the result of both is not clear from the analysis of the available scientific literature.

The currently available toxicological information does not support the view that MCS arises solely from the toxic effects of low-level exposure to chemicals in the environment. Specifically, it does not explain the diverse symptoms affecting multiple organ systems or the diverse range of triggering agents. Furthermore, it cannot be explained why the same chemical trigger can induce different symptoms in different MCS patients. No currently known biological mechanisms, processes or anatomical alterations can adequately explain such divergent effects (Gots & Pirages, 1999).

Currently, the most biologically plausible (and testable) physiological mechanisms could be regarded as neurogenic inflammation resulting from chemical interactions with sensory nerve C fibres, and limbic kindling ie. sensitisation of the limbic system from chemical exposure via olfactory neural pathways and/or psychosocial stress.

Animal studies have demonstrated several pathways providing a conduit for molecules from the nasal passages to the brain bypassing the blood brain barrier. Molecules can be transported from the olfactory region in the nose directly to the brain via retrograde transport in olfactory neurons or into the cerebrospinal fluid via the olfactory epithelium (Illum, 2004). Although the mechanisms governing uptake are still unclear, evidence suggests such an uptake pathway for at least some types of molecules in humans and therefore the potential for chemical sensitisation of the olfactory, limbic, mesolimbic and related pathways of the CNS.

Additional initiators such as psychosocial stress or “life trauma” events have been implicated in the neural sensitisation of the limbic system, which is believed then to become hypersensitive to a range of environmental triggers. Support for the potential of psychosocial cofactors to augment or induce neural sensitisation of the limbic system is drawn from observations in experimental animals of the augmentative effects of stress on blood brain barrier permeability. This theory suggests that normally innocuous, peripherally sequested chemicals encountered under stress may reach the brain and modulate limbic function. This theory emphasises the potential interplay between physiological and psychological components in the aetiology of MCS.

Another important question in determining the aetiology of MCS is whether or not MCS patients are able to discriminate in double-blind placebo controlled challenge studies (using an olfactory masking agent) between reported environmental triggers and placebos. In such

studies, some MCS patients fail to react to their reported triggers and some react to the placebo, suggesting a psychological aetiology for MCS. While there are some studies that report that MCS patients are able to distinguish between the placebo and the actual chemical trigger(s), further investigation of study methodology reveals that these studies may not have been truly "blinded". These studies either use chemical triggers at concentrations above the odour threshold or do not use an olfactory masking agent (Staudenmayer et al. 2003a; Das-Munshi et al., 2006). These latter authors, in a systematic review of provocation studies, conclude that chemically sensitive individuals do react to chemical odours but only when discrimination between active and sham substances is possible and that, on this basis, expectations play a role in reactions.

A fundamental principle of toxicology is that exposures to individual chemicals elicit predictable dose-related adverse effect(s) in predominantly single but also multiple, related organ systems. The symptoms triggered by low-level exposure in MCS subjects generally do not conform to this toxicological principle. Some have suggested that the dose-response relationship displayed by MCS subjects is different to that of the general population, in that it can be altered by several intrinsic factors resulting in a lower sensitivity threshold to a triggering agent. Notably, the limbic kindling hypothesis suggests that the lack of consistent dose-response relationships is due to differing susceptibility factors (eg. cacosmia, toxic exposures, and psychological predispositions) that affect the neural sensitivity of the limbic system. This suggestion raises again the likelihood of an interconnection between physiological and psychological factors in the aetiology of MCS.

Another argument in support of a physiological basis for MCS is that in the absence of an identifiable acute exposure associated with the sensitisation event in MCS, the disorder might be caused by cumulative effects from low-level exposures, resulting in an exceedence of a body-load tolerance threshold. While there are examples of harmful effects from long-term cumulative exposures to low-levels of certain toxins (e.g. metals), this scenario differs from that proposed for MCS, as the toxin can be quantified in the body and its presentation follows a well-defined toxicological paradigm. In contrast, no evidence of accumulation of toxic chemicals in MCS subjects has been found.

Genetic predispositions may additionally play a role in individuals with MCS through altered chemical biotransformational capabilities and susceptibilities to chemical toxic effects. Statistical differences in genotypic profiles for drug-metabolising enzymes have been shown for MCS individuals. Additional information on genetic predispositions is needed to support a hypothesis of altered biotransformational capability as an explanation for MCS.

NOTE: Further studies/references are sought in this area.

Multifactorial models of MCS have been described where physiological processes such as exposure to odours under stressful circumstances coupled with psychological predispositions and subsequent cognitive filtering and feedback mechanisms can result in initiation and progression of illness. From studies of both normal and hypersensitive individuals, perceptions of odour are shown to be a powerful modulator of exposure symptoms. Such multifactorial models should lead to new hypotheses for MCS aetiology that can be tested through research.

3.3 FURTHER RESEARCH TO IDENTIFY POTENTIAL CAUSATIVE MECHANISMS OF MCS

There is considerable debate as to what causes MCS. The literature describes numerous potential causative mechanisms many of which are amenable to further testing. The most credible physiological mechanism for MCS is limbic kindling/neural sensitisation which proposes that sensitisation of the olfactory, limbic, mesolimbic and related pathways of the central nervous system occurs as a result of, or in the context of, chemical exposure. The scientific weight-of-evidence currently suggests that while physiological mechanisms may play a part in MCS, there is also a psychological or psychogenic component in its pathogenesis. Recent medical/scientific opinion suggests that MCS has a multifactorial origin, involving physiological, psychological and social predispositions.

While there are a number of proposed mechanism s warranting further consideration, based on biological plausibility, testability and identified existing research gaps, the following are identified as priority areas for further scientific research and investigation:

- Immunological variables
- Respiratory disorder/neurogenic inflammation
- Limbic kindling/neural sensitisation and psychological cofactors
- Elevated nitric oxide, peroxynitrite and NMDA receptor activity.

Research on these particular hypotheses may elucidate the potential MCS causative mechanisms, and hence improve diagnosis and treatment/management of MCS of patients. Specific comments on each proposed mechanism is provided below.

3.3.1 Immunological variables

No consistent pattern of immunological abnormalities has been found to date that characterises MCS subjects. The role of the immune system in MCS is difficult to assess from many of the published reports because of the lack of standardised protocols, the wide variation in patient test results, and the lack of control for confounding variables that influence the immune system (e.g. stress, smoking).

If the possibility of immune dysregulation as a potential mechanism for causing MCS is to be adequately tested, further work is needed including validated immune measurements with appropriate quality controls, using specific controlled chemical challenges in well-defined clinical groups. These tests should also factor in the potential for adaptation and biochemical individuality.

3.3.2 Respiratory disorder/neurogenic inflammation

The major criticism for this causative mechanism is that altered nasal mucosa and other respiratory changes such as increased nasal resistance alone, even if found consistently, cannot account for the multiple organ system pathology reported in MCS. Multiorgan involvement is dependent on a theory of ‘neurogenic switching’ where antidromic sensory nerve impulses causes release of inflammatory mediators at distant tissue sites. Whether this mechanism is operational and responsible for the symptoms of MCS should be confirmed in DBPC studies examining respiratory changes and referred physiological effects following specific chemical challenges.

3.3.3 Limbic kindling/neural sensitisation and psychological cofactors

The limbic kindling/neural sensitisation theory also suggests a model to explain the diverse array of symptoms experienced by MCS subjects, including those involving multiple organs. However, there are a number of gaps in the available information that would benefit from further research, including:

- Odour perception – the pattern of higher cortical processing of odour information;
- Mechanisms by which kindling/sensitisation might be initiated through investigations of the transport of molecules within olfactory pathways and blood brain barrier permeability changes during challenge testing;
- The role of psychological factors including stress in initiating or contributing to the disorder, noting that an existing psychiatric condition prior to the onset of symptoms has been observed as a strong diagnostic predictor of MCS.

Lehrer (1997) outlines several psychophysiological hypotheses and research strategies that would be useful for exploring psychological factors contributing to MCS.

The important research question relating to the extent to which psychological factors contribute not only to the *initiation* but also to *continued* disability in long-term MCS can be addressed by balanced-placebo challenge tests in which not only the putative eliciting substance(s) but also the expectation of adverse effects are directly assessed. As noted by Weiss (1997), the use of balanced-placebo study designs for testing the power of expectation involves deception procedures in the administration of the study, but with appropriate management of ethical issues would be expected to further elucidate the role of psychological mechanisms in MCS. In addition, with appropriate ethical controls, such study designs incorporating the testing of expectation conceivably could be incorporated in longitudinal repeated studies in individuals.

3.3.4 Elevated nitric oxide, peroxynitrite and NMDA receptor activity

The theory notes that the hypersensitivity reportedly experienced by MCS sufferers can be explained by elevated levels of nitric oxide and peroxynitrite and related increases in the chemical sensitivity of NMDA receptors in the limbic system. This theory links with the limbic kindling/neural sensitisation model of MCS.

Currently, there is no *de novo* scientific evidence to support this theory. However, support for the direct involvement of nitric oxide, peroxynitrite and NMDA receptor biochemistry and a potential pharmacological intervention for MCS might be afforded by trials of the effects in MCS sufferers of agents which down-regulate these reactants, such as nitric oxide scavengers, synthesis inhibitors or NMDA antagonists. A number of agents including dietary supplements have been postulated as being effective in down-regulating nitric oxide, peroxynitrite biochemistry (Pall 2006).

4 DIAGNOSIS, TREATMENT AND MANAGEMENT OF MULTIPLE CHEMICAL SENSITIVITY

Different disease classifications for MCS reflect the differing views regarding the underlying cause and mechanism of MCS. The lack of agreement on an operational definition, or even an appropriate label, has been a hindrance to scientific analysis and an understanding of MCS.

This lack of agreement is reflected also in the lack of agreement on appropriate clinical treatment/management of MCS. Of interest in this respect, therefore, is how medical practitioners, both at the specialist and general practitioner level, currently respond to individuals who show patterns of chemical sensitivity suggestive of MCS.

In order to explore further these questions, the Office of Chemical Safety (OCS) and the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) in 2006 commissioned a survey to identify current gaps in clinical research and education with regards to diagnosis and treatment/management of MCS. The methodology for the survey which formed part of a report into barriers to the clinical diagnosis and management of MCS is detailed in Appendix 1 and findings from the study have been incorporated into this Chapter.

4.1 DIAGNOSIS AND PREVALENCE OF MCS

The lack of an agreed case definition for MCS is particularly problematic when considering estimates of the prevalence of MCS. Prevalence estimates exist but are generally not comparable across studies that use different case definitions. There are numerous studies (including Australian State health surveys) that have examined the extent to which people report sensitivity to chemical(s). However, it is not clear how many of these individuals would be classified as having MCS.

The lack of a case definition means that MCS is often identified on the basis of self-reporting in the absence of a confirmable medical diagnosis.

4.1.1 Studies on the prevalence of MCS in Australia

In NSW, a 2002 survey of adult health conducted by the Department of Health, 24.6% of respondents (from a total of 12,491 individuals) answered “yes” to the question “Do certain chemical odours or smells regularly make them (or their children) feel unwell?”. Moreover, 2.9% answered “yes” to the question “Have you been medically diagnosed with a chemical sensitivity?” The severity of these health effects and their conformity to the 1999 Consensus Criteria (Section 1.2) are not known. Interestingly, the survey did not find significant variations in the proportion of people reporting diagnosed chemical sensitivity based on level of socio-economic disadvantage.

In South Australia, two surveys were commissioned by the State Health Department (September 2002 and June 2004) to determine the prevalence of MCS and general chemical sensitivity. Combining both surveys, in 4,009 randomly selected adults, 16.4% of respondents reported sensitivity or adverse health effects from exposure to one or more chemicals, and only 0.9% reported a medical diagnosis of MCS.

The limited Australian survey information suggests that the prevalence of medically diagnosed MCS in Australia is of a similar order to that reported overseas.

4.1.2 Studies on the prevalence of MCS in other countries

MCS is most commonly reported in western industrialised countries despite the worldwide ubiquitous presence of implicated chemicals. The diagnosis of MCS was reported to be more common in the United States, Canada and Germany than in the United Kingdom (Reid et al, 2001). The best overseas estimates for prevalence of MCS are from the United States where prevalence appears to be less than 1% (Reid et al. 2001).

Mooser (1987), on the basis of personal communications with American clinicians, suggested that 2–10% of persons in the general population have substantive disruption of their lives because of MCS. However, Cullen and colleagues suggested that this range was too high, with only 1.8% of 2759 patients treated at the Yale Occupational and Environmental Medicine Clinic diagnosed with MCS according to the Cullen diagnostic criteria (Cullen, 1987). Cullen et al. (1992) concluded that if only 1.8% of patients in clinics qualified for a diagnosis of MCS, then the rate in the general population would be far lower.

Bell and colleagues reported that 15-22% of a sample of college students reported feeling moderately or severely ill after exposure to at least three of five common substances (ie. pesticides, paint, perfume, car exhaust and new carpet) (Bell et al. 1993a, b). Subsequently, the same investigators found that 28% of college students considered themselves to be "especially sensitive to certain chemicals", but the results were dependent on the type of query. Only 9.7% reported illnesses related to chemicals and only 0.2% of college students reported physician-diagnosed MCS (Bell et al. 1996).

Bell et al. (1993c) also reported that 17% of a group of retired elderly persons participating in a longitudinal study of osteoporosis reported feeling moderately or severely ill after exposure to at least four of five common substances (pesticides, paint, perfume, car exhaust and new carpet). Overall, 4% of participants in studies of the community elderly reported physician-diagnosed chemical sensitivity (Bell et al. 1994).

The results of the 1995 California Department of Health Services Risk Factor Survey of 4,046 randomly selected adults showed that 16% of respondents reported themselves as being unusually sensitive to everyday chemicals. Moreover, 6.3% claimed to have doctor-diagnosed environmental illness or MCS. Less than 1% of the sample (0.6%) reported an unusual sensitivity to chemicals and a medically diagnosed chemical sensitivity that restricted their daily activities (Kreutzer et al. 1999).

Kipen et al. (1995) questioned cohorts of patients visiting different medical clinics. Four percent of patients visiting an environmental and occupational health centre, 15% of patients referred to an occupational clinic, 20% of medical clinic patients, 54% of occupational clinic patients diagnosed with asthma and 69% of MCS patients were identified as reporting symptoms attributable to exposure to 23 or more substances.

Meggs et al. (1996) reported that 33% of a randomly selected rural North Carolina population self-reported chemical sensitivity, with symptoms occurring daily in 4%. Amongst a random sample of 1582 individuals from Atlanta, Georgia, Caress and Steinemann (2003) reported hypersensitivity to common chemicals in 12.6% of respondents, with 3.1% claiming a diagnosis of MCS (Caress & Steinemann 2003; 2004).

Reid et al. (2001) reported a prevalence of MCS in British war veterans of 0.2-1.3% amongst cohorts of several thousand respondents from 3 operational theatres. However, only 30% of those who self-reported MCS met the study criteria for MCS, in this case, that used by Simon et al. (1993) requiring a duration of illness 3 months or more, symptoms reported in at least three organ systems including the central nervous system and reported sensitivity to 4 or more common exposures from a list that included fresh paint, newspapers, perfume, hair spray, and solvent fumes.

Amongst Gulf War veterans, MCS was strongly associated with exposure to pesticides (Reid et al. 2001). In other studies, 30-36% of Gulf War veterans considered themselves unusually sensitive to certain chemicals (Bell et al. 1998; Kipen et al. 1999). In a sample of Gulf War military personnel in Iowa, 3% met study criteria for MCS, with 2% being medically diagnosed with MCS. Deployed military personnel were nearly twice as likely as non-deployed military personnel to report symptoms suggestive of MCS (Black et al., 2000a). A recent systematic review of multi-symptom conditions in war veterans noted that Gulf War veterans were more than 3 times more likely than non-Gulf veterans to report MCS or chronic multi-symptom illnesses (Thomas et al., 2006).

Park and Knudson (2007) reported the prevalence of several disorders associated with medically unexplained physical symptoms based on information from 2002 and 2003 Canadian Community Health Surveys. According to the 2003 survey, the prevalence of individuals claiming a medical diagnosis of MCS in Canada was 2.4%, with the rate for females at least twice that for males. Also, along with CFS and FM, the prevalence of MCS was related to socio-economic status, with the likelihood of reports of MCS increased with decreased household incomes.

In summary, worldwide, there are only a small number of studies that have reported the prevalence of medically diagnosed MCS. In these studies, the prevalence of MCS ranges from 0.2 – 4% for populations or selected population subgroups. A number of other studies have reported the prevalence of chemical sensitivity or general reactions to chemicals, but not necessarily MCS. In these studies, the prevalence ranges from 15 to 36%.

4.2 MCS CASE DEFINITION AND PREVALENCE DATA

At present, it is difficult to determine the prevalence of MCS in the population as the reporting of MCS is based on self-diagnosis or on uncertain medical diagnostic criteria. There have been numerous studies overseas to determine the prevalence of MCS, but most have suffered from poor reporting details that have made it difficult to ascertain which, if any, published case definitions were employed to diagnose MCS subjects.

Notwithstanding the difficulties associated with self-reporting of illness, health surveys such as those routinely conducted by State Government health departments are useful for obtaining a snapshot of the prevalence of individual perceptions of chemical sensitivities in the general community. However, it is important that health surveys utilise questions of sufficient clarity and specificity to discriminate those with MCS (such as defined by the 1999 Consensus Criteria) from those with simple common aversions to certain smells and odours. The susceptibility of MCS population studies particularly to numerous types of epidemiological bias has been acknowledged (Kreutzer, 2002).

The use of strictly validated blinded challenge test is a vital tool in obtaining objective data regarding the presence of any organic dysfunction in those individuals who identify themselves as suffering from MCS. Such methodologies would address the variable quality of currently available studies. Miller et al. (1997) described methods for the controlled scientific study of MCS including the development of a case definition, appropriate sample selection and randomisation with the documentation of objective and subjective responses in appropriately designed DBPC challenge tests. Siegel and Kreutzer (1997) outlined the suitability of challenge testing based on a balanced-placebo design similar to that used in alcohol research where a major focus is to distinguish *expectations* of toxic effects from *actual* effects of chemical exposure.

A fundamental experimental question is whether MCS can be elicited reliably and repeatedly with proper experimental controls. Accordingly, Weiss (1997) recommended that the research approach best suited for MCS studies is the single subject design, where, in contrast with conventional group designs, data are compiled by repeated observations of individual subjects. Such longitudinal studies on individuals clearly would provide repeatability data and bypass the potential difficulty in MCS research of identifying common eliciting substances for group testing.

In Australia, there are few documented systematic records of patients with MCS that would enable appropriate tracking and an understanding of the natural history of people with MCS. Generally the clinical impression formed about these patients is dependent on the specialty, expertise and level of interest of the clinician, the occupation of the patient and the location of patient's residence. Where a case definition is agreed and recognised, the need for referral and subsequent management undertaken is well accepted (see Appendix 1).

A documented nine year longitudinal study of MCS in the USA concluded that individuals remained strongly committed to the diagnosis of MCS, and although some improved since their original interview, many remained symptomatic with their disability continuing to impact on their lifestyle (Black et al., 2000c).

In Australia in 1994, Winder reviewed cases of what he termed at that time "chemically related chronic fatigue syndrome" (Winder, 1994). He considered that early detection and intervention including minimising exposure to the triggers resulted in improved outcomes.

4.3 TREATMENT FACILITIES

Individuals who complain of sensitivity or intolerance to environmental chemicals or other agents are frequently referred to mainstream specialist allergy clinics for care. For example, fifty percent of patients referred to the Allergy Unit, Royal Prince Alfred Hospital (RPAH) present with non-allergic or "vasomotor" rhinitis, ie. unexplained chronic inflammation of the nasal airways with no allergic component. One third of these patients complain of smell intolerance. The treatment of patients who claim extraordinary sensitivity or intolerance to certain smells or odours aims at providing explanation and reassurance, determining any clinically identifiable causes and establishing appropriate avoidance strategies (Loblay, 1993; Sparks 2000a). A strategy of support and trigger avoidance was also endorsed amongst Australian general and specialist medical practitioners involved in the clinical review of MCS (see Appendix 1).

Evidence given to the South Australian Parliamentary Inquiry noted that there were no public hospitals in Australia in 2005 that had a policy regarding management of the hospital environment for people with MCS (Social Development Committee, 2005). Although the Royal Brisbane and Women's Hospital and Health Service District have draft protocols to provide an environment that reduces exposure to incitants for those patients who identify themselves as suffering MCS, the protocols had not moved past draft status. In the past, there have been specific private facilities in Australia catering for the chemically sensitive.

Importantly, the South Australian Parliamentary Inquiry heard that patients with MCS attributed the majority of the benefits they experienced to education, support and acknowledgement of the illness (Social Development Committee Report, 2005).

More recently, the Australian Human Rights and Equal Opportunity Commission has included reference to MCS in their revised Guideline, *Access to Buildings and Services: Guidelines and information* (HEREOC 2007). The Use of Chemicals and Materials section of the Guidelines state: A growing number of people report being affected by sensitivity to chemicals used in the building, maintenance and operation of premises. This can mean that premises are effectively inaccessible to people with chemical sensitivity. People who own, lease, operate and manage premises should consider the following issues to eliminate chemical sensitivity reactions in users:

- the selection of building, cleaning and maintenance chemicals and materials;
- the provision of adequate ventilation and ensuring all fresh air intakes are clear of possible sources of pollution such as exhaust fumes from garages;
- minimising use of air fresheners and pesticides;
- the provision of early notification of events such as painting, pesticides applications or carpet shampooing by way of signs, memos or email.

Dedicated health centres exist overseas for individuals suffering from environmental illnesses. In Canada, the Nova Scotia Environmental Health Centre was established as a medical treatment and research facility dealing with environmentally triggered illnesses. Many of the patients treated at this facility suffer from MCS, FM or CFS. Each patient undergoes routine blood screening and full physical examination including some functional capacity tests. The patient's symptoms are recorded and a diagnosis is made based on diagnostic criteria presented in the literature (MCS: Cullens criteria; CFS and FM: Anon 2003a, b). A diverse range of treatments is available to patients, but most include education, psychotherapy and individual counselling, physiotherapy and sauna programs.

NOTE: Additional reference material on other existing treatment facilities would be welcomed.

4.4 TREATMENT OF MCS

MCS individuals may see a variety of specialist medical practitioners depending on the stage of their illness and the background to their referral. For the majority, the general practitioner is likely to be the first consulted. If the condition is regarded as an allergic response, a

specialist allergist may be seen, or if considered work-related, an occupational physician may be consulted.

As part of a clinical review of practices in Australia, a workshop examining the current diagnostic and therapeutic practices for MCS amongst Australian medical practitioners from a variety of specialties revealed little consensus on effective interventions (Appendix 1). No evidence was forwarded for any medication, dietary supplements or other therapies as a treatment for MCS. Basic management strategies currently used by practitioners involve strategies common to all chronic illnesses - engaging with the patient, encouraging self-management and maintaining a long-term supportive relationship.

Pharmaceutical treatments for MCS currently do not exist. Psychotherapy, biofeedback and relaxation and other behavioural therapies are regarded as efficacious (Wolf 1996; Stenn and Binkley 1998; Sparks 2000a,b; Bornschein et al. 2001).

Gibson et al. (2003) surveyed 917 individuals with self-reported MCS to ascertain the perceived efficacies of 101 treatments including environmental techniques (chemical avoidance, sauna, rotation diet, and/or personal oxygen), nutritional supplements, Eastern-origin (meditation, yoga) or detoxification techniques, holistic (homeopathy, chelation) or body (chiropractic, kinesiology) therapies and prescription medicines. The study reported significant drain on personal resources in seeking treatment for MCS and described respondents' attitudes toward the possibility of a positive treatment outcome. On average, participants consulted 12 health care providers and spent over one-third of their annual income on health care costs. The most helpful treatment/management strategies rated by 95% of respondents were creating a chemical-free living space and chemical avoidance.

In Australia, there are a number of societies and groups that provide specific support and understanding to individuals suffering from MCS. Such groups include:

- Allergies and Intolerant Reactions Association;
- Allergy and Environmental Sensitivity Support and Research Association Inc.;
- Allergy, Sensitivity & Environmental Health Association Qld Inc.;
- Australian Chemical Trauma Alliance Inc.;
- Chemical Sensitivity, Victoria
- Circle of Friends MCS Support Group WA;
- Community Taskforce on Multiple Chemical Sensitivities;
- Fragrance and Chemical Sensitivity Support Group;
- Global Recognition Campaign for Multiple Chemical Sensitivity and Chemical Injury;
- MCS Australia;
- ME/CFS Society (SA) Inc.;
- National Toxics Network;
- South Australian Task Force on Multiple Chemical Sensitivity.

These groups provide support and guidance for MCS sufferers and also present information on a range of treatments. Advocacy and support group websites (both national and overseas) list a wide range of treatments including intravenous vitamins, nutritional supplements, detoxification, chelation therapy, colonic irrigation, desensitisation, use of medication to boost the immune system, antidepressants, antibiotics, antifungals, homeopathy, acupuncture, mind-body therapy, psychotherapy and total or partial avoidance.

However, in terms of a specific treatment, information from these societies and groups do not establish a consensus for the treatment of MCS other than avoidance of chemicals that cause symptoms.

The lack of official recognition of MCS as a distinct clinical entity, together with difficulties in establishing aetiology and inconsistencies in the diagnosis of MCS, are reflected directly within the different views clinical views on the approach to treatment/management of MCS as found in the Australian clinical review. Nevertheless, as the result of interviews with clinicians, responses to questionnaires and subsequently confirmed in workshop discussion, common ground was identified amongst Australian clinicians (see Appendix 1).

The Australian clinical review found that, commonly, people complaining of symptoms attributed to MCS often report that their medical advisers have not listened to their concerns. These people believe that they have been rejected or that their symptoms have been disbelieved. This concern and belief may well impact on their ability to come to terms with their illness or recover their health. Some patients and clinicians have observed that people presenting with symptoms ascribed to MCS experience symptoms that fluctuate over time. This is another complicating factor and a better understanding of the extent to which these occur would be important for clinical management.

Clinicians involved in the clinical review of MCS agreed a set of general principles that are useful for the management of MCS (from Appendix 1).

MCS Clinical Management Principles

- Accept that the person with MCS feels ill and is disabled by the illness;
- Provide an empathic relationship to offer understanding and support;
- Encourage self-management rather than offering or seeking a cure;
- Recognise and explain that no specific therapy has yet been proven to be of benefit;
- Maintain a long-term positive approach.

4.5 CLINCAL RESEARCH NEEDS

The clinical review has highlighted difficulties with agreed criteria for the diagnosis of MCS, identifying an underlying pathological process and treating or managing MCS.

Available reports suggest that MCS individuals do not show a typical dose-response reaction following exposure to triggering agents. Some challenge tests suggest that it is the smell or odour of a triggering agent, rather any of its pharmacological or toxicological properties *per se* that elicit MCS symptoms.

Overall, a number of primary clinical research needs are evident:

- Establishing agreed diagnostic criteria that are acceptable to clinical and scientific groups;
- Determining the prevalence of MCS, for both self-reported cases and those that are medically diagnosed;
- Determining the relative contributions of toxicodynamic and psychogenic mechanisms in the process of the disorder through the use of appropriately blinded challenge tests;

- Determining effective treatment/management protocols for MCS based on positive therapeutic alliances and individual self-management.

4.5.1 Longitudinal Study

To get a better understanding of MCS in Australia there is a need to look more closely at the natural history of people with MCS. A longitudinal clinical and sociological study (ie how MCS develops over time) should assist in identifying elements of MCS and areas that may have been overlooked to date.

Such a study should examine eliciting agents/events, diagnostic experiences, clinical course and impacts of treatment/management strategies. To undertake such a longitudinal study it would be necessary to identify people with MCS who would be prepared to be involved. Appendix 1 findings provides some suggested practical steps in addressing this issue

4.5.2 Education/Training

The development of a clinical education program be investigated. Such a program should be based on evidence currently available, utilise any findings from clinical research in Australia (such as a longitudinal investigation) and consider the practical guidance on approaches to MCS clinical management agreed by participants in the recent clinical review of MCS.

Finally there is a need for better public information in order to address concerns regarding MCS and to assist those who may be affected to seek appropriate help and treatment. Input should be sought from MCS support and advocacy groups, including the SA Government MCS Reference Group, with the aim of informing clinicians, workplaces and communities about what is currently understood by the term MCS and practical ways to assist people who are affected by MCS.

5 APPENDIX 1. A SURVEY OF AUSTRALIAN CLINICIANS APPROACHES TO MULTIPLE CHEMICAL SENSITIVITY

Different disease classifications for MCS reflect the differing views regarding the underlying cause and mechanism of the disorder. The lack of agreement on an operational definition, or even an appropriate label, has been a hindrance to scientific analysis and an understanding of MCS. This lack of agreement is reflected also in the lack of agreement on appropriate treatment/management of the condition. Of interest in this respect, therefore, is how medical practitioners, both at the specialist and general practitioner level, currently respond to individuals who show patterns of chemical sensitivity suggestive of MCS.

In order to address these questions, the Office of Chemical Safety (OCS) and the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) in 2006 commissioned a survey to identify current gaps in clinical research and education with regards to diagnosis and management of MCS. The following is a summary of the methodology and findings from the survey.

5.1 THE SURVEY PROCESS

A survey of clinical diagnosis and management of MCS was conducted by clinical medical consultants in two phases. Phase 1 consisted of a literature survey and interviews with professional organisations, medical practitioners and other stakeholders. Phase 2 consisted of a one-day workshop involving clinicians and/or experts from a range of general practice and specialist medical backgrounds who had been identified as having experience in dealing with people with symptoms associated with chemical sensitivity.

5.1.1 Stakeholder contact

An initial list of professional organisations for contact was determined by the OCS/ NICNAS project team and the clinical consultants. Telephone contact was initially made with representatives from those professional organisations whose members may have a role in the management of people with MCS to explain the study and engage the organisation and the most appropriate contact or organisational representative. All organisations were sent a letter of introduction to the study and the review process, contact details for the consultants and the semi-structured questionnaire for the proposed interviews. A summary of the responses received is shown in Table 3.

Table 3. Summary of responses from key professional organisations

The Australian Medical Association (AMA)	The AMA was unable to provide a nominee for consultation; does not have a position or policy statement on the issue; expressed interest in environmental issues and exposure measurement, requested to be kept informed of the progress and project outcomes.
The Public Health Association of Australia (PHAA)	The PHAA Environmental Health Special Interest Group and the South Australian Department of Human Services co-hosted a workshop at the 2002 Annual Conference of the PHAA, to explore the aetiology of Chronic Fatigue Syndrome (CFS) and MCS. Nominated representatives provided access to workshop materials and outcomes.

The Royal Australian College of General Practitioners (RACGP)	The RACGP does not have a position or policy statement on MCS; nominated involvement of the Australian Integrative Medicine Association (AIMA) and GPs known to be interested in the field; The RACGP requested to be kept informed of the progress and project outcomes.
The Australian Psychological Society (APS)	The APS was unable to find a member with a specialisation or interest in MCS for interview or completion of the questionnaire, and was also unable to provide any information on the possible role of their membership with individuals with MCS.
The Australian Integrative Medicine Association (AIMA)	The AIMA confirmed the nomination of GPs with an interest in MCS and also identified recent research on food intolerance believed to be of relevance to MCS.
Medicare Australia (MA)	A state based senior medical advisor indicated that Medicare Australia was unable to identify problems experienced with practitioners who were specifically involved in the management of patients. He was unable to elaborate further.

Initial contact was sought but no formal response was forthcoming to the introductory letter outlining the background to the project and the questionnaire from:

- The Australian College of Dermatologists
- The Royal College of Pathologists of Australia
- The Royal Australian and New Zealand College of Psychiatrists
- The Australian College of Nutritional and Environmental Medicine.

Two of the above organisations also received follow-up by phone. Additional contacts for interviews were provided by stakeholders during Phase 1 of the study, each of which was followed up with the introductory letter and questionnaire.

5.1.2 Questionnaire

The consultants prepared and circulated a semi-structured questionnaire that formed the basis of subsequent interviews. The questionnaire addressed the following issues:

Experience and Diagnosis

- What has been your experience with MCS?
- What do you consider to be the authoritative evidence for recognising the existence of MCS?
- What diagnostic criteria do you use to determine the presence of MCS? Do you require all of Cullen's criteria be fulfilled? Are there other diagnostic criteria being used?
- Do you use any diagnostic tests to confirm the diagnosis, or would like to use but are not currently available to you?
- What do you consider to be the pre disposing factors to MCS?
- Do you have any information on the prevalence of MCS?
- What factors do you consider might influence the apparent ethnic and geographic differences in the prevalence of the diagnosis of MCS?
- What association (if any) do you consider there might be between MCS and chronic fatigue syndrome?

Treatment/Management Strategies

- Do you consider MCS treatable/manageable?
- Do you consider you can stage MCS?
- What do you regard as successful/unsuccessful strategies for treatment/management?
- How do you define goals for treatment?
- What factors have you found that influence outcome?
- Can you ever consider MCS to be cured/controlled?
- How do you assist with learning to live with the condition.
- What factors appear to influence the course of the condition?

Research and Education

- Are you aware of clinical research currently being undertaken to improve the knowledge and understanding of the condition?
- What do you consider to be the knowledge gaps associated with identifying and treating sufferers of MCS?
- What action is being taken to overcome the education and how knowledge gaps regarding MCS?
- Do you have (or can you suggest any strategies that might improve or overcome gaps in education and knowledge about MCS?

5.1.3 Interviews

The consultants conducted in-depth interviews with individual clinicians but also some representatives from relevant professional and advocacy bodies to ascertain the current views and supporting available evidence regarding:

- Diagnosis of MCS;
- MCS treatment/management strategies;
- Identification of knowledge gaps associated with identifying and treating MCS sufferers;
- Clinical research and education aimed at overcoming knowledge gaps.

Interviews were sought across a broad range of the medical community including general practitioners, psychiatrists, respiratory physicians, psychologists, integrative medicine practitioners and immunologists. Interviews with representatives from MCS support and advocacy groups from most states were also conducted to provide additional background information.

A range of individual clinicians known to have or likely to have experience in MCS, including general practitioners, allergists, occupational physicians, medicine practitioners, professional and advocacy organisations and stakeholders, were contacted initially by telephone to ascertain their interest or to identify the relevant person in their organisation.

All nominated organisations and individuals were sent an introductory letter explaining the project and an accompanying questionnaire for opinion leaders or consumers so that those who had agreed to be interviewed could be fully aware of the intent of the study, the scope of information being sought and have the opportunity to gather supporting information to assist the project consultants.

Interviews were completed with:

- 4 general practitioners (GPs);
- 2 immunologists;
- 1 allergist;
- 2 occupational physicians;
- 2 respiratory physicians;
- 2 psychiatrists;
- 1 ear, nose and throat (ENT) surgeon;
- 1 toxicologist;
- representatives from 4 MCS support and advocacy groups;
- 3 people suffering from MCS.

Completed questionnaires, without interviews, were received from 2 clinicians from Queensland and Victoria.

5.1.4 Workshop

In addition to the semi-structured interviews, the consultants conducted a workshop in Sydney involving some of the clinicians and/or experts from a range of general practice and specialist backgrounds who had been identified as having experience in dealing with people with symptoms associated with chemical sensitivity. Representatives of key stakeholders whose involvement was likely to provide organisational views or opinions were also invited. All workshop participants had been interviewed and were provided with background material and references prior to the workshop.

The workshop sought to reach agreement about:

- Recognising likely presentations that would lead to the diagnosis;
- Defining the range of possible management;
- Determining what research might be undertaken to assist in understanding, MCS including diagnosis and management;
- Determining whether any specific education or training programs would be likely to improve the understanding and management of MCS.

5.2 PROBLEMS ENCOUNTERED

From the beginning of the project, it was evident that a major barrier to progressing the issues surrounding MCS existed, best described as a strong divergence of clinical opinion and a lack

of agreement about MCS in the literature. This was encountered in one-on-one interviews and confirmed at the collaborative workshop. In addition to polarised and strongly held views, two further barriers to progress were evident:

1. A lack of authoritative published research specifically related to MCS

While there are many articles and books published about MCS in the world literature, much of which is featured on the websites of interest and advocacy groups including papers presented at meetings, little evidence could be found in peer reviewed journals that supported the diagnosis of MCS.

In Australia in 1992, an expert working group initially established by the Royal Australasian College of Physicians (RACP) and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) set out to examine MCS but was soon diverted to focus on CFS. Whilst several clinical advocates have declared their belief that MCS is a component of, or related to CFS, others consider MCS a separate entity requiring different approaches to both diagnosis and management.

2. Limited available information on prevalence

Generally, jurisdictions do not collect data specifically identifying MCS. Germany is the only country in which MCS is a recognised ICD10 disease term. Information on prevalence in Australia is based on telephone surveys in NSW and SA ranging from 2.9 per cent to less than one per cent (0.9%) of respondents, may be quite unreliable because of the way in which the questions were framed, particularly between studies, thus hindering the development of longitudinal datasets. Participants in the SA surveys were asked if a medical doctor had diagnosed MCS, while the NSW survey participants were asked if they had been diagnosed with chemical sensitivity.

5.3 THE COMMON GROUND

Responses to questionnaires demonstrated that individual clinical views were polarised, vigorously stated and defended, based mainly on individual belief and limited clinical experience.

As indicated earlier, interviews and literature searches revealed that on one side, some clinicians, together with some of the published literature, proposed that people with symptoms attributed to MCS do have an identifiable condition and that these people suffer from a chronic debilitating syndrome arising from continuing exposure to chemicals. Some of these clinicians considered the underlying mechanism had been defined, at least to their satisfaction, and provided publications to support their position. For others, the reality of the condition was accepted but the cause was still not understood nor satisfactorily explained by the evidence base.

On the other side of the debate, some clinicians, respected overseas medical organisations and at least one local clinical organisation stated strongly that MCS is neither a diagnosis nor a syndrome but a range of sometimes disparate disabilities with some common presenting symptoms. Some described the presentations as a somatoform disorder, with symptoms in the absence of an identifiable general medical condition. These clinicians consider that psychological conflicts become translated into physical problems or complaints.

Other clinicians considered MCS to be a psychopathological condition created, enhanced, and perpetuated by the law and its application, termed a "nomogenic" disorder. They argue that some doctors and lawyers have provided patients presenting with a range of symptoms, some of which may be related and all of which become attributed to a sensitivity to chemical odours, with the identifying label, "MCS". These clinicians consider that patients presenting with such problems are more often likely to have been exposed to chemicals in the course of their work and may be seeking something or someone to be responsible for their ill health and/or to achieve compensation from an employer or some other source to make recompense for the disability.

Nevertheless, as the result of interviews with clinicians, responses to questionnaires and subsequently confirmed in workshop discussion, the following common ground was uncovered in the clinical review:

5.3.1 Initial Presentation

- MCS is a condition with a diverse range of symptoms but with no agreed distinguishing signs.

- Few, if any, people who are subsequently considered to have MCS, present initially with a claim that their illness has followed exposure to chemicals.

- The commonly experienced psychological symptoms may be inevitable, perhaps as the result of exposure, or because of the frustration in seeking to be believed or attempting to find effective treatment, leading to anxiety and/or depression, or perhaps even the cause of some of the other symptoms reported.

5.3.2 Diagnosis

- Specific diagnostic tests are not available in Australia. Proposed diagnostic tests being researched overseas are laboratory based and considered impracticable in every day practice.

- The potential exists for some clinicians to undertake large numbers of diagnostic investigations at great cost, but of little benefit to patient outcomes, to exclude other conditions.

- The diagnosis is generally suggested by a pattern of symptoms and often includes a history of referrals to multiple specialists. The eventual diagnosis (whether MCS or some other condition) is ultimately made by listening carefully to the patient and taking a detailed history. This factor makes diagnosis in primary care situations less likely, or at least significantly delayed because of the relatively short time taken at each encounter in most general practices compared with that of a specialist.

5.3.3 Prognosis and Treatment

- No evidence exists for benefit from any medication, dietary supplements or other therapies despite support for some of the treatments by some clinicians at their interviews or in response to the questionnaire.

- People with the symptoms associated with MCS run a variable course but for most, MCS is a chronic condition.

- The basic management involves engaging with the patient and maintaining a long-term supportive relationship whilst encouraging self-management as with all chronic illness.

- Self-management involves providing the patient with information about the nature of the problems being experienced and guidelines regarding symptom management.

- Clinicians need to accept the patient's complaints as a debilitating and disabling illness irrespective of whether the clinician recognises or accepts the presence of a specific entity, in order to avoid the patient seeking unnecessary referrals and harmful or costly treatment of unproven benefit.

5.3.4 Education

- The lack of exposure to information and education about MCS at undergraduate and postgraduate level is likely to be ongoing given the relatively small amount of time available for minor specialities, including immunology, in the medical curriculum.

5.4 IMPLICATIONS FOR TREATMENT/MANAGEMENT

As noted in the common ground identified during interviews with clinicians and subsequently agreed at the workshop, no consistent or reliable data were available to support any particular treatment. Rather than debate the merits or otherwise of particular forms of treatment of MCS, it was evident that it is more appropriate to talk in terms of management of MCS as this enables both the supporters and non-supporters to agree to some beneficial approaches.

5.4.1 Common MCS treatments

Advocacy and support group websites list a wide range of treatments including intravenous vitamin C and other vitamins, nutritional supplements, detoxification, chelation therapy, colonic irrigation, desensitisation, use of medication to boost the immune system, antidepressants, antibiotics, antifungals, homeopathy, acupuncture, mind-body therapy, psychotherapy and total or partial avoidance. Various treatments appear to be based on particular theories for MCS. At least three of the clinicians interviewed used one or more of these treatments with their patients in line with their understanding of the causality of MCS. Ongoing utilisation of their treatment choices was reinforced by reported benefit in at least some of their patients.

5.4.2 Recognising and responding to MCS individuals

To get a better understanding of MCS in Australia there is a need to look more closely at the natural history of people with MCS. A longitudinal clinical and sociological study might help identify elements of the condition or areas that may have been overlooked to date. From interviews and responses to questionnaires it was apparent that GPs and specialists appeared to see quite different cohorts of people with MCS and so may be contributing unwittingly to the confusion regarding this condition. For example, specialist occupational physicians or immunologists may mainly see individuals with the propensity to react to environmental exposures who may be seeking legal compensation. To establish a case for compensation requires a definitive diagnosis from an authoritative medical specialist. Most of these specialists reject the diagnosis of MCS because they are unable to find objective signs or confirmatory diagnostic tests to provide evidence for the presence of a disease entity. GPs see a different patient population from most specialists. GPs are trained to deal with

undifferentiated illness and often have to cope with uncertainty in diagnosis, especially in the early stages of an illness. Specialists primarily deal with patients with illnesses related to their specialty referred by other clinicians. If unable to reach a definitive diagnosis, specialists may consider the condition to be outside their expertise or experience, or that it does not exist. Such is the case with MCS.

Commonly, people complaining of symptoms attributed to MCS often report that their medical advisers have not listened to their concerns. These people believe that they have been rejected or that their symptoms have been disbelieved. This concern and belief may well impact on their ability to come to terms with their illness or recover their health. Some patients and clinicians have observed that people presenting with symptoms ascribed to MCS experience symptoms that fluctuate over time. This is another complicating factor and a better understanding of the extent to which these occur would be important for clinical management.

5.4.3 Principles for the management of MCS

From interviews, responses to the questionnaire and workshop comments, the clinical workshop agreed to the following principles for the management of MCS:

Accept that the person with MCS feels ill and is disabled by the illness

Clinicians need to accept the patient's complaints as a debilitating and disabling illness irrespective of whether the clinician recognises or accepts the presence of a condition, in order to minimise patients seeking unnecessary referrals and harmful or costly but non beneficial treatment.

Provide an empathic relationship to offer understanding and support

The basic management, as with all chronic illness, involves engaging with the patient and maintaining a long-term supportive relationship whilst encouraging self-management.

Encourage self-management rather than offering or seeking a cure

Self-management involves providing the patient with information about the nature of the problems being experienced and guidance for symptom management. Self-management should include advising ways to minimise contact with perceived triggers as total avoidance generally proves impossible or impracticable.

Recognise and explain that no specific therapy has yet been proven to be of benefit

No evidence for benefit exists for any medication, dietary supplements or other specific therapies. However, symptomatic treatment may help some people.

Maintain a long-term positive approach

Symptoms associated with MCS run a variable course but for most, MCS is a chronic condition. Clinicians should encourage patients to try to come to terms with their disability and develop a positive attitude toward the future.

5.5 SUGGESTIONS FOR CLINICAL RESEARCH

Advice was that further clinical research is needed.

The clinical review identified that a longitudinal clinical and sociological study would provide a better understanding of MCS in Australia by looking at the natural history of people with MCS. Three practical approaches have been suggested to assist in facilitating clinical research were identified and improve patient management. These are:

1. Establish a voluntary register, or similar process, where people who consider they have MCS or an allied condition could record details of their condition, treatment/management and indicate if they were prepared to participate in reviews and research including a longitudinal study in Australia.

2 Consideration be given to establishing an MCS expert clinical working group or similar to assist in :

- establishing criteria for any voluntary register and evaluating/reporting on the information recorded on such a register;
- recommending ways to develop improved clinical and patient guidance;
- identifying opportunities for further research that might include, for example:
    - establishing clinical case-comparison studies in both general and specialist practices and/or
    - exploring the initiation and natural history of sensitivity syndromes involving environmental chemicals by re-examining studies of defined populations that have had reported discrete and sudden chemical exposures; and/or
    - developing a survey instrument to determine prevalence of associated conditions including multi-organ disorders that appear to be linked to MCS.

3 Consideration of a clinical education program be investigated. Using evidence currently available, the outcomes of this scientific review together with the outcomes from the MCS expert clinical working group, and input from MCS support and advocacy groups including the SA Government MCS Reference Group, seek to inform clinicians, employers, workplaces and communities about what is currently understood by the term MCS and proposing ways to assist people who are affected by this condition.

6 APPENDIX 2. VIEWS OF OTHER NATIONAL GOVERNMENTS AND PROFESSIONAL ORGANISATIONS

6.1 US PROFESSIONAL ORGANISATIONS

Several American organisations have issued formal statements about MCS pointing out the shortcomings of the MCS diagnosis, the unreliability and misuse of certain diagnostic procedures and the lack of scientific support for and clinical evidence of the alleged toxic effects from environmental chemicals in these particular patients.

6.1.1 American Academy of Environmental Medicine (AAEM)

In 1965, Randolph founded the American Academy of Environmental Medicine (AAEM), composed mainly of medical and osteopathic physicians practising the principles of clinical ecology. AAEM has published its philosophy in *An Overview of the Philosophy of the Academy of Environmental Medicine* (AAEM, 1992). This statement suggests that a wide variety of symptoms arising from many different organs may result from biological system dysfunction triggered by environmental stressors in susceptible people (Interagency Workshop, 1998).

6.1.2 American Academy of Allergy, Asthma and Immunology (AAAAI)

The American Academy of Allergy, Asthma and Immunology (AAAAI) is the largest medical speciality organisation in the US representing allergists, asthma specialists, clinical immunologists and other allied health professionals. The AAAAI first issued a position statement in 1986 that was updated in 1999. The AAAAI notes an absence of scientific evidence for any particular mechanism for the aetology and production of symptoms in MCS and any immunological or neurological abnormalities in MCS subjects. Causal connections between environmental chemicals, foods and/or drugs and MCS symptoms continues to be speculative.

6.1.3 American College of Physicians (ACP)

The American College of Physicians published a position paper in 1989, which was later adopted by the American College of Occupational and Environmental Medicine (ACOEM) until it drafted its own in 1991. It concluded that there is inadequate support for the beliefs and practices of clinical ecology. The existence of an environmental illness as presented in clinical ecology theory must be questioned because of the lack of a clinical definition. Diagnoses and treatments involve procedures of no proven efficacy (American College of Physicians, 1989).

6.1.4 American College of Occupational and Environmental Medicine (ACOEM)

The ACOEM first issued a position statement in 1991 that was updated in 1993 and 1999. It states that although evidence does not yet exist to define MCS as a distinct entity and there is no single case definition, data are available to support some tentative conclusions. The statement reports:

- 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 link between MCS and exposure to environmental contaminants remains unproven.
- No scientific basis currently exists for investigating, regulating or managing the environment with the goal of minimising the incidence or severity of MCS (American College of Occupational and Environmental Medicine, 1999).

The ACOEM also recognises that there is some indoor air quality problems that can affect human health and thus support regulatory efforts to improve indoor air quality.

6.1.5 American Medical Association (AMA)

In 1992, the AMA stated that until accurate, reproducible, and well-controlled studies are available, it believes that MCS should not be considered a recognised clinical syndrome (American Medical Association Council on Scientific Affairs, 1992). The AMA now has no position statement on MCS.

6.1.6 Californian Medical Association (CMA)

In 1986, the Californian Medical Association Scientific Board Task Force on Clinical Ecology conducted an extensive literature review and reported that there is no convincing evidence supports the hypotheses on which clinical ecology is based, that clinical ecologists have not identified specific, recognisable diseases caused by low-level environmental triggers and that the methods used to diagnose and treat such undefined conditions have not been proven effective (California Medical Association Scientific Board Task Force on Clinical Ecology, 1986).

6.1.7 Other Organisations

Other organisations which have issued statements on MCS include the American Council on Science and Health (Orme and Benedetti, 1994) and the American Health Foundation. A review of the mechanisms of MCS by the Environmental Health and Safety Council of the American Health Foundation concluded that:

- 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 cannot explain its mechanism because limbic kindling itself is not understood as a mechanism and time dependent sensitisation describes a pattern not a mechanism (Ross et al, 1999).

6.2 US GOVERNMENT

In America, Federal and State government interest in MCS has a relatively long history dating from 1979. The issue has been discussed and examined through workshops and conferences by State governments, Federal agencies, the National Academy of Sciences and professional organisations (Read, 2002). Despite this interest, scientific research into this condition has been limited.

6.2.1 Agency for Toxic Substances and Disease Registry (ATSDR)

The ATSDR keeps a watching brief on the issues surrounding sensitivity to low levels of chemicals. In the past, given the need for additional scientific research, the ATSDR has funded MCS conferences to further well-designed scientific research into MCS aetiology. The first meeting was sponsored by the National Academy of Sciences in March, 1991 and

the second was sponsored by the Association of Occupational and Environmental Clinics in September, 1991. Throughout these efforts, ATSDR has served as a conduit of information about the issues surrounding MCS (Interagency Workgroup, 1998).

6.2.2 Department of Defence (DOD)

Due to the work environments that employees of the Department of Defence (DOD) face, the DOD has sponsored several projects to investigate chronic multi-symptom illnesses, focussing on the relationship between Gulf War illnesses and other diseases such as CFS, MCS and FM. Such projects have included an investigation of dysregulation of the normal neuroendocrine-mediated stress response as a possible mechanism underlying these illnesses. Another study examined neuropsychological function in a group of treatment-seeking Gulf War veterans and non-deployed Gulf era veterans. In 2003, the DOD Appropriations Bill provided US$ 5.2 million to further fund this research on chronic multi-symptom illnesses (Department of Defence Appropriations Act, 2003).

6.2.3 Department of Veterans Affairs

The Department of Veterans Affairs has funded three Environmental Hazards Centres for the purpose of conducting research on environmental health and toxicology related to military service. Some of the centres performed research into MCS. Detailed studies of those diagnosed with MCS (according to Cullen's criteria) include psychiatric status, neuropsychological function, symptom reports, occupational and economic outcomes, pulmonary function, neurologic status and evaluation of possible triggers. The results from some of these studies have been published (eg. Black et al. 1999, Gray et al. 2002). Black et al. (1999) noted that of 3695 Persian Gulf-War military personnel, 4.6% met Cullen's criteria for MCS, with most reporting they were on Veteran's affairs disability status or receiving Veteran's affairs disability compensation.

6.2.4 National Centre for Environmental Health (NCEH), Centre for Disease Control

The Centre for Disease Control, NCEH was established to promote health and quality of life by preventing and controlling disease, injury and disability associated with the interactions between people and their environment outside the workplace. The impact of its programs is amplified through close interaction with public health departments in every State and with many public, private, and international organisations. Its major activities include biomonitoring for environmental toxicants, lead poisoning surveillance and prevention, birth defects surveillance and prevention, and exigent public health investigations where environmental exposures may be involved (Interagency Workgroup, 1998).

NCEH does not have any programs directly devoted to MCS, however, a number of its activities are relevant to the issues surrounding MCS. Through its division of Environmental Health Laboratory Sciences, NCEH has a leadership role in measuring more than 200 toxicants in human biologic samples. Analyses of samples from large population studies have established the extent of exposure in the U.S. population to volatile organic compounds, pesticides, halogenated aromatic compounds (eg. PCBs), toxic metals (eg. lead and cadmium), and environmental tobacco smoke. This information helps to clarify relationships between exposures to toxicants and human health effects (Interagency Workgroup, 1998).

Epidemiologic investigations conducted by NCEH have relevance to questions of chemical sensitivities. Epidemiologists in the Division of Environmental Health Hazards and Health Effects have investigated adverse health effects associated with tryptophan ingestion,

inhalation of fuels and other air pollutants and foetal alcohol exposure. A community-based program in asthma prevention explores risk factors and intervention effectiveness for this increasingly important cause of morbidity and mortality. There has been reported no specific funding or legislative mandate within NCEH in the area of MCS (Interagency Workgroup, 1998).

6.2.5 National Institute of Environmental Health Sciences (NIHES), National Institute of Health

The NIHES has provided research support for studies related to MCS and to areas of research associated with MCS outcomes, and has supported a number of workshops and meetings concerning MCS to assist NIEHS in developing new and innovative research ideas to better understand MCS (Interagency Workgroup, 1998).

6.2.6 US Environmental Protection Agency (USEPA)

The USEPA sponsored a Federal government Interagency Workgroup on MCS that was co-chaired by the ATSDR and the NCEH of the Centres for Disease Control and Prevention. 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 provided a public health evaluation of the extent and nature of MCS and recommended future actions for federal agencies to consider.

The workgroup concluded that there is a need for research in the areas of case definition, basic epidemiology and challenge studies are necessary to address the concerns surrounding MCS. These recommendations are consistent with those from several expert workshops held since 1990 (Interagency Workgroup, 1998). The report received some criticism from MCS advocates for procedural problems and not including all available literature (Donnay 1999).

A National Environmental Justice Advisory Council was established in 1993 to provide independent advice to the USEPA on issues relating to environmental justice. In 2000, this council recommended that MCS be a notifiable disease, that existing environmental laws be reviewed to assure protection from chemicals that initiate and trigger MCS and that MCS be included as a factor when setting standards and establishing regulations. In response to these recommendations, the USEPA 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 by the council (Read, 2002).

In January 2002, a US Senate Bill (SB 6302) was passed to allow MCS sufferers compensation under the workers' compensation system. Workers seeking compensation for MCS syndrome must prove that their illness would not have occurred but for workplace conditions. If a worker has been diagnosed with MCS syndrome prior to developing a chemically-related occupational disease in the workplace, the worker does not need to prove that the illness would not have occurred but for the work environment. The worker only has to prove that work-related conditions exacerbated the pre-existing MCS syndrome. The worker can only be compensated for conditions resulting from the workplace exacerbation of the condition, not conditions resulting from the pre-existing illness (Senate Committee on Labour, Commerce & Financial Institutions, 2002).

6.2.7 Social Security Administration and Department of Housing and Urban Development

The US Social Security Administration granted affected individuals protection under the US Social Security Act (Donnay, 1999). In 1992 the Department of Housing and Urban Development stated that MCS is a "handicap" under the Fair Housing Act, and people with MCS can seek protection or "reasonable accommodation" under federal housing discrimination laws (Orme & Benedetti, 1994).

Some American States, including 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).

Some jurisdictions, including the cities of San Francisco, Santa Cruz and the State of Washington, include MCS within their disability access regulations and recommendations. Generally these policies call for well-ventilated, 'chemical-free' rooms that use less toxic building materials, furnishings, floorings and supplies than traditional building methods. These policies require the public to be notified of any areas undergoing renovations or pesticide application prior to commencement, as well as the provision of 'chemically-free' medical treatment facilities.

6.2.8 MCS in the US Courts

In the USA, legal activity and consequences surrounding MCS has been noted to outpace the science (Gots 1995). Some courts have recognised MCS as a compensable disease whereas others disregard causation and award benefits to the plaintiff considered disabled by a somatisation disorder or psychological impairment. This is despite the equivocal scientific evidence that MCS is an organic disease (Barrett, 2000a).

In other instances, chemical sensitivity court cases have been dismissed. Traditionally the validity of scientific evidence presented in courts is evaluated under a "general acceptance" standard, letting the jury decipher which opponent's expert was more credible. Now, some courts are using the precedence set in 1993 by the Supreme Court *Daubert v. Merrell Dow* decision, which requires Federal judges, not the jury, to evaluate the validity of the methodology and its applicability to the case. The Daubert ruling states that the following considerations will bear on admissibility of expert testimony: 1) whether the theory or technique in question can be tested, 2) whether it has been subjected to peer review and publication, 3) whether the reasoning or methodology has a known or potential error rate, and 4) whether it has widespread acceptance within a relevant scientific community (Supreme Court of the United States, 1993).

Some courts have excluded testimony by MCS proponents on the grounds that MCS lacks scientific corroboration and does not fulfil these criteria (see Barrett, 1998 for a list of MCS court cases).

6.3 CANADIAN GOVERNMENT

The Canadian Government first examined the problem of MCS in 1985 and has since sponsored several workshops to aid the understanding of the complex issues surrounding MCS.

In Canada in 2000, the Department of Health Act specifically relating to the environmental illnesses CFS, MCS and FM was amended (Bill C-416) to make provisions for conducting scientific research to establish the existence of environmental illnesses and their associated causes and effects. The amendment also requested information programs be established to inform the general public of such illnesses (The House of Commons of Canada, 2000).

In addition, the Disabled Residential Rehabilitation Program of the federal government's Canada Mortgage and Housing Corporation offered up to US$10,000 in grants and loans for home renovations for people with hypersensitivities (Orme & Benedetti, 2004).

Many municipalities across Canada and the United States, including Halifax and Toronto have passed by-laws and/or federal laws restricting the cosmetic/non-essential use of pesticides. Other communities are limiting the use of pesticides through voluntary measures such as public education and social marketing. In Quebec, by-laws are complemented by provincial legislation that prohibits the sale of pesticides and fertilizers containing banned ingredients (Kassirer et al. 2004).

Some Canadian hospitals have introduced MCS policies providing "chemical-free" emergency and treatment rooms for those patients identifying themselves as suffering from MCS. The municipality of Nova Scotia has established Environmental Health Centres for the treatment and care of people who identify themselves as suffering from chemical sensitivities.

6.4 GERMAN GOVERNMENT

Germany is often reported to be the only country to "officially recognise" MCS, since it is included in the alphabetical index of the German version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-SGB-V) published in November 2000 by the German Institute of Medical Documentation and Information (DIMDI). While MCS is included in the alphabetical listing of the ICD-10-SGB-V, it is important to note that this index is a collection of phrases or diagnoses used by some German clinicians and is not a list of diseases "officially recognised" by Germany. Not all phases are used or indeed recognised by clinicians.

As is the case for MCS, some phrases have not been allocated a unique disease code, as the phrase does not represent a distinct disease entity. Germany's DIMDI has stated that even though MCS may be incorporated in the ICD-10-SGB-V alphabetical listing, this does not imply that it is a recognised disease (M. Schopen, DIMDI, Personal Communication, 2004).

6.5 UNITED KINGDOM PROFESSIONAL ORGANISATIONS

In the United Kingdom, position statements have been issued by both proponents and opponents of MCS being classified as a discrete clinical disorder.

6.5.1 Royal College of Physicians and Royal College of Pathologists

In the UK, the Royal College of Physicians and Royal College of Pathologists have also published reports detailing the non-scientific basis for MCS (The Royal College of Physicians and Royal College of Pathologists, 1995).

6.5.2 British Society for Allergy, Environmental and Nutritional Medicine (BSAENM)

The statements of the BSAENM differ from those of other medical organisations. The BSAENM 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, and 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;
- Environmental exposures to triggering agents should be kept below that which has been 'shown' to initiate sensitivity in susceptible individuals. Suggested levels for ambient volatile organic compounds should be kept below about 5 ppb, a value derived from unpublished data reported to provoke symptoms of SBS in the USA;
- Invoke the precautionary principle;
- Assessments of interaction, immunological adjuvant activity and hormone mimicry should be included in chemical safety assessments, based on the fact that there is anecdotal evidence that suggests that chemical exposure may contribute to the increasing prevalence of allergic disease;
- Recognise that some form of allergy probably contributes to chronic conditions (Read, 2002).

6.5.3 Institute of Occupational Medicine, Edinburgh

The Institute of Occupational Medicine, Edinburgh conducted a comprehensive review of the MCS literature in 1999 for the UK Health & Safety Executive. The purpose of the review was to determine whether there was convincing evidence that low-level exposure to environmental chemicals could result in a clinical response in some people. The review concluded that there was no unequivocal epidemiological evidence for MCS, despite extensive literature, and that although MCS probably does exist, it is sometimes used indiscriminately for undiagnosed disorders resulting in its prevalence being exaggerated. The Institute also concluded that of the range of causal mechanisms proposed, evidence favoured the limbic kindling mechanism (Graveling et al. 1999).

This review was presented to 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 (Read, 2002).

6.6 NEW ZEALAND GOVERNMENT

Submissions relating to MCS were received in response to a number of government discussion documents. The issue was also raised in the Imperial Chemicals Industries chemical fire inquiry that reported all the adverse health effects of firefighters attending the fire at Riverview store in December 1984. In 2002, MCS was also mentioned by the Agrichemical Trespass Ministerial Advisory Committee set up by the Minister for the Environment and in the resulting discussion document on pesticides risk reduction policy (Read, 2002).

Successful claims have been made to the New Zealand Accident Rehabilitation and Compensation Insurance Corporation, although the number is not known. In 1998, the Accident Compensation Appeal Authority granted cover to 3 individuals due to exposure to chemicals in the workplace and place of residence. Other appeals for chemical poisoning have been unsuccessful, due to MCS aetiology being ill-defined (Read, 2002).

6.7 DANISH GOVERNMENT

A review of MCS for the Danish Ministry of the Environment oulined briefly the status of this condition in Denmark (Silberschmidt, 2005).

In Denmark, the expressions odour hypersensitivity and solvent intolerance are commonly used instead of MCS. The condition is not recognised as a disease in its own right and is not registered. According to the review, the level of knowledge of MCS amongst Danish physicians is low.

No comprehensive approach to MCS has been taken by Danish authorities. Such an approach requires further research on the use of and exposure to chemicals, effects on health and the extent of the MCS problem in Denmark.

The Danish MCS Organisation has approached the Danish Environmental Protection Agency regarding the reduction of scents in the environment.

6.8 INTERNATIONAL PROGRAM ON CHEMICAL SAFETY (WHO/ILO/UNEP)

The International Programme on Chemical Safety (IPCS), established in 1980, is a joint programme of three Cooperating Organizations, the United Nations Environmental Programme (UNEP), the International Labour Organisation (ILO) and the World Health Organisation (WHO), implementing activities related to chemical safety. WHO is the Executing Agency of the IPCS, whose main roles are to establish the scientific basis for safe use of chemicals and to strengthen national capabilities and capacities for chemical safety.

In February 1996, a workshop organised by the IPCS in collaboration with several of Germany's Federal health and environmental agencies met in Berlin to discuss multiple chemical sensitivities. Invited participants represented a range of disciplines involved in researching, investigating, and treating MCS and other environmental illnesses. The majority of the invited participants suggested that the term "idiopathic environmental intolerances" (IEI) should be used to describe MCS, because they concluded that the condition’s pathogenesis is unclear, and a relationship between exposure to chemicals and symptoms was unproven. Other conclusions were:

- 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 are necessary;
- Interdisciplinary approaches should be sought for diagnosis and treatment.

The recommendations of the workshop included DBPC challenge studies to distinguish psychogenic from toxicogenic origins and epidemiological research directed at the prevalence of relevant symptoms and correlates such as demographics and time trends and the

concurrent presence of other disease states, such as CFS and sick building syndrome (IPCS, 1996). The workshop also recommended that public information be based on established facts and not on speculation and that coordination occur between responsible health care systems, institutions and insurers in order to coordinate approaches to patients with IEI.

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