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Review of the Available Scientific Evidence on Multiple Chemical Sensitivity Syndrome

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Abstract: ***Background:*** *Multiple Chemical Sensitivity (MCS) Syndrome poses many faces and it is related to previous exposure to substances found in the environment, at well-tolerated concentration by the general population. There are a lot of sources of exposure and there is no typical clinical pattern, as well as several degrees of severity in the subjects affected by MCS Syndrome. For all these reasons, the MCS Syndrome becomes a complex disease with difficult diagnosis and management. The aim of this study is to review and to update the available scientific evidence on MCS Syndrome.* ***Methodology:*** *A systematic revision of the available evidence has been made, and updated the available evidence. The following sources were used: Medline, Embase, PSYCINFO, Toxline, UpToDate, IBSST, CISDOC, The Cochrane Library and Centre for Reviews and Dissemination (CRD). Two reviewers independently made the selection of recovered articles, applying the inclusion and exclusion criteria for the final selection of studies. There were identified 613 studies of which 27 were selected for the 5 analyzed clinical areas: 1) Epidemiology, 2) Clinical manifestations and co-morbid clinical conditions, 3) Diagnosis of MCS syndrome, 4) Physical, Psychological and Social impact on the Quality of Life 5) Therapeutic and prevention approaches for MCS Syndrome.* ***Results:*** *The estimation of MCS´s prevalence can range between 0.02% and 0.04%, increasing to 19% in people with an added diagnosis of allergy. The most frequently affected systems in the MCS Syndrome are the digestive tract, the cardiovascular one and the skin. Also, the mental sphere is affected with certain frequency. The MCS´s diagnosis can be difficult, due to the variety of symptoms the disease can show from the beginning and because of the wide range of different definitions about the same disease that can be made. The clinical suspicion after a correct anamnesis and physical exam and the use of the Quick Environmental Exposure and Sensitivity Inventory (QEESI), in Spanish version can help with the diagnosis. People affected by MCS Syndrome seems to decrease their quality of life in a significant way, even reaching self-isolation in an attempt to reduce the exposition to trigger substances or due to the serious physical deterioration in case of continuous expositions. The more effective therapeutic intervention consists on avoiding new re-exposure to the leading substances.* ***Conclusions:*** *The MCS is frequently associated with a previous allergic subject. It can affect multiple systems simultaneously, most often the gastrointestinal and cardiovascular systems, the skin and the mental sphere. The non-specific symptoms and the lack of consensus about the definition of MCS deter an early diagnosis of the disease. There is a Spanish version of the QEESI of reference. It is believed that the adoption of measures to sensitize the general population about MCS, could influence the reduction of exposures to trigger substances and improve understanding of this disease and people who suffer it. Actually, the best preventive measure is to avoid exposure to the triggering substances.*

Keywords: *Multiple chemical sensitivity; systematic review; low-dose toxicity; risk assessment*

1. INTRODUCTION

Multiple Chemical Sensitivity (MCS) is described as a complex condition that involves a set of symptoms attributed to exposure to extremely low levels of a wide variety of environmental chemical[1]. It involves the exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals[2]. The symptoms experienced by many individuals get them, in some cases, exhaust[3,4].

The pathogenic mechanisms involved in MCS are not clearly established[5-7]. There are several biologically plausible hypotheses that warrant further scientific research to explain the underlying

mechanism or modes of action of MCS[8]. In addition, methods of diagnosis and treatment have not yet been agreed upon by the medical profession[9,10].

Given the uncertainty regarding the mechanisms, criteria for diagnosis and treatment methods of MCS[11,12] there is the need to review new research on MCS to improve the understanding, prevention and treatment of MCS. However, these calls for further investigations have determined priority areas for scientific and research community in the field of health and the environment. Elucidate the biological basis of MCS[13] provide guidelines for clinical diagnosis and improve treatment option[14]. It must also identify the natural history and the true prevalence of this condition[15].

The aim of this review is to update the available evidence in the scientific literature.

2. METHODOLOGY

A systematic revision of the available evidence has been made. The search was done by consulting the following databases: Medline, Embase, The Cochrane Library and the Centre for Reviews and Dissemination (which include the Database of Abstracts of Reviews of Effects, the National Health Service Economic Evaluation and the Health Technology Assessment Database). We have also searched on specialized databases in this field: PsycINFO, Pubpsych, Toxline, OSH, Update and CISDOC. A description of the search strategies is available as supplementary material (upload file Annex 1). The publication date was set between 2010 and 2015, as a Spanish previous review was done in 2010. Two reviewers independently made the selection of recovered articles, applying to the inclusion and exclusion criteria for the definitive selection of studies. Inclusion criteria: Population based case control studies with results of prevalence or incidence of MCS; Original research publications with MCS patients in whom the effectiveness of intervention with one or more drugs or other therapeutic measures is studied; Studies that describe MCS symptoms; Qualitative studies that address physical, psychological and social impact, and quality of life; Narrative and editorial reviews that provide a novel approach or new working hypothesis in the research of MCS. Study exclusion criteria: Papers on the study of electromagnetic radiation; Population with different primary diagnosis of MCS; Studies with different main problem of MCS; Studies dealing MCS but do not respond to the area of interest. Due to heterogeneity of the included studies no statistical analysis was performed (meta-analysis or quantitative synthesis).

3. RESULTS

There were identified 613 studies of which 27 were selected (figure 1 describes the PRISMA flow diagram) for the 5 analyzed clinical areas: 1) Epidemiology, 2) Clinical manifestations and co-morbid clinical conditions, 3) Diagnosis of MCS syndrome, 4) Physical, Psychological and Social impact on the Quality of Life 5) Therapeutic and prevention approaches for MCS Syndrome. Extensive description of included studies (Table 1) and reasons for excluded studies (Table 2) are also reported.

1. Epidemiology: In the observational study done by Lee *et al.* 2013[16] a prevalence of 19.1% of MCS in allergic population is estimated and established risk factors change of address and use household cleaning products. The study of Nogué *et al.* 2011[17] estimated prevalence in the Spanish population between 0.02% and 0.04%.

2. Clinical manifestations and comorbidity: Caccamo *et al.* 2013[18] indicate that patients affected by MCS appear most frequently gastrointestinal and cardiovascular disorders in relation to suspected cases of MCS. In cases of suspected MCS it is most often headache-neurological, respiratory, skin, musculoskeletal and immunological symptoms in diagnosed cases of MCS. 30% of patients have comorbidities, highlighting main remaining comorbidities in chronic fatigue syndrome and fibromyalgia 70%. In Holst *et al.* 2011a[19] erythema intensity induced by capsaicin in MCS patients with eczema and the outbreak area in patients with symptoms induced by odorous chemicals studied. The symptoms studied included in upper airway and downs, CNS, allergic rhinitis, asthma, eczema and food allergy. They performed prick tests (skin tests) to airborne allergens, analyzing the intensity of erythema and measuring the response of the skin neurovascular spectroscopy using polarized light. In the study of Holst *et al.* 2011b[20] reactivity to pain, hyperalgesia, temporal summation effect and neurogenic inflammation in patients with MCS is evaluated. The clinical trial of Berg *et al.* 2011[21] investigates the relationship between skin reactions to various chemicals, and the sensitivity reported by the patient from inhalation of airborne chemicals. Patch tests are performed. Allergic skin responses (RAC) and non-allergic skin responses (NRAC) had statistically significant positive

association with more severe groups compared to the group that does not mind any of the exposures included in the questionnaire on MCS. Individuals relate chemical sensitivity not show an increase in allergic reactions. Katerndahl *et al.* 2012[22] evaluate the prevalence of chemical intolerance, comorbidities and psychiatric disorders in patients with Primary care setting. They are linear relationship between the number of mental disorders and the prevalence of chemical intolerance, stressing that primary care centers, chemical intolerance, is often unrecognized, still prevalent in low-income population, and frequently presented comorbidity with a large class medical and psychiatric conditions, having to make an active search for cases. They also highlight that psychiatric comorbidities contribute to functional limitations and increased use of health care. Skovbjerg *et al.* 2012[23,24] investigate the association between depressive symptoms and four domains related to idiopathic environmental intolerance (IEI), determining whether the association could be confused by the low social support and major life events. Significant correlations are moderate to high scales for symptoms of central nervous system (CNSS); mucosal symptoms (MUSS); consequences for social activities (CSAS); and chemical hypersensitivity (CHS). In addition, the features of personal perception and somatosensory amplification and regional perceptions are associated with IEI. It failed to show association between repressive coping style and IEI, either with alexithymia (inability to identify and verbalize the emotions), but with some properties of it, such as negative emotional reactions, defensiveness and difficulty identifying feelings. The cross-sectional study by Nordin *et al.* 2013[25] investigates whether sensitivity to environmental noise is related to the perception of stress and sensitivity to environmental odors, supporting the hypothesis that noise sensitivity is associated with perceived stress and sensitivity to smell.

3. Diagnosis of MCS: Through a cross-sectional study, Skovbjerg *et al.* 2012[26] evaluated questionnaire translation QEESI applied Danish population, verifying the reliability and validity, and sensitivity and specificity. The authors propose to investigate in the future the combined use of the scales "Chemical intolerance" and "impact on activities of daily living", because it is a shorter, but equally valid alternative to the QEESI complete questionnaire. Barnig *et al.* 2013[27] hypothesis review the pathophysiology of MCS and found no differences between healthy and sick people, or medical identification or cognitive development or serum cortisol. Martini *et al.* 2013[28] made an overview of MCS specifying the critical points of the case definition and diagnosis in relation to the workplace. They propose a diagnostic protocol for suspected MCS, including a first phase with detailed interview using several questionnaires, blood and urine analysis, the signs and indications of the patient and spirometry. A second phase is indicated when suspected MCS and no other diseases or other modified aspects exist. In these cases, the second phase consists of the following tests: psychological evaluation, neurophysiological, allergy testing, genetic polymorphisms, determine different chemicals, metals and other metabolites in biological samples, as well as research on the metabolism and the use of detoxifying agents. In the cross-sectional study of Mena *et al.* 2013[29] translated into Spanish the quick quiz exposure and environmental sensitivity (QEESI) and adapted to the Spanish population. The univariate analysis for the description of the population is made by comparing the median scores between diagnosed and undiagnosed MCS subjects, and assessing the internal consistency of the scales.

4. Physical, psychological and social impact. Quality of Life: Gibson *et al.* 2011[30] conducted a qualitative study to investigate the impact of MCS in their lives. Respondents refer social and occupational isolation; need to take many precautions; they indicate that a cultural effort is needed to create safe environments (work, cinema, transport, etc.) where you can interact with others. Moreover, refer incomprehension, ignorance about their sickness, loneliness, guilty fellness by high demand for maintaining relationships. It is mentioned that a solution may be to educate others about MCS, although not everyone shares this approach. They note that Internet and telephone help maintain social relations in the context of isolation caused by the disease. Finally, they report feeling outside world, as mere observers. In another qualitative study, Soderholm *et al.* 2011[31] intended to clarify how individuals experience living with sensory hyperreactivity (HRS), the impact on accessibility, economic security and social relations. According to the authors, the HRS is a form of intolerance to odors, including MCS and IEI. Difficulties are taking a shuttle, visit public buildings and facilities, and indicate that finding a suitable place to live is almost impossible. With regard to economic security: reduction of income due to the difficulty of living, increased expenses due to HRS, lack of support from the authorities, and difficulties to manage their finances. Finally, with regard to social relations, refer to: socializing has become difficult and traumatic, among other conditions. The study

of Dupas *et al.* 2013[32] presents the social and labor implications for people with MCS, even losing the job.

5. MCS Therapeutic Approach: In 2013 Genuis[33] presented as currently therapeutic alternatives, the use of desensitizing immunotherapy; Profile unfavorable risk / benefit of steroids and immunosuppressive drugs for the treatment of this syndrome; the lack of success of cognitive therapy and other commercial alternatives (Dynamic Neural Retraining System™) and; eliminating xenobiotics by physiological processes (the toxicokinetics phases of metabolism or biotransformation, and excretion) or exogenous interventions, that appear to decrease detoxification immune disorder, and improve clinical status. It indicated that physiological treatments are superior and sustainable compared to psychological therapies and highlights the role of Public Health and the work of health education. The study of Ralph *et al.* 2011[34], regarding a case of a woman with MCS for permethrin, emphasizes environmental research as a tool to make the right treatment and prevention measures. In the same line Waddick 2011[35] highlighted, in a case report, the importance of lifestyle with avoidance of exposure through sustainable urban development. In the United States, Mischley *et al.* 2013[36] describe the results of the use of intranasal reduced glutathione (inGSH), highlighting the efficacy and safety of inGSH for respiratory and central nervous system diseases.

With a preventive strategy, a descriptive study was found, regarding a case of a woman diagnosed with MCS, investigating the clinical changes in relation to changes in exposure and re-exhibition to accidental contaminants. Environmental toxicological research specifically identified as causal origin of MCS clinic patient, accidental exposure to permethrin insecticide biocide properties, so that preventive measures are in line to avoid exposure to this chemical.

4. DISCUSSION AND CONCLUSION

In 1996 a WHO/IPCS Workshop has suggested to use as an appropriate descriptor of MCS the broader term "Idiopathic Environmental Intolerances (IEI)", in order to incorporate "*a number of disorders sharing similar symptomatologies*", and research was strongly encouraged[37]. MCS is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses below those established in the general population to cause harmful effects[38].

Over 15% of the general population has mechanisms excessive response to certain chemicals or environmental stimuli and 5% of cases are pathological and exceed the adaptive capacity of the organism; MCS is an acquired disease, characterized by progressive loss of tolerance to the presence in the environment of various chemical agents[39] such as household cleaning products, colognes, perfumes, solvents or hydrocarbons[40]. In the middle of last century the first cases of these patients became ill when exposed to substances well below harmful levels to health were reported.

Sensitivity to chemicals is a toxicological concept[41], contained in the dose-response relationship[42]. Sensitivity also includes the concept of hypersensitivity[43], although controversy surrounds the nature of effects from very low exposures[44]. Research into the possible mechanisms of MCS is far from complete[45].

Its etiology and pathophysiology remain a mystery, although several inconclusive theories are postulated. Therefore, the diagnosis is based on symptoms presented by patients, as there is no laboratory test blood or urine, and no specific complementary examination in order to confirm the diagnosis[46-49]. The symptoms differ among individuals who have to change their lifestyle to cope with the disease[50,51].

A clear predominance of involvement in females (80%) and the most common chemicals for developing symptoms are household cleaning products and fragrances, toiletries and cosmetics is observed. That is why it has made out a literature review of the MCS and the search for evidence that would link these two variables; there has not been published[9,52].

Fragrances and other odorants could, however, be associated with symptoms as claimed by MCS symptomatics[53,54], because they are recognizable stimuli, but fragrance has not been demonstrated to be causal in the usual sense[55].

Scientific Committee on Consumer Safety recently published (June 2012) an opinion on fragrance allergens in cosmetic products[56]. Fukuyama *et al.* used long-term sensitization followed by low-dose

challenge to evaluate sensitization by well-known Th2 type sensitizers [trimellitic anhydride (TMA) and toluene diisocyanate (TDI)] and a Th1 type sensitizer [2,4-dinitrochlorobenzene (DNCB)]. This long-term sensitization method would be useful for detecting environmental chemical-related hypersensitivity[57].

Even today, MCS is not part of the ICD-10 (International Classification of Diseases) although associated with various diseases[58] and pose a disability in activities of daily living of sufferers[59] and for workers[60-62].

In conclusion, we can say that the uncertainty in the etiological attribution, not being clear causal origin of MCS is maintained. The update also notes that there is no clear diagnosis. More studies are presented to indicate the impact on quality of life. No specific measures found treatment except symptomatic measures. In the area of prevention, it is designated as primary preventive measure avoidance of exposure and re-exposure.

TABLES

Table 1. *Summary of evidence tables of included articles*

Epidemiology

REFERENCE	STUDY / POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	COMMENTS
Lee *et al.* 2013[15], South Korea	**Aims** To evaluate the prevalence and related factors of MCS in patients with allergic diseases. **Design** Observational study. **Period of execution** Not indicated. **Population** 196 patients with allergic diseases.	They classify patients according to scores on the questionnaire QEESI: **Group 1:** very suggestive of suffering MCS (symptoms severity score ≥40 and ≥40 chemical intolerance) **Group 2:** little suggestive of suffering MCS (lower scores) **Statistic analysis** Subsequently, a univariate analysis was performed.	Prevalence of: - Asthma: 39.4% (n = 77) - Allergic rhinitis: 70.4% (n = 138) - Atopic dermatitis: 30.1% (n = 59) 34 patients were included in Group 1. MCS prevalence of 19.1%. Demographic characteristics and patterns of allergic disease were not different between groups. MCS is related to change of address, adjusted OR [95% CI 5.29 (1.39, 20.09)] and the use of household cleaning products more than once a week, adjusted OR [5.20 95% CI (1.19, 22.86)].	The risk of MCS in allergic patients is higher in patients who have changed address or frequently used household cleaning products. In this study, although MCS is not dependent allergic diseases, both are environmental diseases may be related. Further studies are needed to establish relationships between MCS and allergic diseases.	Information on the origin of the sample selection, variable definitions (change of address, use household cleaning products), and MCS prevalence of allergic diseases such failure.

Clinical manifestations and comorbidity

REFERENCE	STUDY	POPULATION	INTERVENTION / COMPARISON	CLINIC / COMORBIDITY	CONCLUSIONS	COMMENTS
Caccamo *et al.* 2013[18], Italy	**Objetive** Compare the distribution of genetic polymorphism of cytochrome P450 and Aryl hydrocarbon receptor (xenobiotic sensor) in 3 cohorts. **Study design** Case-control. **Period of realization** Not specified.	**Inclusion criteria** People from different Italian regions, with full or partial diagnosed with MCS hypersensitivity. **Groups** **MCS Group**: 156 patients were diagnosed by Cullen and QEESI 20 to 30 points. Middle Ages (EM): 49 (11) **SMCs Group: 94 (79M / 15H);** QEESI 10-20 points. MS: 49 years (12)	Comparative description of comorbidities registered in the group of MCS and SMCS in the group	HCS Group (approximate figures *) ≈50% neurological-headache ≈50% Respiratory Musculoskeletal ≈42% ≈37% immunological Gastrointestinal ≈33% Cardiovascular ≈30% Skin ≈29% ≈30% without comorbidities SMCS Group (approximate figures *) ≈58% neurological-headache ≈62% Respiratory Musculoskeletal ≈42% ≈40% immunological Gastrointestinal ≈26% Cardiovascular ≈16% Skin ≈39% ≈6% without comorbidities	DOES NOT APPLY	The study does not aims to analyze differences between groups comorbidities Only about 30% of people diagnosed with MCS have no associated comorbidities, but this figure is reduced to approximately 6% in the case of people with suspected MCS. Clinical data extracted from a chart

REFERENCE	STUDY	POPULATION	INTERVENTION / COMPARISON	CLINIC / COMORBIDITY	CONCLUSIONS	COMMENTS
Berg *et al.* 2011[33], Denmark	**Objetive** Researching general population the relationship between skin reactions to various chemicals, and the **sensitivity** reported by the patient to the **inhalation of airborne chemicals** itself. **Study design** Clinical trial. **Period of realization** June 2006-June 2008	**Recruitment** From 7,931 people in the civil registry. Copenhagen area. Including 3,471 (43.8%). age range between 18 and 69 a. Invitation to participate in a general health checkup (Health 2006)	**Intervention** ***Patch test:*** the answer classifies as (3,460 people): Allergic skin response (RCA): redness and dermis infiltration No allergic skin response (RCNA): irritative response, follicular, or doubtful. ***Prick test:*** (2,232 people) Positive: wheal diameter ≥3mm ***4 groups*** according consequences (severity) attributed to inhalation of chemicals in airborne ***Group 1:*** Undisturbed exhibitions included in the questionnaire. ***Group 2:*** exposure-related symptoms but no impact on daily life. ***Group 3:*** refers adjustments in lifestyles. ***Group 4:*** refers adjustments in social or work life.	**Patch test**: *RCA (univariate analysis):* A> severity of symptoms (groups 1 to 4),> RCA. Statistically significant (p <0.05) for groups 3 and 4 with respect REFERENCE (group 1) *Group 3:* OR 1,37 (IC95%: 1,04 a 1,81) *Group 4:* OR 2,03 (IC95%: 1,10 a 3,74) *RCA (Multivariate analysis *):* There is no association between the severity of symptoms and RCA. No statistical significance (p> 0.05) **RCNA**: *RCNA (univariate analysis):* A> severity of symptoms (groups 1 to 4),> RCA. Statistically significant (p <0.05) for groups 3 and 4 with respect REFERENCE (group 1) *Group 3:* OR 1,55 (IC95%: 1,15 a 2,08) *Group 4:* OR 2,83 (IC95%: 1,55 a 5,15) *RCNA (Multivariate analysis *):* Association seen with> severity of symptoms (group 4) and> RCNA. *Group 4:* OR 2,63 (IC95%: 1,39 a 5,01) p=0,003 No association between severity of symptoms and RCN to the other groups (p> 0.05) were observed **Prick Test**: RESULTS no association between test and severity of symptoms (groups) is identified. RESULTS NOT included in multivariate analysis and not shown	People who refers chemical sensitivity, show an increase in non-allergic skin reactions, basing this information on reading the patch test 48 hours.	Possible limitations described by authors due to reading the patch test 48 hours rather than 72 hours. *: RCA and RCNA, sex, age, eczema, atopic dermatitis, asthma, depression, anxiety, smoking, social status and educational level: more complete information model includes the following variables is described adjustment.

REFERENCE	STUDY	POPULATION	INTERVENTION / COMPARISON	CLINIC / COMORBIDITY	CONCLUSIONS / COMMENTS
Katerndahl *et al.* 2012[34], U.S.	**Objetive** Assess medical and psychiatric comorbidities in a community of people with or without MCS **Study design** Transversal study. **Period of realization** Not indicate	**Recruitment** 2 primary care centers: **Centre A:** Hispanic population with low incomes **Center B:** Hispanic middle class population and non-Hispanic **Sample** 400 patients ≥ 18 years of age: **Activity A:** 270 (68%) **Center B:** 130 (32%) **Reason query: no acute** conditions **Characteristics** *Average age: 47.4 years 14.7* *148 (37%) men and 252 (63%) women* **Groups**	**Intervenyion** All questionnaires filled: sociodemographic characteristics Quick Environmental Exposure and Sensitivity Inventoriy (QEESI). MCS define whether score ≥ 40 for **scale chemical intolerance scale and severity of symptoms.** Apply without discrimination, intolerance and chemical MCS Primary Care Evaluation of Mental Disorders (PRIME-MD). Detection of psychiatric disorders in the previous month. **Statistic analysis** Descriptive asthma, allergies, autism, multiple sclerosis, arthritis, diabetes, gastro-intestinal, mood disorders, chemical intolerance, systemic erythemic lupus: **refer** family and personal	RESULTS shown only statistically significant differences **G1 vs. G2: (personal record):** Allergies: 43 (53%) vs. 129 (40%) Mood altered state: 44 (54%) vs. 64 (20%) chemical intolerance: 19 (24%) vs. 24 (8%) **G1 vs. G2: (family history):** Gastro-intestinal disorders: 21 (26%) vs. 31 (10%) Mood altered state: 31 (38%) vs. 56 (18%) chemical intolerance: 16 (20%) vs. 24 (8%) Systemic Lupus Erythematosus 7 (9%) vs. 9 (3%) **G1 vs. G2: (mental clinic):** Major depression: 69 (85%) vs. 106 (33%) Generalized Anxiety: 63 (78%) vs. 67 (21%) Panic attacks: 44 (54%) vs. 53 (17%) Alcohol: 30, 37%) vs. 63 (20%) Somatization disorders: 74 (91%) vs. 218 (68%) **Relationship mental health and chemical**	1 in 5 people who use health services Primary Care (US) for **non-acute** conditions, presents MCS. Mental disorders are more common in people with MCS and allergies and other mood disorders. The gastro-intestinal, mood disorders, lupus chemical intolerance and family history are most often mentioned by people with MCS **COMMENTS** Autoquestionaries for information There is a pre-selection of those who come for

		MCS (G1): 81 (20.3%) people **Without MCS (G2**): 319 (79.7%) people	history is explored. major depression, generalized anxiety, panic attacks, alcohol abuse and somatization disorders.	**intolerance:** A> prevalence of MCS,> number of possible mental disorders	**non-acute conditions** Participation in the study is paid ($ 5)

REFERENCE	STUDY	POPULATION	INTERVENTION / COMPARISON	CLINIC / COMORBIDITY	CONCLUSIONS
Skovbjerg *et al*. 2012a[35], Denmark	**Objetive** To analyze the association between psychological disorders and idiopathic environmental intolerance * (IEI) and determine whether social support and major life events could be confounding factors **Study design** Transversal study **Period of realization** They do not tell. ***: IEI** disorder characterized by nonspecific symptoms of several attributed by the person to exposure to common chemicals in the air organs.	**Recruitment** 1,024 people invited to participate. **Group 1 (G1):** general population. 787 people **Group 2 (G2):** 237 people. Danish Research Center for symptoms common aerosols and diagnosis of IEI. % Response rate 71.5% **(732 people)** **Analyzed** **G1**: 571 people men: 194; female: 377 mean age 48.1 (12.4) **G2:** 161 people men: 21; female: 140 mean age 53 (SD 10.6) G2> G1 age (p p≤0,001**)**	**Interventions** *Auto shipping questionnaires by mail.* Evaluation depression by Symptom Checklist 92 (SCL-de subscale) Social support perceived (ASP) Recent life events (AVR) Scales: Symptoms of Central Nervous System (ESSNC). Score between 0 and 8. Mucous symptoms (ESM). Score between 0 and 6. chemical hypersensitivity (EHQ). Score between 0 and 33. Implications for Social Activities (ECAS). *Score between 0 and 14.* **Statistic analysis** Comparative analysis Correlation analysis	**Comparative** SCL-de:> symptoms in G2 (p≤0,001) ASP: <social support perceived in G2 (p≤0,001) AVR: No differences between groups ESSNC:> involvement in G2 (p≤0,001) ESM:> involvement in G2 (p≤0,001) EHQ:> involvement in G2 (p≤0,001) ECAS:> involvement in G2 (p≤0,001) **Correlation between variables** *Significant positive correlation between moderate:* ESM and ESP SNC ESM and ECAS ESM and EHQ ESSNC and ECAS ESSNC and EHQ ECAS and EHQ *Remaining positive correlations are low or very low, all significant except between:* ECAS and AVR ESSNC and Age ASP and Age *Very low negative correlation between:* SCL-de and Age AVR and age (p = 0.01)	The association between IIA and psychological disorders (depression symptoms) is not explained by known risk factors for severe depression, such as social support and recent life events The differences between people and group patients in the study suggest that psychological disturbances may be a risk factor or part of the most serious states of IEI, possibly adding to the level of disability, ie, the social and labor.

REFERENCE	STUDY	POPULATION	INTERVENTION / COMPARISON	CLINIC / COMORBIDITY	CONCLUSIONS
Nordin *et al.* 2013[37], United Kingdom	**Objetive** Investigate perceived stress, focusing on emotional factors and environmental sensitivity to odors in people with very high sensitivity to noise compared to people with low sensitivity to noise. **Study design** Transversal study. **Period of realization** They do not tell.	**Recruitment** 134 male college students. *Weinstein's answer questionnaire Noise Sensitivity Scale (NSS)* (classifies noise sensitivity as negative emotional reactions and behavioral disturbances caused by noise) Range between 1 and 105 (a> score> sensitivity) **Groups** **Group 1 (G1):** 16 people high sensitivity Average age: 23a (DE 2.5) NSS Average Score: 85.4 (SD 7.5) **Group 2 (G2):** 16 people low sensitivity Average age: the 24th (SD 2.9) NSS Average Score: 55.2 (SD 6.1)	**Interventions** **Perceived stress** Perceived Stress Questionnaire (PSQ): Range between 0 and 1 (> value> stress) **Sensitivity to odors** Chemical Sensitivity Scale (CSS): range between 1 and 105 (> value> sensitivity) **Statistic analysis** Analysis of variance Spearman correlation	**Perceived stress (PSQ):** G1> G2 stress (p> 0.05) **Sensitivity to odors (CSS):** G1> G2 sensitivity (p> 0.05) **Correlation between:** NSS and PSQ: 0.35 low positive correlation (p <0.05) NSS and CSS: 0,48 moderate positive correlation (p <0.01) PSQ and CSS: 0,58 moderate positive correlation (p <0.001)	The question of whether the relationship between susceptibility to noise and odors reflects a general environmental sensitivity arises

Diagnosis

REFERENCE	STUDY / POPULATION	INDICATOR	RESULTS	CONCLUSIONS / COMMENTS
Mena *et al.* 2013[41], Spain	**Objetive** QEESI translate and adapt to Castilian and Spanish population and analyze their reliability in people with MCS diagnosed in Tertiary Hospital. **Study design** Transversal study. **Sample** **Group 1 (G1):** 77 (74 women) people diagnosed with MCS. Average age: 54.2 years (SD 6.5). **Group 2 (G2):** 154 people. Recruited outpatient without criteria MCS. Average age: 52.3 years (SD 8.7).	**Interventions** Translation QEESI the Castilian, back translation, committee discussion and piloting. **Statistic analysis** For valuation of internal consistency of the scales: Cronbach α.	**Cronbach α of:** Chemical intolerance: 0,81 Other intolerances. 0.85 Severity of symptoms: 0,81 Impact daily life activities: 0.87	This adapted version of QEESI presents, in terms of reliability, good internal consistency. **COMMENTS** Prospective longitudinal studies considered necessary to calculate the ROC curves (AUC) in order to establish cutoff points for each scale Propose other studies to design instruments with better ability to diagnose MCS.

REFERENCE	STUDY / POPULATION	INDICATOR	RESULTS	CONCLUSIONS / COMMENTS
Skovbjerg *et al.* 2012b[38], Denmark	**Objetive** Evaluate the translation of QEESI for Danish population. **Study design** Transversal study. **Period of realization** See below. **Involved** **Group 1 (G1):** 1st questionnaire Shipping: 2,000 people (between 18 and 69 years) 2nd questionnaire Shipping: 200 Danish Civil Registration come (January 2010) **Group 2 (G2):** 1st questionnaire Shipping: 315 people. 183 after contact with Danish Research Centre for Chemical Sensitivities (between January 2006 and January 2010). 132 people diagnosed with MCS hospital between January 1990 and January 2009 2nd questionnaire Shipping: 140 people.	**Interventions** Translation with piloting. Questionnaire sent 2 times (starts and two months) **1st questionnaire responses:** Global: 64.5% G1: 65.3% (1305/2000) G2: 60% (189/315) **2nd questionnaire responses:** G1: 61% (122/200) G2: 80% (112/140) **Statistic analysis** **Reliability:** Internal consistency: Cronbach α Test-retest (same test people at two different times - Home and 2 months): Pearson Correlation **Sensitivity and specificity:** Area under the curve	**Internal consistency:** G1: between 0.64 and 0.94 (x age groups) G2: between 0,83 and 0,91 **Test-retest:** Between 0.84 and 0.96. Positive correlation between high and very high ($p < 0.05$) Overall sensitivity (S): 92.1% overall specificity (E): 93.1% **Intolerance Scale Chemistry (IQ):** S: 89.3% (for cutting point scale 47) E: 89.4% (for cutting point scale 47) Scale impact on daily life (IVD): S: 91.0% (for cutting point scale 21) E: 90.9% (for cutting point scale 21) Combined use IQ and IVD: S: 92.1% (35 point IQ cut and IVD 14) E: 91.8% (35 point IQ cut and IVD 14)	Danish translation of QEESI shows good reliability and validity. Recommend using scales "Chemical Intolerance" and "impact on activities of daily living" as it is a shorter alternative with good S and E.

Physical, psychological and social impact. Quality of life

REFERENCE	STUDY	POPULATION	INTERVENTION	IMPLICATION	CONCLUSIONS / COMMENTS
Gibson *et al.* 2011[42], U.S.	**Objetive** Investigate the long-term impact of the MCS in the lives of patients with MCS, focusing on relationships. **Study design** Qualitative study.	**Inclusion criteria** MCS minimum of 5. **Recruitment** Advertisements. **Sample** 15 women 11 men **Characteristics** Average age: 59 years Range: 31-82 Symptoms Average duration: 23.5 years Range: 5 to 51 years	**Methodology** **Telephone interview:** Yes, and how their relationships with others are affected by having MCS The way they thought they were perceived by others and if there are misconceptions about disability If you have ever felt disconnected from society because MCS **Reading, transcription, discussion group and re-reading.** **Grouping content by topics:** Adequacy of spaces *("primacy of spatiality")*	**Adequacy of spaces:** Social and occupational isolation Need to take many precautions to relate. a cultural effort is needed to create safe spaces (work, cinema, transport, etc.) where you can interact with others. Reaching out to others: Incomprehension, disbelief, ignorance, not ill. Loneliness, guilt by high demand for maintaining relationships. One solution may be to educate the general population about MCS, although not all share.	**Described under discussion:** Respondents living very different lives and see the world from a markedly different than those without MCS perspective. Require constant precautions, tendency to social isolation, it emphasizes the importance of the adequacy of the spaces.

REFERENCE	STUDY	POPULATION	INTERVENTION	IMPLICATION	CONCLUSIONS / COMMENTS
			Reaching out to *others ("reaching for others")* Living in a different world (includes previous issues)	Internet and telephone possible to maintain contact with people. **Living in a different world:** They feel the world outside as mere observers.	Health care providers must broaden their perspectives and create safe spaces for people with MCS.

REFERENCE	STUDY	POPULATION	INTERVENTION	REPERCUSIONES	CONCLUSIONS / COMMENTS
Soderholm *et al.* 2011[43], Sweden	**Objetive** Clarify how individuals experience living with sensory hyperactivity disorder (HRS), the impact on accessibility, economic security and social relations. **Study design** Qualitative study.	According to the authors, time is a form of intolerance odors, including MCS and IEI. **Inclusion criteria** HOURS be diagnosed by a physician with the provocative test of capsaicin, be ≥18 years old and live in Sweden. **Recruitment** Ad on specific web. **Sample** 16 volunteers 12 women met inclusion criteria **Characteristics** Age range: 23 to 64a Symptoms range duration: 1 to 20a	**Methodology** I relate answering three written questions: How do you experience the impact of this condition in its accessibility to society; in their social relationships; in economic security? They use a scale chemical-sensory hyperreactivity sensitivity to quantify emotional reactions and behavioral disorders in everyday life by odors. Cutoff for HRS is **≥43 points.** **Groupings topics:** Accessibility Economic security Social relationships	All they obtained on the sensitivity scale chemical-HRS ≥43 Media **52.3** (range 44-55) Subjects identified categories: **Accessibility:** Take transport is difficult. Visit public buildings and facilities is difficult. Finding a suitable place to live is almost impossible. **Economic security:** Reduction in revenue due to the difficulty of living. Increased expenses have HRS Lack of support from the authorities. Difficulty managing finances. **Social relationships:** Socializing has become difficult and traumatic. Limitation for social activities. Getting support from some people knowing that this limits people. Refusing to change their own social interaction. *Six common themes for the three content areas were identified:* Limitation to participate in society Obligation to behave inconsistently with personality Experience lack of understanding and respect for others experiencing insecurity Being dependent on others Forced to choose between plague and cholera. Alternative sometimes are equally negative.	If you choose to **avoid odors:** Determinants of health (accessibility, financial security, social relations) are adversely affected If they decide **exposed to odors:** Determinants of health can be affected positively, but will get sick with symptoms HRS, with the loss of livestock, not physically able to work, travel and participate in activities and social gatherings.

REFERENCE	STUDY	RESULTS	CONCLUSIONS / COMMENTS
Genuis, 2013[45], Canada	**Objetive** Provide information on the management of MCS. **Study design** Review **Search period** Not specified **Revised databases** MEDLINE, books, magazines toxicology, conference papers, government publications and magazines environmental health.	**Desensitization immunotherapy** **Steroids.** Alternative that is not first line. **Cognitive therapy and neuronal Retraining**: technique from the premise of neuroplasticity and involvement of the limbic system in the MCS, proposes a training by instructions to restructure and modify the operation of the limbic system. RESULTS variables without a clear effectiveness. Moving away from social activities (avoid chemicals and create a free-living chemicals)	Physiological treatments appear to have superior and sustainable RESULTS compared to psychological therapies. As a preventable and reversible condition, people with MCS need of attention directed to avoid exposure to triggers and attention directed to inform these people substances.

Therapeutic management and prevention

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS / COMMENTS
Ralph *et al.* 2011[46], Luxembourg and France (Study addressing	**Objetive** Tracking a case since his diagnosis, investigating changes in	Woman Social worker Occupational exposure unlikely From 2004 to August 2007:	Diagnosing triggers products and reduce or eliminate symptoms of exposure. **Identified home products:** **Biocidal** products (17 products): Azaconazole, chlorothalonil, chlorpyrifos, 4,4'-DDE, 4,4'-DDT, dichlofluanid, dieldrin, endosulfan, Eulan, adjoin, methoxychlor, pentachlorophenol,	Onset of symptoms after exposure to permethrin. syndromes solvents and	The appearance of symptoms of MCS after accidental exposure to permethrin corroborates the cause-effect relationship.

prevention and therapeutic measure)	clinical regarding changes in exposure. **Design** Descriptive, apropos of a case. **Period of realization** From 2007.	baffling symptoms with multiple medical research Severe pain and headaches with visual impairment 24-28 hours after furniture restoration weekend. improvements and exacerbations alternate according restatements	propiconazole, tetrachlorvinphos, tolyfluanid and tribromophenol, tebuconazole **Pyrethrins** (8 products): Permethrin, cyfluthrin, cypermethrin, deltamethrin, fenvalerate, phenothrin, tetramethrin and piperonyl butoxid **Flame retardants** (8 products): 2-ethylhexyl-diphenyl-phosphate EHDPP, tributyl-phosphate TBP, TPP triphenyl-phosphate, tris (2-butoxyethyl) -phosphate TBEP, tris (2-chloroethyl) -phosphate TCEP, tris (3-chloropropyl) -phosphate TCPP; tris (1,3-dichloro-2-propyl) -phosphate TDCP or TDCPP and tris (2-ethylhexyl) -phosphate TEHP. **Bed mattress:** very high levels of permethrin (30 mg / kg of foam). Notable changes to the clinic as exposure to permethrin mattress.	olfactory syndrome are excluded (Permethrin is odorless) The replacement mattress marked improvement in symptomato-logy one woman	Environmental toxicological investigations ensured a diagnosis of existing at a time that could implement treatment measures designed to prevent re-exposure substances.

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS / COMMENTS
Mischley *et al.* 2013[48], U.S.	**Objetive** Describe RESULTS provided by people with prescription **intranasal reduced glutathione (inGSH).**	**Inclusion criteria** You have received one or more prescriptions Ings Between April 2009 and April 2011. **Recruitment** Pharmaceutical base data. **Sample** **300** individuals selected for randomization	Mailed questionnaire. **Individual perceptions about:** Adverse effects Health benefits	Response rate: 23.3% (n = 70) Confirm prescription 94.3% (n = 66) **MCS** Prescription inGSH MCS: 42% (n = 29) **InGSH usage time in MCS - months:** Median (p25; p75); 32.5 (16; 65) negative effects described: 20.7% (n = 6) Health benefits described: 62.1% (n = 18) Improving energy: 17.2% (n = 5) They feel good: 31.0% (n = 9) Improved sense of smell: 10.3% (n = 3) Amelioration of symptoms of MCS: 44.8% (n = 13) ↓ head pain often: 13.8% (n = 4) ↓ sinusitis: 13.8% (n = 4) ↓ otitis: 3.4% (n = 1) **Adverse effects** Irritation of sinuses or nasal passage: 31% (n = 9) Headaches: 20.7% (n = 6) Worsening symptoms MCS: 3.4% (n = 1) Epistaxis: 13.8% (n = 4)	**inGSH** is easy to administer, with few adverse effects and perceived health improvements **Future studies** could be aimed at determining whether the individual perception of improvement can be objectively verified and if these benefits can be inferred to larger population.

REFERENCE	STUDY	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS / COMMENTS
Waddick, 2011[47], U.S.	**Objetive** Analyze residential areas to reduce exposure to contaminants in MCS vulnerable population. **Study design** Case Studies **Period of realization** Not specified	Two healthy residential areas	interviews: 1-Personal 2-Phone Visits to residential areas	Difficulties in **finding safe housing** Planning actions (to address these challenges) Role of **people** **Economy** and finance staff Safe maintenance and property management (housing) Access to affordable and safe housing for vulnerable populations.	In the absence of etiological treatments, more research is needed on ways to create and sustain healthy residential areas, understand and reduce sources of exposure that initiate and trigger the MCS and learn from experiences and strategies used in other countries.

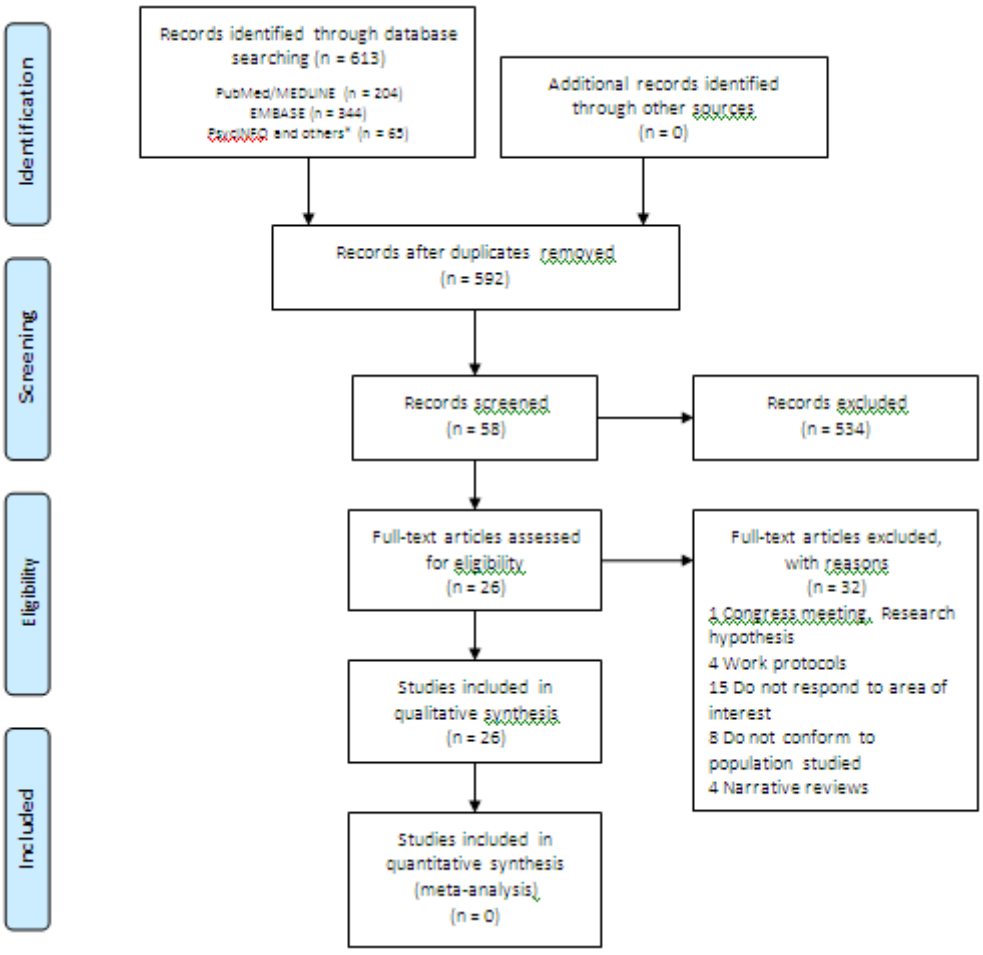
Table 2. *Excluded studies*

REFERENCE	EXCLUSION CRITERIA
EPIDEMIOLOGY	
Baliatsas *et al.* 2014, Holland	It does not fit the study population.
CLINICAL MANIFESTATIONS AND COMORBIDITY	
Baliatsas *et al.* 2014, Holland	It does not fit the study population.
Genuis 2013, Canada	Narrative review.

REFERENCE	EXCLUSION CRITERIA
Tran *et al.* 2013b, Denmark	Study protocol.
De Luca *et al.* 2011, Italy and Malaysia	Narrative review.
Goldstein *et al.* 2011, U.S	It does not address the intervention of interest.
Leer *et al.* 2011, Holland	It does not address the intervention of interest.
Skovbjerg *et al.* 2012c, Denmark	It does not address the intervention of interest.
Skovbjerg *et al.* 2012d, Denmark	It does not fit the study population.
Nogué *et al.* 2011, Spain	Narrative review.
MCS DIAGNOSIS	
Dupas *et al.* 2013, France	Narrative review.
Mazzatenta *et al.* 2013, Italy	It does not address the intervention of interest.
Nordin *et al.* 2013, United Kingdom	It does not address the intervention of interest.
Tran *et al.* 2013a, Denmark	It does not address the intervention of interest.
Baliatsas *et al.* 2012, Holland	It does not fit the study population.
Fujimori *et al.* 2012, Japan	It does not address the intervention of interest.
PHYSICAL, PSYCHOLOGICAL AND SOCIAL IMPACT. QUALITY OF LIFE	
Baliatsas *et al.* 2014, Holland	It does not fit the study population.
Heinonen-Guzejev *et al.* 2012, Finland	It does not address the intervention of interest.
Skovbjerg *et al.* 2012b, Denmark	It does not address the intervention of interest.
Skovbjerg *et al.* 2012c, Denmark	It does not fit the study population.
Skovbjerg *et al.* 2012d, Denmark	It does not address the intervention of interest.
De Luca *et al.* 2011, Italy and Malaysia	Narrative review.
Waddick 2011, U.S	It does not address the intervention of interest.
PREVENTION AND TREATMENT	
Baliatsas *et al.* 2014, Holland	It does not fit the study population.
Tran *et al.* 2013b, Denmark	Study protocol.
Araki *et al.* 2012, Japan	It does not address the intervention of interest.
Hauge *et al.* 2012, Denmark	Study protocol.
De Luca *et al.* 2011, Italy and Malaysia	Narrative review.
Stoppe *et al.* 2011, Germany	It does not fit the study population.
Williams *et al.* 2011, Canada	It does not address the intervention of interest.
Witthoft *et al.* 2013, UK and Germany	It does not address the intervention of interest.
Zaitseva *et al.* 2011, Russia	It does not fit the study population.

IMAGES:

PRISMA 2009 Flow Diagram



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Annex 1. Search strategies

MEDLINE

Dec 2015

#1 "Multiple Chemical Sensitivity"[Mesh]

#2 Multiple[tiab] AND (Chemical Sensitivit*[tiab] OR chemical hypersensit*[tiab])

#3 Multiple[ti] AND chemica*[ti] AND (sensitivit*[ti] OR hypersensitivit*[ti])

#4 Idiopathic Environmental Intoleranc*[tiab]

#5 (#1 OR #2 OR #3 OR #4)

("2011/01/01"[PDat] : "2015/12/15"[PDat])

Epidemiology

incidenc* OR prevalenc* OR epidemiol*

Clinical manifestations and comorbidity

symptoms* OR signs* OR manifestat* OR comorbidit*

Diagnostic

diagnos* OR prognos* OR screen* OR specific*

Quality of life

quality* OR lif* OR impact* OR psychol*

Treatment

therap* OR trial*

Prevention

prevent* OR control*

EMBASE

Dec 2015

#1 "Multiple Chemical Sensitivity"/exp

#2 Multiple:ab AND (“Chemical Sensitivity”:ab OR “chemical hypersensitivity”:ab)

#3 Multiple:ti AND chemica*:ti AND (sensitivit*:ti OR hypersensitivit*:ti)

#4 “Idiopathic Environmental Intolerance”:ab,ti

#5 (#1 OR #2 OR #3 OR #4)

Epidemiology

incidenc* OR prevalenc* OR epidemiol* AND [embase]/lim AND [2010-2015]/py

Comorbilidity

symptoms* or signs* or manifestat* or comorbidit* AND [embase]/lim AND [2010-2015]/py

Diagnostic

diagnos* OR prognos* OR screen* OR specific* AND [embase]/lim AND [2010-2015]/py

Quality of life

quality or lif* or impact* or psychol* AND [embase]/lim AND [2010-2015]/py

Treatment

therap* or trial* AND [embase]/lim AND [2010-2015]/py

Prevention

prevent* or control* AND [embase]/lim AND [2010-2015]/py

PUBPSYCH

Dec 2015

#1 multiple chemical sensitivity

#2 idiopathic environmental intolerance

#1 OR #2

Dates: 2010-2015

PSYCINFO

Dec 2015

S1 - AB "chemicalsensitivit*"

S2 - AB "chemical hypersensit*"

S3 - AB "multiple"

S4 - S1 OR S2

S5 - S3 AND S4

S6 - TI multiple

S7 - TI "chemica*"

S8 - TI "sensitivit*"

S9 - TI "hypersensitivit*"

S10 - S8 OR S9

S11 - S6 AND S7 AND S10

S12 - TI "idiopathicenvironmentalintoleranc*"

S13 - AB "idiopathic environmental intoleranc*"

S14 - S12 OR S13

S15 - TI "multiple chemical sensitivity"

S16 - AB "multiple chemical sensitivity"

S18 - S15 OR S16

S19 - S5 OR S11 OR S14 OR S17, Limiters - Publication Year: 2010-2015

The COCHRANE LIBRARY

Dec 2015

#1 MeSH descriptor: [Multiple Chemical Sensitivity] explode all trees

#2 idiopathic environmental intoleranc* (Word variations have been searched)

#3 multiple chemical intolerance (Word variations have been searched)

#1 or #2 or #3

Treatment

therap* or trial*:ti,ab,kw (Word variations have been searched)

CRD:

Dec 2015

#1 (multiple AND chemical AND sensitivity)

#2 (idiopathic AND environmental AND intolerance)

#3 (multiple AND chemical AND hypersensitivity)

#4 #1 OR #2 OR #3 FROM 2010 TO 2015

TOXLINE:

Dec 2015

1 "idiopathic environmental intolerance" AND 2010:2015 [yr] [not] PubMed [org] [not] pubdart [org]

2 "multiple chemical sensitivity" AND 2010:2015 [yr] [not] PubMed [org] [not] pubdart [org]

CISDOC database

Dec 2015

#1 multiple chemical sensitivity

#2 idiopathic environmental intolerance