

# **Proposal to study the prevalence of multiple chemical sensitivity on a large occupational population: Results of a preliminary field study.**

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## **Goals:**

- 1. Design a Proposal to conduct a prevalence study in a large industrial population for Multiple Chemical Sensitivity.**
- 2. To perform a field study to permit development of a measurement instrument to be used in the prevalence study.**
- 3. To compare attributes in two populations of cases purporting to have multiple chemical sensitivity (MCS), those clinically meeting Cullen's criteria and those meeting the more liberal Agency for Toxic Substances and Disease Registry (ATSDR) conference criteria, and a control group.**

## **Introduction**

**Multiple chemical sensitivity is an emerging clinical problem that is having an increasing impact on the medical and occupational communities. This entity is also called a variety of other names such as 20th Century disease, Chemical Intolerance, Chemical AIDS, and Total Allergy Syndrome. Some investigators include Gulf War Syndrome, Chronic fatigue syndrome, and Sick Building Syndrome. MCS is a unique entity in that it is the only self-reported entity without an objective "gold standard" that has significantly influenced federal regulations (American for Disability Act and HUD rulings), workers compensation and civil court decisions. Legislation has even been introduced in Congress, promoted by grassroots advocacy groups, to recognize MCS as a consequence of indoor air pollution. ( S. 1629, H.R. 5373) <sup>1</sup>**

## **Epidemiology**

**There has been an absence of sound epidemiological studies in regards to this entity. MCS prevalence is unknown and only a few studies have attempted to study this important area. <sup>2,3</sup> Cullen noted that the apparent rate of cases of MCS referred to**

his clinic at Yale over a 53 month period was low (49 cases meeting his strict criteria) between 1986 and 1991. Of these only 16% occurred outside of a work setting. Among the patients whose exposure was job related, 19 (46%) came from the service industry, predominately from education and health care. Seventeen cases (34%) were coded as indoor air pollution. He confirms that MCS patients are generally younger than other patients with occupational or environmental health problems and are predominately female.<sup>4</sup> Mooser describes similar findings regarding sex and age as does Ross.<sup>5,6</sup> Two recent studies of interest are those of Bell<sup>7</sup> and Kipen.<sup>8</sup> Bell studied 637 subjects from a University setting and found that 60% self reported that they react adversely to 5 or more chemicals. Kipen developed an instrument for field studies and found that in 705 subjects self reporting on adverse effects to 122 common substances, MCS patients and asthmatics responded significantly more often than controls. Higher total scores were reported by female patients. Kipen states that no information exists on the prevalence of chemical sensitivity and he did not actually perform a prevalence study. Tollisen reviews the need for a specific case definition with measurable outcomes performed according to the criteria of Bradford Hill and following a double blind randomized protocol.<sup>9,10</sup>

Prevalence studies are typically cross-sectional studies and general conclusions regarding populations are not possible. Nevertheless such studies serve an important role in basic epidemiological investigation of an illness or phenomenon.

Bell Helicopter, the proposed contractor organization, has had increasing workers' compensation claims filed regarding injuries purporting to result from toxic exposures and resulting in MCS. Often such patients are referred to clinical ecologists who reinforce their concerns. These physicians espouse that MCS is a common entity, often under-diagnosed and under-treated. Unfortunately the diagnostic and treatment modalities utilized by the clinical ecologists are unproved and controversial.

As Bell Helicopter has an inventory of over 1500 chemicals compounds and many occur as complex mixtures, and is proactive regarding their worker's safety, this is an appropriate organization upon which to perform the prevalence study. The proposal for the cross-sectional prevalence study is shown in Appendix 1. The focus of this report is to develop the prevalence questionnaire and describe the field trial results.

### Definition

The most widely accepted definition for epidemiological purposes is that of Cullen. "Multiple Chemical Sensitivity is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems occurring in response to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No simple widely accepted test of physiologic function can be shown to correlate with the symptoms. " <sup>11</sup>

### Methodology

Population n=167 non randomized subjects with 85 controls, 28 cases meeting Cullen's criteria after clinical verification and 54 cases who perceive themselves as moderately to severe impaired regarding activities of daily living related to MCS, but do not meet Cullen's criteria. 276 coded questionnaires were administered with 181 returned. Of these, 7 Cases failed the exclusionary criteria clinically. One was deemed psychotic; three had documented occupational illnesses (two cases, occupational asthma and one, carbon monoxide encephalopathy- late); one, systemic lupus with polysystemic involvement; one multiple sclerosis and one with vascular headaches and extrinsic asthma. Nine additional cases were deleted due to incomplete responses. All cases and controls were evaluated by a clinical team consisting of a certified allergist, a certified internist, an occupational physician and a certified psychologist to verify inclusionary and exclusionary criteria. Clinical records of all cases were examined. Twenty eight subjects met Cullen's criteria in regard to a documentable chemical exposure. Cases reporting that they have MCS that did not meet the ATSDR or Cullen's criteria were excluded and not placed as cases or in the control group. (n=6) Controls were patients with chronic illness but

who denied adverse reactivity to chemicals. They included allergic problems, arthritis, diabetics and arteriosclerotic medical problems.

Case-control design Due to non-random design, all cases and controls were tested under the same conditions and evaluated clinically. Inclusionary and exclusionary criteria were followed and applied to both groups.

Questionnaire design The Nominal Self Perceptive Environmental Questionnaire (NSPEE) was designed by a medical clinician with expertise in this field as well as 2 psychologists. The questionnaire, as administered, consisted of 240 dichotomous questions and a 23 question demographic form. The demographics included Cullen's criteria and also directly asked the question of whether the subject felt that chemicals made them ill. Those answering positive graded the severity of response based on activities of daily living. Controls had no adverse response to chemicals. A mild case did not have interference with activities of daily living. Such cases were felt to be common in our society, did not represent a distinct disease and were placed in the control group. Moderate cases had some interference with such activities but did not need to make major changes in their lifestyle to provide reasonable accommodation. The severe group as self reported had interference with their activities of daily living and were required to make significant alterations in their lifestyles and occupational or home environment. (see attached demographics and questionnaire) The 240 variable responses were then programmed to consist of 13 scales similar in design to the Minnesota Multiphasic Personality Inventory (MMPI). The scales measured: (a) perceived chemical involvement, (b) somatic concerns, (c) anxiety, (d) depression, (e) defensiveness, (f) allergy, (g) medical illnesses, (h) control/avoidance behavior, (i) rumination, (j) suspiciousness, (k) neurocognitive dysfunction, (l) chemical exposure and (m) validity. The subjects also completed a Profile of Mood states, Millon Clinical Multiaxial Inventory, revised, Beck Inventory and a Clinical Analysis Questionnaire.

#### Statistical methods:

Questionnaire development: Content reliability studies: (a) Reproducibility test-retest 41 subjects repeated after 30 days. test of proportions. (b) Proportion of response to all variables of all subjects were analyzed: Those variable answered > 95% and < 5% were deleted. (c) Cronbach's alpha testing, commonly used in behavioral data analysis, was used to eliminate redundant questions and increase accuracy (content validity).

#### External Instruments and NSPEE subscales

Comparison with external tests were performed to increase reliability. Statistically the null hypothesis was utilized.

### Hypothesis

H<sub>0</sub>: No true difference exists between the cases and the control.

H<sub>1</sub>: A difference exists between the cases and the control group.

Alpha=.05

The internal subset scales were correlated with four validated external instruments utilizing Pearson's correlation coefficient. Two of these external tests are reported in this paper, Beck Depression Inventory and Profile of Mood States; ANOVA and t tests were utilized when measuring differences within the study groups with continuous variables of the internal or external scales; Pearson's  $\chi^2$  test was utilized for grouping variable with nominal variables in the questionnaire. All results were performed on Statistica (Tulsa, OK.) and reviewed by the department of business computer information systems, University of North Texas.

## Results

### Questionnaire design

Response analysis of 240 questions revealed that 4 questions were answered more than 95% or less than 5% of the time. These were deleted and resulted in deletion of the Sp scale. Inter-item analysis utilizing Cronbach's alpha for all subscales was determined and permitted deletion of 59 additional questions. (Table 1) Two additional scales were deleted due to poor correlation utilizing Cronbach's alpha. (Rm and Df)

Test-retest validation was performed with tests of proportions resulting in all z values being below .581, p value = .281. The null hypothesis that the test-retest are equal is statistically supported. This indicates good correlation in paired test response.

### External instruments and NSPEE subscales

Correlation coefficient between the Beck and Profile of Mood test  $r = .81$ .

*Beck Depression Inventory response mean and standard deviation* for each of the three study groups: The Cullen positive  $\bar{x} = 17.57$   $s = + 9.57$ ; Cullen negative  $\bar{x} = 15.76$   $s = + 9.68$ ; controls  $\bar{x} = 8.12$   $s = + 7.04$ . ANOVA of these three means:  $F =$

14.21076,  $p = .000003$  indicating rejection of  $H_0$ . There was a statistical difference between the groups when controls were considered. In evaluating differences between the Cullen + and Cullen - groups,  $t = .659$ ,  $df = 49$ ,  $p = .5123$ .  $H_0$  was supported. There was no statistical difference between the Cullen + and Cullen - group.

*Profile of Mood States results (means and standard deviation) for the three study groups:* Cullen positive  $x = 51.86$   $s = + 9.86$ ; Cullen negative  $x = 49.43$   $s = + 8.22$ ; Controls  $x = 44.22$   $s = + 6.34$ . ANOVA of the three groups:  $f = 9.678$ ,  $p = .00013$ .  $H_0$  is rejected when controls are included. In evaluating differences between Cullen + and Cullen - cases,  $t = .9544$   $df = 49$ ,  $p = .3445$ .  $H_0$  is supported. Again there was no statistical difference between the Cullen + and Cullen - group.

#### Demographics

Comparisons were made with the study group including controls, and excluding controls (Cullen + and Cullen - cases) for selective variables. (age, sex, education, perception of classical allergic symptoms, prior or current psychological treatment.) Chi square testing was utilized for measurement of differences of the three groups. The findings were: Sex  $x^2 = 11.836$ ,  $p = .0026$ ; Education  $x^2 = 6.425$ ,  $p = .099$  ( $df = 4$ ); Allergies  $x^2 = 37.559$ ,  $p = .000$ ; Psychological  $x^2 = 24.503$ ,  $p = .000$ ; Age  $x^2 = 14.198$ ,  $p = .288$  ( $df = 12$ ). In evaluating the Cullen positive and the Cullen negative group for differences the findings are: Sex  $x^2 = 2.961$ ,  $p = .085$ ; Education  $x^2 = 2.526$ ,  $p = .639$  ( $df = 4$ ); Allergies  $x^2 = 2.666$ ,  $p = .102$ ; Psychological  $x^2 = 2.721$ ,  $p = .386$ ; Age  $x^2 = 4.144$ ,  $p = .657$ .

In comparing all three groups, statistical differences were noted between sex, allergic problems and psychological treatments (between the control group and the cases) but there was no statistical differences on these five variables with the Cullen + and Cullen - groups.

#### Subscales :

Three subscales were eliminated due to nondiscrimination on item reliability testing or low Cronbach's alpha values. The ten remaining subscales were

compared with the study group. The results are shown in Table 2. All scales statistically differentiated the controls from the cases except the validity scale, as would be expected, and the Oi scale. This “other involvement” scale compared the subjects with a variety of other medical conditions and was used to search data but will be deleted from the final questionnaire.

Selective subscales were also correlated with the Beck and Profile of Mood States. The results are: The D subscale correlated satisfactorily Pearson  $r = .70$ , with the POMS and  $.73$  with the Beck. The An scale correlated moderately with the POMS  $r = .65$  and  $.66$  with the Beck. The Nc scale correlated  $r = .60$  with the POMS and  $.65$  the Beck and the So scale  $r = .57$  with the POMS and  $.62$  with the Beck. In comparing psychological instrument scales such correlations are acceptable. There was no significant correlation between any of the other scales. This would be expected as the primary instruments being compared externally measure depression ( Beck)and both depression and anxiety (POMS).

### Discussion

Methodological strengths and weaknesses should be noted. A case-control study from a selected population, as opposed to using a random sampling, inherently has a problem with sampling bias. Recall bias is probably present to some extent as patients who report multiple chemical sensitive have a higher prevalence of illness behavior including hopelessness, anxiety, depression, obsession and fear than controls.<sup>12,13,14</sup> This was dealt with by the realization that some degree of adversity to chemicals is common in the population. This was emphasized by Bell’s study. I felt that it was important to classify those individuals that react adversely to petroleum products, but not to the extent that their personal or occupational relationships are interfered with by such exposures, as belonging to the control group. They can be considered mild MCS problems in a relative sense. Thus those cases chosen here are *significantly* affected by chemicals at least as they perceive the problem. A second problem with case-control studies is the low power of the study in permitting population extrapolation. Often a clear cut cause and effect relationship is not

present. Case-control studies have the advantage of speed, low-cost, the ability to study rare diseases, and the ability to study many attributes all at once.<sup>15</sup> Due to relatively small sample size of this survey population, the predominance of the female gender, the disproportionate amount of Caucasians, and the fact that all groups were more highly educated than the standard population, this study is only applicable to this population. The study did permit inter-item testing, item deletion, and other measures to improve the questionnaire.

There is a further problem with small sample size of one of the case groups. Twenty eight of 82 cases were verified as meeting Cullen's criteria. (Cullen +). This is a marginal amount required to perform adequate statistical evaluations. Such cases however are uncommon and in most medical practices, rare.

This study was designed to utilize a self-reporting questionnaire. There are inherent problems with this type of reporting system.<sup>17</sup> Birdsong recommends that when using questionnaires to estimate worksite exposures, the conservative choice is an extreme-groups design.<sup>18</sup> That is why we chose to place the milder multiple chemical cases with the controls. In conducting a large cross-sectional prevalence study, however, this type of questionnaire must be considered for practical and economical reasons.

Due to the non-random study group, specific exclusionary and inclusionary criteria were established and followed. Clinical examination, as well as retrospective analysis of their record information, was performed to increase accuracy in verifying these cases in the absence of a true gold standard.

In reviewing the literature on multiple chemical sensitivity, it is apparent that there is a general agreement in regard to the definition for epidemiological purposes but a disagreement in regards to who should be included (inclusionary criteria). Cullen has proposed stringent criteria for epidemiological purposes to reduce the amount of malingerers.<sup>19</sup> These are reviewed in Table 3. His criteria have been criticized as being too restrictive and not applicable to the actual clinical setting. The primary point of criticism applies to the fact that a specific and measurable chemical

must be present to initiate this disorder in Cullen's criteria. Clinicians have found many cases fitting the description of MCS with exposure to either a non-measured mixture of chemical fumes (as in remodeling) or no significant demonstrable previous exposure,

A more liberal set of criteria was proposed by the committee of the Proceedings of the Association of Occupational and Environmental Clinics Workshop of Multiple Chemical Sensitivity.<sup>20</sup> This proceeding was cosponsored by the Agency for Toxic Substances and Disease Registry (ATSDR) and is referred here as the ATSDR criteria. These criteria are listed in Table 4. Nethercott et. al. conducted a study to identify clinical diagnostic criteria that experts regarded as major for categorizing patients with MCS. They performed a cross-sectional survey of 148 practitioners with an interest in the condition. Similar criteria to that resulting from the ATSDR conference were reported as a result of this survey.<sup>21</sup>

Exclusionary criteria are also important with a non randomized study. Those chosen for this study and followed by the clinicians are shown in Table 5.

There has not been any published reports comparing attributes, differences or associations between individuals meeting Cullen's criteria and those who meet the ATSDR criteria. Our cases were collected over a 21 month period from designated doctor workers compensation referral, self referral and physician referral and included both types of cases. It was appropriate that some preliminary comparisons be made. The clinicians also investigated all cases self reporting that they complied with Cullen's criteria and revised final statistics based on true positives. They excluded those who originally self reported a distinct and measurable initial exposure but upon further investigation proved that this could not be verified. Fifty subjects originally reported a positive Cullen criteria on the demographic form. This was reduced to 28 after the clinical investigation. The Cullen negative population (ATSDR criteria positive) increased from 34 to 54 after clinical correlation. A control population was added from patients that came into several clinics for traditional allergic diseases or medical problems such as osteoarthritis, hypertension,

counseling, coronary artery disease or chronic obstructive airways disease. Their allergic complaints were more prevalent than that found in a general population (33 out of 85 controls or 38%) since they were, in part, obtained from an allergist practice. Allergies would be expected to be found in approximately 20% of a control group.

### Controversy

Chemical sensitivity was first described in modern literature by Theron Randolph, an instructor in Allergy at Northwestern University Medical School at the time. In a series of abstracts published in the *Journal of Laboratory and Clinical Medicine* beginning in 1954, he shared his clinical observations that allergic type reactions were seen to industrial solvents and liquid fuels, mosquito abatement fogs and mists, motor exhaust, indoor utility gas and oil fumes, chemical additives of foods and drugs, synthetic drugs and cosmetics.<sup>22,23,24,25,26,27</sup> Randolph was a great empiricist publishing in the days where abstracts and clinical cases were popular. Some of his observations and discoveries have been verified such as asthma and urticaria related to certain food additives. In those days, Hans Selye's theory of adaptation and maladaptation (General Stress Theory)<sup>28</sup> was popular. Randolph applied this theory to a subset of individuals who he felt could not adapt to the total stressor load genetically.

Following the discovery of specific atopic antibody, IgE by Johansson<sup>29</sup> and Ishizaka and Ishizaka<sup>30</sup> in 1960, traditional allergists gradually became advocates of a more scientific methodology using response to reagin (IgE), specific to a variety of antigens, as the cornerstone of their "science" of allergy. Randolph felt that prior to this discovery, the allergist was more interested in exploring adverse environmental interrelationships independent of the "mechanism" of action. He employed the original definition of allergy coined by Von Pirquet referring simply to a state of altered reactivity.<sup>31</sup> In recent years Selner has addressed this issue in his presidential speech to the American College of Allergy, Asthma and Immunology in which he emphasized the need for allergists to acquire new concepts and skills to

appreciate adverse environmental interrelationship independent of their traditional restricted domain of interest. He states that public pressure, regulatory concerns and competition fiscally by the “clinical ecologists” necessitate this change. Thus far, unfortunately the official allergic community has not picked up this challenge. In recent years however the occupational physician has incorporated these concepts in his area of interest. The recent name change in his college to the American College of Occupational and Environmental Medicine exemplifies this. MCS along with the closely related sick building syndrome are some of the “baggage” that we, as scientists, must inherent.

As time progressed, physicians began to notice an increasing number of MCS patients. Frustration grew as these patients were not helped by traditional methods. Physicians did what they always do when they don’t understand something, they referred these cases to psychiatrists. The clinical ecologist movement, an offshoot of Randolph’s original ideas, became more vocal and developed increasingly controversial methods of helping these patients. These methods include sauna techniques based upon finding very low levels of chemicals in the patients blood and lowering these levels with depurational methods, the establishment of provocation and neutralization methods to cancel out the adverse idiosyncratic reactions. Usually a variety of substances unrelated to the historic triggering agent was investigated based on the total load concept. Antioxidants, avoidance and education were utilized.<sup>32</sup> Sometimes an illness model was promoted by these physicians and primary and secondary psychological issues were not appreciated or accounted for. Criticism grew of the ecological methods which did not conform to the tenants of immunological, medical or toxicological methodology.<sup>33,34,35,36,37,38</sup> and a series of more rigid studies was undertaken to discredit the ecologists.<sup>39,40,41</sup> Position statements followed<sup>42,43,44,45,46</sup> and the field of clinical ecology became more isolated from the rest of the medical community.

In recent years, there are increasing clinical reports of individuals who allege to have adverse reactions to chemicals such as solvents, pesticides, detergents,

paints, cosmetics, carpeting, formaldehyde, methyl tertiary butyl ether and a variety of volatile organic mixtures. These individuals are alleged by the clinical ecologist to have become sensitized in an induction stage, then responding in a subjective polysymptomatic fashion when re-exposed to lower doses (many multiples below TLV or PEL values). This is termed triggering and the phenomenon may spread to foods, pollens, molds and other chemicals whose classes are unrelated to that found in the original exposure. A variety of complaints are reported from MCS patients. These include vertigo, neurocognitive dysfunction including panic attacks, anxiety, depression, short term memory dysfunction, obsessive compulsive behavior, depression, mixed or vascular type cephalgia, fibromyalgia activation, arthritis or arthralgia, gastrointestinal pain, nausea, vomiting, extreme fatigue and panic episodes, chest pain, bronchospasm, visual blurring and even transient blindness, paresthesias, burning pain of a non dermatome type, rhinitis/sinusitis, pseudoseizures, and syncope. It is my observation that an individual patient with this disorder will have a specific pattern of reactivity usually with three or four symptoms. Sometimes one type of chemical will induce one pattern of symptoms and another class of chemicals, such as perfume, will induce a different response. Like chronic fatigue syndrome and fibromyalgia, with whom MCS shares many features,<sup>47</sup> this entity often impacts the workplace.

One reason for the popularity of this ecologic theory is the lack of training of physicians in medical toxicology as well as traditional allergy in the medical school curriculum. Often the ecologist is seen as the only individual to refer such an individual to. In addition there is a large segment of the general public that is disenchanting with the standard medical community. This is likely to get worse instead of better with managed care with its dehumanizing effect. This theory fits in with many lay individual's idea that their chronic problems are the responsibility of others (government laxity, greed from the chemical manufacturers and food processors) and not something that they control or are responsible for. Finally, there is increasing public awareness of the inherent dangers of chemicals in our

environment. Toxic spills, train derailments with evacuations, and toxic dump sites near schools all bring media coverage to perpetuate these concerns. Added together it is likely that the current underground environmental movement (clinical ecology) will someday emerge as a significant movement in shaping the opinion of politics and medicine. Multiple chemical sensitivity is an issue that will not go away and patients with this entity must be separated from the controversial issues of theories, mechanisms and treatments that surround clinical ecology. Until we know better, the worse thing that we can do is deny their symptomatology exists and support them physically and psychologically with prudent medical treatment.

Claims by clinical ecologists lack scientific credibility, in that no precise objective test can validate their illness, no pathophysiological mechanism has been documented, and the literature published by the advocates of this theory has largely been anecdotal, lacks controls, and poor statistical methodology.

*Allergy and reactivity:* It is true that some individuals react to a variety of agents including some chemical compounds as an allergy. These cases demonstrate a reproducible, well defined immunological response, a secondary inflammatory response that is well demonstrated and altered end organ physiology. All of these are absent in cases of MCS. Those cases that were misclassified on self reporting as MCS but in fact were an allergy ( diisocyanate asthma) were not included in the controls or the MCS cases.

There is a tendency in the literature to confuse allergy with immunodeficiency. Atopy or allergy results in the overproduction of IgE in 90% of genetically predisposed subjects. Chemicals, internally, are not known to play an important role in true allergy with only a few exceptions regulated by OSHA. These are Captafol, a fungicide, Cobalt, Isophorone diisocyanate, Phenthiazine, Phenyl glycidyl ether, plicatic acid, subtilisins, and Toluene-2,4 diisocyanates.

It is noted that allergic individuals are more prone to overreact to fumes and gases as an irritant due to underlying inflammatory processes in the mucosa. Also neurocognitive changes are present in allergic individuals independent of multiple

chemical sensitivity.<sup>48</sup> The statistics demonstrated in this study are consistent with those of others who have shown a higher incidence of allergic disease in MCS patients than in controls.

#### *Theories of mechanisms:*

There are three prevailing theories of the probable mechanism for multiple chemical sensitivity: The immunologic, the toxicologic and the psychological/neurologic.

#### *The immunologic theory*

This theory is the most common one proposed by the ecologists. It is their opinion that various chemicals can gradually accumulate in the adipose and other tissue and lead to impairment of detoxification mechanisms. A resultant state of auto-intoxication is produced by an abnormal “total load”. This load is contributed by food polypeptides due to altered intestinal permeability, is amplified by unknown genetic factors and in many cases traditional allergies. They use the concept of total load to reduce the burden for foods, inhalants and other factors on the immune system. This is, in fact, the cornerstone of their treatment other than education to permit more skillful avoidance of the offending substances. They also acknowledge that stress, in general, co-contributes to this overview. This combination of factors results in altered immunological function. Usually this represents altered T cell ratios, alterations in natural killer cell numbers or activity, more activation of the T lymphocytes and mild to moderate anergy on skin testing.<sup>49,50</sup> Secondary alterations in Candida intestinal levels, due to reduced cell mediated surveillance, then augment the disorder. Such studies have not been reproduced by other investigators.

<sup>51,52,53,54,55,56</sup> Though interesting, there is no biological plausibility for this theory. If these dynamics are occurring, our current state of medical knowledge is unable to verify this hypothesis. Interestingly, Rea, who has published four volumes describing investigation of 20,000 MCS patients, has stated that he does not know the cause of MCS.<sup>57</sup>

The immune (“allergic”) system concept has been published earlier by ecologists and reviewed by Meggs who offers an overview of immunological

mechanisms and a speculative but possible immunological orchestration related to environmental exposures.<sup>58</sup> Production of IgG antibodies, a high incidence of associated atopy, production of autoimmunity and more recently immunotoxic modulation of the immune system by environmental chemicals have all been proposed.<sup>59</sup> This field has intensified interest with the publication of numerous materials pertaining generically to the subjects of immunotoxicology, neurotoxicology, and psychoneuroimmunology.<sup>60,61,62,63</sup> A review of the literature related to immune aberrations found in MCS indicates bias, and poor or no patient selection criteria. Many of the theories such as haptenic formation are unproved thus far. Methodological problems may have accounted for low interleukin-1 values.<sup>64</sup> A small number of case series describe elevated immunoglobulins, anti-chemical antibodies, autoantibodies, elevated levels of TA1-positive cells and various changes in lymphocyte subsets.<sup>65,66,67</sup> None of these shows a consistent trend of immunologic abnormality. Some suffer from a lack of a control group and small sample size.<sup>68,69</sup>

Confounding variables were not appropriately stressed in any of the immunological studies reviewed. These include nutritional deficits. This is important as malnutrition is the most common cause of immunodeficiency worldwide and selective nutrient deficiencies can influence portions of the immune response. Many of these MCS cases are on severe restricted diets, often self imposed, or may have recently fasted.

It has not been verified that individuals suffering from MCS have a higher prevalence of autoimmune diseases (not just low level autoantibodies.) Nor has it been proven that such patients have a higher rate of infection, cancer or other disorders known to be linked to immune regulatory problems.

The role of the nervous system and its link to the immune system is gradually becoming known and is a likely confounder. I suspect that any group of subjects with a high amount of psychological diseases verses controls will also have a higher amount of minor immune abnormalities on the basis of psychoneuroimmunological factors alone.

#### *Toxicologic theory*

Efforts to determine the amount of “toxic buildup” proposed by the ecologist have not been successful. Generally these physicians measure panels of substances in parts per billion in the blood with only intra-laboratory controls to compare to. There is no general population study for blood test ‘normals’ for most chemicals. The fact that in most cases of MCS, there is no precise measurable chemical agent causing the clinical response, is relevant to toxicologic criticism of the ecologists hypothesis. In addition, there is no demonstrable dose response curve. Is this condition related to a genetic predisposition? Perhaps, but this is not necessarily a defect in detoxification mechanisms. It is known that genetic polymorphism occurs in the population and in fact adverse effects can be found with slow acetylators. Debrisoquine evaluations might be interesting in this subset of individuals. Receptor sensitivity relationships in the central nervous system or periphery have been discussed but no concrete differences have yet been documented. No specific defect has been located in regard to absorption, distribution, pharmacokinetics, biodegradation, or elimination. Most respectable toxicologists have not “lowered “ themselves to even conduct studies on these subjects and their discussions of the subject are descriptive or critical opinions only.

<sup>70,71</sup> Most would state the following about this phenomenon, as defined in a manner similar to Cullen’s:

- MCS does not allow specificity or consistency for biological reactions to the effects of chemicals.
- MCS does not provide a testable hypothesis.
- MCS is contradictory to the fundamental principles of toxicology
- The current testing procedures are so subjective that they are useless.
- There is no evidence that the responses attributed to MCS are any other than would occur by chance.
- The MCS literature attaches an emotional bias to chemicals.

Toxicologists thus examining this subject understand that it does fulfill the nine factors widely used by epidemiologists as cited by Sir Austin Bradford Hill <sup>72</sup> and summarized for use in experimental animals by Barceloux.<sup>73</sup> Note that Cullen’s criteria specifically

states that that no test of organ system function is to be positive. The concept of adaptation, so that a chemical may or may not have an effect, is foreign to the toxicologist. Most of the literature on MCS as cited by Waddell consists of uncontrolled studies and case reports.<sup>74</sup> In King's study, frequently used by the ecologists to defend their position, there was no dose response established and the subjects correctly identified the placebo (insufficient blinding).<sup>75</sup>

#### *Psychological/neurological theory*

The last theory is expressed by the opponents of the concept of MCS. It is the psychological theory. There are several schools of thought to account for this disorder. The behavioral conditioning theory stipulates that an unconditioned stimulus such as a chemical can produce an unconditioned response. Repeated exposures lead to a conditioned response resulting in this syndrome.<sup>76,77</sup> Schottenfeld theorized that amplification of somatic symptoms plays a part in the genesis of MCS.<sup>78</sup> Black believes that it is basically a non-entity and should be termed a phenomenon rather than a disease or syndrome.<sup>79</sup> Generally most studies indicate an increased incidence of depression, anxiety and somatoform disorders though none has proven that these disorders cause the problem. The clinical impression that a majority of subjects with MCS had significant premorbid psychopathology has been reported in a controlled study but this has not been verified by additional rigorously designed scientific studies.<sup>80</sup> The conclusion that there is an increased incidence of obsessive compulsion, mood disorders, and somatoform disorders that preceded MCS has also not been conclusively verified though our study also suggests their presence.<sup>81</sup> The field of psychiatry, as well as the DSM IV, deals with descriptive, qualitative, subjective data. A common error of psychiatric studies is to hold a more vigorous standard for medical criteria than for psychiatric criteria with MCS or similar problems, such as chronic fatigue syndrome and fibromyalgia. There is a possibility that the MCS created a decompensation of a latent premorbid psychological type rather than the opposite. Davidoff and Fogarty are the first to make a critical review of the numerous papers written regarding the psychological origins of MCS.<sup>82</sup> Ten articles met their criteria. Only

one study reviewed was found to have less than eight methodological errors.

<sup>83,84,85,86,87,88,89,90,91</sup> Black's article compared index subjects to first degree relatives of psychiatrically normal subjects using standard psychiatric tests. Analysis reveals a questionable sample source, an unspecified status of the MCS index patients, asthmatic and other local irritative phenomenon were not excluded properly, and no selection criteria for index subjects were established. Self reporting data is relied upon (as it is in 5 out of 10 of the studies reviewed by Davidoff). Uncontrolled investigator bias was found in Black's study but also in all 10 studies. Unjustifiable conclusions were reached in 8 out of 10 studies. Inadequate controls were present in all 10 studies. Insufficient information regarding methodology was present in 6 out of 10 studies. Doty's article had the least methodological errors but had a sample size that was too small and a questionable sample source. This does not exclude a psychological basis for MCS. It only indicates the need for psychiatrists to follow appropriate methodology in conducting studies on this illness,

### Summary

Though no current theory of multiple chemical sensitivity can account for the phenomenon, there is no doubt that increasing numbers of patients are having a constellation of complaints affiliated with low level exposure to various chemical agents. The present study provided a clinically validated questionnaire, in the absence of a gold standard, to conduct future investigations regarding multiple chemical sensitivity. The different characteristics of the control group and the cases, which either qualified for Cullen's criteria or not, were also reviewed. There was no appreciable difference between the cases but there was between the controls and the cases. More basic research regarding the prevalence, incidence, natural history, treatment, pathophysiology and psychopathology of multiple chemical sensitivity is required.

### Appendix 1

## Research Proposal

### Organization and Personnel

**Principle investigator: Stevan Cordas D.O. Occupational Consultants of Texas.**

**2921 Brown Trail Bedford Texas 76021**

**Co-investigators:**

- 1. Nancy Didrikson Ph.D. 543 Bedford-Eules Road Hurst Texas 76035**
- 2. Joseph Doster Ph.D. University of North Texas, Department of Behavioral Medicine. Denton Texas 76455.**
- 3. Kellie Keeling Ph.D. (Cand.) University of North Texas, Department of Business Computer Information Systems Denton Texas 76455**
- 4. Industrial Hygiene division at Bell Helicopter.**

**Organization where Study is proposed to be conducted: Bell Helicopter, military division. Hurst Texas 76020**

**Sufficient commitment shall be made at the beginning of this study to ensure its timely and proper completion. Agreements in regard to the importance and cooperative spirit in relationship to this project will be undertaken with union officials, management and a work team consisting of representatives of management, the labor union, industrial hygienists, shift supervisors, and workers. The work team concept permits the most efficient implementation of the questionnaire including a grassroots method of educating the workforce, dissemination of the questionnaire, and motivation to return it. Collection will be coordinated by the industrial hygiene personnel that have full access to all parts of the plant-site and then picked up by the senior investigator.**

**Time frame anticipated: 30 days for union, management and work team organization, education and approval; 30 days for dissemination of questionnaire; 30 days for collection with a specific cutoff date; 14 days for optical scanning and statistical analysis; 45 days for preparation of manuscript describing the project. The results are projected to be published in peer reviewed medical literature. (total 150 days)**

Ownership of the manuscript will be that of the principal investigator.

Management of the organization will examine the draft before submission for publication and offer constructive changes.

Population information a stratified random sample of 1000 employees exposed to solvent fumes and 1000 salaried personnel not generally exposed, from a total work population of 11,750 workers will be utilized. We anticipate a response rate of over 50%.

Written consent shall be provided which includes the purpose of the study, the name and phone number of the contact investigator to answer any questions and confidentiality information, since their name or badge number will not be used in our coding method. In addition the consent will contain information about how to complete the questionnaire and the requested return time frame involved. In addition there will be a statement of the voluntary nature of participation in the study and the right not to proceed and possible benefits for the worker and the organization will be explained.

Archiving will be done by the senior investigator off premises of the organization and confidentiality of patient records will be maintained.

#### Methods

Subjects: projected n=1000. Randomly selected from an industrial population. >11,000

Study design: . Cross-sectional prevalence study utilizing a clinically validated questionnaire (167 questions). Selection criteria will be applied to the random group. (a) employment for at least 90 days without evidence of MCS. (b) No preexisting medical or legal claims purporting to have chemical related injury. Coding will be assigned as to whether they were occupationally exposed to petroleum based vapors, fumes or gases and whether they were not. In addition a modified demographic questionnaire consisting of 5 questions will be provided. (age, sex, job title, smoking history, length of employment, self perception of impairment of activities of daily living related to chemical

exposures - none, mild, moderate or severe.) Answers will be processed per NCS optical scanning format. Statistical validation by Statistica (STAT SOFT, Tulsa, OK.) using proportions and odds ratios for comparison of dichotomous variables. Differences between exposed verses non-exposed groups will be determined by z approximation of binomial population as a small expected frequency is projected to be present in the two groups.

Table 1

*Cronbach's alpha values and # of items deleted*

Scale	iV	An	Cb	Pc	In	Al	Nc	D	So	Oi
raw alpha	.01*	.86	.65	.94	.00*	.76	.91	.91	.89	.52*
alpha after deletion	.01	.87	.82	.95	.00	.77	.92	.91	.89	.53
# items deleted	0	5	4	4	0	1	1	10	10	2

\* These scales contain items that would not be expected to correlate. Additional deletions: Df scale (16 items deleted), Rm scale (8 items deleted), Sp scale (1 item deleted), and <5% rule (4 items deleted).

Variables before deletion = 240, variables after = 177.

Table 2

*NSPEE subscale values (mean and standard deviations)*

Scale	iV	An	Cb	Pc	In	Al	Nc	D	So	Oi
x	1.0	9.40	9.71	11.90	2.18	4.37	7.85	10.62	15.86	2.54
	2									
s	.87	4.71	3.74	8.28	1.19	2.36	4.70	6.75	7.31	1.87
F**	.51	15.96*	62.27*	127.02	6.75*	14.82	47.25	13.70	40.13	19.31
				*		*	*	*	*	*
t***	-.91	.56	1.05	.84	.11	-1.65	-.10	.08	-.31	-2.54*

\* Statistically significant  $p < .05$

\*\* ANOVA differences between control, Cullen + and Cullen -

\*\*\* Student t differences between Cullen + and Cullen -

Legend: iV = Validity; An = Anxiety; Cb = Control behavior; Pc = Perceived

chemical involvement; In = Chemical exposure; Al = true allergic; Nc =

neurocognitive; D =depression; So = somatic concerns; Oi = other illnesses

**Table 3**  
**Cullen's criteria**

- The disorder is acquired in relation to some documentable environmental exposure(s), insult (s), or illness (s).
- Symptoms involve more than one organ system.
- Symptoms recur and abate in response to predictable stimuli.
- Symptoms are elicited by exposures to chemicals of diverse structural classes and toxicologic modes of action.
- Symptoms are elicited by exposures that are demonstrable.
- Exposures that elicit symptoms must be very low, by which we mean many standard deviations below "average" exposure known to cause adverse human responses.
- No widely available test of organ system function can explain symptoms.

**Table 4**  
**ATSDR conference criteria**

- Change in health status identified by the patient.
- Symptoms triggered regularly by multiple unrelated chemical stimuli at dosages that are far below those established in the

**general population to cause harmful effects. (traditional allergens are excluded)**

- **Symptoms experienced for at least six months.**
- **Symptoms ameliorated by non exposure to the chemical stimuli.**
- **A defined set of symptoms reported by patients.**
- **Symptoms that occur in three or more organs systems.**
- **Exclusion of patients with other medical conditions that might account for these symptoms.**

#### **Table 5**

##### **Exclusionary Criteria**

- **Exclusion of all subjects with known occupational injury or illnesses that produce traditional toxicological responses. (an exception is chronic solvent encephalopathy)**

- Exclusion of all subjects with incomplete responses to the questionnaire.
- Exclusion of all subjects with standard medical illnesses, that with reasonable medical probability account for their symptoms
- Exclusion of all subjects with localized irritative responses to chemical stimuli as the sole presenting manifestations. (example is conjunctivitis, rhinitis, reactive airways disease).
- Presence of psychosis as defined by the Diagnostic and Statistical Manual of the American Psychiatry Association (DSM IV)

#### **References:**

1. Ashford, NA, Miller CS, editors. **Chemical Exposures: Low Levels and High Stakes.** New York. Van Nostrand Reinhold 1991; xvii
2. Board on Environmental Studies and Toxicology; Commission on Life Sciences. *Epidemiology.* Multiple Chemical Sensitivities: Addendum to Biological Markers in Immunotoxicology. National Research Council. Washington DC. National Academy Press 1992; 11-12
3. National Research Council, Board of Environmental Studies and Toxicology. **Workshop on Health Risks from Exposure to Common Indoor Household Products in Allergic or Chemically Diseased Persons.** 1987 July 1,
4. Cullen MR, Pace PE, Redlich CA. **The Experience of the Yale Occupational and Environmental Medicine Clinics with Multiple Chemical Sensitivities, 1986-1991.** In: **Proceedings of the Association of Occupational and Environmental Clinics**

**Workshop on Multiple Chemical Sensitivities. Advancing the Understanding of Multiple Chemical Sensitivity. Toxicology and Industrial Health. ed. Rest KM 1992; 8 (4): 15-19**

- 5. Mooser S.B. The epidemiology of multiple chemical sensitivities. In: Workers with Multiple Chemical Sensitivities. State of the Art Reviews. Occ Med Cullen MR editor. 1987 Oct.-Dec.; 2 (4): 663-668**
- 6. Ross GH. Treatment options in Multiple Chemical Sensitivity. In: Proceedings of the Association of Occupational and Environmental Clinics Workshop on Multiple Chemical Sensitivities. Advancing the Understanding of Multiple Chemical Sensitivity. Toxicolo. and Indust. Health. Rest KM editor 1992; 8 (4): 87-95**
- 7. Bell IR, Schwartz GE, Peterson JM, Amend D. Self-reported Illness from Chemical Odors in Young Adults without Clinical Syndromes or Occupational Exposures. Arch Env Health 1993; 48 (1): 6-13**
- 8. Kipen HM, Hallman W, Kelly-McNeil K, Fiedler N. Measuring chemical sensitivity prevalence: a questionnaire for population studies. Am J Public Health 1995; 85 (4): 574-7**
- 9. Tolleson L. Multiple Chemical Sensitivity: Controlled Scientific Studies as Proof of Causation. Reg. Toxicol Pharmacol 1993; 18: 32-43**
- 10. Hill AB The environment and disease. Association and causation. Proc. R. Soc. Med. 1965; 58: 295-300**
- 11. Cullen MR. Multiple Chemical Sensitivities in Maxcy- Rosenau-Last Public Health & Preventive Medicine: 13th edition Eds. Last, J.M., Wallace, R.B. Norwalk, Appleton & Lange. 1992: 459-62**
- 12. Bolla-Wilson K, Wilson RJ, Bleeker ML Conditioning of physical symptoms after neurotoxic exposure. J. Occup. Med.. 1988; 30 (9): 684-686**
- 13. Selner JC, Staudenmayer H. Neuropsychophysiologic Observations in patients presenting with environmental illness. In: Proceedings of the Association of Occupational and Environmental Clinics Workshop on Multiple Chemical**

- Sensitivities. Advancing the Understanding of Multiple Chemical Sensitivity. Toxicology and Industrial Health. Rest KM editor. 1992; 8 (4):145-155**
- 14. Simon GE, Katon WK, Sparks PJ. Allergic to life: Psychological factors in environmental illness. Am. J. Psychiatry. 1990; 147: 901-906**
  - 15. Riegelman RK, Hirsch RP. editors. Studying a Study and Testing a Test: How to Read the Medical Literature. Second Edition. Boston: Little, Brown & Company 1989:68-69**
  - 16. Monson RR, editor. Occupational Epidemiology. Second Edition. Boca Raton: CRC Press 1990 53-54**
  - 17. Staudenmayer H., Selner JC. Failure to Assess Psychopathology in patients Presenting with Chemical Sensitivities. JOEM 1995; 37 (6): 704-709**
  - 18. Birdsong WH, Lash AA, Thayer S, Kumekawa E, Becker CE. The Validity of Study Group Assignments Based on Occupational Histories Obtained from Questionnaires, JOM 1992; 34(9): 940-945**
  - 19. Cullen MR. Multiple Chemical Sensitivities in Maxcy- Rosenau-Last Public Health & Preventive Medicine: 13th edition Eds. Last, J.M., Wallace, R.B. Norwalk, Appleton & Lange. 1992: 459-62**
  - 20. Rest K M. in Proceedings of the Association of Occupational and Environmental Clinics Workshop on Multiple Chemical Sensitivities. Advancing the Understanding of Multiple Chemical Sensitivity. Toxicology and Industrial Health. ed. Rest KM 1992; 8 (4):**
  - 21. Nethercott, Jr., Davidoff LL, Curbow, B. Multiple Chemical Sensitivities Syndrome: Toward a Working Case Definition. Arch. Env. Health Jan/Feb 1993 48:1:19-26**
  - 22. Randolph T. Allergy Type Reactions to Industrial Solvents and Liquid Fuels. (abstract) in J Lab Clin Med. 1954 44 (6): 910-911**
  - 23. Randolph T. Allergy Type Reactions to Mosquito Abatement Fogs and Mists. (abstract) in J Lab Clin Med. 1954 44 (6): 911-912**
  - 24. Randolph T. Allergy Type Reactions to Motor exhausts. (abstract) in J Lab Clin Med. 1954 44 (6): 912**

25. Randolph T. Allergy Type Reactions to Indoor Utility Gas and Oil Fumes. (abstract) in J Lab Clin Med. 1954 44 (6): 913
26. Randolph T. Allergy Type Reactions to Chemical Additives of Foods and Drugs (abstract) in J Lab Clin Med. 1954 44 (6): 913-914
27. Randolph T. Allergy Type Reactions to Synthetic Drugs and Cosmetics (abstract) in J Lab Clin Med. 1954 44 (6): 914
28. Selye H. editor. Selye's Guide to Stress Research. 1983 New York. Scientific and Academic Editions. Vol. 1-3
29. Johansson, SGO, Bennich HH and Berg T. The Clinical Significance of IgE. Prog. Clin. Immunol. 1972; 1: 1
30. Ishizaka K, Ishizaka T. Human reaginic antibodies and immunoglobulin E. J. Allergy 1968; 42: 330
31. Scanlon RT, Bellanti JA Immunology III ed. Bellanti JA. Philadelphia, WB Saunders. 1985; 349
32. Ross GH. Treatment options in Multiple Chemical Sensitivity. In: Proceedings of the Association of Occupational and Environmental Clinics Workshop on Multiple Chemical Sensitivities. Advancing the Understanding of Multiple Chemical Sensitivity. Toxicolo. and Indust. Health. Rest KM editor 1992; 8 (4): 87-95
33. Gots RE. Medical Hypothesis and Medical Practice: Autointoxication and Multiple Chemical Sensitivities. Reg. Toxicolo. Pharmacolo. 1993; 18: 2-12
34. Terr AI. Multiple Chemical Sensitivities. J. Allergy Clin. Immunol. 1994; 94 (2): 362-365
35. Terr AI. Immunological issues in "Multiple Chemical Sensitivities" Reg. Toxicolo. Pharmacolo. 1993; 18: 54-6
36. Tolleson L. Multiple Chemical Sensitivity: Controlled Scientific Studies as Proof of Causation. Reg. Toxicol. Pharmacol. 1993; 18: 32-43
37. Waddell WJ. The Science of Toxicology and its Relevance to MCS. Reg. Toxicol Pharmacol. 1993; 18: 13-22

38. **Gotts RE, Hamosh TD, Flamm WG, Carr CJ. Multiple Chemical Sensitivities: A Symposium on the State of the Science. Reg. Toxicol Pharmacol. 1993; 18: 61-78**
39. **Staudenmayer H, Selner JC, Buhr M. Controlled chamber challenges in 20 patients with multisystem symptoms attributed to hypersensitivity to exposure to multiple chemicals. Regul. Toxicol. Pharmacol.1993; 18: 44-53**
40. **Albright, JF, Goldstein RA. Is there evidence of an immunologic basis for multiple chemical sensitivity? Toxicol. Ind. Health 1992; 8:215-219**
41. **Black DW, Rathe A, Goldstein RB Environmental illness: A controlled study of 26 subjects with '20th Century Disease' JAMA 1990; 264 (24): 3166-3170**
42. **California Medical Association Scientific Task Force on Clinical Ecology. Clinical Ecology-a critical appraisal. West. J. Med. 1986; 144: 239-245**
43. **American Academy of Allergy and Immunology. Position Statements- Controversial Techniques. J Aller Clin Immunology. 1981; 67 (5): 333-338**
44. **American Academy of Allergy and Immunology. Position Statements-Clinical Ecology. J. Aller. Clin. Immunology 1986; 72 (8): 269-271**
45. **American College of Physicians. Clinical Ecology. Ann. Int. Medicine 1989; 111 (2): 168-178**
46. **Council of Scientific Affairs, American Medical Association. Clinical Ecology. J. Am. Med. Assoc. 1992; 282: 3465-3467**
47. **Buchwald D, Garrity D. Comparison of Patients with Chronic Fatigue Syndrome, Fibromyalgia, and Multiple Chemical Sensitivities. Arch Intern Med 1994; 154: 2049-2053**
48. **Avner SE, Kinsman RA. Psychologic Factors and Allergic Diseases in Allergic Diseases from Infancy to Adulthood. Second Edition. Eds. Bierman CW, Pearlman DS. Philadelphia: W. B. Saunders 1988: 300-315**
49. **Ross GH . History and Clinical Presentation of the Chemically Sensitive Patient. In: Proceedings of the Association of Occupational and Environmental Clinics Workshop on Multiple Chemical Sensitivities. Advancing the Understanding of**

**Multiple Chemical Sensitivity. Toxicology and Industrial Health. ed. Rest KM 1992; 8 (4):21-28**

- 50. Rea WJ, Bell I, Suits C, Smiley R. Food and Chemical Susceptibility after environmental chemical overexposure; Case histories. Ann. Allergy 1978; 41: 101**
- 51. Sparks PJ, Daniell W, Black DW, Kipen HM et al. Multiple Chemical Sensitivity Syndrome: A Clinical Perspective ii. Evaluation, Diagnostic Testing, Treatment, and Social Considerations JOM 1994; 36 (&): 731-737**
- 52. Psychoneuroimmunology. ed. Ader R. 1981 Academic Press New York**
- 53. Kipen HM, Fielder N, Maccia C, Yurkow E, Todaro J, Laskin D. Immunologic evaluation of chemically sensitive patients. Toxicol. Ind. Health 1992; 8: 125-135**
- 54. Terr AI. Immunological issues in "Multiple Chemical Sensitivities" Reg. Toxicolo. Pharmacolo. 1993; 18: 54-6**
- 55. Albright, JF, Goldstein RA. Is there evidence of an immunologic basis for multiple chemical sensitivity? Toxicol. Ind. Health 1992; 8:215-219**
- 56. Terr, A. Environmental Illness, a clinical review of 50 cases. Arch. Intern. Med. 1986; 146: 145-49**
- 57. Rea WJ Chemical Sensitivity Lewis Publishers Boca Raton FL.1992-1994 vol. I-IV**
- 58. Meggs WJ Immunological Mechanisms of Disease and the Multiple Chemical Sensitivity Syndrome. In Multiple Chemical Sensitivities: Addendum to Biological Markers in Immunotoxicology. National Research Council. Board on Environmental Studies and Toxicology; Commission on Life Sciences. National Academy Press Washington DC 1992; 155-168**
- 59. Levin AS, Byers VS. Environmental illness: A disorder of immune regulation. State Art. Rev. Occup. Med. 1987;2 : 669**
- 60. Neuroimmunomodulation: The State of the Art. Eds. Fabrs N, Marcovic BM, Spector NH, Jankovic BD. Annals of the New York Academy of Sciences 1994; 741:1-69**
- 61. Toxicology of the Immune System: A Human Approach. eds. Burrell R, Flaherty DK, Sauers LJ. Van Nostrad Reinhold. New York. 1992**

62. **Environmental Neurotoxicology. National Research Council. National Academy Press. Washington D. C. 1992**
63. **Identifying and Controlling Immunotoxic Substances: Background Paper. Congress of the United States. Office of Technology Assessment 1991**
64. **Simon G, Daniell W, Stockridge H, Claypolle K. Rosenstock L. Immunologic, psychologic, and neuropsychological factors in multiple chemical sensitivity. Reg. Toxicol. Pharmacol. 1993; 18: 44-53**
65. **McGovern JJ Jr., Lazaroni J A, Hicks MF, Adler JC, Cleary P. Food and Chemical sensitivities. Clinical and immunological correlates. Arch Otolaryngol. 1983; 109: 292-7**
66. **Thrasher JD, Broughton A, Madison r. Immune activation and autoantibodies in humans with long-term inhalation exposure to formaldehyde. Arch. Environ. Health. 1990; 45: 217-23**
67. **Thrasher JD, Madison R, Broughton A, Gard Z. Building -related illness and antibodies to albumin conjugates of formaldehyde, toluene diisocyanate, and trimetallic anhydride. Am J. :Ind Med. 1989; 15: 187-95**
68. **Kipen H, Fielder N, Maccia C, Yurkow E Todaro J et al. Immunologic Evaluation of Chemically Sensitive Patients. Proceedings of the Association of Occupational and Environmental Clinics Workshop on Multiple Chemical Sensitivities. Advancing the Understanding of Multiple Chemical Sensitivity. Toxicology and Industrial Health. ed. Rest KM 1992; 8 (4): 125-135A**
69. **Terr A. Immunological Issues in multiple chemical sensitivities. Reg. Toxicol. Pharmacol. 1993; 18:54-60**
70. **Kurt TL Multiple chemical sensitivities--a syndrome of pseudotoxicity manifest as exposure perceived symptoms. J Toxicol Clin Toxicol 1995;33(2):101-5**
71. **Spyker DA. Multiple Chemical Sensitivities- Syndrome and Solution. Clinical Toxicology 1995; 33 (2): 95-99**
72. **Hill AB The environment and disease. Association and causation. Proc. R. Soc. Med. 1965; 58: 295-300**

73. Barceloux DG Halogenated solvents. In **Hazardous Materials Toxicology: Clinical Principles of Environmental Health**. eds. Sullivan JB Kreiger GR. Williams and Wilkins Baltimore 1992: 732-747
74. Waddell WJ. The Science of Toxicology and its Relevance to MCS. *Reg. Toxicol Pharmacol* 1993; 18: 13-22
75. King DS Can allergic exposure provoke psychological symptoms? A double-blind test. *Biol. Psychiat.* 1981; 16: 3-19
76. Guglielmi RS, Cox DJ, Spyker DA. Behavioral treatment of phobic avoidance in multiple chemical sensitivity. *J. Behav. Ther. Exp. Psychiatry* 1994 Sep; 25 (3): 197-209
77. Shusterman D, Balmes J, Cone J. Behavioral Sensitization to Irritants/Odorants After Acute Overexposures. *J. Occ. Med.* 1988; 30 (7): 565-567
78. Schottenfield RS, Cullen MR Occupation-induced posttraumatic stress disorder. *Am. J. Psychiatry* 1985; 142: 198-202
79. Black DW, Rathe A, Goldstein RB Environmental illness: A controlled study of 26 subjects with '20th Century Disease' *JAMA* 264 (24): 3166-3170
80. Brodsky CM. Psychological factors contributing to somatoform disorders attributed to the workplace The case of Intoxication. *J Occup. Med.* 1983; 25: 459-64
81. **Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV).** American Psychiatric Association, Washington DC
82. Davidoff AL, Fogarty L. Psychogenic Origins of Multiple Chemical Sensitivities Syndrome: A Critical Review of the Research Literature. *Arch Env Health* 1994; 49 (5): 316-324
83. Black DW, Rathe A, Goldstein RB Environmental illness: A controlled study of 26 subjects with '20th Century Disease' *JAMA* 264 (24): 3166-3170
84. Simon GE, Katon WJ, Sparks PJ. Allergic to Life: Psychological Factors in Environmental Illness. *Am J Psychiatry* 1990; 147: 901-906

85. Rosenberg S, Freedman MR Scmaling KB, Rose C. Personality Styles of Patients Asserting Environmental Illness J Occ Med 1990; 32 (8) 678-681
86. Studdenmeyer HS, Selner JC. Neuropsychophysiology during relaxation in generalized "universal" reactivity to the environment. A comparison study. J. Psychosomat Res 1990; 34: 259-70
87. Stewart DE, Raskin J. Psychiatric assessment of patients with "20th Century Disease". ("total allergy syndrome") Can. Med. Assoc. J. 1985; 133: 1001-06
88. Brodsky CM. Psychological factors contributing to somatoform disorders attributed to the workplace The case of Intoxication. J Occup. Med. 1983; 25: 459-64
89. Terr, A. Environmental Illness, a clinical review of 50 cases. Arch. Intern. Med. 1986; 146: 145-49
90. Doty RI, Deems DA, Frye RE, Pelberg R, Shapiro A. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivity. Arch Otolaryngology - Head Neck Surg. 1988; 114:1422-27
91. Schottenfield RS, Cullen MR Occupation-induced posttraumatic stress disorder. Am. J.. Psychiatry 1985; 142: 198-202

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