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Multiple Chemical Sensitivity

Review of the State of the Art in Epidemiology, Diagnosis, and Future Perspectives

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Objective: Systematic bibliography analysis of about the last 17 years on multiple chemical sensitivity (MCS) was carried out in order to detect new diagnostic and epidemiological evidence. The MCS is a complex syndrome that manifests as a result of exposure to a low level of various common contaminants. The etiology, diagnosis, and treatment are still debated among researchers. **Method:** Querying PubMed, Web of Science, Scopus, Cochrane library, both using some specific MESH terms combined with MESH subheadings and through free search, even by Google. **Results:** The studies were analyzed by verifying 1) the typology of study design; 2) criteria for case definition; 3) presence of attendances in the emergency departments and hospital admissions, and 4) analysis of the risk factors. **Outlook:** With this review, we give some general considerations and hypothesis for possible future research.

Learning Objectives

- Become familiar with the history and current concepts of multiple chemical sensitivity (MCS), including the recently proposed "evolutive framework."
- Discuss the findings of the present review of recent research on MCS, including the types, characteristics, and findings of the studies identified.
- Discuss the implications for patient evaluation and further research on MCS.

Multiple chemical sensitivity (MCS) is currently included in the broader definition of idiopathic environmental intolerance (IEI), which also includes physical risk factors such as electromagnetic fields. It is a complex disease, a multisystem disorder that manifests as a result of exposure to various environmental contaminants (solvents, hydrocarbons, organophosphates, heavy metals) at concentrations below the ''Threshold Limit value'' (TLV) that are considered toxic doses for the general population.[1–4]

At the beginning of the '50, the allergist Theron G. Randolph[5] was the first to note that some patients became sick after exposures to a wide range of substances, either job-related, either, broadly speaking, environmental, in concentrations below those considered toxic for most individuals. Dr. Randolph and his colleagues speculated the possibility of allergic reactions and maladjustment to explain the symptoms that are attributed to MCS. It is considered that chronic exposure to subtoxic doses, as well as any acute exposures, can, in some people with, perhaps, a particular metabolic and genetic predisposition, lead to a gradual process of substance sensitization.

However, because of the difficulty of finding unique and incontrovertible diagnostic markers, from the '60 to date, the syndrome was analyzed in its different aspects: metabolic, genetic, immunological, epidemiological, etiological, symptomatic, therapeutic, and the criteria for case definition were gradually revised. Currently, the Cullen criteria,[6] with or without Lacour revision,[7] and the year 1999 criteria of the consensus[8] are the most accepted. To perform an initial screening, different questionnaires are used: ''Environmental Exposure and Sensitivity Intolerance'' (EESI) or its short version ''Quick Environmental Exposure and Sensitivity Inventory'' (QEESI),[9–11] ''Huppe questionnaire,''[12] ''Chemical sensitivity scale for sensory hyperreactivity'' (CSS-SHR),[13] German questionnaire on chemical and environmental sensitivity (CGES).[14]

From the symptoms point of view, some industrial experts have compiled the following nonexhaustive example of evolutive framework of the syndrome, presented in Italy in Bill N 1922[15]:

Stage 0 - Tolerance: in this stage, the individual is normally able to adapt to the environment that surrounds him, unless limits for certain hazardous substances are exceeded.

Stage 1 - Sensitization: this stage could be experienced as a result of chronic exposure to low doses and/or after individual acute exposures. The patient may complain of the following disorders: dermal, ocular and respiratory tract irritation, itching, fatigue, muscle and joint pain, headache, nausea, tachycardia, changes in blood pressure, balance problems, sensations of cold or fever, dyspnea, cognitive problems and asthma, insufficient peripheral circulation, immune disorders and gastrointestinal diseases, etc.

Stage 2 – Inflammation: chronic inflammation in load of different tissues, organs, and systems. Various disorders development, detectable through specialist examination: dermatitis, vasculitis, immune, endocrine, metabolic diseases, food and environmental allergies (dust, pollen, etc), arthritis, colitis, rhinitis, dyspnea, asthma, muscle fatigue, fainting, cognitive delays, poor peripheral circulation, bleeding, etc. The persistence and aggravation of this stage depends on the exposures, their avoidance, and undergo therapy. After an exposure, symptoms may persist and oscillate for days, if not weeks.

Stage 3 - Deterioration: chronic inflammation produces damage to tissues and organs. CNS (central nervous system), kidneys, liver, lungs, immune system, circulatory, vascular, dermal are affected. Lupus, ischemia, heart failure, cancer, autoimmunity, neurodegenerative and psychiatric syndromes, hemorrhagic forms, porphyria are the most common diseases in this stage.

Given that most of the chemicals implicated are common environmental pollutants, it is practically impossible to avoid them completely and therefore individuals who have the disease will be, depending on the stage reached, more vulnerable than the general population.

Moreover, given the diagnostic difficulty, in the early stages, it is possible that nor the doctors nor the patients find the causal link between the symptoms reported and the exposures. The MCS could therefore not be diagnosed as such and be confused with other diseases.

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In confirmation of the foregoing considerations, basically two different scientific approaches are lined up[16–18]:

(1) toxicological, mostly supported by ecologist clinicians, recognizing the excursus described above;
(2) psychiatry-psychosomatic, which tends to report the source of such disturbances to the psyche, as an endogenous self-induced cause and not as a consequence of excessive and abnormal reaction to an albeit reduced chemical exposure.

International and National Recognition

Although the theme is still debated due to lack of uniformity of opinion in the scientific community, some countries such as Germany and Austria and some agencies and provisions in the United States such as the Environmental protection Agency (EPA) and the American Disability Act (ADA) have recognized this pathology.[1] IEI can be codified as clinical condition using the WHO ''International Classification of Diseases,'' revision of the year 2010 (ICD10) by mean of the following codes:

(1) J68.9: unspecified respiratory conditions due to inhalation of fumes, gas, and chemical vapors;
(2) T78.4: unspecified allergies (allergic reaction Nitrous Oxide System (NOS)-hypersensitivity NOS-idiosyncrasy NOS).

Due to the nonspecific nature of these codes, diagnostic difficulties, and multiplicity of symptoms reported, only explorative epidemiological estimates can be performed.

In Italy, the Health Authorities of different regions and the Ministry of Health have formally requested a technical-scientific opinion to the Italian National Institute of Health (I.S.S) for establishing care protocols for patients with symptoms related to MCS.[19]

From the analysis of the literature on the topic, IIAAC/SCM working group drew the following indications for a diagnostic and therapeutic path:

(1) chemical risk characterization; clinical, instrumental, and laboratory examinations; forms for description of subjects and for a summary of the results of the diagnostic process. When necessary, treatment should be symptomatic according to best practices and evidence-based medicine;
(2) encouragement of research projects that include controlled clinical trials.

Following the opinion expressed by the Italian Superior Health Council, the Health Ministry does not recognize MCS as a rare disease due the difficulty of nosologic recognition.

However, it is to point out that, in some cases, the severity of the condition has led to changes in lifestyle or even the withdrawal from work, also determining the onset of litigation and request of compensation.[16]

Also, as the symptomatology is related to chemical exposure, some professional groups could be at more risk. The Italian ''National Institute for occupational accident insurance'' (INAIL) was involved in the legal-medical and workplaces surveillance aspects of the syndrome.[20]

AIM

Starting from the conclusions set out in the review carried out by the Working Group of the Italian National Institute of health,[19] it was decided to analyze the literature of these last 17 years in order to verify the methodology of studies, diagnostic evidences, and related opinions.

METHODS

A systematic bibliographic research was performed for a 17-year period (date first article May 1998 to date last article December 2015) in several scientific databases: PubMed, Web of Science, Scopus, and the Cochrane library. Free searches on MCS as keyword were performed combined with specific Mesh subheadings: etiology, diagnosis, and epidemiology. Only the studies in English or Italian language were analyzed.

The following main topics were considered in the research:

(1) type of study design
  - experimental with chemical stimulation
  - observational (cross-sectional, case–control, cohort study)
(2) definition of ''case'', with inclusion and exclusion criteria;
(3) presence of attendances at the emergency department (ED) and hospital admissions;
(4) analysis of the risk factors;

In principle, reviews and discursive or generic articles and commentaries have been excluded, while the most relevant articles were included for the purpose of this research, collected through references from various sources.

Studies performed on some population groups or individuals at risk were not included: military personnel (Gulf war, Cambodia), individuals presenting a sensitization from dental amalgams, and individuals exclusively sensitive to electromagnetic fields.

As a result of the research criteria above indicated, $n = 73$ scientific papers were selected for the analysis.

RESULTS

Experimental Studies on Humans (Provoked Exposure)

The application of the above indicated selection criteria lead to the identification of 27 articles[14,21–46] in which experimental chemical provocation studies were performed on individuals with MCS or suspected.

Analysis of Inclusion criteria

In most of the studies, individuals were selected who had multiple symptoms related to chemical sensitivity, based on the correspondence to: Cullen criteria and/or 1999 US Consensus criteria with or without Lacour revision of 2005[21–35] and based on the results from interviews or questionnaires aimed to assess the intolerance to chemical exposure.[36–41] The questionnaires administered included the QEESI[29,30]; Chemical Sensitivity Scale[25,42]; CGES.[14,43,44]

Analysis of Exclusion criteria

Exclusion criteria, when present, are heterogeneous and more or less strict depending on the experimental design. Haumann et al,[14] in 2003, and Lee in 2007,[38] for example, have chosen male individuals (M) to eliminate any potential problems such as, for example, those due to cyclical hormonal changes in women of childbearing age. In other studies, only women (F) are present,[28,29,31,33,35–37] that is, moreover the gender most affected by the syndrome.

Among the criteria for exclusion, when deemed and specified by the authors, in some studies, conditions are included such as smoking, pregnancy and/or breast feeding,[21–24,30,37,41] alcohol or drug abuse or therapy.[21,22,30,33,37,41] Some diseases are also considered as exclusion criteria: for example, diabetes, cancer, HIV, neurological and psychiatric diseases, disorders of affect, radiation and trauma to brain, renal and hepatic diseases, hypothyroidism, olfactory dysfunction and also pulmonary and cardiovascular or endocrine diseases,[21,22,30,33,37,41,44–46] chronic fatigue syndrome,

fibromyalgia, irritable bowel syndrome,[23,24,30,41] anosmia and allergic rhinitis hypertension, hyperlipidemia,[30] or generically neurological and immunological problems that can mimic MCS and diseases of the upper respiratory tract.[27] In general, the different authors have identified their exclusion policies without referring to any specific and harmonized consensus document, even if Lacour at al[7] produced some tables where they had listed a number of diseases that can overlap this syndrome and which have to be ruled out and others that do not exclude MCS diagnoses.

Emergency Department and Hospital Admissions

Normally, there is no specific information regarding attendance at ED and hospital admissions, although sometimes the subjects were recruited from the Hospital/clinical waiting rooms or from specific Research Centre for this syndrome.

Analysis of Risk Factors

Only for provocation studies, a review has been made by Das Munshi et al[47] up to year 2006. The current review is updated to year 2015.

The results of our review are summarized in Table 1. We subdivided the articles on the basis of imaging and nonimaging studies with a classification of the different studies in groups defined by the following common criteria: (1) study design (presence/absence of controls), (2) level of exposure to substances, (3) modality of provoked exposure, (4) results, and (5) type of conclusion (psychosomatic vs toxicological approach).

We have also specified the type of imaging analysis, as they have a different resolution power.

Studies where the chemical stimulation is represented exclusively by carbon dioxide in concentrations of between 5% and 35%[48] and by capsaicin[49,50] are not included in this classification.

The observed studies present different substance exposure modes: aerosols with facemask or by dynamic olfactometer,[21,22,32,36,42,43] chemical room at controlled temperature and humidity[14,23–25,33,37,40,41,44–46] or smelled through bottle,[28,31] and soaked paper discs or even through sticks.[26,27,29,30,43] Substances may be harmless as the smells of banana, coconut, chocolate, vanilla, cedar, and lavender oil.[21,22,26,27,29–31] Some are toxic such as volatile organic compounds (VOCs), alcohols, and solvents in general,[14,23–46] but their concentrations are always below the legal limits. Many authors agree that stress is an important risk factor and some speculate a psychosomatic origin of the syndrome.[14,30–32,37,40] Other researchers tend to rule out this theory in favor of a neurogenic inflammatory origin and hyper-reactivity to stimuli of the limbic system[21,22,25,46] associated with frontal and prefrontal cortex hypo-activity in MCS cases with respect to controls as detected by positron emission tomography (PET), single photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI) analysis.

The analysis of the articles has led us to deduce the following schematization (Table 1) based on the derivative conclusions dividing them into three large groups:

A = toxicological theory; B = psychological theory; C = no conclusion.

Imaging Studies

These studies did not lead to homogeneous result probably due to differences in type of exposure, substances used, the different selection criteria adopted in dividing the suspect MCS (sMCS), from the controls also with regard to the severity of the symptoms, and possibly to the different power resolution in the Imaging techniques used.

In addition, the number of tests and the sample are often limited. On the basis of these considerations, we highlight some studies,[21,22] in which, following olfactory stimulation, a hyperactivation of the amygdala and the olfactory cortex is detected in sMCS, not counterbalanced by the activation of frontal and prefrontal areas as otherwise evidenced by the controls. These metabolic differences would be the basis of the different responses to olfactory stimuli between sMCS and controls and would suggest authors toxicological theory of hyperreactivity and limbic sensitization with neuronal inflammation. To the same conclusion also comes Orriols et al,[25] although the results are different from those noted by the authors mentioned above, but anyway indicative of brain dysfunctions in the processing of the stimulus. Diametrically opposite is the opinion of the authors Azuma et al[30] and Hillert et al.[31] According to them, the reiteration of olfactory stimulation would cause emotional responses[30] and the reduction of the activation of the olfactory regions in the MCS, according to top-down regulations.[31]

Nonimaging Studies

Regarding our bibliographic research, we highlight that only in three studies,[34,35,46] the authors substantially propose the toxicological hypothesis of neuronal sensitization, while in several others,[14,26,32,37,40,41,42,45] the authors speculate a psychological response in sMCS, compared with controls, or anyway anxiety as a risk factor to the development of syndrome. According to these authors, both the changes in some physiological parameters such as heart rate, pressure, and respiration between sMCS and controls, rather than the exact opposite, that is, the lack of modifications of some other parameters (eg, cortisol level), following the stimulation, would be a proof of emotional nature of the problem.

As outlined in the table, several other studies show controversial results, inducing the authors to come to no conclusion.[23,24,27–29,33,39,43]

The previous considerations for the Imaging Analysis regarding the importance of a greater standardization are also valid for Nonimaging studies.

Observational and Longitudinal Epidemiological Studies

In the current review, we analyzed about

(1) 24 cross-sectional studies of prevalence;
(2) 22 cohort and case–control studies.

Analysis of Inclusion Criteria

In most of the epidemiological studies, people are recruited following interviews and through the compilation of different kinds of questionnaires[51–60] or standardized questionnaire as the EESI or QEESI,[61–74] CGES,[75] Huppe,[76] Environmental medicine questionnaire (EMQ), or chemical sensitivity scale for sensory hyperreactivity (CSS-SHR),[50,77] Chemical Odor Intolerance Index (CII).[78,79] Sometimes, the syndrome has been diagnosed by doctors without pointing out the diagnostic procedure.[80,81] The inclusion criteria described by Cullen with or without Lacour revision were also cited in some articles.

Analysis of Exclusion Criteria

Exclusion criteria were not standardized but decided by individual authors, depending on the study model, so that we have both: studies in which these criteria are made explicit[66–69,72,75,79] and others where they are not specified.[57–59,61,64,82,83]

Emergency Department and Hospital Admissions

Normally, there is no specific information regarding the prevalence of attendances at ED or hospital admissions, although sometimes the subjects were recruited from the Hospital/clinic

TABLE 1. Imaging and Nonimaging Analysis After Chemical Provocation Study on Humans: Results and Conclusions

	Type of Imaging Analysis	Reference	sMCS/Controls*	Substances Level	Exposure Mode	Results	Conclusions on Toxicological and/or Psychological Theory
Imaging Analysis	PET	[21,22]	26/11	Harmless	Aerosol with facial mask	Both in controls than in MCS decreases the metabolism of 18F- FDG in the *putamen* and *hippocampus* during stimulation with vanilla (OC) than is the case with pure saline (NC). There is an increased metabolism in the *amygdala* and *olfactory cortex* during stimulation with vanilla in MCS patients with respect to controls. Only controls demonstrate an activation of frontal and prefrontal areas, which is absent in MCS. The authors conclude that the results obtained are consistent with the theory that attributes to the MCS an increased responsiveness of both central nervous system and of olfactory center.	Speculate toxicological theory (neurogenic inflammation)
	SPECT	[25]	8/8	Dangerous below TLV	Exposure chamber	It is noted that in the MCS respect to control group, showed basal brain hypoperfusion in small cortical areas of parietal, temporal, and front-orbital lobes. After chemical challenge, the odor processing related brain areas (hippocampus and amygdala) are hypoactivated. In neuropsychological tests, MCS patients show a reduced ability to concentrate, store, and even slower response, following exposure to chemicals.	Speculate toxicological theory
Nonimaging Analysis		[34,35,46]	48/57	Dangerous below TLV	Exposure chamber or dynamic olfactometer	In these studies, the patients showed both physical and psychic symptoms only in presence of chemical exposure.	Speculate toxicological theory
Imaging Analysis	NIRS	[30]	16/17	Harmless	Sticks test	The reiteration of proof determines MCS patients an activation of the frontal portion. Not all olfactory stimuli lead to the same result though	Speculate psychological theory

TABLE 1. (*Continued*)

	Type of Imaging Analysis	Reference	sMCS/Controls*	Substances Level	Exposure Mode	Results	Conclusions on Toxicological and/or Psychological Theory
	PET	[31]	12/12	Dangerous and/or harmless	Bottle	The MCS, unlike controls, activate less areas of the brain involved in odors processing. Also in MCS, the Anterior Cingulate and Precuneus-Cuneus regions are activated, which are directly related to emotions.	Speculate psychological theory
Nonimaging Analysis		[14,26,32,41,42,45]	110/91	Dangerous below TLV and/or harmless	Exposure chamber or sticks test or dynamic olfactometer	No statistically significant differences respect to some physiological parameters were found in MCS, and/or between MCS and control, before and after treatment. The only differences found in some studies were probably due to a psychosomatic response.	Speculate psychological theory
		[37,40]	87 sMcs, controls not specified				
Imaging Analysis	MRI	[38]	10/no controls	Dangerous below TLV	Not specified	Two individuals have been recognized with organic syndrome, two individuals with MCS/IEI, while the others show symptoms of hypocondria.	No conclusion *results assessed on a case by case analysis based on the clinical evaluation of the individual patient*
		[36]	25/26		Dynamic olfactometer	Olfactory system is not hyperactive. The authors found only hyperactivity of the thalamus and inferior frontal gyrus in IEI than the control. In MCS group, the superior frontal gyrus is hypoactive with respect to control group.	No conclusion
Non imaging Analysis		[44]	84 (smell annoyance 29, general annoyance 39, magnetic field 16) 53 controls	Dangerous below TLV and/or harmless	Exposure chamber or sticks test or dynamic olfactometer bottle	Limited and/or controversial results	No conclusion
		[23,24,27–29,33,39]	158/177				
		[43]	39 healthy (low and high sMCS)				

MCS, multiple chemical sensitivity; sMCS, suspect MCS; TLV, threshold limit value.

waiting rooms or from specific Research Centre for this syndrome.[61,64–68,76,82,83]

Analysis of Risk Factors

Beside specific questions about exposure to chemicals and related symptoms,[51–92] some studies[51–53,58,59,62–65,68,71,75–77,79,80,82,83,86,88,90,92] have carried out questionnaires to assess the psychological condition (DSM-IV, SCL 90, NEO, CIDI, etc). Sociodemographic surveys have also been performed and surveys on the simultaneous presence of other diseases such as asthma, allergies, cardiorespiratory problems, autoimmune diseases, cancer, etc.[51,52,54,57,58,61–66,68,70,72,74,76,78,82–87,89] These information are useful to get a feedback on the prevalence of symptoms and to characterize the individual social, psychological, and physical conditions of the observed persons. It was found that women are more affected than men,[57,89] and that the socioeconomic and cultural level is medium up to high. Due to the diagnostic difficulty, the lack of standardized criteria for case definition, and the different prominence given to the syndrome in different countries, the estimated prevalence is variable from a minimum of 1% to more than 15%.[53,57,64,87,88]

According to psychiatric and psychological test results, some authors have detected a frequent association between levels of anxiety, depression, psychotic disorders, and MCS,[50,58,59,64,71,75–77,80,82,83,86,88] results that led some of them to suppose that both stress[50,58,59,75,77] and/or female gender[50] may represent risk factors. An increase in the prevalence of other diseases in cases versus controls was also detected: asthma, allergies, atopic dermatitis, autoimmune, neurological, gynecological, cardiopulmonary diseases, etc.[51,54,61,68,78,85]

Some researchers are trying to determine whether this syndrome causes an inflammatory condition without concurrent infections, with the release of the related chemical mediators and dysregulation of the immune system. In the study by Dantoft et al,[68] the levels of 14 interleukins (ILs) and inflammatory factors in blood samples of Danish individuals were analyzed. IL-1β, IL2–4–6, the IL4/IL13, and the alpha factor of tumorous necrosis are increased in comparison to controls. Nevertheless, in a challenge study,[24] the same authors found no differences in the concentrations of inflammatory mediators detected in nasal fluids in MCS cases versus controls.

Changes in cytokine levels may be indicative of an inflammatory process that is not generated from the nose after olfactory stimulations. In this scenario, the sensitivity to substances may also be caused by different polymorphisms involved in the detoxification of xenobiotics, which could lead to an accumulation of oxidizing substances and subsequent damage. In some studies,[69,72,74] various polymorphisms of Cyp 450 (Cyp 2C9, Cyp 2C19, Cyp 2D6, etc) were analyzed, also including glutathione transferase and peroxidase (glutathion S-Transferase M1, glutathion S-Transferase T, glutathion S-transferase P), aldehyde dehydrogenase, superoxide dismutase (SOD_2), and paraoxonase (PON1).[69,73,74] The SOD_2 polymorphism[69] and a specific variant of NOS_3[67] seem to be associated with the syndrome and increased levels of oxidative stress. Glutathione both reduced and oxidized are decreased in the MCS cases and there is also an altered pattern of cytokines,[74] different from that observed in the study of Dantoft et al.[68] Controversial results, positive[72] and negative,[74] were observed for some frequencies of Cyp isoforms. Caccamo et al[72] have studied the prevalence of some haplotypes of the Cyp 450 family (cyp 2C9*2 and Cyp 2C9*3; Cyp 2C19*2 and CYP 2D6 ht) in MCS cases, suspected cases, or patients with fibromyalgia and chronic fatigue and in controls. They have discovered a higher frequency of the haplotypes mentioned above in MCS patients that could be evaluated, together with others, as possible risk factor of MCS.

The recent study by the team of Gugliandolo et al[66] noted a decrease in the levels of oxidized/reduced glutathione and Coenzyme Q10 and a greater damage in lymphocytes in MCS patients than controls. These findings led to conclude that there is an increase in oxidative stress due to the decreased activity of detoxifying enzymes. An increased concentration of free radicals and peroxynitrite can be detected, with subsequent release of cytokines.

Among epidemiological papers of particular importance are cohort and case–control studies of workers exposed to various chemicals[60,69–71,73,90–93] joined in some cases with chemical provocation essays.[25,38–40] It should be noted that in these kinds of studies, mainly male workers were involved, due mostly to the type of occupation. There is a small occurrence of MCS diagnoses.[90] It could be caused by the ''healthy worker'' effect, which can be explained by selective or self-selective processes both for the access to the employment phase and for the continuation of the activity. The bias of the healthy worker effect is a known factor in the field of occupational medicine and is involved in underestimates of morbidity and mortality if the follow-up of the worker is not conducted in a comprehensive manner.[70,94]

Particularly relevant among cohort studies is the one conducted by the team of Davidoff et al.[60] They took into account a cohort of workers employed in the excavation of a tunnel under the service area of a disused petrol pump. In some well documented cases, workers were exposed to gasoline vapors over the allowed limits. During working hours, some workers developed symptoms similar to those reported to MCS. Considering the sociocultural and psychological characteristics of the sample, the authors do not consider likely easy suggestibility with associated psychosomatic symptoms. Furthermore, the same authors in a subsequent study[92] believe that psychological questionnaires such as the Minnesota Multiphasic Personality Inventory (MMPI-2) may be misleading because it might be the State of chronic disease, not accurately diagnosed, to lead to a gradual isolation of patients whether within family or in social and working life, helping to aggravate the psychological state of anxiety and frustration. In another study,[89] seven patients with previous occupational exposure to neurotoxic undergo PET with F18 radioactive tracer of deoxyglucose (FDG). Compared with controls, there is a hypometabolism in cortical and hypermetabolism in limbic areas. The authors consider this involvement of the CNS as the possible cause of symptoms similar to panic attacks.

CONCLUSION

Although over the years, the researchers have made several steps toward a better definition of this syndrome, it is still not possible to diagnose MCS with absolute certainty, as the many and diverse symptoms that patients complain following ''low-dose" exposures to chemicals, not well defined in most cases, are common to various pathologies, both physical and psychic. It is still lacking an adequate agreement about the definition of ''case'' and about proper inclusion and exclusion criteria of patients in the studies.

As to the personal risk factors, experts basically agree on the predominance of the female than male gender and on the association with medium-high social and cultural categories. On the contrary, some epidemiological researches have tried to analyze the importance of certain genetic polymorphisms involved in the detoxification process, in order to highlight differences that might be involved in the variability of the response and then the increased vulnerability to chemical insults. The results, however, still limited in number, are currently conflicting for the part concerning the importance of genetic variability component rather than epigenetic mutation. Even the profession does not seem to always play a major role, though some risk categories have been identified.

In recent years, several experimental studies were performed with exposure of susceptible individuals to chemicals both toxic and harmless, aimed to analyze both the psycho-physiological changes such as heart and respiration rate,[14,23,31,45] concentration and memorization ability, and changes in brain activity in different areas.[21–23,25,31,36]

The conclusions are still uncertain and controversial, although a greater involvement of the activity of the limbic system and of the autonomic nervous system at the expense of cortical areas is broadly confirmed.

The versatility of the methods used in the existing studies and the lack of standardized protocols in toxicology, especially for human trials, makes evaluating the efficiency of the test and the accuracy of the conclusions even more complicated.

DISCUSSION AND OUTLOOK

From the analysis of the results observed in the current review, it is difficult to assess the weight of the self-induced psychological component compared with the physiological one, considering that exposition to high doses of specified substances has straight effects on the CNS, mimicking a psychiatric syndrome.[95–97] Lacking clarifications on the etiology, diagnosis, and excursus of the syndrome, patients may feel unfairly labeled as mentally ill, with high disrepute and impacts on their lives.[92] It is a major importance from an ethical–professional and legal point of view to take into account this aspect before reaching to conclusions.

In the hypothesis that both factors can also coexist, studies should focus more on the bio-toxicological and physiological parameters changes, as a result of exposure to toxic substances below the TLV, as already thoroughly expressed in previous opinion both by the working group coordinate by the Italian National Institute of Health[19] and by Italian ''National Institute for occupational accident insurance'' (INAIL).[20]

It could also be considered that some solvents can cause sensitization of the myocardium to endogenous catecholamines, with possible arrhythmias up to atrial fibrillation and cardiac arrest.[97] Such an eventuality, even though still not detected in any epidemiological study so far, could lead to an increased risk of cardiopulmonary disease[78] or death in patients with MCS, as a result of even reduced environmental and professional exposure, a *fortiori ratione* in case of a clinical trial. For these reasons, sensitization trials on human could be hazardous because of the possible damage and stress possibly inflicted to the individual. However, to properly evaluate this syndrome, subjects should be exposed to subtoxic doses at concentrations to be evaluated with accuracy and for an appropriate period of time, in order to detect cases of bioaccumulation with detoxification difficulty. Another issue is the need to re-evaluate whether to make increasingly stringent exclusion criteria. Considering that MCS is a syndrome that progresses to increasingly serious stages, with the gradual onset of multiple pathologies, the multi-pathology criterion for exclusion from the sample[7] may be acceptable as a precautionary measure to avoid further risk to the patients. On the contrary, this criterion could become counterproductive if is adopted to deny the presence of MCS as it may have been the MCS itself the determinant of the onset of other diseases (autoimmunity, heart disease, respiratory, neuropsychiatric, etc).[1,7]

Moreover, the absence of stronger evidence in MCS diagnosis protocols, based on specific measures of exposure to chemicals and their biological and physiological effects, could lead to an erroneous estimation of the impact of MCS on the population health status. This is a major problem especially in the field of prevention, particularly for groups at greater risk. We should at least draw up validated and harmonized guidelines for this type of essays, which involves serious ethical issues, and have an appropriate number of repeatable tests just like it does for the toxicological evaluation of chemical substance in the in vivo experiments on animals.

As evidenced, this syndrome, along with other occupational disease, such as toxic-organic solvent psycho-syndrome or chronic toxic encephalopathy,[95,96] can play an important role in the appreciation of suitability to the task, with all the repercussions that this can cause, up to the request of disability. From the statistical and epidemiological point of view, it would be appropriate to detect temporary or permanent unfitness to chemical risk, or even the reasons for sudden changes in position that could occur in different working environments.

A careful analysis of case studies occurring in the workplace[20] may highlight cases of MCS without the need to perform ad hoc experiments. Executing appropriate and consistent environmental controls for chemical risk is an important factor to prevent both accidents and occupational diseases in workplaces with exposures above the limits and to prevent workers to stay in contaminated places.[70] These considerations are particularly relevant in the light of the development of portable electronic devices (ie, eNose) that could highly facilitate the task.

Personal electronic tools, adequately set on defined exposure limits and equipped with audible warning on thresholds exceeding, would be appropriate. The fact that these instruments are wearable by the worker is important to monitor exposure in real time, as with evaporation, substances disperse in the environment. When a suspicion of intoxication, albeit at low doses, arises, it is important to check the biomarkers such as, for example, the presence of the substance or its metabolites in body fluids (blood, urine) as well as the physiological and neurophysiological parameters, also in order to rule out exposures to higher than accepted doses. A careful analysis of both medical and working records could highlight the factors characterizing the phenomenon for the MCS.

As the syndrome might, at a low dosage, mimic a more or less strong poisoning, it is possible, in our opinion, that MCS patients arrive at ED with symptoms similar to those of an intoxication, in which the nervous and cardiovascular system are primarily involved.[97]

As highlighted in the above indicated studies, the analysis of the patient at anamnestic and etiological level is of great importance. In particular, it should be inquired about the differences in timing and mode of manifestation between endogenous psychiatric syndromes and those caused by chemicals in order not to err on the diagnosis, as symptoms can overlap.

In this regard, more information gathering would be useful in order to perform longitudinal epidemiological studies.

REFERENCES

1. De Luca C, Raskovic D, Pacifico V, Chung Sheun Thai J, Korkina L. The search for reliable biomarkers of disease in multiple chemical sensitivity and other environmental intolerances. *Int J Environ Res Public Health*. 2011;8:2770–2797.
2. Scientific review report. Multiple chemical sensitivity: Identifying key research needs- November 2010 Report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and the Office of Chemical Safety and Environmental Health (OCSEH). Google free search.
3. De Santis M. Malattie da intossicazione cronica e/o ambientale. International Conference of the network of public health institutions on rare diseases (NEPHIRD). Istituto Superiore di Sanità, Roma 20-23 Settembre 2006. Rapporto Istisan 08/11; rapporto ISSN 1123-3117. Google free search.
4. Magnavita N. MCS –Riflessioni in tema di sensibilità chimica multipla. Diapositive Università Cattolica di Roma. Google free search.
5. Randolph TG. Human ecology and susceptibility to the chemical environment. *Ann Allergy*. 1961;19:518–540.
6. Cullen MR. The worker with multiple chemical sensitivities: an overview. *Occup Med*. 1987;2:655–661.
7. Lacour M, Zunder T, Schmidtke K, Vaith P, Scheidt C. Multiple chemical sensitivity syndrome: suggestions for an extension of the US. MCS case definition. *Int J Hyg Environ Health*. 2005;208:141–151.
8. Bartha L, Baumzweiger W, Buscher DS, et al. Multiple chemical sensitivity: a 1999 consensus. *Arch Environ Health*. 1999;54:147–149.
9. Miller CS, Prihoda TJ. The environmental exposure and sensitivity inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicol Ind Health*. 1999;15:370–385.
10. Miller CS, Prihoda TJ. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. *Toxicol Ind Health*. 1999;15:386–397.

11. QEESI Questionnaire. drs Claudia Miller Department of Family & Community Medicine. University of Texas School of Medicine San Antonio. Available at: http://familymed.uthscsa.edu/qeesi.pdf. Google free search.
12. Wiesmüller GA, Niggemann H, Weiβbach W, et al. Sequence variations in subjects with self -reported multiple chemical sensitivity (sMCS): a case control study. *J Toxicol Environ Health A*. 2008;71:786–794.
13. Nordin S, Millqvist E, Löwhagen O, Bende M. A short chemical sensitivity scale for assessment of airway sensory hyperactivity. *Int Arch Occup Environ Health*. 2004;77:249–254.
14. Haumann K, Kiesswetter E, van Thriel C, Blaszkewicz M, Golka K, Seeber A. Breathing and heart rate during experimental solvent exposure of young adults with self reported multiple chemical sensitivity (sMCS). *Neurotoxicology*. 2003;24:179–186.
15. Italia. Disegno di legge N 1922 –Atto parlamentare di iniziativa dei Senatori Balboni, Gasparri, Tomassini, Cursi, Bianconi; D'Ambrosio Lettieri, Massidda, Gramazio, Rizzotti, Ghigo, Saccomanno, Calabrò, Di Giacomo, De Lillo e Tofani. Disposizioni in favore dei soggetti affetti da sensibilità chimica multipla (MCS). Senato della Repubblica 16 legislazione. Google free search.
16. Winder C. Mechanism of multiple chemical sensitivity. *Toxicol Lett*. 2002;128:85–97.
17. Bornschein S, Förstl H, Zilker T. Idiopathic environmental intolerances (formerly multiple chemical sensitivity) psychiatric perspectives. *J Intern Med*. 2001;250:309–321.
18. Magnavita N. Cacosmia in healthy workers. *Br J Med Psychol*. 2001;74: 121–127.
19. MCS. Attività del gruppo di lavoro sulla intolleranza idiopatica ambientale ad agenti chimici (IIAAC) denominata anche sensibilità chimica multipla (SCM). Google free search.
20. Martini A, Iavicoli S, Corso L. Multiple chemical sensitivity and the workplace: current position and need for an occupational health surveillance protocol. *Oxid Med Cell Longev*. 2013;2013:351457.
21. Alessandrini M, Micarelli A, Chiaravalloti A, et al. Involvement of subcortical brain structures during olfactory stimulation in multiple chemical sensitivity. *Brain Topogr*. 2016;29:243–252.
22. Chiaravalloti A, Pagani M, Micarelli A, et al. Cortical activity during olfactory stimulation in multiple chemical sensitivity: a ^{18}F-FDG PET/CT study. *Eur J Nucl Med Mol Imag*. 2015;42:733–740.
23. Andersson L, Claeson AS, Dantoft TM, Skovbjerg S, Lind N, Nordin S. Chemosensory perception, symptoms and autonomic responses during chemical exposure in multiple chemical sensitivity. *Int Arch Occup Environ Health*. 2016;89:79–88.
24. Dantoft TM, Skovbjerg S, Andersson L, et al. Inflammatory mediator profiling of n –butanol exposed upper airways in individuals with multiple chemical sensitivity. *PLoS One*. 2015;23:1–15.
25. Orriols R, Costa R, Cuberas G, Jacas C, Castell J, Sunyer J. Brain dysfunction in multiple chemical sensitivity. *J Neurol Sci*. 2009;287:72–78.
26. Zucco GM, Militello C, Doty RL. Discriminating between organic and psychological determinants of multiple chemical sensitivity: a case study. *Neurocase*. 2008;14:485–493.
27. Ojima M, Tonori H, Sato T, et al. Odor perception in patients with multiple chemical sensitivity. *Tohoku J Exp Med*. 2002;198:163–173.
28. Caccappolo E, Kipen H, Kelly- McNeil K, et al. Odor perception: multiple chemical sensitivities, chronic fatigue, and asthma. *J Occup Environ Med*. 2000;42:629–638.
29. Alobid I, Nogue S, Izquierdo-Dominguez A, et al. Multiple chemical sensitivity worsens quality of life and cognitive and sensorial features of sense of smell. *Eur Arch Otorhinolaryngol*. 2014;271:3203–3208.
30. Azuma K, Uchiyama I, Takano H, et al. Changes in cerebral blood flow during olfactory stimulation in patients with multiple chemical sensitivity. A multichannel near infrared spectroscopic study. *PLos One*. 2013;8:1–6.
31. Hillert L, Musabasic V, Berglund H, Ciumas C, Savic I. Odor processing in multiple chemical sensitivity. *Hum Brain Mapp*. 2007;28:172–182.
32. Papo D, Eberlein –König B, Berresheim HW, et al. Chemosensory function and psychological profile in patients with multiple chemical sensitivity: comparison with odor –sensitive and asymptomatic controls. *J Psychosom Res*. 2006;60:199–209.
33. Joffres MR, Sampalli T, Fox RA. Physiologic and symptomatic responses to low-level substances in individuals with and without chemical sensitivities: a randomized controlled blinded pilot booth study. *Environ Health Perspect*. 2005;113:1178–1183.
34. Saito M, Kumano H, Yoshiuchi K, et al. Symptom profile of multiple chemical sensitivity in actual life. *Psychosom Med*. 2005;67:318–325.
35. Östberg K, Ørbaek P, Karlson B, Akesson B, Bergendorf U. Annoyance and performance during the experimental chemical challenge of subjects with multiple chemical sensitivity. *Scand J Work Environ Health*. 2003;29:40–50.
36. Andersson L, Claeson AS, Nyberg L, Stenberg B, Nordin S. Brain responses to olfactory and trigeminal exposure in idiopathic environmental illness (IEI) attributed to smells: an fMRI study. *J Psychosom Res*. 2014;77:401–408.
37. Fiedler N, Kelly–Mc Neil K, Ohman-Strickland P, Zhamg J, Ottenweller J, Kipen HM. Negative affect and chemical intolerance as risk factors for building-related symptoms: a controlled exposure study. *Psychosom Med*. 2008;70:254–262.
38. Lee HS, Hong RZ, Gil HO, et al. Pesticides –initiated idiopathic environmental intolerance in South Korean farmers. *Inhal Toxicol*. 2007;19:577–585.
39. Georgellis A, Lindelöf B, Lundin A, Arnetz B, Hillert L. Multiple chemical sensitivity in male painters; a controlled provocation study. *Int J Hyg Environ Health*. 2003;206:531–538.
40. Lee YL, Pai MC, Chen JH, Guo YL. Central neurological abnormalities and multiple chemical sensitivity caused by chronic toluene exposure. *Occup Med (Lond)*. 2003;53:479–482.
41. Fiedler N, Kelly–Mc Neil K, Mohr S, et al. Controlled human exposure to methyl tertiary butyl ether in gasoline: symptoms, psychophysiologic and neurobehavioural responses of self reported sensitive persons. *Environ Health Perspect*. 2000;108:753–763.
42. Andersson L, Bende M, Millqvist E, Nordin S. Attention bias and sensitization in chemical sensitivity. *J Psychosom Res*. 2009;66:407–416.
43. Van Thriel C, Kieswetter E, Schäper M, Juran SA, Blaszkewicz, Kleinbeck S. Odor annoyance of environmental chemicals: sensory and cognitive influences. *J Toxicol Environ Health A*. 2008;71(part A):776–785.
44. Östberg K, Persson R, Karlson B, Ørbaek P. Annoyance and performance of three environmentally intolerant groups during experimental challenge with chemical odors. *Scand J Work Environ Health*. 2004;30:486–496.
45. Bornschein S, Hausteiner C, Römmelt H, Nowak D, Förstl H, Zilker T. Double -blind placebo-controlled provocation study in patients with subjective multiple chemical sensitivity and matched control subjects. *Clin Toxicol*. 2008;46:443–449.
46. Kimata H. Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self reported multiple chemical sensitivity. *Int J Hyg Environ Health*. 2004;207:159–163.
47. Das Munshi J, Rubin J, Wessely S. Multiple chemical sensitivities: a systematic review of provocation studies. *J Allergy Clin Immunol*. 2006;118:1257–1264.
48. Poonai N, Antony MM, Binkley KE, et al. Carbon dioxide inhalation challenges in idiopathic environmental intolerance. *J Allergy Clin Immunol*. 2000;105:358–363.
49. Ternesten- Hausseus E, Bende M, Millqvist E. Increased capsaicin cough sensitivity in patients with multiple chemical sensitivity. *J Occup Environ Med*. 2002;44:1012–1017.
50. Andersson L, Johansson A, Millqvist E, Nordin S, Bende M. Prevalence and risk factors for chemical sensitivity and sensory hyperreactivity in teenagers. *Int J Hyg Environ Health*. 2008;211:690–697.
51. Gundersen H, Harris A, Bråtveit M, Moen BE. Odor-related chronic somatic symptoms are associated with self reported asthma and hay fever: the Hordaland health study. *Iran J Allergy Asthma Immunol*. 2015;14:19–27.
52. Baliatsas C, van Camp I, Hooiveld M, Yzermans J, Lebret E. Comparing nonspecific physical symptoms in environmentally sensitive patients: prevalence, duration, functional status and illness behavior. *J Psychosom Res*. 2014;76:405–413.
53. Palmquist E, Claeson A-S, Neely G, Stenberg B, Nordin S. Overlap in prevalence between various types of environmental intolerance. *Int J Hyg Environ Health*. 2014;217:427–434.
54. Trabacchi V, Riccò M, Pasquarella C, Signorelli C. Multiple chemical sensitivity syndrome: study on young adult population. *Ig Sanità Pubbl*. 2009;65:363–376.
55. Berg ND, Linneberg A, Dirksen A, Elberling J. ·Phenotypes of individuals affected by airborne chemicals in the general population. *Int Arch Occup Environ Health*. 2009;82:509–517.
56. Berg ND, Linneberg A, Dirksen A, Elberling J. Prevalence of self reported symptoms and consequences related to inhalation of airborne chemicals in a Danish general population. *Int Arch Occup Environ Health*. 2008;81: 881–887.
57. Caress SM, Steinemann AC. A national population study of prevalence of multiple chemical sensitivity. *Arch Environ Health*. 2004;59:300–305.
58. Skovbjerg S, Christensen KB, Ebstrup JF, Linneberg A, Zachariae R, Elberling J. Negative affect is associated with development and persistence of chemical intolerance: a prospective population-based study. *J Psychosom Res*. 2015;78:509–514.

59. Eek F, Karlson B, Österberg K, Östergren PO. Factors associated with prospective development of environmental annoyance. *J Psychosom Res*. 2010;69:9–15.
60. Davidoff AL, Keyl PM, Meggs W. Development of multiple chemical sensitivities in laborers after acute gasoline fume exposure in an underground tunneling operation. *Arch Environ Health*. 1998;53:183–189.
61. Jeong I, Kim I, Park HJ, Roh J, Park JW, Lee JH. Allergic disease and multiple chemical sensitivity in Korean adults. *Allergy Asthma Immunol res*. 2014;6:409–414.
62. Sierra RG, Alvarez Moleiro M. Evaluation of suffering in individuals with multiple chemical sensitivity. *Clin Y Salud*. 2014;25:95–103.
63. Heinonen-Guzejev M, Koskenvuo M, Mussalo-Rauhamaa H, Vuorinen HS, Heikkilä K, Kaprio J. Noise sensitivity and multiple chemical sensitivity scales: properties in a population based epidemiological study. *Noise Health*. 2012;14:215–223.
64. Katerndahl DA, Bell IR, Palmer RF, Miller CS. Chemical intolerance in primary care settings: prevalence, comorbidity, and outcomes. *Ann Fam Med*. 2012;10:357–365.
65. Skovbjerg S, Berg ND, Elberling J, Christensen KB. Evaluation of the quick environmental exposure and sensitivity inventory in a Danish population. *J Environ Public Health*. 2012;2012:304314.
66. Gugliandolo A, Gangemi C, Calabrò C, et al. Assessment of glutathione peroxidase-1 polimorphisms, oxidative stress and DNA damage in sensitivity related illnesses. *Life Sci*. 2016;145:27–33.
67. De Luca C, Gugliandolo A, Calabrò C, et al. Role of polymorphism of inducible nitric oxide synthase and endothelial nitric oxide synthase in idiopathic environmental intolerances. *Mediat Inflamm*. 2015;2015:245308. Epub ahead of print.
68. Dantoft TM, Elberling J, Brix S, Szecsi PB, Vesterhauge S, Skovbjerg S. An elevated pro-inflammatory cytokine profile in multiple chemical sensitivity. *Psychoneuroendocrinology*. 2014;40:140–150.
69. Cui X, Lu X, Hiura M, Oda M, Miyazaki W, Katoh T. Evaluation of genetic polymorphisms in patients with multiple chemical sensitivity. *PLoS One*. 2013;8:e73708.
70. Cui X, Lu X, Hiura M, et al. Prevalence and interannual changes in multiple chemical sensitivity in Japanese workers. *Environ Health Prev Med*. 2014;19:215–219.
71. Cui X, Lu X, Hisada A, Fujiwara Y, Katoh T. The correlation between mental health and multiple chemical sensitivity: a survey in Japanese workers. *Environ Health Prev Med*. 2015;20:123–129.
72. Caccamo D, Cesareo E, Mariani S, et al. Xenobiotic sensor and metabolism related gene variants in environmental sensitivity related illnesses: a survey on the Italian population. *Oxid Med Cell Long*. 2013;2013:Article ID 831969.
73. Fujimori S, Hiura M, Cui XY, Lu X, Katoh T. Factors in genetic susceptibility in a chemical sensitive population using QEESI. *Environ Health Prev Med*. 2012;17:357–363.
74. De Luca C, Scordo MG, Cesareo E, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. *Toxicol Appl Pharmacol*. 2010;248:285–292.
75. Österberg K, Persson R, Karlson B, Eek C, Ørbaek P. Personality, mental distress, and subjective health complaints among persons with environmental annoyance. *Hum Exp Toxicol*. 2007;26:231–241.
76. Eis D, Helm D, Mühlinghaus T, et al. The German Multicentre study on multiple chemical sensitivity (MCS*). Int J Hyg Environ Health*. 2008;211:658–681.
77. Bailer J, Witthöft M, Rist F. Psychological predictors of short- and medium term outcome in individuals with idiopathic environmental intolerance (IEI) and individuals with somatoform disorders. *J Toxicol Environ Health A*. 2008;71:766–775.
78. Baldwin CM, Bell IR. Increased cardiopulmonary disease risk in a community –based sample with chemical odor intolerance. Implications for women's health and health care utilization. *Arch Environ Health*. 1998;53:347–353.
79. Bell IR, Patarca R, Baldwing CM, Klimas NG, Schwartz GER, Hardin EE. Serum neopterin and somatization in women with chemical intolerance, depressives and normal. *Neuropsychobiology*. 1998;38:13–18.
80. Black DW, Okiishi C, Schlosser S. The Iowa follow up of chemically sensitive persons. *Ann NY Acad Sci*. 2001;933:48–56.
81. Altenkirch H. Multiple chemical sensitivity (MCS) –differential diagnosis in clinical neurotoxicology: a German perspective. *Neurotoxicology*. 2000;21:589–598.
82. Hausteiner C, Mergeay A, Bornschein S, Zilker T, Förstl H. New aspects of psychiatric morbidity in idiopathic environmental intolerances. *J Occup Environ Med*. 2006;48:76–82.
83. Skovbjerg S, Rasmussen A, Zachariae R, Schmidt L, Lund R, Elberling J. The association between idiopathic environmental intolerance and psychological distress, and the influence of social support and recent major life events. *Environ Health Prev Med*. 2012;17:2–9.
84. Berg ND, Linneberg A, Thyssen JP, Dirksen A, Elberling J. Non allergic cutaneous reactions in airborne chemical sensitivity: a population based study. *Int J Hyg Environ Health*. 2011;214:239–245.
85. Caress S, Steinemann AC. Asthma and chemical hypersensitivity: prevalence, etiology, and age of onset. *Toxicol Ind Health*. 2009;25:71–78.
86. Bornschein S, Hausteiner C, Drzezga A, et al. Neuropsychological and positron emission tomography correlates in idiopathic environmental intolerances. *Scand J Work environ health*. 2007;33:447–453.
87. Caress S, Steinemann AC. Prevalence of multiple chemical sensitivities: a population –based study in the Southeastern United States. *Am J Public health*. 2004;94:746–747.
88. Park J, Knudson S. Medically unexplained physical symptoms. *Health Rep*. 2007;18:43–47.
89. Hojo S, Ishikawa S, Kumano H, Mijata M, Sakabe K. Clinical characteristics of physician-diagnosed patients with multiple chemical sensitivity in Japan. *Int J Hyg Environ Health*. 2008;211:682–689.
90. Bornschein S, Hausteiner C, Pohl C, et al. Pest controllers: a high –risk group for multiple chemical sensitivity (MCS). *Clin Toxicol*. 2008;46:193–200.
91. Ralph B, Martine O, Jacques R. Double-blind non controlled chemical challenge with environmental toxicological assessment in a multiple chemical sensitivity case. *J Neurol Sci*. 2011;306:154–156.
92. Davidoff AL, Fogarty L, Keyl PM. Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. *Arch Environ Health*. 2000;55:165–175.
93. Heuser G, Wu JC. Deep subcortical (including limbic) hypermetabolism in patients with chemical intolerance: human pet studies. *Ann N Y Acad Sci*. 2001;933:319–322.
94. Li C-Y, Sung F-C. A review of the healthy worker effect in occupational epidemiology. *Occup Med (Lond)*. 1999;49:225–229.
95. Visser I, Wekking ME, de Boer AGEM, et al. Prevalence of psychiatric disorders in patients with chronic solvent induced encephalopathy (CSE*). Neurotoxicology*. 2011;32:916–922.
96. Baker EL. A review of recent research on health effects of human occupational exposure to organic solvents. *J Occup Med*. 1994;36:1079–1092.
97. Olson Kent R. *Acute intoxications, poisons,pharmaceutical substances and drugs. Second Edition by Tiziana della Puppa.* Springer 2007, English version: Poisoning &Drug overdose; Google free search.

