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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

MCS Report
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Review of Multiple Chemical Sensitivity - Draft Report

Thank you for the opportunity to contribute to the latest Review of Multiple Chemical Sensitivity Draft Report.

The latest draft report at first appears to be a well balanced review of MCS, but on closer inspection it seems to continue to be biased toward a psychogenic model. The review places too much emphasis on viewing the MCS issue as purely physiological VS psychological. There are several physiological models all of which are plausible and given the acknowledged complexity of MCS and multisystem symptoms it is likely that all of these contribute some part to the overall syndrome. ASEHA finds the paper unacceptable unless the bias changes and the studies reviewed presented impartially. This view is also held by Prof Martin Pall, who is
1 Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University, who also contends that the author(s) of the Draft report make false unsupported undocumented claims

Although the report now points out that a lack of characterized physiological mode of action is insufficient proof of psychological activity we are left to conclude that the constant reference to psychogenic studies throughout the report reflects an intentional bias and remains in the document to influence readers towards a psychogenic etiology. This can only result in individuals who are desperately in need of medical care being trivialized and their genuine medical need not met (RACP, 2002.). Psychogenic treatment will not resolve health problems such as poisonings that are physical in origin. The report has not considered that there is controversy amongst psychiatrists about whether or not 'somatisation disorder' is a valid diagnosis (Crombez et al, 2009; Noyes, Stuart and Watson, 2008; Pridmore 2009)

NICNAS needs to explain to the people of Australia why it would consistently take this approach. This is a very serious matter that is deserving of a response.

While there were some improvements in the new Draft Report of the Review of MCS, it is still not rigorous science and this is supported by Prof. Martin Pall's comments in relation to the manner in which his work was misinterpreted. We endorse his comments and have included them as part of our response

In summary ASEHA has found a number of major errors in the way the draft report presents and we are concerned about the following issues:

- The report has not sufficiently researched the role of each of the proposed physiological modes of action that contribute to the multisystem disorder. For example, the review noted the lack of validated tests for Immunological deregulation but has missed an article co authored by Mitchell CS an author referenced in the Draft Report. The authors of this article "Hoover et al, 2003 Reproducibility of Immunological Tests Used to Assess Multiple Chemical Sensitivity Syndrome" evaluated certain immunological measurements to ascertain that they meet the minimal requirement for validity and highlight where inconsistencies can be minimised (Hoover et al, 2003).
- The use of the term IEI from peer reviewed work does not make it an official and acceptable term. IEI implies there is no known cause of reactions and is a term often used by detractors of MCS.
- Many statements in the report were not referenced and some references cited do not appear in the list of reference material.

- Testing issues - There are tests diagnostic of chemical sensitivity, some exist in the occupational area but are not available to civil society. We covered this in our last input and like most of our work it was ignored. For example, a relevant article by Gordon 2003 titled "Approaches to testing for food and chemical sensitivities" was missed. This article provides guidelines for a range of tests to assist in diagnosis.
- Genetics was poorly represented in the new draft, in particular those genes that determine the rate of metabolism of xenobiotics. The statistical significance of these is underrated. Evidence for genetic susceptibility is ignored (Pall M L, 2010)
- Chemical sensitivity caused by toxic chemical exposure – studies by eminent occupational physicians with experience in diagnosing and treating MCS e.g. Cullen, MIller, Ziem, Meggs, Kilburne were ignored. The work by Prof. Martin Pall which was submitted to the last round of the review was misrepresented. Martin Pall is a credible science professional.
- The latest authoritative publication on MCS that was set for toxicologists, regulators and others who have important roles dealing with the impact of toxicants on human health. The authors of this publication are convinced that MCS is a toxicological phenomenon. The chapter by Prof Martin Pall is important to the understanding of MCS (Pall ML, 2009).
- MCS is caused by chemical acting as toxicants – it cannot have a psychological etiology (Pall ML, 2010)
- Chemicals that cause MCS are not necessarily unrelated – this was also covered in our last submission and ignored. More recently Prof Martin Pall clarified the issue in his response to the new Draft Report
- The Review of MCS Draft Report appears more political than scientific (Pall ML, 2010)
- Evidence for genetic susceptibility is ignored in the Draft Report (Pall ML, 2010)
- MCS is not necessarily an olfactory phenomenon or a response to odours (Pall ML, 2010) The issue of odours/fumes is covered by existing NICNAS literature.
- Much relevant data was ignored in the draft report and the review cannot be scientific due to substantial flaws (Pall ML, 2010)
- Numerous, critical errors in fact and interpretation make the Draft Report a misrepresentation and a misleading document.
- NICNAS is happy to accept self reporting on psychogenic studies but not anywhere else. Most psychological studies are done by surveys with no science involved.
- In relation to diseases of chemical aetiology, this is a difficult issue as the general public are not educated with regard to the toxic nature of the products to which they are exposed. If they become ill from chemical exposure, any diagnosis is difficult as most GPs are not educated in chemical caused diseases and there are no diagnostic tools available to them. As a result individuals with chemical induced disease are not able to be diagnosed.
- The review has not included a GIT model – reactive intestinal dysfunction syndrome. The work done by the Allergy Clinic at the Prince Alfred Hospital in Sydney on phenolic sensitivities is in effect a gut model of multiple chemical sensitivity as many chemicals, both naturally occurring and manmade, are phenolic compounds. (Loblay, Swain., 1988)
- The discussion in the review on the use of dedicated treatment facilities (environmentally controlled units) left the overall impression that they were not of much use and this view would not provide the impetus to a government to initiate building of such a facility. These types of units are already in use in some medical facilities for allergy testing.

MCS is an important public health problem because of the potential health, disability and welfare costs. This is confirmed in the New Zealand report p. 25 which states that *'whatever the etiology it (MCS) is an important public health problem with potential for significant morbidity and economic loss as those with MCS are often disabled and some become totally disabled in terms of employment'* (Read, D. 2002). Other costs of MCS to the community include economic factors such as compensation to poisoned victims of chemicals and the cost to industry in lost sales and dangerous chemicals being withdrawn from the marketplace. Loss of employment may also be a consideration. However, the decrease in quality of life and inability to contribute to society also creates a significant cost. ASEHA believes the economic cost to industry and the economy could be overcome by a shift in fundamental thinking of industry and government in new policy that is focused on green chemistry. This should provide new opportunities for the research and development of chemicals of greatly reduced toxicity and the production of new chemicals and products that are less harmful to the health and wellbeing of the environment, employees and consumers.

Dorothy M Bowes (Mrs) and Dr Sharyn Martin, PhD for ASEHA Qld Inc April 14, 2010

Comments on the review
The comment in summary of revisions P2 on the reasons for not including papers describing neurological effects of pesticides and solvents that their properties and effects on the nervous system occur via well characterised exposure etc (p2) cannot be substantiated.

A Medline search would produce many articles on ongoing research on modes and mechanism involved in adverse effects of solvent and pesticides on neurological mechanisms as well as many other body systems. Ex. Parkinson's disease – recent research is finding evidence of a pesticide cause – the mechanism is far from finalised.

According to Kezic et al 2006 in an article on Chronic solvent induced encephalopathy (CSE) *"The biological mechanism by which organic solvents induce CNS impairment is not known" "Generally believed that the solvent itself is responsible for the acute effects, while reactive metabolic intermediates of the solvent are responsible for long term effects."* Kezic et al, 2006.

Browne et al, in 2006 published an article on the involvement of paraoxonase polymorphism on neuronal reactions in chronic, sub-threshold pesticide exposure. The article states that "*although the short term effects of acute OP poisoning understood to a great extent, the long term consequences of acute poisoning and chronic, sub threshold exposure are still not clear.*"

A review of Oxidative Stress and Neurotoxicity by Sayre et al, 2008 states that there is increasing awareness of ubiquitous role of oxidative stress in neurodegenerative disease states such as Alzheimer's, Parkinson's, and neurodegenerative and neuroinflammatory disorders. Oxidative stress is a common link and is described in detail in M Pall's research.

On Mutli symptoms, Low Levels and Mixture of chemicals
The use of the term '**low levels'** and the use of the term '**ambient levels'.** Ambient levels are more relevant to the much of discussion as we are now rarely exposed to one chemical at a time. Consumer products in the form of detergents, disinfectants, fragrances, cosmetics, toiletries abound in our lives, These are sometimes used and applied to the skin more than once per day (underarm deodorant, perfume, cosmetics – all often refreshed throughout the day) and can be highly volatile mixtures that can result in chemical sensitivity to more than one chemical i.e. multiple chemical sensitivity. In addition to consumer products, we are also exposed to multiple chemicals in ambient air, indoor air, from building materials/products, furnishings, carpets and other chemical laden products.

3

While the review was focusing on articles that directly mentioned MCS, a knowledge of research on low levels and mixtures of chemicals would have added to understanding some aspects of MCS that are contentious such as low levels and mixtures. For example, research on the effects of exposure to low levels of environmental chemicals is an ongoing process and while the emphasis of most of this work has not been directed at MCS, the findings and implications of this research is essential to understanding MCS. Recent research highlights the uncertainties in defining no dose levels and provides evidence of chemicals displaying a broad spectrum of activity at molecular and pathway levels (Judson et al, 2010; Woodruff et al, 2010).

As toxicity information is limited or nonexistent for thousands of chemicals that have high potential for significant human exposure Judson et al, 2010 evaluated the use of in vitro assays to understand the types of molecular and pathway perturbations caused by environmental chemicals and build models of in vitro toxicity. They tested 309 chemicals and their findings showed that chemicals are active across multiple human genes and pathways. The higher the number of low concentration in vitro pathway hits, the lower the observed lowest toxic dose in vivo. The most important conclusion they came to is how multifunctional chemicals can be, they can hit many molecular targets and perturb many pathways, meaning that a single molecular target is not going to explain the whole effect. (Judson et al, 2010).

An article by Woodruff et al, 2010 evaluates the use of upstream endpoints to improve risk assessment. They found that exposure to a chemical can influence disease processes through multiple modes of action and can also increase the risk of more than one overt effect. Disease status, susceptibility and chemical background (maternal during pregnancy as well as lifetime exposures) are critical to consider when assessing the implications of exposure as they can put a portion of the population in the dose range where small incremental exposures can increase the risk of downstream effects. These findings suggesting "that the assumption of a threshold dose level below which no deleterious effects occur may not apply..." (Woodruff et al, 2010)

Use of published, peer reviewed literature only
Using only published, peer reviewed literature on sensitivities and a symptoms is restrictive to the draft report and invalid. NICNAS continually contradicts itself on this point as many of the psychological studies used

will be dependent on anecdotal reports taken for surveys to prove or disprove viewpoints. Most psychological studies are surveys and are available in large volumes because they are cheap to produce and require little science. Similarly, general practitioners who are usually the first line of approach to the medical system depend on patient reporting of symptoms to identify problems and make a diagnosis. While the diagnosis may depend on blood work or other forms of diagnostic techniques to validate it, sometimes the diagnosis is made from the patient description of the symptoms. In the case of new and emerging diseases or those that are not well understood and do not have diagnostic criteria, a clinical diagnosis is often made i.e. a diagnosis made following a long period of observation. MCS is currently such a disease.

What chemicals trigger the symptoms of MCS?
The number and type of classes of chemicals documented by M. Pall was misreported and dealt with in Prof M Pall's Comments on the review March 5 2010. (Pall ML, 2010)

It is clear from the literature surveyed in the Draft Report with regard to which chemicals can trigger MCS that almost any chemical is likely to do this. Pall noted which chemicals were consistent with his hypothesis for his NO/ONOO theory for MCS. Theoretically chemicals that can initiate MCS should also be able to trigger symptoms and this would be consistent with known mechanisms of allergy/sensitisation where a reaction could occur on each subsequent exposure. Conversely, many individuals can be ill as a result of exposure to a chemical(s) and not know the illness is the result of chemical exposure. It can take a long time for individuals to work this out. Reactions will also be dependent on the unique biochemical and genetic susceptibility of the individual involved.

Problems sorting out which chemicals are involved in MCS are compounded further because of the volume of chemicals in our environment, and effects of mixtures of chemicals cannot be overlooked. Combinations of chemicals can have an enhanced effect. It would now be difficult to work out which chemicals are responsible for individual reactions.

MCS Definition
Various definitions have been postulated. We need one that is clear about what is happening and why e.g.

Multiple chemical sensitivity is a complex condition that involves a broad array of symptoms across multiple body organs following chemical exposures to chemically unrelated substances. Adverse reactions can occur to ambient levels of toxic chemicals(s) contained in air, food and water. The nature of these adverse reactions depends on the tissues(s) or organ(s) involved, the chemicals and pharmacologic nature of the substance(s) involved (i.e. duration of time, concentration, and virulence of exposure), the individual susceptibility of the exposed person i.e. nutrient state, genetic make up (gene/environment interaction), state of health, gender, age, and toxic load at the time of exposure), and the length of time and amount and variety of other body stressors (i.e. total load) and synergism at the time of reaction(s). (Rea, W J. 1992)

4

Does MCS have an ICD
Germany listed MCS in their ICD-10 which makes MCS an acceptable and appropriate disease classification - regardless of the NINCAS bias. The failure of Australia to recognise MCS in its Australian version of ICD-10 is due disinterest in Australia to recognise the problem. We have few relevant clinical specialists who know anything about MCS or display an interest. There is a group of specialists representing occupational physicians and Immunology/Clinical Allergy who are opposed to MCS and whose views are known by NICNAS and the community. MCS needs to be included in the Australian version of ICD classifications. It is absurd that CFS and FM have classification codes and MCS does not. In many cases the only difference between them is the specialty or the personal bias of the doctor making the diagnosis.

Lack of recognition of MCS should not stop Australian authorities from collecting data on MCS and from initiating some of its own studies. The 24.6% of adults identified in the NSW Adult Health Survey of 2002 represents a significant percentage of the population with no services and unmet need. Any government should be sensitive to numbers like that.

Is MCS related to other syndromes or disorders?
Long-term medical conditions reported in the Australian Health Survey of 2007-2008 that can co-exist with chemical sensitivity were arthritis (15%), asthma (10%), hay fever and allergic rhinitis (15%). The most commonly reported conditions among children and young adults that can co-exist with chemical sensitivity were respiratory conditions (17%) of children under 15 years and 28% of persons aged (15–24 years), with asthma being the most prevalent for children aged under 15 (10%) and hay fever and allergic rhinitis for those aged 15–24 (17%). Respiratory conditions were also common in older people 65% years and over (29%). The cost of asthma treatment to the community could be significantly reduced if the allergic/sensitivity basis were explored and some simple avoidance procedures put in place. Although the NHS collects information on all long term conditions, it has a particular focus on chronic diseases such as

arthritis and osteoporosis, asthma, cancer, diabetes, heart and circulatory conditions, mental health and obesity.

In many cases the causation or trigger of the these chronic diseases is not diagnosed and avoidance as a management strategy is not applied. This means the role of chemical sensitivity in chronic disease in Australia is not recognised or explored and yet this lack of public health strategy can place an undue strain on health services. Recent research indicates that arthritis, hypertension, cardiac disease, diabetes, cancer, osteoporosis, GIT disorders can all be related to environmental chemicals.

The cost of those diseases that are most associated with ageing could be dramatically reduced with allergen and chemical avoidance and a significant saving to the Australian health bill could be gained by managing allergy/chemical sensitivities as a public health measure. There is no mention in the AHS of the body burden of toxic chemicals that can cause or contribute to chronic ill health, yet a large body of data now exists to validate the body burden of environmental chemicals.

Allergy and chemical sensitivity was the subject of a survey by Meggs et al (1996). The objective of the study was to determine the self-reported prevalence of allergy and chemical sensitivity in a rural population in North Carolina, the frequency and type of symptoms for each condition and to determine demographic groups affected. They found an association between allergy and chemical sensitivity for 16.9% of the survey population. Meggs et al concluded that if the prevalence of sensitivity to chemical irritants is equivalent to that of allergy as was found in the study, then support for scientific investigation of chemical sensitivity is justified (Meggs WJ. Dunn KA, Bloch RM, Goodman PE, Davidoff AL. 1996). This study shows the relevance of allergy to MCS. Unfortunately, the allergy statistics are likely to be conservative as most individuals are never referred for specialist allergy testing and when asked if they have allergy or not many deny they suffer from allergy but often display classic symptoms of allergic complaints, or on questioning will volunteer that they have an allergic disease. The relationship between allergy and MCS needs to be explored.

Studies of GWS are pertinent to the discussion of MCS, in that like MCS, GWS is a chronic multisystem illness as a result of exposure to pesticides and chemicals (Gever, 2008 - Veteran's Affairs Advisory Panel; Golomb 2008). According to a Veterans Affairs (VA) advisory panel, Gulf War illness is caused by pyridostigmine bromide (pills taken by U.S. troops to neutralize the effects of nerve gas attacks) and by exposure to neurotoxic insecticides. Symptoms of GWS typically include a combination of memory and concentration problems, persistent headache, unexplained fatigue, and widespread pain, and can also include chronic digestive difficulties, respiratory symptoms, and skin rashes. Multiple insecticides and bug repellents were widely used during the war and subsequent studies have found dose-response effects with these agents, as well as neurocognitive deficits and neuroendocrine alterations in Gulf War veterans. According to the report "All available sources of evidence combine to support a consistent and compelling case that pesticide use during the Gulf War is causally associated with Gulf War illness".

5

3. Mechanisms and Modes of Action of MCS

While the mode of action in MCS is subject to discussion and there is not a widely accepted definition of the problem, multiple chemical sensitivity describes sensitivity to more than one chemical or multiple chemicals. This can occur at any exposure(s) and as we live in a sea of chemicals where mixtures are more the norm than the exception, sensitisations to more than one chemical (multiple sensitisations) can be expected.

Allergy and sensitisation are two mechanisms that are valid for MCS and must be left in the discussion on mechanisms. According to Klaassen et al, 1995, in Casarett and Doull's Toxicology, allergy and sensitivity are toxic responses. There are already models of MCS that cover initiation and triggering. They can include multiple substances and various organ systems can be involved. Chemical sensitivity is sensitisation to a substance. Multiple chemical sensitivity is chemical sensitisation to more than one substance. Similarly, pesticides and solvents which cause neurotoxic effects cannot be removed from the MCS model as many are known chemical allergens/sensitisers. MCS cannot be distinguished from other environmental intolerances. According to Kaassen et al, the terms allergy, sensitivity, hypersensitivity are all used to describe the same state. Intolerance is sometimes used in the same context.

Allergy vs Sensitisation – direct quote

'Chemical allergy is an immunologically mediated adverse reaction to a chemical resulting from previous sensitisation to that chemical or a structurally similar one. The term 'hypersensitivity' is most often used to describe this allergic state, but 'allergic reaction' and 'sensitisation reaction' are also used to describe this situation when preexposure of the chemical is required to produce the toxic effect, (Goldstein et al 1974; Loomis, 1978). Once sensitisation has occurred, allergic reactions may result from exposure to relatively very low doses of chemicals, and therefore population-based dose-response curves for allergic reactions have seldom been obtained. Because of this omission, some people assumed that allergic reactions are dose related. Thus they do not consider the allergic reaction to be a true toxic response. However, for a

given allergic individual, allergic reactions are dose-related. For example, it is well known that the allergic response to pollen is related to the concentration of pollen in the air. In addition, because the allergic response is an undesirable, adverse, deleterious effect, it obviously is also a toxic response. Sensitisation reactions are sometimes very severe and may be fatal.' (Klaassen C D, Amdur M O and Doull J. Eds. 1995. Chapter 2, Principles of Toxicology p. 16)

Examples of agents that induce allergic reactions

Compound	**Exposure**	**Type of reaction**
Formaldehyde	Disinfectants, cosmetics, deodorants, paper, dyes, photography, textiles, inks, wood products, resins	Type IV
Pthalic anhydrides	Saccharin production	Type I
B Subtilis	Detergents	Type I
Pesticides	Food, exterminators, farm workers	Type I, IV
Ethylenediamine	Plastic industry	Type I
Food additives (azo dyes, BHA, BHT)	Ingestion of processed foods	Type I
Antimicrobials (e.g. parabens, EDTA, mercurials)	Cosmetics, shampoos, creams, lotions	Type IV
Resins and plasticisers	Plastics, glues, nail lacquers, wood products, resins	Type I, IV
Platinum compounds	Metal refining	Type I
Nickel	Jewellery, garment fasteners	Type I, IV
Chromium	Leather products, printing	Type IV
Gold, mercury	Medicinal treatments, photography	Type II, III, IV
Beryllium	Manufacture of alloys	Type I, IV
Drugs (penicillin, quinidine, tetracycline)	Medicinal treatments	Type I, II, III, IV

Amdur, Doull and Klaasen, Eds. 1991 p. 303

Many individuals are allergic to multiple allergens e.g. mould, dust and pollen. Some individuals suffer from pollen-food allergy syndrome, or oral allergy syndrome, which can cause anaphylaxis and is an example of cross reactivity between pollens and foods e.g. ragweed pollen can cause reaction to melons, those with birch pollen allergy may react to apples. In the same way cross reactivity between chemicals may occur. In the phenolic model of food intolerance, various substances are implicated and cross reactivity occurs between foods high in phenolic compounds e.g. salicylates, benzoates, amines, terpenes and strong odours from fragrances (Loblay and Swain, 1986). Cross reactivity to strong odours can occur when some individuals are placed on a diet in which salicylates have been severely restricted. As a result, some individuals experience heightened sensitivity to odours and fumes which can aggravate symptoms (Loblay and Swain, 1986). Phenolic compounds in food can affect various organ systems and have been shown in studies to result in the following systemic symptoms: lethargy, headache, gastrointestinal, myalgia, cerebral, rhinitis, uriticaria, mouth ulcers, asthma/eczema (Loblay and Swain. 1986). While transient depression has been noted as part of a reaction to phenolic compounds in food and is sometimes severe enough to provoke suicidal thoughts, Loblay and Swain claim that '*delusions, hallucinations or thought disorders are not typical and require independent psychiatric assessment.'* (Loblay and Swain. 1986).

6

Pharmacological reactions to food can affect the gastrointestinal tract, respiratory tract, and central nervous system either alone or in any combination. Loblay and Swain (1986) list the most commonly recognisable syndromes as recurrent uriticaria and/or angioedema, migraine and irritable bowel syndrome. Symptoms across various organ systems include:

- respiratory tract symptoms include nasal congestion, sinusitis, pharyngeal irritation and asthma;
- GIT symptoms include mouth ulcers, nausea, abdominal cramps and diarrhea;
- CNS symptoms can be bizarre and result in patients being misdiagnosed as neurotic or hysterical if the diagnosis of food intolerance is not recognised. CNS symptoms include headache, lethargy and myalgia with impairment of memory and concentration, mental agitation, depression, dysphasia, visual disturbances, tinnitus, dizziness, autonomic disturbances, parasthesias, neuralgias. '*Symptoms may affect one or more organ systems simultaneously, or may change from one organ system to another with time'* Loblay & Swain, 1986).

Pharmacological reactions to foods should be included in the MCS Clinical Review as a GIT model of chemical sensitivity as should the RIDS theory – Reactive Intestinal Dysfunction Syndrome postulated by Lieberman and Craven (1998). A new 'reactive syndrome' was described that had similarities to the clinical syndromes Reactive Airway Dysfunction Syndrome (RADS) and Reactive Upper Airway Dysfunction Syndrome (RUDS). The authors propose that at least 5 neuropeptides are common to both the respiratory tract and digestive tract and the abnormal secretion of these neuropeptides, or the abnormal numbers of their receptors, play a role in what is perceived clinically as RADS, RUDS, and RIDS. The large surface

areas of the lungs and gut render them particularly vulnerable to their constant environmental exposures (Lieberman and Craven. 1998).

Proposed model for MCS

Definition ASEHA rejects the suggestion that modes of action such as chemical allergy and sensitisation are not part of MCS. We propose the following definition of MCS:

Multiple chemical sensitivity is a complex condition that involves a broad array of symptoms across multiple body organs following chemical exposures to chemically unrelated substances. Adverse reactions can occur to ambient levels of toxic chemicals(s) contained in air, food and water. The nature of these adverse reactions depends on the tissues(s) or organ(s) involved, the chemicals and pharmacologic nature of the substance(s) involved (i.e. duration of time, concentration, and virulence of exposure), the individual susceptibility of the exposed person i.e. nutrient state, genetic make up (gene/environment interaction), state of health, gender, age, and toxic load at the time of exposure), and the length of time and amount and variety of other body stressors (i.e. total load) and synergism at the time of reaction(s) (Rea, W J. 1992).

The discussion generally ignores the genetic component and the toxic nature of chemicals that can cause chemical sensitivity and trigger reactions. Dr Martin Pall in his response to the Draft Report dealt with this and we endorse his comments (Pall ML, 2010). There is no skin or GIT model and these should be represented.

More Specific Comments on mechanisms.

3.1.1 Immunological dysregulation
Abnormal findings have been documented in MCS and this does suggest an as yet identified immune dysfunction. The review states that it could not envisage immunological dysregulation changes could explain the symptomology of MCS yet Hoover et al, 2003 noted that "*hyperactivity of the immune system by environmental stimuli could explain both the diversity of symptoms in MCS and the very low levels of chemical exposures with which these symptoms have been associated*". He then goes on to qualify this statement.

7 In any discussion on MCS it is relevant to review the evidence of ill health due to environmental chemical exposure. Hererth et al, 2009 analysed immune markers of inflammatory reactions in children as a result of indoor renovation. They found that floor covering induced the strongest inflammatory reactions and IL-8 and MCP-1 were the most suitable markers. (Hererth et al, 2008).

3.1.2 Respiratory disorder
Allergy can also cause multi system dysfunction – anaphylaxis and can occur following **inhalation** or **ingestion** of the offending substance (allergen). It is therefore presumptuous to suggest that respiratory changes cannot account for sensitivity to non-inhaled chemicals.

3.1.6 Altered xenobiotic metabolism
It was not sufficiently acknowledge that the study of toxicology at the genomic level has potential but is still in the early stages. Prof. Martin Pall has covered the inadequacies in the genetics of this review in his Comments on the scientific review March 5 2010 and will not be repeated here (Pall ML, 2010).

Comments on other aspects.

P32 "*The chemical sensitivity in this rat line is not related to precipitating xenobiotic chemical exposures*." Where is the evidence for this statement? I am unaware of any such research.

P33 Author inadvertently made an observation, the significance of which was missed.
On Mechanisms: P33 "*A confounding factor in implicating alterations in xenobiotic metabolism in MCS is that the genes for which certain polymorphisms are overrepresented in MCS groups also have known functions not just in the metabolism of certain xenobiotics but also in the metabolism of normal endogenous products. For example, the paraoxonase gene family has ubiquitous antioxidant and anti-inflammatory roles and appears to be central to a range of cardiovascular, metabolic, neurological and infectious illnesses* (Camps et al., 2009)."

On Investigations: P48 "*A confounding factor in implicating alterations in xenobiotic metabolism in MCS is that the genes for which certain polymorphisms are overrepresented in MCS groups also have known functions not just in the metabolism of certain xenobiotics but also in the metabolism of normal endogenous mediators.*" If the (xenobiotic) polymorphisms overrepresented in MCS have functions in xenobiotic metabolism, as well as endogenous mediators/products that are central to a range of cardiovascular,

metabolic, neurological illnesses, then this may provide a link to the idea of multisystem harm. If these polymorphisms can modify responses to xenobiotics they may also disturb the production of those endogenous mediators/products involved in systems for which people with MCS display symptoms. This means that there is some evidence that a multisystem/multisymptoms disease can perhaps be mediated through genetic variation in detoxification genes.

3.2.2 DBPC Challenge studies

We have raised the issue of placebo controlled studies previously and such studies need to be discounted in the MCS draft as the placebo substances can be suspect and this flaws the studies. Placebo studies are fraught with difficulties. It would be difficult to find a substance that was an acceptable placebo for an entire group of individuals with a moderate level of allergy and/or MCS i.e. one substance that would not affect any individual in the study in any way at all. Anything substance is a potential problem and the study respondents would need to be tested for the placebo to ensure that it is truly inert to all involved.

Researchers that use volatiles as placebos either do not know what they are doing when they design studies or they have used the volatile to deliberately bias the study findings.

Some of the problems the review found with the physiological models were – subjective & self reported no validated diagnostic tests and does not explain the multiple symptoms. The psychological model does not provide a testable mechanism or defined mode of action. The testing is subjective and self reported (on the part of the patient), as is the interpretation of the results by the researcher. The demonstration of regions of the brain that show altered activity in MCS compared to 'normal's' demonstrates a physiological response that does not in itself validate a psychological diagnosis.

Placebo, DB challenges studies etc cannot 'correct' for the fact that

a) the majority of people normal or otherwise, are likely to have a body burden of toxins,
b) chemical contaminants are ubiquitous in all buildings
c) The ubiquitous nature of solvents means that most people are exposure to solvents within the course of a normal day. Ch 24 Casserret and Doull P982 . and
d) "Most solvent exposures involve a **mixture of chemicals**, rather than a single compound. Our knowledge of the toxicity of solvent **mixtures is rudimentary** relative to the toxicology of individual solvents" p 983

8

These facts mean that there are too many confounding factors to make sense of any results unless they were performed in an Environmentally Controlled Unit. For an assessment/comparison to be valid, all participants would need to detox in an Environmentally Controlled Unit to obtain baseline levels prior to testing AND/OR assessing the level of chemicals in all participants prior to testing.

For these reason ASEHA is opposed to double blind placebo controlled studies and rejects those already in place as unsuitable studies for inclusion in the Draft Report.

Other Comments

p40 "Also reflecting a range of views on modes of action, the heterogeneity of symptoms (Section 2.2) and chemical triggers (Section 2.3) reported in MCS has raised questions as to whether MCS is a single nosological entity with a single mode of action." Within the context of nosology defined as 'the science of the classification of diseases' a Nosological entity is nonsensical.

P41 This whole section is out of context to the title of the section and does not provide any relevant discussion on the direction of further research except to make an unsubstantiated comment. First paragraph p 41, I question whether this paragraph can be substantiated.

P42 The first paragraph is another nonsensical paragraph not referenced, that seems to be used for the purpose on attempting to explain 'dose response' on a psychogenic model.

P53 last paragraph on MCS case definition and prevalence. Again a paragraph where a reference is used to conclude a psychogenic cause. It should be becoming apparent that the "commitment to a diagnosis" occurs as they are still chemically sensitive, just as someone with diabetes remains "committed" to their diagnosis.

Para "It is debatable..." p55 is a biased discussion

P57 2nd paragraph on clinical research needs. No references for the statement and again used to purport a psychogenic origin.

P60 last para section 4.2 Again out of context and opportunity to push psychogenic diagnosis

Conclusion

By focusing the discussion in Section 4.6 Clinical Research Needs (p57-58) on challenge and DBPC studies that have many flaws, and reducing the issue to one of physiological VS psychological, the review shows that it is not serious about presenting a fair and unbiased document. There was no mention of any of the other physiological diagnostic processes that are showing promise in elucidating the mechanism/s of MCS.

There is a lot at stake here:

- for those with MCS chronic ill health, social isolation, little to no income and little to no medical, legal, economic or social assistance;
- for those regulating chemicals and their use, a finding that the current procedures are insufficient to protect the whole population and a rethink of chemical regulation is required; and
- for those producing/using chemicals restrictions that would have an economic impact on their business.

We can appreciate that it may be difficult for a Department that monitors and regulates chemicals and their use, to envisage that their protocols and processes are not as safe as they thought and therefore wonder whether an impartial report could be produced under such conditions.

Individuals with allergic disease also experience attitude problems when seeking health care or when hospitalisation is necessary. If a lot of allergies are present it can be difficult for medical staff in a health care facility to work with. Several ASEHA members have personal experiences that allergies can be ignored, in spite of medical documentation to support their existence i.e. we are not believed. This puts vulnerable individuals in an untenable situation – people can die. A similar situation exists for those with chemical sensitivity who display multiple medication sensitivity or both allergy and medication sensitivities. The higher the numbers of allergies/sensitivities the less they are likely to be believed and the higher the likelihood that they will suffer an adverse reaction. A good example of medication sensitivity is phenolic sensitivity which takes in aspirin allergy and MOST medications. Unfortunately, it is not an uncommon situation for medical staff to ignore even documented allergy and lives are at risk. Uncertainties that impact adversely on the lives of those with chemical sensitivities need to be resolved.

Toxicology is a relatively new science and like other branches of the sciences is not sufficiently developed to provide answers to many questions. New branches of science are constantly opening up and this review should be ongoing as eventually one of these new branches of science is likely to isolate mechanisms responsible for causing and triggering MCS. However, having said that we already know some of those mechanisms and NICNAS needs to come out of denial to allow MCS to be included in health and welfare planning and service delivery. In particular issues of access to goods and services need to be pursued immediately as the continued failure by government (Correspondence Attorney General) to allow this is a breach of the basic human rights of every person with environmental sensitivities, in particular those with MCS and severe allergy. In the meantime, NICNAS is purposely and unnecessarily narrowing the scope of the MCS Clinical Review to avoid taking action that might lead to regulation to protect civil society from the dangers of chemicals in the environment and consumer products that have the potential to poison them and damage lives. Such action would cost jobs unless major R & D was undertaken to develop and produce green chemicals that are less harmful to the environment and human health. Government needs to be at the forefront of this development as it would be a significant saving in health care costs, save lives and the planet.

There are so many things wrong with the Draft Report that we did not have time in the specified period to address them all. We also did not have access to all of the references or time to check the NICNAS interpretation of them. The Draft Report in its current form can serve no purpose other than to prolong the suffering of those with chemical sensitivity and increase the chance of more people becoming chemically sensitive.

RECOMMENDATION

The Review of Multiple Chemical Sensitivity Report should be a document that is scientifically credible and socially responsible. It should be an authoritative document that can be quoted with certainty and used to inform scientists, regulators, government, the chemical industry, the medical profession and civil society. It should not be biased, misrepresented and flawed as is currently the case as it falls very short of being a rigorous 'scientific review'. NICNAS need to rectify this.

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