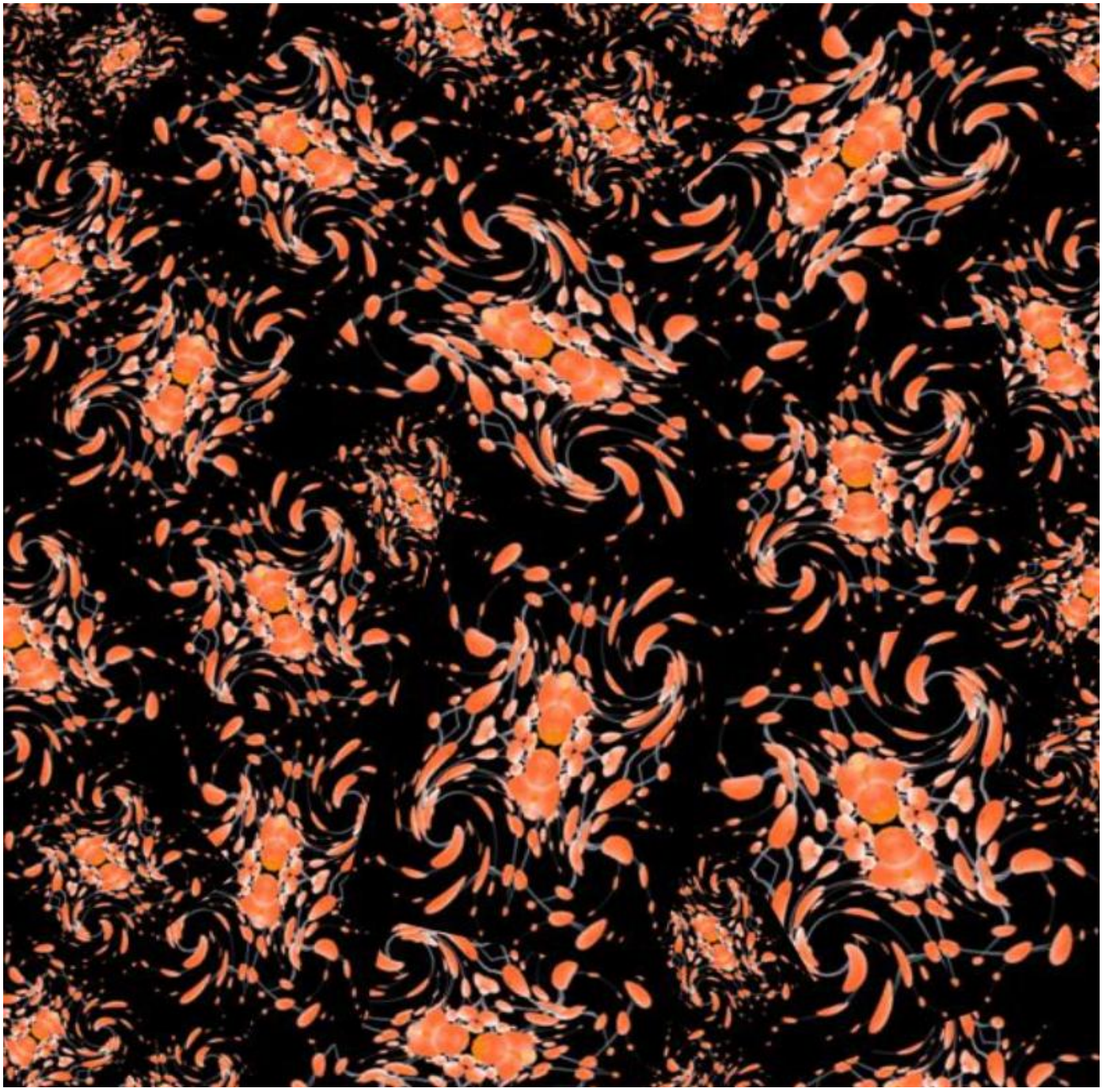
Scientific Review Report

Australian Government
Department of Health and Ageing
NICNAS OCSEH

Multiple Chemical Sensitivity:
identifying key research needs



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

Report prepared by the
National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and the Office of Chemical Safety and Environmental Health (OCSEH)

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PREFACE

What this review is about

Multiple Chemical Sensitivity (MCS) is a term used to describe a condition presenting as a complex array of symptoms linked to low level exposure to chemicals. There is uncertainty about the event(s) and the underlying biological mechanisms that lead to symptoms. This uncertainty has hampered the development of a clinical basis for the diagnosis and treatment of individuals with MCS.

Those with MCS often face situations where their symptoms may be poorly understood or mis-diagnosed, and may be provided with health care that is less than optimal. Difficulties with the diagnosis of MCS are accompanied by a lack of consensus for its treatment other than avoidance of agents that may trigger symptoms.

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

Scope of the review

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

The report therefore examines evidence about:

- Identifying MCS, symptoms and triggers;
- Mode(s) of action for chemical interactions within MCS;
- Approaches to clinical diagnosis and treatment of MCS.

The report also highlights research efforts and further activities that would enhance diagnosis, treatment and better clinical management practices of MCS in Australia.

Conduct of the review

The review has two key areas of focus. Firstly, it reviews scientific information to identify biologically plausible hypotheses to explain the underlying mechanisms of MCS. The elucidation of the biological basis for MCS will undoubtedly 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, to better support the diagnosis and management of individuals with MCS, the review identifies current diagnosis and treatment practices and gaps in clinical research and medical education in Australia. The review findings point to specific priorities for further scientific and clinical research on MCS.

ABBREVIATIONS

AAAAI	American Academy of Allergy, Asthma and Immunology
AAEM	American Academy of Environmental Medicine
ACOEM	American College of Occupational and Environmental Medicine
ACP	American College of Physicians
ACTA	Australian Chemical Trauma Alliance Inc.
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
AOEC	Association of Occupational and Environmental Clinics
ASCEPT	Australian Society of Clinical and Experimental Pharmacology and Toxicology
ASCIA	Australasian Society of Clinical Immunology and Allergy
ASEHA	Allergy, Sensitivity and 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
CFS	Chronic fatigue syndrome
CMA	Californian Medical Association
CNS	Central nervous system
CTMCS	Community Taskforce on Multiple Chemical Sensitivities- WA
DBPC	Double-blind placebo controlled
DOD	Department of Defence, USA
DoHA	Australian Government Department of Health and Ageing
EPA	U.S. Environmental Protection Agency
FM	Fibromyalgia
GRCMCS and CI	Global Recognition Campaign for Multiple Chemical Sensitivity and Chemical Injury
IEI	Idiopathic environmental intolerance
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
MCS Australia	Multiple Chemical Sensitivity Australia
MCS	Multiple chemical sensitivity
ME/CFS	Myalgic encephalopathy/Chronic fatigue syndrome.
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
NRC	National Research Council
NTN	National Toxics Network
OCSEH	Office of Chemical Safety and Environmental Health
OSHA	Occupational Safety and Health Administration
RACP	Royal Australasian College of Physicians
RPAH	Royal Prince Alfred Hospital
SATFMCS	South Australian Task Force on Multiple Chemical Sensitivity
SBS	Sick building syndrome
SHR	Sensory hyperreactivity
TILT	Toxicant-induced loss of tolerance
TRP	Transient receptor potential
UNEP	United Nations Environmental Programme
VOC	Volatile organic compound
WHO	World Health Organization

1 EXECUTIVE SUMMARY

1.1 OVERVIEW

Multiple Chemical Sensitivity (MCS) is the most common term used to describe a condition presenting as a complex array of symptoms linked to low level chemical exposures. The underlying mode(s) of action of MCS, i.e. the biological mechanisms by which the chemical sensitivity occurs, remain uncertain.

A common theme reported by individuals is experiences of heightened responsiveness to chemicals at extremely low exposure levels. The agents linked with MCS symptoms in susceptible individuals are numerous and chemically diverse. They include individual chemicals and chemical products encompassing air pollutants, workplace and domestic chemicals, agricultural chemicals, therapeutics and foods.

Similarly, the symptoms experienced by individuals from exposures are diverse and involve multiple organ systems. Although non-specific neurological symptoms are common, overall there is no characteristic symptom profile that identifies MCS. Nevertheless, reported symptoms can, in some cases, be debilitating.

Numerous modes of action have been postulated for MCS. These include immunological changes, respiratory/neurogenic inflammation, limbic sensitisation, elevated NMDA receptor activity, altered metabolism as well as behavioural conditioning and psychological disorders. Alternative names for MCS in part reflect views on particular modes of action.

Several attempts have been made to establish diagnostic criteria for this disorder. A set of 'Consensus Criteria' developed in 1999 describes 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 and survey purposes. Worldwide, a small number of available studies indicate the prevalence of medically diagnosed MCS at 0.2% – 4%. In Australia, only limited surveys of the prevalence of chemical sensitivities and MCS in the community have been conducted. South Australian state health surveys reported a prevalence of medically diagnosed MCS of 0.9%.

At this time, worldwide, MCS is not an internationally classified disorder, with only Germany and Austria (via adoption of German diseases documentation) listing MCS in their national disease classifications.

Presently, a diagnosis of MCS is based commonly on self-reported symptoms and chemical exposure histories. The symptom profile of MCS is indistinguishable from other multi-symptom disorders. No laboratory tests currently exist for diagnosing MCS. Different case definitions and the lack of a characteristic symptom profile and objective laboratory biomarkers for MCS have impeded recognition of the disorder as a distinct clinical entity.

There are no standardised treatments for MCS. Current treatments advocated for MCS include dietary changes, nutritional supplements, detoxification and desensitisation techniques, holistic or body therapies, as well as prescription medicines and behavioural therapies. The most common management regime for MCS is avoidance of agents that trigger symptoms.

1.2 FINDINGS

1.2.1 Research into biological mechanisms underpinning MCS

There is considerable debate as to what biological mechanisms (modes of action) are responsible for the state of chemical sensitivity in MCS. The literature describes numerous potential causative modes of action, both physiological and psychological in nature, many of which are amenable to further testing. MCS may have a multifactorial origin.

An understanding of mode of action and how chemicals interact with organ systems would be assisted by more detailed identification of the chemical species and the exposure scenarios responsible for symptoms in MCS.

Finding 1: Targeted research into 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 modes of action for MCS are highlighted for further scientific research and investigation as priorities:

- Immunological variables;
- Respiratory disorder/neurogenic inflammation;
- Limbic kindling/neural sensitisation and psychological factors;
- Elevated nitric oxide, peroxynitrite and NMDA receptor activity;
- Altered xenobiotic metabolism.

1.2.2 Clinical research needs

An Australian clinical review has highlighted differences with criteria used for the diagnosis of MCS and methods to treat MCS.

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

- Standardising diagnostic criteria that are acceptable to, and utilised by, clinical and scientific groups;
- Determining the prevalence of MCS in the community, for both self-reported cases and those that are medically diagnosed;
- Exploring initiating/triggering agents/events and modes of action in MCS through the use of well designed and conducted blinded challenge tests and longitudinal studies of illness course;
- Determining and documenting effective treatment/management protocols for MCS based on long-term 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 should assist in identifying key elements of MCS such as how MCS is initiated and/or triggered and how sensitivities vary over time.

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. Findings in Appendix 1 provide some practical suggestions to address this issue.

Finding 3: **Education/training**

A survey of clinical approaches to MCS of Australian medical practitioners identified a lack of coverage of MCS within the current Australian medical curriculum given the relatively small amount of time devoted to minor specialties. Other than hospital protocols containing practical measures to assist inpatients with chemical sensitivities, there are also currently no clinical guidelines available to inform medical practitioners as to how to provide appropriate care for MCS individuals.

The development of a clinical education program should 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.

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 complex condition involving a broad array of physical and psychological symptoms, attributed to exposure to low levels of a wide variety of environmental chemicals.

MCS is a condition within the sphere of "environmental sensitivities", a descriptor used in a wider sense to describe a variety of reactions to environmental factors including chemicals and physical phenomena such as electromagnetic radiation, at levels commonly tolerated by the majority of people (Sears, 2007).

In terms of sensitivities involving chemicals, the terms "MCS" and "chemical sensitivity" (sometimes known as "chemical intolerance") are often used interchangeably. However, "chemical sensitivity" in its wider context can describe several distinct types of reactions encompassing classical adverse toxicological reactions, immunological "allergic" sensitivities, individual chemical idiosyncrasies and intolerances through to aversions to particular odours. Broadly, on the basis of Consensus Criteria, MCS is distinguished from other types of chemical sensitivities or intolerances predominantly on the basis of reactions to multiple, diverse chemical substances, the wide spectrum of non-specific symptoms reported in multiple organ systems and the extremely low levels of environmental exposures linked to responses.

The initial concepts to explain MCS were developed by the allergist Theron G. Randolph who, in the 1950's, observed that patients became 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 symptoms in individuals that resemble what is referred to most frequently today as MCS (Randolph, 1961). From these ideas evolved the discipline of *clinical ecology*, based on diagnoses of 'environmental illness' in individuals with multiple symptoms attributed to environmental factors. Reflecting a rise in the general recognition of environmental medicine, the Society for Clinical Ecology founded by Randolph and colleagues in 1965 changed its name in 1984 to the American Academy of Environmental Medicine.

Today, the principles and practices of clinical ecology continue, but they differ from those of the traditional medical specialties of allergy and immunology even to the extent of different interpretations of the terms "allergy" and "sensitivity" and a lack of recognition by many professional medical bodies (Ashford and Miller, 1998).

Although MCS is the most common term, there have been many terms used in the scientific literature and public media to describe the condition encompassing a range of symptoms linked to environmental chemical exposures (Sears, 2007). 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)
- Acquired Intolerance to Solvents
- Total Allergy Syndrome

In many cases, specific terms reflect particular views of individuals or groups regarding the underlying pathogenesis of MCS. Use of the descriptor Idiopathic Environmental Intolerance (IEI) was favoured by many, but not all, participants at an International Programme on Chemical Safety (IPCS) workshop on multiple chemical sensitivities organised by the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). The term was suggested on the basis that it does not make inferences with regards to causative agents (Anonymous, 1996; Lessof, 1997).

As well as being known by different names, some see MCS not as a single defined disease entity, but as a collective term describing a range of symptoms associated with environmental exposures that may represent more accurately a class of disorders (Ashford, 1999; Altenkirch, 2000; Lacour et al., 2005).

2.2 WHAT ARE THE SYMPTOMS OF MCS?

The range of symptoms associated with MCS is very broad. Indeed, a feature of MCS is the wide variety of symptoms that are expressed in multiple organ systems. For example, a literature review by Labarge and McCaffrey (2000) identified 151 symptoms associated with MCS. There are common symptoms reported but there appears to be no consistent characteristic symptom picture for MCS. In an earlier study of symptom prevalence, the most expressed symptoms amongst 200 chemically sensitive individuals (diagnostic criteria not known) reporting to a US environmental health centre fell into 3 groups, namely, those affecting the central nervous system (CNS), the respiratory system and the gastrointestinal system (Table 1) (Ross, 1992).

Table 1. Percentage Prevalence of Symptoms Reported for MCS (Ross, 1992)

Symptom	Prevalence (%)[#]
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

Amongst those referred to an environmental specialist health centre (Nova Scotia Environmental Health Centre), symptoms of environmental sensitivities amongst 351 individuals (diagnosed according to the criteria of Cullen, 1987) and the 1999 Consensus Criteria – see Section 2.5) commonly featured fatigue, difficulty concentrating, forgetfulness and irritability (Joffres et al., 2001). In a study of the discriminant validity of MCS case definitions and reported symptoms, four particular symptoms showed the most discrimination of environmental health clinic patients from general practice patients. These were having a stronger sense of smell, feeling spacey, feeling dull or groggy, and having difficulty concentrating, all of which involve the nervous system (McKeown-Eyssen et al., 2001).

A more recent comprehensive literature review of symptom profiles also noted the preponderance of non-specific CNS symptoms, such as headaches, fatigue and cognitive deficits in self-reported MCS cases (Lacour et al., 2005).

In Australia, websites of allergy and chemical sensitivity community associations list a diverse variety of symptoms affecting almost all body systems reported by those with MCS. An inquiry into MCS by the Social Development Committee of 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 commonly reported were concentration or memory problems, nausea/stomach complaints, muscle pain, dizziness, fever, fatigue, depression and eczema (Social Development Committee, 2005). Other testimonies provided at the Inquiry attested to the wide variability in symptoms, in type, severity and timecourse. A similar wide range of symptoms was reported in oral and written submissions to a 2004 West Australian Parliamentary enquiry into health complaints linked to emissions from the Alcoa refinery at Wagerup (West Australian Legislative Council, 2004).

Although investigations of cause-effect relationships between chemical exposure events and symptoms can be conducted i.e. whether symptoms are the direct result of exposures (Winder, 2002), the lack of a characteristic, empirically validated symptom profile for MCS is regarded by some as an impediment to comprehensive diagnostic procedures, clinical practice and scientific investigation (Lacour et al., 2005).

2.3 WHAT CHEMICALS TRIGGER THE SYMPTOMS OF MCS?

In the literature, the range of chemical agents linked with MCS symptoms in susceptible individuals is remarkably extensive and diverse. Early descriptions of environmental illness implicated the following broad categories of chemical agents (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.

Ashford and Miller (1998) outlined an array of chemicals and chemical product types that have been shown, or have the potential, to be problematic for those with MCS. These authors grouped these substances as:

- Outdoor air pollutants e.g. pesticides, solvent vapours, fuel and paint vapours, combustion products, tar fumes, diesel and auto exhaust, industrial air pollution;
- Indoor air pollutants, domestic and workplace chemicals e.g. industrial and domestic indoor air, especially in "tight" buildings and spaces, combustion products from gas or oil-fired heaters, sponge rubber bedding, padding and upholstery, plastics, insecticides, perfumes, paints, deodorisers, cedar closets, cleaning agents, disinfectants, mothballs, newsprint and other printed materials, fabrics in clothing, bedding and window coverings, particleboard, carpeting and carpet padding; odours of virtually any description especially petrochemical odours but also natural odours from woods or cooking foods;
- Foods, food additives and contaminants e.g. corn and corn sugar, pesticide residues, fumigants, fungicides, sulphur treatments, artificial colours, sweeteners, preservatives, ripening chemicals such as ethylene oxide, protective waxes, packaging materials;
- Water contaminants and additives ingested but also those encountered whilst showering and bathing;
- Drugs and consumer products e.g. aspirin, barbiturates, sulphonamides, diluents, excipients such as cornstarch or lactose, flavouring agents, coatings, preservatives, mineral oils, petroleum jelly, ointments, lotions, laxatives, synthetic vitamins, adhesive tape, cosmetics, perfumes, shampoos, personal hygiene products, denture adhesives, bath salts and oils, waterbeds, synthetic fabrics, felt tipped pens, polishes, cleaners, chlorinated swimming pools, skin alcohol, radio contrast dyes, contact lenses, plasticisers leaching from medical devices.

In a 2003 population study of MCS in the USA, out of 12 possible reaction triggers for which particular survey responses were sought, the products reported to make the largest percentages of respondents sick were cleaning agents, pesticides and perfumes. Car exhaust, barber shops/beauty salons, new carpets, new furniture, chlorine in household water and fresh ink were also common triggers (Caress and Steinemann, 2003).

In Australia, respondents to a South Australian state health survey conducted in 2002 and 2004 were asked about specific chemical classes associated with chemical sensitivity. Most chemically hypersensitive individuals noted perfumes as of concern (82.5%), with tobacco smoke, new building or renovation, pesticides and herbicides, petrochemicals, vehicle smoke, and other chemicals in decreasing order of concern (Fitzgerald, 2008).

The Australian Chemical Trauma Alliance (ACTA), in a written submission to the Parliament of South Australia Inquiry into MCS (Social Development Committee, 2005), listed the following chemicals, products and non-chemical agents as common triggers for MCS:

- Pesticides;
- Fragranced products such as perfumes, aftershave and deodorants;
- Virtually all volatile organic compounds (VOCs), 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 South Australian Parliamentary 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 containing numerous individual chemical compounds, for example, from the Alcoa alumina refinery at Wagerup (West Australian Legislative Council, 2004). For this emission source, an emissions inventory was developed for an environmental study listing 27 individual compounds or classes of compounds (Donoghue and Cullen, 2007).

In contrast to the array of predominantly chemical products associated with MCS, Pall (2009) identified seven different chemicals or chemical types implicated in MCS – organophosphorous/carbamate, organochloride and pyrethroid pesticides, organic solvents, carbon monoxide, hydrogen sulphide and mercury/mercurial compounds. These chemicals/chemical types are reputed to possess a common characteristic in that they are able to stimulate N-methyl-D-aspartate (NMDA) receptor activity, a key component of the NO/ONOO cycle theory for MCS (see Section 3.1.4).

Agents that trigger symptoms are often distinguished from those that initiate the MCS condition. Ashford and Miller (1998) highlighted a two-step process of initiation (causation) and triggering (subsequent reactions) in MCS. It is considered by some that chemicals that induce or initiate MCS via a single large exposure or chronic low level exposure may be different to those that subsequently trigger symptoms once the condition is established. In addition, the range of chemicals involved in triggering is regarded as often greater than that involved in initiation – the phenomenon known as “spreading”. However, others suggest that the types of chemicals involved in these separate processes appear to be similar, suggesting similar mechanisms of action in initiation and triggering (Pall, 2009).

Initiation versus triggering was investigated in the population study of Caress and Steinemann (2003). In this study, 13% of the survey population of 1500 individuals claimed an unusual sensitivity to common chemical substances, with 3% claiming a medical diagnosis of MCS. Of those claiming unusual sensitivity, less than half (40%) were “sure” or “pretty sure” what exposures produced their original chemical sensitivity. The chemical types most indicated as initiating sensitivities were pesticides, harsh cleaners or solvents, new construction materials and gasoline or other petroleum products. The chemical types most implicated in subsequently triggering chemical sensitivities were cleaning agents, pesticides and perfumes. This population study indicates at least an overlap between types of chemicals that initiate and those that trigger MCS.

In Australia, 11 of 14 hypersensitive respondents in the South Australian State health survey indicated that as well as identifying chemicals that trigger symptoms, they did know what initially caused their sensitivity. However, detail of these chemical types responsible for sensitivity is not available (Fitzgerald, 2008).

In conclusion, MCS is associated with a diverse range of individual chemicals as well as chemical products. It is not clear whether individuals with MCS can commonly identify particular chemical exposures responsible for their condition. Also, the extent to which different chemicals are implicated in separate initiation and triggering events is not clear.

2.4 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 based on repeated observations in the Yale University Occupational Medical Clinic of recurrent problems in workers following chemical exposures. Cullen (1987) described the condition as follows:

> "*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 to Cullen's case definition. Ashford and Miller (1991) advocated an operational definition for MCS that proposed that a patient could be shown to have MCS by removal from the suspected offending agents and by rechallenge, after an appropriate interval, under strictly controlled environmental conditions. Causality could be inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge. They also advocated challenges for research purposes performed in a double-blind, placebo-controlled (DBPC) manner.

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 (Kreutzer, 2000). 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 DBPC challenge testing rather than via self report.

Others also noted limitations of 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, i.e. the physician relies entirely on the patient's reports of symptoms and exposure when making a diagnosis (Gots et al., 1993; Waddell, 1993; American Academy of Allergy, Asthma and Immunology, 1999).

The IPCS 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 (Anonymous, 1996). One of the principal (but not unanimous) conclusions from the workshop was that use of the term MCS should be avoided because it makes an unsupported judgement on causation. Instead, use of the descriptor "Idiopathic Environmental Intolerances" was suggested (Anonymous, 1996; Lessof, 1997).

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 (5)" (Nethercott et al., 1993). An additional criterion was included subsequently by Bartha et al. (1999), namely, (6) that "symptoms be displayed in multiple organ systems" to distinguish MCS from single organ system disorders e.g. migraine that may also meet these five criteria.

These six criteria of Bartha et al. (1999) (Table 2) are referred to as the '1999 Consensus Criteria' and are commonly included in research definitions.

Table 2: 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

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 and their association with chemical exposures.

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 (e.g. 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 whom some measurable change is produced e.g. bronchospasm (Eaton et al., 2000).

Other case definitions have been proposed but not substantially tested or widely acknowledged (Simon et al., 1990; Kipen and Fiedler, 2002). In Japan, diagnostic criteria for MCS based on a symptoms and objective examination checklist were devised under the auspices of the Ministry of Health, Labour and Welfare in 1997 (Hojo et al., 2008). 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 cited in Australian surveys. For example, although they were not used, the Consensus Criteria were quoted in the New South Wales (NSW) Department of Health Adult Health Survey in 2002 where questions on general chemical sensitivity (not specifically MCS) were included (NSW Department of Health, 2002).

2.5 DOES MCS HAVE A DISEASE CLASSIFICATION?

The International Classification of Diseases (ICD) published by the WHO is the international standard diagnostic classification system for diseases and health conditions. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological and quality purposes, ICD records also provide a common basis for the compilation, analysis and interpretation of national mortality and morbidity statistics.

Individual countries are free to adopt their own version of the ICD. 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). At this stage, Austria has adopted the German ICD-10 for its use and therefore MCS is included also in the Austrian ICD-10 (R. Schlögel, personal communication).

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. 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, experts from 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 consulted.

The proposal to assign a unique classification code for MCS in 2003 was rejected. The experts concluded that there was a lack of clinical or laboratory evidence of a pathological process, difficulties in delineating patients from others within a wide spectrum of intolerance/irritation from smells and fumes in the general population, a lack of internationally accepted diagnostic criteria or validated diagnostic tests and a lack of clarity of the relationship between MCS and other syndromes with overlapping clinical features e.g. chronic fatigue syndrome or fibromyalgia (J Rust, NCCH, personal communication, 2004).

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

2.6 DO INDIVIDUALS WITH MCS SHARE COMMON CHARACTERISTICS?

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; Ashford

and Miller, 1991; Cullen et al., 1992; Sparks et al., 1994; Lax and Henneberger, 1995; Miller and Mitzel, 1995; Fielder and Kipen, 1997; Levy, 1997; Kreutzer et al., 1999; Eis et al., 2008).

In the first phase of their population study of MCS, Caress and Steinemann (2003) reported similar results for gender, but that MCS occurred across education and income levels and most often within the agebands < 20 and 21-35 years of age. The population survey also reported that the majority of respondents could not identify any original cause of their condition. Less than one fifth indicated a "chemical" or "pesticide" exposure as responsible for their hypersensitivity.

A more recent Canadian survey also revealed a female predominance amongst MCS subjects with the greatest percentage of MCS cases occurring at 45-64 years of age. The survey also reported that MCS (together with other medically unexplained physical symptoms) were more common in low income households, but did not show a clear relationship between MCS and educational status (Park and Knudson 2007).

Race/ethnicity or geography also do not appear to be significant risk factors for MCS (Kreutzer et al., 1999; Caress and Steinemann, 2003; Eis et al., 2008).

Different explanations have been offered to account for the overrepresentation of females amongst MCS patients. These include different reactions in females in noticing, defining and acting on symptoms, increased vulnerability of the female immune system, the likelihood of more frequent exposure to chemical exposures in poorly ventilated homes and even a greater prevalence in females with major depressive or somatisation disorders (Labarge and McCaffrey, 2000).

Ashford and Miller (1998) claimed that the following separate groups with different chemical exposure experiences show a heightened reactivity to low level exposure to chemicals:

- Industrial workers exposed occupationally to chemicals;
- Occupants of "tight buildings", including office workers and school children;
- Residents of communities whose air or water is contaminated by chemicals;
- Individuals who have had personal and unique exposures to various chemicals.

These groups are claimed by these authors to differ demographically. For example, industrial workers are regarded as predominantly male, blue collar workers, whereas those with chemical sensitivity from tight buildings and those with "personal and unique" chemical exposures are regarded as a heterogeneous group, but predominantly female, white collar or professional workers.

Industrial workers were the first individuals to attract qualitative descriptions of MCS in medical clinics (Cullen, 1987), suggesting initially that MCS may be linked to occupational, and therefore potentially intense, chemical exposures. However, a subsequent quantitative study by Cullen and co-workers of all MCS patients seen at the Yale University Occupational Medical Clinic from 1986 to 1992 revealed only low rates of MCS occurring in industrial sectors associated with the highest rates of chemical and physical injuries. Only approximately 27% of MCS subjects were occupationally exposed to chemicals such as in the construction and manufacturing industries, suggesting paradoxically that exposure

backgrounds with low levels of chemical exposures are more likely to be associated with MCS than those with high exposures (Cullen et al., 1992).

Similarly, of 200 individuals with MCS (case definition not described) seen at an environmental health centre in Dallas, USA, less than 5% worked in labour or trade employment. By far, the largest percentage (25%) consisted of homemakers, suggesting an association between certain domestic chemical exposure events and MCS (Ross, 1992). Similar to the demographic findings from other studies, the majority of MCS patients in this study were women, presenting for evaluation predominantly in their 30's or 40's.

At another occupational health clinic, Lax and Henneberger (1995) identified 35 of 605 new patients presenting between 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.

One explanation for the relative paucity of individuals with MCS who are concurrently exposed to chemicals occupationally is the migration of workers with chemical sensitivities away from chemical-intensive industries - the "healthy worker effect" (Ashford and Miller, 1998). Unfortunately, the extent to which occupational migration biases the analysis of MCS from occupational chemical exposures is unclear. Population surveys of MCS are subject to several biases, important common ones being the reliance in case definitions on the self-report of personal experiences and the subjectivity of observations and interpretations of investigators (Kreutzer, 2002).

A recent study investigated whether pest controllers with frequent exposure to a chemical class commonly associated with MCS, pesticides, show increased risk of developing MCS (Bornschein et al., 2008). Results for a cohort of 45 active pest controllers (44 men and one woman) identified from companies in Bavaria, Germany, showed no increased prevalence of chemical sensitivity (assessed using a German version of the Quick Environmental Exposure and Sensitivity Inventory) compared to environmental medicine clinic outpatients. Although the results are in line with previous observations, the authors noted the possibility of a healthy worker effect, limiting the validity of these findings. They suggested this could be addressed by longitudinal surveys of professional activities before and after onset of MCS.

Military involvement has been associated with increased prevalence of multi-symptom conditions including MCS (see Section 2.7). MCS is more common in groups deployed to war theatres than those not deployed (Black et al., 2000a; Thomas et al., 2006) and it has been suggested that chronic neurological symptoms common in MCS may result from stress and/or genetically impaired metabolism of organophosphates commonly used in these theatres (Haley et al., 1999).

As well as individual demographics and experiences, wider societal factors may influence a predisposition to reporting or being diagnosed with MCS. Awareness of chemical sensitivity in general is likely to be proportional to the level of community environmental activism and practice of clinical ecology or environmental medicine (Ashford, 1999). Climate and related cultural practices e.g. amount of time spent indoors, choice of building materials and furnishings, ventilation practices for buildings, and different culturally-related uses of classes of chemical products may also affect the prevalence of chemical sensitivity, including MCS (Ashford, 1999).

Little information is available to determine whether particular demographic susceptibilities for MCS exist in Australia. The 2005 South Australian Parliamentary 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 link between occupational exposures to chemicals and MCS in Australia, supportive studies providing epidemiological data are lacking.

Overall, available data indicate that some demographic characteristics are overrepresented amongst cases of MCS e.g. gender, but overall there does not appear to be a strong, defining demographic risk profile for MCS.

2.7 IS MCS RELATED TO OTHER SYNDROMES OR DISORDERS?

The multiple subjective non-specific symptoms and timecourses associated with MCS have been reported to be noticeably similar to other multi-organ or multi-symptom conditions that have ICD classifications such as chronic fatigue syndrome (CFS), fibromyalgia (FM) and post-traumatic stress disorder (PTSD) (Aaron et al., 2001; Bornschein et al., 2001; Pall, 2002; Lacour et al., 2005).

Buchwald and Garrity (1994) compared 30 adults 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.

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). One study investigating the medical conditions of navy personnel deployed in the Gulf War reported a higher prevalence of CFS, PTSD, MCS, irritable bowel syndrome and a number of other conditions compared to other navy personnel (Gray et al. 2002). Similarly, a subsequent systematic literature review revealed greater reporting of multi-symptom conditions, including CFS and MCS, in Gulf War veterans compared to non-Gulf veterans (Thomas et al., 2006).

The significant overlap in symptoms between these syndromes has suggested shared aetiological mechanisms (Pall 2001, 2002). However, different multi-symptom conditions are regarded to be triggered by distinct, different 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 2002; 2003).

In addition to CFS, FM and PTSD, several other multi-symptom syndromes have been associated with MCS (see Table 3).

Table 3. Syndromes that may be associated with MCS (from Staudenmayer et al., 2003b)

Syndrome	Possible Triggers
Sick building syndrome	Poor building ventilation and VOCs
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	Major infection
Fibromyalgia	Physical trauma
Post traumatic stress syndrome	Severe psychological stress
Irritable bowel syndrome	Food intolerances and allergies, stress

The sick building syndrome (SBS) is a poorly understood condition temporally related to working in particular buildings. Similar to MCS, persons with SBS experience diverse symptoms that include eye, nose and throat irritation, headaches, cough, difficult breathing, fatigue, dizziness and difficulty in concentrating. SBS is thought to result predominantly from poor building ventilation causing a build-up of biological contaminants or vapours from sources that include building materials, furnishings and office equipment (Burge, 2004). Occasionally, some people with SBS report that they later develop MCS (Hodgson, 2000). Contaminants in the indoor environment are similarly implicated in Aerotoxic syndrome (Winder, 2002).

Self-reported health complaints attributed to dental amalgam have been compared to MCS (Malt et al., 1997) and the evidence linking amalgam dental restorations to a wide variety of diseases has been reviewed (Dodes, 2001). Exposures to electromagnetic radiation has been associated with a dermatological syndrome consisting of symptoms of dermal irritation but more recently also to a general syndrome of non-specific sensory, nervous, respiratory and gastrointestinal system complaints similar to MCS (Levallois, 2002).

The symptomatology of MCS is indistinguishable from that of other multi-system disorders which have established ICD classifications. These disorders are sometimes deemed as conditions caused by, or that predispose to, or that exist as comorbid conditions with MCS (Staudenmayer et al., 2003b; Lacour et al., 2005). Some are of the view that a diagnosis of these other multi-symptom disorders should exclude a diagnosis of MCS (Lacour et al., 2005).

3 MECHANISMS OF MULTIPLE CHEMICAL SENSITIVITY

The literature on MCS highlights differences in views regarding the underlying mechanisms through which MCS occurs. Indeed, the heterogeneity of symptoms has given ground for doubt as to whether MCS is a single disease entity with a specific aetiology and pathogenesis (Altenkirch, 2000; Lacour et al., 2005).

The underlying biological basis for MCS and its range of variable symptoms remains unresolved. Indeed, a review by Winder (2002) identified dozens of possible causative mechanisms.

Generally, the debate on mechanisms of MCS has aligned traditionally to views as to whether MCS symptoms are due to psychosomatic responses to perceived chemical toxicity or to a physiological/pathological interaction between chemical agents and organ systems. While some believe MCS is purely a psychological disorder, others consider it to be an overt, albeit poorly understood, physiological response to chemical exposure. Given the increasingly recognised complex interplay between behavioural traits and physiological functions, 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., 2006; Das-Munshi et al., 2007; Haustener et al., 2007; Bauer et al., 2008; Goudsmit and Howes, 2008).

It is important to note that the use of the broad terms psychological, psychogenic or psychosomatic in this report acknowledges an incomplete understanding of the neurochemical processes involved in behavioural susceptibilities and responses. The exacerbation of a variety of different disease states by psychological influences is well documented in the literature and on this basis the possibility that psychological processes influence the development and/or course of MCS is considered (Sorg, 1999).

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 understanding the molecular basis for an effect.

In the toxicological sciences, the concept of mode of action is becoming increasingly important in interpreting toxicological data for risk assessment and in recommending additional relevant research.

3.1 OVERVIEW OF POSSIBLE MCS MODE (S) OF ACTION

With a view towards understanding mode(s) of action, a review of the available literature was undertaken to identify which scientific reports of the mechanisms of MCS are commonly discussed as reflecting the most biologically plausible and scientifically testable hypotheses.

This analysis identifies those theories that warrant further research/testing and these are presented below (in no specific order).

Given difficulties in characterising MCS, this review is not exhaustive but covers major hypotheses.

3.1.1 Immunological dysregulation

Theories of immune dysregulation propose that MCS is caused by a chemically induced disturbance of the immune system leading to cell damage, in turn resulting in immunological dysfunction (Levin and Byers, 1987; 1992; Meggs, 1992, 1993).

Within these theories, a distinction is made between a putative abnormal disturbance of immune mechanisms thought to be responsible for inducing the heightened chemical sensitivity in MCS, and immune sensitisation as the mechanism for chemical sensitivity involving classical allergic reactions reflected by predictable tissue reactions or changes in specific immune parameters. Immune (allergic) sensitisation alone *per se* would not be regarded as indicative of MCS as it is common, well characterised single organ phenomenon that does not meet the MCS Consensus Criteria of multiple organ involvement.

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. Early immunological testing of MCS patients did not find levels of immunoglobulins, complement, B-cell, T-cell or T-cell subsets in MCS subjects outside normal limits that would indicate either allergic sensitisation or aberrant immune reactivities (Terr, 1986). Subsequent studies have reported out of range values in individual MCS patients for immunoglobulins, complement components, peripheral blood lymphocyte subsets, activated T cells or abnormal serum antibodies to tissue antigens and chemical-protein conjugates (Thrasher et al. 1990; Fiedler et al., 1992; Heuser et al. 1992; Kipen et al. 1992; Levin and Byers, 1992; Rea et al. 1992). However, across these studies, there were no consistent findings suggestive of immunological reactivity in MCS.

Overall, it had been suggested from these early studies that a consistent pattern of immunological reactivity or abnormality indicative of a specific immunological deficit in MCS had yet to be found (Simon et al. 1993; Graveling et al. 1999; Labarge and McCaffrey, 2000). More recently, although more subjects with idiopathic environmental intolerance (IEI - defined on the basis of reported chemical sensitivities, symptoms and avoidance behaviour) reported allergies compared with somatoform disorder (SFD) or normal control subjects, total serum IgE, a common marker of allergic disease, showed no consistent changes with IEI, SFD or in normal controls (Bailer et al., 2005).

A long term sensitisation method was described recently to identify very weak immediate and delayed type hypersensitivity reactions in an animal model of low level chemical allergy (Fukuyama et al. 2008). In a modification of the local lymph node assay (LLNA), levels of serum IgE, IgE expressing B cells, major histocompatibility complex (MHC) expressing lymphocytes and a range of proinflammatory cytokines were monitored following low level repeated dermal exposures to several known allergic sensitisers in mice. Although studies in humans have yet to be conducted by these authors, they suggest that this sensitive assay methodology could be used to identify low level allergic reactions to weakly immunogenic chemicals such as those reported as triggers in MCS.

Given the extent to which the chemicals implicated in MCS are structurally diverse, it is difficult to envisage a common change in immune parameters or adverse effect on immune function that would reflect or explain the symptomatology of MCS. Overall, some researchers have hypothesised that allergic or immunotoxicologic reactions could be contributing factors in at least a subset of MCS patients (Selner and Staudenmayer, 1992; Albright and Goldstein 1992; Meggs, 1992) but others have concluded that there is an absence of a consistent pattern of immunological reactivity or abnormality in MCS (Simon et al. 1993; Graveling et al. 1999; Labarge and McCaffrey, 2000). Unfortunately, the role of the immune system in MCS is difficult to assess from available reports because of an absence of testable immune hypotheses and choice of tests based on specific hypotheses, the lack of standardised protocols including for the selection of cases and controls and wide variations in the quality control of immunological testing (Mitchell et al., 2000).

Reports also lack controls for common variables that influence the immune system e.g. age, stress, infections, smoking or drugs (Salvaggio, 1991; Gad, 1999).

Consistent changes in certain immunological markers have recently been reported in a study of potential dysfunctions of chemical defenses in MCS (De Luca et al., 2010). An array of metabolic and immunological markers was studied amongst MCS individuals, individuals with suspected MCS and healthy control individuals. MCS and suspected MCS were diagnosed according to Cullen's criteria (1987) and responses to a modified Quick Environmental Exposure and Sensitivity Inventory (QEESI). Serum levels of immunomodulatory cytokines (interferon gamma, interleukin 8 and 10, macrophage chemotactic protein 1, platelet-derived growth factor and vascular endothelial growth factor) were statistically significantly elevated in 77 MCS individuals compared to 52 healthy controls. From these results, in addition to alterations in serum metabolic markers seen in MCS and suspected MCS individuals, the authors concluded that dysfunctions of chemical defenses in MCS may be related to metabolising/antioxidant enzyme expression and activity mediated by proinflammatory agents.

Research challenge: If further research on immune sensitisation or immune dysregulation in MCS is to be justified, it requires validated immune measurements with appropriate quality controls in well-defined clinical groups. Specific evaluations of immunological markers in population-based studies and during specific chemical challenges could be applied additionally to prospective, longitudinal evaluations of immune function and dysfunction in MCS individuals (Mitchell et al., 2000).

3.1.2 Respiratory disorder/neurogenic inflammation

The respiratory disorder/neurogenic inflammation theory suggests that MCS represents an amplification of non-specific immune responses to low-level irritants, initiated by the interaction of chemical irritants with sensory nerves in the respiratory mucosa. In essence, this theory contends that inhaled chemicals bind to receptors on sensory nerve C-fibres in the respiratory mucosa which triggers the local release of inflammatory mediators from nerve endings, leading to altered function of the respiratory system (Bascom, 1992; Meggs, 1993; 1999). The airways are particularly sensitive to damage by airborne chemicals, particulates and infectious agents, and although MCS is also associated with chemical exposures via the skin or gastrointestinal tract, airborne chemicals are common initiators/triggers (Sorg, 1999) (Section 2.3) and respiratory symptoms are common complaints (Section 2.2).

As well as neurogenic inflammation at the site of chemical stimulus within the respiratory mucosa, 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).

The upper and lower airways are richly innervated with multiple subsets of nociceptive, parasympathetic and sympathetic nerves containing an array of ion channel receptor proteins, including members of the transient receptor potential (TRP) ion channel superfamily. TRP ion channels have a wide range of sensing properties and subsets of nociceptive primary sensory neurons contain proinflammatory neuropeptides which are released from nerve terminals after TRP receptor stimulation, thereby causing airways neurogenic inflammation (Nassini et al. 2010). Multiple levels of complexity in nasal innervations and TRP ion channel proteins, in addition to reactivities to multiple exogenous chemicals and endogenous proinflammatory agents observed for ion channels such as TRPA1 (Bessac and Jordt, 2008; Tai et al., 2008) are regarded as a rational basis for a spectrum of sensory responses to airborne chemicals in conditions including MCS (Bessac and Jordt, 2008; Baraniuk and Merck, 2009).

In a variety of airways diseases, including those associated with chemical exposures, neurogenic inflammation mediated via sensory nerves contribute to acute defensive responses and chronic effects (Nassini et al., 2010). Asthma-like symptoms described as irritant-induced asthma, occupational asthma or reactive airways dysfunction syndrome (RADS) can occur after accidental exposures to a range of airborne pollutants. Moreover, resultant airways inflammation, tissue remodelling and psychological impacts from exposures severe enough to result in worker's compensation claims can persist for years (Malo et al., 2009).

Because of a link between MCS and airborne chemical exposures, evidence for neurogenic inflammation in the airways has been sought in MCS individuals. Meggs and Cleveland (1993) conducted rhinolaryngoscopic examinations of the nose and throat in 10 MCS sufferers and reported chronic inflammatory changes in the nasal region and/or pharynx in all subjects. Another study although not conducting histological examinations reported significantly higher total nasal resistances and higher respiratory rates in 18 MCS sufferers (diagnosed on the basis of an environmental questionnaire and medical histories) compared to controls (Doty et al., 1988; Doty, 1994).

The potential induction of neurogenic inflammation by volatile organic compounds (VOCs) was investigated in a challenge study with 25 individuals with self-reported MCS (Kimata, 2004). Plasma levels of substance P (SP), vasoactive intestinal peptide (VIP) and nerve growth factor (NGF), but not histamine, were elevated in these individuals compared to normal or atopic eczema/dermatitis syndrome (AEDS) patients. Moreover, VOC exposures from a newly painted room sufficient to induce irritation, headache, nausea or dizziness in these MCS individuals increased plasma levels of these substances. In contrast, lower level VOCs (same room but 2 months after painting) were without effect. VOCs had no effect on plasma levels in normal subjects or AEDS patients. Exposure to the higher level VOCs also enhanced skin wheal responses induced by histamine in these MCS individuals. The results suggest plasma SP, VIP, NGF and histamine as biochemical markers for triggering events in MCS. Unfortunately, exposures were not conducted in a blinded fashion and therefore the

role of stress or expectation in subject responses is unclear. Also, the extent to which MCS reported by individuals conformed to the Consensus Criteria was not clear.

As well as studies of airways inflammation, the sensitivity and specificity of chemosensory reactions have been tested in controlled challenge studies in MCS on the basis of reports of a heightened sense of smell in MCS patients. Despite recording higher total nasal resistances and respiratory rates, 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 (Doty et al., 1988; Doty, 1994).

Hummel and colleagues also 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 i.e. how odours are perceived, rather than differences in sensitivity or chemical sensory processing.

Caccappolo et al. (2000) assessed general odour detection ability using phenylethyl alcohol and pyridine in 33 MCS subjects (diagnosed according to Cullen's criteria) and compared these to CFS patients, asthma patients and normal controls. Similar to previous studies, no differences were found in odour detection thresholds or ability to identify odours in MCS subjects compared to these control groups.

Others have also reported unaltered odour detections between similarly diagnosed MCS subjects and normal matched control individuals suggesting no alteration in olfactory-sensory function in MCS, but MCS individuals were reported to experience more unpleasant reactions to common odours (Ojima et al., 2002) and increased subjective ratings of irritation of the nose, eyes and airways (Georgellis et al., 2003).

Increased subjective airways irritation or "sensory irritation" is a common observation in MCS individuals (Doty et al., 1988; Fernandez et al., 1999; Dalton and Hummel, 2000; Österberg et al., 2003). However, it is also common in the wider population (Holst et al. 2009) where the term odour intolerance is sometimes used to describe heightened airways reactivity to airborne chemicals (Millqvist 2008). In general, sensory irritation can arise from exposures to a variety of chemical classes and early studies showed desensitisation of chemical-induced irritant responses with the respiratory irritant capsaicin, specific for the ion channel receptor TRPV1 (Nielsen, 1991).

Individuals with chronic cough (regardless of the putative cause) have increased sensitivity to the irritant effects of capsaicin and increased expression of TRPV1 on airways epithelial nerve fibres (Groneberg et al. 2004). MCS individuals (diagnosed using Cullen's criteria) also show statistically significantly increased cough sensitivity to capsaicin with tidal breathing tests compared to health controls (Ternesten-Hasséus et al., 2002). However, this sensitivity depends on the testing procedures, with only marginal, non-statistically significant increased sensitivity observed compared to healthy individuals using single breath inhalation testing (Holst et al., 2009).

Sensory hyperreactivity (SHR) is a discrete diagnostic condition within cases of airways sensory irritation defined as a combination of increased cough sensitivity to inhaled capsaicin and a high score on questionnaires examining behavioural consequences of self-reported odour sensitivity. Respiratory symptoms and behavioural/lifestyle changes as a result of chemical sensitivity are seen in both SHR and MCS. As a result, a resemblance between SHR and MCS is drawn, although the diagnosis of SHR implies that a single organ is affected, whilst MCS is defined as a multi-organ disorder (Millqvist 2008).

Although studies have shown that MCS individuals display increased cough sensitivities with particular breathing tests using capsaicin, objective tests of irritation measuring cough reflex thresholds using capsaicin alone are not diagnostic for MCS. Non-MCS individuals with chronic airways irritation also show increased sensitivities as do patients such as those with eczema who display even greater responses than those with MCS (Holst et al., 2009).

As an animal model of sensory irritation in MCS, Anderson and Anderson (1999) in a series of studies in mice examined the acute biological effects of air emissions from common consumer products associated frequently with MCS such as colognes, fabric softeners, air fresheners and mattresses. In chamber tests using pneumotachography, mice exposed to diluted volatile emissions from these products showed air flow limitations and changes in breathing patterns suggestive of sensory irritation. Neurobehavioural changes were also noted. Air samples taken from rooms in which these products were left to offgas, and from sites of complaints of poor air quality, also caused similar effects. For some chemical mixtures (eg some fabric softeners, vinyl mattress covers), but not others (e.g. solid air freshener), respiratory compromises as well as neurobehavioral changes increased with subsequent identical exposures, suggesting increased sensitivity over time to particular combinations of airborne chemicals. Unfortunately, the authors were not able to characterise emissions sufficiently to explain the sensitising potential of some products but not others. However, such direct measurement of sensory irritation in animals from airborne chemicals, especially well characterised individual chemicals and/or mixtures, may be a helpful model to explore neurogenic inflammation in MCS.

Research challenge: The available information suggests that MCS individuals do not have heightened sensitivities with regards to the detection of odours. However, there may be inflammatory effects in the upper airways in at least some MCS individuals. It would be useful to examine these effects in larger cohorts. Nasal lavage studies used to quantify irritant-induced inflammation in allergic rhinitis and asthma could be used to examine MCS (Peden 1996).

Recent work suggests that the majority of sensory neuronal inflammatory signalling in the airways involves TRPV1 and TRPA1 ion channels to the extent that these are considered prime candidates for pharmacological anti-inflammatory and anti-tussive treatments (Bessac

and Jordt, 2008; Nassini et al., 2010). Moreover, the sensitivity of TRPA1 to multiple exogenous and endogenous pro-inflammatory substances is viewed as an explanation for broad chemical sensitivities observed in individuals with RADS which may also extend to less clearly defined conditions such as MCS (Bessac and Jordt, 2008).

Parallels are also drawn between SHR and MCS. However, whether such broad chemical sensitivities in SHR and RADS can account for all of the airborne chemicals implicated in MCS is not known. The expression and function of TRP ion channel receptors as well as the prevalence of tissue remodelling in the airways warrants study in MCS individuals.

The mechanisms by which alterations in the respiratory mucosa and/or functional respiratory changes alone account for the multiple organ system effects in MCS are not known. The involvement of a neurogenic switching mechanism to explain multiple organ effects (Meggs and Cleveland, 1993; Meggs, 1995; 1999) has yet to be demonstrated in MCS (Graveling et al., 1999). Also, MCS is associated with chemical exposures not just via inhalation but also exposures via the skin or gastrointestinal tract. Moreover, although respiratory symptoms are reported in MCS, they do not appear to be the predominant symptom type with neurological symptoms being the most common (Section 2.2).

Overall, further investigations would be helpful in determining the prevalence of airways hyperreactivity in MCS and the extent to which airways hyperreactivity is linked to multiple chemical reactivities and multi-organ symptomatology characteristic of MCS. In this respect, trials in MCS individuals examining the effects of agents which block TRPV1 and TRPA1 ion channels may be instructive.

3.1.3 Limbic kindling/neural sensitisation

Many studies of MCS symptomatology note that disturbances related to the CNS are common (see Section 2.2). The limbic kindling/neural sensitisation model suggests that repeated perturbations of the CNS (in particular the limbic system) from a variety of environmental stressors may induce and amplify multiple organ responses to environmental chemicals.

The limbic system is a group of interconnected brain structures involved in olfaction, emotions, learning and memory. The limbic system also participates in the regulation of many cognitive, endocrine and immune functions. The olfactory bulb is close anatomically to limbic structures and olfactory neurons have been suggested as a potential conduit for chemicals to reach the CNS. Consequently, Bell and colleagues postulated that olfactory-limbic neural sensitisation could lead to polysymptomatic conditions involving multiple organs, such as MCS (Bell et al., 1992; 1997; 1998).

Sensitisation in the context of neurological and behavioural studies commonly refers to the ability of repeated exposures to external stimuli e.g. drugs, chemicals, stress, to induce progressive increases in neurochemical and/or behavioural responses in individuals. In essence, neural sensitisation refers to a nonimmunological form of response amplification in an organism mediated via the nervous system. Numerous studies in animals and some in humans have demonstrated a variety of acute and chronic changes in brain physiology and/or behaviour in response to repeated electrical or chemical stimuli (Antelman, 1994; Gilbert, 1995; Sorg et al., 1998; Sorg, 1999; Labarage and McCaffrey, 2000). Ashford and Miller (1998) outlined a number of human studies showing how chemical and cognitive modulation

of the limbic system can induce behavioural and other responses consistent with those seen in MCS.

Kindling is a form of neural sensitisation defined classically as the ability of a repeated, intermittent electrical or chemical stimulus previously unable to induce a response, to induce a permanent susceptibility to seizure activity in later applications. Researchers have proposed limbic kindling as a type of neural sensitisation that may occur in MCS where chemical stressors (pharmacological or environmental) are able to induce physiological effects that then are amplified with the passage of time (Bell et al. 1992; Miller, 1992; Antelman, 1994). More recently, it has been recognised that whereas there is evidence for neural sensitisation in chemical sensitivity and MCS, evidence for a limbic kindling component in neural sensitisation is limited (Bell et al., 1999a).

Regardless of the evidence for kindling as a mechanism for neural sensitisation, overall, 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 neural sensitisation model claims that increases in limbic neuronal network excitability as a result of stimuli from environmental stressors may augment reactivity to low-level chemical exposures. Moreover, this model emphasises interaction between nervous, immune and endocrine systems within the central nervous system as an explanation of the wide variety of symptoms expressed in MCS.

Neural sensitisation models of MCS infer a potential involvement of olfactory neurons. Both animal and human studies have demonstrated direct neurological pathways from the olfactory region of nasal cavity to the brain and close association between the olfactory bulb and the limbic system within the brain. Therefore, the nose offers potentially a direct pathway into the limbic system for many environmental molecules via the nasal mucosa and olfactory nerves bypassing the blood brain barrier. However, although nose to brain transport of substances 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).

One issue with the involvement of chemicals in a limbic kindling mechanism for MCS is the levels of chemical exposures necessary for kindling to occur. Chemical kindling/neural sensitisation described 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. However, this does not appear to be the case (see Section 2.6).

Arnetz (1999) proposed an integrated model for MCS based on sensitisation of the limbic system induced or augmented not just by chemicals but by a range of environmental stressors including psychosocial stress or “life trauma” events. Once sensitised, the limbic system then reacts to a greater number of triggering events that include chemicals, noise and electromagnetic radiation (Arnetz, 1999).

Several animal models lend support to this psychosocial stress-related model of neural sensitisation in MCS. Friedman et al. (1996) demonstrated that in mice, stress significantly

increased blood brain barrier (BBB) permeability to peripherally administered Evan's blue–albumin, plasmid DNA and the acetylcholinesterase inhibitor pyridostigmine, suggesting that peripherally acting chemicals administered under stress can reach the brain and affect centrally controlled functions (Friedman et al., 1996).

In a rat model of neurological impairment in Gulf War Syndrome, Abdel-Rahman et al. (2002) showed that the combination of restraint stress and low dose repeated exposures to pyridostigmine and the pesticides DEET and permethrin produced BBB disruption and neuronal cell death in the cingulate cortex, dentate gyrus, thalamus and hypothalamus in excess of that seen with either stress or chemicals alone. A follow up histopathological study of the same animals (Abdel-Rahman et al., 2004) revealed neuronal cell death also in areas not associated with BBB disturbances. Liver damage was also observed in animals subject to combined stress and chemical exposures in excess of that seen with stress or chemicals alone. In this model, several mechanisms (BBB breakdown, compromised liver clearances) appeared to be involved in inducing neural damage and this integrated model of chemical toxicity from combined stress and low level chemical exposures could be further investigated.

In another series of rat models, Sorg et al. (2001) described the ability of repeated formaldehyde inhalation exposures to produce behavioural sensitisation in female rats to subsequent psychostimulant (cocaine) injections, suggesting low level formaldehyde-induced altered dopaminergic sensitivities in mesolimbic pathways. Behavioural sensitisation (measured by locomotor activities) was observed with 20 day, but not 7 day formaldehyde exposures.

In other studies, formaldehyde exposures also enhanced fear conditioning responses to odour (orange extract) in male rats, but not female rats. In these, the enhanced fear conditioning was explained by limbic sensitisation and/or enhanced odour responses from increased airways irritation. Low level repeated formaldehyde exposures themselves were also reported to alter locomotor patterns in male (but not female) rats and also alter sleep patterns in male rats upon withdrawal. These studies provide models of at least certain aspects of MCS such as cross sensitisation to different chemicals and behavioural alterations including anxiety and fatigue related to low level chemical exposure.

Human neurological studies have also been conducted in an attempt to objectively measure functional changes in the CNS of MCS individuals. A neuropsychological study by Brown-DeGagne and McGlone (1999) examined the cognitive profile of MCS subjects within the framework of the olfactory-limbic sensitisation 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.

Early electroencephalographic (EEG) studies in normal subjects suggested the ability of airborne chemicals at levels below olfactory thresholds to alter EEG activities and mental performances (Lorig, 1994). Neural sensitisation (increased EEG delta activity) was demonstrated in a challenge study in a subset of chemically intolerant individuals who had not made lifestyle changes due to chemical intolerance but not in chemically intolerant individuals who had made lifestyle changes (Bell et al., 1999b). Neural sensitisation (increased EEG alpha frequency amplitudes) was also demonstrated after repeated

intermittent exposures to chemicals both in chemically sensitive (CS) women and sexually abused (SA) women but not in normal controls (Fernandez et al., 1999). Sensitisation also observed with room air exposures in CS and SA subjects suggesting a role for non-chemical stimuli in this study. Both these studies provide objective measures of neural sensitisation in laboratory settings but they appear to be influenced by psychological states of the subjects. Also, the extent to which these chemically intolerant subjects would be regarded as having MCS is unknown.

Similarly, Joffres et al. (2005) in a pilot study reported significant changes in skin conductance in 10 individuals with MCS diagnosed using the Consensus Criteria compared to 7 control subjects but also noted the importance of identifying potentially confounding anxiety responses.

Brain imaging studies using single proton emission computed tomography (SPECT) have been conducted in individuals with CFS and MCS as well as for investigating specific neurotoxic exposures not directly related to MCS (Heuser et al., 1994; Simon et al., 1994). Early studies of MCS were difficult to interpret because of clinical variability, lack of strict diagnostic criteria and uncharacterised neuropathology (Mayberg, 1994). A subsequent review of SPECT studies of individuals who reported chemical sensitivity (inclusion criteria and relationship with MCS unknown) also noted the need to establish the specificity and relevance of changes by comparisons with challenge studies in chemically naïve, healthy controls (Ross et al., 1999).

Positron emission tomography (PET) showed areas of cortical hypometabolism and limbic hypermetabolism suggesting limbic involvement in a small cohort of individuals (7) with both MCS (according to Cullen's criteria) and neurotoxic injury compared to normal controls (Heuser and Wu, 2001). In 12 subjects with MCS alone, PET revealed mild glucose hypometabolism in one patient, however, compared to normal control subjects, MCS patients did not show neurotoxic or neuroimmunological brain changes of functional significance (Bornschein et al., 2002b). Similarly negative findings were reported by the same research group in subsequent PET and neuropsychological studies of 12 patients with well characterised idiopathic environmental intolerance compared to 17 healthy controls. No consistent or characteristic neuropsychology or functional imaging patterns for the intolerant subjects could be found (Bornschein et al., 2007).

Another 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.

A similar hypoperfusion of odour processing areas was shown also in a recent small case control study of 8 MCS individuals identified using the Consensus Criteria (Orriols et al., 2009). Using SPECT following non-blinded airborne chemical challenges, MCS individuals

showed statistically significant hypoperfusion of olfactory, right and left hippocampus, right parahippocampus, right amygdala, right thalamus, right and left Rolandic and right temporal cortex regions compared to healthy age-, sex-, educationally- and socioeconomically-matched controls. The authors postulated that reduced inhibitory signalling from these olfactory areas may explain heightened chemical sensitivity.

Research Challenge: Overall, results from small studies of brain function in MCS individuals are mixed and the experimental needs outlined in early reviews of neurophysiological studies still apply. Objective measurements of neural sensitisation in MCS individuals require further controlled studies of well characterised individuals using standardised clinical criteria. The behavioural state of subjects during EEG and brain imaging studies would appear to be of particular importance. Control subjects with similar exposure histories but without subjective complaints may be better controls than age-, sex-, educationally- or socioeconomically-matched subjects (Mayberg, 1994). Interpretation of imaging studies would be assisted by further controlled challenge studies, in particular using subthreshold exposures, in chemically sensitive subjects (Mayberg, 1994) and also normal subjects (Ross et al., 1999).

Despite these research needs, there remain several types of observations that support a neural sensitisation model for MCS (reviewed by Bell et al., 1999a; 2001). In animals and humans, sensitisation can induce a variety of physiological and behavioural effects. A key feature of the sensitisation that occurs in MCS is a two step process – initiation whereby a single strong or multiple low level or moderate exposures to a stimulus can increase subsequent responses, and elicitation where the same or a cross-sensitising stimulus activates an amplified response. There are similarities between neural sensitisation models and MCS with regards to a spreading of responses where, over time, reactions are seen to a wider variety of chemical stimuli than those responsible for the sensitised state (Ashford and Miller, 1998).

3.1.4 NMDA receptor activity and elevated nitric oxide and peroxynitrite

Pall (2002; 2003) hypothesised that the hypersensitivity reportedly experienced by MCS sufferers can be explained by increases in N-methyl-D-aspartate (NMDA) receptor activity coupled with stress-related increases in nitric oxide and the oxidative product peroxynitrite. This hypothesis is the main subject of a recent extensive review of MCS by this author (Pall, 2009) and so will only be outlined in brief here.

This theory suggests that hypersensitivity arises through limbic kindling/neural sensitisation and/or neurogenic inflammation processes involving short-term environmental stressors that stimulate NMDA receptors also producing elevated levels of nitric oxide and peroxynitrite. A cycle of interconnected reactions, known as the NO/ONOO cycle, then acts to increase the stimulation and hypersensitivity of NMDA receptors and inducing extreme chemical sensitivity. The cycle involves:

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 effects including increases in blood brain permeability, leading to increased access of chemicals to the central nervous system.

More recent developments of this theory also implicate increased activity of TRP receptors in the CNS and peripheral nervous systems which can increase nitric oxide levels and stimulate NMDA receptor activity (Pall, 2004; 2007a, b; 2009). Overall, this theory implicates seven individual chemicals or chemical classes - organophosphorous/carbamate, organochloride and pyrethroid pesticides, organic solvents, carbon monoxide, hydrogen sulphide and mercury/mercurial compounds, as initiating cases of MCS through their ability to increase NMDA receptor activity.

Five distinct principles and types of evidence are identified for the NO/ONOO cycle mechanism theory as an explanation for MCS and other multisystem illnesses (Pall, 2007a, b; 2009):

- Short term stressors act by raising nitric oxide synthesis and levels of nitric oxide and/or other cycle elements.

- Initiation is converted into chronic illnesses through chronic elevation of cycle elements.

- Symptoms and signs are generated by elevated nitric oxide and/or peroxynitrite, inflammatory cytokines, oxidative stress, NMDA and TRPV1 receptor activity and/or other aspects of the cycle.

- Fundamental mechanisms are local. The cycle components nitric oxide, superoxide and peroxynitrite have quite limited diffusion distances in biological tissues and the mechanisms involved in the cycle act at the level of individual cells. The local nature of the cycle biochemistry provides for wide variations in tissue impacts leading to variations in symptoms and signs from one individual to another.

- Therapy for MCS and other multisystem illnesses should focus on down-regulating NO/ONOO cycle biochemistry.

A neural sensitisation mechanism involving several NO/ONOO cycle elements notably NMDA activity, nitric oxide and intracellular calcium is hypothesised to be responsible for central nervous system symptoms. Peripheral sensitivities expressed in the respiratory or gastrointestinal tracts, lungs, skin and other tissues are hypothesised to occur via local neurogenic inflammatory mechanisms also involving NO/ONOO cycle elements including nitric oxide, local oxidative stress and peroxynitrite elevation, TRP receptors, mast cell activation and release of inflammatory cytokines.

Research challenge: The plausibility of this theory is based on established biochemical mechanisms some of which have been implicated in human studies. In addition, the role of cycle components has been implicated in a number of animal studies regarded as animal models for MCS involving neural sensitisation and other mechanisms (reviewed by Pall, 2009). It also provides an explanation for MCS that potentially unifies other theories for MCS such as neurogenic inflammation and neural sensitisation.

Overall, however, the complex role of multiple NO/ONOO cycle components requires confirmation in MCS subjects for this theory to be a demonstrated mechanistic explanation for MCS. There is currently an overall lack of convincing evidence from studies of MCS individuals that directly demonstrates the presence of much of the hypothesised biochemistry

purported to possess a causal role in chemical sensitivity. Moreover, given the central role of nitric oxide, peroxynitrite and NMDA receptors in this theory, the effects of agents that disrupt this biochemistry, such as nitric oxide scavengers, synthesis inhibitors or NMDA antagonists also have not been investigated adequately in MCS. Anecdotal reports exist of the efficacy of several agents including the NMDA antagonist dextromethorphan and the nitric oxide scavenger hydroxocobalamin in MCS (Pall, 2002; 2007a, b; 2009), but overall, more information is needed to determine the effectiveness of selective agents that inhibit NO/ONOO biochemistry in MCS as evidence for this mode of action in MCS.

Another method of determining the contribution of at least one important component of the NO/ONOO cycle would be to measure levels of nitric oxide in MCS individuals before and after chemical challenge. Because nitric oxide is stable in the gas phase it could be measured in expired air (Pall, 2007b).

Another consequence of the NO/ONOO theory for MCS is that it implicates specific individual chemicals and classes of chemicals on the basis of a common ability to increase NMDA receptor activity. Notwithstanding the extreme broadness of certain classes of chemicals implicated in this theory eg. organic solvents, the plethora of chemicals and chemical products implicated in MCS raises the question as to whether multi-organ sensitivities observed in MCS can be explained adequately by this mechanism for all chemicals elicitants.

Interestingly also in the context of this theory, psychological stress is acknowledged as a potential environmental stressor in several other multisystem illnesses such as CFS, FM and PTSD held by the proponents of this theory to be related to MCS, but not in MCS itself, despite evidence from other studies for at least a contributory role. Finally, given that this hypothesis is linked at least in part to the limbic kindling/neural sensitisation and neurogenic inflammation theory, this hypothesis would benefit from addressing the same identified research needs as for these models.

3.1.5 Toxicant-induced loss of tolerance (TILT)

Miller (1997) proposed another disease theory, TILT, to explain chemical sensitivity, including MCS. This theory suggests that acute or chronic chemical exposures can cause susceptible persons to lose their tolerance to previously tolerated chemicals, drugs and foods. TILT is described in the context of two step process – *initiation* from repeated low level or a single high level chemical exposure, and subsequent *triggering* from everyday common chemical exposures. 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 in detail to account for the initial loss of tolerance or the apparent spread of sensitivity to other unrelated chemicals in MCS. Tolerance breakdown may involve the cholinergic nervous system, neural sensitisation or multiple neurotransmitters and genetic polymorphisms, underlying parallels between chemical intolerance and addiction (Miller 2000). 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 (Ashford and Miller, 1998; 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 (1997), a dedicated environmental medical unit is required to control masking from background chemical exposures and studies to date generally have failed to unmask patients before challenge. Whereas such studies in a dedicated facility would reveal the reliability, or otherwise, of reactivities to chemical triggers, it is unclear to what extent they would elucidate the TILT theory for MCS as no precise physiological mechanism has been proposed to explain the chemical sensitivity.

3.1.6 Altered xenobiotic metabolism

Another postulated mechanism for MCS is genetically based differences in the abilities of MCS individuals to metabolise chemicals.

Although in absolute terms the prevalence of MCS amongst Gulf War veterans is low (less than 7%), Gulf War veterans are approximately three and one half times more likely to report multi-symptom conditions including MCS, compared to non-Gulf veterans (Thomas et al., 2006). Also, in British Gulf War veterans, MCS has been strongly associated with exposure to pesticides (Reid et al., 2001).

In a genotypic study of Gulf War veterans, Haley et al. (1999) reported an association between chronic neurological symptoms and PON1 paraoxonase/arylesterase gene polymorphisms. Studying 20 healthy control subjects (10 deployed and 10 non-deployed personnel) and 25 Gulf War veterans with neurological symptoms ranging from impaired cognition to various manifestations of confusion/ataxia, veterans were significantly more likely than the well controls to possess the PON1 R allele (QR heterozygous or R homozygous). This allele encodes an R allozyme associated with impaired metabolism of organophosphate chemicals such as sarin and chlorpyrifos to which Gulf War veterans were thought to have been exposed at low levels. These findings are interpreted to support the theory that neurological impairment in veterans may result from exposure to particular environmental chemicals in the absence of protective alleles of the polymorphic PON 1 gene.

A subsequent case control study examined gene polymorphisms for selected metabolic enzymes including PON1 in 203 MCS women and 162 normal control women (McKeown-Eyssen et al. 2004). MCS participants were chosen by questionnaire based in part on the case definition of Nethercott et al. (1993). This study reported that women with MCS showed higher hepatic cytochrome P450 isozyme CYP2D6 gene activity and NAT2 “rapid” acetylator gene activity compared to controls. The CYP2D6 gene encodes the monoxygenase enzyme debrisoquine hydroxylase which metabolises endogenous neurotransmitters and a variety of xenobiotics. The NAT2 gene encodes an N-acetyltransferase isozyme which metabolises aromatic amines.

The study also found an overrepresentation in MCS cases of the PON1 QR heterozygous genotype, similar to the study of Haley et al. (1999) in Gulf War veterans. However, in contrast to the Haley et al. (1999) study, no association was found between MCS and the homozygous PON1 R genotype. Also, no associations were found for PON2 or MTHFR C677T genes, the latter which encode methylenetetrahydrofolate reductase involved in Vitamin 12 and folate metabolism, processes that have been implicated in nonspecific neurobehavioural symptoms in MCS (McKeown-Eyssen et al., 2004).

Another cross-sectional study of gene variants in cases of self-reported chemical sensitivity (determined using an Environmental Exposure and Sensitivity Inventory) revealed that a

cohort of 273 chemically sensitive individuals more frequently possessed the NAT2 "slow" acetylator genotype or genetic deletions for glutathione S-transferases (GSTM1 or GSTT1) compared to a cohort of 248 less chemically sensitive individuals (Schnakenberg et al., 2007). The differences in these findings with respect to the NAT 2 genotype compared to McKeown-Eyssen et al. (2004) showing greater prevalence of NAT2 "rapid" acetylator genotype was explained by differences in case inclusion criteria, noting that cases were not assessed against the specific criteria in common MCS case definitions such as of Cullen (Schnakenberg et al., 2007).

A more recent case control study of the role of genetic variations in MCS examined gene polymorphisms for 5HTT, NAT1, NAT2, PON1, PON2 and SOD2 in 59 self-reported MCS individuals compared to 40 normal controls from the same anthroposphere i.e. living surroundings (Wiesmüller et al., 2008). MCS individuals were screened for inclusion additionally by a standardised, validated MCS questionnaire. In contrast to previous studies, no significant differences were found in the proportions of gene polymorphisms between MCS and normal control individuals. Differences in results for NAT2 and PON1 polymorphisms from previous studies were attributed to the comparatively small sample size but also to differences in case inclusion criteria in this study.

These authors also drew similarities between these results and those of a larger German multicentre study of MCS (Eis et al., 2008). In self-reported MCS outpatients recruited from environmental medicine units, no overrepresentations in any of 17 candidate genes associated with enzyme polymorphisms related to xenobiotic metabolism, toxicologically relevant receptors, carrier proteins or mediators of inflammation were detectable. Unfortunately, no details of this genetic analysis were provided in the Eis et al. (2008) paper.

Another German study showed a statistically significant overrepresentation of UDP-glucuronosyltransferase UGT1A1 gene polymorphisms amongst 42 patients suffering from environmental disease (MCS and/or CFS and/or FM) in southern Germany (Müller and Schnakenberg, 2008). Unfortunately, no details (numbers of subjects, diagnostic criteria, genetic analyses) were provided for the MCS individuals in this study.

Genetic susceptibility factors in MCS were also studied recently by Berg et al. (2010). These investigators examined the prevalence of polymorphisms for the genes CYP2D6, NAT2, PON1, MTHFR and CCK2R (cholecystokinin 2 receptor, putatively linked to panic disorder – see Section 3.1.8) in 96 physician diagnosed MCS individuals (Cullen's criteria) and a population sample of 1027 individuals. No statistically significant differences were found for allelic frequencies in a case-control analysis of MCS individuals and matched non-chemically sensitive individuals from the population sample. A statistically significant difference in CCK2R allele (21) frequency was observed in the case-control analysis when using the entire population sample as the control group. However, no statistically significant differences were seen in allelic frequencies (including for CCK2R) within the population sample between groups of individuals stratified according to severities of self-reported discomfort with common airborne chemicals.

These results did not confirm earlier associations for CYP2D6 or NAT2 (McKeown-Eyssen et al., 2004) or PON1 alleles (Haley et al., 1999; McKeown-Eyssen et al., 2004). For CCK2R, allele 21 was statistically significantly overrepresented in contrast to a previous study showing overrepresentation of CCK2R allele 7 in MCS individuals (Binkley et al., 2001) (Section 3.1.8). Consequently, the authors suggested that MCS may represent a

heterogeneous disorder and that depending on the chemical exposure, a given metaboliser phenotype may confer either protection or increased risk of harm. Consequently, a future strategy may be to study groups of individuals stratified according to reported exposures or symptoms.

Polymorphisms of xenobiotic-metabolising enzymes were also studied by De Luca et al. (2010) amongst 133 MCS individuals, 93 individuals with suspected MCS and 218 healthy individuals. MCS and suspected MCS were diagnosed according to Cullen's criteria and responses to a modified Quick Environmental Exposure and Sensitivity Inventory (QEESI). Allelic variants for the cytochrome P450 isoforms CYP2C9, CYP2C19, CYP2D6 and CYP3A5, as well as UDP- glucuronosyltransferase UGT1A1 and glutathione S-transferases GSTP1, GSTM1 and GSTT1 were examined. No statistically significant differences were reported between MCS cases (proportions of MCS and suspected MCS individuals in test cohorts not stated) and healthy controls.

The negative results for CYP2D6 were similar to that of Berg et al. (2010) who were also unable to verify a previous statistically significantly increased prevalence for CYP2D6 in MCS (McKeown-Eyssen et al., 2004). Neither did this study confirm previous reports of a statistically significant overrepresentation of UGT1A1 polymorphisms amongst environmental disease (MCS/CFS/FM) patients (Müller and Schnakenberg, 2008).

As well as genetically based determinants of xenobiotic-metabolising capability, these authors also assayed numerous plasma metabolic and cytokine indicators of enzyme function. An array of enzymatic and non-enzymatic metabolic parameters and cytokine levels were significantly altered in MCS and/or suspected MCS individuals compared to healthy controls. The authors concluded that dysfunction of chemical defenses in MCS may not depend predominantly on genetic susceptibilities but on non-genetic modifications of metabolising/antioxidant enzyme expression and/or activity mediated by proinflammatory agents (De Luca et al., 2010).

A genetic rat model of cholinergic hypersensitivity originally established to study depression displays behavioural characteristics similar to those reported in MCS (Overstreet and Djuric 2001). The cholinergic system is pervasive and involved in many physiological and behavioural functions. Flinders Sensitive Line (FSL) rats were selectively bred for sensitivity to anticholinesterase organophosphates as an animal model of depression. This line exhibits fatigue and reduced appetite but exhibits normal hedonic responses and cognitive functions and also responds to antidepressant drugs. However, this line also demonstrates greater sensitivity to several other classes of chemical compounds and along with fatigue and abnormal sleep and appetite superficially resembles at least part of the clinical picture of certain MCS individuals.

The chemical sensitivity in this rat line is not related to precipitating xenobiotic chemical exposures. Also, the displayed behavioural characteristics do not completely reflect the cluster of symptoms commonly reported in MCS, and in some respects, differ notably e.g. absence of cognitive dysfunction. However, this may be a useful model for insights into certain subpopulations of MCS individuals.

Across available studies, current genetic profiling does not provide a clear genotypic characterisation of MCS individuals. Differences in gene polymorphisms between studies have been attributed to differences in case inclusion criteria (Schnakenberg et al., 2007), the

small size (representativeness) of certain studies (Wiesmüller et al., 2008), normal differences in allelic frequencies across different populations and differences in chemical exposures responsible for the MCS condition (Pall, 2009; Berg et al, 2010). A confounding factor in implicating alterations in xenobiotic metabolism in MCS is that the genes for which certain polymorphisms are overrepresented in MCS groups also have known functions not just in the metabolism of certain xenobiotics but also in the metabolism of normal endogenous products. For example, the paraoxonase gene family has ubiquitous anti-oxidant and anti-inflammatory roles and appears to be central to a range of cardiovascular, metabolic, neurological and infectious illnesses (Camps et al., 2009). Also, the environment of chemical exposures may be critical in determining whether the biotransformative activities of one or more metabolically relevant genes are related to MCS in individuals. Gene products may have a detoxifying role for certain toxicants, but for others, through metabolic activation may produce secondary toxicants which themselves confer specific symptoms of chemical sensitivity in some individuals. This process of toxication or metabolic activation of xenobiotics to harmful products is well known in toxicological science, but the extent to which this process is active in MCS is not known.

Research challenge: The hypothesis of altered xenobiotic metabolism as an explanation for MCS would benefit from additional genetic or biochemical profiling of biologically plausible xenobiotic related genes/gene products in carefully diagnosed MCS individuals. The hypothesis would benefit from correlating genetic/biochemical profiles with confirmed chemical initiators/triggers.

3.1.7 Behavioural conditioning

Conditioning is a form of psychobiological learning, whereby in its simplest form repeated pairing of a previously neutral (conditioned) stimulus with a biologically active (unconditioned) stimulus eventually results in the ability of the neutral stimulus to induce conditioned biologic responses (Bell et al., 1999a). 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; Bolt and Kiesswetter, 2002). 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).

Several experimental trials of conditioned reactions in healthy subjects demonstrated that subjects can acquire and then lose somatic symptoms and altered respiratory behaviours in response to odorous chemical substances, if these odours were associated with unrelated symptom-inducing physiological challenges (hyperventilation from exposure to CO_2 enriched air) or information on adverse health impacts (Van den Bergh et al., 1999; 2001; Devriese et al., 2000, 2004; Meulders et al., 2010). Conditioning in these trials could be replicated by mental cues and images alone indicating that conditioning stimuli may occur psychologically as well as physiologically. The occurrence of conditioning in healthy subjects suggests the possibility that the symptoms of MCS in certain individuals may be the result, perhaps in part, of a conditioned response.

In the above trials, mental evocation of images associated with CO_2 challenges and hyperventilation elicited increases in symptoms but only when the imagined situations were stressful i.e. odours were foul smelling. Conditioning only occurred with actual or imagined

exposures to foul smelling odours, not to neutral or pleasant odours. Moreover, once symptoms were learned, they also generalised to new odours but only provided that they shared a negative affective valence i.e. were foul smelling. In MCS, the spreading of responses is thought by some to occur through similar stimulus generalisation where other odorous agents or even the perception of exposure may begin to elicit the conditioned response (Bolla-Wilson et al., 1988; Devriese et al., 2000; Lehrer, 2000).

One question regarding the role of odours as a conditioning response in MCS is whether MCS individuals have heightened abilities to detect odours. MCS individuals do not appear to possess greater ability to detect odours, but do report increased subjective sensory irritation (See Section 3.1.2).

A review of chemosensory function by Dalton and Hummel (2000) concluded that differences between MCS subjects and controls in reactions to intranasal challenges with odours appear to reflect changes in cognitive perceptions 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 i.e. 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 and Hummel, 2000).

The potential role of stressful events in MCS has also been hypothesised in the context of conditioning. Pennebaker (1994) in noting that virtually all diseases have physical symptoms that are influenced by psychological processes, reported that subjects who report higher rates of physical symptoms are often people who have suffered traumatic experiences before reporting their symptoms. Deployments to war zones have been associated with increased prevalence of MCS and multi-symptom conditions (Black et al., 2000a; Gray et al., 2002; Thomas et al., 2006; also see Sections 2.3 and 4.1.2), although overall, the prevalence of MCS in such individuals overall is low (less than 7%) (Thomas et al., 2006). In the population survey of MCS by Caress and Steinemann (2003), questions were asked about mental or emotional problems prior to the onset of hypersensitivity. Only 1.4% of respondents indicated such a history, but unfortunately, the extent to which these results could be extrapolated to the presence or absence of potentially precipitative traumatic or stressful events is not clear.

Sparks (2000b) suggested that MCS is 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 conditioning approaches to MCS therefore should aim towards symptom desensitisation and the prevention of reinforcement of illness behaviour (Sparks, 2000b). More recent reviews of behavioural and social factors in MCS suggested that MCS 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 was also proposed by Österberg et al. (2006) who identified the need for cognitive-behavioural therapy via a large scale treatment study to validate this model and establish effective treatment regimes. In a study to identify early psychological determinants for the development of MCS, these authors 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.

Criticisms of the conditioning theory for MCS include observations of the diversity of symptoms elicited from diverse chemicals in MCS individuals. Although stimulus generalisation is viewed as an explanation for this spreading of susceptibilities, the extent of this generalisation is regarded by some as unlikely. Moreover, the elicited symptoms should be the same as those experienced during the original chemical exposure, however, MCS individuals have similar non-specific symptoms to different chemicals (Bell et al., 1999a). Additionally, the severity of symptoms often vary with time, susceptibilities are also associated with non-odorous chemicals and in many cases of MCS, there appears to be no substantial initial toxic event that would constitute the unconditional stimulus (Sparks, 2000b).

It is possible that particularly strong conditioning stimuli for some individuals (toxic exposure, stressful event) may broaden the range of chemical stimuli amenable to generalisation. Similarly, cognitive backgrounds and convictions of threats may establish new conditioning experiences leading to stimulus generalisation. Also, regular anticipatory anxiety and hyperventilation in a chemical context may act as unconditioned stimuli (Van den Bergh et al., 2001). It has been suggested that symptoms induced by hyperventilation share similarities with those observed in MCS individuals (Lehrer, 1997; Leznoff 1997; Leznoff and Binkley, 2000). However, the extent to which these mechanisms including the propensity to hyperventilation relate to MCS, or even exist in MCS individuals, is not known.

Research challenge: Behavioural conditioning as a paradigm describes the formation of associative connections, subject to cognitive and emotional factors and external stimuli that modulate both the probability of association formation and their expression in symptoms. Conditioning is viewed by some as a theoretical framework for examining critical processes underlying MCS symptoms, but not as a specific explanation for MCS (Van den Bergh et al., 1999). For example, notably, behavioural conditioning does not explain the diverse range of symptoms reported by MCS sufferers and as much as behavioural conditioning can be demonstrated in laboratory trials, the extent to which conditioning is responsible for MCS has not been established.

The study of behavioural conditioning in MCS would benefit from longitudinal studies of MCS individuals in which eliciting and triggering events (both physical and psychological) are identified and related. In addition, an analysis of cognitive-behavioural systemic desensitisation treatments aimed at the extinction of conditioned responses would be of benefit. These should be designed to detect changes in MCS reactivities and distinguish

between alterations in avoidance behaviour and changes in cognitive predispositions. The potential role of hyperventilation in MCS could be tested by comparing respiratory parameters in MCS individuals with controls (Lehrer, 1997).

3.1.8 Psychological/psychiatric factors

Psychological/psychiatric factors in MCS individuals have been seen either as the *cause* of MCS, an *effect* of having MCS, a *predisposing factor* in the development of MCS, or a *co-morbid* occurrence with MCS.

Various investigators claim that 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 and Kipen, 1997; Labrage and McCaffrey, 2000; Staudenmayer, 2000). The importance of interactions between biological, psychological and social factors in the aetiology of psychological disorders has been noted for some time (Barlow, 1993) and indeed the usefulness and limitations of neuropsychological testing in MCS has been reviewed (Bolla, 2000).

Some researchers also view some individuals with MCS as susceptible to iatrogenic influences where those providing treatment may inadvertently provide inappropriate psychological support to symptoms and concepts of illness (Black, 1995; Labrage and 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 across studies ranges between 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 toxic chemical exposures as the most probable cause of symptoms.

Similarly, in a public health survey in which 65 volunteers attributing hypersensitivity to indoor air pollutants were studied, 38 (58%) were reported by Eberlein-Konig et al. (2002) from professional psychological evaluations to show a psychosomatic or psychotic disorder.

In contrast to these rates of professionally diagnosed morbidities, in a larger population survey of MCS, Caress and Steinemann (2003) noted that only 1.4% of voluntary respondents to their survey reported depression, anxiety or other emotional problems prior to their MCS. However, over one third (38%) reported emotional problems after their hypersensitivity manifested, indicating that for many, psychiatric effects resulted from their MCS condition and were not the primary cause.

Associations between particular psychological dispositions and MCS have 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 and 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 and 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 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 an association between panic disorder and MCS comes from genotypic analysis of MCS subjects, which showed overrepresentation of panic disorder-associated cholecytokinin B receptor alleles 7 (Binkley et al., 2001) and 21 (Berg et al., 2010). However, this latter study found no evidence of a disposition to panic behaviour related to any CCK2R alleles in a population sample of individuals not diagnosed with MCS but who were stratified on the basis of degrees of discomfort related to inhalation of airborne chemicals.

Moreover, the cholecytokinin B receptor has also been implicated in modulating NMDA activity, an important putative central mechanism for MCS (Pall, 2002) (See Section 3.1.4), directly highlighting difficulties with simplistic characterisations of psychological versus physiological dispositions as factors in MCS.

Some researchers have reported that the strongest predictors of MCS are, firstly, histories of somatisation i.e. 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). The common feature of somatoform disorders is the presence of physical symptoms that cannot be fully explained by known general medical conditions, a situation similar to MCS (Labrage and McCaffrey, 2000). 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. Others have previously reported significant inconsistencies in the features of self-reported MCS individuals and somatoform disorder, such as higher age of onset, predominance of severe cognitive symptoms and environmental attribution in MCS (Miller and Mitzel, 1995).

Recent longitudinal studies of psychological factors in MCS and somatoform disorders showed both conditions were temporally stable and present at 1 year follow-up (Bailer et al., 2007) and at 32 months follow-up (Bailer et al., 2008). Both MCS and somatoform individuals scored significantly higher than healthy controls on measures of somatic symptoms and psychological predictors for somatisation. These authors concluded that trait anxiety and symptom perception, interpretation and attribution contribute substantially to the persistence of typical somatoform symptoms in both conditions.

In additional studies by this same group, MCS individuals were distinguished from somatoform disorder and healthy controls by an enhanced trait of absorption (related to suggestibility, openness to experience and fantasy proneness) both at baseline and at 32 months follow-up (Witthöft et al., 2008). Interestingly, another study of bodily sensations and symptom perceptions in MCS found the traits of somatosensory amplification and autonomic perception enhanced in MCS individuals compared to a population control group, but not so the trait of absorption (Skovbjerg et al., 2009). This difference was attributed to different questionnaire formats and also to different control groups, in this latter case a population

control group not of healthy individuals but of individuals sensitive to odorous chemicals but who had not pursued medical care.

In a study of cognitive responses to trigger and symptom words in MCS and somatoform disorder, negative associations towards MCS trigger words were found enhanced in MCS individuals compared to somatoform disorder individuals or health controls. However, emotional intrusion effects (assessed by the speed of responses) to symptom words were similar for both MCS and somatoform individuals compared to controls, suggesting a symptom focussed attentional style in both conditions (Witthöft et al., 2009). Although such psychological studies indicate alterations in cognitive-emotional processing in MCS individuals, they cannot address the issue of causality i.e. whether such cognitive alterations are a cause of MCS (and therefore a risk factor) or a consequence of the chronic condition. Such a question could be addressed either by longitudinal studies preceding illness or by controlled psychological therapeutic studies in MCS individuals.

Hausteiner et al. (2007) recommended treating MCS as a somatoform disorder also with special emphasis on the role of threat beliefs. An integrative psychiatric approach to MCS was regarded as 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.

Reviews of behavioural and social factors in MCS suggested that MCS 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). Joffres et al. (2005) concluded that the reporting of symptoms in MCS may result from a complex set of interactions between aspects of personality, attitudes, culture and social climate as well as any pathologic changes.

Numerous chemical challenge trials involving MCS individuals have also been conducted in an attempt to distinguish physiological and psychological factors in responses to chemical elicitants. 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.

The strength of this overall conclusion from this systematic review has been challenged (Goudsmit and Howes 2008) on the basis of underestimates of the methodological inadequacies of individual provocation studies under review. These authors accept that MCS may be the result of interplay between psychological and physiological processes, but conclude that the systematic review may have overstated the role of psychological factors in MCS.

One physiological explanation for findings of psychological/psychiatric morbidities in MCS may be the effects of neurotoxic agents implicated in MCS such as solvents and pesticides that directly affect mood and emotions. In spite of the documented effects of common neurotoxins, it is possible that complaints resulting from exposures to such agents may remain, at least initially, misdiagnosed and regarded as psychogenic in origin. Also, in the presence of medical symptoms in the absence of objective pathophysiologic findings, the diagnosis of multiple organ symptom complaints frequently default to psychogenic explanations (Sykes, 2006) that, in some cases, may perpetuate discrimination and dismissal for MCS individuals. However, clearly, the absence of pathophysiologic findings in MCS cannot be construed as direct evidence for psychogenic causations (Labarge and McCaffrey, 2000). Also, it should be noted that as much as behavioural profiling studies suggest that certain behavioural dispositions may occur in individuals with environmental sensitivities, they cannot provide definite evidence for psychological/psychiatric influences as a cause of such conditions.

With regards to whether psychopathological issues cause, or are the result of MCS, 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, including those with MCS, may be inevitable and inappropriate with “one shot” psychological profiling. Therefore, although profiling data may be useful in determining the current mental health status of individuals, distinguishing pre-existing psychopathology and psychopathology secondary to organic disease in MCS with such profiling may be difficult. Recent discussion in the psychosomatic research literature on somatoform disorders highlights the difficulties in distinguishing and classifying physical and mental disorders and the dubious nature of dualism between mind and body inherent in the concept of “medically unexplained symptoms” (Creed, 2009).

That said, it has been suggested that proper care of MCS patients requires identifying the existence of both psychological and pathophysiological dysfunction (Gots and Pirages, 1999). There is also evidence that psychotherapeutic interventions may assist individuals with MCS. Gibson et al. (2003) reported that whilst a majority of individuals in a large study of self reported MCS claimed no noticeable effect from psychotherapy to *cure* their MCS, a majority found psychotherapy very, or somewhat, helpful in assisting in *coping* with their MCS. Others also advocate multimodal therapy to improve the prognosis of MCS, which is regarded as a multifactorial disorder involving biological, psychological and social influences (Bauer et al., 2008).

Research challenge: Despite evidence of psychological predispositions and psychiatric comorbidity in MCS, an important question is the extent to which these are the *cause* or an *effect* of an individual’s MCS condition. The lack of evidence for a physiological cause for MCS should not be interpreted as indicating support for a primarily psychiatric explanation.

Simplistic "one shot" psychological profiling may be problematic in distinguishing pre-existing psychopathology and psychopathology secondary to organic disease in MCS. The study of psychotherapeutic interventions in MCS might best focus on supporting and enhancing coping strategies rather than providing a cure. For the study of psychological factors as a cause of, or a contributing factor in MCS, as well as controlled chemical challenge studies or studies of the effectiveness of psychological therapies, longitudinal studies preceding symptoms of illness in high-risk populations may be a valuable research strategy (Davidoff et al., 2000).

3.1.9 Other proposed mechanisms

3.1.9.1 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 and Ziem, 1995; Ziem and 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 and McCaffrey, 2000).

3.1.9.2 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 VOCs 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) 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 FURTHER RESEARCH FOR ELUCIDATING MODE(S) OF ACTION

The mechanisms responsible for symptoms in MCS individuals are still debated. Numerous modes of action have been postulated to explain MCS. However, discussion in the scientific literature has centred around a smaller number based on biological plausibility. To some extent, the multiplicity of names for MCS (Section 2.1) reflects different views on modes of action. Also reflecting a range of views on modes of action, the heterogeneity of symptoms (Section 2.2) and chemical triggers (Section 2.3) reported in MCS has raised questions as to whether MCS is a single nosological entity with a single mode of action.

MCS is described as involving a two step process of initiation of sensitivities followed by subsequent triggering of symptoms. These separate processes are encompassed particularly by the toxicant-induced loss of tolerance (TILT) mode of action hypothesis. However, significant questions remain as to what extent the chemicals involved in each process are different, how frequently a spreading of sensitivities to additional chemicals occurs and what biological mechanism(s) are responsible for facilitating this spreading.

In the early literature on MCS, debate on the mechanisms by which MCS occurs polarised to potential physiological responses to chemical exposures versus psychogenic responses to perceived chemical injury. The exposure levels associated with triggering of symptoms in MCS individuals are extremely low and some theories for modes of action infer additional susceptibility factors. Accordingly, an integrated approach to considering MCS has also been advocated, that similar to other multi-symptom conditions, MCS results from a complex interplay between predisposing psychosocial factors and physical exposures. These multifactorial models of MCS describe how physiological processes such as exposure to chemicals under stressful circumstances coupled with psychological predispositions and subsequent cognitive filtering and feedback mechanisms result in initiation and subsequent triggering of illness. Indeed, the term “stressors” as causative agents in multi-symptom illnesses include psychological stressors as well as physical agents such as chemicals, electromagnetic radiation, infections or physical trauma.

Given the multiplicity of potential stressors for MCS, it is possible that between individuals, or even within the same individual, different modes of action may be present which ultimately manifest as sensitivities to multiple chemical agents.

A central role for chemical exposures is commonly, but not universally, accepted for MCS. The evidence for environmental chemical exposures as a primary cause of MCS has been reviewed systematically by several authors using the Hill criteria for assessing environmental disease (Ashford and Miller 1998; Staudenmayer 2003a, b; Pall, 2007b; Pall, 2009). Hill (1965) described nine separate criteria that could be used to distinguish *association* versus *causation* in assessing evidence linking environmental factors to environmental disease.

The strength of evidence supporting an environmental chemical causation for MCS varies for different Hill criteria and arguably there are criteria for which additional information would be particularly helpful to inform discussion on mode(s) of action in MCS. These are the specificity of association with regards to identifying the exact chemical initiators and/or triggers and whether a biological gradient of responses with regards to chemical exposures exists in MCS individuals.

3.2.1 Chemical initiators/triggers and biological gradients

One fundamental issue for understanding mode(s) of action in MCS is identifying what chemicals can initiate and/or trigger MCS. Numerous case definitions and diagnostic criteria for MCS refer to the involvement of multiple unrelated chemicals (Section 2.4) and the array of chemicals/chemical products reported for MCS is vast (Section 2.3). In the context of particular claimed modes of action for MCS, specific chemicals and chemical classes are implicated (Pall, 2009) (Sections 2.3 and 3.1.4) whilst specific chemicals (ammonia and butyric acid used in experiments to test behavioural conditioning to odours) are claimed *not* to be implicated in MCS (Pall 2010). This is, for example, despite cleaning agents being common elicitants (Section 2.3) with glass cleaners (which frequently contain ammonia) identified as problematic for a majority of MCS individuals in particular surveys (Miller and

Mitzel 1995). Similarly, food additives and certain foods are common elicitants and butyric acid is both a natural food component and additive. Clearly, overall, the identification of chemical species implicated in MCS is poor, relying mostly on identification of chemical uses or chemical mixtures/products e.g. pesticides, solvents, perfumes, cleaning products, particular foods, or biological material (e.g. mold) rather than identifying particular specific chemical identities.

From a toxicological point of view, understanding mode(s) of action in MCS would benefit from detailed information on chemical functional groups shown to be implicated in MCS and how they interact with biological tissues. Without detailed information on the chemistry involved in MCS cases, determining mechanistically how chemicals initiate and/or trigger a state of chemical hypersensitivity in MCS is difficult.

An additional aspect of elucidating mode(s) of action in MCS as well as risk management for MCS individuals is to what extent chemical exposures and symptoms follow a dose-response relationship. External dose is one determinant of the biological effects of xenobiotic chemicals and dose response is an important aspect of toxicological risk characterisation. For many, but not all, chemical toxicants, a threshold dose can be observed or extrapolated below which no biological responses occur. The assumption of a threshold dose and the nature of dose response relationships in the absence of experimental data depend critically on, and are informed by, understandings of mode(s) of action. For example, advocates of purely psychogenic mode(s) of action for MCS suggest that expectations of chemical exposures, rather than exposures themselves, are responsible for the MCS condition and that as such a threshold external dose cannot be demonstrated.

There have been few scientific studies on dose response in either initiation or symptom triggering in MCS. Exact response thresholds in general are difficult to determine due to the nature of dose response curves at very low levels (Sorg, 1999). A recent trial of the effects of different VOC exposures in chemically sensitive groups recorded mild increases in self-reported symptom ratings across several orders of magnitude increases in odour concentrations of phenylethyl alcohol (PEA) in MCS individuals (diagnosed according to the criteria of Cullen). However, in contrast, no changes in symptom ratings were recorded with similar increasing odour concentrations of pyridine (Caccappolo et al., 2000; Fiedler and Kipen, 2001). Also, for PEA, although aesthetic ratings (pleasantness, safety, intensity) by MCS individuals were statistically significantly different from controls at each increasing non-zero dose, trigeminal ratings (burning, stinging/pricking and temperature) were only so at one intermediate dose. Although these data suggest a positive dose response for some subjective symptom ratings for one chemical in MCS individuals, more information is required to establish how the provocation of symptoms from chemical exposures in MCS individuals is dose related.

3.2.2 Challenge studies for determining causation

A particular difficulty for elucidating causalities, biological gradients and mode(s) of action in MCS is establishing adequate designs for scientific studies in which the effects from defined chemical exposures are tested. The Consensus Criteria for a diagnosis of MCS includes the requirement that symptoms are reproducible upon repeated chemical exposures. Some early advocates of a definition of MCS suggested an operational definition based on removal from suspected offending agents and by rechallenge, after an appropriate interval, under strictly controlled conditions. Causality was inferred by the clearing and recurrence of symptoms respectively (Ashford and Miller 1991).

Unfortunately, establishing causality and reproducibility of effects from chemical exposures have been hampered by the reliance of symptom self reporting in the absence of confirmatory laboratory tests and the potential for confounding by multiple chemical exposures, exposure routes, exposure durations and predisposing psychosocial factors encountered in daily life. Although it is not a new idea, and with only limited animal models reflecting particular aspects of MCS, advancing an understanding of MCS would still benefit from further study of the reproducibility of symptoms and symptom type in appropriately diagnosed MCS individuals under controlled exposure conditions.

An important operational question in determining the mechanistic nature of MCS is whether or not, and how reliably, MCS individuals are able to discriminate in controlled challenge studies between reported environmental triggers and appropriate placebos. Given the potential role of expectation in MCS, a particularly useful methodology for such studies is the double blind placebo controlled (DBPC) design using an appropriately benign olfactory masking agent. A systematic review by Das-Munshi et al. (2006) of challenge studies of MCS revealed numerous challenge study designs, but only two of this DBPC type, likely reflecting the practical difficulties in conducting this type of test.

From the review of Das-Munshi et al. (2006), while there are some challenge studies of various designs that report that MCS patients are able to distinguish between placebos and actual chemical trigger(s), others do not, and the most common question raised is whether the study methodologies or their conduct ensures that participants are truly “blinded”. Some 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).

Through the systematic review, Das-Munshi et al. (2006) concluded that chemically sensitive individuals do react to chemical odours but only when discrimination between active and sham substances is possible. Goudsmit and Howes (2008) critiqued this systematic review and this conclusion and outlined a number of important methodological weaknesses across some challenge studies reviewed by these authors. For several double and single-blind challenge studies that utilised olfactory masking (chemical mask or nose clips), they highlighted the small numbers of participants in some studies, the potential for stress, apprehension or comorbid psychiatric disorders to confound results, issues with the selection of subjects (physician diagnosed MCS versus self-reported MCS versus chemically-sensitive), the potential for reactions to masking chemicals, and problems with the identification of chemical triggers in laboratory trials as part of the study versus those identified in daily life.

It is debatable as to the extent to which such single issues identified in studies are sufficient to confound overall study conclusions. For example, it is unclear whether speculations regarding stress, apprehension, or co-morbid psychiatric disorders in certain challenge trials (in the absence of information confirming the presence or otherwise of such conditions in participant cohorts) are sufficient to dismiss the trial results (regardless of the outcome) or, rather, strengthen the notion that psychological issues may play a role in participant’s sensitivities. Also, it is debatable whether the method of identification of chemical triggers, in prior laboratory trials or via reports of daily experiences, significantly compromises the results from double blind testing of sensitivities to such triggers in the laboratory.

That appropriate challenge studies for MCS are difficult to conduct is evident even from a cursory consideration of elements of the current diagnostic criteria for MCS – extreme sensitivity to multiple unrelated chemicals manifesting as non-specific symptoms in multiple organs. It is also underlined by considering arguably the most single cited challenge study in the MCS literature, the DBPC study of Staudenmayer et al. (1993). It is one of only two DBPC challenge studies conducted to date of individuals with chemical sensitivity utilising chemical masking. In this study, 20 physician referred patients with a diagnosis of chemical sensitivity were tested in a purpose built, filtered air environmental chamber. A tolerated olfactory masker was used to provide participant blinding. Participants were exposed in a blind fashion to individual chemicals, the choice of which was dependent upon individual's clinical history. Staff handling participants and recording results were also blinded to the challenges.

Challenges were considered positive if any objective clinical signs were observed, or the subject reported a reaction during challenge, or a postchallenge symptom rating increased to moderate or severe. Overall, these authors concluded that none of the participants were able to demonstrate reliable response patterns across the series of challenges.

Criticisms of this study have been published previously and also summarised recently in a toxicological review of MCS (Pall, 2009). The first criticism is that mint was used as a masking agent, which is reported to initiate EEG sensitisation in humans and so may not be a neutral placebo (Bell et al., 1999a; Fernandez et al., 1999). However, the report of Staudenmayer et al. (1993) indicates that mint was only one of three masking agents employed which were tested in prior trials for tolerance and is defended by noting that if sensitisation to the masking agents was occurring, every exposure to placebo should, but did not, result in symptoms (Staudenmayer et al., 2003b). Also, sensitivity to the masking agent does not explain negative responses to active plus masking agent.

The second criticism is that patients can become desensitised when exposed to various chemicals and that the protocol did not allow a substantial period away from chemical exposures prior to commencement of the study. However, the study protocol indicates chemical avoidance and confirmation of no symptoms present in participants as a prerequisite of entry to the process for testing for tolerance to the masking agent, although discusses neither the avoidance nor the symptom testing to achieve this baseline.

The last criticism is that patients were not chosen using a standard case definition of MCS, raising questions as to whether they were MCS sufferers. However, the report indicates that patients were referred by physicians for evaluation, they presented with a belief of sensitivity to multiple chemicals, described themselves as "universal reactors", "allergic to the 20th century", having "chemical hypersensitivity" or "multiple chemical sensitivity", and presented with a range of multiple organ symptoms.

The point here is not that the study of Staundenmayer is immune to criticism, but that there are numerous practical difficulties and potential points of argument with the conduct and reporting of challenge studies of MCS. These arise essentially from difficulties with the diagnostic criteria as well as observations of variabilities in the timecourse of reactivities following exposures that are not described by current diagnostic criteria.

In summary, the following specific issues for challenge studies of MCS have been outlined (Ashford and Miller, 1998; Sorg, 1999; Kreutzer, 2000; Labarge and McCaffrey, 2000; Das-Munshi et al., 2006; Goudsmit and Howes, 2008; Pall, 2009):

- Adequate entry and exclusion criteria and characterisation of participant cohorts;
- Isolation of individuals from background exposures to allow a "deadapted state" i.e. not in a state of tolerance, prior to challenge studies;
- Adequate blinding of participants through use of olfactory masking agents or devices that themselves do not evoke reactions in participants;
- Identification and trial of challenge substances relevant to the participant cohort;
- Appropriate challenge time periods and challenge doses;
- The potential for delayed responses in individuals that induce false negatives (participants do not immediately react) or false positives (reactions are delayed confounding subsequent challenges);

3.2.3 Investigations for key modes of action

Studies in the scientific literature on MCS have not only identified and discussed individual modes of action for MCS but also suggested particular research directions. Some of these, such as the need for identifying objective biomarkers for MCS and conducting population surveys and challenge studies which are adequately controlled, have been advocated repeatedly.

While there are a number of individual proposed biological mechanisms or modes of action identified for MCS, based on biological plausibility, testability and identified existing research gaps, the following are identified as potential priority areas for further scientific investigation:

3.2.3.1 Immunological variables

The role of the immune system in MCS is currently difficult to assess from published reports because of an absence of testable immune hypotheses, the lack of standardised protocols and wide variations in the quality control of current immunological testing. Current reports also lack controls for common confounding variables that influence the immune system e.g. age, stress, infections, smoking or drugs.

If immune dysregulation or as yet to be identified low level immune sensitisation are to be adequately tested as potential modes of action for MCS, further work is needed including validated immune measurements with appropriate quality controls in well-defined clinical groups. Specific evaluations of immunological markers in population-based studies and during specific chemical challenges could be applied also to prospective, longitudinal evaluations of immune function and dysfunction in MCS. A modification of the local lymph node assay involving long term low level sensitisation has been recently described as an animal model of low level chemical allergy in MCS (Fukuyama et al., 2008). Similar measurements of proinflammatory cytokines, immunoglobulins and lymphocyte subsets could be used in an attempt to identify putative low level allergic reactions to weakly immunogenic chemicals such as those reported as triggers in MCS.

3.2.3.2 Respiratory disorder/neurogenic inflammation

The respiratory disorder/neurogenic inflammation theory suggests that inhaled chemicals bind to receptors on sensory nerve C-fibres in the respiratory mucosa which trigger the local release of inflammatory mediators from nerve endings, leading to altered function of the

respiratory system. Small studies have found macroscopic and functional evidence of chronic inflammatory changes in the upper airways in some MCS individuals and increased subjective ratings of airways irritation by MCS individuals. However, studies do not reveal increased olfactory sensitivity in MCS.

A 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. In addition, this mechanism cannot account for reported sensitivity to non-inhaled chemicals.

Multiorgan involvement is dependent on a theory of 'neurogenic switching' where antidromic sensory nerve impulses causes release of inflammatory mediators at distant tissue sites. Currently, there are few data supporting the existence of a neurogenic switching mechanism in MCS although one recent small study showed elevated levels of substance P, vasoactive intestinal peptide and nerve growth factor in the plasma of MCS individuals compared to normal or atopic eczema/dermatitis syndrome patients.

Whether this mechanism is operational and responsible for the symptoms of MCS could be explored by measuring vasoactive mediators in larger cohorts. Studies could also include nasal lavage studies such as those used to quantify irritant-induced inflammation in allergic rhinitis and asthma and challenge studies examining respiratory changes and referred physiological effects following exposures to specific chemical triggers.

Parallels are drawn between SHR and MCS and in recent years there has been increasing interest in the role of airways TRP ion channel receptors in respiratory irritant responses. The function and distribution of different TRP receptors in the airways provides a mechanism whereby airways sensitivities may be mediated by multiple airborne chemical agents. Whether such sensitivities can account for all of the airborne chemicals implicated in MCS is not known. The expression and function of such receptors in the airways warrants study in MCS individuals carefully distinguished from those with SHR alone.

An animal model of SBS showed changes in respiratory function and neurobehaviour in mice with exposure to selected consumer products and building air (Anderson and Anderson, 1999). Moreover, effects increased with subsequent exposures suggesting a selective induction of sensitivity. This model could be explored further. It would be important to determine whether the increased respiratory and neurobehavioural sensitivities to common products as well as purified chemical agents can be quantified reliably in this model. If so, it could be used to explore the nature of this sensitivity and why some chemical emissions appear to produce sensitisation whilst others do not.

3.2.3.3 Limbic kindling/neural sensitisation and psychological factors

The limbic kindling/neural sensitisation theory also provides a model to explain the diverse array of symptoms experienced by MCS subjects, including those involving multiple organs.

There are mixed results from attempts at examining higher cortical processing of odour information by electrically recording or imaging brain function in MCS and other chemically sensitive individuals. The experimental needs outlined in early reviews of neurophysiological studies still apply. Objective measurements of neural sensitisation in MCS individuals require further controlled studies of well characterised individuals using standardised clinical criteria. The behavioural state of subjects during EEG and brain imaging studies appears to be of

particular importance. Control subjects with similar exposure histories but without subjective complaints may be better controls than age-, sex-, educationally or socioeconomically matched subjects (Mayberg, 1994). Interpretation of imaging studies would be assisted by further controlled challenge studies, in particular using subthreshold exposures, in chemically sensitive subjects (Mayberg, 1994) and also normal subjects (Ross et al., 1999).

Given the primacy of olfactory pathways in this hypothesised mode of action for MCS, mechanisms by which kindling/sensitisation might be initiated could be explored through investigations of the transport of molecules within olfactory pathways and blood brain barrier permeability changes. These could be compared during challenge testing in MCS individuals and appropriate control subjects.

Several animal models lend support to an integrated model of neural sensitisation and neurological injury resulting from combined stress and low level chemical exposures. The role of psychological factors including stress in initiating or contributing to MCS should be further explored, both through confirmation of the results from these animal models as well as through studies of MCS individuals. Lehrer (1997) outlines several psychophysiological hypotheses and research strategies that could be useful for exploring psychological factors contributing to MCS in individuals.

An important research question relates to the extent to which psychological factors contribute not only to the *initiation* but also to *continued* disability in long-term MCS. This 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 Siegel and Kreutzer (1997), the use of balanced-placebo study designs for testing the power of expectation similar to those used in alcohol research 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.

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 difficulties in MCS research of identifying common eliciting substances for group testing and groups containing MCS individuals with widely varying types and severities of reactions.

Due to the sensitivity of the limbic system to multiple internal and external influences, the limbic kindling/neural sensitisation model has particular implications for the design of challenge studies. The operative factor in examining manifestations of chemical sensitivity within this model is the individual, not the toxicant or the stressor (Bell et al., 1999; 2001). Certain masking agents used in challenge studies have been linked themselves to EEG sensitisation in human subjects (Bell et al., 1999a; Fernandez et al., 1999) and therefore the choice of masking agent is important. For group testing, parallel groups should be considered rather than crossover designs to avoid carryover effects between active and sham treatments. Also, reliance on individual's subjective judgments of chemical reactions should be avoided. Rather, standardised mood and symptom ratings, cognitive tests and objective functional tests at rest and during challenge should be employed (Bell et al., 1999a).

3.2.3.4 Elevated nitric oxide, peroxynitrite and NMDA receptor activity

This 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 and TRPV1 receptors in the CNS and peripheral tissues. This theory links with the limbic kindling/neural sensitisation and neurogenic inflammation models of MCS.

This proposed theory is based on established biochemical mechanisms some of which have been implicated in human studies including other multi-symptom illnesses. In addition, the role of cycle components has been implicated in animal studies regarded as animal models for MCS involving neural sensitisation and other mechanisms.

However, the role of these cycle components needs to be demonstrated adequately in MCS subjects for this theory to be confirmed as an adequate explanation for MCS. For example, given the central role of nitric oxide, peroxynitrite and NMDA receptors in this theory, the effects of agents that disrupt this biochemistry have not been investigated adequately in MCS. Limited reports exist of the efficacy in different multi-system illnesses of numerous agents including dietary supplements that downregulate this biochemistry (Pall, 2006, 2007a, b), and efficacy of the NMDA antagonist dextromethorphan and the nitric oxide scavenger hydroxocobalamin has been reported anecdotally in MCS (Pall, 2002; 2007b; 2009). However, overall, more information is needed including clinical trial data on the selective inhibition of NO/ONOO cycle biochemistry in MCS for this to be accepted as a confirmed mode of action for MCS.

A method of determining the contribution of at least one important component of the NO/ONOO cycle would be to measure levels of nitric oxide in MCS individuals before and after chemical challenge. Because nitric oxide is stable in the gas phase it could be measured in expired air (Pall, 2007b).

One complication for this theory is that it implicates only specific chemicals or classes of chemicals which can increase NMDA activity. However, a wide spectrum of chemicals/chemical products is implicated in MCS and it is not known whether this theory can account for all agents reported as elicitants in MCS. This theory would benefit then from further characterisation of the precise chemical agents linked to MCS and confirmation, or otherwise, of their properties in increasing NMDA receptor activity.

3.2.3.5 Altered xenobiotic metabolism

MCS is also postulated to arise from genetically-based differences in the abilities of MCS individuals to metabolise chemicals.

There are numerous studies in the literature linking genetic polymorphisms with specific disorders including those arising from chemical toxicity, reflecting the complexity by which genes interact with environmental agents to mediate individual responses. In the shadow of the Human Genome Project, emerging toxicogenomic technologies now permit sequence analysis, as well as gene transcript, protein, and metabolite profiling on a genome-wide scale. The application of genomic technologies to toxicology allows genotypes and toxicant-induced genome expression, protein, and metabolite patterns to be used to screen compounds for toxic effects, to monitor individuals' exposure to toxicants, to track cellular responses to different doses, to assess mechanisms of action, and to predict individual variability in sensitivity to toxicants (Committee on Applications of Toxicogenomic Technologies to

Predictive Toxicology and Risk Assessment, National Research Council, 2007). Clearly, these new technologies could be utilised to explore genomic susceptibilities in MCS.

Humans vary in their responses to environmental factors, including chemicals, because of differences in gene sequences, gene expression and epigenetic modifications such as DNA methylation which also affect gene expression. Consequently, it is recognised that to some extent the same level of exposure to a chemical compound may give rise to different biologic effects in different individuals.

Unfortunately, across available studies, current genetic profiling does not provide a clear genotypic characterisation of MCS individuals. Differences in gene polymorphisms between studies have been attributed to differences in case inclusion criteria, the small size (representativeness) of certain studies, normal differences in allelic frequencies across different populations and differences in chemical exposures responsible for the MCS condition. A confounding factor in implicating alterations in xenobiotic metabolism in MCS is that the genes for which certain polymorphisms are overrepresented in MCS groups also have known functions not just in the metabolism of certain xenobiotics but also in the metabolism of normal endogenous mediators.

The hypothesis of altered xenobiotic metabolism as an explanation for MCS would benefit from additional genetic or biochemical profiling of biologically plausible xenobiotic related genes/gene products in larger cohorts of carefully diagnosed MCS individuals. This hypothesis would clearly also benefit from attempts not just to identify specific genetic profiles in MCS cohorts but also to correlate variations in metabolic activities with confirmed chemical triggers. MCS is linked to a plethora of individual chemical agents and chemical products and although it is thought by some that there are common chemical agents linked to the sensitivities in MCS, identification of common chemical elicitants/triggers would allow elucidation of particular metabolic pathways for genomic study.

There are recognised challenges in using toxicogenomic technologies to understand the human health impacts of chemicals (Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment, National Research Council, 2007). There are frequently many genes with small effects on the sensitivity of an individual to a particular toxic agent, which in combination defines an individuals' overall susceptibility to health effects. Interactions between gene variations, as well as additional gene-environment interactions and epigenetic processes play a significant role in determining sensitivity to particular environmental exposures. For MCS individuals, this is likely to be especially so, given the diversity of chemical agents implicated in the pathogenesis of MCS and the multiplicity of adverse health effects.

Also, understanding the distribution of nucleotide polymorphisms in the human gene pool is currently only modest and natural human variability (as opposed to experimental inbred animal strains) makes the understanding of human disease complex and the need for large scale epidemiologic studies obvious.

Unfortunately, toxicogenomic epidemiologic research is difficult, requiring multidisciplinary teams to measure toxicogenomic-derived markers, environmental exposures and to conduct clinical assessments. For MCS, measuring human responses to environmental chemicals in epidemiological studies as well as experimentally in challenge studies is particularly difficult given the extremely low levels of sensitivities, the multiplicity of chemical agents to which

sensitivities are claimed and the lack of objective laboratory markers to quantify theses sensitivities.

4 DIAGNOSIS, TREATMENT AND MANAGEMENT OF MULTIPLE CHEMICAL SENSITIVITY

Difficulties in attempts at establishing diagnostic criteria for MCS are reflected in clinical medical practice. For MCS, clinicians are confronted with a range of self-reported symptoms with which individuals present, differing views on modes of action for MCS, no characteristic diagnostic markers for the disorder and challenges in determining the types and levels of chemical exposures responsible for symptoms.

In terms of treatment or management of MCS, the commonly used Consensus Criteria for MCS include the observation of improvement of symptoms upon removal of triggers, but other than for this avoidance strategy, different views on how MCS should be treated and/or managed may arise from different understandings of the mode(s) of action for MCS. Of interest 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 and Environmental Health (OCSEH) 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 objective biomarker 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 chemicals. However, depending on the type and extent of questioning regarding the nature of their chemical sensitivity, and the extent to which their experiences fulfil available criteria for MCS, it may not clear how many of these individuals would be diagnosed with MCS and not common, well defined sensitivities such as specific allergies.

4.1.1 Studies on the prevalence of MCS in Australia

In NSW, in a 2002 Department of Health survey of adult 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?” Females were more likely to report sensitivity to chemical odours than males, and older individuals (over 65 -75 years) were less likely to report sensitivity to chemical odours. There were no differences in reporting rates between urban and rural areas (NSW Department of Health, 2002).

The survey also requested information on medical diagnoses, with 2.9% answering “yes” to the question “Have you been medically diagnosed with a chemical sensitivity?” Regarding medical diagnoses, there were no significant differences in reporting rates in medical diagnoses between males and females. However, reporting rates were significantly lower for young people (16-24 years). There were no significant differences in reporting rates for diagnosed sensitivity between urban and rural areas. The severity of these health effects and

their conformity to the 1999 Consensus Criteria (Section 2.4) are not known. The survey did not find significant variations in the proportion of people reporting either sensitivity to chemical odours or 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 0.9% reported a medical diagnosis of MCS. Similar to the NSW health survey, more females than males reported a medical diagnosis of MCS and there were no differences in reporting between urban and rural environments (Fitzgerald, 2008).

The prevalence of 0.9% from limited surveys of medically diagnosed MCS in Australia is of a similar order to that reported overseas (below).

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.

On the basis of personal communications with American clinicians, early estimates suggested that 2%–10% of persons in the general population had substantive disruption of their lives because of MCS (Mooser 1987). 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). They 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 (Cullen et al., 1992).

Studies of college student populations revealed that 15%-22% reported feeling moderately or severely ill after exposure to at least three of five common substances (i.e. 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).

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.

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, and of these, inexplicably only about half also reported unusual chemical sensitivity, raising questions as to how this figure relates to MCS. Only 0.6% reported an unusual sensitivity to chemicals plus a medically diagnosed chemical sensitivity that restricted their daily activities (Kreutzer et al., 1999).

In North Carolina, Meggs et al. (1996) reported that 33% of randomly selected individuals in this state 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 and 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 of 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, USA, 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. The prevalence of MCS amongst such individuals is reported to be less than 7% (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, the prevalence of MCS ranges from 0.2% to 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, determining the prevalence of MCS in the Australian population is complicated by surveys that do not request sufficient information for self-reported or medically diagnosed chemical sensitivity to determine whether the sensitivity corresponds to MCS as defined by published diagnostic criteria. There have been numerous studies overseas to determine the prevalence of MCS, but most also have suffered from a lack of information about which, if any, published case definitions were employed to diagnose MCS subjects.

Accordingly, estimates of the number of people with MCS vary widely. It is important to distinguish between cases of common sensitivities or aversions to particular chemicals, cases of well defined toxicological effects or injuries related to particular chemicals, and MCS. Inclusion criteria based on simple self-affirmation of chemical sensitivity/intolerance as used in some laboratory studies and population surveys cannot distinguish these groups. Vastly different outcomes in studies would be expected between individuals who possess common aversions to single (or even multiple) chemicals with little or no symptomatology, those who have well characterised toxicological reactions to chemicals (such as immune sensitisation), those who suffer overt toxic injury involving defined organ systems, and those that would be regarded as having MCS as assessed against defined criteria such as the Consensus Criteria.

Notwithstanding the difficulties associated with the 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. Difficulties with population-based MCS research have been discussed and standardised questions to elucidate experiences of chemical sensitivity in the population have been suggested (Kreutzer, 2002).

In Australia, there are few documented systematic longitudinal 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 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).

4.3 TREATMENT FACILITIES

In the absence of specialist environmental sensitivities treatment facilities, individuals who express general environmental sensitivities in Australia are sometimes referred to mainstream specialist allergy clinics for care. For example, around half of patients referred to the Allergy Unit, Royal Prince Alfred Hospital (RPAH) present with non-allergic or "vasomotor" rhinitis, i.e. unexplained chronic inflammation of the nasal airways with no allergic component. One third of these patients complain of smell intolerance. For individuals who claim extraordinary sensitivity or intolerance to certain smells or odours, current treatment aims at providing explanation and reassurance, determining any clinically identifiable causes and establishing appropriate avoidance strategies (Loblay, 1993). Support and trigger avoidance for chemical sensitivities was also endorsed amongst Australian general and specialist medical

practitioners involved in the clinical review of MCS (see Appendix 1) and similar strategies have been advocated overseas (Sparks 2000a).

Evidence given to the South Australian Parliamentary Inquiry indicated that in the past there were specific facilities in Australia catering for the chemically sensitive. However, particular facilities e.g. in Sydney, were closed because it was concluded that the treatments provided by the facility were not effective (Social Development Committee, 2005).

Evidence also provided to the Inquiry noted that at the time there were no public hospitals in Australia in 2005 that had a policy regarding management of the hospital environment for people with MCS. 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. 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, 2005).

In November 2009, hospital guidelines for catering for inpatients and hospital visitors with MCS and chemical hypersensitivity based on the Royal Brisbane Hospital model were published by the Western Australian Department of Health. Similar guidelines for MCS for South Australian hospitals have also been released recently (May 2010) by the South Australian Department of Health.

Overseas, dedicated health centres exist 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: Cullen's criteria; CFS and FM: Anonymous 2003a; 2003b). A diverse range of treatments is available to patients, but most include education, psychotherapy and individual counselling, physiotherapy and sauna programs.

Clinics devoted to environmental illnesses including MCS are operational also in Germany (Bauer et al., 2006) and Japan (Hojo et al., 2008).

4.4 TREATMENT/MANAGEMENT STRATEGIES

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. In a recent survey of Danish general practitioners, the majority (74%) referred individuals with chemical sensitivities to other medical specialties, the most common of which was allergology (Skovbjerg et al., 2009).

Established pharmaceutical treatments for MCS currently do not exist. Psychotherapy, biofeedback and relaxation and other behavioural therapies are described for some cases as efficacious (Wolf, 1996; Stenn and Binkley, 1998; Staudenmayer, 2000; 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 techniques (meditation, yoga), 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 in this survey were creating a chemical-free living space and chemical avoidance. These authors also reported that whilst a majority of individuals (65%) claimed no noticeable effect from psychotherapy to cure their MCS, a majority (65%) found psychotherapy very or somewhat helpful in assisting in coping with their MCS. Others also claim that the prognosis of MCS is strongly affected by access to multimodal therapy and an understanding between doctor and patient of a multifactorial model of disease (Bauer et al., 2008).

A recent survey of Danish general practitioners with experience of multiple chemical sensitivities also uncovered disparate views on causes and treatments. The majority (65%) perceived the aetiology of their MCS cases as multifactorial, with 28% a somatic/biologic and 7% a psychological aetiology. Amongst the practitioners, treatment advice ranged from avoiding chemical exposures associated with symptoms (75%), avoiding all chemical exposures (12%), not avoiding chemical exposures (linked to perceived psychological aetiologies) (3%), to providing no clinical advice (10%) (Skovbjerg et al., 2009).

Some advocacy and support group websites (national and/or overseas) note a wide range of treatments that are, or have been, used 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 does not establish a consensus for the treatment of MCS other than management by avoidance of chemicals that cause symptoms.

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 and Environmental Health Association Qld Inc.;
- Australian Chemical Trauma Alliance Inc.;
- Circle of Friends MCS Support Group WA;
- Community Taskforce on Multiple Chemical Sensitivities;
- 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 some also present information on a range of treatments.

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.

Although dedicated to management rather than medical treatment, the Human Rights and Equal Opportunity Commission in Australia recently included reference to MCS in their revised Guideline, *Access to Buildings and Services: Guidelines and Information* (HREOC 2007). The section on use of chemicals and materials in the Guidelines states:

> "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."

The South Australian Department of Transport, Energy and Infrastructure has recently published a *Disability Access Checklist Guide for Government Owned and Leased premises* (2010). Part 3 of the guide includes a checklist for MCS. The guide was developed using information in the HREOC's guideline referred to above.

4.5 CLINICAL APPROACHES TO MCS IN AUSTRALIA

In Australia, clinical medical approaches to MCS involve not only general practitioners but also potentially a variety of medical specialists.

In order to determine currently how medical practitioners in Australia respond to individuals with patterns of chemical sensitivity suggestive of MCS, a survey of clinical approaches to the diagnosis and management of MCS was commissioned by the Office of Chemical Safety and Environmental Health (OCSEH) and the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) in 2006. The survey comprised a literature survey, interviews with professional organisations, medical practitioners and other stakeholders, and a workshop to examine the diagnostic and therapeutic practices for MCS currently used by Australian medical practitioners.

Further detail regarding the background and outcomes for this survey are available in Appendix 1.

The workshop 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.

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 different 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 expressing 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 affected 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.

4.6 CLINICAL RESEARCH NEEDS

Views expressed in the scientific literature on MCS and also through the Australian clinical survey of MCS (Appendix 1) highlight subtly different approaches to diagnosing MCS (despite the availability of Consensus Criteria), differing views on the underlying pathological process(s) in MCS and differing approaches to treating or managing MCS other than recommending the avoidance of initiators and/or triggering agents.

Information from available reports is currently insufficient to establish whether reactions in MCS individuals from chemical exposures conform to a dose-response relationship. Dose response is an important aspect of characterising health risks from toxicological agents. Some challenge tests of inhaled chemicals suggest that it is the odour of an airborne triggering agent, or an expectation of harm from exposure, rather than any pharmacological or toxicological properties *per se* that elicits MCS symptoms. Although not all chemicals or chemical products implicated in MCS are airborne, a pivotal role for inhaled chemicals is suggested from particular hypothesised modes of action for MCS such as respiratory

disorder/neurogenic inflammation, limbic kindling/neural sensitisation and behavioural conditioning which involve limbic excitability, olfaction and respiratory function.

Unfortunately, the design, conduct and reporting of current challenge tests for MCS and their conclusions with regards to physiological versus psychological mechanisms are highly debated (see Section 3.2.2). However, as much as arguments continue as to whether MCS is *primarily* physiological or *primarily* psychological in nature from individual tests, current systematic reviews of the scientific literature on challenge testing conclude at least that MCS may be the result of interplay between physiological and psychological influences. If so, this has implications for treatment.

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

- Standardising diagnostic criteria for MCS that are acceptable to, and utilised consistently by, clinical and scientific groups;
- Determining the prevalence of MCS, for both self-reported cases and those that are medically diagnosed using standardized criteria;
- Exploring initiating/triggering agents/events and modes of action in MCS through the use of well designed and conducted blinded challenge tests and longitudinal studies of illness course;
- Determining and documenting effective treatment/management protocols for MCS based on positive, long-term therapeutic alliances and individual self-management.

Prevalence estimates need standardised criteria and surveys of sufficient power to distinguish MCS from other types of chemical sensitivity. A recently developed and validated symptom profile inventory (the Idiopathic Environmental Intolerance Symptom Inventory) could be utilised for reliably and rapidly studying symptom prevalence in MCS. This inventory has advantages over previously used inventories for chemical sensitivity such as the Chemical Sensitivity Scale, The Chemical Odour Sensitivity Scale, the Chemical Odour Intolerance Index or the Quick Environment Exposure Sensitivity Inventory as it deliberately assesses specific symptoms linked to MCS rather than just groups of symptoms or merely the severity of reactions (Andersson et al., 2009).

Challenge testing is helpful to elucidate modes of action. For example, the NO/ONOO cycle theory implicates only those chemicals that can upregulate this biochemistry. However, there is a wide spectrum of chemicals implicated in MCS and any that provoke MCS symptoms and physiological effects unrelated to this biochemistry would suggest additional modes of action. Challenge testing can also explore the relative contributions of physiological and psychological influences in responses to chemical exposures.

Both clinical challenge testing and longitudinal studies could additionally be employed to explore potential therapeutic agents, such as those which downregulate NO/ONOO biochemistry, thus exploring mode of action as well as potentially establishing an avenue of treatment.

4.6.1 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 (i.e. how MCS is initiated and how sensitivities vary 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. Findings in Appendix 1 provide some suggested practical steps on how a longitudinal study could be established.

4.6.2 Education/Training

There is unlikely to be coverage of MCS within the current Australian medical curriculum given the relatively small amount of time devoted to minor specialties. Notwithstanding the recent availability of MCS hospital guidelines in Western Australia and South Australia, there are also currently no clinical guidelines for medical practitioners to provide appropriate care for MCS individuals.

In order to improve the quality of care provided by medical practitioners, the development of a clinical education program for MCS should 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.

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

This appendix contains detail regarding the background, process, issues and outcomes for the 2006 survey of clinical approaches to MCS of Australian medical practitioners. Key outcomes from this survey are included in discussions of the treatment of MCS (Sections 4.4) and clinical research needs (Section 4.5).

The medical approach to individuals with case histories suggestive of MCS is likely to involve not only general practitioners but also a variety of medical specialists depending on the background to their referrals and the stage of their illness. Although Consensus Criteria exist for diagnosing MCS, application of these criteria, and even knowledge of MCS itself, is likely to vary significantly between medical practitioners depending on their specialties and their understandings, if any, of the mechanisms by which the disorder manifests. A lack of standardised approaches to MCS is likely then also to be reflected in different approaches to 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 and Environmental Health (OCSEH) 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 survey was conducted by BMP Healthcare Consulting Pty Ltd.

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 contact list of professional organisations and individuals with experience in dealing with MCS was determined by the OCSEH/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 4.

Table 4. 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 Australasian 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 Australasian 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. Workshop participants are outlined below (in alphabetical order):

Dr Michael Bollen AM: Consultant, BMP Healthcare Consulting
Dr Jonathan Burdon: Respiratory Physician, Past President of the Thoracic Society
Dr Mark Donohoe: General Practitioner with a special interest in MCS
Dr David Elder: Occupational Physician
Dr Jim Fitzgerald: Toxicologist, SA Department of Health

Dr David Gillis: Immunologist, currently Queensland representative on the Australasian Society of Clinical Immunology and Allergy (ASCIA) Council
Dr Vicki Kotsirilos: General Practitioner, Founding President of the Australasian Integrative Medicine Association (AIMA)
Dr Colin Little: Allergist
Dr Rob Loblay: Immunologist, Royal Prince Alfred Hospital
Dr Moira Somers: General Practitioner with a special interest in MCS
Dr Sue Whicker: Consultant, BMP Healthcare Consulting

Two additional participants in the workshop wished to remain anonymous.

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 for characteristic biological markers 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 and Austria (via adoption of the German disease classifications) are the only countries in which MCS is a recognised ICD-10 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 comparatively limited clinical experience with MCS within overall caseloads.

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 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.

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

- Insufficient evidence exists in the literature 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 issues 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

Some advocacy and support group websites (national and/or overseas) note 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 chemical 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 expressing 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 issues 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

The clinical review identified that further clinical research is needed and 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 were suggested to assist in facilitating clinical research and improve patient management:

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 conditions including multi-organ disorders that appear to be associated with 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 identify ways to assist people who are affected by this condition.

6 APPENDIX 2 - VIEWS OF NATIONAL GOVERNMENTS AND PROFESSIONAL MEDICAL ORGANISATIONS

The health issues surrounding MCS have been considered by professional medical organisations and by governments. The following information on position statements on MCS and MCS government policy is not intended to be exhaustive, but indicates how the issue has been addressed by key overseas bodies with environmental health regulatory responsibilities and professional interests. Further information on references to MCS by organisations and jurisdictions at various levels is available (Hileman, 1991; Donnay, 1998, 1999; Labarge and McCaffrey, 2000; Read, 2002; Silberschmidt, 2005).

6.1 US PROFESSIONAL ORGANISATIONS

6.1.1 American Academy of Environmental Medicine (AAEM)

In 1965, Randolph founded the Society for Clinical Ecology, later renamed the American Academy of Environmental Medicine (AAEM), composed mainly of medical and osteopathic physicians practising the principles of clinical ecology. AAEM has published its overall philosophy in *An Overview of the Philosophy of the Academy of Environmental Medicine* (AAEM, 1990). According to the model of environmental medicine outlined in this overview, environmentally triggered illnesses occur when homeodynamic interactions among biological functions are compromised by external or internal stressors. Environmental substances as well as physical phenomena such as vibration, noise, electromagnetic radiation etc. are potential stressors that are capable of contributing to homeostatic imbalances. Internal stressors include psychological stress, genetic limitations, malnutrition etc.

A separate 2008 position statement on “chemical sensitivity” by the AAEM notes that it is a chronic, sometimes disabling, primarily physical condition consisting of a hyperreactivity to environmental pollutants in highly susceptible individuals (AAEM, 2008). The statement does not refer specifically to MCS.

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) first issued a position statement on MCS in 1986 that was updated in 1999. The AAAAI notes an absence of scientific evidence for any particular mechanism for the aetiology 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 continue to be speculative (American Academy of Allergy, Asthma and Immunology, 1999).

6.1.3 American College of Physicians (ACP)

The American College of Physicians published a position paper on clinical ecology 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). This statement does not specifically address MCS and it is unclear whether this position on clinical ecology is still held.

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 are some indoor air quality problems that can affect human health and thus supports 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). More recently, a guide for health professionals on indoor air quality co-sponsored by the AMA as well as the American Lung Association, the Environmental Protection Agency and the Consumer Products Safety Commission notes that definition of MCS is elusive and its pathogenesis as a distinct entity is not confirmed. The guide also notes that the current consensus is that complaints in cases of claimed or suspected MCS should not be dismissed as psychogenic, and that a thorough workup is essential (American Lung Association, Environmental Protection Agency, Consumer Product Safety Commission and American Medical Association, 2009).

6.1.6 Californian Medical Association (CMA)

Whilst not addressing MCS specifically, 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 that supports the hypotheses on which clinical ecology is based. 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). There are conflicting views as to whether this is still a CMA position (Orme and Benedetti, 1994; Donnay, 1999). According to the CMA, to date, this view has not been officially sunsetted (Y. Choong – personal communication).

6.1.7 Association of Occupational and Environmental Clinics (AOEC)

The Association of Occupational and Environmental Clinics (AOEC) is a network of individual clinics and individuals committed to improving the practice of occupational and environmental medicine through information sharing and collaborative research. The AOEC

has not published a position statement on MCS, but in 1991 cosponsored a workshop for its members on advancing the understanding of MCS. The workshop covered clinical experiences, diagnosis and treatment, research studies and mechanisms (Rest, 1992).

6.1.8 National Academy of Sciences – National Research Council (NRC)

The National Research Council of the National Academy of Sciences does not have an official position on MCS but has published two books addressing MCS. The first, *Biologic Markers of Immunotoxicology*, a consensus document prepared by the Subcommittee on Immunotoxicology, noted that SBS, MCS and illnesses from environmental toxicants in general are areas of increasing national concern, with significant but uncounted patient populations suffering morbidity and disability. However, members of the subcommittee are of the view that there is insufficient evidence that MCS is an immunologic problem (Subcommittee on Immunotoxicology, Committee on Biologic Markers, Board on Environmental Studies and Toxicology, National Research Council, 1992). The second, *Multiple Chemical Sensitivities*, published as an addendum to *Biologic Markers of Immunotoxicology*, consisted of papers presented at a 1991 workshop on MCS cosponsored by the National Academy of Sciences and the Environmental Protection Agency (Board of Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, 1992).

6.1.9 Other Organisations

Other health related organisations in the US that have issued reviews of MCS include the American Council on Science and Health (ACSH) (Orme and Benedetti, 1994) and the American Health Foundation. In 1994, the ACSH noted that many who believe they have MCS suffer greatly and although some are sensitive to small amounts of specific chemicals, the Council does not conclude that MCS describes a general hypersensitivity to chemicals. The paper also questions the value of further research, on the basis of a lack of clear definition for MCS and untestable hypotheses.

A review of olfactory mechanisms in MCS by the Environmental Health and Safety Council of the American Health Foundation (unrelated to the current American Health Foundation founded in 2002) (American Health Foundation, 2003), concluded that there was no convincing evidence that any olfactory mechanism underlies induction of a sensitised state or triggering of symptoms in MCS. However, fragrances and other odourants could be associated with symptoms because they are recognisable stimuli (Ross et al., 1999).

6.2 US GOVERNMENT

In America, interest in MCS within federal government health departments and agencies has a relatively long history dating from 1979 with the issue being discussed and examined through several workshops and conferences (Read, 2002).

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 supported MCS conferences to further well-designed scientific research into MCS aetiology. One meeting by the National Academy of Sciences on MCS was held in March 1991. Another meeting on MCS in September 1991 was cosponsored with the Association of Occupational and Environmental Clinics. Another meeting on low level chemical exposures and neurobiologic sensitivity sponsored by the ATSDR was held in 1994. The proceedings from these meetings are available in a combined publication (Mitchell 1995).

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. 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 (e.g. 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 Veterans affairs disability compensation.

In 2008, the Research Advisory Committee on Gulf War Veterans' Illnesses published a detailed report on the health of Gulf War veterans which examined MCS (Research Advisory Committee on Gulf War Veterans' Illnesses, 2008). The report noted both similarities and differences between Gulf War illness and other multisymptom disorders found in the general population. The report recommended studies that determine the extent to which objective measures distinguishing CFS, FM and MCS patients from healthy controls are also associated with Gulf War illness.

6.2.4 National Institute of Environmental Health Sciences (NIEHS), National Institute of Health

The NIEHS 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.

6.2.5 Environmental Protection Agency (EPA)

In 1991, the EPA requested that the National Research Council organise a workshop on MCS. The papers presented at this workshop cosponsored by the National Academy of Sciences and the Environmental Protection Agency were published as an addendum to *Biologic Markers of Immunotoxicology* (Board of Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, 1992).

The EPA also initiated a federal government Interagency Workgroup on MCS that was co-chaired by the ATSDR and the National Centre for Environmental Health 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 (Interagency Workgroup on Multiple Chemical Sensitivity, 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. 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 EPA 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 EPA stated that the state of knowledge regarding the definition, causes and treatment of MCS was insufficiently defined to warrant the type of regulatory action called for by the council (Read, 2002).

More recently, a guide for health professionals on indoor air quality co-sponsored by the EPA as well as the American Lung Association, American Medical Association and the Consumer Products Safety Commission notes that definition of MCS is elusive and its pathogenesis as a distinct entity is not confirmed. The guide also notes that the current consensus is that complaints in cases of claimed or suspected MCS should not be dismissed as psychogenic, and that a thorough workup is essential (American Lung Association, Environmental Protection Agency, Consumer Product Safety Commission and American Medical Association, 2009).

6.2.6 Occupational Safety and Health Administration (OSHA)

The Occupational Safety and Health Administration (OSHA) of the Department of Labor notes that MCS is a highly controversial issue. In theory, MCS is an adverse physical reaction to low levels of many common chemicals. Chemical sensitivity is generally accepted as a reaction to chemicals but debate continues as to whether MCS is classifiable as an illness. There is insufficient scientific evidence to confirm a relationship between possible causative theories and symptoms (Occupational Safety and Health Administration, 2008).

6.3 CANADIAN GOVERNMENT

Several workshops on MCS have been sponsored by the Canadian government. In 1990, the Department of National Health and Welfare in Canada convened a workshop on MCS to develop priorities for research and identify health needs of MCS patients (Health and Welfare Canada, 1990). In 1992, a second workshop examined multiple chemical sensitivities and their relevance to psychiatric disorders (Health Canada, 1992).

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).

The Canadian Centre for Occupational Health and Safety notes MCS and SBS as important issues with respect to indoor air quality (Canadian Centre for Occupational Health and Safety, 2008).

Many municipalities across Canada including Halifax and Toronto and in the United States 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). The province of Nova Scotia has established an environmental medicine clinic, the Nova Scotia Environmental Health Centre, 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).

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 (Royal College of Physicians and Royal College of Pathologists, 1995).

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

In 2000, the BSAENM issued a lengthy report on MCS (Eaton et al., 2000) which included discussion on individuals at risk, eliciting agents, possible mechanisms, patient management and research priorities. In summary, the report concluded that:

- There is increasing disquiet about the safety of chemical exposures and there should be efforts generally to reduce exposures;
- Environmental exposures to triggering agents should be kept below that which has been 'shown' to initiate sensitivity in susceptible individuals. Suggested levels for ambient VOCs should be kept below about 5 ppb, a value derived from unpublished data reported to provoke symptoms of SBS in the USA;
- The priorities for clinicians are to halt a perceived increase in prevalence of MCS, improve recognition and management of MCS, and increase awareness of the difficulties faced by MCS patients to avoid extreme avoidance behaviours by those with MCS;
- Government should enact the precautionary principle, including restricting exposures to chemicals with the greatest potential for public exposures and with any history of long term adverse effects;
- Independent, adequately funded research needs to be conducted to improve prevalence monitoring and to establish effective diagnosis and treatment;
- Medical education regarding environmental exposures needs to be improved.

6.5.3 Institute of Occupational Medicine, Edinburgh

The Institute of Occupational Medicine, Edinburgh conducted a review of the MCS literature in 1999 for the UK Health and 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. Committee members noted MCS was a condition largely defined by the patient and that there was no consistent pattern of symptoms or exposure data to define the condition. The Committee agreed that, on the basis of current knowledge, there was insufficient evidence to make comments on potential mechanisms or to recommend further research in this area. (Anonymous, 1999).

6.6 NEW ZEALAND GOVERNMENT

According to a review on multiple chemical sensitivities commissioned by the New Zealand Environmental Risk Management Authority (Read, 2002), no position statements on MCS were identified for New Zealand organisations. However, submissions relating to MCS have been received in response to a number of government discussion documents. MCS was also raised in the Imperial Chemicals Industries chemical fire inquiry that reported all the adverse health effects of fire-fighters 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).

A technical report into the burden of occupational disease and injury in New Zealand was commissioned by the National Occupational Health and Safety Advisory Committee (Driscoll et al., 2004). In an entry for MCS, the report noted that there are no occupational exposures clearly related to the development of MCS in the New Zealand workforce and there are no New Zealand studies of MCS in relation to work. Occupational exposures reported to precipitate typical symptoms in persons who are said to be chemically sensitive included adhesives, industrial air contaminants, fumigants, photocopy toner, smoke, soldering fumes, solvents, sulphur residues, utility gas and paint vapour.

6.7 DANISH GOVERNMENT

A review of MCS for the Danish Ministry of the Environment outlined 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 no comprehensive approach to MCS has been taken by Danish authorities. According to the review, the level of knowledge of MCS amongst Danish physicians is low.

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 German federal health and environmental agencies met in Berlin to discuss multiple chemical sensitivities (IPCS, 1996). Invited participants represented a range of scientific disciplines but focussed on occupational and environmental medicine and toxicology. 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 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 unexplained disease states, such as CFS and Gulf War Veterans illnesses. 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 (Anonymous, 1996).

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