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DOCUMENTATION TO REQUEST THE RECOGNITION OF MCS IN THE WHO

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INTRODUCTION

The purpose of this document, entitled **Multiple Chemical Sensitivity**, is to gather some of the most relevant aspects of this disease. It includes the biological and physiological aspects most widely studied during the last few decades in relation to its etiopathogenesis and development.

The report's aim is, firstly, for the disease to be recognized in the international ICD-11 as Multiple Chemical Sensitivity, thus encompassing under one single term an illness with different names in the countries in which it has officially been recognized, and secondly, for Multiple Chemical Sensitivity to be included in the public health systems of those countries where it is still pending recognition.

In most countries across the world, affected individuals currently survive outside the protection which their States should grant them, without adequate medical care, without treatment, without access to social security protection systems, without adaptations to their workplaces and educational or cultural centers, etc. Furthermore, and as a consequence of this marginalization from public institutions, sufferers become socially and family isolated, being often stigmatized as psychiatric patients due to the lack of understanding of doctors and family members.

These dramatic situations could be avoided or alleviated to a great extent if Multiple Chemical Sensitivity is recognized in the ICD-11, with the consequent introduction in respective state health systems, the training of doctors and health professionals and more comprehensive information about the disease to the general public.

Some of the most important national and international scientific publications available on this disease have been reviewed to prepare this report, as well as documents published in those countries where Multiple Chemical Sensitivity has been recognized in their national ICD appendixes.

1) DIFFERENT NAMES FOR THE SAME DISEASE

Multiple Chemical Sensitivity (MCS), also known in Spanish by its acronym SQM, is a disease described in the United States since the early 1950s by Theron Randoplh, who observed how some people developed specific symptoms when exposed to very low levels of substances present in the environment, in the workplace or at home. It is also known as "Chemical Sensitivity", "Disease of the 20th century", "Universal Allergy", "Chemical Response Syndrome", "Toxic Induced Loss of Tolerance", "Multiple Sensory Sensitivity Syndrome" or "Idiopathic Environmental Illness".

Other names have also been used to approximate its particular locations, e.g., *"Gulf War Syndrome"* from the first Gulf War (1990-91) and *"New Building Syndrome",* which develops in poorly ventilated buildings with new furnishings where there is a high presence of Volatile Organic Compounds (VOCs). As will be discussed below, VOCs alone can trigger Chemical Sensitivity in some people.

There are other illnesses whose characteristics are closely related to those of MCS, such as the "*Sick Building Syndrome*", more characterized by poor ventilation, content of asbestos or other toxic materials, presence of fungi and high load of electromagnetic radiation, or the "*Chinese Restaurant Syndrome*", where the high content of monosodium glutamate causes the development of symptoms similar to those of MCS.

This multitude of names and origins reflects the medical and scientific challenge of studying such a complex disease. Its understanding is essential to achieve early diagnosis and therefore avoid the development of more severe and disabling symptomatology.

Both Multiple Chemical Sensitivity (MCS) and Chemical Sensitivity (CS) will be hereinafter used to refer to the disease in this report.

The most frequently used terms recognize that affected individuals understand that chemicals and the environment are associated with their disease.

2) DEFINITION

The Canadian Human Rights Commission defined the disease in 2007 as follows:

"Multiple Chemical Sensitivity (MCS) is the term most commonly used to describe a complex syndrome that presents as a set of symptoms linked to a wide variety of

agents and components found in the environment, with such reactions occurring after exposure at levels commonly tolerated by most people."

This definition is included in the Spanish Consensus Document of the Ministry of Health, 2011.

In 2021, a Consensus on the clinical and therapeutic management of this disease was published in the *International Journal of Environmental Research and Public Health* (see *Damiani et al., 2021*) by a set of Italian experts and medical researchers on MCS. In this paper, the disease is defined as follows:

"Multiple Chemical Sensitivity (MCS) is a multisystem, recurrent, environmental disorder that flares in response to different exposures (i.e., pesticides, solvents, toxic metals and molds) under the threshold limit value (TLV) calculated for age and gender in the general population. MCS is a syndrome characterized by cutaneous, allergic, gastrointestinal, rheumatological, endocrinological, cardiological and neurological signs and symptoms."

MCS disease overlaps with other coexisting co-morbidities such as Fibromyalgia (FM), Chronic Fatigue Syndrome (CFS), and Electrohypersensitivity (EHS). It is a multisystem, chronic course disease, characterized by inflammatory and degenerative processes.

Case definition

In 1987, Cullen defined what is currently known as "Multiple Chemical Sensitivity", stating a series of characteristics of the disease. However, this definition lacked consensus, as it did not include all the nuances of the disease. Finally, in 1999, an **International Consensus** established case definition criteria based on **internationally observed patterns consistent with the disease** (*Bartha. Consensus Criteria, 1999*). These criteria received the approval and consensus of 34 North American researchers and clinicians, all of whom had extensive experience treating hundreds of patients with MCS. These case definition criteria introduce, with respect to *Cullen*'s definition, the nuance of avoidance as a therapeutic element.

The case definition is therefore established by the International Consensus as follows:

- ✓ Symptoms are reproducible with repeated chemical exposure.
- ✓ The condition is chronic.
- ✓ Low levels of exposure cause manifestations of the syndrome (such levels are lower than usual or previously tolerated).
- ✓ Symptoms improve or resolve when the triggers are removed.
- ✓ Responses occur to multiple, chemically unrelated substances.

- ✓ Symptoms involve multiple organ systems.

As indicated by *McKeown-Eyssen et al., 2001,* there are many other typical features of this disease which are not included in the Consensus case definition. In addition to the above criteria, having a strong sense of smell in most people, feeling dazed and dull and having difficulty concentrating were also suggested. *Lacour 2005* confirms and extends these criteria, adding the aspects of: worsening of quality of life and organ functions, with recurrent and reproducible symptoms that always affect the central nervous system with a characteristic hypersensitivity to odors, in addition to at least one other symptom in another organ system.

3) SYMPTOMS

Pall 2009 states that MCS is a complex disease often initiated after acute exposure to some chemical compound. In most cases, however, there is no particular exposure event and it is chronic **exposure to various compounds at low doses** that may initiate most cases.

Once the disease has been triggered, those affected report sensitivity or intolerance to low levels of a broad spectrum of chemicals. Symptoms reported from chemical exposure are diverse and variable from patient to patient, but they all include pain, especially headaches, muscle and joint pain, confusion, cognitive impairment, asthmatic-type symptoms, rhinitis, sleep disturbance, fatigue, and even psychiatric symptoms in some individuals such as anxiety, depression, and less frequently rage and anger. *Pall 2009* refers to previous studies reviewing the symptoms of those affected, such as the review by *Sorg's 1999*, where a total of 41 different symptoms are listed, many of which occurred only in a minority of people. *Sorg* states that among the most common symptoms following chemical exposure in patients with MCS are extreme fatigue, headaches, gastrointestinal problems, dizziness, anxiety, depression, upper respiratory irritation, muscle and joint pain, and difficulty concentrating. In *Miller 2001*, 74 symptoms are listed and divided into neuromuscular, head-related, musculoskeletal, gastrointestinal, cardiac, airway-related, cognitive and others. In *Lacour* 2005, nonspecific complaints concerning the central nervous system (headaches, fatigue, cognitive deficits) are listed as the most characteristic among those affected.

Relationship between chemical exposure and MCS

Hooper 2011 highlighted that multiple studies have documented that chemical contamination is spreading throughout the planet. Most strikingly is the fact that umbilical cord blood contains hundreds of toxic compounds, which implies that already

in the uterus, when cell replication is highest, there is no protection against toxic compounds.

In the study by Eis et al., 2008, 287 different chemicals were identified in the umbilical cord blood of newborns. Of those chemicals, 17 were toxic to the brain and nervous system, 208 could cause developmental problems, and 108 could cause cancer in humans and animals.

Chemical and electromagnetic pollution is advancing at an unprecedented pace in human history. What were once diseases typically associated with occupations (painters, shepherds, carpet makers, etc.) are now spreading to non-occupational settings.

Numerous scientific publications have reported a pattern of chemical exposure preceding the development of MCS, either a high-level exposure or a constant low-level exposure to toxicants. Evidence of disease onset following exposure to low levels of toxicity is reported in *Ashford and Miller 1998* and *Sorg 1999*. Twenty-four different studies showing chemical exposure prior to disease onset are reported in *Pall 2007*, and twelve further studies showing chemical exposure prior to disease onset are cited in *Miller 2000*. *Pall 2009* also details additional studies that confirm the occurrence of MCS disease after chemical exposure.

Pall 2009 shows that exposure to organic solvents, which is present in the "Sick Building Syndrome," appears to initiate cases of MCS. Two of the most striking cases of "Sick Building Syndrome" were the Environmental Protection Agency building in Washington, D.C., where approximately 200 people became ill with MCS (See *Miller 2001*) and the *Brigham and Women's Hospital* in Boston, part of the Harvard Medical School complex. This episode is described in *Kawamoto et al., 1997*, where the use of chemicals was subsequently reduced and airflow increased, which led to a substantial decrease in new cases of MCS and related illnesses. This fact suggested a causal relationship between chemical exposure and the onset of the disease.

Epidemiological studies are cited in *Pall 2009* that have estimated the prevalence of MCS in various occupations, including those expected to have significant chemical exposure to some types of chemicals implicated in MCS as a consequence of work. A higher prevalence of MCS was reported in several occupations involving such chemical exposure, again suggesting a causal role for chemical exposure. Two examples of the development of occupational MCS from exposure to VOCs are shown in *Zibrowski and Robertson, 2006*, who showed a higher prevalence of MCS symptoms among laboratory technicians exposed to organic solvents compared to similar technicians with no apparent exposure, and in *Yu et al*., *2004,* who found a high prevalence of MCS symptoms among painters exposed to solvents compared to chemically unexposed controls.

Pall 2009 also shows that there are at least seven groups of chemicals that initiate cases of MCS, as seen below. Along with chemicals, another important element that triggers the illness is the mold present in infected "sick" buildings, as an increase in nitric oxide (NO) and inflammatory cytokines in the nasal passages has been reported to occur in some occupants. Similar responses have also been seen in the lungs of people similarly exposed to mold.

Nitric oxide and inflammatory cytokines are important aspects of MCS, as explained throughout the following pages.

Figure 1: Major classes of chemicals associated with multiple chemical sensitivity (MCS). Psychiatry an Evidence Based Text. Chapter 50: Multiple Chemical Sensitivity

Table 50.5 Major classes of chemicals associated with multiple chemical sensitivity (MCS)

Chemical class	Known biological activities	Common sources/uses
Highly substituted, poly- or per-halogenated organic compounds with chlorine, bromine or fluorine atoms*, e.g. DDT, DDE, lindane, hexachlorobenzene, hexachlorocyclohexanes, PCBs, aldrin, dieldrin, PBDEs, perfluorooctanoic acid polymers and derivatives	Carcinogenic, mutagenic, kidney and liver damage, endocrine disruption	Household and agricultural pesticides as sprays and dusts, electrical insulation, flame-retardants, non-stick kitchen utensils, stain-resistant fabrics
Organophosphates, nerve agents	Nerve toxins, immune dysregulation, inhibition of key enzymes	Various pesticides in agriculture, fisheries, herbicides, engine oils
Phthalates, nonylphenol, bisphenol A and B*	Endocrine disruption	Polymers, plasticizers, toys, babies' pacifiers, dialysis tubing
VOCs, aliphatic and aromatic compounds*, formaldehyde, aldehydes, esters, ketones, acids, alcohols, toluene	Disruption of brain function, nerve damage, carcinogenic	Ubiquitous in fragrances, perfumes, household goods, solvents, fuels, paints, polymers
PAHs	Carcinogenic, mutagenic	Burning fuels, exhaust fumes, power stations
Heavy metals: mercury*, lead, cadmium, arsenic, organometallics, tributyltin*	Neurotoxicity, tissue damage, endocrine disruption	Anti-fouling paints, fuels, preservatives, pesticides, electrical goods, crematoria

*Bioaccumlative and biomagnified through the food chain.

DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodichlorophenylethene (major metabolite of DDT); PAHs, polyaromatic hydrocarbons; PBDEs, polybromodiphenylethers; PCBs, polychlorobiphenyls; VOCs, volatile organic compounds.

In order to understand how the body is able to manage chemical exposure, it is required to consider individual factors, including absorption, distribution, metabolism, excretion, genetics, age, gender, environment and nutritional status.

4) BIOLOGICAL/PHYSIOLOGICAL BASES OF THE DISEASE

This section details some of the main physiological bases of the disease.

☑ NEURAL SENSITIZATION, including the limbic system

It should be noted that a large number of the symptoms associated with this disease are attributed to the Central Nervous System.

Changes in brain function of affected individuals have been shown on PET (Positron Emission Tomography) scans of the brain in patients with MCS — *see Heuser and Wu, 2000*, who observed hypermetabolism in the deep subcortex, including the limbic subcortex, in these affected individuals.

Changes in EGG brain activity (see *Lorig et al.; 1999*, *Bell et al., 1999b*; *Muttray et al., 1995*; *Ross et al., 1999*; *Schwartz et al., 1994*; *Fernandez et al., 1999*) and SPECT scans have also been seen in MCS (see *Simon et al., 1994*; *Heuser et al, 1994*; *Fincher et al., 1997*).

Some authors have proposed a model of neural sensitization and neurogenic inflammation [CORRECT] whereby chemicals would also act by increasing sensitization in the brain, particularly in the limbic system. See *Bell et al., 1992*; *Bell et al., 1999*; *Anntelman 1994*; *Rossi 1996*; *Friedman 1994*; *Sorg et al., 1997*, *Meggs 93 and 95*, *Miller 97*; *Halley et al., 2000*.

Figure 2: **Basal ganglia wrapped round the thalamus, deep in the brain**. *Source: Psychiatry an Evidence Based Text. Chapter 50: Multiple Chemical Sensitivity***.**

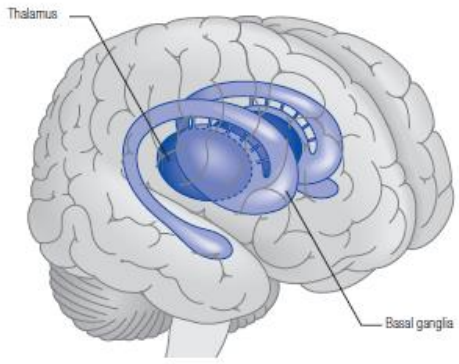

Figure 50.9 Basal ganglia wrapped round the thalamus, deep in the brain

Changes seen in deep brain structures are consistent with the penetration of toxic chemicals into the blood-brain barrier. *Ashford and Miller 1998* suggest that the entry

of chemicals occurs either via the bloodstream or via intraneuronal transport, along the olfactory pathway.

Figure 3: **Potential interactions between Chemical Sensitivity and the domains of neurogenic inflammation, perceptual and central integration, and non-neurogenic inflammation**. *Source: Psychiatry an Evidence Based Text. Chapter 50: Multiple Chemical Sensitivity***.**

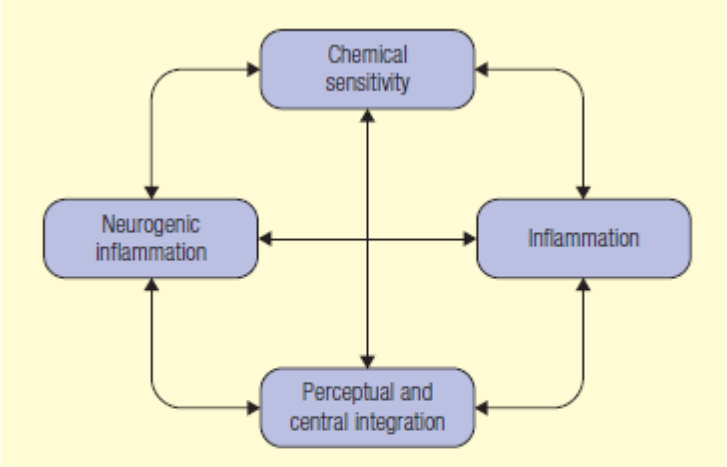

Figure 50.8 Potential interactions between chemical sensitivity and the domains of neurogenic inflammation, perceptual and central integration, and non-neurogenic inflammation

☑ VICIOUS METABOLIC CYCLE: NO/ONOO$^-$ cycle

Human metabolic systems are identical in all cells and are responsible for the conversion of matter into energy in the form of Adenosine Triphosphate (ATP) molecules to perform all functions necessary for life.

In affected individuals, a vicious biochemical metabolic cycle is set in motion, the so-called NO/ONOO$^-$ or nitric oxide-peroxynitrite cycle.

In Chapter 92, **MCS. Toxicological Questions and Mechanisms**, in the *Encyclopedia of Toxicology: General and Applied Toxicology*, the author *Pall ML (Pall, 2009)* describes the etiological mechanisms of MCS and other related diseases. He provides interesting genetic studies, studies in animal models, and studies that argue each of the proposals.

This compendium is one of the most rigorous encyclopedias of toxicology, as every chapter has been reviewed by three other toxicologists, thus avoiding methodological or study design errors, which have been observed in other works. This work is a worldwide reference in the field of toxicology precisely because of its great rigor .

One of the key points to the development of MCS is the excessive activity of the NMDA receptor (N-methyl-D-aspartate), since chemicals act precisely here, in many cases indirectly, by increasing the activity of these receptors. The pathway or route by which this increase in NMDA activity is produced will not be the same in all cases — it will differ depending on the group of toxicants to which the individual is exposed. *Pall 2009* reports that all seven groups of chemicals seen in the scientific literature that initiate cases of MCS (each group encompassing many different compounds) act as toxicants in the disease **because they indirectly produce excessive NMDA receptor activity**.

The seven groups are described as follows:

- ✓ Organophosphates and cabamates

In the case of organophosphate and carbamate toxicants (such as some pesticides and organophosphate flame retardants), the effect occurs because they act by inhibiting the enzyme *acetylcholinesterase* (responsible for the catabolism of acetylcholine) and thus producing an **increase in acetylcholine**. As a consequence, muscarinic **receptors are stimulated**, thus producing an increase in **glutamate release**, which leads to a **stimulation of the NMDA receptor** and other glutamate receptors. Multiple studies show that the effect of organophosphates can be largely diminished by using NMDA antagonists, an indication that NMDA receptor activation plays a major role in the effect these toxicants have in the human body.

- ✓ Pyrethroid pesticides

They also initiate cases of MCS, acting to produce **long-term sodium-channel opening** (*Narahashi et al., 1995; Valentine, 1990; Wu and Liu 2003; Bradberry et al., 2005; Proudfoot, 2005*). This in turn, produces **increased NMDA stimulation** (*Wu and Liu, 2003; Yu, 2006; Doble, 1996*).

- ✓ Organochlorine compounds, including pesticides

Organochlorine pesticides (chlordane, lindane, dieldrin and aldrin) have all been shown to **lower GABAA** (γ-aminobutyricacid) **receptor activity** (*Gant et al., 1987; Corrigan et al., 1994; Cassidy et al., 1994; Brannen et al., 1998; Narahashi et al., 1995*) and this, in turn, is well known to produce **elevated NMDA activity** (*Blaszczak and Turski, 1998; Watanabe et al., 1995; Tusell et al., 1992*). In fact these same citations show that seizure activity produced by these GABAA antagonists, including these pesticides, is blocked by NMDA antagonists, showing that the elevated NMDA activity produced by such toxicants has a key causal role in the mechanism of seizure generation.

- ✓ Organic solventes

These chemicals are the predominant set of chemicals that trigger reactions on a day-to-day basis in MCS patients.

Pall and Anderson 2004 argued that the probable target for such organic solvents in MCS is the **vanilloid receptor** (*transfer receptor potential (TRP)V1*). That paper was extensively documented with 222 citations and with specific references.

- ✓ Mycotoxins

Somemycotoxins are known TRPV1 agonists, so it is possible that the role of moulds in MCS may be explained through the role of the TRPV1 receptor in many cases.

- ✓ Other chemicals

Chemical sensitizers, including toluene diisocyanate (TDI) and eugenol, which produce local sensitivity to a wide range of chemicals, are known TRPV1 agonists. MCS patients often report sensitivity to chlorine gas from swimming pools or from drinking water, and chlorine acts as a TRPV1 agonist *in vivo* (*Morris et al., 2005*), producing an irritant response.

TRPV1 stimulation produces neurogenic inflammation and also reactive airways disease often called reactive airways dysfunction syndrome (RADS), a form of asthma showing reaction to a spectrum of chemicals similar or identical to those involved in MCS. Both RADS and neurogenic inflammation are often aspects of MCS cases (*Meggs, 1994; Meggs, 1997*).

Other authors (*Johansson et al., 2002; Millqvist, 2000; Ternesten-Hasse´us et al., 2002; Millqvist et al., 2005; Millqvist et al., 2008)* have published a series of papers showing that MCS patients are hypersensitive to capsaicin, the classic TRPV1 agonist, again providing support for a TRPV1 role in MCS.

Three other apparent initiators of cases of MCS are carbon monoxide, hydrogen sulfide and mercury.

- ✓ Carbon monoxide

Carbon monoxide has been reported to produce such increased NMDA activity and NMDA antagonists block or lower the toxic responses to carbon monoxide exposure (*Thom et al., 2004; Liu and Fechter, 1995; Penney and Chen, 1996; Ishimaru et al., 1992*).

- ✓ Hydrogen sulfide (H2S)

Hydrogen sulfide can also produce increased NMDA activity and again its toxic effects are lowered by NMDA antagonists (*Cheung et al., 2007; Qu et al., 2008; Kamoun, 2004*).

- ✓ Mercury

Mercury, acting through its metabolic product methylmercury, also acts to produce increases in NMDA activity, and again methylmercury toxicity is lowered by NMDA

antagonists (*Juarez et al., 2005; Allen et al., 2002; Faro et al., 2002; Miyamoto et al., 2001; Zhang et al., 2003; Rossi et al., 1997*). Methylmercury acts to produce such increased NMDA activity, at least in part, by lowering the transport of the glutamate, the most important physiological NMDA agonist (*Juarez et al., 2005; Allen et al., 2002*).

Figure 4:

Pathways for action of pesticides and organic solvents. Each chemical class implicated in the initiation of cases of MCS can act along a distinct pathway to generate increases in NMDA activity, as shown in the figure. Each arrow represents a mechanism by which one parameter stimulates another. Some inhibitory (negative) interactions are also indicated. Both the organophosphorus/carbamate toxicants and the organochlorine pesticides have double negative interactions. Such negative interactions, together with the arrows in the figure, indicate that each of the four classes of compounds acts along one of these pathways, leading to an increase in NMDA activity.

Chapter 92. MCS. Toxicological Questions and Mechanisms. General and Applied Toxicology.

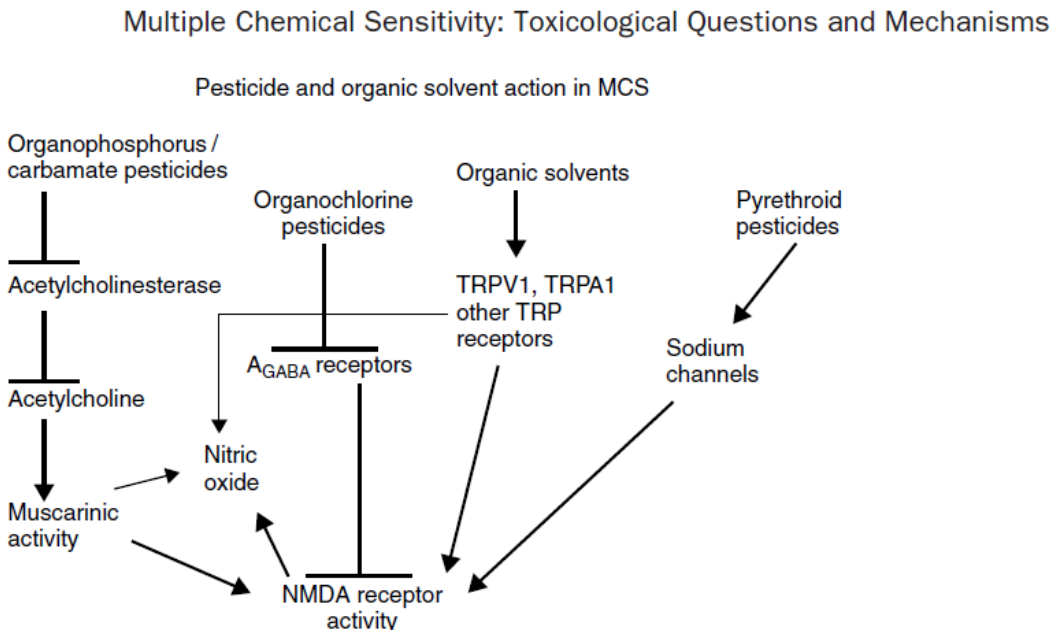

Figure 1. Pathways for action of pesticides and organic solvents. Each chemical class implicated in the initiation of cases of MCS can act along a distinct pathway to generate increases in NMDA activity, as shown in the figure. Each arrow represents a mechanism by which one parameter stimulates another. Some inhibitory (negative) interactions are also indicated. Both the organophosphorus/carbamate toxicants and the organochlorine pesticides have doubl- negative interactions. Such negative interactions, together with the arrows in the figure, indicate that the each of the four classes of compounds acts along one of these pathways, leading to an increase in NMDA activity

As a consequence of NMDA receptor activation, the level of **nitric oxide (NO)** increases, which leads to the **NO/ONOO$^-$ cycle** being set in motion. **NO** reacts with the

Superoxide ion which is generated mainly in the mitochondria in small amounts as part of the normal synthesis of Adenosine Triphosphate (ATP), the main energy molecule in the body. NO and Superoxide bind together to form **Peroxynitrite ($ONOO^-$)**, a strongly oxidizing molecule. This therefore generates oxidative stress, which is one of the main characteristics of MCS and all its overlapping syndromes.

Oxidative stress activates the **genetic transcription factor NFkB**, increasing **Nitric Oxide Synthase (i NOS)** enzyme activity and inflammatory cytokine levels (e.g. **interleukin 6, IL-6**), which also stimulate **i NOS**. At the same time, **calcium ion (Ca^{2+})** is released from intracellular stores into the cell, leading to cell apoptosis and stimulating the activity of enzymes **Neuronal Nitric Oxide Synthase (n NOS)** and **Endothelial Nitric Oxide Synthase (e NOS)**. In addition, oxidative stress and superoxide stimulate the **vanilloid receptors, TRPV1**, which are chemoreceptors found on C-nerve fibers. Vanilloid receptor and NO evoke stimulation of glutamate NMDA receptors' excitation, thus completing the cycle. These interactive positive feedback loops are vicious and destructive biochemical cycles. Understanding them provides a more complete picture of the illness and explains the signs and symptoms of all the syndromes that overlap with MCS.

Figure 5: $NO/ONOO^-$ cycle. *Source: MCS: Toxicological Questions and Mechanisms.*

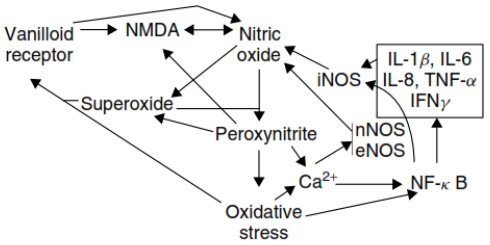

Figure 2. Vicious ($NO/ONOO^-$) cycle diagram. Each arrow represents one or more mechanisms by which the variable at the foot of the arrow can stimulate the level of the variable at the head of the arrow. It can be seen that these arrows form a series of loops that can potentially continue to stimulate each other. An example of this would be that nitric oxide can increase peroxynitrite, which can stimulate oxidative stress, which can stimulate NF-κB, which can increase the production of iNOS, which can, in turn increase nitric oxide. This loop alone constitutes a potential vicious cycle and there are a number of other loops, shown diagramatically in the figure that can collectively make up a much larger vicious cycle. The challengein these illnesses, according to this view, is to lower this whole pattern of elevations to get back into a normal range. You will note that the cycle not only includes the compounds nitric oxide, superoxide and peroxynitrite, but a series of other elements, including the transcription factor NF-κB, oxidative stress, inflammatory cytokines (in box, upper right), the three different forms of the enzymes that make nitric oxide (the nitric oxide synthases iNOS, nNOS and eNOS), and two neurological receptors, the vanilloid (TRPV1) receptor and the NMDA receptor. (The figure and legend are taken from the author's web site with permission.)

Subsequent work by the same author increases to 11 the groups of chemical families that indirectly produce NMDA receptor activation.

Experiments in animal models confirm the link between MCS and excessive NMDA activity. The antagonist of this receptor, dextromethorphan, has been found to decrease the response to chemical substances in patients with MCS.

Studies of genetic polymorphisms have shown that in the CCK-B gene, the allele of the gene that acts indirectly to produce an increase in NMDA activity is associated with an increased MCS prevalence, *Binkley et al., 2001.*

Bell and other scientists who present the model of neural sensitization as a key element in patients with MCS, suggest that the likely mechanism for such sensitization is the so-called **Long Term Potentiation (LTP)**. This mechanism **involves an increase in NMDA activity**. It has also been shown in many animal models of MCS that excessive NMDA activity plays an important role in this disease.

Conclusions

The NO/$ONOO^-$ cycle is based on five principles (*Pall 2009*):

- ✓ The factors that initiate cases of multisystem diseases act by increasing NO synthesis and subsequent levels of $ONOO^-$ and/or other elements of the cycle.

- ✓ Initiation becomes a **chronic disease** due to the fact that the reactions occurring in the cycle take place on an ongoing basis, so that the various elements of the cycle such as NO, $ONOO^-$ and others will chronically show high values.

- ✓ MCS symptoms and signs are caused by high NO levels and/or other relevant consequences of the proposed mechanism, including high levels of ONOO, NO, inflammatory cytokines, oxidative stress, increased NMDA receptors, TRPV1 and other aspects of the cycle. This fact reveals the immune activation and characterizes the **inflammatory, oxidative and degenerative processes** that take place in this disease.

- ✓ Due to the components involved, NO, superoxide and ONOO- have fairly limited diffusion distances in biological tissues, and since the mechanism involved in the cycle acts at individual cell level, **the main mechanisms are local in nature**. This entails that there can be variations in the impacted tissue and it may differ from one affected individual to another. That explains the differences in symptoms from one individual to the next. **Those differences do not rule out the presence of systemic effects, they only mean that there are also local effects.**

- ✓ Therapy should aim to down-regulate the biochemistry of the NO/ONOO- cycle. In other words, it should focus on reducing the cause of the illness, not only on treating the symptoms.

Pall 2009 (*Chapter 92. MCS. Toxicological Questions and Mechanisms*, in the Encyclopedia *General and Applied Toxicology*), from where this whole section has been extracted, states that, while what has become the NO/ONOO− cycle has produced fairly complete explanations of such illnesses as CFS and FM and also of a number of additional, well-established diseases, it alone did not produce a compelling explanation for the complexities of MCS. It was only when fused with a previous model, the neural sensitization model, that a much more complete explanation became apparent.

The fusion of both models (neuronal sensitization and neurogenic inflammation, and NO/ONOO- cycle) explains the main challenging aspects of the disease, such as its chronicity, diversity of effects and involvement of many body systems, given that the impacted tissues can be diverse.

The neural sensitization model proposed by Bell and her collaborators (*Bell et al., 1992; Bell et al., 1999a; Bell et al., 2001a*) and others (*Antelman, 1994; Rossi, 1996; Friedman, 1994; Sorg and Prasad, 1997*), where chemicals were proposed to act to greatly increase neural sensitization in the brain, particularly in the limbic system. The notion here is that if chemicals can act to produce such neural sensitization, greatly increasing the activity of synapses over large regions of the brain, that this could explain the basic mechanism of MCS.

The neural sensitization interpretation of MCS never generated explanations of how the various classes of chemicals may work nor how the roughly 1000-fold increase in chemical sensitivity that appears to occur in many MCS patients might be generated, nor the similarities to CFS and related illnesses. It did provide a framework to explain the chronic nature of chemical sensitivity, namely long-term changes in synaptic sensitivity.

The **LTP** mechanism is involved on a highly selected basis in strengthening synaptic interactions in the process of learning and memory. In the process of neural sensitization, changes in each synapse involve changes in both the presynaptic and the postsynaptic neurons.

LTP is known to involve, as key elements in a complex overall mechanism activated in the postsynaptic neuron, several elements of the NO/ONOO- cycle, notably NMDA activity, NO and intracellular calcium. Superoxide, another cycle elemental, so has a

role, albeit a complex one. Increased NMDA activity in the postsynaptic neuron has a role, as do the increases in intracellular calcium and NO produced by such NMDA stimulation of the postsynaptic neuron. NO produced in the postsynaptic neuron acts as what is called a retrograde messenger, diffusing back to the presynaptic neuron and causing it to be more active in neurotransmitter release, including the release of glutamate, the major physiological agonist of the NMDA receptors. LTP involves not only increased glutamate release, but also changes in the postsynaptic neuron, making its synapses more sensitive to stimulation.

One point that needs to be made is that we have a striking convergence between the demonstrated role of each of the chemicals implicated in MCS, producing increased NMDA activity, and the essential role of NMDA receptors in LTP. This convergence provides, therefore, for the first time, an explanation for that pattern: only chemicals leading to increased NMDA activity may be expected to produce an up-regulation of the LTP mechanism.

Whereas the normal, highly selective role of LTP in learning and memory will not be expected to involve any substantial NO/ONOO- cycle elevation, a massive stimulation of NMDA activity over substantial regions of the brain, produced by chemical exposure, will be expected to involve substantial NO/ONOO− cycle elevation.

Conclusions reached by this author have been obtained through the study and interrelation of numerous well-established and proven scientific principles whose authors are cited with great rigor in this work (*Pall 2009*). Many of the proposed mechanisms of action have been contrasted in experiments with animal models in MCS. The author of this publication (reviewed, as mentioned above, by three other toxicologists to ensure that no methodological errors were made) acknowledges the need for further research in this direction, admitting verbatim "*…the extraordinarily low level of research support that has been available for MCS studies."*

☑ METABOLISM OF TOXINS

The liver is the main but not the only organ of metabolism and it is essential for the elimination of both exogenous and endogenous compounds, and thus xenobiotics from the body. Metabolic processes have been extensively studied and involve a series of well-defined chemical reactions. The understanding and study of phase I and II of endogenous and exogenous molecules metabolism is of particular importance, especially in understanding the significance of detoxification in people with MCS.

Phase I consists of a large family of enzymes, for instance mono-oxygenases and cytochrome P-450 enzymes that introduce oxygen atoms into organic compounds that are highly lipid-soluble, thus creating highly reactive intermediates. In phase II, these

intermediates conjugate with a variety of molecules to create water-soluble products that can be excreted in the urine. In a later phase III, excretion of lipid compounds in the feces takes place. Human CYP enzymes play a central role in the excretion of numerous key endogenous compounds, and have been extensively studied for their relationship to the metabolism of ISO drugs and carcinogenic compounds.

There are basically six conjugation pathways in phase II:

- Glutathione conjugation
- Amino acid conjugation
- Methylation
- Sulphation
- Acetylation
- Glucuronidation

Human CYP plays an important role in the transformation of many endogenous compounds. It has nevertheless been most studied for its relationship to the metabolism of certain drugs and carcinogenic compounds (e.g. Polycyclic Aromatic Hydrocarbons, PAHs).

Metabolism and elimination of xenobiotics have become a significant area of study within toxicology. CYP450s are involved in the metabolism of approximately 75 percent of drugs and xenobiotics and are present in many key areas of the body, including mitochondrial membranes, the blood-brain barrier, the gastrointestinal tract and the liver.

Many of the xenobiotics found widely distributed in the environment are PAHs. Phase I metabolism transforms PAHs into highly reactive compounds such as epoxides, which in turn are conjugated in phase II into polar compounds, which can be then excreted in the urine. If phase I process is not carried out appropriately and does not conjugate with phase II, then **reactive oxygen species (ROS)** are created. These species can prove to be very destructive and lead to oxidative damage, which may cause tissue damage, a feature of all multisystem diseases, including MCS, FM, CFS and EHS.

Hence the importance to highlight that the ratio at which phase I produces activated intermediates has to be balanced or lower than the ratio at which phase II conjugates and excretes toxins in the urine via the kidneys, or in the bile and feces via the intestine, and in sweat. As mentioned above, if phase I happens faster than phase II, active intermediate metabolites will be produced that are more toxic than the original ones and very destructive.

Many drugs are P-450 enzyme inhibitors, which can result in a build-up of medication and foreign chemicals (xenobiotics) that increases side effects and toxicity. Examples of inhibitory drugs include cimetidine, ciprofloxacin, diltiazem, erythromycin,

ketoconazole, verapamil, and a number of selective serotonin reuptake inhibitors (SSRIs).

For a deeper understanding of these aspects, the following books are recommended:

Jakoby WB, Enzymatic Basis of Detoxification. Vol. 1, Academic Press. 1980. This book explains in detail the catalytic mechanism and physiological expression of the enzymes involved in detoxification phase I and phase II, including the action of the enzymes alcohol dehydrogenase, aldehyde oxidase, superoxide dismutase, glutathione peroxidase and monoamine oxidase, as well as the action of cytochrome P-450. The book explores the metabolism of xenobiotics and what specific enzymes do.

***Jakoby* WB**, Enzymatic Basis of Detoxification. Vol. 2, Academic Press, New York (1980). This volume elaborates on the biochemistry of all the conjugation pathways.

Malnutrition and high toxic body load

It should be noted that, for all these biochemical reactions to take place, the body needs to be provided with the appropriate enzymes that catalyze each one of the reactions, as well as the nutrients that act as coenzymes, assisting in each of these processes. Some authors have proved a low nutritional status on those affected by MCS and related illnesses — see *Jacoby, 1980, Ross et al., 1989, Rea 1986, Cox et al., 1991, Romano et al., 1994, Rogers 1990*. Due to the lack of an adequate nutritional reserve, the cofactors are not available to assist in these reactions, which leads to an inability to detoxify properly, thus causing an accumulation of toxins and increasing what is known as the **toxic body load** (burden). This in turn accumulates more toxicity in the organism and makes affected individuals more vulnerable to the impact of toxic chemicals in the body, since the capacity for homeostatic regulation is altered.

Other studies have linked high toxic body load with Chemical Sensitivity (CS) disease and related illnesses, as shown in *Rea 1987*, who confirms the existence of a high concentration of hydrocarbon organic compounds that shows higher in people with Chemical Sensitivity. Another instance is that of *Pan et al., 1987/88*, where a large concentration of aliphatic hydrocarbon solvents was found among those affected. In *Rea 1986*, a high concentration of organochlorine pesticides and chlorinated solvents is found in the blood of people with Chemical Sensitivity.

In *Ziem 1999*, the author calls attention to the fact that toxic injury from repeated exposure to solvents, pesticides, fragrances, etc., can cause a decline of the immune, endocrine and nervous systems; impairment of the detoxification, energy and neurotransmitter metabolism; protein, mineral and nutrient deficiencies; as well as

gastrointestinal changes such as yeast infection, parasites, reduced pancreatic enzyme function, gluten intolerance, reduced secretory IgA levels and adrenal insufficiency.

In *Carrasco NJ 2009*, the author shows how malnutrition and environmental toxicity are influencing illnesses in recent generations, going so far as to state that this coming generation may be the first in which children are sicker than their parents, since advanced disease processes previously only seen in adults are now occurring at the age of seven.

It should also be taken into account that those affected by MCS carry genetic polymorphisms that prevent detoxification from occurring as efficiently as in the rest of the population. This may explain why people do not react in the same way to the same chemical exposure.

For a better understanding of all these factors, the following books are recommended:
Rea, William J.: Chemical Sensitivity, Volume I, Lewis Publishers, Boca Raton, Florida, 1992.
Rea, William J.: Chemical Sensitivity, Volume 3, Lewis Publishers, Boca Raton, Florida, 1996.
Rea, William J.: Chemical Sensitivity, Volume 4, Lewis Publishers, Boca Raton, Florida, 1997.

☑ GENETICS

Marshal et al., 2011 states that genetic polymorphisms have been found in chemically sensitive people compared to control groups which seem to indicate that these people have greater difficulty than the majority of the population in metabolizing and excreting chemicals commonly found in the environment and in drugs. Although relatively recent, the science of epigenetics and how environmental stimuli can have an effect by turning on or off metabolic enzymes expression, is evolving very rapidly.

As stated in *Genuis, 2008*: "*Just as a loaded gun needs to be triggered to unload destruction, epigenetic research confirms that disease is often the result of vulnerable genes being triggered by specific determinants. Mounting evidence suggests that without activation, some disease processes will not develop, and removal of the initiating trigger may allow developing illness to abate or subside.*"

In an Italian study by *De Luca et al., 2010*, patients diagnosed with or suspected of having MCS were compared to healthy controls. Although the various tested genes were not observed to be different in the combined "case" population, several metabolizing enzymes were actually found to be different. The authors of this study concluded that ***"The altered redox and cytokine patterns suggest an inhibition of metabolizing and antioxidant enzyme expression/activity in MCS. Metabolic***

parameters indicating accelerated lipid oxidation, increased nitric oxide production and glutathione depletion in combination with increased plasma inflammatory cytokines should be considered in the biological definition and diagnosis of MCS."

Pall 2009 shows that there are genetic studies on the increased susceptibility or tendency to suffer from MCS. Three studies are named in which chemicals play a causal role in initiating MCS cases.

In the first of those studies, *Haley et al., 1999*, Gulf War veterans, including those who suffered from MCS, also suffered from related illnesses such as FM or CFS. Gulf War veterans were subjected to more than a dozen stressors that may have played a significant role in the onset of the disease, such as exposure to organophosphorus toxicants (sarin, cyclosarin). *Haley et al., 1999* reported that those veterans who carried a form of the gene for PON1 that made them less able to metabolize these neurotoxicants were more likely to develop neurological symptoms. This provides substantial evidence that sarin/cyclosarin gases played a crucial role in the development of the disease in those whose enzyme encoded by the PON1 gene showed reduced activity, making them less able to detoxify toxicants and more prone to develop the disease. Concerning the PON1 gene, *Mackness et al., 2003* also reported that, among farmers who used organophosphates for washing sheep, those whose allele for PON1 yielded a lower pesticide metabolism suffered from chronic disease, compared to farmers who reported better health.

The second and third studies were conducted on civilian population with MCS compared with control groups. One was the Canadian study by *McKeown-Eyssen et al., 2004*, and the other one was a German study by *Schnakenberg et al., 2007*.

Both studies showed that the three different genetic polymorphisms involved in the metabolism of chemicals that were also involved in the initiation of MCS cases, had a statistically significant influence on susceptibility. In the *Schnakenberg et al., 2007* study a very high level of statistical significance was found for each of these three genes, so the probability of obtaining these results by chance if there was no true correlation is less than 1 in 10^{11}. In *McKeown-Eyssen et al., 2004* an 18-fold increased risk of developing MCS was shown when interactions happened between the metabolizing enzymes of CYP2D6 and NAT2 genes.

Pall 2009 concludes that "*From the three major studies conducted on this topic (Haley et al., 1999, McKeown-Eyssen et al., 2004, and Schnakenberg et al., 2007), we have a pattern of evidence showing that genes that metabolize chemicals otherwise implicated in MCS initiation, have substantial influence on the susceptibility to develop MCS. These results support the inference that chemicals acting as toxicants cause many cases of MCS and that those chemicals must be in their toxic form in order to so act. Therefore, alleles of polymorphic genes that either decrease or increase the metabolism of these chemicals will influence the susceptibility to MCS."*

Figure 7: Genetic polymorphisms influencing MCS susceptibility. *Source: MCS: Toxicological Questions and Mechanisms.*

Table 1. Genetic polymorphisms influencing MCS susceptibility

Gene	Study	Function—chemical metabolism	Comments
PON1	H, M	Detoxification of organophosphorus toxicants	—
CYP2D6	M	Hydroxylation of hydrophobic compounds	Hydroxylation of compounds without hydrogen binding group may be expected to lead to greater activity as a TRPV1 agonist
NAT2	M, S	Acetylation	May produce more or less activity depending on the specific compound involved
GSTM1	S	Provide reduced glutathione for conjugation	Should increase detoxification and excretion
GSTT1	S	Glutathione conjugation	Should increase detoxification and excretion
GSTP1	S	Glutathione conjugation	Should increase detoxification and excretion; only statistically significant role was in conjunction with specific alleles of other genes

H, Haley *et al*. (1999); M, McKeown-Eyssen *et al*. (2004); S, Schnakenberg *et al*. (2007).

Hooper 2011 points out the significance of studying genes carried by people with MCS. The relevance of genetic variations in the metabolization of drugs and xenobiotics was acknowledged in the scientific literature at the beginning of the 21st century. See *Nebert DW 2000, Ma MK, et al., 2000.*

"The underlying genetic predisposition of each patient will reflect combinations of slow or poor metabolizer phenotypes or fast or extensive metabolizer phenotypes. If these enzymes take part in the same metabolic pathway for any given drug or environmental agent, such genetic variability could be synergetic and lead to as much as 30- or 40-fold differences in molecule activation or degradation. The end result may be large interindividual differences in the risk of environmental toxicity." Cory-Slechta et al., 2008.

In *Wiesmuller et al., 2008* no link was found with some allele frequencies, but only NAT1, NAT2, PON1 and PON2 were considered. *Hooper 2011* notes in this regard that CYP2D6 or GST genes were not considered, and so it is a complex field of study due to the large number of genetic variants of the numerous enzymes involved in xenobiotic metabolism. It is however urgent to address this subject area as it will be very fruitful in order to understand the widespread variations in MCS.

Cui et al. 2013 comes to the conclusion that highly sensitive patients presented a greater association with SOD2 polymorphisms.

Caccamo et al. 2013 studied genetic polymorphisms associated with phase I and phase II metabolizing enzymes by comparing, in the three patient cohorts used for the study,

the frequencies of genetic polymorphisms for metabolizing enzymes in P-450 (CYP) cytochrome and, for the first time, also the frequency of Aryl hydrocarbon xenobiotic receptor (AHR). A significantly higher frequency of CYP2C9 ∗ 2, CYP2C9 ∗ 3, CYP2C19 ∗ 2, CYP2D6 ∗ 4 and CYP2D6 ∗ 41 polymorphisms was found in patients compared to controls. This fact confirms that these genetic variants represent a genetic risk factor for diseases related to Environmental Sensitivities.

It is therefore important to factor in the presence of genetic polymorphisms in those genes involved in the biochemistry or transformation of molecules participating in processes which are crucial for detoxification and disintoxication.

CONCLUSION

As can be seen, all the physiological/biochemical bases set out in this section, together with others proposed in the scientific literature, do not contradict each other, but are different pieces of the same puzzle that have to be put together for a complete understanding of the disease.

5) DIAGNOSIS

MCS diagnosis is well established in Spain in the Consensus Document on Multiple Chemical Sensitivity, 2011 of the Spanish Ministry of Health, and the Scientific Evidence Update on Multiple Chemical Sensitivity (MCS), 2015.

A reliable compendium on this aspect can be found on page 57, Section III of the Consensus Document: *Conclusions and Recommendations Agreed by the Drafting Group*. In a clear and concise manner, it describes case definition, diagnostic criteria, etiopathogenesis, anamnesis, physical examination and additional tests, mentioning as well various questionnaires that support the diagnosis of MCS. Particular emphasis is also placed on the avoidance of triggering substances to prevent symptoms as the only known tool, while proposing a health care algorithm.

The diagnosis of MCS is a clinical diagnosis, based on the presence of symptoms and signs. To this end, it is required to conduct a reliable anamnesis with a detailed clinical history as well as a history of environmental exposure, not only in the workplace, but also in the home, in the hobbies field, etc.

The QEESI questionnaire is the most widely used diagnostic tool in the scientific literature and has been validated by clinicians. It allows using a symptom severity rating scale. The QEESI test showed a sensitivity of 92% and a specificity of 95% in discriminating between chemically sensitive people and the common population.

Regarding the aforementioned additional tests that can be performed to assess the general condition of the patient, the Spanish Consensus Document proposes some of them. In this section we will present some of those reflected in scientific literature:

It is important to stress that MCS disease has no pathognomonic biomarker, that is to say, there is no specific test that confirms or excludes the disease.

The following are some **indicative additional tests** suggested in different articles that can be performed to help in the assessment of the patient's general condition in relation to the disease he/she is suffering from.

The Spanish *Consensus Document, 2011, Ministry of Health* states:

"Performing a thorough physical examination, in relation to the symptoms exhibited, paying attention to the existence of signs, if any: erythema, hoarseness, attention and speech disorders, distension or increased abdominal perimeter, tachycardia, arrhythmia, tachypnea, motor hyperactivity, motor incoordination, bradypsychia, vulvovaginitis, asterixis."

"Requesting additional tests shall be considered individually, based on the clinical picture, the physical examination and the suspicion of a related illness (for instance, thyroid function analysis, basal cortisol, RF, ANA, 25 OH-D, PTHi, prolactin, ferritin, Vitamin B12 or folic acid)."

The French working group (*Belpomme et al., 2015, Belpomme and Irigaray 2020, 2022*) suggests the following tests in their studies:

- Histamine, as a marker of inflammation.
- 6-OHMS, as a marker of chronic insomnia.
- HSP27 and HSP70, as markers of cellular stress.
- Anti-myelin P0 antibodies, as an autoimmune marker.
- Pulsed Cerebral Echo-Doppler, to measure cerebral blood flow.
- Nitrotyrosine, as a marker of oxidative stress ($ONOO^-$).
- hs-CRP (hypersensitive C-reactive protein).

Belpomme's work concludes that those affected by MCS (and also those affected by EHS) share common disease mechanisms, such as a low degree of inflammation, due to which patients show hyperhistaminemia, autoimmune response and presence of oxidative and nitrosative stress. It has also been found that the 6-hydroxymelatonin (6-OHMS)/creatinine ratio in 24-hour urine was normal or significantly decreased in a high number of subjects. Hypoperfusion in the capsulothalamic area has been seen in patients when measuring cerebral blood flow in the temporal lobes with pulsed brain ultrasound computed tomosphygmography in patients with MCS and also with EHS (Electrohypersensitivity).

Other clinicians have recommended:

- ATP profile test: measurement of ubiquinone, cytochromes, etc. in order to assess mitochondrial involvement.
- Stress tests, to measure functional limitation, may be indicative.
- NIRS: Near infrared spectroscopy. Women exposed to organophosphates show impaired delivery of oxygen after exercise (*Verdaguer-Codina, Valls-Llobet, Pujol Amat 2004*).
- Autoimmunity tests, e.g. antibodies to rule out Hashimoto's thyroiditis, etc.
- Brain SPECT imaging to assess brain dysfunction, or other tests such as PET or EEG. Imaging tests are proposed based on findings of the presence of brain dysfunction, which can show in the test. However, it should be taken into consideration that in moderate or severe MCS sufferers, these tests can severely impact their health. It is also crucial to consider the fact that they are not definitive markers.
- Assessment of underlying chronic inflammatory processes, using the inflammatory risk factor with genetic polymorphism testing in relation to IL1-alpha, IL1-beta, TNFα, and IL1RA receptor. The risk factor is graded from 0 to 5.
- Assessment of all enzymes linked to the ability of eliminating toxic and carcinogenic substances: SOD (Mg-dependent), copper- and zinc-dependent SOD, glutathione peroxidase and transferase, catalase...
- Assessing the presence of allergic phenomena: LTT tests (lymphocyte transformation tests, Melissa test and sensitization test).
- Assessing the presence of mercury and other heavy metals in blood (plasma, intraerythrocytic), hair and urine. This is a key assessment when there has been occupational exposure, there are or there have been mercury amalgams or a high fish intake.
- Many inflammatory and toxic processes are due to substances measurable in the biological fluids and tissues themselves, via blood, urine and hair analysis, as well as in fat biopsy. Presence of solvents, pesticides, heavy metals, PAHs, and persistent organic compounds can be thus identified. It is not always easy to detect the presence of these substances, hence its importance. It is known that such substances can determine inflammatory diseases (*Rea, W. J. 1997 Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol. 4, Lewis Publishers, Boca Raton*).
- Assessing whether affected individuals have dental implants or other types of prostheses, and whether there are inflammatory-reactive phenomena, not

from an allergy point of view, but on a toxic basis. Titanium provocation test, for instance, allows us to check if there is reactivity. The patient's lymphocytes are put in contact with titanium microparticles so that inflammatory cytokines produced by the lymphocytes can be measured. For other types of metals, Melisa tests can be performed with different profiles, subject to the metals in prostheses and implants (*Rea, W. J. 1997 Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol. 4, Lewis Publishers, Boca Raton*.)

- Fungi can be another major causal element, as they produce millions of toxins that can cause inflammation and other symptoms. It is crucial to measure fungi at home and in the workplace.

In this section we will present the contributions of the Italian Consensus Document 2021 (*Damiani et al., 2021*) which, following the clinical history and environmental exposure history, recommends:

- Prescribing the following tests in <u>a first consultation</u>:

1. Serum protein electrophoresis;
2. Ferritin serum;
3. Sodium (Na), magnesium (Mg), zinc (Zn) serum;
4. Creatine phosphokinase (CPK) serum;
5. Cholinesterase serum/plasma/erythrocyte;
6. Erythrocyte sedimentation rate (ESR);
7. C-reactive protein (CRP) serum;
8. Immunoglobulin E (total IgE) serum;
9. Interleukin-2 receptor (sIL-2R) serum;
10. Basal serum cortisol;
11. Basophil activation test on chemicals known for adverse reactions.

- Additionally, *Screening tests*: Brief Environmental Exposure and Sensitivity Inventory (BREESI), and Quick Environmental Exposure and Sensitivity Inventory (QEESI©) for diagnostic purposes to maintain international comparability and adequate accuracy.

Other systemic diseases that may meet the *Lacour 2005* criteria, such as porphyria and macrocytosis, should be excluded.

- Subsequent further specialized evaluations are proposed in patients with MCS:

a) <u>Allergologic/Dermatologic Assessment (I Level):</u>

1. Total immunoglobulin E (IgE) dosage and, only in the case of a clinical suspect, specific or recombinant IgE assays (Immuno Solid-Phase Allergen Chip (ISAC®) and in vitro multiplex allergy tests (i.e., Allergy Explorer-ALEX® and ALEX2®)).
2. Patch tests are regarded as a second choice as they can cause MCS flares to the patients.
3. A lymphocyte transformation test (LTT) is optimal only for testing metal allergies and has approval/approbatory medical-legal validity only for metal allergies.

b) Otorhinolaryngology (ORL) Assessment (I Level)

1. Upper airway endoscopy [11, 60-66].

2. Olfactometry with "Sniffin' Stick" stick tests (threshold, discrimination and odor identification) and olfactory-related questionnaires.

3. An otoneurological evaluation (pure-tone audiometry and impedance examination, auditory brainstem response and otoacoustic emissions, hyperacusis and dizziness-related questionnaires, posturographic examination).

4. Positron emission tomography (PET) with a pure olfactory stimulus.

c) Dental Assessment (I Level)

Mercury-containing dental amalgam fillings release metal ions (i.e., mercury, silver, tin, copper, gold, and nickel) in the oral cavity, resulting in toxicity (i.e., neurotoxicity, immune-toxicity and hormonal dysfunction) and potential allergic reactions.

Dental prostheses and metal crowns may release gold, palladium, chromium, beryllium, cobalt and titanium. Ceramics and dental porcelain can release aluminum into the saliva and dental resin-based composite restorations can release zirconium.

Blood/serum, urine and saliva analyses are suggested in order to check metal toxicity.

Toxic metals screening in blood:

1. Mercury (Hg) in whole blood.
2. Lead (Pb) in whole blood.
3. Aluminum (Al) in whole blood/serum.
4. Cadmium (Cd) in whole blood.
5. Nickel (Ni) in whole blood.

Toxic metals screening in urine:

1. Mercury (Hg) in 24-hour urine specimens.
2. Arsenic (As) in 24-hour urine specimens.

The chewing-gum-stimulated saliva test represents a non-invasive and accurate method of detecting metals released in saliva.

d) Neurological Assessment (I Level)

Despite MCS patients often displaying a normal neurological exam, environmental exposures may negatively modulate the nervous system (spatial disorientation, short-term memory loss, tinnitus, tremors, convulsions) in susceptible subjects. Thus, the neurological armamentarium may also include the following clinical and instrumental tests:

1. Pupillography
2. Simple and choice reaction time tasks
3. Balance tests
4. Visual contrast tests
5. Visual color tests

6. Tests of the perception of vibrations
7. Electroencephalography (EEG)
8. Single-photon emission computed tomography (SPECT)

An assay of the serum S100B protein is recommended to evaluate the permeability of the blood-brain barrier that may be altered by MCS triggers. A neuron-specific enolase (NSE) assay in serum is suggested to evaluate current or previous mercury-related neurological signs and symptoms.

e) Endocrinologic Assessment (I Level)

Several metals as well as chemicals may interfere with the physiology of the endocrine glands, in particular the thyroid and the hypothalamic-pituitary-adrenal axis. Recently, epidemiologic studies further confirmed the association between MCS and endocrine disorders (i.e., hyposurrenalism, dysthyroidism and hyperprolactinemia).

Experts agreed on the assessment of endocrinopathies in MCS patients following the Italian Association of Clinical Endocrinologists (AME) or the Italian Society of Endocrinology (SIE) guidelines.

f) Cardiological Assessment (I Level)

MCS patients display a wide range of comorbidities, including cardiovascular ones.

As well as the epidemiological association between MCS and tachycardia, arrhythmia, mitral valve prolapse and anomalies in the electrocardiogram results, the cause-effect link is far from being elucidated. Rea and colleagues postulated a synergic detrimental effect of a dysregulated autonomous central nervous system with vasoconstriction due to MCS triggers in susceptible patients (i.e., diabetes and/or hypertension).

Experts agreed on the assessment of cardiovascular disorders in MCS patients following the Italian Federation of Cardiology (IFC), the Italian Society of Cardiology (SIC) and the Italian Association for Cardiovascular Prevention and Rehabilitation (AICPR) guidelines.

g) Rheumatologic Assessment (I Level)

Several MCS patients may display an association with autoimmune diseases (such as Hashimoto's thyroiditis, systemic lupus erythematosus (SLE) or Sjogren's syndrome), corroborating the MCS immunological pathogenetic hypothesis.

Experts agreed on the assessment of rheumatologic disorders in MCS patients following the Italian Society of Rheumatology (SIR) guidelines.

h) Anesthesiologic Assessment (I Level)

Anesthesiologic management of MCS patients remains challenging in real life and should avoid all environmental exposures capable of triggering an MCS flare.

Remarkably, MCS patients do not display an increased risk of anaphylaxis related to anesthetics (both local and systemic), but may experience transient postoperative symptoms currently interpreted as self-limited flares. Anesthesiologists should carefully collect the pharmacological history of MCS patients to avoid anesthetics that previously provoked anaphylaxis and/or intraoperative signs and symptoms. Preoperative anesthetic-related allergy tests should not be performed to avoid sensitization phenomena.

Experts agreed on the assessment of potential anesthesiologic disorders in MCS patients following the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) guidelines.

i) Public Health / Occupational Medicine Assessment (I Level)

Chemical, physical and biological evaluations should be performed at the working site and at home to detect recognized MCS triggers for patients with a positive QEESI© test.

j) Genetic Assessment (II Level)

Although the MCS genetic fingerprint is far from being fully elucidated, phase I and II detoxification enzymes (cytochromes P450 (CYPs), glutathione S-transferases (GSTs), N-acetyltransaferases (NATs) and antioxidant enzyme (SOD2) gene polymorphisms have been linked to MCS. These polymorphisms may decrease xenobiotic catabolism and increase oxidative stress. Thus, the gene expression is epigenetically modulated by exposure, both internal and external, leading to potential hypersensitivity and MCS.

Thus, experts agreed that MCS-related polymorphism screening remains not diagnostic but only a complementary test.

k) Metabolic Assessment (III Level)

Metabolism perturbations due to or provoked by environmental exposures are currently under evaluation and the preliminary data suggest anomalies in the detoxification metabolism (i.e., glutathione transferase, catalase, superoxide dismutase), energetic metabolism (i.e., intracellular adenosine triphosphate (ATP) in erythrocytes and platelets) and inflammatory response (pro-inflammatory serum cytokines). These promising biomarkers evaluated on serum, whole blood and peripheral blood mononuclear cells (PBMCs) are detected with methods validated only in experimental conditions and are not applicable to daily clinical practice. Thus, experts agreed that biochemical tests should be reserved for an experimental setting.

6) TREATMENT

The first and most important treatment tool is **the avoidance** of triggering substances. The aim is to have a home free of chemicals and electromagnetic radiations, as this is the option that succeeds in improving symptoms in most cases. However, when there is a moderate to severe degree of the disease, numerous symptoms occur even when the person is not being exposed to triggers. Such symptoms are exacerbated by exposure.

Given the fact that some sufferers have a large constellation of symptoms that decrease when triggering substances are avoided, some authors claim that *reduction of the total toxic load to enhance and reinforce internal toxic elimination processes is the desirable goal of treatment, as well as the downward reduction of NO/ONOO- cycle activity.* (*Marshal 2011) (Pall 2007a: Explaining 'Unexplained Illnesses', Chapter 15 - Treatment) (Rea WJ 1997: Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol. 4, Lewis Publishers, Boca Raton*.)

Dr. Miller states, "*Specific tolerated supplements might be cost prohibitive, but if patients do not maintain proper nutrition, a burden of harmful substances can increasingly accumulate in the body and they can find themselves so overloaded that even minimal amounts of the chemical triggers they must avoid will initiate severe symptoms that can be disabling and last for days or much longer periods of time…"*

Rea WJ 1997 reports that low-dose immunotherapy has helped many chemically sensitive patients in the process of improving their symptoms. *Genuis 2013* also reports the use of desensitization immunotherapy aimed at decreasing the hypersensitivity immune response associated with exposure in susceptible individuals.

Genuis 2013 claims:

"[…] *Psychotherapeutic interventions have so far failed to achieve success." "In general, physiological treatments appear to consistently have superior and sustained results compared to psychological therapies."*

"[…] *The preferred medical management designed to restore health entails the removal of the initial body load of primary toxins. Reducing the toxic load through innate toxic elimination mechanisms or through clinical detoxification interventions for persistent pollutants appears to consistently decrease immune dysregulation associated with CS and gradually ameliorate clinical manifestations of CS."*

It should be born in mind that such proposed treatments are long term and, although they do not achieve cure, they do manage to increase the margin of tolerance and decrease symptoms in most cases. Their effectiveness is subject to the implementation of changes in everyday life to avoid triggering substances. It must be considered that for people who suffer from such a large number of symptoms which forces them to

voluntary isolation in order to feel better, any improvement in their symptoms would go a long way to providing a better quality of life.

CONCLUSIONS

It is in our view significant to highlight the reflections that have been published on this disease in the *Enciclopedia Práctica de Medicina del Trabajo* ("Practical Encyclopedia of Occupational Medicine") by the Spanish National Institute for Occupational Health and Safety (INSST).

"*En prevención primaria, conocer en más profundidad la SQM resulta fundamental pues puede tener como efecto colateral una mejora de las condiciones medioambientales de la población general. En cuanto a la prevención secundaria, la detección precoz en los circuitos de atención primaria y servicios de riesgo laboral, puede ser una buena medida para evitar la amplificación y cronificación del mecanismo de sensibilidad junto con la evitación de la exposición y reexposición a los agentes desencadenantes." (p. 240).*
["In primary prevention, a more in-depth understanding of MCS is essential because it can have the collateral effect of improving the environmental conditions of the general population. As for secondary prevention, early detection in primary care circuits and occupational risk services can be a good measure to avoid the sensitization mechanism from getting intensified and becoming chronic, together with the avoidance of exposure and re-exposure to triggering agents."]

***"Conviene hacer hincapié en que el sufrimiento de algunas de las personas afectadas puede llegar a ser importante como consecuencia de los padecimientos físicos de la enfermedad y de las limitaciones de vida a que frecuentemente se ven sometidas, al reducir drásticamente su capacidad laboral y su autonomía personal por la necesidad de evitar aquellos entornos que, por propia experiencia, han comprobado que les causan reacciones indeseadas o adversas**." (p. 241)*
["It should be emphasized that the suffering of some of those affected can become significant as a result of the physical ailments of the disease and the limitations in their lives to which they are frequently subjected, by drastically reducing their ability to work and their personal autonomy due to the need to avoid those environments that, from their own experience, have been proven to cause unwanted or adverse reactions."]

The recognition of MCS and associated diseases in Europe is a result of:

- The European Parliament Resolution of September 4, 2008, on the Mid-term Review of the European Environment and Health Action Plan 2004-2010, which includes MCS within the growing number of diseases linked to environmental

factors and considers that Environmental Medicine should be supported and promoted within the European Union.

- The Parliamentary Assembly of the Council of Europe, Doc. 11788. 20 January 2009, under the title *"Environment and health: better prevention of environment related health hazards"*, sets out the concern within the European Union for environmental health. Specifically, point 37 mentions:

  "To add to these recent concerns in environmental health, in recent years a number of new diseases or syndromes have made their appearance, such as:"

  - MCS (Multiple Chemical Sensitivity)
  - CFS (Chronic Fatigue Syndrome)
  - Dental mercury amalgam syndrome
  - Hypersensitivity to electromagnetic fields
  - Sick Building Syndrome
  - Fibromyalgia

LATEST MCS PREVALENCE STUDIES IN THE UNITED STATES, AUSTRALIA, UK AND SWEDEN

Latest MCS prevalence studies in some countries:

- **Steinemann, A**. National Prevalence and Effects of Multiple Chemical Sensitivities. Journal of *Occupational and Environmental Medicine*: March 2018 - Volume 60 - Issue 3 - p e152–e156.

This study assessed the prevalence of MCS in the United States, differentiating between those people diagnosed with MCS by a physician and those who self-reported Chemical Sensitivity. June 2016 data show that **12.8% of the population had medically diagnosed MCS** and **25.8%** self-reported Chemical Sensitivity based on noticing particular sensitivity to everyday and scented chemicals.

- **Steinemann, A**. Prevalence and effects of multiple chemical sensitivities in Australia. *Preventive Medicine Reports.* Volume 10, June 2018, Pages 191-194.

Results showed that across the country **6.5% had medically diagnosed MCS** and **18.9%** reported having Chemical Sensitivity based on noticing special sensitivity to everyday chemicals and fragrance chemicals, and 19.9% reported one of the situations or both.

- **Steinemann, A**. Chemical sensitivity, asthma, and effects from fragranced consumer products: National Population Study in the United Kingdom. *Air Quality, Atmosphere & Health.* 2019, Volume 12, Issue 4, pp. 371–377.

The study reported that **6.6%** of the UK population is **medically diagnosed with MCS** and **16.3%** report having Chemical Sensitivity based on noticing particular sensitivity to everyday chemicals and fragrance chemicals.

- **Steinemann, A**. Chemical sensitivity, asthma, and effects from fragranced consumer products: national population study in Sweden. *Air Quality, Atmosphere & Health.* 2019, Volume 12, Issue 2, pp. 129–136.

The study shows that **3.6% of the Swedish population suffer from medically diagnosed MCS** and **18.5%** report having Chemical Sensitivity based on noticing special sensitivity to everyday chemicals and scented chemicals.

Consensus Document on MCS, 2011. **Spanish Ministry of Health, Social Policy and Equality.**

Actualización de la Evidencia Científica sobre Sensibilidad Química Múltiple (SQM) ["Scientific Evidence Update on Multiple Chemical Sensitivity (MCS)"] / **Mónica Valderrama Rodríguez** [et al.] – **Madrid: Spanish Ministry of Health, Social Services and Equality**, 2015. – 92 p.; 24 cm. – (Reports, studies and research) (Health technology assessment reports. IACS).

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Appendix I

Compilation by A. Donnay of scientific documentation published up to 1999 which investigates and concludes that MCS is a physical disease. www.mcsrr.org

Appendix II

Compilation by A. Steinemann.

Patients with Multiple Chemical Sensitivity urge the World Health Organization to consider this pathology as a nosological entity and to include it in the International Classification of Diseases (ICD). This recognition would lead to a global categorization and, as a result, those affected would have a better diagnosis, treatment, adaptations to their environment and, consequently, a better quality of life. Also, at a medical and scientific level, health professionals would have more resources and knowledge of this pathology and research would be promoted, which is necessary to know in more detail its aetiology, symptoms and effects. And on a general level, it will contribute to raising awareness in society as a whole in order to prevent its effects. In other words, this demand is not only for those who suffer from the disease but for future generations who may contract the disease.

We are at a turning point where the planet is increasingly suffering from the effects of climate change. This global challenge we face has multiple consequences. One of the most obvious are the deaths and illnesses caused by poor air quality, the proliferation of chemicals or the emission of greenhouse gases. As climate change increases, the number of people affected by Multiple Chemical Sensitivity is also on the rise. Multiple Chemical Sensitivity is a chronic pathology that arises in response to exposure to toxic substances and chemical compounds that are harmful to health. Moreover, following the pandemic caused by Covid-19, the prevalence of this disease has increased due to the massive use of bleaches and disinfectant products that were used against the SARS-CoV-2 virus.

The daily life of patients with this disease is an ordeal. Exposure to substances such as perfumes, shower gels, cleaning products or tobacco fumes worsen their quality of life. This is why they cannot lead a normal life. Any social, work or family event is truncated because they suffer from this pathology. The routine of people with MCS is disrupted when, for example, hairdressers are forced to give up their work due to exposure to hairspray or farmers are unable to continue their work due to contact with pesticides.

For the world's largest health organization to recognize Multiple Chemical Sensitivity as a disease as a nosological entity and in the International Classification of Diseases would mean that patients would not have to wait years or even decades for a proper diagnosis and that they would be diagnosed in a clear, direct and simple way. In addition, recognition by an organization belonging to the UN such as the WHO would mean the unification of criteria for the diagnosis and treatment of this pathology, as well as its presence in computerized health systems.

There are already countries that recognize this disease with this specific nomenclature *Multiple Chemical Sensitivity* in their annexes to the ICD, and all of them are part of the northern hemisphere. Germany (2000) http://www.csn-deutschland.de/dimdi_icd-schreiben.pdf , Austria (2001) http://www.csn-deutschland.de/icd-10_austria.pdf , Luxembourg (2007) http://www.csn-deutschland.de/ministere_de_la_sante.pdf , Japan (2009) http://www2.medis.or.jp/stdcd/byomei/update/DFF/data/281/ver281a-b.pdf , Switzerland (2010), Denmark (2012), Spain (2014) https://istas.net/descargas/DOCUMENTO%20DE%20CONSENSO%20SQM%202011.pdf and Finland (2014).

In addition, they have published some official documents such as those of Spain:

- Recomendaciones clínico-asistenciales. Sensibilidad Química Múltiple. Servicio Canario de Salud. (2020)
- Protocolo de atención ás persoas con sensibilidade química múltiple. Xunta de Galicia. (2019)
- Protocolo SQM para Urgencias de la Comunidad de Madrid. (2018)
- Ficha de prevención SQM. UGT Cataluña. (2017)
- Mejora de Atención de las Personas con SQM. Servicio Andaluz de Salud. (2017 / actualizado 2018)
- La Comunidad de Madrid ha reconocido la SQM como patología excepcional en los procesos de incapacidad temporal por enfermedad común para obtener la mejora del 100 por 100 de la prestación a todos los empleados públicos, incluido el personal de la administración de justicia. BOCM 23 de mayo de 2017
- Sensibilidad Química Múltiple. Catsalud, Generalitat de Cataluña.
- Actualización de la Evidencia Científica sobre Sensibilidad Química Múltiple (SQM) Informes de Evaluación de Tecnologías Sanitarias. Ministerio de Sanidad, Servicios Sociales e Igualdad. (2015)
- Documento de Consenso Sensibilidad Química Múltiple. Ministerio de Sanidad, Servicios Sociales e Igualdad. (2011)
- Enciclopedia de Medicina del Trabajo. INSST. (2018)

That is why patients with MCS need the World Health Organization to serve as a reference and example for other countries and regions, and today we are sending this request together with doctors and researchers from all over the world who are experts in this disease.