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A volunteer community organisation providing support for people with allergy, food and chemical sensitivity

A participating organisation of National Toxics Network

Response to the NICNAS/OCS Scientific Review of Multiple Chemical Sensitivity pre-release consultation draft

Introduction

The proposed MCS report is badly drafted and is unlikely to address the myriad of serious problems faced by individuals with MCS in the Australian community. Such individuals have been poisoned by substances in the environment, in particular man made chemicals that now abound in our lives. As long as government fails to address the issues surrounding exposure to the multitude of chemicals we encounter on a daily basis, the issue of MCS and other environmental sensitivities cannot be satisfactorily addressed e.g.:

- concentrations of chemicals in all of our environments – domestic, workplace, wider environment
- the lack of toxicology for most of these, both singly and as mixtures,
- the recognition of poisonings at government and medical level,
- treatment and management,
- co-existing morbidities between MCS and other diseases e.g. airway disease
- education of the public re MCS and chemical usage. Often people are shocked to find that the chemicals they are using are not as safe as they thought - especially once their health has been damaged and they cannot get help. This demonstrates the need for government action to encourage people to reduce chemicals in their lives.
- The opportunity to develop green chemicals that are non toxic and sustainable

We are especially concerned about the impacts of gene technology and nanotechnology on human health and the environment as we haven't caught up with existing technology yet.

Some criticisms of the document are as follows:

- It is clear there is a genetic component to MCS and there is little evidence that OCS/NICNAS reviewed scientific and medical literature on recent research into genetic mechanisms.
- It cannot be claimed that MCS is not an organic disease until all avenues of investigation have been explored.
- The socio-economic impact of MCS and other environmental sensitivities have not been investigated.
- The health impact of environmental pollution on humans has not been adequately investigated. While it is clear there is an environmental impact from chemical pollution and wildlife is under threat, humans are a threatened species as well.

We found the review draft to be a biased document that overall has the propensity to impede rather than assist individuals with MCS to access necessary safe health and welfare services and to take part in society. References to the psychological/psychiatric basis of MCS were constant throughout the document and a primary 'psychological/psychiatric' pathogenesis cannot be justified. This view has changed in recent years as studies that previously supported a psychological aetiology have been discredited. The pre-release report has included a further 13 references published after 2006 when the BMP consulting group report was completed. Of these eight were clearly added to lend weight to the psychological/psychiatric basis of MCS. This data can work as a dismissal of MCS rather than an attempt to understand and implement measures that would ease the pain and suffering of those with MCS. The persistence in demonstrating a psychological/psychiatric basis does not appear to be by the Australian Psychological Society, as on p41 of the report states that "*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."* MCS is a serious and disabling illness with no single diagnostic test and it is clear that a range of factors contribute to its pathogenesis.

As was the position with the CFS Guidelines in 2002, research into the aetiology, pathology and treatment of MCS is necessary. We need to learn from the CFS Guidelines controversy and the MCS review should not go down that path especially as there are many overlaps and it looks to be the same condition. If the review finds for a primary psychogenic diagnosis and after some research MCS/CFS/FM are found to be the same condition or the pathophysiology of MCS is found, the government will look ridiculous on the World stage.

It is reprehensible that Medicine cannot acknowledge things it does not understand. Although the pathogenesis of MCS is not fully understood, this does not make it right to decide MCS is a psychological problem (Read. 2002 p. 25, para. 4). Such an approach cannot be justified either medically or ethically. The reference to a belief system is immoral as the language in the document can influence doctors and contribute to the thinking that individuals with MCS have psychological problems. Clearly, it is the medical profession and the government who have the belief system and this absolutely must change if we are going to be able to move forward. We acknowledge a psychological overlay, some individuals can become depressed when they are unable to get medical, social and welfare assistance. Some become isolated, some suicidal and for these individuals psychological counselling or psychiatric interventions as a part of the overall medical care of MCS may be applicable. The feeling of being isolated, desperate and helpless happens with many diseases and should always be seen in perspective - as it is with those other conditions.

If the belief system/psychogenic approach in the document is not changed, individuals with MCS will experience prejudice in their efforts to get safe and appropriate health care; they will not be believed and will continue to be trivialised by clinicians in their efforts to have their needs safely and properly addressed. This needs to be avoided as individuals with MCS usually have other diseases, some of which are chronic, painful and disabling conditions. These are not necessarily related to MCS, and can be diseases requiring health interventions. Such conditions can be missed or left untreated if an individual is thought to have a psychological problem and individuals with MCS will simply go on suffering the most appalling physical distress, compounded by insults and inhumanity**.**

Lack of education about the dangers of chemicals and MCS can also add to the distress of individuals with MCS. Their self-management efforts can be misunderstood by the general public and police, who may then involve local mental health services. Some individuals with MCS have been detained in a mental health facility which is basically dangerous for them (Sears, M E 2007). Once detained they are in an unsafe environment in which they can be exposed to triggering substances that can cause them more harm, and if medicated can suffer dangerous reactions – individuals with MCS can die as a result of chemical exposure. We need the best outcome from this review to ensure that this NEVER happens again.

ASEHA reviewed four other reports for comparison with the Australian document, these were the Institute of Occupational Medicine, Edinburgh (Gravelling); the NZ report (Read) the Danish report (Silberschmidt) and the Canadian Human Rights report (Sears). We consider the Canadian report to be the most relevant because they have dedicated facilities for diagnosis and treatment of individuals with environmental sensitivities including MCS and their work is evidence based.

ASEHA is of the opinion that the model for MCS should be an integrated model that encompasses a medical, social and disability approach. We also think that the model for MCS should not be looking at various body systems but should take a whole of body approach.

Some research needs to be carried out to ascertain how many people in the community have MCS and the socio-economic cost of these. The government needs to look at:

- lost tax revenue,
- lost productivity,
- health and welfare costs.

In its current form the OCS/NICNAS report will:

- contribute nothing to the MCS debate,
- clinicians will not lose their bias,
- the debate will remain polarised and
- individuals with MCS, especially the very severe sufferers, will remain disadvantaged as they will continue to be considered as psychiatric cases;
- they will not taken seriously;

- not be included in health and disability policy,
- not included in service planning and delivery;
- their issues of access to essential services will continue to be ignored;
- some may even be erroneously detained by psychiatric services, further harmed or traumatized,
- their human rights will continue to be ignored and
- their fundamental needs will not be met – all of which is unacceptable.

Individuals with MCS need to be protected by legislation to ensure that they are treated with dignity and respect, can access necessary services in a safe and timely manner and are not erroneously detained by psychiatric services, local police or under notice by national security organisations when they need to wear a mask.

We have to wonder why the federal government has abrogated its duty of care to those in the community with MCS. We need positive feedback and progress from OCS/NICNAS so that we can access safe and appropriate health and allied care and welfare services, and have our human rights observed. Currently, we are subject to human rights abuses that we do not expect in a developed country. Those of us who know we have MCS now are just the thin edge of the wedge, many, many, more will follow. The cost of allowing the debate to remain polarised and not do anything about MCS and its causes will be much more expensive in years to come than currently is the case.

Overall, we found the draft report of the MCS clinical review to be a controversial document with the underlying message that people with MCS have a psychological problem rather than a physical disease that needs treatment. This is an unacceptable approach and absolutely must be changed. As a whole of government approach to MCS, if the relevant changes are not made in the final NICNAS/OCS Scientific Review of MCS, it will be unacceptable to the MCS community and others.

Prepared by Dr Sharyn Martin, PhD and Dorothy M Bowes for ASEHA Qld Inc 28 October 2008

RESPONSES TO MCS REVIEW PAPER
2.1 What is MCS

Comments: P8 Lack of agreement on cause and pathogenesis, and operational definition is hindering investigations and clinical recognition. There is even a lack of agreement on a common term to describe the disorder. We would like to see the term Idiopathic Environmental Intolerances (IEI) replaced with the Canadian term '***environmental sensitivities'*** The term IEI is not acceptable as it implies no known cause. However, there IS a cause; individuals with MCS have been poisoned by environmental chemicals. *'The Canadian government uses the term Environmental Sensitivities to describe a wide variety of reactions to chemicals, electromagnetic radiation and other environmental factors at exposure levels commonly tolerated by many people. Environmental Sensitivities does not describe a single simple condition with a universal cause (Sears, M E 2003 p. 3)'. The term MCS is not superseded by 'Environmental Sensitivities' and should in future be known as MCS/ES instead of MCS/IEI.*

Supporting Information
Canadian Term. Environmental Sensitivities (ES) describes a variety of reactions to chemicals, electromagnetic radiation and other environmental factors at exposure levels commonly tolerated by many people. Environmental sensitivities does not describe a single simple condition with a universal cause. (Sears, M E 2007 p. 3)

2.2 What are the symptoms of MCS
The signs and symptoms pertaining to MCS are complex and related to multiple organs. The predominating symptoms in MCS are generally exposure related CNS effects, with other symptoms and signs representing functional disturbances in other organ systems as a result of pre-existing conditions such as asthma, allergy or part of the chronic ill health that develops with MCS. (Lacour et al 2005). Symptoms and signs related to specific exposures may also be influenced by the substance - eg pesticide, perfume, paint exposure and can be different in different individuals. Symptoms related to a specific acute exposure are generally more severe than those experienced at other times.

Symptoms of chemical exposures have been well documented in various research studies over a period of years. We should accept the research already done rather than reinvent the wheel and spend any possible research funding unwisely. Symptoms of specific chemicals can vary according to the individual. Individuals can process chemicals in different ways depending on genetics, state of health, predisposing factors and others. The level of sensitivity may also depend on the level of exposure.

2.3 Is MCS related to other syndromes or disorders
There are 3 issues here

1. MCS as a part of a constellation of diseases and conditions that can be adversely affected by low levels of chemicals in the environment, known as Environmental Sensitivities. A possible link between these diseases is perturbations of the inflammatory process.
2. MCS may represent the extreme end-point of spectrum of symptoms related to chemical hypersensitivity resulting from damage to xenobiotic metabolizing processes or other metabolic processes
3. The same chemicals and groups of chemicals that cause adverse health reactions in MCS, have been shown to cause reproductive, developmental and other effects in humans and are at the heart of programs to reduce the chemical load in the environment. There are many sources of data such as MSDS (IPCS. 2004), fact sheets, toxicology studies, environmental health criteria monographs, and a proliferation of research articles. All support a physiological/pathological interaction between chemical agents and organ systems.

Supporting Evidence

1. Overlap with other disorders.
There are many existing co-morbidities between MCS and other diseases so the symptoms of many diseases can be expected to overlap. (MCS Referral and Resources) (see appendix). MCS/hypersensitivity to chemicals has been associated with allergy and other disorders such CFS & Fibromyalgia (Meggs et al, 1996; Caress and Steineman, 2005; Lacour et al, 2005). It has been suggested that allergy may be a risk factor in chemically sensitivity patients for the development of respiratory disorders such as RADS and food allergy/sensitivity (RIDS) Meggs et al, 1996; Caress and Steineman, 2005.

People with environmental sensitivities may also have conventional allergies and indeed exhibit more allergies than the general population with considerable overlap between asthma and MCS (Sears, M EM 2007 p. 23). Allergy (IgE or non-IgE mediated) is a marker of MCS – many with nasal allergy are sensitive to fragrances/chemicals. Up to 50% of individuals with nasal allergy can experience symptoms from non-allergic irritants many of which are linked to indoor air quality problems. This is known as non-allergic rhinitis and overlaps with what occupational physicians call occupational rhinitis (Shusterman, D & Murphy M. 2007)

MCS is defined by multiple symptoms affecting multiple organs that wax and wane in response to varying chemical exposures at or below previously tolerated levels. Sjogrens Syndrome (SS) is a common autoimmune disease and systemic features are common between the two diseases, leading to considerable morbidity and occasionally mortality (Migliore, A et al. 2006)

2. MCS as chemical hypersensitivity end point.
In a 1991 conference Levin an immunologist, suggested that MCS may be the prodromal phase of other serious diseases such as autoimmune diseases, (Rest, K A. 1992 p. 3) Levin and Byers claim that in their experience, MCS patients with persistent symptoms who are followed for long periods of time often develop cancer or severe autoimmune disease such as systemic lupus, multiple sclerosis, adult onset diabetes. In their view, these patients had a genetic propensity to such an illness which has been triggered by chemical exposure. The first symptoms of this triggering were MCS (Levin, A S and Byers, V S. 1992 p.100)

Individually different effects of exposure to comparable levels of chemicals might be explained by dissimilar response sensitivity to chemicals, with MCS being the clinical endpoint of this altered sensitivity. Over a 4 hour exposure period MCS subjects showed increasing symptom score (sensory irritations – nasal and ocular) while control subjects did not. The results lead the authors to conclude that the time course of sensory irritation was affected by self-reported chemical sensitivity while the symptoms of bad smell were not affected by the influence of MCS (Van Thriel et al 2002).

A study by Zibrowski et al, 2006, of olfactory sensitivity in medical laboratory workers exposed to organic solvent mixtures found that these workers reported symptoms similar to those found in chemical intolerance and may represent the early stages of the altered sensitivity suggested by van Thriel et al, 2002. (Zibrowski and Robertson, 2006).

3. Chemical effects on the population.
The ASEHA website www.asehaqld.org.au on the Children's Health page lists a number of initiatives to reduce the chemical load in the environment.

- *Rhinitis, eczema and asthma in children* was linked to concentrations of *phthalate* found in household dust (Bornehagg, C G et al. 2004).
- *Perfluorinated compounds* previously in stain repellents may be *affecting the human immune system*, according to new research published in *Toxicological Sciences* (**2008**, DOI 10.1093/toxsci/kfn059). After studying mice orally exposed to perfluorooctane sulfonate (PFOS) daily for 28 days, a group of researchers observed that the animals' immune systems were affected at much lower levels than ever reported. PFOS was a key ingredient in the original formulation of 3M's Scotchgard, a stain-repelling spray.
- Occupational exposure to *formaldehyde* often indicates *discomfort in the upper airways*. The objective of the study was to determine whether chronic formaldehyde exposure causes symptoms of direct irritation and whether it affects all exposed people, atopic and non-atopic, by formaldehyde-induced hyperreactivity or by an immunologically mediated reaction (type I). 50% of the study group experienced hyperreactivity. Two workers sensitised by a long term occupational exposure to formaldehyde returned a positive RAST test. (Wilhelmsson, B and Holstrom, M. 1992).
- *Air pollution* is a bigger killer than road accidents according to Dr Tom Beer, CSIRO Atmospheric research scientist. Each year, on average, *2,400 of the 140,000 Australian deaths are linked to air quality and health issues* - much more than the 1,700 people who die on our roads. That's an average of a death every four hours. This number increases if long-term effects of air toxics on cancer are included. (Anon. Air pollution bigger killer than road accidents. Sydney Morning Herald, March 2, 2004)
- *Babies' DNA* can be damaged even before they are born if their mothers breathe air polluted with *polycyclic aromatic hydrocarbons*. A team of researchers at the Columbia University Center for Children's Environmental Health in New York studied umbilical cord blood of newborns for chromosomal damage. The study showed that environmental exposures to

specific combustion pollutants during pregnancy can result in chromosomal abnormalities in fetal tissues that can cause susceptibility to cancers. The study was published in the February 2005 issue of the Journal Cancer Epidemiology Biomarkers and Prevention. (Reuters, USA. February 16, 2005).

- *Chemicals* known to the State (California) to cause *cancer or reproductive toxicity*. 2003. (California, EPA. Office of Environmental Health Hazard Assessment.) http://www.oehha.ca.gov/prop65/prop65_list/files/31403LSTa.htm
- *VOCs* are a diverse group of relatively low-molecular weight compounds that are all liquid at room temperature and are highly lipophilic. Researchers sought to determine whether reported symptoms of mothers and infants were associated significantly with the use of household products that raised indoor air levels of TVOCs. Higher TVOCs were associated with air freshener and aerosol use. *Infant diarrhea and earache* were statistically significantly associated with air freshener use and diarrhea and vomiting with aerosol use. *Headache* experienced by mothers 8 months after birth was significantly associated with the use of air fresheners and aerosols; maternal depression was significantly associated with the use of air fresheners. The results of the study suggest a link between the use of products that raise indoor air levels of TVOCs and an increased risk of certain symptoms among infants and their mothers. (Farrow, A et al. 2003.)

2.4 What Triggers Symptoms of MCS

Comments on review:
The last paragraph on p. 11 in this section "Reported triggering agents for MCS are diverse and often chemically unrelated. Research reports suggest that there is likely to be a psychogenic component in the aetiology of MCS" but it cannot be concluded from the information presented in this section. This effect was not discussed and this statement has not been referenced. The information presented prior to this statement referenced reports on what various triggers are associated with MCS with reference to the importance of distinguishing between 'inducing chemicals' and those chemicals that later trigger symptoms.

This paragraph ignores literature on the adverse health effects of chemicals such as VOCs pesticides, phenolic compounds, terpenes as separate groupings of substances. A list of triggers was provided in ASEHAs response to the Questionnaire. These are well documented and that research should be accepted.

Supporting information:
***Some points of interest in the Australian Worksafe Standard are as follows*:**

Odour and chemical interactions validated
Chapter 9 Odour thresholds p.14

- 9.1 odours can serve as a useful warning signal as to the presence of a substance in the environment;
- 9.2 there may be interference from other substances;

Avoidance validated
Chapter 11 Effects on the skin p. 16

- 11.1 some substances can readily penetrate the skin and this method of exposure can pose a far greater danger than inhalation exposure;
- 11.3 some substances such as solvents can accelerate or alter the rate of skin absorption;
- 11.6 it is 'good practice' to avoid any unnecessary contact with all chemical substances (Worksafe Standard. 2005)

In a two year period more than 500 employees from a Nova Scotia hospital were examined due to indoor air quality and in the course of seven months many had developed chemical hypersensitivity including MCS. The majority identified odours as the most common triggering factor. This led to hospital management and the labour union issuing a ban on fragrances and fragrance containing products in the hospital. Many other sectors in the area have since taken similar initiatives (Silberschmidt, M. 2005 p. 77).

Triggers can be an individual problem and is an area where testing of substances would be advantageous. Once people are initially sensitised to low levels of environmental factors, they may experience reactions triggered by a broader range of exposures if the condition is not recognised and addressed. (Sears, M E. 2007). Recently reported doctor diagnosed environmental sensitivities

indicate approx. 1 million Canadians experience sensitivities. (Sears, M E. 2007 p. 6) . A review by Canada's federal regulators has determined that chemicals once thought to be benign are potentially dangerous for the physical health of Canadians (Mittelstaedt, M. 2006)

The most common triggers in chemical sensitivity can be classified and 'related' by their intended purpose/use. The most common triggers found by Caress et al, 2002 were cleaning products (88.4%0, tobacco smoke (82.6%), perfume (81.2%), pesticides (81.2%) and car exhaust (72.5%). Sensitivities may be initiated by a range of environmental factors and once the condition is initiated, reactions may be triggered by a broadening array of incitents. Environmental sensitivities may affect every system in the body, so multiple symptoms are possible, with variation among individuals. (Sears, M E 2007 p. 20)

Mixtures of chemicals may contain substances to which an individual is sensitised but the connection is not made. Exposure to multiple chemicals is ubiquitous in today's environment. Each neurotoxic contaminant may cause negligible effect but in combination with other toxic chemicals may trigger decreases in brain function (Grandjean P et al, 2007).

Increased susceptibility to developing chemical sensitivity may begin in utero and continue through persisting exposure to these same chemicals. A study of pregnant women found that exposure **to** common household chemicals during pregnancy was associated with persistent wheezing and lung function abnormalities in their non-atopic children. It was thought that this may result from prenatal developmental effects or postnatal irritant effects on the developing airway (Henderson et al, 2007).

Sensitisers/Irritants

The Australian Worksafe Standard validates **sensitisation and low level exposures**

Chapter 12 Sensitisers p. 17

- 12.1 Some substances (TDI, Formaldehyde) can cause a specific immune response in some people. This is known as 'sensitisation';
- 12.2 Following sensitisation 'an affected individual may subsequently react to exposure to minute levels of that substance'. Although low values have been assigned the exposure standard may not be adequate to protect a hypersensitive individual and persons who are sensitised to a particular substance should not further be exposed to that substance.

Chapter 15 Mixtures of substances p. 28

- 15.12 At present the understanding of interaction effects is incomplete. The knowledge that such effects occur is reason to maintain the concentrations of individual substances as low as is practicable under complex exposure conditions (Worksafe Standard. 2005).

Some substances are known sensitisers or irritants. Many man made chemicals on the market do not have adequate toxicology data to support any use, their toxicity is unknown and safety unproven. Product labelling needs to be improved. Chemicals in the product need to be listed to allow people to chose whether or not they wish to be subjected to such chemicals, while credible information about those chemicals and their health impacts needs to be freely available to the general public on request. A University of Washington study of top-selling laundry products and air fresheners found the products emitted dozens of different chemicals, including chemicals regulated as toxic or hazardous under federal laws (US) but none of those chemicals were on the product labels (University of Washington. 2008)

Toluene diisocyanite is one of many known sensitisers' that can cause a specific immune response in some people. This may manifest as a skin rash, an asthmatic condition or inflammation and in some individuals may be extremely severe. Following sensitization an affected individual may subsequently react to minute levels of that substance and although low exposure values have been assigned to strong sensitising substances they may not be sufficient to protect a hypersensitive individual. (Worksafe Standard. 1995. Ch. 12, Sensitisers).

As with other VOCs, terpenes and terpenoids are a class of chemicals that encompass some 5000 substances. Terpene and terpenoid sensitivity is quite common among chemically sensitive individuals and as terpenes can cause ongoing aggravation of chemical sensitivities they are a deterrent to recovery. Over 5000 terpenes are known and many have been synthesized in the laboratory. Terpenes are the odours and colours of many plants and building materials e.g. pine, cedar (Rea, W J. 1992. V.2; p. 979). Terpenes are classified into 6 categories, mono, sesqu, di, tetra, tri and poly terpenes. Some examples of terpenes are: mono -citronella, fragrances; sesqu - oil of

cubeb; di - the phytol-building block of chlorophyll and vitamin A; tetra - carotenoids, tomato pigment; tri - liver and vegetable oil, cholesterol; poly – latex from the rubber tree. Essential oils are terpenes, they are the aromatic odours extracted from many plants. Terpenes are common in the natural environment, from trees and plants, including grasses. Terpenes are used as solvents in industry (Rea, W J. 1992 v.2, p 979-989). Dermatologists use a terpene mixture to patch test for fragrance allergy as they cause allergic disease (www.dermnetnz.org)

Individuals with phenolic sensitivities react to both naturally occurring and synthesized phenolic compounds in food, as well as in the environment. Swain, Soutter and Loblay in their Book 'Friendly Food' pp.23-25 state that individuals with phenolic sensitivities in food find that their sense of odour becomes more acute when phenolic substances in their foods are restricted. They comment on a range of substances that can cause reactions e.g. perfume, motor exhausts, petrol fumes, paint, smoke and other irritants, toiletries, cosmetics and cleaning products, flavours and aromas such as peppermint and menthol, VOCs in the domestic indoor environment from carpets, underlay, chipboard, furnishings, air fresheners and other fragranced products, cooking odours, smoke etc and medications (Swain et al, 2004).

Chlorinated hydrocarbon levels were measured in 22 patients with CFS as defined by the Centers for Disease Control (CDC), in 17 patients with CFS symptoms who had an exposure to toxic chemicals that excluded them from the research definition of CFS; and in 34 controls matched for age and sex. The objective of the study was to determine whether serum levels of chlorinated hydrocarbons are elevated in patients with CFS. Organochlorine pesticides (OCPs) were detected in all serum samples and the results of the study suggest that serum levels of OCPs may have an aetiological role in CFS. There were no significant differences in OCPs between CFS patients and those with CFS and a history of toxic exposure and therefore the exclusion of the exposed group from the CDC research definition of CFS was invalid. The role of low-level OCP bioaccumulation in the development of CFS symptoms requires further investigation (Dunstan, R H et al. 1995)

Influence of the current state of knowledge of sensitisers
There is another issue here and that is the lack of knowledge about the toxicity and sensitising potential of many chemicals in common usage in industry and domestic markets.

***Some points of interest in the Australian Worksafe Standard are as follows*:**
Introduction p. 5

- 1.2 exposure standards are based only on current knowledge;
- 1.4 exposure standards do not guarantee protection for every worker because of individual susceptibility and biological variation, and it is inevitable that some workers will suffer adverse health impacts;
- 1.6 atmospheric exposure standards only consider absorption by inhalation and are only valid on the assumption that skin absorption cannot occur.

Most substances used are untested/lack data
Chapter 2. Unlisted substances p. 6

- 2.1 most substances used in industry have not been assigned exposure standards. This does not imply that the substances are safe or non-hazardous;
- 2.2 there is a lack of data on health effects of some substances to assign a standard.

Lack of biological tests
Chapter 8. Biological monitoring p. 13

- 8.3 there is limited knowledge of suitable and definitive biological tests for most substances (Worksafe Standard. 2005)

Part 2 Interpretation p. 70
'Exposure Standard' means an airborne concentration of a particular substance in the workers breathing zone, especially to which according to current knowledge, should no cause adverse health effects nor cause undue discomfort to ***nearly all workers*** . (Worksafe Standard. 1995).

According to a 2007 survey by the World Allergy Organization's Specialty and Training Council about 22% of the population in 33 countries is estimated to suffer from some form of allergic disease. Occupational and environmental chemicals account for some proportion of allergic diseases and prompted the Japanese researchers to compare International criteria for designating sensitizers. Substances designated as sensitizers were found to differ according to the organization and country.

The authors found that while classification of chemical substances that cause cancer are relatively consistent amongst the various organizations, the supporting evidence for sensitizing chemical substances is not consistent. Neither is the information regarding irritants that induce bronchial asthma or dermatitis (Murakami et al 2007).

Reasons for inconsistency are many and include individual susceptibility, not all people will develop allergic reactions in response to sensitizers and those few that do may not be well documented. There are also differences in the grouping of substances amongst various organizations. This resulted in only 9 substances being designated as sensitizers by all organizations. The globally harmonized system (GHS) UN 2005 of classification and labelling of chemicals is hoped to provide/promote a consistent designation of sensitizers amongst national, international organizations as well as the development of testing guidelines and classification criteria for mixtures (Murakami et al 2007).

The challenge for occupational health is in setting OELs for numerous chemicals being introduced for which the extent of their ability to cause adverse health effects is unknown. Gaffney et al, 2007 discusses the challenge and importance of identifying sensitizers in the setting of appropriate occupational exposure limits (OEL) in order to minimize diseases due to exposure to airborne chemicals. The article states that of the 600 substances for which an OEL has been established, approximately 66% are sensory irritants. In setting OELs, Gaffney observed that often there is inadequate knowledge about the toxicology of these chemicals to set an OEL and irritation potencies are not recognized until they are manufactured or used in large quantities. The authors acknowledge that there are some workers who due to prior exposure to chemicals have a heightened sensitivity to the presence of chemicals and that the large degree of inter-individual variation makes attempting to characterize the risk difficult. They discuss the importance of taking into account those individuals who are hypersensitive to chemicals and highlight a 1997 study that found improvements made in buildings air quality (such as replacing carpets and ventilation systems) could save between $12 and $125 billions dollars in worker productivity alone. Such interventions to improve air quality and make employees more comfortable will help to increase a workplaces morale and productivity (Gaffney et al, 2007).

2.5 Can MCS be clinically defined
A clinical diagnosis is acceptable for some diseases – why not MCS!!!

Comments: The definition of MCS is sufficiently documented by Cullen and is still in use with some modifications by most environmental specialists. We should not be wasting time with this unless a better definition has been documented. We need to move forward with what we have got until evidence based research provides something better. Hopefully this will come from Canada who have medical facilities dedicated to environmental sensitivities and can gather the evidence based data required to resolve many of the current problems and biases.

Supporting Information:
MCS is accepted as a physical disease in Denmark, Canada, New Zealand, and by the Institute of occupational Medicine, Edinburgh (Silberschmidt, M. 2005; Sears, M E. 2007; Read, D. 2002; Gravelling, R A et al. 1999). Why is Australia different?

'Most international experts within the field agree that on the basis of epidemiological data, MCS is a reality' (Silberschmidt, M. 2005 p.90).

Levin and Byers in the AOEC workshop on MCS in 1991 claim that MCS is easy to diagnose and treat. They list diagnostic tests in their presentation as do Ashford and Miller in their book (Levin A S & Byers V S. 1992; Ashford N A and Miller, C J. 1998 Appendix B p. 359)

Rea and Miller ensure that when testing is done, offending agents are removed and symptoms cleared prior to challenges. Rea and Miller test in environmental control units to ensure the tests are not compromised. (Rea, W J. 1998; Ashford, N and Miller, C. 1998)

Lacour et al suggest that diagnostic procedure follows the guidelines for CFS which are extended by diagnostic clarification of functional disturbances in other organ systems (Lacour, M. 2005 p.1)

Testing for MCS p. 12
In our response to the OCS Questionnaire, we included the diagnostic tests used by Rea and Miller in their environmental health centers. Some of these were also psychological tests. Canada has a

government funded environmental health centre and expertise from them should be sought to allow OCS/NICNAS to move forward with of MCS.

Clinical evidence of underlying pathological process for MCS p. 14
Double blind placebo controlled challenge testing. In some studies substances used as placebos are not inert and may trigger reactions. Care needs to be taken that in studies where placebos are used that these are truly inert substances that cannot trigger reactions. Individuals may need to be allergy tested with respect to planned placebos.

A criticism made by references in the MCS review of double blind studies, is that some do not use an 'olfactory masking agent', but the masking agent itself may cause a reaction and therefore bias a studies conclusion toward psychological when subjects are unable to distinguish. So many different and conflicting reports means that NO conclusion should be drawn until some consistency and appropriate testing protocols are established. The study by Staudenmayer et al, 1993 should be discounted for this reason.

Another problem with this type of invasive challenge testing is that the individual is likely to have adverse reactions to the chemicals during the challenge. This is not for the benefit of the individual.

Other types of testing
Dermatologists have used patch testing for decades. They use a mix of terpenes to test for fragrance allergy. (www.dermnet.org.nz). For some chemicals the term chemical allergy is appropriate (Amdur, M O et al. 1991 Chapter 2; Bernstein, D I. 1996). Allergists use skin tests i.e. scratch or prick tests to test for allergy. Some Environmental Medicine practitioners use intradermal testing to test for chemical reactivity. Methods used by practitioners of environmental medicine need to be investigated without bias.

Genova Diagnostics www.GDX.net have a range of diagnostic tests to assist in the diagnosis and management of MCS. The tests include Detoxification Profile, Oxidative stress markers and Genetic Predisposition analysis.

It is only though further targeted research into the causes of chemical sensitivity that a range of tests for MCS will be available. Given the ubiquitous nature of chemicals in our environment we doubt that it is possible now when studies are planned to find controls.

While MCS is considered a controversial diagnosis by the medical profession, it is recognized as a disability.
Acceptance of MCS as a disability by Human Rights organizations is an acceptance that regardless of whether or not MCS is clinically or scientifically defined it results in human ill health and suffering. Science and medicine will eventually elucidate the mechanism of MCS as it has done for other diseases that were originally viewed as psychosomatic such as asthma, allergy, stomach ulcers and RSI, but in the meantime individuals with MCS are in dire need of assistance with their health, finding appropriate housing and the ability to earn an income.

The Australian Human Rights Commission accepts MCS as a disability (Personal correspondence) and recently amended their building access guidelines to allow access to those who are sensitive to chemicals. The Canadian Human Rights Commission on June 15, 2007 approved their Policy on Environmental Sensitivities. They state that environmental sensitivities is a medical condition and a disability entitled to the protection of the Canadian Human Rights Act which prohibits discrimination on the basis of disability.

WHO and MCS Although WHO do not officially acknowledge MCS they have several programs where the emphasis is on special precautions when handling chemicals. WHO Programs include: Children's Environmental Health; International Program on Chemical Safety; Strategic Approach to International Chemicals Management; Inter-organisation program on the Sound Management of Chemicals; Intergovernmental Forum on Chemical Safety.

2. Does MCS have a disease classification
There is a substantial overlap between MCS/CFS/FM and in general, demographic and clinical factors and health locus of control do not clearly distinguish patients with CFS, FM and MCS. Symptoms typical of each disorder are prevalent in the other two conditions (Buchwald, D and Garrity, D. 1994)

P15 **The lack of recognition of MCS as a clinical entity and subsequent classification within the health systems significantly limits the collection and analysis of morbidity.**
MCS was first documented by occupational health physicians in 1979 (Cullen, M R. 1987) at the Yale Occupational Medical Clinic and we have procrastinated about it for twenty-nine years. Do we have to wait another twenty-nine years for the problem to be diagnosed and treated because the medical profession, regulatory authorities and the government have a belief system that prevents MCS and other new diseases from being recognised and services provided to those suffering needlessly in the community (Kilburne, K 2003; Hileman, B. 1991). The classification of diseases is important for recognition of the condition and to initiate research into the mechanism/s.

The OCS/NICNAS Scientific Review of MCS acknowledges on p15 that the collection and analysis of morbidity data for MCS is limited because of a lack of recognition and overlap with other diseases. This is a circular argument that will not be resolved until someone takes the initiative to begin the process. The Australian Hazard Assessment Database (AHEAD) was mentioned by the review but has yet to publish any data as suggested on p16.

The ICD is used as a basis for the provision of health care within Canada. ICD-9 includes some relevant categories such as ill-defined conditions, injury and poisoning by drugs and biological substances, and late toxic effects of non-medical substances. While the latest version of ICD-10 does not list environmental sensitivities, the related conditions of chronic fatigue and fibromyalgia have been included. Other possible related conditions e.g. arthritis due to hypersensitivity are also listed. In the update of ICD-10, wood preservatives have been recognised as causing disease (Sears, M E 2007 p. 8)

Applying the Hill Criterion to MCS
Martin Pall (2008) and Ashford & Miller (1988, p. 273) in their book 'Chemical Exposures: Low levels and high stakes" evaluated MCS against the nine criteria offered by Sir Austin Bradford Hill that have been widely used by epidemiologists to assist them to make a causal relationship.

1. Strength of Association i.e. between the exposure and the illness. Ashford & Miller cite Percival Pott in the UK in 1775 who observed around a 200-fold increase in scrotal cancers among chimney sweeps as opposed to those not exposed to tar or mineral oils. Pall cites evidence suggesting that chemicals can have a role in chemical sensitivity i.e. the great increase in synthetic organic chemical and pesticide production - approximately 15 fold between 1945 and 1980; increasing medical and scientific interest as a possible surrogate measure of increased MCS incidence. Increase in sick building syndrome with US EPA reporting that 50% of complaints were related to sick building syndrome. There exists a parallel between increased chemical production and decreased air flow and apparent increased MCS initiation. There is genetic evidence that genes determine the rate of metabolism of chemicals and can influence the prevalence and incidence of MCS.

2. Consistency. Have a number of people in different places at different times observed the association? Hill considered this to be important for rare hazards or conditions. A number of observers have independently described chemical sensitivity arising in individuals exposed to organophosphate pesticides. Pall quotes observations made in a number of countries around the world including the USA, UK, at least nine European countries, Australia, Canada and Japan. Miller notes that numerous investigators from different geographic regions have published strikingly similar descriptions of individuals who report disabling illnesses after exposure to recognised environmental contaminants.

3. Specificity of Association. The more an association is made between specific exposures and specific types of disease, the clearer the case for causation. Miller states that while research on MCS inducing exposures might reveal strong specific associations, with respect to triggering, initially there might appear to be a lack of specificity in terms of exposures and symptoms. However, individuals with MCS report specific symptoms in relation to specific exposures. Unlike cancer or heart disease, cause and effect for symptom triggering MCS can be tested in humans providing direct measurement of the specificity of the association. Pall argues that chemicals might act via increased NMDA activity and/or increased nitric oxide and peroxynitrite and that there is a substantial argument for specificity through the common response mechanism of NMDA stimulation – even though diverse chemicals are implicated in MCS initiation and in eliciting symptoms in sensitive individuals.

4. Temporality. Does the exposure precede the illness? Some critics claim that tendencies for depression or somatoform disease in many MCS patients precedes their 'initiating' exposure event. Miller claims that large numbers of MCS patients show no evidence of prior psychopathology. The

strongest evidence for temporality is the temporal cohesiveness between exposure and onset of symptoms that has been observed in large exposed groups e.g. US EPA's sick building occupants and sick Gulf War Veterans, many of whom report new-onset intolerances and have no evidence of psychiatric problems predating their exposure. Pall, in chapter 13 of his book (2007a), quotes some 30 citations that report chemical exposure precedes illness initiation with an addition 12 citations in his 2008 paper. Pall further states that these 42 citations are by no means a comprehensive list and that there are likely to be many more.

5. Biological gradient. An association that follows a dose-response curve strongly suggests causality. Hill acknowledges it can be difficult to obtain a satisfactory measure of exposure. However, Miller suggests that a dose-response relationship similar to allergic conditions may also apply to chemical sensitivity. To begin with there is the first, sensitising exposure in a susceptible individual, with subsequent exposures and the sensitised person responding in proportion to the dose, but at a much lower dose than most people. MCS is also suggestive of a dose response relationship and the longer an MCS sufferer remains in an exposure situation, the more severe the symptoms become and the longer they persist. In contrast to cancer or some other environmentally related disease, the triggering phase of chemical sensitivity can be tested for a dose-response relationship thus obviating the need speculating about a biological gradient.

6. Plausibility. Hill comments it is helpful if the causation we suspect is biologically plausible, but that what is plausible depends upon the biological knowledge of the time. Miller interprets this as *'the association we observe may be new to science or medicine and we must not dismiss it too lightheartedly as just too odd.*' She claims there are medical conditions that have features strikingly similar to MCS and are well-accepted e.g. reactive airways dysfunction syndrome and multiple drug allergy syndrome. These parallel clinical observations may be signs of biological plausibility for MCS.

7. Coherence. The cause-and-effect relationship under scrutiny should not conflict with other generally known facts about the disease e.g. the pathology or biochemistry of the illness. Miller states *'As little research on MCS has been done, so far this has not been a problem.'*

8. Experiment. Experimental evidence can provide the strongest support for a cause-and-effect relationship.
Miller claims that perhaps the reason MCS sufferers are so insistent that chemicals are causing their symptoms is the strength of evidence when they deliberately avoid and then are re-exposed to triggering substances. MCS is a testable hypothesis via direct challenge and elimination studies, in contrast with other environmentally induced illnesses such as cancer. Miller goes on to state that experimental conditions must be optimized so that there is unmasking in an environmental control unit if the most robust effect is to be seen. Lack of funding currently is a deterrent to this.

9. Analogy. Under certain circumstances, cause-and-effect can be inferred by analogy. The sensitivities reported by MCS patients are similar to those reported by those who have recently quit smoking and experience a heightened sensitivity to tobacco smoke. There are also close associations between 'addiction' and MCS in which caffeine, food cravings and binge eating are reported and MCS sufferers report going through 'withdrawals' or 'detox'. During this time the symptoms they report are reminiscent of those reported by drug abusers going through withdrawal, yet MCS sufferers usually avoid even mildly addictive substances. Other analogies to MCS are reactive airways dysfunction syndrome (RADS) and toluene diisocyanate (TDI) sensitivity. Especially RADS, where a single major exposure may lead to airway hyperresponsiveness to multiple, chemically unrelated inhalants. We then need to ask the question 'if the airways can develop heightened sensitivity to multiple chemicals in this way, by analogy, why can not the central nervous system do this as well?'.

To Hill's criteria Miller added a tenth that would apply to symptoms (or illnesses) that are primarily subjective in nature.

10. Unique symptomatology. 'The more obscure or unique a symptom is, particularly if it is reported by several independent exposure groups (e.g. industrial workers, white collar professionals, Gulf War veterans), the greater the likelihood of causation. For MCS it would be difficult to imagine that the curious symptom of odor intolerance, which has been reported by demographically diverse groups following various exposure events, could be 'invented' by them all. Equally unexpected and counterintuitive are MCS patient's practices of avoiding fragrances, foods, alcoholic beverages and other substances that they formerly relished. Why would people give up things like pizza, chocolate and beer unless they made the subjects ill? Why would a mechanic who loved his job and used to think that WD-40 would make him a wonderful perfume, suddenly report that odours at work made him

ill if, in fact, they did not? Why would doctors, lawyers, teachers and others say they quit their professions because of severe mental confusion around fragrance and engine exhaust if this were not the case? Scientifically, it would be absurd to dismiss such eccentric behaviours in otherwise sane individuals without searching exhaustively for a plausible biological basis.

Reasons For Slow Acceptance

According to Dr Kaye Kilburn there are numerous factors that slow the acceptance of chemicals as a major cause of disease the same as those that created opposition to fecal contamination of water causing cholera.

The 13 explanations (described below) for delayed acceptance of the reality of chemical brain injury illustrate a cultural lag in medical thinking and society as a whole. Acceptance of a new idea can take 2 – 3 generations. Remember recognition of cigarette smoking and cancer in the 1950s,asbestos in the 1960s, nuclear (ionizing) radiation in the 1960s. Half a generation has passed so maybe we will see chemical sensitivity recognised by 2010 – unless many decision makers brains have also been damaged… (Kilburn, K E. 2003)

The work already done by Miller and other occupational physicians, clinical ecologists and those researchers who have published over the last 20 plus years should be recognised and accepted.

There is no reason why a system for gathering data on MCS via individuals in the health care system cannot be established – with their consent.

Factors seen by Kilburn , 2003, for slow acceptance of chemical damage are:

- Concealed damage – subtle tests may be needed for the ID of chemical brain injury
- Psychic resistance to vulnerability – reluctance of individuals to consider that the brain could be vulnerable is an emotional defense – the brain barrier does not filter out anaesthetics
- It is all in your head – physicians dismiss unfamiliar problems with this phrase implying that the problems are psychosomatic. Few consider that the symptoms could be caused by chemicals instead prescribing more chemicals (drugs) and further poisoning patients
- Acceptance of mind altering drugs. While we are aware of the impacts on the brain of alcohol and illicit chemicals such as cocaine, many physicians prescribe mind altering drugs e.g. prozac to improve mood. Such connections should not be ignored.
- Not an imminent threat. Chemical brain damage is not considered an imminent or personal threat such as anthrax, terrorist piloted airliners, Bhopal or Sarin in a subway, However, chemical warfare is effective on many people. They were not susceptible – just in the wrong place when the exposure event occurred.
- Competition from other threats – or an explanation for indifference. Recognition that helicobacter pylori caused peptic ulcer was a minor newsmaker; enormous concern followed /AIDS and associated problems, AIDS is a serious brain infection and intoxication; the menace of emerging infections – antibiotic resistance is the result of short sighted practices. Clearly anthrax, smallpox and similar agents resemble sarin and the Bhopal spill in being extremely difficult to guard against.
- Delay in acknowledging health risks. Cigarette smoke was associated with lung cancer in the 1950s; non-smokers rights were recognised and indoor smoking curtailed. Cigarette companies lobbied for smokers under the pretence of guarding the rights of smokers – but protecting profits; the banning of asbestos required 75 years – longer than for cigarette smoke – and the companies protected profits until they filed for bankruptcy. The health of workers appears to take a back seat to profits.
- Economic interests – these may discourage prevention – even of cancer e.g. chimney sweeps avoided scrotal cancer by not entering chimneys; radon lung cancers in miners in the late 19th Century; Rehm's aniline dye workers. Enormous expensive institutions do research on cancer and dedicated public organisations pursue the biologically implausible myth of cancer cures. A large reduction in lung cancer mortality occurred when people quit smoking – the power of avoidance as a treatment strategy; it is safe to assume that other cancers can be prevented by the cessation of exposure to cancer-causing chemicals e.g. PAHs, PCBs.
- The promise of the human genome mapping –the genome mapping is seen as the key to human disease. There are hollow claims that we must know the site at which the chemicals affect the genome to stop inhalation or withdraw them from use – thus ignoring the lessons since cholera.
- Splintering of medical and surgical practice – this process is creating experienced technicians who cannot see and understand the interplay of factors in their patients. Therapeutic

oncologists wield powerful chemicals to cure the first cancer and cause the second. Few academic departments train doctors or surgeons who consider problems in whole patients.

- Neurology has been slow to consider causes – perhaps the slowness is caused because neurology focuses on the structure of the brain and not its function. Apart from the EEG to confirm seizures, the CAT scanner and MRI to confirm localized lesions, neurology is ancient and largely obsolete.
- The idea that chemicals damage brains and may cause chronic brain diseases has been met with resistance in Neurology. Examples of specific organic solvents that cause damage are n-hexane and acrylamide which destroy nerves; hydroxyquinoline produces optic atrophy and permanent vision loss; ethambutol (used to treat TB) causes optic neuritis and colour blindness; manganese causes Parkinson's Disease and this has now been associated with herbicides and MPTP (street drug).
- Failure to recognise potential harm from low chemical concentrations in spite of awareness that the brain has enormous amplified capacity (sensitivity to low levels of chemicals). Occupational toxicology has a rich history e.g. the disturbance of brain function by mercury, palsy and psychosis by lead (Kilburne, K E. 2003)

2.7 Do individuals with MCS share common chemical exposures

There is no clear distinction but there are generalizations. For example, a group of MCS people would all find difficulty if they were in a room with, - others wearing highly scented perfumes, aftershaves and deodorants, - where the carpet was new, - the room had been recently cleaned with harsh cleaning products or treated with pesticides and - the walls had just been painted. But as to whether any individual MCS person could stand next to someone wearing an essential oil or eat one of the biscuits at morning tea would depend on whether they had a terpene sensitivity or specific food allergy/intolerance respectively.

VOCs are a common group of chemicals to which most people with MCS would adversely react. Which of these might cause the most severe or least severe reactions would depend on the nature of the individuals sensitizing chemical compound and their genetic predisposition.

Perfumes are another 'group' of diverse chemical substances that can produce symptoms from irritation to migraine to asthma in both MCS individuals and the rest of the population.

3. Causes of MCS
There being a single causative mechanism for MCS is unlikely due to the large range of chemicals with different modes of action; individual predisposing factors such as genetic susceptibilities, state of health; other environmental factors. That OCS/NICNAS doubt the physical basis of MCS is reprehensible.

The introduction discusses the Mode of action and Mechanism of action. A hypothesized mode of action should be supported by experimental evidence involving the molecular basis for an effect. In MCS the generalized mode of action is firstly sensitization by a specific chemical/s and secondly following this sensitization a spreading effect is observed.

In terms of a mechanistic action, the 2007 review on Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment, acknowledges that mechanistic insight is required for understanding the pathobiology underlying adverse responses to chemical exposures but 'the scarcity of comprehensive assessments of multiple exposures (to chemicals) in real time or with adequate resolution has slowly progressed. The developing area of Toxicogenomic may help resolve the underlying molecular mechanisms involving the several hypothesised physical modes of action. So far abundant evidence suggests that 1) chemical or physical injury is mediated by, or reflected in changes in mRNAs, proteins and metabolites and 2) individual variations in their gene Single Nucleotide Polymorphisms (SNPs) and mutations can alter the susceptibility to these effects. This type of research is only in it's infancy and the cause of MCS will eventually be resolved through this research. MCS cannot in the meantime be assigned to the psychiatric/psychological realm because of lack of knowledge. Investigations into the Mechanism of these actions are ongoing.

3.1.1 Immunological dysregulation.
There is still a lot of research potential in this area. For example, the distinction between IgE and non IgE mediated 'allergic' reactions. The studies by Kimata, 2004 and Hasegawa et al, 2005 on eczema/dermatitis and rhinitis respectively both found responses that differed from the usual 'allergic' response. In the case of Kimata 2004, enhanced wheal response to VOC exposure did not correspond to elevated histamine levels. In the Hasegawa 2005 study MCS patients with 'allergic rhinitis' IgE levels were relatively low and decreased reactivity and sensitivity of histamine release from peripheral blood following challenge with chemical compounds were observed.

The concept of nitric oxide (NO), synthesized by many cell type, is involved in immunity and inflammation was highlighted in 2001 by J Coleman.

3.1.2 Respiratory disorder/ neurogenic inflammation
Focus on DBPC studies that are inconsistent in methodology are unlikely to produce any consistent results.

3.1.3 Limbic kindling/neural sensitisation
The conclusions drawn in the review paper reflect a bias toward fitting the information to exclusively fit a psychiatric model.

Comments on Odour sensitivity and MCS p.20

The Australian Worksafe Standard validates odour and chemical interactions
Chapter 9 Odour thresholds p.14 states

- 9.1 odours can serve as a useful warning signal as to the presence of a substance in the environment;
- 9.2 there may be interference from other substances (Worksafe Standard. 2005)

Smells/odours/vapours/fumes are often **toxic** e.g. fragrances, which are a mixture of 100 or more chemicals, largely solvents and of unknown toxicity. The odours/fumes can be very dangerous, they can irritate the lungs as does cigarette smoke and affect the CNS e.g. migraine. Odour thresholds for many VOCs are probably considerably lower than previously known. In subgroups of individuals with airway symptoms induced by chemicals and odors there seems to be a sustainable physiological mechanism behind the reactions. Airway reaction to chemical stimuli and odors is an essential protective physiological mechanism to prevent inhaling harmful substances, but it may also be a symptom of diseases of the nose and lungs. In the general population, self-reported odor intolerance, often called chemical sensitivity, is a frequent symptom with a reported prevalence of 16-33% (Millqvist, E. 2008)

MCS is called odour hypersensitivity in Denmark and is considered a condition with many health complaints from different organs which occurs in some people when exposed to low concentrations of chemicals (Silberschmidt, M. 2005 p. 90)

Recent studies indicate that there are changes in levels of nerve growth factor in nasal secretions following inhalation (Millqvist, E et al. 2005)

Cacosmia. Ryan et al (1988) studied the relationship between occupational exposure to mixtures of organic solvents, neurobehavioral functioning and complaints of cacosmia. Cacosmia was defined as nausea, headaches, and subjective distress in individuals exposed to environmental odours. A battery of cognitive tests were administered to subjects with and without a history of solvent exposure and exposed workers were found to be impaired across a wide range of cognitive domains (Ryan, C M et al. 1988 p.1).

3.1.4 Elevated NO, peroxynitrite and NMDA receptor activity
Problems with this section have been addressed by Professor Martin Pall in his comments and Article Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms, 2008.

3.1.7 Psychiatric disorder
Debate as to whether MCS is psychogenic due to perceived chemical toxicity or physiological/pathological interaction between chemical agents and organ systems is alluded to in introductory information P 17.

Some people become ill because they are reacting to substances in their environment that they do not know are there. They have no idea they are reacting to something, they just feel unwell.

The NICNAS/OCS Scientific Review of Multiple Chemical Sensitivity pre-release consultation draft is a biased document and out of touch with the realities of individuals who have to live with MCS.

MCS can be summed up by the words – loss, loss and more loss Pamela Reed Gibson, PhD

To make the case that individuals with MCS are psychiatrically disturbed all of the following conditions would have to be satisfied:

1. **Any physical cause for the psychiatric symptoms would have to be ruled out.**

2. **The psychiatric symptoms would have to have caused the MCS.**

3. **The groups with MCS would have to have more psychiatric symptoms than people with other chronic physical illnesses (Gibson, P R. 2000 p. 157 Associate Professor of Psychology, James Madison University, Harrisburg, Virginia USA)**

Supporting evidence:
The Sears 2007 Canadian review indicates that physical factors contribute to environmental sensitivities. There remain many unanswered questions regarding sensitivities and the interplay between biochemical, neurological and psychological processes. It is important for society to come to a common understanding, in order to offer the most efficient, effective care to people with environmental sensitivities. (Sears, M E 2007 pp. 21-24)

Living with chronic ill health
We do recognize that there are psychological problems associated with living with chemical sensitivity, but similar pressures exist for other conditions and diseases that affect a persons whole life. 'Recent research with better defined patient populations concluded that psychiatric symptoms are more likely to stem from, rather than to cause, symptoms of environmental sensitivities. Development of sensitivities usually pre-dates symptoms of depression and anxiety in people with sensitivities, with 1.4% of patients identifying problems before the onset of sensitivities and 38% reporting the development of depression, anxiety and other symptoms after sensitivities became apparent. Although emotional and behavioural problems, including depression, are more frequently found in people with sensitivities and fibromyalgia than in the general population, psychological symptoms cannot be accounted for by psychiatric illness alone. People dealing with a poorly recognized chronic illness that affects their brain, impairs their quality of life and earning potential, and has impacts on family and friends, would be under psychological distress. They could be expected to report anxiety and depression'. 'Adding to the complexity are recent findings that environmental factors such as

pesticides and moulds have been shown to be associated with symptoms such as depression and anxiety'. (Sears, M E 2007 pp. 21-24)

The relationship of anxiety and depression to chemical sensitivity is controversial. In a study to assess relationships between self reported chemical sensitivity, allergy and medical illnesses to anxiety and depression, a random telephone survey was conducted in North Carolina. 71% completed the survey. Anxiety was positively associated with chemical sensitivity, allergy and medical illnesses. Depression was comparable to anxiety in associations with chemical sensitivity and allergy, while it was more related to other illnesses. The relationship between chemical sensitivity, allergy and medical illnesses is not unique and does not support the contention that chemical sensitivity is somatised anxiety (Bloch, R M and Meggs, W J. 2007)

Evidence against psychiatric/psychological mode

Caress et al, 2002 found that only 1.4% of subjects reporting hypersensitivity to common chemical products had a prior history of emotional problems, whereas 27.7% developed problems after the emergence of hypersensitivity to chemicals.

MCS patients do not have either somatic or psychologic symptoms under chemical free conditions and symptoms may be provoked only when exposed to chemicals (Saito, M et al. 2005)

'Physicians seeking the most efficient and effective treatments have found that when people with environmental sensitivities were placed in an uncontaminated environment in which their physical symptoms resolved, their psychological symptoms also resolved. Successfully alleviating symptoms of sensitivities (with safe housing, workplaces, food, water, etc.) is necessary before other psychosocial interventions may be helpful. In a large patient survey regarding treatments, avoidance of incitants was reported to be the most effective strategy, followed by meditation and prayer to address the psychological aspects of the condition'. (Sears, M E 2007 pp. 21-24)

Seeber et al, 2002, found that influences of trait anxiety and chemical sensitivity on reports of annoyance, bad odor or irritation are only weak. While there was a correlation between odor or bad smell and annoyance, reports of sensory irritation did not correlate to annoyance. In this study measures of self reported irritation were sufficiently reliable to show a dose-response relationship to various sensory irritants.

The New Zealand MCS report states …*It is important not to conclude that because a biological cause has yet to be determined then MCS should be considered a psychological disorder*. (Read, D. 2002 p. 25)

Institute of Occupational Medicine, Edinburgh. Graveling et al in their literature review found that for a small number of people MCS does exist and the available evidence seemed to strongly support a physical mechanism rather than a psychological basis. (Graveling, R A et al. 1998 p. 1)

Potential reasons for erroneous diagnosis

When abnormal psychological/psychiatric data are obtained on personality tests or from interviews administered to patients who report symptoms of MCS, investigators typically attribute these to either psychiatric traits or psychogenic origins of illness. This study evaluated the plausibility of non psychiatric explanations of psychologic/psychiatric symptom data. The study results show the strategy of administering psychometric tests to ill populations for the purposes of evaluating psychiatric illness or traits, and/or psychogenic origins of illness was shown to be potentially misleading (Davidoff, A L et al. 2000)

'Although nasal biopsies of individuals with MCS have revealed tissue abnormalities and greater numbers of nerve fibers and symptoms induced by chemicals have been shown to be accompanied by elevated nerve growth factor, there are no consistently informative and non-invasive diagnostic tests (e.g. blood or urine tests) for environmental sensitivities. Consequently doctors base their diagnosis on patient-reported symptoms and triggers of sensitivities. Self-reporting is standard for psychological symptoms, bringing some to the conclusion that sensitivities may be psychologically based. This has broad implications for treatment, workplace accommodations, compensation and liability'. (Sears, M E 2007 pp. 21-24)

Problems associated with using psychiatric/psychological label

'A priori labelling of these symptoms as psychogenic has done tremendous harm; It has hindered the ability of affected individuals to seek help, and also the amount of research conducted. It is time to

recognise that we cannot separate the psyche from the physical dimensions of the human being and that we must understand and support ES (environmental sensitivity) sufferers' (Joffres, M R et al. 2001)

'The controversy and confusion regarding the aetiology of MCS translate into poor medical diagnosis and treatment for patients. In an earlier article we reported that persons with MCS reported seeing a mean of 8.2 physicians each, waiting 7.5 years for a diagnosis spending a considerable amount of money on their health, receiving misdiagnoses, and suffering iatrogenic harm' (Gibson, P R et al. 1998).

Some problems associated with psychotherapists:

- Inadequate medical screening (p. 158)
- Not listening to what patients say (p. 158)
- Fitting new problems into old categories (p. 159)
- Psychological intervention for individuals with MCS has been anything but supportive (p. 159)
- People reported having felt harmed by mental health providers e.g. prescribed psychoactive drugs (p. 159)
- Gender bias in mental health especially affects women (p. 160).
- Inappropriate psychological labelling was distressing e.g. depression, schizophrenia, post traumatic stress disorder … because individuals were affected by chemicals (p. 161)
- Contamination of depression inventories with somatic items (p. 161)
- Inappropriate test methods (p. 162)
- Ignoring studies that support physical explanations (p.162) (Gibson, PR 2000)

'After the 2001 9/11 World Trade Center collapse ….many were exposed to substances of varying toxicity. Many developed… environmental sensitivities and other symptoms. There is a concern that conditions may be ineffectually treaded as post-traumatic stress, whereas symptoms were reported to diminish or resolve when a sauna detoxification regimen…was used to enhance elimination of contaminants.' (Sears, M E. 2007 p. 24)

'Research shows that psychological interventions are not entirely effective. For example, cognitive - behavioural therapy, used to desensitize one to the fear of sensitivity to substances, only partially reduced symptoms in a single case. Medication and psychological interventions may be used to treat phobia or panic disorder, but for individuals with environmental sensitivities, lasting benefits have been achieved only by avoiding incitants. In a survey of 917 people with multiple chemical sensitivities, tranquilizers and antidepressants were the least effective therapy and caused harm (possibly because of a genetically-determined inability to metabolize them). In another study, psychological treatment of medically unexplained physical symptoms provided no additional benefit compared to care by a general practitioner'. (Sears, M E 2007 pp. 21-24)

History of false psychogenic attribution in medicine

There is a long history of false psychogenic attribution in medicine. Each of the following diseases has been falsely claimed to have an aetiology that is largely or completely psychological and has subsequently been proven to be a real physiological disease:

Multiple sclerosis
Parkinson's Disease
Lupus
Interstitial cystitis
Migraine
Rheumatoid arthritis
Asthma
Gastric and duodenal ulcers
Ulcerative colitis

The most recently rejected psychogenic claim is for gastric and duodenal ulcers. The bacterium *Helicobacter pylori* plays a major role in the development of these. Two Australian physicians were awarded a Nobel Prize in 2005 for this work. It is tiresome that in 2008, the medical profession still take this approach as it prejudices people's efforts to get medical assistance.

An Example - CFS, welfare rehabilitation and ethics

The study was based on former activity levels in CFS subjects (athletes), identifying differentiating variable and discussing ethical issues. *Patients who had a working diagnosis of CFS, FM, MCS which was referred to collectively as CFS syndromes were studied*. Referral bias is an important confounder

in CFS studies in a practice setting; in this case the outpatient private psychiatric practice was set in the traditional specialists quarter in Brisbane. Socioeconomic status could also bias the outcome.

While twice as many CFS patients had welfare problems (40% vs 20% of controls) this was largely a product of referral because 30% were referred wholly for medicolegal assessment. Those with welfare problems suffered lengthy and acrimonious struggles to receive benefits. Previous high achievements were rarely mentioned in medicolegal reports yet would seem highly relevant. While depression was common it does not seem to be an adequate explanation for the turnarounds in lifestyles.

The DSM-IV classification scheme has produced benefits for psychiatry sufferers but not for CFS sufferers. It provides no guidance as to whether CFS (remember we are talking about CFS syndromes that includes MCS and FM) should be listed on axis I (psych) or axis III (medical). Together with criterion BI for undifferentiated somatoform disorders – 'after appropriate investigation, the symptoms cannot be fully explained by a known general medical condition…' leaves practitioners free to list those with a medical orientation on axis III or those with a psych orientation on axis I.

In the RACGP CFS Clinical Practice Guidelines they suggest that somatisation and somatoform are unhelpful diagnostic labels that are best avoided in patients with CFS and that unless there is direct evidence of malingering, speculative judgments about unconscious motivation should be avoided. '*The psychoanalytical concept of 'secondary gain' has been misused in medicolegal settings and does not rest on a solid empirical base'.*

'It is all too easy for practitioners to collude with the insurance industry in unethical 'deny benefits' at all costs practices. These cases included 'expert' reports in which clinicians seemed oblivious to the fact that compensation neurosis is an outdated oversimplification of complex issues (Cantor, C and Neulinger, K. 2003)

3.1.8 Belief system

The diagnoses clinicians make as practitioners depends on their own beliefs, prejudices, education, background etc. While the symptoms can be almost identical the diagnosis can vary according to the specialty of the clinician e.g. neurophysician/neuromyasthenia; psychiatrist/somatisation disorder; immunologist/post viral fatigue syndrome; rheumatologist/polymyalgia rheumatica; naturopath/candida. Psychiatrists have most success in treatment with patients that adopt the psychiatric belief system that the symptoms are generated by emotional conflict and the same is true for the other specialties. In terms of a diagnosis, it depends who has made the diagnosis and what their beliefs are about the cause of the condition. Two people with the same symptoms may get two different diagnoses (Presentation by Robert Loblay to the Allergy Association Australia, Brisbane Branch Kedron Park, Brisbane December 5, 1988).

When a patient reports symptoms they should be believed regardless of the belief system of the treating clinician. Because of the 'belief system' by clinicians, individuals with MCS can be regarded suspiciously, not treated with dignity and respect and not given appropriate care. In this position such a patient can be exposed to allergens/triggers and more harm caused. Many individuals with MCS fear being detained erroneously by psychiatric services in an unsafe environment for them and if medicated can suffer more harm than good because they are physically unable to metabolise medications which are chemicals. **Their primary treatment i.e. avoidance must be observed in all circumstances.**

3.1.9 Odour Perception

Issues regarding problems associated with the provocation studies used in the MCS review have been addressed in the previous sections and comprehensively addressed by Professor Martin Pall.

The Australian Worksafe Standard validates odour and chemical interactions

Chapter 9 Odour thresholds p.14 states

- 9.1 odours can serve as a useful warning signal as to the presence of a substance in the environment;
- 9.2 there may be interference from other substances (Worksafe Standard. 2005)

3. Commentary on Overview of Possible MCS Mode(s) of action

P28 3.2 Commentary of the proposed models of modes of action. This commentary related only to the psychiatric/psychological analysis. The review's statement that no currently known biological

mechanism, process or anatomical alteration can adequately explain such divergent effects is referenced from a 1999 paper and ignores research over the last 9 years.

Heightened responsiveness to chemicals at various levels including low levels. P29 In response to low level exposures, for a long time we could only measure to a specific concentration and it was assumed that substances did not exist or cause problems below the level of detection. Once we could measure lower concentrations we then knew that substances were still present and could cause problems. Today, the new science of nanopathology indicates that nanoquantities of some substances e.g. metals are sufficient to create developmental problems in the newborn. Nanoquantities of chemicals are dangerous as they can cross blood barriers and access the various body systems (Gatti, A M et al. 2007)

There are still many more potential avenues to investigate, such as

- Viral agents e.g. hepatitis, EBV – some of these damage the liver and it lacks the ability to metabolise chemicals.
- Individuals can have a genetic predisposition to chemical sensitivity, such individuals may lack CP 450 enzymes in the liver and other organ systems to metabolise chemicals and medications (which are also chemicals).
- Cells also have detoxification mechanisms e.g. efflux transporters and some substances e.g. synthetic musk compounds destroy these. This allows pollutants to lodge in cells which then cannot protect themselves and are open to ongoing insults by chemical exposures (Epel, D et al. 2008). This could be a factor in reactions to chemicals that are thought not to be chemically related.

Rowat in 1998 describes integrated defence system (IDS) overlaps as a disease model with examples for MCS. The CNS and immune system communicate with each other and over evolutionary time, integrated defense system messengers have developed to coordinate the communications. These include the stress response; acute phase response; non-specific immune response; immune response to antigen; kindling; tolerance; time-dependent sensitisation; neurogenic switching and traumatic dissociation. Three IDSs were explored and their overlap examined (Rowat, S T. 1998)

Studies that suggest a potential molecular mechanism of action

Biological methods and limit values have been applied in occupational and environmental medicine based on the assumption that individuals do not differ significantly in their ability to detoxify chemicals. With the emergence of toxicogenomics it is however becoming clear that there is wide inter-individual differences in xenobiotic metabolism. It is also becoming clear that those diseases for which environmental sensitivity applies – many of these diseases are associated with adverse effects from common chemicals

The genetic makeup of chemical sensitivity is complex and it is likely that only in few rare instances a single gene mutation conveys significant sensitivity to normal levels of exposure. It is more likely that there will be many genes with small to moderate effects on susceptibility that will define susceptibility to toxic chemicals. Interactions between these gene variations, as well as gene-environment interactions and epigenetic processes are likely to play a significant role in determining sensitivities to particular exposures (Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology, 2007).

The NIEHS Environmental Genome Project (EGP) are working towards identifying and characterizing common sequence polymorphisms in many of the genes with suspected roles in determining chemical sensitivity. The results of which will be used to identify and protect susceptible individuals from disease and reduce adverse exposure and environmentally induced diseases (Waters et al, 2003).

‘People may be genetically pre-disposed to sensitivities. As a result of genetic polymorphisms, some bodies have less effective enzymes for detoxifying chemicals and metabolizing drugs. This is more prevalent in patients with multiple chemical sensitivity and in Gulf War veterans who became ill. Interestingly, these genes are also more common in children who developed leukemia (the very young are particularly susceptible because the immature liver has low enzyme levels). In multiple chemical sensitivity patients, a higher prevalence of a gene that has been associated with a biochemical basis for panic disorder has been found’. (Sears, M E 2007 pp. 21-24) Gulf War victims are nine times more likely to have a genetic defect that makes them susceptible to chemical warfare agents and similar chemicals than their healthy comrades. (Cox News Service. 1999)

Influences of age, gender, disease and genetics on toxicokinetic and toxicodynamic processes.
Lindeman et al, 2002 suggests that in the elderly a combination of reduced organ function, disease and use of pharmaceuticals contributes to enhanced chemical sensitivity reflected in an increased incidence of adverse drug reactions in this population. Many pharmaceutical and chemicals are metabolized by the same xenobiotic metabolizing enzymes such as the cytochrome P450s. In rodents Mori et al, 2007 found a marked age related decrease in expression of 4 members of the Cyp3a family critical for drug metabolism (Mori et al, 2007). Studies in epigenetics have discovered that epigenetic changes can occur over a person's lifetime as a result of dietary and other environmental exposures. Feinberg et al, JAMA June 25 issue.

Humans vary in their responses to environmental factors because of variability in their genes and their genes epigenetic modification. This means that the same level of exposure to a chemical substances may produce different biological responses in different people. The genetic contribution of gene variations in differing human susceptibilities to toxic effects of pharmaceuticals and other chemicals are now being explored through identification of SNPs that are associated with variation in drug toxicity and responsiveness and chemical toxicities. There is substantial evidence that genetic variations in many genes influence individual responses to toxic agents (Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology, 2007).

These are a few examples of influence of variations in the genome:

- Influence of variations of the PON1 genotypes and neuronal reactions in chronic sub-threshold pesticide exposure. Browne et al, 2006.
- Genetic polymorphisms of xenobiotic enzymes have been found to modify the risk of solvent induced encephalopathy. Kezic et al, 2006. In this same group of patients Visser et al, 2008 found that patients with Chronic Solvent-induced Encephalopathy had reduced dopamine D2 receptor binding ratios predictive of impaired psychomotor speed and attention.
- Polymorphisms of the glutathione-S-transferase (GST) gene are known risk factor for some environmentally related diseases.
- Increased risk factor in asthma and allergy. Polymorphisms of the glutathione gene was found to modify the effect of diesel exhaust particles on allergic inflammation. The concern is that there is a high frequency of polymorphisms of these genes in the population and therefore have clinical and public health relevance especially for sensitized individuals living in the urban environment. (Tamer et al, 2004; Gilliland and Diaz-Sanchez, 2004)
- Polymorphisms of glutathione-S-transferase (GSTT1 and GSTM1) have been found to modulate serum levels of lipid parameters (triglyceride, total cholesterol and high density lipoprotein cholesterol). The study also found that there were significant differences between males and females, with the number of active GST genotypes correlating with variations in lipid levels in females. (Saadat, 2007). Gender polymorphism differences
- Studies are showing that different xenobiotic metabolizing Cytochrome P450 (CYP) enzymes present in the lung and lung-derived cell lines are likely to contribute to activation of pulmonary toxins. Interindividual differences in the expression of these enzymes may explain different risk of developing lung toxicity (including cancer) by chemical substances that require metabolic activation. Castell et al, 2005.
- Kelada et al, 2003 reviewed the literature on the role of genetic polymorphisms in environmental health and concluded that the evidence suggests that the health effects of many different types of exposures can be modified by polymorphisms. Associations of particular exposures and biomarkers or effect and polymorphic variants include immunotoxicity of organochlorine compounds with gene variants of CYP – CYP1A1, CYP1A2 and AHR; exposure to heterocyclic amines and the development of colon and breast cancer with variants of NAT2 and NAT2 and SULT1A1 respectively. Literature is also documenting polymorphisms of various xenobiotic enzymes and the effect on function, inducibility, expression levels, activity, substrate specificity or whether the enzyme is produced at all. Kelada et al, 2003.
- Parkinson's disease. The potential risk for developing Parkinson's disease with dementia include pesticide exposure and at least one defective copy of the CYP2D6 gene.
- MCS is associated with variations in NAT2, GSTT1 and GSTM1 Schnakenberg et al 2007; and CYP2D6 and NAT2 McKeowyn-Eyssen et al, 2004

3.3 Further Research to identify causative mechanisms of MCS
Again the main emphasis was on trying to establish a psychiatric/psychological cause that does not appear in any way to be for the benefit of individuals with MCS. The potential of Toxicogenomics in elucidating the mechanisms behind MCS and related conditions is enormous.

Professor Martin Pall has addressed the areas of greatest research need in *Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms* that will assist in elucidating the Mechanism/s involved in developing MCS.

Potential of Toxicogenomic Research
Assessment of individual variation Combinations of epigenetic and genetic approaches are required to assess the risk of disease caused by environmental toxicants.

Gene expression profiles in response to chemicals Individual variability in gene expression can reflect individual variability due to mutations in the gene, its promoter or other regulatory regions, and epigenetic effects.

Gene-Environment interactions. Where genetic variability dictates the differential responses of an individual to environmental exposures. EG PON1 gene polymorphisms with occupational exposure to pesticides and GWS. And CYP2E1 gene mutations and drinking water contaminants (commonly trihalomethanes from chlorination) associated with effects on fetal growth. Recent studies indicate a significant genetic role in susceptibility to air pollution (Kleeberger, 2003).

Gene-gene interactions. Gene-gene interactions are important for understanding susceptibility to chemical sensitivity, where one gene modifies the effect of another on disease or adverse reactions. For example McKeown study where an association of a gene-gene interaction was found between NAT2 and CYP2D6. Gene-gene interaction between CYP2D6 and CYP 3A4 have been found to influence the metabolism of many commonly used pharmaceuticals.

Epigenetic Variability. Epigenetics – reversible heritable changes in gene function without a change in nuclear DNA sequence. Eg DNA methylation – can turn genes on or off. Epigenetic variation can alter gene expression and is implicated in individual variation in susceptibility and disease. Environmental factors such as infection, diet and chemical exposures are known to affect DNA methylation.

Xenobiotic Metabolising Enzymes (XMEs) - encompassing Phase I and II enzymes
A review of the literature on xenobiotic metabolizing enzymes and processes yields a large number of potential areas to explore. Research is demonstrating individual differences in SNPs in genes encoding xenobiotic metabolizing enzymes and the significant effect on an individual's ability to tolerate pharmaceutical medications. In MCS there are reported drug intolerances and it is entirely possible that SNP variations seen in individuals with medication sensitivity that may also occur in chemical sensitivity. There are a number of polymorphisms (SNPs) found in drug and xenobiotic metabolizing enzymes (XMEs) involving both phase I and II enzymes. Numerous studies have shown an association between adverse reactions to pharmaceuticals and XME mutations and/or polymorphisms.

XMEs have broad substrate specificity, and any one XME may metabolise several different compounds - drugs and xenobiotics, just as more than one enzyme may metabolise the same substrate. These enzymes may be constitutively expressed or induced by the presence of specific substrates. XMEs are widely distributed through the body and present in several subcellular compartments. The richest source of Phase I Cytochrome P450 (CYP) enzymes is liver microsomes, but they are also expressed in extrahepatic tissues/organs such as the respiratory tract, gastrointestinal tract and skin. Tissues differ enormously in their capacity to biotransform xenobiotics and this has important toxicological implications in terms of tissue-specific chemical injury. Levels and activities of each P450 enzyme have been shown to vary from one individual to the next due to environmental and/or genetic factors. When environmental factors influence P450, considerable variation maybe observed during repeated measures of xenobiotic transformation in the same individual, *such variation is not observed when P450 alterations are genetically determined* (Casseret & Doull, 7th ed). To date there are no studies to determine if this is the case in MCS or whether some of the differences in MCS is related to genetic variation or environmental exposure resulting in genetic alteration through epigenetic mechanisms.

Potential research areas of xenobiotic metabolism using cytochrome P450 as an example

Oxidative Damage
Bioactivation of xenobiotics and pharmaceuticals by cytochrome P450s can result in the production of reactive products/intermediates. These reactive intermediates can cause "mechanism based inactivation" of P450 leading to detrimental clinical effects. Mechanism based inactivation occurs with higher frequency with P450s because of the reactivity of the intermediates. Inactivation of P450s that form reactive intermediates may lead to toxicity, carcinogenesis or mutagenesis (Hollenberg, 2007) .

Current Scientific Project: Professor Edward T Morgan etmorgan@emory.edu Emory University Dept of Pharmacology. Project Title Regulation of CYP proteins by reactive nitrogen species. Project started 2004 and project end in 2009. The abstract describes that they had obtained compelling evidence that NO generated during an inflammatory response causes a rapid NO-dependent down regulation of rat liver CYP2B proteins. The current project proposal is to investigate the hypothesis "that modification of CYP2B proteins by reactive nitrogen species results in their targeted proteolytic degradation, and to identify the specific amino acids targeted on human CYP2B6." Their research would also investigate the regulation of human 3A4, 2D6, 2E1 and 2C enzymes by NO in cultured human hepatocytes.

Within the NIEHS Environmental Genomics Group
http://www.niehs.nih.gov/research/atniehs/labs/lmg/eg/index.cfm Douglas A. Bell, Ph.D (A Principal Investigator) Tel (919) 541-7686 , Fax (919) 541-4634, bell1@niehs.nih.gov P.O. Box 12233, Mail Drop C3-03, Research Triangle Park, North Carolina 27709
"Having uncovered the genetic basis for several phenotypes in carcinogen metabolism, the group has developed high-throughput genotyping assays and worked with epidemiologists to further explore the gene-environment interaction component of disease. … One of the current Projects concerns - Discovery and functional analysis of genetic factors predisposing to oxidant injury. The group is analysing SNPs in genes that are regulated by oxidative stress, and carrying out functional genomics studies to elucidate their significance as susceptibility factors."

Other Studies include Genetic variation in human toxicological responses, Identification of sequence variants that modulate exposure responses. Evaluation of the role of those variants in environmentally-induced disease

Extrahepatic sites of xenobiotic metabolism – Demonstration of multi organ symptoms
Metabolism of xenobiotics occurs in different tissues and is significant to the resulting balance of detoxification and activation Guengeric, 2008. What is the relevance of extrahepatic sites of xenobiotic metabolizing enzymes (XMEs) to the multi organ symptomology and spreading phenomenon of MCS. Ding and Kaminsky, 2003 suggest that there are links between metabolism of xenobiotics in the respiratory system and aetiology of MCS and asthma. Some extrahepatic tissues are important entry points for xenobiotic – Ex Respiratory atmospheric contaminants, GI tract for oral ingestion, the Skin for dermal absorption. Cytochrome P450s (CYPs) and other XMEs in these tissues contribute to first pass clearance of xenobiotics and may also influence the tissues burden of foreign compounds or bioavailability of therapeutic compounds. Ding and Kaminsky, 2003.

The chemical toxicity of a given compound is linked to its metabolic fate in the target tissue. The regulation of CYP maybe different in extrahepatic tissue compared with the liver therefore leading to a tissue selective response to chemical exposures. Some CYPs preferentially expressed in extrahepatic tissue and may lead to unique extrahepatic metabolites and tissue specific consequences in cellular toxicity and organ pathology. Acute pulmonary inflammation in mice exposed to asphalt fumes is not macrophage mediated inflammation, but mediated through metabolic enzyme systems critical for inhaled chemicals.

Bieche et al, 2007 investigated tissue distribution of mRNA expression of 23 human CYP isoforms of CYP families 1 to 3 in 22 different human tissues (pooled samples). They were able to confirm previous studies of CYP distribution and provide more information about little known CYP isoforms and their expression. Some of the CYPs were preferentially expressed in extrahepatic tissues, eg 2F1 expression in the respiratory tract. 2F1 metabolises naphthalene, a pulmonary toxin in mice, and could play a role in addition to the 1A family in the metabolism of PAH's and other atmospheric contaminants in the respiratory tract and in the production of mutagenic &/or carcinogenic metabolites. (Bieche et al, 2007)

Seliskar and Rozman, 2007 suggest that for cytochrome P450's that are expressed in many tissues or cell types, their tissue or cell type specific expression might be associated with their special physiological role. Most cytochrome P450 will reside in a single subcellular compartment in a certain cell, but there are others such as CYP2E1 that have been found to be simultaneously localised in different subcellular compartments. This may be a significant factor in MCS. Baines et al, 2004 found that more MCS cases than controls had detectable choloform, with choloroform levels higher in MCS cases. Choloroform is metabolised by CYP 2E1 and Kezic et al, 2006 found higher frequencies of a variant for the CYP 2E1 gene in individuals with chronic solvent induced encephalopathy (CSE). Individuals with CSE show central nervous system impairment not unlike that seen in MCS (Kezic et al, 2006). There have been no studies to date on whether genetic polymorphisms of the CYP 2E1 exist in MCS individuals and whether any variations may correlate with choloform levels in the body. Pollack in 1998 suggested that CYP 2E1 induction by one chemical could result in enhanced toxicity of other chemicals. (Pollack, 1998)

A review by Backes and Kelley in 2003 found evidence supporting the potential for enzymes of the P450 system to interact with POR (P450 reductase enzyme) as well as interactions between multiple P450 enzymes (Backes and Kelley, 2003).

Extrahepatic CYP1A isoenzymes are found in dermal Langerhans cells and are able to metabolise prohaptenic xenobiotic such as the PAH, dimethylbenz-[a]-anthracene, to haptens. Haptens can activate specific T cells that mediate contact hypersensitivity, presumed through the presentation of haptenated peptides. Individuals carrying polymorphisms especially combined I and II defects might be at higher risk for allergic and autoimmune disorders induced by xenobiotics. Griem et al, 1998

Cytochrome P450 2A13 is predominantly found in the respiratory tract (nasal mucosa & lung). A study by Ling et al, 2006 found that CYP 2A13 expression can be modulated by airway inflammation (respiratory specific) and epigenetic silencing of the genes promoter plays a role in the genes tissue specific expression (Ling et al, 2006)

Relevance of constitutional versus inducible expression of XMEs
There is a distinction between constitutive and inducible cytochrome P450 enzymes. Where inducible enzymes are expressed following xenobiotic activation of “xenobiotic” receptors, constitutively expressed hepatic cytochrome P450 enzymes may be regulated by tissue-enriched transcription factors. Constitutively expressed enzymes are responsible for eliminating various hydrophobic xenobiotics from the body by oxidation reactions. (Gonzalez and Lee, 1996).

Identification of common pathways for XMEs
For example while there are a number of different cytochrome p450 enzymes that have common and overlapping substrate specificity, but there is a common enzyme NADPH P450 oxidoreductase (POR) that is required by all cytochrome P450 enzymes to function. It was initially thought that mutations in this gene would be lethal, but recent research has found SNPs that are not lethal but show evidence of phenotypic/ pathological changes.

For microsomal cytochrome P450s, NADPH P450 oxidoreductase (POR) is the only source of electrons that are necessary for enzyme catalysis. A number of mutations & SNP in the POR gene have been discovered, with different POR mutations seeming to affect different P450s to variable degrees. Defects in POR may cause disorders in hepatic drug and xenobiotic metabolism as well as affecting functioning of all steroid microsomal P450s. Change in the activity of P450 by variant POR could lead to changes in toxic dosage of drugs and xenobiotics. Different P450s have variable affinities for POR and mutation/polymorphisms in POR could have different effects on different P450 enzymes.

Fluck et al, 2007 has proposed that defects in POR could cause disorders in hepatic drug and xenobiotic metabolism as well as affect functioning of all steroid metabolizing enzymes. Mechanisms by which CYP receives electrons from NADPH depends on the subcellular localization of the P450.
1) In endoplasmic reticulum (microsomes) NADPH transfers its electrons via the POR enzyme
2) In mitochondria (most P450 involved in steroid hormone biosynthesis & Vitamin D metabolism) electrons are transferred from NADPH to P450 via an iron sulphur protein Ferredoxin and Ferredoxin reductase
3) Certain P450 reactions can be supported by hydroperoxides in the absence of POR and NADPH

Polymorphisms in the POR gene can affect POR and P450 catalysed drug oxidation reactions. Hart et al, 2008 found 1) interindividual variations of the POR enzyme activity, 2) significant associations

between the activity of POR and activity of most drug metabolising P450 enzymes and 3) a significant influence of SNPs in the POR gene and POR activity. They proposed that POR is a rate limiting step in P450 mediated catalysis and is an important factor in drug metabolism.

If this is a process by which MCS and related environmental sensitivities develop, is it the POR of microsomal XME or is mitochondrial CYP affected because of ferredoxin reductase variations. Are there any differences in catalytic activity if electrons are supplied via POR or hydroperoxides

Cell Receptors
The Vanilloid receptor as putative target of diverse chemicals in MCS has been proposed by Pall and Anderson, 2004. Regulation of Phase I and II enzymes by various receptors such as Ahr. Research is showing evidence of phase I/II xenobiotic enzyme perturbations that might be relevant to MCS. There is a large amount of research on cell receptors and their involvement in various cellular processes.

Medication Sensitivity, links with XMEs
Idiosyncratic drug reactions occurs ~ 1/10 individuals and has been *difficult to predict with animal models & even in clinical trials.* The pharmaceutical industry is leading research into polymorphisms in cytochrome P450 enzymes because of their significant role in the activation and metabolism of pharmaceutical drugs (Hollenberg, 2008).

As there is broad substrate specificity amongst XMEs, testing of chemically sensitive individuals against the CYPs involved in drug metabolism may show some patterns in correlation between known pharmaceutical important CYP SNP. Similar procedures for testing for polymorphism to medications (susceptible SNP) could be used substituting chemicals known to activate one or several of the cytochrome P450s.

Research into adverse drug reactions has determined some of the critical cytochrome P450s (CYPs) involved in drug metabolism. Genetic variability (polymorphisms) in these enzymes may influence a patients response to commonly prescribed drugs (Lynch and Price, 2007). A common feature of chemical sensitivity is intolerance of many pharmaceutical medications. Niedoszytko et al, 2006 found that patients with IEI showed positive skin test reaction to several commonly used antibiotics, nonsteriodal anti-inflammatory drugs, myorelaxants, verapamil and anaesthetic agents. It would be interesting to test individuals with Environmental Sensitivities on the same panels used to predict the risk of adverse drug reactions. Suzuki et al 2004, found that substances likely to be unusable in MCS are Lidocaine, caffeine, aspirin, chlorphenylamine, maleate, minocycline hydrochloride, levofloxacin. There are now microarray assay (high throughput assay system mainly used in pharmaceutical industry) methods available for testing for gene mutations and variations responsible for adverse drug reactions/interactions.

Roche Diagnostics. The CYP2 and CYP3 families are considered to be of particular importance in drug metabolism. The CYP3A4 enzyme is present in higher levels in the liver and is affected more by environmental factors (direct, concurrent mediation, gender, age, overall health, hormones, hepatic disease, inflammation, nutrition etc) than by inherited variations. CYP2D6 activity can however be influenced by inherited variation as well as environmental factors.

Roche AmpliChip CYP450 Test – CYP2D6 and CYP2C19 selected for testing as research showed that genetic variations of these modify patient ability to metabolise drugs. CYP2C19 gene metabolises many anti-convulsants, proton pump inhibitors, benzodiazepines and anti-malarials. CYP2C19 and 2D6 involved in metabolism of certain tricyclic antidepressant drugs.

Validated assays for human cytochrome P450 activities have been analysed by Walsky and Obach in 2004 to be used to study drug interactions that could be modified for testing various substrates in chemically sensitive individuals.(Walsky and Obach, 2004).

As discussed earlier, polymorphisms in the POR gene may also contribute to variations in drug metabolism.

4.0 Diagnosis, treatment and management of MCS

P34. …reports of MCS increased with decreased household income conflicts with the information contained on p15 where MCS subjects….. above-average socioeconomic status. The unfortunate truth is that these above average socioeconomic status individuals will, through the course of an illness not acknowledged and measures taken to minimize the effect not taken, suffer economic hardship.

P35. An alternative explanation to that of Black et al, 2000c is that MCS is a disabling disease due to continued exposure to chemicals ubiquitous in the environment, rather than a commitment to the diagnosis.

4.4 Treatment of MCS

We have already presented this and our position remains the same. Chemical avoidance is the best known treatment. Avoidance of the offending substance is validated in the Australian Worksafe Standards.

Chapter 11 Effects on the skin p. 16

- 11.1 some substances can readily penetrate the skin and this method of exposure can pose a far greater danger than inhalation exposure;
- 11.3 some substances such as solvents can accelerate or alter the rate of skin absorption;
- 11.6 it is 'good practice' to avoid any unnecessary contact with all chemical substances (Worksafe Standard. 2005).

The theory that an illness was caused by toxins might be strengthened if elevated levels are found upon chemical analysis of the blood, urine, hair or tissue. However, toxins are ubiquitous in our bodies, so information must be considered in the context of exposure history and symptoms. Conversely, not detecting a toxic chemical in the blood or urine is not evidence that it did not precipitate illness. The chemical may have been metabolized and excreted, or it may have been sequestered in fat, organs or bone and therefore be at lower levels in the blood or urine by the time they are sampled. Nevertheless, monitoring levels of toxic chemicals and biomarkers such as enzymes may play an important role in following patient progress. Establishing standard monitoring is necessary for other research regarding environmental sensitivities and for studies of methods to reduce body burdens (e.g. heat, exercise and medications such as chelating agents that will accelerate excretion). Lack of availability and access to analytical expertise and services, as well as lack of funds to pay for tests, may limit the ability to identify and monitor biomarkers and toxin levels (Sears, M E 2007 p. 27)

Diagnosis of people with environmental sensitivities involves systematically identifying and treating conditions contributing to ill health, then determining if remaining symptom patterns meet the diagnostic criteria. Early recognition, avoidance of symptom-triggering agents, environmental control, treatments that may reduce residual toxins and recovery of normal biological processes are key to regaining health for people with sensitivities. Without safe food, water, shelter and workplaces, people with environmental sensitivities may become severely debilitated and unemployed (Sears, M E 2007 p. 28).

An example of an appropriate approach to treatment (Canada)

Once a diagnosis of environmental sensitivities has been established, there are a variety of strategies for treating and living with the condition. Avoidance of symptom triggers and removal of toxic chemicals stored in the body are key to treating environmental sensitivities. Safe housing, school or workplace, and food and water are top priorities. Drinking purified or spring water may lower exposure to water-based contaminants. Home and workplace cleanups/renovations, and possibly air filtration both at home and at work, may be necessary. (Sears, M E. 2007 p. 27)

Food sensitivities are common in people with environmental sensitivities and may be managed with an elimination or rotation diet. One example of food intolerance that is commonly missed is coeliac disease, an autoimmune response to gluten in many grains. It is assessed up to the age of 6 in Italy, but in Canada testing is not routine and may be preceded by months of symptoms. The delay between onset of symptoms (some of which are vague and may be missed by physicians) and diagnosis with a simple test leads to deterioration of health and well being with serious possible consequences including neurological problems and diabetes. As with the broader range of environmental sensitivities, celiac disease is chronic; the related malabsorption and 'leaky gut' may lead to diverse toxicities; it is under-diagnosed; and the most effective and important treatment is gluten avoidance.(Sears, M E. 2007 p. 27)

Clinical management strategies (Canada)
Once exposure to incitants is eliminated, helpful interventions include:

- treating gastrointestinal infections which, if untreated, can lead to absorption of internal toxins and large-molecule food antigens, or conversely, may lead to poor absorption of nutrients;
- regimens to enhance detoxification and elimination such as sauna and exercise therapy;
- reduction of heavy metal contamination using oral and intravenous chelation for toxic metals (shown to be safe to treat lead in children; it is currently in clinical trials for children with autism);
- oral and intravenous vitamins;
- securing hormonal homeostasis, given that many of the toxins observed are endocrine disruptors;
- correcting biochemical irregularities;
- desensitization for foods and/or inhalants;
- psychological, social and spiritual support;
- occupational accommodation; and
- financial support for safe workplaces, housing, food and water. (Sears, M E 2007 p. 28)

Denmark
The first Division of Environmental Medicine in Canada was established in the province of Nova Scotia in the beginning of the 1990's. During a two-year period, more than 500 employees from the local hospital were examined due to indoor climate problems. In the course of seven months many had developed chemical hypersensitivity, including MCS. Because a majority was of the opinion that odours were among the most common triggering factors, the health authorities, in collaboration with the hospital management and the labour union, issued a ban on perfume and scent-containing products in the hospital. The ban was implemented and followed up in a 'soft' manner with good results (Silberschmidt, M. 2005 p. 77).

4.5 Clinical Research Needs
P 39 Again an emphasis has been placed on challenge tests that suggest smell or odor is the triggering agent. This statement is not referenced and the studies using double blind placebo controlled are flawed and potentially biased. All other relevant information to a physical cause has been ignored.

Suggested Medical approach:

- An EHC should be built as a priority to gather data on MCS and other environmental sensitivities. The EHC should be a facility where doctors and other health care professionals can visit to take part in research and training programs to facilitate information, diagnostic, treatment and management techniques into the health care system. Gathering unbiased evidence based data will be beneficial in many areas.

- The government should consult with the Canadian Nova Scotia Environmental Health Center for assistance re the above to take advantage of work already done.

- A consultant from the EHC in Nova Scotia should be brought to Australian to get the ECU, the diagnostic process started and to effect a training course in MCS for doctors, nurses and other hospital staff

- ASEHA suggests that we try to rate MCS on a symptom scale as per disability impairment. That approach may work and at least gives some basis for diagnosis, treatment and for evaluating the success of any treatment approach. It will also give a clearer picture of co-existing morbidities.

- A question on the next census to gather data on the percentage of the Australian population suffering from MCS.

- Some costing of MCS and environmental sensitivities needs to be undertaken to assess the socioeconomic cost of MCS and environmental sensitivities to the community. These will justify the educational approach and the regulatory need for action.

- A clinical diagnosis is acceptable for some diseases and should be available for MCS

- Modify the Canadian or SA CFS Guidelines to diagnose MCS
- A Body burden testing program of humans as per the US CDC Exposure Reports needs to be initiated to ascertain the chemical body load of Australians.
- A Precautionary approach to MCS should to be taken by government and the medical profession.
- The genetic basis of MCS should be investigated
- Fragrance free policies for health and allied care facilities including nursing homes and respite facilities need to be developed and implemented over a period of time. This work should begin immediately as a humanitarian response that will allow individuals with MCS access to essential services – the same as others in the community who do not have MCS.
- Access to complimentary medicines and treatments in the absence of tolerance of drug/medical treatments e.g. Traditional Chinese Medicine. Acupuncture, Homoeopathy, Naturopathy, Bowen therapy, chiropractic, myopractic.
- Access to disability aids such as masks, air filters, oxygen, assistance with home modifications to allow MCS sufferers to stay in their homes, assistance with relocation costs. (Sears, M E. 2007)

FACTORS NOT COVERED BY THE MCS REVIEW

Impacts on individuals and their families

One million Canadians are less productive or underemployed and need to modify their homes
Half a million Canadian adults:

- are unable to do paid work
- are isolated
- are facing additional costs such as organic food and uncovered medications, medical services and assistive devices which can total $10,000 per year and are
- are depleting their savings and superannuation plans
- Hundreds of thousands of Canadian adults are relatively homeless,
- thousands are homeless
- Many experience failed marriages and family tension
- Some are suicidal

Socio-economic impacts of MCS and other related diseases

An area that has been ignored by this review is the socio-economic impact of MCS other than to try to suggest that low income maybe a triggering factor. Millions of Canadians suffer physical, emotional and financial hardship as a result of environmental illness. As many as one third of Canadians suffer from some form of environmental sensitivities with environmental sensitivities affecting more women than men and increasing with age(Sears, M E 2007 p. 6). This would be true of any nationality. In a 2003 survey 3.6% of all Canadian nurses experienced chemical sensitivities (Sears, M E 2007 p. 4)

The total estimated financial cost of environmental illness to Canada is estimated at $13 billion per year - $10+ billion per year in lost productivity; $1+ billion per year is eroded from the tax base
$1+ billion each year in health care costs which is avoidable if the illness were diagnosed and treated in a timely manner and $1+ billion dollars per year in avoidable disability payments. (Kassirer, J and Sandiford, K 2000)

Environmental Illness is one of the most expensive health care conditions in Canada along with heart disease, musculoskeletal disease and cancer. Around 7 million individuals suffer significant symptoms, increased absenteeism and impaired abilities at work due to normally safe exposures to some of the common chemicals and moulds found in their homes and at work. Around half a million adult Canadians are unable to do paid work due to a disability associated with Environmental Illness (Sears, 2007).

Health utilisation costs directly related to MCS have been estimated at approximately $1.581 annually per patients (Fox, R A et al. 2007). Prevalence studies predict that approximately 15% of the US population suffers from MCS and direct health care utilisation costs amount to a staggering $71.8 billion per year (Muir, T and Zegarac, M. 2001).

Societal costs of air pollution.

Pervin et al investigated the societal costs of air pollution in relation to ill health. The criteria air pollutants considered responsible for air pollution are known to be harmful to human health and can result in a significant amount of morbidity and premature death. However, exposure to air pollutants damages the health of everyone, especially 'at risk' groups. Studies reviewed for the Pervin report included some OECD and non-OECD countries. Most of the studies found air pollutants to be the main sources of respiratory and cardiovascular disease and contributory factors to environmental sensitivities (various allergies, headaches, eye irritation, cough and others). They also only focused on human health damage and ignored costs related to damage to crops, forests, buildings and degradation to visibility and the ecosystem. While establishing threshold levels for air pollution is an important issue, currently there is no scientific basis for setting thresholds in the evaluation of the health impacts or air pollution. The costs are as follows:

Country	Direct Health	Non Health	Productivity losses	Intangible costs	Total societal cost
France	US$6.60 -11.25 mill	Not estimated	US&5,10 – 8.72 ,mill	Not estimated	US$13.43 – 22.95 mill
Tokyo	US$6,860 mill	US$833 million	US$6,330 million	Not estimated	US$14,023 mill
California	$5.2 million	Not estimated	Not estimated	Not estimated	$5.2 million
Belgium	Not stated separately	Not stated separately	Not stated separately	Not stated separately	$1.5 billion approx
Canada	US$674 mill	Not estimated	US 2,696 mill	US$3,370 mill.	US$6,740 mill.

Mexico City	Not reported	Not reported	Not reported	Not reported	US$760 mill.
Russia	Not estimated	Not estimated	US$28.8 – 80.01 mill	Not mentioned	US$28.8 – 80.01 mill
Taiwan	US$5510,491 – 804,298	Not estimated	US$117,575 – 244,477	Not mentioned	US$628,074 – 1,048,775
Indonesia	US$115 mill	Not estimated	US$65 mill	Not estimated	US$180 mill
Shanghai	US$67.82 mill	Not estimated	US$557.58 mill	Not mentioned	US$625.4 mill
Beijing	US$956.841	Not estimated	$226,617 mill	Not mentioned	US$1184 mill
India	US$119.11 mill	Not estimated	US$18,783.99 mill	Not mentioned	US$18,983.10 mill
Hong Kong	US$33.02 – 57.79 mill	Not estimated	US$437.66 – 462.43 mill	Not mentioned	US$495.45 mill

Pervin T et al. 2008.

Cost of COPD to the Australian economy

The cost of Chronic Obstructive Pulmonary Disease in Australia is high.

- Recent research shows that up to 1 in 6 people over 45 have COPD, affecting over 1 million Australians
- COPD is the fifth biggest killer of Australians
- COPD is the 3rd leading cause of human and economic burden of disease (following coronary heart disease and stroke).
- Disability of COPD is viewed as similar to paraplegia and AIDS.
- The estimated direct and indirect costs of COPD are $800-900million annually.
- COPD goes largely unrecognised and under-diagnosed.
- Less than 25% of the study participants who were found to have COPD had been diagnosed by a doctor.

Abramson MJ. 2005; AIHW. Chronic Diseases Mortality; Mathers C, Vos T, Stephenson C. 1999; Crockett AJ, Cranston JM, Moss JR. 2002. www.lungnet.com.au.

Cost of Asthma to the Australian community

In recent years asthma has been recognised as a common health problem affecting between 8-9% of the Australian population or 1.4 million people, yet there has been little effort to ascertain the economic impact of the disease. The quantifiable costs of asthma, namely the medical related and indirect costs of lost productivity, have been evaluated by The National Asthma Foundation of Australia in an effort to fill this void and understand the total quantifiable cost and prevalence of asthma in all age groups as well as the impact of asthma severity and control on cost for adult sufferers. However, no attempt was made to place a financial value on the intangible yet significant "quality of life" costs:

- In 1991, the cost burden of asthma to the community was estimated to be around $585 to $720 million;
- This consists of around $320 million in medical related costs and around $260 to $400 million in indirect costs from lost productivity with 45%-55% due to lost productivity.
- The medical related costs of asthma amount to around $320 million with 35% of the medical cost, or $120 million due to pharmaceutical prescriptions and devices.
- Close to $100 million, arises from some 3 million medical consultations, predominantly GP services, provided annually to asthmatics outside the hospital system.
- Hospitalisation costs are estimated at approximately $60 million and includes the costs of caring for asthmatics as hospital inpatients and in the emergency and outpatient departments. The total cost figure is based on average hospital costs of $358 per day and total asthma bed days of 155,000 per year.
- Indirect medical costs of around $30 million are due to the fact that asthma can exacerbate other medical conditions and increase the cost and demands placed on the health system.
- The cost of allied therapies represents another $8 million while ambulance transport amounts to $5 million of the total cost.
- The indirect cost of asthma was estimated at $260 to $400 million and are costs incurred by an individual, an individual's family or the community because of the adverse consequences asthma may have on an individual's work and social activities. These costs were valued on a time basis at the GDP hourly rate.
- Asthma related absenteeism accounts for over 60% of indirect costs of asthma.
- Around $110 million, the equivalent of 0.5 days per year for each working asthmatic, is absenteeism directly due to asthma.

- Another $90 to $120 million can be incurred as a result of employed caregivers having to stay with a sick asthmatic child.
- Apart from resulting in absenteeism, asthma can limit the effectiveness of employees at work. This cost has been estimated between $40 and $100 million, based on assumptions of lost productivity in the range of 10% to 25% and a total of around 1.8 million work affected days. It excludes the costs of lost productivity from asthmatics taking time off work to attend consultations. The value of this foregone output represents an additional $20 to $60 million.

The total cost, although substantial, is not comprehensive as the potentially significant impact asthma has on an individual's quality of life has been excluded. http://www.nationalasthma.org.au/html/home/index.asp

Figures from the Australian Bureau of Statistics show that the mortality rate of asthma has been increasing since 2005. The incidence of asthma has risen worldwide with Australia having the highest prevalence. http://www.nationalasthma.org.au/html/about/index.asp

Cost of allergy to the Australian economy
According to a 2007 report by the Australian Society of Clinical Immunology and Allergy (ASCIA) the financial cost of allergy to the community was $7.8 billion. $5.6 billion was lost productivity, $1.2 billion was direct health system expenditure, $261.5 million was spent in other indirect costs such as allergy aids and home modifications, $783 million was deadweight loss from transfers including welfare payments and lost taxation revenue. The personal cost of allergy to those affected is estimated to be $21.5 billion.

In Australia there is a lack of recognition of the impact of allergic and immune disorders on quality of life and even less recognition of the economic impact on society and individuals who suffer from allergic disease. Allergy is a chronic immunological disorder that occurs when a person's immune system mounts an abnormal response to allergens that do not normally bother other people. Examples of allergy are allergic rhinitis or hay fever, allergic asthma, food allergy, sting and insect bites.

Australia and New Zealand have the highest incidence of allergic disorders in the developed world. 4.1 million Australians have at least one allergy, this represents 19.6 %of the population. The working aged population is most affected with 78% of people who suffer from allergy aged between 16-64 years. There are 7.2 million cases of allergy in Australia meaning there is an average of 1.74 comorbid allergies per person. ASCIA and Access Economics. 2007. The Economic Impact of Allergies. www.allergy.org.au/content/view/325/76/

Australia
Federal Finance Minister at the time (November 2006), Nick Minchin, warned of spiraling costs if the link between environmental chemicals, cancer and chronic illness was ignored. He claimed that common sense tells you there is a relationship there and its impact on the health budget 'keeps you awake at night'. He was opening a new CRC for Contamination Assessment and Remediation of the Environment (CARE) at the University of SA Mawson Lakes Campus, North Adelaide. (Roberts, J. 2006)

While we do not have a lot of data for MCS in Australia, we have used a CFS study due to the substantial overlap between MCS/CFS/FM and the possibility that they may be the same disease.

CFS Study. The financial burden of CFS was calculated by direct and indirect costs related to the disorder. The statistics were drawn from a survey of patients with CFS and Medicare data on the incidence and fees charged for scheduled items for those surveyed.

Forty two patients with CFS were identified in a population-based prevalence study. The conservative estimate of costs in the Richmond Valley with a prevalence of 37.1 cases per 100,000 was $396,000. If extrapolated to the Australian population it was estimated that CFS would generate an annual cost of at least $59 million (Lloyd, A R and Pender, H. 1992). It is unfortunate that this study does not include lost productivity, tax dollars, disability payments, avoidable suicides and erosion of human rights

United States
Toxic chemicals Sicken and kill thousands of people in California each year and cost the state an estimated $2.6 billion in medical expenses and lost wages (Chea, T. 2008)

A 1997 study that found improvements made in buildings air quality (such as replacing carpets and ventilation systems) could save between $12 and $125 billions dollars in worker productivity alone (Gaffney et al, 2007)

CHANGES REQUIRED

Government abrogating its duty of care to individuals with chemical poisonings/MCS

Various Australian groups who have documented chemical poisonings have tried to gain recognition and compensation. The cost of poisonings to the community is already high in terms of medical and socio-economic costs. To do nothing about MCS will cost much, much more……

Some groups include;

- the Deseal/Reseal Workers in the Air Force who are still struggling for a reasonable amount of compensation and for the government to behave in their best interests;
- Vietnam Veterans who were drenched with carcinogenic pesticides and who have illnesses the government does not want to recognise;

More recently individuals who live around the ALCOA plant in WA and who have been poisoned by noxious fumes are struggling for recognition, health care and compensation.

Regulatory need

Some occupational and environmental chemicals cause allergic diseases. To prevent chemical allergies, it is essential to identify the chemical substances that cause sensitisation and to eliminate such sensitisers from daily life. Information for evaluating sensitisation of chemical substances is needed. The article by Murakami et al, 2007 compared criteria for sensitisers among national organisations in various countries and international organisations to make out a list of sensitisers. The definition of sensitising chemicals and the designation of respective sensitisers according to various occupational health organisations were studied with 1389 chemical substances designated as sensitisers (Murakami, T. 2007) Current toxicology methods of assessment are inadequate. The challenge for occupational health is in setting OELs for numerous chemicals being introduced for which the extent of their ability to cause adverse health effects is unknown (Gaffney and Paustenbach, 2007).

When confronted with the harm they have caused, corporations typically blame the victims, deny the problem and try to avoid responsibility for the harm caused. The manufacturers of products that have harmed human health would rather silence the messenger than acknowledge that their products are not safe. The chemical manufacturing industry has launched an anti-MCS campaign designed to create the illusion of controversy about MCS and cast doubt upon its existence. MCS sufferers have been labelled neurotic and doctors that help them as quacks; scientific studies that support MCS 'flawed'; lab tests that show physiological damage in MCS sufferers as unreliable; anyone helping MCS sufferers as cruel for reinforcing 'beliefs' that they are ill; using medical doctors and the legal system to discredit MCS suffers so that their claims are denied, or block testimony that supports MCS (McCampbell, A. 2001; Hileman, B. 1995)

In the last 100 years there has been a proliferation of man-made chemicals and in that time we have also experienced great increases in cancer, brain damage, asthma and other epidemic degenerative diseases such as arthritis and coronary artery disease. We reek with chemicals and human health has been sacrificed to economic growth and profits. Chemicals are costing us dearly. They have injured human brains in many people who are not aware they have been chemically exposed. Unless this pandemic is stopped it threatens our existence (Kilburne, K. 1999)

The pesticide industry is a major business worldwide with annual sales in 2001 estimated at US$30 billion per year. Manufacturers claim it is hard to get people to use pesticides responsibly, they call this product stewardship. In spite of this it was estimated at the time of the report that up to 25 million people were poisoned by pesticides per year. While governments and manufacturers believe that pesticides can be used safely, most of the victims are in developing countries. Many do not speak or read English. A BBC crew went to SE Asia to document the 'Toxic Trail' and reported that farmers are literally bathing in toxic cocktails. Multinational corporations disclaim responsibility for what happens to their products, leaving the responsibility to governments who do not have the regulatory capacity to cope (British Broadcasting Commission. 2001)

Conclusion

OCS/NICNAS should move forward with recognition of MCS as a physical disease, it is already a recognised disability (personal correspondence HREOC) and disability access barriers need to be removed so that chemically sensitive individuals can access health care, nursing homes and other necessary facilities/services so that their human rights can be observed and evidence based data on MCS can be gathered. Government has a duty of care to the population and it is time to stop procrastinating.

As consumers of health services we are disempowered by our treating clinicians. They do not believe us unless there are signs and symptoms that fit their criteria. Patients presenting with a lot of symptoms that do not add up to something clinicians understand are immediately suspected of somatisation disorder. This includes individuals with chronic degenerative diseases such as allergy that can impact on various organ systems. In a hospital admission, patients have to identify diseases, allergens e.g. pollens, latex, medication allergies, fragranced products and other substances that trigger reactions e.g. medical equipment e.g. adhesive tape, plastic tubing and then have to ask to see the dietitian due to food allergy, IBS or metabolic disorder that affects diet. The latter really is like the straw that broke the camels back and the clinician has decided by now that this patient has psychological problems.

Case study one: Deborah a 40 year old woman with severe MCS and EMS who cannot find a house in which she can safely live. She lives in her car most of the time as the house she is currently renting causes reactions as it is not a low toxic home. While looking for another more suitable house, a real estate agent disbelieved her as he thought she was a psychiatric case. He called the police who notified local psych services. Deborah's mother said she was schizophrenic and she was detained against her will for seven hours while subject to a psychiatric assessment. Deborah is not schizophrenic according to her GP. Her mother, like the real estate agent and the police do not understand her problems. The latest development with Deborah is that she has become suicidal because she cannot get any help, she is very ill, cannot find a safe place to live and since she was detained by the local psychiatric service is now constantly visited by Police in her area. Recently, she drove off into the bush to end her life and the local police, a TV station crew and some individuals drove around the area looking for her. She was found, safe, but in a highly volatile and distressed state and taken to a house in the local area occupied by another chemically sensitive person. She did not tolerate the house and became unstable again. We are unable to find her a safe place to live, rest and recover and be able to care for herself. We fear for her life.

Case study two: People can die from fragrance exposure. Valentina was a 78 year old woman with emphysema and severe chemical sensitivities. Her lungs were particularly sensitive to fragrances and many other chemicals. She could lose consciousness on contact with fragrance and would need to be revived. She could not find air that was clean enough for her lungs to tolerate so spent a lot of time on oxygen struggling to breathe. She lived in a rural area but was constantly exposed to smoke from wood stoves and people burning rubbish etc. Because of the smoke she had several emergency admissions to hospital. She would ring the ambulance and ask them not to wear any fragrances or fragranced products when they came to transport her to the hospital. However, they invariable arrived smelling fragranced and on several occasions she arrived unconscious at the Emergency Room and needed to be resuscitated. She would then be placed in a ward and would suffer more fragrance exposure as almost everything in the hospital is fragranced e.g. hand washes, staff that tended her, surgical scrub and disinfectants/detergents. Unfortunately, she was not believed and her efforts to protect herself from losing consciousness were mistaken for somatisation disorder and eventually she would have to discharge herself from the hospital and go home where she lived alone and then struggled to cope without any medical care. In September of 2007, she suffered smoke inhalation from surrounding human burning and called an ambulance to transport her to the local hospital. Once again her request for fragrance free ambulance staff was ignored and she arrived at the hospital unconscious. Yet again she was revived and placed in a ward where she was subjected to fragrances from staff and products, so she demanded to see the hospital administrator and had herself moved to another part of the hospital where there were to be no fragrances. Unfortunately that area of the hospital was worse than what she had left behind and she resigned herself to the fact that she would die in the hospital. (She communicated this to ASEHA executive) We suspect she was subjected to fragrance through the night, lost consciousness and either nobody noticed or there was nobody to revive her in time…….. we will never really know. She was dead the next morning when an ASEHA executive rang to check on her. Over a period of days the hospital ignored all of ASEHAs efforts to ensure Valentina was safely accommodated and nursed. (For around 12 months prior to this event ASEHA had provided the hospital with information about MCS, nursing notes, information about fragrances/fragranced products and fragrance free products – all ignored)

The bias towards MCS in the NICNAS/OCS Scientific Review of MCS is blatantly obvious and unacceptable. As CFS and FM are recognised and MCS is not, this raises questions about the morals and ethics of decision makers with respect to their bias and conflicts of interest. If the decision makers go on sanctioning the commercial sector by allowing the adverse health impacts to continue the community can then assume they have accepted the whole population as a sacrificial community and are morally and ethically bankrupt. Government needs to distance itself from the commercial sector and other pressure groups with self interests.

While the cost of taking actions to reduce chemicals that can harm humans and the environment may be expensive – to do nothing will be even more costly.

Actions needed to proceed:

Bring someone from the Dallas Environmental Health Centre or the Nova Scotia Environmental Health Centre to:

- advise the government on MCS;
- assist to establish medical and nursing training programs;
- assist to establish protocols to allow persons with MCS necessary access to health care, health and allied care facilities, nursing homes, respite, housing and necessary welfare services;
- advise the government on the establishment of programs for persons with MCS disability so that they can access assistive devices e.g. masks, air filters, as per other medical, disability aids and home modifications;
- advise the government on the needs of persons with MCS disability so that they can realize their full potential and take part in society the same as persons who do not have MCS disability.

The Nova Scotia Environmental Health Centre deals with all environmental sensitivities including CFS and FM so their expertise could be useful to progress management of these disabilities as well as for MCS.

Research needs

- Ascertain how many chemically sensitive individuals there are in the population;
- their level of sensitivity i.e. low, medium, high;
- investigate the socioeconomic cost of MCS in Australia;
- what their medical needs are including access to complimentary therapies;
- what their health and allied care needs are;
- what their aged care needs are;
- what their disability access issues are e.g. hospitals, nursing homes, housing, public transport, schools and detriments to access;
- their disability needs i.e. assistive devices such as masks, air filters, oxygen etc and home modifications;
- what their social needs are;
- what their welfare needs are;
- Body burden testing as per the US CDC NHEXAS program;
- Studies into the incidence of MCS in those with a high body burden. However, this is not a complete approach as some chemicals e.g. organophosphates do not accumulate in the body and yet can cause MCS;
- Studies into the impact of chemical exposures on DNA and future generations;
- Investigate the role of gene polymorphisms in MCS;
- Research into xenobiotic metabolizing Enzymes e.g. CYP450;
- Investigate links between XMEs and medication sensitivities;

Any studies designed for Australia should be done in consultation with and under the supervision of either the Environmental Health Centre, Dallas, Texas, or The Environmental Health Centre, Nova Scotia, Canada. There are many pitfalls when individuals who do not understand chemical sensitivities try to design studies for MCS. Booth testing is particularly unethical and will not be tolerated. There are many other ways to test for chemical reactions.

ASEHA strongly recommends that a consultant from either Dallas or Nova Scotia should be brought to Australia to assist with MCS research, training and educational programs. OCS/NICNAS should also

contact Australian specialists who have established Environmental Control Units in the past e.g. Dr Colin Little, Dr Mark Donohoe.

Public education that chemicals are not necessarily safe and can damage human health and the environment. Some specific areas that need to be addressed are:

- fragrances and fragranced products
- wood smoke
- low chemical housing – some work has already been done here – needs to be improved with easier access for the population
- educate Australians to use less chemicals in every aspect of their lives
- educate Australians to use less toxic chemicals in their lives
- MCS should be given an ICD code in line with CFS and FM which could be the same condition.
- Encourage chemical manufacturers to develop green chemistry which in turn will cater to the consumer swing to 'natural' products and open up new markets. In the food industry natural and allergy foods are a growing market and becoming lucrative. In the UK the UK 'free from' food market is currently being driven by increased public awareness of food allergy and intolerance and has already experienced sales growth of more than 300% since the year 2000; In 2005, the 'free from' market which includes dairy, gluten and wheat free products, was worth an estimated £90 million and is set to continue its strong growth; According to a report by Euromonitor in 2006 the UK market for gluten free foods alone amounted to £47 million making it the third largest market in the world for gluten free products after the USA and Italy; Sales of lactose free products increased by 29% since 2002 and reached £23 million in 2006. (foodnavigator.com/europe 24 September 2008)
- **A growing lucrative 'natural' market.** A UK based company, Create Flavours, has introduced a range of nut flavours that are natural and nut free. These include peanut and hazelnut which are difficult to produce. The company claims these were produced with in-house technologies and natural ingredients and opens up a new range that their dairy and bakery customers are keen to exploit. The natural, nut free range, opened up nut flavours for individuals with allergen restrictions or for foods with nut free considerations. These days both retailers and consumers are scrutinising ingredients more carefully and creating pressures to remove potentially allergenic ingredients while shifting to natural foods. This trend is growing world wide. The company claim that this part of their market is growing quickly with most of their attention devoted to servicing it and that in the future the majority of their trade would come from these flavours. Starling, S. 2008 Create Flavours favour nut free nut flavours. Foodnavigator/Europe.com 3 Sept 2008

Regulatory approach to chemicals:

Assurances that levels of chemicals do not exceed government standards for exposure: Safe levels are a compromise between industry's commercial needs and consumer protection and do not guarantee that harm cannot occur. The use of males to set exposure limits neglects the fact that women react differently to toxins

- Remove known sensitisers in products for personal or domestic use,
- Remove known carcinogens from products for personal or domestic use,
- Phase out lipophilic substances that have been found to build up in the environment and humans
- Phase out endocrine disrupters and neurotoxins that can impact on humans and the environment
- Labeling requirements of products need to be improved and should contain a list of any substances such as sensitisers, allergens, carcinogens, endocrine disruptors, neurotoxins or lipophilic substances. Labels should also contain health warnings as per cigarette packets.
- Reduce the penetration enhancers, strength and life of fragrances in all products to ensure they are not discernable any more than one meter from point source and that they degrade in a short space of time.
- All health and allied care facilities, including respite centers and nursing homes, should be fragrance free zones. IAQ should be frequently monitored to ensure a low VOC environment. This is beneficial to all involved in health and allied care including the workers.
- Alter the building code to remove products that can cause health impacts, this will ensure that individuals with MCS and other environmental sensitivities can access safe housing, health and allied care facilities, workplaces and public buildings. While some work has already been done to reduce solvent based paints much more can be done.

Building access

- The building code needs to be upgraded to ensure that building products used are low in VOCs.
- Indoor air levels low in VOCs and biological contaminants urgently need to be set for all indoor environments, including the domestic environment.
- High emission products need to be phased out of the building code.

Labeling

- Labels should list all ingredients with warnings that the product may contain dangerous chemicals.
- All ingredients need to be listed or be freely available from the manufacturer.
- The label should also include the health impacts of the ingredients as per cigarette packets.

Information about chemicals

A list of all chemicals used in products and their known health impacts should be freely available from NICNAS to allow people the right to choose whether they wish to expose themselves to chemicals and risk an adverse health event. Information about mixtures of chemicals where available should also be available.

Fate of the MCS Clinical Review

The MCS clinical review should be ongoing until the science has caught up with the problems related to chemicals that are unleashed on the population and unravel the diseases they cause. Currently such science does not exist and consumer health and safety can be compromised by many ingredients of freely available products. Most people think that because products are available on supermarket shelves that the government has assessed them and they are safe to use. Education of the general public is essential and urgently needed in order to change this belief system.

References

Abramson MJ. Respiratory symptoms and lung function in older people with asthma or chronic obstructive pulmonary disease. MJA 4 July 2005; 183(1):S23-S25

AIHW. Chronic Diseases Mortality.
Found at: http://aihw.gov.au/cdarf/data_pages/mortality/index.cfm

Amdur, M et al. 1991. Casarett & Doull's Toxicology: The Basic Science of Poisons. 4th Ed, Pergamon, NY.

Anon. 1999. Gulf War victims seen nine times less likely to have protective gene. Cox News Service June 17, 1999

Ashford, N A and Miller, C S. 1998. Chemical Exposures: low levels and high stakes. 2nd Ed. Van Nostrand Reinhold, NY.

Baines CJ, McKeown-Eyssen GE, Riley N, Cole DEC, Marshall L and Jazmaji V (2004) Case-control study of multiple chemical sensitivity, comparing haematology, biochemistry, vitamins and serum volatile organic compound measures. Occupational Med. 54:408-418

Bakes W and Kelley R. 2003. Organisation of multiple cytochrome P450s with NADPH-cytochrome P450 reducatse in membranes. Pharmacol Ther. 98(2):221-233.

Bernstein, D I. 1996. The role of chemical allergens. *Regulatory Pharmacology & Toxicology 24:S28 – S 31.*

Bieche I, Narjoz C, Asselah T, Vacher S, Marcellin P, Lidereau R, Beaune P and Waziers I. 2007. Reverse transcriptase-PCR quantification of mRNA levels from cytochrome (CYP)1, CYP2 and CYP3 families in 22 different human tissues. Pharmacogenetics and Genomics. 17:731-742.

Bloch, R M and Meggs, W J. 2007. Comorbitity patterns of self-reported chemical sensitivity, allergy and other medical illnesses with anxiety and depression. *J Nutr & Env Medicine 16(2):136 – 148.*

Bornehagg, C G et al. 2004. The association between asthma and allergic symptoms in children and phthalates in house dust: A nested case control study. *Environmental Health Perspectives 112:1393-1397)*

Buchwald, D and Garrity, D. 1994. Comparison of patients with chronic fatigue syndrome, fibromylagia and multiple chemical sensitivities. *Arch Intern Med 154: 2049 - 2053.*

British Broadcasting Commission . 2001. Toxic Trail. Documentary. www.ToxicTrail.org/

Browne RO, Moyal-Segal LB, Zumsteg D, Yaron D, Kofman O, Berger A, Hermona S and Friedman A. Coding region paraoxonase polymorphisms dictate asscentuated neuronal reactions in chronic, sub-threshold pesticide exposure. 2006. The FASEB Journal. 20, E1103-E1113.

Cantor, C and Neulinger, K. 2003. Premorbid functioning, welfare issues and ethics in chronic fatigue syndrome. *Australian Psychiatry 11(3):312 – 318*

Caress SM, Steinemann AC, Waddick C. 2002. Symptomology and etiology of multiple chemical sensitivities in the southeastern United States. Arch Environ Mealth 2002 Sep-Oct; 57(5); 429-36

Castell JV, Donata MT, Gomez-Lechon MJ. 2005. Metabolim and bioactivation of toxicants in the lung. The in vitro cellular approach. Exp Toxicol Pathol. 57 (Suppl 1): 189-204

Chea, T. 2008. Chemical-related illnesses cost state. Associated Press 61 Jan 2008.

Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology. 1007.

Crockett AJ, Cranston JM, Moss JR. Economic Case Statement. Chronic Obstructive Pulmonary Disease. Australian Lung Foundation, Sept 2002

Cullen, M R. 1987. Workers with multiple chemical sensitivities. Occupational Medicine: State of the Art Reviews 2(4):Oct-Dec 1987

Davidoff, A L et al. 2000. Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. *Archives of Environmental Health 55(3): 165 – 175.*

DermNet NZ. 2008. Fragrance mix allergy. www.dermnet.org.nz

Ding X and Kaminsky. 2003. Human extrahepatic cytochrome P450: Function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. Annual Reviews Pharmacol. Toxicology. 43: 149-173.

Dunstan, R H et al. 1995. A preliminary investigation of chlorinated hydrocarbons and chronic fatigue syndrome. *Med J Aust 163:294-297*

Epel, D et al. 2008. Efflux transporters: Newly appreciated roles in protection against pollutants. *E S & T Online news 42(11): 3914-3920*

Farrow, A et al. 2003. Symptoms of mothers and infants related to total volatile organic compounds in household products. *Archives of Environmental Health. 58(10):633-*

Feinberg et al, JAMA June 25 issue.

Fluck C, Nicolo C and Pandey A. 2007 Clinical, structural and functinal implications of mutations and polymorphisms in human NADPH P450 oxidoreductase. Fundamental and Clinical Pharmacology 21: 339-410.

Fox, R A et al. 2007. The impact of multidisciplinary, holistic approach to management of patients diagnosed with MCS on health care utilisation costs: an observational study. *J Alt Complement Med Mar. 13 (2):223-9)*

Gaffney SH, and Paustenbach J. 2007 A proposed approach for setting Occupational Exposure Limits for sensory irritants based on chemosensory models. Ann. Occup. Hyg. Vol 51(4): 345-356

Gatti, A M Ee al. 2007. Evidence of environmental pollution translocation from mother to foetus. Laboratory of Biosciences, Department of Neuroscience, Italy. Project QIRT – 2002 – 157 (2002-2005). An RID project funded by the European Commission.

Gilliland FD, Li YF Saxon A, Diaz-Sanchez D. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomized, placebo-controlled crossover study. Lancet. 363(9403): 119-25.

Gibson P R et al. 1998. Social support on persons with self-reported sensitivity to chemicals. *Research in Nursing & Health 21: 103 – 115*

Gibson, P R. 2000. Multiple Chemical Sensitivity: A survival guide. New Harbinger Publications Inc, Oakland, Ca.

Grandjean, Philippe; David Bellinger, Åke Bergman, Sylvaine Cordier, George Davey-Smith, Brenda Eskenazi, David Gee, Kimberly Gray, Mark Hanson, Peter van den Hazel, Jerrold J. Heindel, Birger Heinzow, Irva Hertz-Picciotto, Howard Hu, Terry T-K Huang,Tina Kold Jensen, Philip J. Landrigan, I. Caroline McMillen, Katsuyuki Murata, Beate Ritz, Greet Schoeters, Niels Erik Skakkebæk, Staffan Skerfving and Pal Weihe. 2007. The Faroes Statement: Human Health Effects of Developmental exposure to chemicals in our environment. Basic & Clinical Pharmacology and Toxicology 102, 73-75.

Graveling, R A et al. 1999. A review of multiple chemical sensitivity. *Occupational and Environmental Medicine 56(2):73-85*

Hart S, Wang S, Nakamoto K, Wesselman C, Li Y and Zhong X. 2008. Genetic polymorphisms in cytochrome P450 oxidoreductase influence microsomal P450-catalyzed drug metabolism. Pharmacogenetics and Genomics. 18:11-24.

Hasegawa M, Ohtomo M, Mita H, Aklyama K. 2005. Clinical aspects of patients with MCS – from the standpoint of allergy. Aregui – Japanese Journal of Allergology. 54(5): 478-54.

Henderson J, Sherriff A, Farrow A, Ayres JG. 2007. Household chemicals, persistent wheezing and lung function: Effect modification by atopy?. Eur Respir J 2007 Oct

Hileman, B. 1991. Special Report Multiple chemical sensitivity. *Chemical & Engineering News 69(29):1 – 38*

Hillert L, Musabasic V, Berglund H, Ciumas C and Savic I. 2007 Odor processing in multiple chemical sensitivity. Human Brain Mapping. Vol 28(3) Mar 2007, 172-182.

IPCS. 2004. ICSC:0482 Sodium hypochlorite (solution active chlorine,10%). International Program on Chemical Safety.

Joffres, M R Et al. 2001. Environmental sensitivities: Prevalence of major symptoms in a referral center: The Nova Scotia Environmental Sensitivities Research Center Study. *Environmental Health Perspectives 109(2): 161 – 165.*

Kassirer, J and Sandiford, K. 2000. Socio-economic impacts of environmental illness in Canada. Environmental Illness Society of Canada.

Kelada SN, Eaton DL, Wang SS, Rothman NR and Khoury MJ. 2003. The role of genetic polymorphisms in environmental health. EHP 111(8): 1055-64.

Kezic S, Calkoen F, Wenker MAM, Jacobs John JL, and Verberk MM. Genetic polymorphisms of metabolic enzymes modifies the risk of chronic solvent-induced encephalopathy. Toxicology & Industrial Health. 22; 281-289.

Kezic S, Calkoen F, Wenker M, Jacobs J and Verberk M. 2006. Genetic polymorphisms of metbaolic enzymes modifies the risk of chronic solvent-induced encephalopathy. Toxicol Ind Health 22: 281-289.

Kilburne, K H. 1998. Chemical brain injury. New York, Van Nostrand/Reinhold/John Wiley & Sons)

Kilburn, K H. 2003. Why is chemical brain injury ignored. *Archives of Environmental Health 58(3): 132-134*

Kimata H. Effect of exposure to volatile organis compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity. International Journal Of Hygiene and Environmental Health. Vol 207(2); 2004, 159-163.

Klaassen C. 2008 Casserr & Doull's Toxicology The basic Science of Poisons. 7th Ed. McGraw Medical , NY

Kleeberger, S.R. 2003. Genetic aspects of susceptibility to air pollution. Eur. Respir. J Suppl. 40:52s-56s.

Lacour, M et al. 2005. Multiple chemical sensitivity (MCS) – suggestions for an extension of the US MCS-case definition. *Int.J.Hyg.Environ-Health 208: 141-151*

Levin, A S and Byers, VS. 1992. Multiple chemical sensitivities: A practicing clinicians point of view. *Toxicolgy and Industrial Health 8(4):95 – 105*

Lloyd, A R and Pender, H. 1992. The economic impact of chronic fatigue syndrome. *Medical Journal of Austalia. 157:559 – 601*

Lynch T and Price A. 2007. The effect of Cytochrome P450 metabolism on drug response, interactions, and adverse effects. American Family Physician. 76(3):391-396.

Lindeman B, Soderlund EJ and Dybing E. 2002. Factors contributing to interindividual variability to chemical toxicity. Tidsskrift for Den Norske Laegeforening 122 (6): 615-8 (Abstract Only)

Ling G, Wei Y, Ding X. 2007. Transcriptional regulation of CYP2A13 Expression in the respiratory tract by CCAAT?Enhancer Binding Protein and epigenetic modulation. Molecular Pharmacology 71:807-816.

MCS Referral and Resources. 2000. MCS Diagnostic codes for MCS. www.mcsrr.org/resources/diagnosticcodes.html

McCampbell, A. 2001. Multiple chemical sensitivities under siege. *Townsend Letters for Doctors and Patients. January 2001 pp.20 – 27.*

Mathers C, Vos T, Stephenson C. 1999 The Burden of Disease and Injury in Australia. ISBN 1-74024-019-7. AIHW Cat. No. PHE-17

Migliore, A et al. 2006. Casual association or related diseases? *Arch Env Occup Health 61(6):285 – 7.*

Millqvist, E et al. 2005. Changes in levels of nerve growth factor in nasal secretions after capsaicin inhalation in patients with airway symptoms from scents and chemicals. *Environmental Health Perspectives 113:849 – 852*

Millqvist, E. 2008. Mechanisms of increased airway sensitivity to occupational chemicals and odors. *Current Opinion in Allergy and Clinical Immunology 8:135 – 139.*

Mittelstaedt, M. 2006. Canada's chemical reaction. *Globe and Mail 27 May, 2006.* www.theglobeandmail.com

Mori K, Blackshear PE, Lobenhofer EK, Parker JS, Orzech DP, Roycroft JH, Walker KL, Johnson KA, Marsh TA, Irwin RD and Boorman GA. 2007. Hepatic transcript levels for genes coding for enzymes associated with xenobiotic metabolism are altered with age. Toxicol. Pathol. 35(2):242-251

Muir, T and Zegarac,M. 2001. Societal costs of exposure to toxic substances: Economic and health costs of four case studies that are candidates for environmental causation. *Environmental Health Perspectives 109: Suppl 6: 885 – 903*

Murakami T, Oyama T, Isse T, Ogawa M, Sugie T and Kawamoto T. 2007. International Comparison of Criteria for Evaluating Sensitization of PRTR-Designated Chemical Substances. Environmental Health and Preventative Medicine Vol 12, 56-65

Niedoszytko et al, 2006 Drug intolerance in patients with idiopathic environmental intolerance syndrome. Int J Clin Pract 2006, 60, 10, 1327-1329.

National Research Council, Board of Environmental Studies and Toxicology. 1987. *Workshop on Health Risks from Exposure to Common Indoor Household Products in Allergic or Chemically Diseased Persons*, July 1, 1987

Pall, M L. 2008. Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms.

Pollack J. 1998. A short review of the problems posed by xenobiotics in chemical mixtures and the role of mixed function oxidases. Int.J.Hyg.Environ 8:157-163.

Rea, W J. 1998. Chemical Sensitivity. Vols 1 – 4. CRC Press, Boca Raton

Read, D. 2002. Multiple Chemical Sensitivities. ERMA, NZ

Reinhartz, A. 2006. Cognitive impairment and olfactory panic from occupational exposure to VOCs. *Am.J.Ind.Med. 49:862-864.*

Rest, K M Ed. 1992. Advancing the understanding of Multiple Chemical Sensitivity. Proceedings of the Association of Occupational and Environmental Clinics (AOEC) Workshop on Multiple Chemical Sensitivity. *Toxicology & Industrial Health 8(4): 1-263*

Roberts, J. 2006. Toxin cancer link may lead to cost spiral. *The Australian 25 November 2006*

Rowat, S C. 1998. Integrated defense system overlaps as a disease model: with examples for multiple chemical sensitivity. *Environmental Health Perspectives 106, Suppl. 1:85-109, Feb 1998.*

Ryan, C M et al. 1988. Cacosmia and neurobehavioral dysfunction associated with occupational exposures to mixtures of organic solvents. *Am J Psychiatry 145(11); 1442-1445*
Saadat M. 2007. Influence of genetic polymorphisms of glutathione S-transferases T1 and M1 on serum lipid parameters. Saudi Med J. 28(11): 1645-7.

Saadat M. 2007. Influence of genetic polymorphisms of glutathione S-transferases T1 and M1 on serum lipid parameters. Saudi Med J. 28(11): 1645-7.

Saito, M et al. 2005. Symptom profile of MCS in actual life. *Psychosomatic medicine 67:318 – 325.* American psychosomatic Society.

Sears, M E. 2005. The medical perspective on environmental sensitivities. Canadian Human Rights Commission.

Seeber A, van Thriel C, Haumann K, Kiesswetter E, Blaszkewicz M and Golka K. 2002 Psychological reactions related to chemosensory irritation. International Archives of Occupational and Environmetnal Health. 75(5): 314-25

Shusterman, D and Murhpy, M. 2007. Seasonal allergy patients also bugged by non-allergic irritants. AAAI Meeting 2007. Abstract 551, presented Feb. 25.

Silberschmidt, M. 2005. Multiple chemical sensitivity, MCS. Environmental project no. 988 2005. Danish Ministry of the Environment, Environmental Protection Agency.

Starling, S. 2008 Create Flavours favour nut free nut flavours. Foodnavigator/Europe.com 3 Sept 2008

Suzuki et al 2004. The problems of multiple-chemical sensitivity patients in using medicinal drugs. J. of the Pharmaceutical Society of Japan.

Swain, A Soutter, V Loblay, R. 2004. Food allergies & intolerances. In Friendly Food p. 6 - 25. Allergy Unit. Royal Prince Alfred Hospital, Camperdown, NSW.

Tamer L, Caliko M, Ates NA, Yildirim H, Ercan B, Saritas E, Unlu A, Atik U. 2004. Glutatione-S-transferase gene polymorphisms (GSTT1, GSTM1, GSTP1) as increased risk factors for asthma. Respirology 9(4): 493-8.

University of Washington. 2008. Toxic chemicals found in common scented laundry products, air fresheners. www.physorg.com/news136035644.html

Van Thriel C, Haumann K, Kiesswetter E, Blaszkewicz M and Seeber A. 2002. Time courses of sensory irritations due to 2-butanone and ethyl benzene exposure: influences of self-reported multiple chemical sensitivity. Internationla Journal of Hygiene and Environmental Health. 204(5-6): 367-9.

Visser et al, 2008. Frontal-striatial-thalamic impairment in chronic solvent-induced encephalopathy. Annals of Neurology. Apr 2008

Walsky R and Obach R. 2004. Validated assays for human cytochrome P450 activities. Drug Metabolism and Disposition. 32(6): 647-660.

Waters MD, Selkirk JK and Olden K. 2003. The impact of new technologies on human population studies. Mutation Research. 544(2-3): 349-60.

Wiesmuller GA, Van Thriel C, Steup A, Bachert C, Clinic EN, Blaszkewicz M, Golka K, Kiesswetter and Seeber A. 2002 Nasal function in self reported chemically intolerant individuals. Arch Environ Health 57(3):247-54.

Wilhelmsson, B and Holstrom, M. 1992. Possible mechanisms of formaldehyde-induced discomfort in the upper airways. *Scand J Work Environ Health 1992 Dec;18(6):403-7*

Worksafe Standard. Exposure standards for atmospheric contaminants in the occupational environment. Guidance note and national exposure standards. 1995

Zibrowski EM and Robertson JMcD. 2006. Olfactory sensitivity in medial laboratory workers occupationally exposed to organic solvent mixtures. Occupational Medicine 56: 51-54.

APPENDIX 1

Relationship of MCS to other diseases
Some diseases and disorders that may overlap with MCS (MCS Referral & Resources)
Adrenal disorder (255)
Allergy (473)
Anemia, hemolytic (282, 283)
Arthritis, arthralgias (various)
Asthma (493, or 506.30 if from fumes)
Attention Deficit Disorder (314.0)
Autism, infantile (299.))
Brain, hypoxic injury (348.1)
Brucellosis (023)
Candida (112)
Chronic Fatigue Syndrome (780.71)
Depression, Chronic Manic, SAD (various)
Dermatitis, atopic (691.8)
Diabetes (250)
Encephalopathy, toxic (349.82)
Epilepsy (various seizure disorders)
Fibromyalgia (729.1)
Food intolerance (579.8)
Gastroenteritis & Colitis, toxic (558.2
Hay fever (477)
Heart disease (various)
Hemochromatosis (275.0 or 285.0 with refractory anemia)
Hypotension (various)
Hypothyroidism (244)
IgA deficiency (279)
Inflammatory bowel disease (558.9)
Irritable bowel syndrome (564)
Lyme disease (088.81)
Malabsorption (579)
Mast Cell Disease (202.6, 757,33)
Migraine (346)
Mitral valve prolapse (424.0)
Multiple sclerosis (340)
Myasthenia gravis (358.0)
Myofascial pain syndrome (729.1)
Neuromyasthenia (049.8)
Neurasthenia (049.8) Cardiac N. (306.2) Gastric N. (306.4)
Post viral N. (780.7)
Poisoning (9**.**) from external causes such as:

- **carbon monoxide (986.*, from E876.* or E868.*)**
- **pesticides (989.4 from E863.4)**

Pellagra (265.2)
Polyps, nasal (471.*)
Porphyrin disorder (277.1)
Raynaud's syndrome (443.0)
Reactive airways dysfunction syndrome (RADS)
Reactive upper airway dysfunction syndrome (RUDS)
Reactive intestinal dysfunction syndrome (RIDS)
Rhinitis, chronic (472.0) or allergic (477.9)
Scleroderma (710.1)
Sinusitis (various)
Sjogren's syndrome (710.2)
Systemic lupus Erythematosus (721.*)
Temperomandibular joint disorder (524.6)
Tinnitus (388)
Urticaria (708.*)
Vasculitis (various)
Vulvodynia (625.9)
Wilson's syndrome (275.1)

Signs, symptoms and ill-defined conditions
Chest pain (786.5 and others)
Dyspnea and respiratory Abn (786.0 and others)
Blurred vision (368.8)
Dizziness, vertigo, equilibrium disturbance (780.4)
Excess thirst (783.5)
Flushing (782.62)
Gait, abnormal (781.2)
Involuntary movements (781.0)
Memory disturbance (780.9)
Nausea and vomiting (787.0)
Pain, abdominal (789.0)
Rash (782.1)
Palpitations (785.1)
Skin sensations, abnormal (782.0)
Sleep disturbances (7809.5 and others including insomnia and restless leg syndrome)
Smell and taste disturbances (781.1)
Tachycardia (785.0)
Throat pain (784.1)
Urinary frequency (788.41)
Vestibular abnormalities (794.16)
Voice disturbances (784.4)

Disease and disorders that overlap with MCS (Lacour)
Cerebrovascular diseases
Degenerative disease of the CNS
Inflammatory disease of the CNS
Sleep apnoea
Narcolepsy
Chronic diseases of the bronchial system
Chronic lung disease
Chronic disease of the coronary vessels
Coronary insufficiency
Arterial hypotenia not necessarily responsive to medication
Insulin dependent diabetes mellitus
Obesity
Chronic hepatopathy
Chronic inflammatory bowel disease
Chronic kidney disease creatinine >1.5mg/dl
Hypothyroidism/hyperthyroidism
Adrenal insufficiency
Pituitary insufficiency
Cushings syndrome
Porphyrias
Anemia
Oncological disease
Collagen vascular disease
Primary systemic vasculitides
Other immunopathies
Chronic hepatitis viral infection
HIV infection
Lues
Chronic borrelia infection
Toxoplasmosis
TBC
Other chronic infections
Multiple arthralgias
Soft tissue rheumatic disorders or other rheumatic complaints
Food intolerance and associated abdominal complaints
Contact and environmental allergy and irritations e.g. erythema, urticaria, edema or other skin eruptions
Auditory complaints e.g. hyperacusia, Otitis media, tinnitus, Menniere's syndrome
Mucosal irritation or other respiratory complaints from common allergens, environmental allergens or irritants.
Dysethesia, muscle weakness or other complaints of the extremities
Cardiac arrhythmias, palpitations or other cardiac complaints,

Pain or other disturbances of the urogenital tract, infections, cycle associated complaints, kidney stones, appendicitis
Chronic fatigue syndrome
Fibromyalgia
(Lacour, M et al. 2005 p. 146/147)