Comments of the pre-release copy of the “Scientific Review of Multiple Chemical Sensitivity” by Martin L. Pall

Dear Drs.

I am very appreciative of the review that you are attempting to put together – it is a daunting task, and I say that as one who has just completed such a wide ranging review (see attached). I know the challenges is doing this and no doubt those challenges are vastly multiplied when many people are involved. So I hope that my criticisms will be taken in the light of the fact that I very much appreciate what you are trying to do and the difficulty accomplishing your task. I also hope that you will read carefully my own review to examine my reasoning, in a number of areas, coming to conclusions that differ from those in your draft document.

My own review was requested by a group of toxicologists and although I am not certain at this point that it will be published, having just submitted it, I am very appreciative of the recognition of being asked to write the first requested publication in a toxicology series to be written on MCS. This clearly shows that what has become known as the NO/ONOO- cycle mechanism has generated some considerable respect among toxicologists. A similar conclusion can be reached by the fact that a book by Dr. Hans-Ulrich Hill, a German toxicologist, and two of his colleagues was recently published in German on MCS (Hill: Multiple Chemikalien Sensibilität (MCS)), and was largely focused on the NO/ONOO- cycle fusion model of that illness. I am the keynote speaker at this December’s meeting the the European Environmental Medicine Association and their entire two-day meeting is dominated by the NO/ONOO- cycle, an amazing amount of recognition. I will end up that trip, which includes talks in five countries, at the European Parliament in Strassbourg, the only non-European asked to participate in a special session on environmental medicine.

Having worked intensively for four and a half months on the attached MCS toxicological review, I am not going to try to reiterate the many points found therein. Most of my response to your draft document is to simply ask you to read carefully my own MCS toxicology review, and where appropriate specific citations cited in it. You will find that it differs from your own draft in quite a number of important points and I would hope you will carefully consider those differences.

What I am going to do here is to discuss the single most important of those differences and then go through your draft document briefly pointing out some others.

In my judgment, THE most important set of work to be published on MCS and the past decade, is the set of genetic studies of susceptibility to MCS, the studies of Haley and coworkers (1999), McKeown-Eyssen and her colleagues (2004) and Schnakenberg and his colleagues (2007). These collectively show that five genes, all having important roles in the metabolism of chemicals otherwise implicated in the initiation of MCS cases, all have statistically significant roles in determining susceptibility to MCS. These provide convincing evidence, in my judgment, that chemicals act as toxicants in the initiation of MCS and these chemicals must be in their most active form in order to have the highest activity in such initiation. So, for example, in the PON1 gene polymorphism, those forms that have lower activity in metabolizing organophosphorus toxicants are associated with higher incidence and prevalence of MCS. The same pattern is true for two genes that help determine the rate of glutathione-dependent detoxification and for a cytochrome P450 gene that in this case produces increased apparent activity in initiating cases of MCS. Your own treatment of this topic only discusses two genes and only considers it in the context of liver-dependent detoxification although this type of metabolism occurs at some level in many tissues of the body. The PON1 encoded enzyme, paraoxonase, circulates in the blood and is active essentially all over the body. PON1 has been reported to determine susceptibility to Alzheimer's, ALS, autism and other brain-related diseases so it should not be surprising that it does so in MCS as well. The role of PON1 in MCS is supported not only by the Haley et al and McKeown-Eyssen studies but also by two British studies of somewhat less apparent relevance by Mackness et al (all of these are cited my own review). Since the Nobel prize winning classic work of Beadle and Tatum in the 1940's, genetics has been the most powerful approach towards determining biological mechanism and the three main studies of MCS susceptibility must be viewed as very strong evidence for chemicals acting as toxicants in the initiation of cases of MCS. All of these effects must be viewed as environment X gene interactions and the influence of alleles of these genes will differ, therefore, with the chemical exposures that impact different populations.

You correctly point out that the effect of the NAT2 alleles in the McKeown-Eyssen study and that in the Schakenberg study were both statistically significant but were in opposite directions. So does that

mean that they are both flawed? Actually it does not. There are a whole series of carcinogenesis studies of NAT2 alleles showing opposite effects in different studies and these were ascribed to different chemical exposures in different populations (see for example Thier et al, Int J Hyg Environ Health 2003; 206:149; Furet et al, Therapie 2002; 57:427; Hein, Toxicol Lett 2000; 112-113;349). While low acetylation has been most often associated with increased carcinogenesis, there are examples of the opposite pattern (Chen et al, Carcinogenesis 2001; 22:1993) and it has been reported that fast acetylators are more active in producing meat-derived metabolites that lead to DNA breakage (Kiss et al, Eur J Cancer Prev 2000; 9:429). There are even studies showing that specific polymorphic forms of the NAT2 enzyme can be more active in acetylating some substrates but not others (Hein et al, Int J Cancer 2006; 119:1208), so their effects on acetylation different compounds may be expected to differ from one another. It follows that given the fact that the chemical exposure in the Canadian population studied in McKeown-Eyssen may differ in chemical exposure from that of the German population studied by Schnakenberg, there is no necessary conflict in the interpretation of the two studies.

In conclusion we have three large studies implicating together five genes influencing the metabolism of chemicals otherwise implicated in the initiation of MCS. This provides compelling evidence, in my judgment, that chemicals act as toxicants in the initiation of cases of MCS.

Other specific comments:

The page numbers here are numbered starting with the cover page of my copy, since the the pages did not seem to be numbered.

p. 6, Executive Summary: There are several claims that I will challenge and are challenged in my review. Specifically the claim that its etiology (pardon my American spellings) is ill-defined; that <u>any level of exposure</u> is reported to elicit similar severity of symptoms; and that this involves a response to odors.

Fiedler and Kipen (Ann NY Acad Sci 2001; 933,24) show in Figs 4 and 5 of their study, fairly reproducible dose-response studies in MCS patients that are substantially left-shift as compared with those of normal controls, suggesting these patients are on the order of 1000 times more sensitive than normals. So your statement of any exposure eliciting similar severity of response is inconsistent with their

data and as far as I can determine, completely unsupported. I think it is fair to state that we need much more study of this area, but your statement should be deleted, in my view.

There is no evidence whatsoever that the olfactory receptors have any essential role in MCS and there is considerable evidence against this view. In contrast, we have substantial evidence implicating other receptors (see my review). We have evidence that people with no sense of smell (anosmics) are still chemically sensitive. That people blocked nasal passages, either because of nasal congestion or the use of a nose clip are still chemically sensitive. And we have Millqvist's repeated studies showing sensitive response to capsaicin, a compound with no odor and a compound where the response is produced from the upper respiratory tract, not from the nasal epithelia. You yourself cited one of the critical studies from Hillert et al (2007) which shows that hyperresponsiveness of the olfactory system is <u>not</u> involved in MCS. I know that there are many claims that MCS is a response to odors. But if you look at the evidence, you will see that these claims are wrong and your document should reflect the science. MCS is a response to chemicals, many of which have odors, not a response to odors.

Again you state that (p.8) "Challenge tests suggest that it is the smell or odor of a triggering event, rather than any pharmacological or toxicological properties per se that elicit MCS symptoms", providing no documentation for this claim. I think this is incorrect. We have now eight different classes of chemicals that can initiate cases of MCS and most if not all of these elicit symptoms in those who are already chemically sensitive. All eight of these are known to produce increases in NMDA activity and in animal models there is evidence that members of each of these eight classes can have their toxic responses greatly lowered by using an NMDA antagonist, showing that increased NMDA activity is required for the toxic responses. Since these act indirectly along different pathways to produce an NMDA response, it is that response that is in common, not the initial target of the chemical. You owe it to the MCS sufferers and their health care providers to examine this literature carefully, in my no doubt biased judgment.

The diagnosis of MCS is currently based mainly on self-reported symptoms, as you suggest. However, one of the things that I found in reviewing the literature for my toxicology review, is that there are a whole series of objectively measurable responses to low level chemical exposure in which MCS patients characteristically differ from those of controls. At least three of these can easily be used in clinical settings

to objectively confirm the diagnosis of MCS. One or more of these should be established as specific biomarker tests for MCS, something that should be relatively easy to do and something that will dramatically change the entire view of the medical community to MCS. It is essential, in my view, that research funding be provided to accomplish this critical task.

On page 11, you state that "chronic toxic encephalopathy, CFS, RADS, FM irritable bowel syndrome or Gulf War syndrome are induced or exacerbated by ambient chemical triggers" (citing Staudenmayer et al, 2003b). While it is true that CFS and FM cases without comorbid MCS do not respond in general to chemical exposures (there is a literature reporting, however, that organophosphorus pesticides can initiate cases of CFS, but I suspect that these will have comorbid MCS). But that statement for RADS, irritable bowel syndrome and Gulf War syndrome is simply inconsistent with the scientific literature. Look up the literature on RADS – you will see that it is both initiated by chemical exposure and produces sensivity to chemicals in the lungs. In fact there is a literature showing that many people with asthma are chemically sensitive and that many cases of occupational asthma appear to be initiated by chemical exposure. There are five studies of Gulf War syndrome veterans showing that they have MCS symptoms (cited in my review). And while chemical sensitivity in irritable bowel syndrome needs further study, it has been clear for quite a while now that IBS patients have elevated TRPV1 (vanilloid) responsiveness and will, therefore, have increased chemical responsiveness to chemicals that act as TRPV1 agonists (some of this is discussed in the Pall and Anderson 2004 paper).

I have gone through the Staudenmayer et al papers carefully, especially their 2003a paper. They have repeatedly and egregiously failed to objectively assess the scientific literature in such blatant ways that this goes way beyond any difference of opinion or perpective. This is documented in my toxicology review and in Chapter 13 of my book "Explaining 'Unexplained Illnesses'". It is my strongly held opinion that if you wish to use Staudenmayer as a possible source for relationships relating to MCS, you need to independently assess the primary literature to determine whether there is any truth whatsoever to his claims.

p. 15. My understanding is that the German insertion of MCS in their ICD code is, in fact, official recognition, but in any case, you need to document any statement on this with something other than a personal communication.

p. 15, bottom quotes a statement from Rust that there is “no clinical or laboratory evidence of an underlying pathological process ...” . I realize that this is a quote but especially as it is a personal communication and is completely undocumented, it provides support for a position that is perhaps, the least supportable statement in your scientific review. I realize that psychogenic advocates have made grandiose claims to this effect, but there are dozens of studies that contradict this view. Rust is right (top of p. 16) that there is a wide spectrum of intolerance/irritation in the general population and indeed within those diagnosed as having MCS as well. But if that were sufficient reason to prevent a disease from being recognized in the ICD code, probably half of the diseases so recognized would not be there.

p. 16, center. There are epidemiological studies showing that those with higher chemical exposure have increased MCS prevalence and of course, the genetics we discussed also documents this (see my review). But it is fair to state that we need much more epidemiological study on this. It should also be pointed out that industries have often prevented such studies, apparently fearing that elevated MCS prevalences among their workers might open them to legal liability.

I have spent a lot of time working on this and will jump to the comments you have made on what is now called the NO/ONOO- cycle fusion model of MCS (p. 23). I am, of course, especially appreciative of an opportunity to comment on this.

Let me first correct a few specific things. The role of viral and bacterial infections is to initiate cases of CFS and FM, not MCS. This may be important because while such infections can increase nitric oxide levels, they do not act via the NMDA receptors to do so. As far as I can determine, all agents that initiate cases of MCS and elicit symptoms in those already chemically sensitive can act, in most cases indirectly, to increase NMDA activity. And this helps explain how they can initiate neural sensitization in the brain, given the known role of NMDA receptors in that process.

There are a couple of things in the last paragraph of this section of your review that need some comment. Malathione is an organophosphorus pesticide and acts like the other organophosphorus and carbamate pesticides as an acetylcholinesterase inhibitor. So this needs to be corrected.

You are correct in indicating that the long chain alcohols were shown by Peoples and Ren (2002) to be inhibitors of the NMDA receptors. Having said that, the key issue with regard to these various chemicals is whether the net effect, both direct and indirect leads to increased NMDA activity. To my knowledge, we don't have any data on the effect long chain alcohols NMDA activity *in vivo*, so it is not possible to infer from Peoples and Ren what the net effect of these compounds may be. However, there is another solvent that has been similarly reported to inhibit NMDA activity, toluene. Yet when toluene was tested in vivo in the rat, it was shown to stimulate NMDA activity, not inhibit (Bale et al, Toxicol Sci 2007; 98:159). And toluene, acting as a pure solvent, and unlike the long chain alcohols, has been shown to initiate an animal model of MCS. So at this point, unless there is some data that I am not familiar with, the Peoples and Ren study does not provide any evidence allowing us to infer that there are some chemicals that initiate MCS that do not act to increase NMDA activity and that paper is therefore, irrelevant to the issue at hand.

One other issue raised in that last paragraph is how do multiorgan systems generate chemical sensitivity symptoms? I have argued that each of these is generated locally and the peripheral sensitivity responses are, therefore, not produced by neural sensitization in the brain. They may, however, involve some of the same mechanisms involved in chemically initiated central sensitization including the NO/ONOO- and may also involve some additional mechanisms including neurogenic inflammation, as argued by Meggs and also mast cell activation/degranulation.

With regard to the second to the last paragraph in this section, I assume what you mean by de novo is evidence for predicted aspects of the NO/ONOO- cycle fusion model that was not known when I wrote up my 2002 FASEB Journal paper. There are a number of such de novo types of evidence – the breakdown of the blood brain barrier in MCS patients reported by Kuklinski and in an animal model reported by Abou-Donia and his colleagues. Inflammatory responses to low level chemical exposure in MCS patients but not in normal or abnormal controls, reported by Kimata. There are clinical observations that the NMDA antagonist, dextromethorphan, is blocks or greatly lowers responses to chemicals in MCS patients and Grace Ziem has clinical observations that the nitric oxide scavenger hydroxocobalamin also lowers chemical reactions in the chemically sensitive. We also have clinical trial data on the effectiveness of multiple NMDA antagonists in the related illness, fibromyalgia and of hydroxocobalamin in the related illness chronic fatigue syndrome. You are wrong about there

being NMDA antagonist or nitric oxide scavenger studies in MCS, but it is fair to state that we need vastly more study on these issues.

There is animal model data arguing for important roles for nitric oxide, peroxynitrite, NMDA receptors, inflammatory responses including inflammatory cytokines, neural sensitization mechanisms, TRPV1 (vanilloid) receptor role and several additional aspects of the NO/ONOO- cycle fusion model. Your review completely ignores all animal model data of MCS, but animal models are often essential to establish biological mechanisms.

There are also a series of objectively measurable MCS-specific responses to low level chemical exposure that confirm a number of important aspects of the NO/ONOO- cycle fusion model as responses triggered specifically by chemical exposure in MCS patients. These include a sequence of responses, starting with TRPV1 stimulation leading in turn to increased NMDA activity; inflammatory responses to chemical exposure; and responses strongly suggesting neural sensitization mechanisms. One of the more interesting of these, the Hillert et al, 2007 study, which was largely dismissed in your own draft review, is consistent with a neural sensitization response in the limbic system, triggered by chemicals acting via the TRPV1 (vanilloid) receptor.

I would urge you to look over carefully my own review and if you have any questions about it, I will try to respond quickly to them: martin_pall@wsu.edu

I would add that I will be doing a lot of traveling over the next three months being scheduled to give talks in nine locations in six countries, so I can't guarantee a rapid response but will try to accomodate.

Martin L. Pall