SCIENCE INTEGRITY KNOWLEDGE

MULTIPLE CHEMICAL SENSITIVITY: LITERATURE REVIEW AND STATE OF THE SCIENCE

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Table of Contents

List of Tables

List of Figures

Appendices

Glossary

$5H_{TT}$ (SLC6A4)	Serotonin transporter
ACC	Anterior cingulate cortex
ACQ	Agoraphobic Cognitions Questionnaire
AEDS	Atopic eczema/dermatitis syndrome
AhR	Aryl hydrocarbon receptor
ALDH2	Aldehyde dehydrogenase 2
ANS	Autonomic nervous system
BOLD	Blood Oxygenated Level Dependent
BSAENM	The British Society for Allergy, Environmental and Nutritional Medicine
CCK2R/CCK2	Cholecystokinin 2 or B receptor
CCHS	Canadian Community Health Survey
CCSIT	Cross-Cultural Smell Identification Test
CFS	Chronic Fatigue Syndrome
CGES	Chemical and General Environmental Sensitivity Questionnaire
CGES	German Questionnaire on Chemical and Environmental Sensitivity
Chemical AIDS	Chemical Acquired Immune Deficiency Syndrome
CHHS	Canberra Hospital and Health Services
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CNS	Central Nervous System
CO_2	Carbon dioxide
CoA	Commonwealth of Australia
COMT	catechol-*O*-methyltransferase
COSS	Chemical Odor Sensitivity Scale
CSS/CSS-SHR	Chemical Sensitivity Scale or Chemical Sensitivity Scale for Sensory Hyperreactivity
CXC8	Chemokine CXC-Motif Ligand 8
CYP450	Cytochrome P450
DASS	Depression Anxiety Stress Scales
DEET	N,N,-diethyl-meta-toluamide
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
ECRHS	European Community Respiratory Health Survey
EEG	Electroencephalogram
EHS	Electro-hypersensitivity
EMF	Electromagnetic Field
EMQ	Environmental Medicine Questionnaire
ES	Epileptic seizures
ESQ	Environmental Sensitivity Questionnaire
EWS	Environmental Worry Scale
FDG	18F-2-fluoro-2-deoxy-d-glucose
FFT	Fast Fourier Transform
FM	Fibromyalgia
fMRI	Functional MRI
FSS	Functional somatic syndrome
GABA	gamma-aminobutryic acid
HPAA	Hypothalamus-pituitary-adrenal axis
HR	Heart rate
IBS	Irritable Bowel Syndrome
IEI	Idiopathic Environmental Intolerance
IEI-LIQ	IEI Life Impact Questionnaire
IEISI	Idiopathic environmental intolerance symptom Inventory
ILC	Innate Lymphoid Cells
INF-γ	interferon-gamma
KSP	Karolinska Scales of Personality
MCP-1	Monocyte Chemotactic Protein-1
MCS	Multiple Chemical Sensitivity
MDD	Major Depressive Disorder
ME	Myalgic Encephalomyelitis
MI	Mobility Inventory for Agoraphobia
MMPI	Minnesota Multiphasic Personality Inventory
MMSE	Mini Mental State Examination
MOC	Medial olivocochlear
MOS SF-36	Medical Outcomes Study Short Form 36
MTHR/MTHFR	Methylene tetrahydrofolate reductase
MUPS	Medically Unexplained Symptoms
NAT	N-Acetyltransferase
NES	Nonepileptic seizures
NIRS	Near-infrared spectroscopy
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
NOS2	Nitric oxide synthase
NOSQ	Nordic Occupational Skin Questionnaire
NSEHC	Nova Scotia Environmental Health Centre
OAS	Odour Awareness Scale
OFC	Orbitofrontal cortex
OLF	Olfactory cortex
OTI	Odour Tolerance Index
PBL	Peripheral blood lymphocytes
PEA	Phenylethylalcohol
PEMF	Pulsed electromagnetic fields
PET	Positron emission tomography
PFC	Prefrontal cortex
PHQ-15	Patient Health Questionnaire
PON1	Paraoxonase 1
PSS	Perceived Stress Scale
PTSD	Post-Traumatic Stress Disorder
QEESI	Quick Environmental Exposure and Sensitivity Inventory
Q-LL	Questionnaire of Living Conditions and Living Factors

GAD	Generalized Anxiety Disorder
GHLCS	German Health Locus of Control Scale
Gpx	Glutathione peroxidase
GST	Glutathione transferase
SAS	Somatosensory Amplification Scale
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission
SCID	Structured Clinical Interview, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
SCL	Symptom Checklist
SDS	Self-rating Depression Scale
SFD	Somatoform disorder
SHS	Sick house syndrome
sMCS	Self-reported multiple chemical sensitivity
SNOMED CT®	Systematized Nomenclature of Medicine -- Clinical Terms
SOD2	Superoxide dismutase 2
SOPs	Standard Operating Procedures
SOW	Scope of Work
SPECT	Single Photon Emission Computer Tomography
SPT	Static Posturography Test
STAI	State-Trait-Anxiety-Inventory
QOD	Questionnaire of Olfactory Disorder
Q-OEUM	Questionnaire of the Outpatient Unit of Environmental Medicine
raCC	Rostral Anterior Cingulate Cortex
RADS/RUDS	Reactive (upper) Airways Dysfunction Syndrome
rCBF	Regional cerebral blood flow
TE	Chemically Intolerant Toxic Encephalopathy or Chronic Toxic Encephalopathy
TEOAE	Transient-Evoked Otoacoustic Emission
TILT	Toxicant-Induced Loss of Tolerance
TNFα	Tumor Necrosis Factor α
TRP	Transient Receptor Potential
TRPV	Transient Receptor Potential Vanilloid
UCTS	Ultrasonic Cerebral Tomosphygmography
UGT	UDP-glucuronosyl transferase
UPSIT	University of Pennsylvania Smell Identification Test
UTHS	University of Toronto Healthy Survey
VEGF	Vascular Endothelial Growth Factor
VIP	Vasoactive intestinal peptide
WOE	Weight of Evidence

EXECUTIVE SUMMARY

Alberta Health has made a commitment to people living in the area of Peace River, Alberta to complete a comprehensive, critical literature review regarding the state of knowledge surrounding Multiple Chemical Sensitivity (MCS) as a medical condition and to help identify potential actions that could support individuals with MCS. Stemming from this, a Request for Proposal was developed by Alberta Health, with defined objectives provided within the Scope of Work. As required by the Statement of Work issued by Alberta Health upon reward of the contract to Intrinsik Corp., a critical, state of science review of the existing research regarding MCS has been completed. Although this work was initiated by Alberta Health in response to concerns expressed by residents of the Peace River area, the Statement of Work is not focused on evaluating the specific symptoms reported by residents in this area or any association with certain chemical substances or emission sources.

The key objectives of this review are to:

1. Identify the lines of research into MCS and the key theories that are used to define it, and describe the state of the science.
2. Synthesize research across major relevant fields, and attempt to describe the answers to the following research questions:
    - *What factors, both human and environmental, contribute to the development of MCS in individuals?*
    - *What are the markers or symptoms of MCS?*
    - *What are the health outcomes of MCS?*
    - *What clinical responses to MCS have been tested and how effective were those responses?*[1]
    - *What public health responses to MCS have been tested, and what is the evidence for their effectiveness?*

To achieve these objectives, a comprehensive, systematic literature search and review was completed of the peer-reviewed scientific literature and the available grey literature. Over 4,000 documents (peer-reviewed and grey combined) were uncovered in the initial search, and through careful application of pre-defined inclusion and exclusion criteria, and ratings for quality and relevance, a focused list of over 140 peer-reviewed literature papers and over 20 grey literature documents were identified. These papers included recently published epidemiological, clinical and experimental studies involving human subjects. Literature based on self-diagnosed MCS or self-reported MCS is presented in an Appendix to the report, as it provides useful insight. However, this information was excluded from the main body of the report due to lack of the diagnosis of MCS by a clinician or researcher using one of the many available diagnostic frameworks available for MCS.

[1] This research question was removed from further consideration in the report at the request of Alberta Health, as a result of scoping discussions following the completion of the literature search. The clinical information identified in the literature search is available within the annotated bibliography within Appendix A.

The state of knowledge regarding MCS has been evolving over time and is represented in the literature by several different terms. To date, several diagnostic frameworks and nomenclature have been published, but there is no clear consensus evident among practitioners or researchers, and none of the frameworks appear to be universally agreed upon or used by researchers. A wide range of symptoms have been associated with MCS, encompassing sensory, neurological, physical, gastrointestinal and behavioural effects. These effects have been associated with a variety of triggers or stimuli, but there is no clear pattern with respect to chemicals or substances.

In addition to providing an overview of what is known about MCS with respect to symptoms, triggers and prevalence, in order to provide a current review of the state of the science review of MCS, literature identified during the comprehensive search and screening processed was sorted and organized topically by lines of research identified previously in comprehensive reviews of MCS by the Commonwealth of Australia (CoA 2010) and Rossi and Pitidis (2017). These lines of research included:

- Toxicant Induced Loss of Tolerance
- Immunological dysregulation
- Genetic factors
- N-methyl-D aspartate Receptor Activity and Nitric Oxide/Peroxynitrate
- Neurological Sensitization and Neurogenic Inflammation
- Neurological Abnormalities
- Behavioural and Psychiatric Factors

A qualitative weight of evidence approach was applied to the peer-reviewed literature identified in this review, and qualitative ratings for the consistency and utility of the study data were applied within each of the above categories using defined criteria. This approach was used to compare and contrast the areas of research. Using a “heat-map” tabular approach and a graphical representation of the ratings, the two areas of research emerged as having the most support:

1. Olfactory processing dysfunction
2. Neurologic sensitization and neurogenic inflammation

These two areas were found to overlap with some of the most commonly reported symptoms in the literature in patients with diagnosed MCS. It is possible that the biological processes involved in MCS may involve olfactory processing, neurogenic sensitization and neurogenic inflammation, as these involve the nervous system and the reaction of the brain to stimuli (irritant and olfactory) and irritation effects on mucosal membranes of the eye and respiratory tract.

At this time, the overall weight of evidence with respect to MCS is rated as **Moderate: generally good evidence from one line of research but evidence missing from others.** Further study of the various lines of research for MCS will likely continue to enhance the state of knowledge, which will likely contribute to advances in the management of MCS.

Like the analysis of the scientific data for MCS, the management of MCS from both a public and occupational health perspective has been reported to be quite complex and considered to varying degrees by governmental organizations. Individuals with MCS have reported many challenges with respect to accessing quality care, and health care providers are limited by the lack of a universal set of diagnostic criteria and common terminology.

This review has revealed that there is a fundamental need for the diagnostic criteria for MCS to be reviewed, updated and harmonized to help ensure appropriate and consistent diagnosis of the condition. This need was evident throughout the entire review and impacts everything from the development of a concise clinical profile, the consistent diagnosis of patients within and between centres, the design of research studies, to effective clinical management and health care provision.

There is also a need for well-designed studies that examine more than one potential endpoint, and for longitudinal studies to better understand the interaction between the various possible lines of research and to obtain additional clarity with respect to what factors may pre-dispose individuals to MCS.

1.0 INTRODUCTION

Multiple Chemical Sensitivity (MCS) is a complex, chronic health condition that can involve a spectrum of various clinical signs and symptoms in affected individuals (Rossi and Pitidis, 2018). Although MCS was first identified in the 1950s, since the 1990s there have been developments in the understanding of MCS with respect to diagnosis, symptoms and prevalence. Despite this, the causes and mechanisms of MCS are not well understood and the condition has been subject to controversy.

Alberta Health has made a commitment to the public within the area of Peace River, Alberta to complete a comprehensive, critical literature review regarding the state of knowledge surrounding MCS as a medical condition and to help identify potential actions that could support individuals with MCS in general, based on the findings of the review. Stemming from this, a Request for Proposal was developed by Alberta Health, with defined objectives provided within the Scope of Work.

The key objectives of this review, as defined by the Scope of Work (SOW) provided by Alberta Health, are to:

- Identify the lines of research into MCS and the key theories that are used to define it, and describe the State of the Science (SOS);
- To synthesize research across major relevant fields of research, and attempt to describe the answers to the following research questions:
- What factors, both human and environmental, contribute to the development of MCS in individuals?
- What are the markers or symptoms of MCS?
- What are the health outcomes of MCS?
- What clinical responses to MCS have been tested and how effective were those responses?[2]
- What public health responses to MCS have been tested, and what is the evidence for their effectiveness?

Based on Alberta Health's SOW, this review is not intended to:

- Represent a comprehensive historical review of the condition;
- Serve as an investigation or inquiry related to the specific symptoms, health issues or exposures reported by individuals within the Peace River, Alberta area nor is it intended for diagnostic purposes for the specific treatment or management of individuals in the area of Peace River, Alberta;

[2] This research question was removed from consideration in the report at the request of Alberta Health. The clinical information identified in the literature search is available within the annotated bibliography within Appendix A.

- Provide an evaluation of potential causative or triggering exposures of individuals within the Peace River, Alberta area or elsewhere;
- Serve as a complete meta-analysis of all available data or include an evaluation of statistical relationships between multiple studies.

2.0 METHODOLOGY

A comprehensive, systematic literature search was completed that involved the identification of relevant literature in peer-reviewed or "white literature" and "grey" databases (literature published elsewhere).

The objective of this review is to utilize the peer-reviewed scientific publications and grey literature to describe the state of science of MCS in response to the research questions defined in the SOW for this project (presented in Section 1.0). Specific databases were searched using the terms outlined in Sections 2.1 and 2.2 for the peer reviewed and grey literature searches, respectively.

Peer-reviewed literature refers to published literature that has undergone critical peer evaluation that is widely accessible through on-line electronic databases such as PubMed, Web of Science, *etc.*

Grey literature refers to documents or research produced by organizations (e.g., government, academia, business and industry) that are not published by a commercial publisher.

Section 2.3 outlines how the collected information was used in the report.

2.1 Review of Peer-Reviewed Literature

Step 1 Literature Identification

The search terms provided in Table 1 represent the common, scientific terminologies used to describe MCS, and were used in searching the databases presented in Table 2. These terms were identified from the information summarized within Graveling et al. (1999), Labarge and McAffrey (2000) and WHO IPCS (1996).

To help focus the results of the database searches on the articles of the most relevance, inclusion and exclusion criteria (Table 3) were developed and applied against the database search results during the initial screening (consisting of the removal of duplicates and a review of titles and abstracts). Primary research articles published from January 1, 2000 to May 4, 2017 were reviewed[3]. This timeframe was selected based on:

- The findings of the initial literature searches;
- The availability of comprehensive literature reviews published in 1999 to 2000 (e.g. Graveling et al. (1999), Labarge and McAffrey (2000)); and
- The publication dates of the most common diagnostic frameworks for MCS (Bartha et al. (1999), Cullen (1987), Nethercott et al. (1993), NRC (1992), WHO IPCS (1996)).

Alberta Health agreed to this approach before the search was completed.

[3] The original research work for this project was completed in 2017. A version of this report was submitted to Alberta Health in Q1 2018. Additional edits were completed in response to external reviewer comments in Q4 2019, but the initial literature search strategy was not updated.

Table 1: Summary of Search Terms Used in the Peer-Reviewed Literature Search

Search Terms
("multiple chemical sensitivity*" OR "idiopathic environmental intolerance" OR "toxicant induced loss of tolerance") AND (cause OR marker OR symptom OR prevalence OR outcome OR diagnosis OR treatment OR review)

Table 2: Databases Searched for Peer-Reviewed Literature

Databases
PubMed (Medline)
Scopus
Web of Science
PsychINFO
ProQuest (for peer-reviewed literature only)

Step 2a Screening - Title and Abstract Review

In the next stage of the literature search, two researchers independently reviewed all 2,539 titles and abstracts, and applied inclusion and exclusion criteria to determine which studies would be included in the next stage of screening. This approach, outlined in Table 3, where articles highlighting several overlapping symptoms are excluded to focus the review on documents specifically related to MCS, is consistent with the comprehensive review of MCS completed by Graveling et al. (1999). In addition, review papers, studies with no abstract, case studies, and studies that involved surveys of self-reported (non-physician confirmed) MCS were also eliminated, as agreed upon in consultation with Alberta Health. Any discrepancies between the two researchers were resolved by consensus or by a third researcher.

Table 3: Summary of Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Available in English	Not available in English
Published January 1, 2000 to May 2017	Published before January 1, 2000
Human studies (occupational or population)	Animal studies
Studies of xenobiotic chemicals that include a chemical sensitization or challenge	Not related to study objectives
Multiple organ systems are affected (as defined by Graveling et al. (1999))	Studies that do not specifically mention and focus on "multiple chemical sensitivity"; "multiple chemical sensitivities"; "idiopathic environmental intolerance", "toxicant induced loss of tolerance" in the Title, Abstract or Keywords
	Sensitivity to electromagnetic frequencies (EMF)
	Sensitivity to noise or light

Step 2b Screening - Evaluation of Studies for Topical Content

Next, studies were coded or 'binned' by a third researcher as to how they related to the key research objectives and the key lines of research for MCS[4] (agreed upon in a letter from Alberta Health of August 8, 2017), including the following terms:

- Symptoms or markers (also captures outcome);
- Prevalence;
- Management (intended to capture both clinical and public health management);
- immunological dysregulation ("immune");
- Respiratory disorder or neurogenic inflammation ("respiratory");
- Neuro sensitization/limbic kindling ("neural"), including olfactory ;mechanisms
- NMDA receptor activity, nitric oxide and peroxynitrate ("NMDA oxidation");
- Loss of tolerance ("tolerance");
- Altered xenobiotic metabolism ("metabolism"); and
- Behavioural and psychological factors ("psychology").

The purpose of this step was to help organize the information to facilitate review. The number of studies that passed through this phase of the literature screening was 183. Once a more detailed review of the text was completed, the coding was changed as necessary to help ensure that the study was included in the most appropriate section of the report. Some studies included material that were relevant to more than one line of research, and this was noted during the screening process.

Step 3 Eligibility and Inclusion- Full-Text Review

In the assessment of the literature to formulate a list for inclusion in the annotated bibliography, a qualitative ranking of study quality was completed by two reviewers based on full-text copies of the identified studies, where a qualitative ranking of one, two or three stars (*, ** or ***) were used to rate studies according to quality (low to high) were applied based on the following factors:

- Were the study objectives, design and results clearly presented?
- How many individuals/subjects were included in the study (e.g. case studies vs. population >10)?
- Were control subjects used?
- Did the study provide information of value and relevance to the objective?

Studies that were identified as being relevant to the project objectives and had a quality ranking of at least two stars (**) were included for further consideration. A total of 141 studies remained

[4] As identified by the most recent comprehensive review document by a governmental agency, – the Australian NICNAS/OCSEH, Commonwealth of Australia (CoA, 2010) document entitled "A Scientific Review of Multiple Chemical Sensitivity: Identifying Key Research Needs". This list of headings was modified during the compilation of this report to reflect the content of the literature, once it was reviewed in more detail.

after this final phase of literature screening. Brief summaries of these studies as well as the 42 that were excluded are included in Appendix A (Tables A-1 and A-2, respectively).

A visual summary of the above described process is provided within Figure 1.

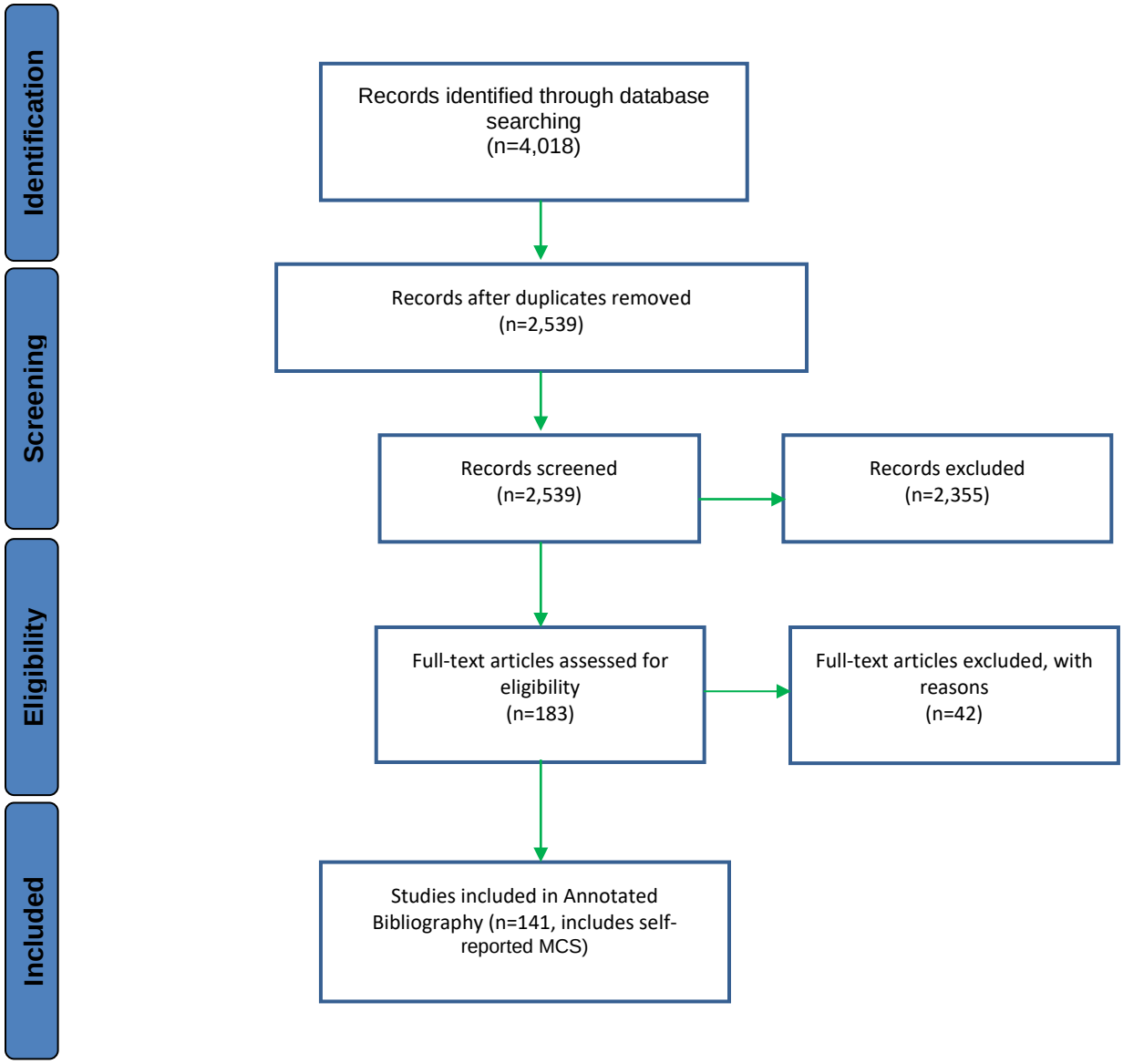

Figure 1: Summary of the Primary Literature Search Methodology

Following the generation of the annotated bibliography using the process outlined in Figure 1, three additional papers, and several recent review articles (n= 13) regarding MCS or related aspects (that were excluded as part of the 42 articles that did not meet eligibility requirements but provided useful background or context for the project) were identified. In addition, much of the literature regarding diagnostic criteria for MCS did not meet the inclusion criteria but was collected and reviewed within Section 3.4 (n=5).

The 141 articles identified in the process outlined in Figure 1 included both diagnosed and self-reported MCS. This was completed as the lack of a single, universally-accepted set of diagnostic criteria and the complexity of MCS has resulted in a wide variety of study designs.

The focus on this review is on studies of diagnosed MCS. However, it is recognized that studies of self-reported MCS are also of value to the body of scientific evidence for MCS as a whole, and many of the self-reported MCS studies are well designed. Summaries of studies identified during the literature search and screening that included patients with self-reported MCS are presented in Appendix C to this report.

2.2 Grey Literature Review

The objective of this search was to identify relevant reviews or studies of MCS from various levels of government, academia, non-profit organizations and industry using the Google search engine. In addition, the references of grey literature documents that were collected were examined to identify any additional documents of potential relevance.

Step 1 Grey Literature Search

The search terms outlined in Table 4 were used. Relevant publications were selected from the first 30 pages of results generated (*i.e.,* the first 300 results, sorted by relevance).

Table 4: Search Terms for Grey Literature Search

Search Terms
("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "idiopathic environmental intolerance" OR "toxicant induced loss of tolerance")

Step 2 Screening of Grey Literature

The criteria listed in Table 5 were then applied to identify relevant documents to be included in the study, which were the same as those applied in the evaluation of the peer-reviewed literature with the exception that only documents published by an established government agency, academic institution, non-profit organization, or industry association were eligible for inclusion. This criterion was applied to limit the review to scientific documents prepared by qualified experts.

Table 5: Summary of Inclusion and Exclusion Criteria for Grey Literature

Inclusion Criteria	Exclusion Criteria
Available in English	Not available in English
Published after January 1, 2000	Published before January 1, 2000
Human studies (occupational or population)	Animal studies
Published by an established government agency, academic institution, non-profit organization, or industry association	
Studies of xenobiotic chemicals that include a chemical sensitization or challenge	Not published by an established government agency, academic institution, non-profit organization, industry association
	Studies that do not specifically mention and focus on "multiple chemical sensitivity"; "multiple chemical sensitivities";

Multiple organ systems are affected (as per Graveling et al. 2000)	"idiopathic environmental intolerance", "toxicant induced loss of tolerance" in the Title, Abstract or Keywords
	Sensitivity to electromagnetic frequencies (EMF)
	Sensitivity to noise or light

A total of 29 grey literature documents were selected from this search for a more detailed review to determine their suitability for inclusion in the annotated bibliography and report.

Step 3 Eligibility – Review of Grey Literature

Similar to what was completed for the peer-reviewed literature review, the identified grey literature documents were assessed for content and relevance, and a qualitative ranking (of *, ** or ***, from lowest quality to highest quality) was applied with respect to quality, taking into consideration the following:

- Did the document provide a weight of evidence or position statement regarding one or more of the research objectives and mechanisms identified for this project?
- Did the organization or author appear to be a legitimate source of scientific information (e.g., is the organization a professional society or governmental agency)?
- Were the sources of the information cited, and if so, clearly?
- Did the study provide information of value and relevance to our objectives?

Studies that were identified as being relevant to the project objectives and had a quality ranking of at least two stars (**) were included for further consideration. With respect to the grey literature documents, several documents were brief factsheets or reviews that did not cite scientific information sources. Some of the documents identified were historical reviews and did not provide information regarding the current state of the science on MCS and its management, as is the interest of Alberta Health. A total of 21 documents remained after this final phase of screening. A list of references and brief summaries of these documents (as well as the documents that were excluded from further consideration) are provided in Appendix B (Tables B-1 and B-2 for the included documents and excluded documents, with rationale). The documents that were retained included comprehensive reviews, discussions or policies or procedures regarding the management of MCS patients, position papers and general overviews.

2.3 Review of Information

The studies of diagnosed MCS identified in the process outlined in Section 2.1 and the grey literature described in Section 2.2. were evaluated and organised in order to create a useful summary of the available information. How this was achieved for the different categories of information is described in Sections 2.3.1 to 2.3.3.

2.3.1 Overview of MCS

MCS is a complex topic to provide a complete and thorough review of due to the volume of research and opinions that have been generated. This review is not intended to represent a complete historical summary of the work completed to date on MCS. There are many documents of interest cited within the peer-reviewed and grey literature summarized in this

report. There are a number of references published before the inclusion date of the year 2000 used in this literature review due to some of the diagnostic frameworks emerging before this time.
The information included in this review was summarized within the following sub-sections to provide the reader with a sense of the complexity of the topic, the wide range of symptoms, triggers and overlapping conditions, and the variety in diagnostic frameworks that are used in the literature. Where possible, information regarding the prevalence of clinician diagnosed MCS is provided in the report, and prevalence information for self-reported MCS is outlined in Appendix C.

2.3.2 Lines of Research

Biological factors that may be involved in MCS have been identified from the body of evidence collected as part of Sections 2.1 and 2.2. These were sorted into different categories by lines of research based on the results of the literature search.

Assessments of the various lines of research associated with MCS have been reported in the Australian review CoA (2010) and also in a review by Rossi and Pitidis (2017). The following review is intended to build upon the foundations set by these two documents.

The literature identified in Section 2.0 was evaluated in detail. Based on more comprehensive document reviews, some studies that were 'binned' in the annotated bibliography (Appendices A and B) were moved between categories based on relevance. If a study included information that was relevant to more than one category, then it was included in all applicable lines of research discussions. For the purposes of this review, the following headings were used to organize the available information into the following lines of research into MCS:

- Toxicant Induced Loss of Tolerance
- Immunological Dysregulation
- Genetic Factors:
  - Genes Related to Metabolism
  - Genes for Immunological Modulators
  - Genes for Neurological Mediators
- N-methyl-D aspartate (NMDA) Receptor Activity and Nitric Oxide/Peroxynitrate
- Neurological Sensitization and Neurogenic Inflammation
- Neurological Abnormalities:
  - Olfactory Processing Dysfunction
  - Vestibular and Auditory Dysfunction
  - Other Neurological Factors
- Behavioural and Psychiatric Factors:
  - Behavioural and Psychological Responses to Stimuli
  - Comorbidity with Various Psychological/Psychiatric Conditions with MCS

The above-listed categories are intended to organize the information in a manner that facilitates critical review and evaluation. It is also recognized that it is difficult to determine if effects reported in the literature within the various sections are involved in the etiology of MCS or are consequences of MCS.

To date, a *weight of evidence* (WOE) approach or *evidence integration* process typically used in the evaluation of chemicals and toxicological endpoints has not been utilized to examine MCS. Several approaches and examples for evaluating and comparing the WOE across multiple lines of research or hypotheses have been documented in the literature in recent years, although these are generally aimed at the assessment of modes-of-action related to a single chemical agent (rather than a disease condition, such as MCS). In this section, we have utilized an evidence-based approach to provide an examination of the peer-reviewed scientific literature with an evaluation of the WOE for each of the identified lines of research. The intent of this analysis is to contrast and compare the types and quality of information available for each line of research. This exercise also helps to identify data gaps and limitations within the state of science for MCS.

The approach to analysing the WOE for this report is in the spirit of or inspired by qualitative and quantitative WOE frameworks available within the scientific literature. By necessity, this review evaluates only human studies as no animal model exists for MCS. A common scoring framework could not be established for the review due to the variability in study designs, clinical signs, and symptoms. Furthermore, dose-response data were generally lacking.

The general steps captured within the current review include:

1. The evaluation of individual publications, with documents being determined to be of sufficient quality to be carried forward into the overall WOE framework or not;

2. The assessment of individual lines of research, including both positive (statistically significant for MCS patients) and negative (not-statistically significant for MCS patients) findings from the studies reviewed, to provide a balanced evaluation;

3. An assessment of the WOE for all lines of research combined; and,

4. A characterization of potential limitations, gaps and uncertainties.

Steps 1 and 2 are discussed within Sections 4.1 to 4.7. For Step 2, criteria for Consistency and Utility were applied for the studies evaluated within each Section, with consistency being the level of agreement between studies, and utility referring to the overall relevance and quality of the studies (SCENIHR, 2012). Additional information regarding this approach is provided in Section 4. In developing these criteria, consideration was given to the use of the MCS diagnostic frameworks and epidemiological study design, as these two variables are most likely to influence the quality and overall integrity of the data. As noted within Sections 3.1 to 3.6, there is considerable variability in how MCS has been diagnosed and assessed. Similarly, experimental and case-control study designs were given a higher rating than cross-sectional studies or other observational study designs. The evaluation of the studies of self-reported MCS identified during the literature search and screening are presented under the same headings within Appendix C.

2.3.3 Public Health Management

The available literature from the peer-reviewed and grey literature identified in Sections 2.1 and 2.2 was extracted and summarized within Section 5 of this report to provide a section that is exclusively focused on approaches that have been used by public health and occupational organizations to assist individuals with MCS. The challenges reported by individuals with MCS within the literature evaluated in this review are presented to provide additional context as to the experiences of these individuals.

3.0 OVERVIEW OF MCS SYMPTOMS, DIAGNOSIS AND PREVELANCE

The focus of this review was on recent information and is intended to provide an up-to-date summary of the scientific literature regarding the symptoms, diagnosis and prevalence of MCS.

In general, the literature regarding MCS is complicated by the absence of universally accepted diagnostic criteria or a clinical case definition for MCS, and the lack of a clear consensus regarding the progression of MCS within affected individuals. In addition, there is a reported lack of consistency in the terminology used in the assessment of MCS subjects, and communication practices by health practitioners and public health organizations (Sampalli et al., 2011).

The sections that follow provide a general overview of the commonly reported symptoms of MCS reported in individuals with clinician- or researcher-defined MCS, the most common diagnostic frameworks available, as well as the estimated prevalence of MCS in Canada and internationally. It is not intended to provide a complete historical overview of MCS.

3.1 A Short History of the Long Evolution of MCS

The theory that some people may be more sensitive than others to common environmental exposures emerged in the 1940s and 1950s from theories developed by an allergist, Theron Randolph, and his colleagues. In 1961, this group developed the first conceptual framework that described MCS as a distinct clinical entity that involved responses in multiple organ systems that arose from an inability to adapt to chemicals, with responsiveness evident at low concentrations (CoA, 2010; WHO IPCS, 1996).

Over time, various terminologies have been used to describe MCS (as noted within CoA 2010, Sears, 2007 and WHO IPCS, 1996), including (but not limited to):

- Chemical sensitivity or intolerance
- Chemical allergy
- Chemical Acquired Immune Deficiency Syndrome (Chemical AIDS)
- Environmental hypersensitivity
- Environmental illness
- Environmental sensitivity
- Idiopathic environmental intolerance (IEI)
- Toxicant-induced loss of tolerance (TILT)
- Total allergy syndrome

- 20th Century disease

The literature regarding the features and suspected mechanisms of MCS has evolved over decades. As discussed in Section 3.4, various case definitions and diagnostic criteria have been developed for MCS[5]; however, clear consensus on how to accurately diagnose MCS, its mechanisms of effect, or appropriate clinical or public health management techniques have not been developed.

Further complicating the issue of defining MCS is the existence of many overlapping conditions, many of which are also ambiguous with respect to clinical definition or mechanism of effect. A listing of some of the reported overlapping conditions noted in the grey literature is provided in Section 3.6.

Despite these uncertainties, increasing recognition is being given to scent sensitivities and non-consensual exposures to chemicals (e.g., tobacco smoke, fragrances, pesticides, vehicle emissions/idling) in occupational and public settings (Marshall et al., 2010; Sears, 2007). Some governmental agencies in Canada and the United States are classifying MCS as either a health condition or as a disability requiring accommodation (Marshall et al., 2010). Additional discussion of the management of MCS within public settings is provided in Section 5.

3.2 What Are the Symptoms Associated with MCS?

A diverse range of symptoms have been attributed to MCS. An overview of some of the most commonly reported symptoms in the available literature for individuals with diagnosed MCS is presented in Table 6. The literature that presents MCS symptoms is complicated by the lack of universally accepted diagnostic criteria or a clinical case definition for MCS, and the lack of a consensus regarding the progression of MCS within affected individuals. Without a clear set of diagnostic criteria for MCS that is universally agreed upon and applied in the literature, it is difficult to ascertain what symptoms clearly are associated with MCS.

Table 6: Summary of Common Symptoms of MCS Reported in the Literature

System	Reported Symptoms in Diagnosed MCS Patients (References cited in alphabetical order below Table)
Cardiovascular System	Chest pain [e] Higher pulse rate [c] Lower pulse rate variability [c] Tachycardia [e]
Dermatological System	Alopecia [e] Facial swelling [e] Itching [r] Skin effects [h,r] Skin rash [e] Sweating [t]
Ears	Buzzing [e] Sudden deafness [e] Tinnitus [e]
Eyes	Burning or irritated eyes [e, j,s,t] Impaired vision [e] Itching eyes [e, j] Weeping eyes [e]
Gastrointestinal System	Abdominal pain [r] Digestive problems [e, h] Nausea [e]
Genitourinary System	Decreased libido [k]

[5] Reference citations for these various definitions and criteria are as follows: Cullen (1987), Nethercott et al. (1993), NRC (1992), WHO IPCS (1996), Bartha et al. (1999), Lacour et al. (2005)

	Unspecified adverse effects [h]
Hematological/Immunological System	Frequent infections [e]
Musculoskeletal system	Foot pain [s] Joint pain [e,h,j,r,v] Muscle pain [e,h,j,r,v] Muscle weakness [r]
Neuropscyhological	Anxiety or nervousness [d,e,g,h,p,q,u] Clumsiness [k] Depression [b,d,g,h,q,s,u,v] Dizziness or impaired balance [e,h,l,s] Dullness [k] Exhaustion [e ,j] Fatigue [b,e,h,j,k,n,v] Feeling spacey [k] Headache [e,j] Impaired concentration [e,f,j] Impaired verbal memory [f,j,k,v] Impaired verbal learning ability [f] Insomnia [e,v] Irritability [h,j, k] Lightheadedness [e,j] Negative mood [o,r] Paresthesia [e] Panic attack [p,q] Somatic symptoms [b,d,e,v]
Upper Respiratory System	Altered odour perception [e] Facial pressure [a] Hoarseness [j,t] Increased odour intensity [c, j, k] Itching [a] Irritation [a,e,n,t] Post-nasal drip [a] Nasal obstruction [a, j] Odour hypersensitivity [a] Rhinorrhea [a, e, j, k,t] Sneezing [a,j] Sore throat [s] Swelling of nose or throat [e]
Lower Respiratory System	Heavy breathing [t] Increased cough reflex [l, m,t] Respiratory irritation [f] Respiratory distress [e,s] Shortness of breath [s]

[a] Alobid et al., (2014), [b] Azuma et al., (2015), [c] Andersson et al., 2016, [d] Bailer et al., 2004, [e] Bornschein et al., 2002, [f] Bornschein et al., 2007, [g] Caccappolo van Vliet et al., 2002, [h] Garcia-Sierra et al., 2014, [i] Holst et al., 2010, [j] Joffres et al., 2001, [k] McKeown-Eyssen et al., 2001, [l] Micarelli et al., 2016a,b,c, [m] Nogami et al., 2004, [n] Osterberg et al., 2003, [o] Papo et al., 2006, [p] Poonai et al. 2000, [q] Poonai et al., 2001, [r] Saito et al., 2005, [s] Shinohara et al., 2004, [t] Ternesten-Hasseus et al., 2002, [u] Tonori et al., 2001, [v] Weiss et al. 2017

As discussed in Section 4, technical advancements have contributed to the weight of evidence surrounding regarding MCS; however, there are many limitations associated with the available literature that are related to the difficulties in determining individual case definitions for the purposes of tracking incidence and prevalence versus treatment.

3.3 What Triggers Symptoms in Sensitive Individuals?

There is a large variety of chemicals that have been reported to be associated with MCS. It is not clear whether the same substances that are reported to trigger MCS symptoms are also responsible for the development of the condition. A summary of the most commonly reported substances or categories of chemicals reported in the literature to be associated with MCS is presented in Table 7. While many of the items provided are a specific compound or substance, many of these items are non-specific with respect to their chemical composition and could include hundreds to thousands of substances (e.g., air pollution, exhaust, perfume and fragrances, food additives).

Table 7: Summary of Commonly Reported Triggers of MCS

Building, household and office triggers	Environmental triggers	Personal products	Other triggers
Building materials Cleaning products Electrical appliances Fresh paint Fresh ink or newsprint Office machines Paint thinner New carpeting or furniture Solvents Varnish	Air pollution Animal dander Car exhaust Herbicides Fertilizers Flavourings Insecticides Mould and mycotoxins Pesticides Pollen Preservatives Sulphites Tobacco/cigarette smoke smoke	Air fresheners Fabric softeners Hair spray and beauty products Nail polish New clothing New furniture or mattresses Perfumes and fragrances	Alcohol Chlorine in household water Chemical weapons Dental materials (including mercury amalgam) Electromagnetic fields and radiation Food packaging Food toxins and additives Formaldehyde Fresh asphalt and tar Fuels Implants and medical devices Organic chemicals Pharmaceutical drugs and anesthetics Soft plastics

Bailer et al. (2006); Black et al. (2000a); Brülls et al. (2006); Caress et al. (2002); Chun et al. (2006); Chun et al. (2010); CoA (2010); Eaton et al. (2000); García-Sierra and Moleiro (2014); Gibson and Lindberg (2007); Gibson and Vogel (2009); Hausteiner et al. (2005); Sears (2007)

The potential for the agents listed in Table 7 to be associated with odours or sensations seems to be the only 'common thread' between the chemicals. No specific chemicals or substances have been clearly identified as being known to be triggers for MCS, which presents challenges for both avoidance and management.

3.4 Overview of Common Diagnostic Frameworks

Within the literature review summarized in Section 4, the most commonly cited diagnostic frameworks used by researchers in studies published after the year 2000 were those of Cullen, (1987) and the 1999 consensus criteria. In some instances, the WHO and IPCS definition of IEI (idiopathic environmental intolerance - terminology used interchangeably with MCS) was applied, or the frameworks of Nethercott et al. (1993), NRC (1992), Bartha et al. (1999) or Lacour et al. (2005). A comparison of these frameworks with respect to case definitions and criteria has been included as Table 8. While some modifications have been made over time, another diagnostic framework has not been published in the last 13 years despite recent research on MCS.

The Cullen (1987) criteria were the first to be formally developed and published, and were based on the experiences and observations within a particular clinic. The seven criteria (also listed in Table 8 for direct comparison with the other frameworks) are as follows:

1. Disorder is acquired in relation to a documentable environmental exposure(s) or insult(s) or illness[6];

[6] Exposure(s), insult(s) or illness were defined by Cullen (1987) as "some untoward encounter with their environment and specifically excludes patients with longstanding health problems'.

2. The symptoms experienced involve more than one organ system;
3. Symptoms recur and abate in response to predictable stimuli;
4. Symptoms are elicited by exposure to chemicals of diverse structural classes and toxicologic modes of action;
5. Symptoms are elicited by exposure that are demonstrable and that the subject is aware of;
6. Exposures that elicit symptoms must be very low, below exposure levels known to be associated with adverse health responses in humans; and,
7. No single widely available test of organ system function can explain the symptoms (Cullen 1987).

However, these criteria have been criticized as being both too stringent and too subjective and non-specific with respect to the evaluation of the exposure-symptom relationship (CoA, 2010; Labarge and McCaffrey, 2000). In 1993, Nethercott et al. (1993) proposed somewhat less stringent criteria, based on a survey of 148 medical practitioners. Some notable modifications made by Nethercott et al. (1993) were the removal of the requirements for a documentable environmental exposure, insult or illness to have taken place before the symptoms occurred, the involvement of multiple organ systems, and assessment of the patients for other conditions to exclude them from having contributed to the symptoms. Several experts working under the banner of the National Research Council (NRC, 1992) developed three case criteria for use in research (but not for clinical diagnosis), and stated that pre-existing conditions should not prevent individuals as being considered as chemically sensitive. The NRC criteria were even less specific than the Nethercott criteria, and are focused more on the perceptions of sensitivity than symptoms (NRC, 1992). A few years later in 1996, a workshop of experts decided that MCS should be referred to as a condition that is captured by the umbrella of illnesses known as IEI, but no criteria were specified (WHO IPCS, 1996).

Clinicians in Japan (Hojo et al., 2007) developed a set of criteria for use in the Japanese population in 1998, which consisted of sub-sets of major and minor criteria[7], and an MCS diagnosis required two positive responses to major symptoms and four responses to minor symptoms. In comparison to the other frameworks available at the time, the Japanese framework was less specific than both the Cullen (1987) and Nethercott et al. (1993) criteria.

The next iteration of general diagnostic criteria (Bartha et al., 1999) evolved from a consensus reached by 34 clinicians and researchers that clearer diagnostic criteria for MCS were needed. The Bartha et al. (1999) rendition was more comparable to the Cullen (1987) criteria, with the exception that a documentable environmental exposure, insult or illness was required to fulfill the definition for MCS. Bartha et al. (1999) also required that symptoms involve more than one organ system.

The most recent set of criteria identified were the modifications of the Bartha et al. criteria by Lacour et al. (2005). The specific modifications made by Lacour et al. (2005) included the addition of the restriction that the reported symptoms had to have been present for more than six months and were in association with functional or lifestyle impairment, that the symptoms involved the central nervous system (CNS) in association with odour hypersensitivity, and the CNS plus at least one organ system was involved in the symptoms reported (Lacour et al., 2005). In addition to the proposed criteria, a list of several diseases and disorders that may

[7] This framework was not included in the summary within Table 8, as the criteria are population-specific.

overlap with MCS was provided, along with proposed tests to aid in excluding other disease conditions (Lacour et al., 2005).

Based on the review of literature, a well-defined standardized set of criteria for the diagnosis of MCS does not appear to have consistently or universally been adopted by practitioners.

3.5 Other Metrics for Evaluating MCS

In addition to the diagnostic frameworks, various metrics for evaluating chemical sensitivity and associated symptoms have been developed and have appeared in the MCS research literature. These metrics have been used as a means of identifying self-reported MCS subjects and of comparing reported symptoms between groups.

Perhaps the most commonly used of these is the Quick Environmental Exposure and Sensitivity Inventory (QEESI©), a system developed specifically as a screening questionnaire for MCS (Miller, 1998). This inventory was developed to aid in the identification of individuals with MCS, given the lack of a generally accepted case definition or set of case criteria. The QEESI© includes four scales: Symptom Severity, Chemical Intolerance, Other Intolerance, and Life Impact. For each scale, there are 10 items that are assigned scores ranging from "0" (no problem) to "10" (severely disabling). An additional index evaluates the degree of masking, or ongoing exposures that could affect the ability to be aware of intolerances or the intensity of responses. The QEESI© is intended to be used to characterize and compare study populations for research, to aid in obtaining information regarding symptoms and intolerances, and in workplace or community investigations (Miller, 1998). In a population of four patient groups and controls (a total number of 421 individuals recruited through advertisements and following the completion and submission of an exposure and sensitivity inventory), the QEESI© (when all scales were utilized) was determined to have a sensitivity of 92% and a specificity of 95% with respect to the ability to differentiate chemically sensitive individuals from controls. Miller and Prihoda (1999), the developers of the QEESI©, noted that there are some inherent weaknesses associated with the scales, due to the use of self-reported and retrospective information, and the potential for other medical conditions to have contributed to symptoms in the past.

Four studies published by Hojo et al. (2003, 2005, 2007, 2009) presented the results and proposed modifications of the QEESI© for the Japanese population. As outlined in Hojo et al. (2009), the "Other Intolerance" subscale within QEESI© is not as relevant or reliable within the Japanese MCS patients. Studies comparing the QEESI© results in both Japanese and American populations have found significant differences in the scores for diagnosed MCS patients and a high degree of variability in some of the sub-scores, with these differences possibly being attributable to differences in lifestyles (Hojo et al., 2007).

The British Society for Allergy, Environmental and Nutritional Medicine presented a set of criteria to define Toxicant Induced Lack of Tolerance (TILT), a condition related to MCS that is often used interchangeably in the literature. Features of this system included: remission occurring in the patient after the simultaneous avoidance of all chemical, food, inhalant and drug triggers and the symptoms returning with the re-introduction of a particular incitant; and re-exposure to an incitant results in the same pattern of symptoms, but only if the challenge is completed within four to seven days following the last exposure (Eaton et al., 2000).

A Canadian interpretation of MCS has been published by the University of Toronto; the Healthy Survey (UTHS) is based on the case definition of Bartha et al., 1999) combined with clinical experience with MCS symptoms (McKeown-Eyssen et al., 2000). The UTHS is a self-reporting questionnaire that requires input regarding 171 distinct symptoms and whether and how often

the subjects have experienced them in the last 12-months. The UTHS achieved agreement with respect to symptoms in 13 different body systems and in the overall number of symptoms reported (McKeown-Eyssen et al., 2000). A combination of four symptoms reported in the UTHS by patients was found to have the ability to identify MCS (specifically: having a stronger sense of smell, feeling dull/groggy, feeling "spacey", and having difficulties concentrating, McKeown-Eyssen et al., 2000). The same clinic at the Women's College Hospital has developed a list of suggested tests for MCS (Marshall et al., 2010) that are not clearly specified within the source document but are generally noted as including blood and urine tests for organ function status, toxic metals, nutritional status and also allergy tests.

Nordin et al. (2004) describes the Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR), which is a tool for evaluating reported chemical sensitivities associated with daily activities for clinical and epidemiological use. The CSS-SHR consists of a list of statements regarding how individuals feel or respond to odours, smells or certain substances (e.g. aftershave, cigarette smoke, exhaust). Individuals are asked to rate each statement as to how strongly they agree or disagree with each statement, and these are scored by study administrators.

The overall reliability of the CSS-SHR has been found to be good. In a study of 22 patients with diagnosed sensory hyperreactivity compared to controls (n=124), the CSS-SHR generated data with an approximately normal distribution. All 22 of the patients with sensory hyperreactivity demonstrated an increased cough sensitivity to capsaicin, which is indicative of C-fibre mediated hypersensitivity of sensory nerves before the CSS-SHR evaluation was completed (Nordin et al., 2004). Other available surveys or systems used for MCS symptom screening include the Chemical Odor Sensitivity Scale, Hüppe questionnaire (Hüppe et al., 2000 - in German), Environmental Sensitivity Questionnaire (ESQ), Patient Health Questionnaire (PHQ-15), the IEI Life Impact Questionnaire (IEI-LIQ) and the German Questionnaire on Chemical and Environmental Sensitivity (CGES) (Bailer et al., 2006; Rossi and Pitidis, 2017). However, these tests were used to varying degrees to evaluate and compare sensitivity, but not for the purposes of diagnosis. Other than the CSS-SHR, details regarding what these individual tests consisted of and how they compared could not be readily identified.

Two unique MCS scales, intended to be more specific with respect to types of symptoms reported (one with six domains and the other with four) were developed and compared in a clinical population by Kutosogiannis and Davidoff (2001). As part of this analysis, the number of patients diagnosed by physicians, traditional specialists (including allergists, otolaryngologists, etc.), and clinical ecologists were compared. The highest prevalence of MCS diagnoses was found to be in the clinical ecologist group (11% and 37% of all diagnosis, using each the 6- and 4-domain systems, followed by occupational physicians (8% and 27%), allergists (2% and 13%, and otolaryngologists (1% and 5%). Overall, the specificity of identifying MCS was determined to be high, but the sensitivity low (Kutsogiannis and Davidoff, 2001).

Despite the on-going research efforts related to MCS, there continues to be a need for more consistency and clarity with respect to a case definition and diagnostic criteria.

Table 8: Comparison of Certain Common Diagnostic Frameworks for Multiple Chemical Sensitivity

	Cullen (1987)	Nethercott et al. (1993)	NRC (1992)	WHO IPCS (1996)	Bartha et al. (1999)*	Lacour et al. (2005)
Case definition	"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 far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms"	Not explicitly stated	Not explicitly stated	Idiopathic environmental tolerance (IEI) is: "An acquired disorder with multiple recurrent symptoms, associated with diverse environmental factors tolerated by most people, and cannot be explained by any known medical or psychiatric disorder"	Not explicitly stated	Not explicitly stated
Diagnostic features or criteria	1. Disorder is acquired in relation to a documentable environmental exposure(s) or insult(s) or illness; 2. The symptoms experienced involve more than one organ system; 3. Symptoms recur and abate in response to predictable stimuli; 4. Symptoms are elicited by exposure to chemicals of diverse structural classes and toxicologic modes of action; 5. Symptoms are elicited by exposure that are demonstrable and that the subject is aware of; 6. Exposures that elicit symptoms must be very low, below exposure levels known to be associated with adverse health responses in humans; and, 7. No single widely-available test of organ system function can explain the symptoms.	1. The symptoms are reproducible with exposure; 2. The condition is chronic; 3. Low exposure levels result in manifestations of the syndrome; 4. Symptoms improve or resolve when the stimuli are removed; and, 5. Responses occur to multiple and chemically-unrelated substances.	1. Sensitivity to chemicals; signs or symptoms related to chemical exposures at levels tolerated by the general population, that is distinct from other hypersensitivity phenomena (e.g. IgE-mediated immediate hypersensitivity reactions, contact dermatitis, hypersensitivity pneumonitis; 2. Sensitivity express as signs and symptoms in one or more organ systems; and, 3. Signs and symptoms that "wax and wane" with exposures.	Not specified beyond the working definition (above)	1. The symptoms are reproducible with exposure; 2. Condition is chronic; 3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome; 4. Symptoms improve or resolve when the incitants are removed; 5. Response occur to multiple chemically unrelated substances; and, 6. Symptoms include multiple organ systems.	1. A chronic condition of at least 6 months duration, that causes significant lifestyle or functional impairment; 2. Symptoms the recur reproducibly in the CNS in association with self-reported odour hypersensitivity; 3. Symptoms occur in multiple organ systems – obligatory in the CNS and accompanied by at least one symptom of another organ system; 4. Symptoms occur in response to low levels of exposure; 5. Symptoms result from exposure to multiple unrelated chemicals; and, 6. Symptoms improve or are resolved when incitants are removed.
Other	Case definition and criteria developed from the experience of Cullen and his team of specialists	Case definition and criteria developed based on the results of a cross-sectional survey of 148 medical practitioners from various disciplines. The 6 identified criteria were selected by at least 50% of surveyed practitioners.	Pre-existing concurrent conditions should not exclude patients from consideration. Case criteria for research purposes (not clinical).	Workshop recommended that the definition of MCS be discontinued as it infers an unsupported judgement regarding causation, and is not a clinically defined disease, and that IEI be used	Developed based on information from Nethercott et al. 1993, and data from a 1989 survey. The main modification is the addition of the 6th criterion	Represents and extension of the Bartha et al. 1999 criteria

*commonly referenced as the "1999 Consensus Criteria" or "1999 Archives of Environmental Health Criteria

3.6 How Common is MCS?

The information regarding the prevalence of MCS provides insight into factors that may influence the development of MCS.

Due to the lack of a clear case definition, diagnostic criteria or set of symptoms associated with MCS, it is difficult to provide a concise estimate of the prevalence of MCS within any population. An overview of the recent literature regarding the reported prevalence of MCS is provided. Much of the available information is based on self-diagnosis or reporting. Where possible, information that is based purely on self-reported or self-diagnosed MCS is presented in Appendix C, to permit the focus of the report on MCS diagnosed by medical professionals.

3.6.1 MCS in the General Population

In Canada, the most recent information available regarding the prevalence of MCS was identified in the 2014 Canadian Community Health Survey (CCHS, as summarized in Park and Gilmour (2017)). The results of this survey indicate that 2.7% of the Canadians surveyed aged 25 or older (a total of approximately 671,500 individuals) self-reported as having been diagnosed with MCS. However, clinical assessments or the application of one of the available sets of diagnostic criteria were not applied as the survey was completed via telephone or mail. These data are based on the responses of individuals to a series of survey questions, rather than formal medical diagnoses. As a result, there may be variability within the surveyed population as MCS diagnosis. Additional characteristics of the population are presented in Appendix C.

Some international information regarding the prevalence of MCS was also identified. In contrast to the CCHS data from Park and Gilmour (2017), notable variation was apparent depending on the diagnostic criteria used, and whether patients were self-reporting as having MCS or were diagnosed by physicians. A recent review by Rossi and Pitidis (2017) reported that the estimated prevalence of MCS across several countries has been found to range from 1% to more than 15%. The variation in prevalence estimates have been suspected to vary as a result of the diagnostic differences or in relation to demographic differences between subjects (Jeong et al., 2014).

Depending on the criteria that were used to evaluate patients, Azuma et al. (2015b) determined that prevalence estimates range from 4.4% to 24.1% in the Japanese population. In the general German adult population, Hausteiner et al. (2005) determined that the prevalence of self-reported MCS and physician-diagnosed MCS was 9% and 0.5%, respectively. Within the Korean adult population, Jeong et al. (2014) determined that the prevalence was 16.4%. It was noted by Jeong et al. (2014) that when participants were grouped as allergic or non-allergic participants, the allergic participants had higher estimated prevalence of MCS (19.5% vs 11.3%).

In Australia, the Commonwealth of Australia (2010) reported that through combining two surveys commissioned by the State Health Department in 2002 and 2004, the prevalence of physician-diagnosed MCS was 0.9% and reported self-diagnosed MCS was 16.4%.

3.6.2 MCS Within Occupational Settings

Occupational exposure has been shown to impact the prevalence of MCS. However, studies that have examined the prevalence of MCS within various occupations have involved the use of patients with self-reported MCS, as opposed to diagnosed MCS.

Previous military involvement has been associated with higher prevalence of MCS (Black et al., 2000; Reid et al., 2001).

The use of pesticides in pest-controllers has also been studied in relation to MCS, although the available information has not found an association between occupational pesticide exposure and MCS (Bornschein et al., 2008; CoA, 2010).

In painters who are regularly exposed to various chemicals from paint, a higher rating of symptoms was reported in workers with diagnosed MCS compared to controls (Georgellis et al., 2003), although no significant differences with respect to smell sensation or the frequency of CNS effects were observed between the groups.

The potential for the "healthy worker effect" to have influenced the results of studies of MCS in occupational populations should be considered. Since healthy individuals tend to be selected for employment, they commonly have lower disease incidence than the general population.

3.6.3 Summary

In summary, MCS is a condition that has been reported to affect approximately 2-3% of the Canadian population (based on self-reporting), and varying proportions of the international community. However, the lack of a clear set of universally accepted and applied diagnostic criteria and the reporting metrics (e.g., the use of self-reporting) impacts the comparability of these data. When self-reported MCS is considered (as described in Appendix C), MCS is more commonly reported. As noted in Appendix C, factors that have been identified as being associated with MCS diagnosis include female sex, middle age, and occupational chemical exposure.

3.7 What Conditions Overlap with MCS?

One of the many challenges that have been identified in relation to studying MCS is the number of health conditions that overlap with MCS with respect to symptom profile or potential etiology. Several of these conditions, like MCS, are not well defined with respect to diagnosis, symptom profile or cause.

Information on overlapping conditions identified during the literature review is summarized in Table 9. Several of these conditions can also be considered as environmental sensitivities, which as noted in Sears (2007) "does not describe a single, simple condition with a universal cause". The Statistics Canada data from the 2014 Canadian Community Health Survey (CCHS) recorded symptoms that didn't have a distinct etiology, consistent findings from physical or laboratory assessments, or clear diagnosis as Medically Unexplained Physical Symptoms (MUPS) (Park and Gilmour, 2017). Thus, the number of potentially overlapping conditions and associated symptom profiles may lead to increased variability with respect to how a patient may be diagnosed. The available information may include individuals with both self-reported and diagnosed MCS, as the list of potentially overlapping conditions was compiled primarily from the grey literature.

Table 9 Summary of Conditions that Have Been Reported to Overlap with MCS

Addictions
Allergies
Arthritis or rheumatism
Asthma
Bipolar disorder
Brain tumour
Bronchitis
Cataracts
Celiac disease
Chronic Fatigue Syndrome (CFS)
Chronic Toxic Encephalopathy (TE)
Dental amalgam-induced mercury toxicity
Diabetes
Electromagnetic fields sensitivity
Electric or magnetic fields
Fibromyalgia (FM)
Food intolerances
Gulf War Syndrome
Heart disease
High blood pressure
Hypothyroidism or other thyroid condition
Infection
Irritable Bowel Syndrome
Major Depression
Medically Unexplained Physical Symptoms (MUPS)
Metabolic or mitochondrial dysfunction
Migraine
Mood disorders
Myalgic encephalomyelitis (ME)
Panic disorder
Physical trauma
Porphyria
Post-infectious neuromyasthenia
Post-Traumatic Stress Syndrome (PTSD)
Post-viral fatigue syndrome
Reactive (upper) airways dysfunction syndrome (RADS/RUDS)
Sick Building Syndrome
Severe psychological stress
Somatoform Disorders
Ulcers
Sources: CoA (2010); Eaton et al. (2000); Labarge and McCaffrey, (2000); Marshall et al. (2010); Park and Gilmour (2017); Sears (2007)

4.0 MCS – LINES OF RESEARCH

Factors that may contribute to the development of MCS have been identified and sorted into different categories by lines of research based on the results of the literature search.

Assessments of the various lines of research associated with MCS have been reported in the Australian review CoA (2010) and also in a review by Rossi and Pitidis (2017). As noted previously, the review of information in this section intended to build upon the foundations set by these two documents.

As described in Section 2.3.3, a qualitative, evidence-based WOE approach has been used to examine the lines of research for MCS, with an aim to contrast and compare the types and quality of information available for each line of research through application of qualitative ratings. This exercise also helps to identify data gaps and limitations within the state of science for MCS.

The general steps captured within the current review include:

1. The evaluation of individual publications, with documents being determined to be of sufficient quality to be carried forward into the overall WOE framework (or not);

2. The assessment of individual lines of research, including both positive (statistically significant for MCS patients) and negative (not-statistically significant for MCS patients) findings from the studies reviewed, to provide a balanced evaluation;

3. An assessment of the WOE for all lines of research combined; and,

4. A characterization of potential limitations, gaps and uncertainties.

Steps 1 and 2 are discussed within Sections 4.1 to 4.7 below. For Step 2, the criteria for Consistency and Utility (Table 10) were applied for the studies evaluated within each Section, with consistency being the level of agreement between studies, and utility referring to the overall relevance and quality of the studies (SCENIHR, 2012). In developing these criteria, consideration was given to the use of the MCS diagnostic frameworks and epidemiological study design, as these two variables are most likely to influence the quality and overall integrity of the data. As noted within Sections 3.1 to 3.6, there is considerable variability in how MCS has been diagnosed and assessed. Where possible, the diagnostic frameworks used in each of the studies were noted. More weight was assigned to studies that incorporated one of the defined diagnostic criteria. However, no preference was given to one diagnostic framework over another. Experimental and case-control study designs were given a higher rating than cross-sectional studies or other observational study designs. The evaluation of the studies of self-reported MCS identified during the literature search and screening are presented under the same headings within Appendix C.

Table 10: **Criteria for the Evaluation of Weight of Evidence (Adapted from SCENIHR, (2012))**

Evaluation of Consistency	Evaluation of Utility
High: most studies have consistent findings within the same direction or reaching the same general conclusion **Moderate**: majority of studies have a mixture of findings in the same direction **Low:** little agreement between studies **Very low:** due to a lack of studies, an assessment of consistency was not possible	**High:** studies generally are of experimental, case-control/case-cohort design and involve the use of one of the established diagnostic frameworks, or the use of larger study populations, adequate information regarding the selection, exclusion criteria and statistics are provided **Moderate:** studies involve a mixture case-control, cross-section or other observational study design, and a range of study population sizes (10 to 50 per group), adequate information regarding the selection, exclusion criteria and statistics are provided **Low:** studies are primarily cross-sectional or generally observational in nature, adequate information regarding the selection, exclusion criteria or statistics are not provided **Very Low:** very limited or no primary studies available

All lines of research were collectively evaluated within a WOE table provided in Section 4.8. A list of limitations, gaps and uncertainties is provided in Section 6.0 that was not restricted to the WOE analysis, but also includes observations based on the information presented throughout the report and the evaluation of self-reported MCS in Appendix C.

4.1 Toxicant Induced Loss of Tolerance (TILT)

Toxicant Induced Loss of Tolerance (TILT) differs from the other lines of research presented in Section 4 of this report, as it represents a suspected disease process or series of events, rather than a specific change or difference in MCS patients vs. controls.

TILT involves a two-step process where a stressor (chemical, physical, or biological or a combination thereof) triggers a subsequent loss of tolerance to several different chemicals, foods or environmental factors (e.g., light, heat), resulting in an array of chronic illness symptoms that arise from low-level exposures to agents that were previously tolerated (Eaton et al. 2000). The concept of TILT was first developed by an American researcher (Miller, who also helped develop the QEESI ©, discussed in Section 3.5) and further explored through her research with Gulf War veterans who reported various symptoms attributed to chemical exposures received while deployed in the Middle East (Miller 2001)[8].

No peer-reviewed scientific research papers were identified that specifically investigated TILT that were found during the literature search and review with a post-2000 publication date. Discussions of case studies (Genuis 2013; 2014) proposed that chemical sensitivity is elicited by a cascade of activity, that begins with an impairment of tolerance to chemicals and subsequent hypersensitivity, followed by an antigenic incitant or trigger (that may be in the form

[8] Additional information regarding TILT is available within the following publications and resources:
- Miller (2001). https://nyaspubs.onlinelibrary.wiley.com/doi/abs/10.1111/j.1749-6632.2001.tb05810.x
- Ashford, N and C. Miller. Chemical Exposures: Low Levels and High Stakes. Second Edition. John Wiley and Sons, 1998. ISBN 0-471-29240-0
- https://tiltresearch.org/about-tilt/

of chemicals, pollens, foods, etc.) that elicits an immune response consisting of antibodies and cytokine release, which in turn result in signs and symptoms in multiple organ systems.

In the grey literature, reviews by the CoA (2010) and Eaton et al. (2000) described TILT as being the concept that acute or chronic chemical exposures can cause susceptible individuals to lose their tolerance to certain substances to which they previously had no adverse reaction. TILT is described as a two-step process involving an initiating exposure (i.e., chronic low level or acute high level) followed by a triggering phase from common household chemicals, pharmaceuticals and foods. The Sears (2007) review further notes that there is an element of adrenergic or "fight or flight" response, followed by adaptation, and the loss of this adaptation in chronic stress or a surge of stress. None of the review documents provided further detail of the potential physiological or biochemical processes involved in TILT.

However, aspects of what is discussed as a lack of tolerance within TILT in the literature is covered in other lines of research (namely, the assessment of immune dysregulation, genetic factors, olfactory processing and neurological dysfunction).

The **consistency** of this line of research in relation to MCS involving the processes defined within TILT is considered to be **Very Low** due to the lack of peer-reviewed studies that have evaluated TILT in the context of patients with diagnosed MCS. The overall **utility** of the information is also **Very Low**, due the lack of identification of primary studies of sufficient quality published after the year 2000.

4.2 Immunological Dysregulation

Various immunological parameters have been studied in MCS patients to date. This section provides an overview of the information that met the inclusion criteria. A summary of the available information is provided in Section 4.2.1, followed by a more detailed description of the literature in Section 4.2.2.

4.2.1 Summary for Immunological Dysregulation

Most of the studies examining immunological parameters were of case-control design. As shown in Table 11, at least 3 different diagnostic frameworks were used across the studies of immune dysfunction. Other studies relied upon self-reported (rather than diagnosed) MCS and are summarized in Appendix C The number of subjects examined also varied widely across the studies, as did the parameters studied.

The case-control studies of Baines et al. (2004) and Dantoft et al. (2014) both identified significantly different immunological profiles for MCS patients vs. controls. But, as suggested by Dantoft et al. (2015) and Eis (2008), these profile changes may be systemic rather than local. This is enhanced by the observation of Dantoft et al. (2014) that increases in plasma IL-1β, IL-2, IL-4, IL-6 were evident in the MCS group. DeLuca et al. (2010) observed changes in various immunomodulators, where some parameters were increased and others were decreased. In opposition to all these suggestions are the findings of Dantoft et al. (2017), where no evidence of up-regulation of genes associated with the production of various immunomodulators. Further, likely because of the variability in the parameters studied and the differences in the study designs, there is no apparent consistency with respect to a particular immunomodulatory substance being increased or decreased across studies. There is little consistency or

reproducibility evident in the data, likely as a result of the variety of endpoints being evaluated in the various studies.

A high prevalence of various types of allergies and sensitivities have been reported (Pigatto et al., 2013); however, the findings are limited by issues related to study design and the potential influence of inherent bias.

Overall, the **consistency** of the information regarding the involvement of immunological dysfunction in MCS is rated as **Low** due to the inconsistencies in the observations, and the **utility** of the data is rated as **Low-Moderate** due to the number of prospective case-control studies and the use of diagnosed MCS subjects. The inconsistent results are suggestive of a still emerging research area, with the findings suggesting a need for further study of immunological (including cytokine) profiles, the relationship between allergic hypersensitivity and MCS, and the role of the immune system in MCS. The information reviewed demonstrates that further study of both gene expression and clinical concentrations of both pro- and anti-inflammatory cytokines and chemokines, as well as parameters related to allergy, should be evaluated in more detail, with an aim to providing a higher level of specificity and reproducibility within the dataset.

A comparison of study design features of the primary literature presented in this Section is presented in Table 11. Within this Table, studies that found statistically significant differences for MCS patients are indicated by a (+) and green shading and studies with no statistically significant differences for MCS patients are noted with a (-) and light blue shading.

Table 11: Summary of Findings Regarding MCS and Immune Dysfunction

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[3]
Baines et al. (2004)	194 MCS 223 controls	Case-Control	Yes	Nethercott, (1993)	UTHS	Decreased lymphocytes, altered haemoglobin, increased ALT and vitamin B_6 levels (+)
						No association with TSH, folate or serum vitamin B_{12} (-)
Dantoft et al. (2014)	150 MCS 148 controls	Case-Control	Yes	Bartha et al. (1999) and Lacour et al. (2005)	QEESI© SCL-92	Increased plasma IL-1β, IL-2, IL-4, IL-6, decreased plasma IL-13. QEESI© scores (+)
						Borderline or no difference in IL-5, IL-8, CXC-8 or IgE (-)
Dantoft et al. (2015)	18 MCS 18 controls	Case-Control	Yes	Bartha et al. (1999) and Lacour et al. (2005)	CSS, SCL-90; PSS, SAS	No differences in cytokines or chemokines[4] in upper airway lavage fluid (-)
Dantoft et al. (2017)	18 MCS 17 controls	Case-Control	Yes	Bartha et al. (1999) and Lacour et al. (2005)	-	No evidence of gene transcription of immune regulation or inflammation[5](-)
DeLuca et al. (2010)	133 MCS 218 controls	Case-Control	Yes	Cullen (1987)	QEESI©	Increased expression of IINF-γ, IL-10, IL-8, MCP-1, VEGF, PDGF (+)
						No difference in expression of other (undefined) cytokines or chemokines (-)
Eis et al. (2008)	45 MCS	Case-Control	Yes	Cullen (1987)	DSM-IV, CIDI, EMQ,	No differences in inflammatory mediators (not defined) in nasal

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[3]
	208 controls					lavage fluid following provocation with 2-propanol (-)
Pigatto et al. (2013)	41 MCS No controls	-	Yes	Cullen (1987)	-	Pre-existing allergy (+)

Acronyms: CIDI: Composite International Diagnostic Interview, CSS: Chemical Sensitivity Scale, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Version IV, EMQ: Environmental Medicine Questionnaire, , MCS: multiple chemical sensitivity, PSS: Perceived Stress Scale, QEESI©: Quick Environmental Exposure and Sensitivity Inventory, SAS: Somatosensory Amplification Scale, SCL-90: Symptom Checklist 90, UTHS: University of Toronto Health Survey, - : not defined

[1] Defined and published diagnostic criteria were required for a study to receive a 'yes' and be considered to have relied upon diagnostic criteria. The use of questionnaires as a diagnostic tool was counted as a screening questionnaire, rather than a diagnostic framework, as the questionnaires rely upon self-reporting, while a clinical diagnosis relies on both self-reporting an assessment by a practitioner.

[2] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[3] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue. Due to a lack of a reference group, the significance of results was difficult to determine in some studies, and findings are presented in grey.

[4] The substances evaluated in this study included: Th1/CD8+/NK cells, innate lymphoid cells (ILC), Th2, eosinophils (ILC2), type-17 (Th17, neutrophils ILC17), Interferon-γ, interleukin-1β, interleukin-2, interleukin-4,interleukin-5, chemokine CSC motif ligand 8, interleukin-8, interleukin-10, interleukin-12p70, interleukin-13, tumour necrosis factor, chemokine CCL1/eotaxin-1, chemokine C-C motif ligand 4, macrophage inflammatory protein 1β, CCL26/eotaxin-3, CCL17/thymus activation-regulated chemokine, CXC10/INF-inducible protein-10, CXC8/IL8, CCLS2/monocyte chemotactic protein-1 (MCP-1), CCL22/macrophage-derived chemokine and CCL13/MCP-4, interleukin-17A, total protein.

[5] Genes controlling the following were evaluated: IL-1β, IL-2, IL-6, IL-8, IL-10, TNFα, NOS2, inducible nuclear factor of x light polypeptide gene enhancer in B cells 1 (NFKb1)

4.2.2 Review of Immunological Literature

Reviews identified in the grey literature (CoA, 2010; Eaton et al., 2000; Marshall et al., 2010; Sears, 2007) and through the primary literature search (Busby, 2017; Genuis and Kyrillos, 2017; Rossi and Pitidis, 2017) noted the potential role of the immune system in MCS.

Some studies have suggested that MCS is the result of immune dysregulation resulting from chemically-induced disturbance of the immune system (CoA, 2010). Studies have found both positive and negative evidence of allergic markers through the examination of markers of both innate and humoral immunity (immunoglobulins, complement, B- and T-cells, lymphocytes and chemical-protein conjugates) (CoA, 2010). Both allergies and asthma have been observed to be overlapping diagnoses with MCS by clinicians in Canada and the US (Marshall et al., 2010). The concept of immune system dysregulation in MCS has been challenged by some researchers on the basis of the structural diversity of chemicals to which people are exposed, the lack of a consistent pattern or abnormal immune function, and the degree of variability in the quality of the available studies (CoA, 2010).

A summary of the findings of the studies that evaluated altered immunological activity in relation to diagnosed MCS is provided below. Features of each study (e.g., subject numbers, use of diagnostic framework, design type, results) are highlighted in Table 11. Studies involving self-reported MCS and immune dysfunction are summarized in Appendix C.

Immune dysregulation indicative of low-level chronic inflammation has been observed in association with MCS, although the findings have been inconsistent. A case-control study by Baines et al. (2004) studied clinical chemical and hematological parameters in blood in 194 diagnosed MCS subjects and 223 controls. Concentrations of several VOCs were measured in

blood to assess recent exposures, including: chloroform, benzene, ethylbenzene, styrene, trimethylbenzenes (1,3,5- and 1,2,3-), methylpentane (2- and 3-), hexane, xylenes (*m&p*), and 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (*p,p*^{1}-DDE). Significant differences between cases and controls were observed in mean cell hemoglobin concentrations (adjusted Odds Ratio (OR) 2.13, 95% CI: 1.20 – 3.77), lymphocytes (adjusted OR 0.37, 95% CI: 0.20 – 0.67), vitamin B_6 ($p < 0.05$) and alanine aminotransferase ($p < 0.05$) (ALT) levels. Only serum chloroform concentrations appeared to increase the likelihood of being a case (OR 2.78, 95% CI: 1.73-4.48, $p < 0.001$), with more cases than controls having detectable serum chloroform ($p = 0.001$). Cases were found to have lower serum concentrations of other VOCs. However, the differences in the VOC concentrations could be associated with behaviours and factors not evaluated in this study (e.g., avoidance) and the levels and frequencies to which people were exposed in their daily environments. Folate, vitamin B_6, vitamin B_{12} serum concentrations were determined to be unlikely to be involved in MCS. Baines et al. (2004) concluded that the findings, particularly of the lower lymphocyte counts observed in cases, suggest that immune dysfunction may play a role in MCS.

Dantoft et al. (2014) completed a case-control study of 150 diagnosed MCS patients recruited from Danish clinics and 148 age- and sex-matched controls. This study compared plasma concentrations of several cytokines and immunoglobulin E responses to common inhaled allergens between groups. The observed differences in plasma concentrations of interleukin-1β, interleukin-2, interleukin-4, interleukin-6 were found to be significantly higher in MCS cases than in controls ($p < 0.05$), and significantly decreased ($p < 0.0007$) in interleukin-13 for cases vs. controls. QEESI© scores were significantly higher for MCS cases than controls for symptoms, chemical intolerances and life impact ($p < 0.001$). The MCS group also reported higher rates of depression and anxiety ($p < 0.001$), and fair to poor self-rated health scores ($p < 0.001$). A decrease in tumor necrosis factor α (TNFα) was observed in cases relative to controls, but these were determined to be of borderline significance ($p = 0.05$). No statistically significant differences in interleukin-5, interleukin-8, chemokine CXC-motif ligand 8 (CXC8) or allergen-specific IgE responses were found between cases and controls. It was concluded by Dantoft et al. (2014) that MCS cases presented a distinct systemic immune mediator profile, consisting of increased levels of certain pro-inflammatory cytokines and interleukin-2 with an inverse regulation of interleukin-4 and interleukin-13 (which are mediated by Th2 lymphocytes), and that this profile is suggestive of low-grade systemic inflammation.

Evidence of a distinct immune mediator profile was not evident in epithelial lining samples collected from MCS subjects and controls taken from the upper airway following exposure to n-butanol within a controlled chamber (Dantoft et al., 2015). Dantoft et al. (2015) reported that although the symptoms were reported to be more intense by the MCS group (18 diagnosed subjects) compared to controls (18), no significant differences in any of the cytokines or chemokines collected from upper airways were observed. Eis et al. (2008) reported a similar finding, where various inflammatory mediators in nasal lavage fluid were sampled from MCS patients (45 diagnosed subjects) following provocation with an odorant.

In a study of gene transcription comparing MCS patients with controls, Dantoft et al. (2017) did not observe any statistically significant increases in the transcription of genes related to immunomodulating cytokines in 18 subjects with diagnosed MCS relative to controls (17). In this study, patients were exposed to 3.7 ppm n-butanol within a controlled chamber for a duration of 60-minutes. Gene expression levels were assessed before, immediately after (within 15-minutes), and 4-hours after exposure cessation. Dantoft et al. (2017) note that it was not possible to distinguish MCS patients from controls based on the expression of 17 pre-selected genes.

A study of several genes regulating cytokines, chemokines and growth factors were compared between subjects with diagnosed MCS (133) and healthy controls (218) by De Luca et al. (2010). The MCS group demonstrated significantly increased levels of various parameters relative to the control group: interferon-gamma (INF-γ) (p= 0.000002), interleukin-10 (p =0.003), interleukin-8 (p = 0.0002), macrophage chemotactic protein (MCP-1) (p = 0.006), vascular endothelial growth factor (VEGF) (p = 0.001) and platelet-derived growth factor PDGF) (p = 0.02). De Luca et al. (2010) proposed that these mediators may be the result of accelerated lipid peroxidation and a subsequent inflammatory response. The authors also suggest that the levels of INF-γ and IL-10 observed indicates the presence of activated Th1 lymphocytes and an on-going regulatory T-cell population effect, a potential characteristic of an autoimmune response (De Luca et al., 2010).

A retrospective case study completed by Pigatto et al. (2013) reported that 92.3% of the 41 MCS subjects included in the study had positive results for allergic responses to metals. Approximately 30.8% of the MCS subjects were also found to have evidence of hormonal disorders that were suggestive of endocrine dysregulation. The presence of mercury-containing dental amalgam fillings were associated with increased mercury concentrations in biological samples (blood, urine, saliva, scalp hair), and 33% of the subjects were found to have developed MCS after mercury-amalgam filling removal procedures that were deemed unsafe or inadequate by the investigators (Pigatto et al., 2013).

Primary research articles that specifically evaluate autoimmune-related aspects of MCS were not specifically identified during this review other than the gene-expression study by De Luca et al. (2010).

4.3 Genetic Factors

Another area of research for MCS is study of the involvement of various genetic factors. Several studies have been published regarding genetic profiles between individuals, or in the expression of genes associated with the production of enzymes or endogenous substances (e.g. neuropeptides, immunomodulators) related to various physiological functions.

A summary of the available information is provided in Section 4.3.1, followed by sections outlining useful background information and summaries of the individual studies.

4.3.1 Summary of Findings Regarding Genetic Factors

Overall, there is no clear, consistent genetic profile for MCS.

Statistically significant relationships in the frequency of genetic variants (alleles, genotypes, haplotypes) were reported for a few genes that control the expression of the metabolic enzymes CYP2C19, CYP2D6, NAT2, NOS and SOD2. However, there were inconsistent results regarding the involvement of certain genes and enzymes related to metabolism with respect to MCS.

A non-statistically significant increase in active CYP 2D6 was reported by Berg et al. (2010) for diagnosed MCS individuals, statistically significant increases in polymorphisms for CYP2D6*4 and CYP2D6*41 were observed by Caccamo et al. (2013), and increased CYP 2D6 expression was observed by McKeown-Eyssen et al. (2004). All three of these studies involved case-control design and the use of diagnosed MCS subjects.

Caccamo et al. (2013) identified that the haplotype CYP2C19 Ht *1/*2-CYP2D6 Ht *1/*4-AHR Arg554Lys was statistically associated with diagnosed MCS subjects, and not individuals with suspected MCS, fibromyalgia, CFS or the control group. De Luca et al. (2010) did not find any differences in the frequencies of either alleles or genotypes for CYP2C19, and no other studies of the particular haplotype studied by Caccamo et al. (2013) were identified.

Conflicting results have been reported regarding the role of the paraoxonase enzymes PON1 and PON2 in MCS studies involving Gulf War veterans. It has been previously suggested that neurological impairment in these individuals is the result of reduced PON activity, which would affect the metabolism of substances such as organophosphates pesticides and nerve agents (CoA, 2010). Variation in PON expression was reported in diagnosed MCS cases by McKeown-Eyssen et al. (2004) (PON1-55 and PON1-192 specifically). No differences in PON1 genotypes were observed by Berg et al. (2010) when the results of MCS patients were compared with a control group selected from the general population.

NOS activity was significantly increased in diagnosed MCS subjects (De Luca et al. 2010), but this enzyme was less studied than the CYP isoforms, NAT, and PON.

Only one study was identified that examined the gene expression of immunomodulators (Dantoft et al., 2017), which does not permit the comparison of results across studies.

For neuromodulatory genes, two studies with diagnosed MCS patients were identified (Binkley et al. 2001, Dantoft et al, 2017) that examined several endpoints.

In general, the genetic studies involved relatively small sample sizes although some larger study populations were included in some papers. The review by CoA (2010) reached a similar conclusion, and also noted that additional studies of the genetic and biochemical profiles in individuals with MCS would be of value. The weight of evidence regarding genetic metabolic profiles and their role in MCS is emerging rather than conclusive. Table 12 presents a summary of the available studies of diagnosed MCS that included the evaluation of genetic factors. Within this Table, studies that found statistically significant differences for MCS patients are indicated by a (+) and green shading and studies with no statistically significant differences for MCS patients are noted with a (-) and light blue shading.

Several additional studies not presented in this section involved self-reported MCS rather than diagnosed MCS, and are summarized in Appendix C. Within the available studies that involved diagnosed MCS individuals, four diagnostic frameworks were used. One study (Eis et al., 2008) did not state what genes or variants were evaluated, and only that no differences were found.

The overall **consistency** of the study findings for metabolic, immune and neurological genetic factors is rated as **Low**. Due to the existence of several prospective case-control studies that included the use of diagnosed MCS, the ratings are moderate for the metabolism and neurological genetic factors, but low for the immune factors, resulting in an overall rating of **Low-Moderate** for **utility**.

Table 12: Summary of Findings Regarding Diagnosed MCS and Genetic Factors

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[4]
Genes Related to Metabolism						
Berg et al. (2010)	96 MCS 1,207 controls	Cross-Sectional Nested Case-Control	Yes	Cullen 1987	Other questionnaires[3]	Incidence of gene variants CYP2D6, NAT2, PON1, MTHFR, CCK2R (-)
Caccamo et al. (2013)	156 MCS 94 sus. MCS 113 controls	Case-Cohort	Yes	Cullen 1987	QEESI©	Gene polymorphisms in CYP2C9*2, CYP2C9*3, CYP2C19*2, CYP2D6*4 and CYP2D6*41 (+)
DeLuca et al. (2010)	133 MCS 218 controls	Case-Control	Yes	Cullen 1987	QEESI©	Decrease in GSH and catalase, increase in NOS (+)
						No difference in gene expression of CYP450 isoforms, GSTs, UGT (-)
Eis et al. (2008)	45 MCS 208 controls	Case-Control	Yes	Cullen 1987	DSM-IV, CIDI, EMQ	No differences in variants of 17 (unspecified) genes (-)
McKeown-Eyssen et al. (2004)	203 MCS 162 controls	Case-Control	Yes	Nethercott, 1993	UTHS	Increased expression of CYP2D6 and NAT2, and gene interactions between them (+)
						No differences in expression of NAT1, PON1 or PON2 or MTHFR-C677T genotype, or serum nutrients (-)
Genes Related to Immune Modulators						
Dantoft et al. (2017)	18 MCS 17 controls	Case-Control	Yes	Bartha et al. (1999) and Lacour et al. (2005)	-	No difference in gene transcription of mediators of immune regulation, stress response, inflammation (-)
Genes Related to Neurological Modulators						
Binkley et al. (2001)	11 IEI 11 controls	Case-Control	Yes	Simon et al. (1993)	DSM-IV	Excess CCK-B allele 7 expression (+)
						No difference in dopamine D4 axon 11 expression (-)
Dantoft et al. (2017)	18 MCS 17 controls	Case-Control	Yes	Bartha et al. (1999) and Lacour et al. (2005)	-	No significant differences in expression of $5H_{TT\ 1A}$ or 2A receptors, adrenergic β1 or β1 receptors, or COMT (-)

Acronyms: CIDI: Composite International Diagnostic Interview, DSM-IV: Diagnosis and Statistical Manual of Mental Disorders, Version IV, EMQ: Environmental Medicine Questionnaire, QEESI©: Quick Environmental Exposure and Sensitivity Inventory; UTHS: University of Toronto Health Survey, - not defined

[1] Defined and published diagnostic criteria were required for a study to receive a 'yes' and be considered to have relied upon diagnostic criteria. The use of questionnaires as a diagnostic tool was counted as a screening questionnaire, rather than a

diagnostic framework, as the questionnaires rely upon self-reporting, while a clinical diagnosis relies on both self-reporting an assessment by a practitioner.

[2] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[3] "other' was noted when was not evident that a formally standardized questionnaire was used

[4] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue. Due to a lack of a reference group, the significance of results was difficult to determine in some studies, and findings are presented in grey.

4.3.2 Background Information for Genetic Factors

The metabolism or biotransformation of chemicals (both endogenous and exogenous) can generally be divided into four categories of enzymatic processes (see Table 13). For each process, several specific enzymes involved in mammalian metabolism have been identified. Examples of each of these processes and enzymes are presented in Table 13, focusing on enzymes discussed through this section of the review. A chemical can be processed by more than one enzyme. Several important genetic components are involved in metabolism, and those that are mentioned within the studies summarized in this section are presented in Table 14.

The lists of enzymes presented in Tables 13 and 14 below do not present complete, comprehensive lists, but summarize a listing only of the enzymes and genes discussed within the reviewed literature to be associated with MCS.

Table 13 Categories of Metabolic Enzymes with Relevant Examples (Klaassen, 2018)

Process	Enzyme	Examples of Enzymes with Polymorphisms
Hydrolysis	Paraoxonase	PON1
Reduction	Superoxide dismutase (SOD)	SOD2
Oxidation	Alcohol dehydrogenase (ALDH)	ALDH2
	Glutathione peroxidase	Gpx
	Cytochrome P450 (CYP450)	CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A5
Conjugation	Glutathione transferase (GST)	GSTM1, GSTP1, GST T1
	N-acetyltransferase (NAT)	NAT2
	UDP-glucuronosyltransferase (UGT)	UGT1A1

In addition to the regulation of metabolic/biotransformation processes, there are many genes that control the expression of other enzymes or molecules with important functions, some of which are discussed in Table 14. Several other genes that control other processes, such as immune regulation (i.e., interleukins, tumour necrosis factor, nitric oxide synthase), sensory ion channels, serotonin receptors, adrenergic receptors, substance P receptor, nerve growth factor, and the sphingosine-q-phosphate pathway (Dantoft et al., 2017) have also been identified in relation to MCS or overlapping disorders such as fibromyalgia and chronic fatigue syndrome (CFS).

Table 14: Examples of Genes With Important Biological Functions (Binkley et al., 2001; Klaassen, 2018)

Gene	Function
Aryl hydrocarbon receptor (AhR)	Receptor for a transcription factor that can increase the expression of other enzymes, affecting the metabolism of various compounds
Cholecystokinin B (CCK-B) or Cholecystokinin 2 (CCK2)	Receptors for CCK, a neuropeptide that is active in the brain and gut. CCK has been identified as being related to panic disorder and anxiety behaviours
Dopamine D4 receptor exon III	Influences behaviour via the dopaminergic system
Serotonin Transporter (5HTT)	Protein that transports the neurotransmitter serotonin from synapses to presynaptic neurons. Influences serotonin, which has a number of physiological functions, including on behaviour
Methylene tetrahydrofolate reductase (MTHR)	Enzyme involved in the metabolism and conversion of amino acids, and in the metabolism of vitamin B_{12} and folate
Catalase	Reduces hydrogen peroxide to oxygen and water. Can influence oxidative stress among other functions

In some instances, the genetic polymorphism for metabolic enzymes can be an underlying cause of disease, as they can affect the reactive capability of chemicals following exposure (i.e. making them more or less capable of inducing tissue damage).

4.3.3 Genes Related to Metabolism

The studies reviewed below primarily discuss the evaluation of potential differences in the incidence of polymorphisms[9] (existence of more than one type or variant) in the above listed genes.

Berg et al. (2010) examined the frequencies of variants (allele, genotype and haplotype) in five genes: cytochrome P450 2D6, arylamine N-acetyltransferase 2 (NAT2), paraoxonase 1 (PON1), methylene tetrahydrofolate reductase (MTHFR) and cholecystokinin 2 receptor (CCK2R). This study involved 96 diagnosed MCS subjects and 1,207 controls. An increasing (but statistically non-significant) association between MCS and with a higher number of active CYP2D6 alleles was observed. No significant differences in polymorphisms of PON1-55 in the L allele were observed. No significant relationship between gene variants and MCS was identified (Berg et al., 2010).

The only Canadian study identified related to metabolism was by McKeown-Eyssen et al. (2004), where 203 diagnosed MCS cases were compared with 162 controls with respect to the existence of polymorphisms in CYP2D6, NAT1, NAT2, PON1, PON2, and MTHFR. A significant difference in the genotypes for CYP2D6 ($p = 0.02$) and NAT2 ($p = 0.02$) were identified between cases and controls. Specifically, individuals with higher CYP2D6 activity (homozygous active) were determined to be at an increased risk for MCS (OR 3.36, $p = 0.01$), and MCS cases were more likely to be fast acetylators (high NAT2 expression, OR 4.14, $p = 0.01$). A potential for gene-to-gene interaction between CYP2D6 and NAT2 was identified,

[9] Polymorphisms are indicated in the text by the inclusion of an asterisk (*) beside the acronym for the enzyme.

suggesting that the two enzymes may interact in the metabolism of either endogenous or exogenous chemicals,

For the two paraoxonases (PON1, PON2), MCS cases were more likely to be heterozygous for the genes PON1-55 or PON1-192. McKeown-Eyssen et al. (2004) suggested that differences in the genetics within linked sites in the PON cluster of genes (rather than any of the types evaluated in the study) may account for the variation in PON expression. It was also suggested that the observed differences could result in altered metabolism of both endogenous and exogenous chemicals, and in protein derangements in individuals with MCS.

Caccamo et al. (2013) evaluated subjects with diagnosed MCS (156) or suspected MCS (94), fibromyalgia, or CFS, and 113 to compare the frequency of several gene polymorphisms. The frequency of five specific polymorphisms (CYP2C9*2, CYP2C9**3, CYP2C19*2, CYP2D6*4 and CYP2D6*41) were found to be significantly higher in patients with MCS, suspected MCS, or FM/CFS relative to controls. No significant difference between case groups and controls were observed for the AhR Arg554Lys gene when evaluated on its own. But, when considered within haplotypes in combination with CYP2C19*1/*2 and CYP2D6*1/*4, this AhR variant was significantly different between MCS and suspected MCS subjects. Caccomo et al. (2013) proposed that future research on the use of CYP2C9*3 be used as a marker for sensitivity related illnesses, such as MCS. The most frequent haplotype (9%) that was statistically significant only in the diagnosed MCS cases ($p < 0.001$) that was not present in any of the other groups was the CYP2C19 Ht *1/*2-CYP2D6 Ht *1/*4-AHR Arg554Lys. In suspected MCS cases, the most frequently detected haplotype was CYP2C9 Ht *1/*2-CYP2D6 Ht*1/*4, which was not detected in any of the other groups ($p < 0.05$).

A study of several genes controlling metabolism, certain cellular processes and cytokines were compared between subjects with diagnosed MCS (133) and healthy controls (218) by De Luca et al. (2010). No differences in the frequencies were detected between the two groups for CYP P450 isoforms (CYP2C9, CYP2C19, CYP2D6 and CYP3A5), UDP-glucuronosyl transferase (UGT1A1), glutathione S-transferases (GSTP1, GSTM1, GSTT1). However, GST activity was significantly reduced (as indicated by the significantly diminished levels of both reduced and oxidized glutathione) in both the MCS and suspected MCS groups relative to controls. Catalase activity was significantly reduced in MCS subjects compared to suspected MCS and control subjects. Nitric oxide synthase (NOS) activity, however, was significantly increased in MCS subjects. GSTs and catalase are considered to be stress proteins, and are considered to be antioxidant enzymes, and the diminished activity of these substances is likely to result in oxidative stress at a molecular level, but may also affect the activity of other biological processes (i.e. polyunsaturated fatty acid metabolism, inflammatory reactions). De Luca et al. (2010) proposed that MCS is the result of various biochemical and immunological dysfunctions that are not likely genetically related, that cause a diminished antioxidant defence and favour the increased formation of oxidants. This in turn triggers increased lipid peroxidation and systemic inflammation with an element of autoimmunity.

4.3.4 Genes for Immunological Modulators

Dantoft et al. (2017) completed a case-control study with a small number of subjects (18 with diagnosed MCS and 18 controls) that examined the transcription of 17 genes in samples of leukocytes isolated from blood samples before and after a controlled 50-minute exposure to n-butanol. While no statistically significant differences in gene transcription were observed at baseline between the MCS group and controls, higher rates of transcription were observed for genes controlling the expression of the immunomodulating cytokines IL-6 ($p = 0.03$) and IL-10

(p = 0.074). No statistically significant differences between MCS subjects and controls were observed in the transcriptions of other genes related to immune regulation, stress response, sensory detection, and inflammation. But, as Dantoft et al. (2017) note, significant differences in the reactions and physiological responses to the MCS subjects relative to controls were apparent.

4.3.5 Genes for Neurological Mediators

Binkley et al. (2001) evaluated the role of 22 allelles related to neuropeptide cholecystokinin B (CCK-B) and the dopaminergic system (via polymorphisms in the dopamine D4 receptor exon portion of the gene). CCK-B has been previously associated with the incidence of panic disorder (Binkley et al., 2001) as well as multiple other physiological functions. Groups of 11 subjects with diagnosed IEI and age-matched controls were compared following the extraction of blood samples. An excess of CCK-B receptor allele 7 was identified in the IEI group (OR of 6.9, 95% CI: 1.1-55.6), which was statistically different than the control group. However, no statistically significant differences between the groups were identified for any of the other 21 alleles for CCK-B or for dopamine D4. The study authors note that this finding suggests that individuals with IEI may be genetically pre-disposed to panic disorder; however, further study is needed (Binkley et al., 2001).

The case-control study discussed above in Section 4.2.2 by Dantoft et al. (2017) also evaluated the expression of genes coding for $5H_{TT}$ (HTR1A and HTR2A), as well as for certain adrenergic receptors (adrenergic β1 and adrenergic β2 receptors), and catechol-*O*-methyltransferase (C*O*MT). No significant differences were observed between the diagnosed MCS cases and controls.

In a German multi-centre, case-control study published by Eis et al. (2008), a total of 26 variants of 17 genes that could be related to genetic susceptibility to MCS were examined from blood samples collected from 205 patients. No significant differences were identified. However, the identities of the genes and the characteristics of the study design could not be verified from Eis et al. (2008), as cross-references to documents only available in German were provided as sources.

4.4 N-methyl-D-aspartate (NMDA) Receptor Activity and Nitric Oxide/Peroxynitrate

While this line of research overlaps with studies covered in other areas (e.g. genetics, neurogenic inflammation and neural sensitization), this area of research generally lacks a body of clinical evidence (positive or negative) to support it by different research teams. However, many of the aspects of this theory (modifications in NOS expression, the potential involvement of inflammatory response, activation of the nervous system, and the involvement of sensitization) are all covered within this review under other lines of research. In particularly, there appears to be some overlap between the NMDA receptor activity and NO/ONOO hypothesis and the discussion of metabolic and genetic differences, The study by De Luca et al. (2015) has added a novel perspective to this line of evidence, examining gene expression related to NO; however, further research is needed. This information is presented within Table 15, with the significant differences for MCS patients indicated by a (+) and green shading.

The **consistency** of the evidence for the involvement of the NMDA receptor, nitric oxide and peroxynitrate in MCS is considered to be **Very Low** due to the lack of peer-reviewed studies with positive or negative results, and the overall **utility** of the information is **Very Low**.

Table 15: Summary of Findings Regarding MCS and N-methyl-D-aspartate (NMDA) Receptor Activity and Nitric Oxide/Peroxynitrate

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[3]
DeLuca eta (2015)	170 MCS 108 suspected. MCS 89 FM/CFS 196 controls	Case-Cohort	No	-	QEESI©	Increased plasma NO, and frequency of NOS2A gene variant (+)

Acronyms: QEESI©: Quick Environmental Exposure and Sensitivity Inventory

[1] Defined and published diagnostic criteria were required for a study to receive a 'yes' and be considered to have relied upon diagnostic criteria. The use of questionnaires as a diagnostic tool was counted as a screening questionnaire, rather than a diagnostic framework, as the questionnaires rely upon self-reporting, while a clinical diagnosis relies on both self-reporting an assessment by a practitioner.

[2] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

It has been hypothesized by a research team led by Pall (2001) that the hypersensitivity response that is characteristic of MCS is the result of N-methyl-D-aspartate (NMDA) activity and subsequent release of nitric oxide (NO) and peroxynitrate (CoA, 2010; Marshall et al., 2010). This area of research is centred on the concept that NMDA receptors (present in the brain, peripheral nervous system, bronchi, gut and cell membranes throughout the body) are activated by chemical stressors, and this receptor-binding activity releases NO and peroxynitrate, which then cycle through interrelated reactions (termed the NO/ONOO cycle), causing the release of inflammatory cytokines and resulting in oxidative stress and a chronic elevation of NO, peroxynitrate, cytokines and NMDA receptor activity (Pall, 2001; CoA, 2010). It has also been proposed that increased central nervous and peripheral nervous system stimulation also result in increased NO and NMDA activity. Various chemical classes have been associated with these changes, including organophosphate and carbamate insecticides, organic solvents, carbon monoxide, hydrogen sulphide and mercury (CoA, 2010; De Luca et al., 2015; Marshall et al., 2010). It has been suggested that increased peroxynitrate may contribute to neurological sensitization and chronic inflammation in MCS patients (Sears, 2007), and sensitization of the respiratory and gastrointestinal tracts (CoA, 2010).

Only one study was identified that examined the role of oxidative stress, inflammation and genes controlling the enzyme nitric oxide synthase (NOS) in MCS. In the case-control study by DeLuca et al. (2015), 367 patients with diagnosed IEI were recruited, and 170 of these individuals were clinically diagnosed with MCS, while the remaining subjects had either suspected MCS, fibromyalgia or CFS. A total of 196 healthy controls were also recruited for comparison purposes. Blood samples were collected and genotyping for several polymorphisms of variants of NOS2. Variations in the numbers of repeats of (CCTTT) were related to the regulation of the transcription of the NOS2 gene, with increased repeats increasing NO production (De Luca et al., 2015). Sixteen allele repeats (CCTTT) within the NOS2A -2.5kb microsatellite were significantly associated with higher serum concentrations of nitrites/nitrates and were present in MCS and SMCS patients and controls at significantly different frequencies. Less repeats, particularly 8 repeats of (CCTTT) was associated with protective effects against IEI disorders, including MCS. Significantly ($p = 0.037$) higher ratios of nitrite/nitrate concentrations in plasma were observed in patients with a wildtype genotype for the NOS variant NOS3-786TT relative to other genotypes.

4.5 Neurological Sensitization and Neurogenic Inflammation

Symptoms involving the upper and lower airways are commonly reported among MCS sufferers, and one potential biological mechanism is airway sensory hyperreactivity attributable to neurogenic inflammation. Neurogenic inflammation is not isolated to the respiratory tract, as studies investigating dermal exposures and neurogenic inflammation were also identified.

4.5.1 Summary for Neurological Sensitization and Neurogenic Inflammation

All the studies reviewed in this section involved a relatively small number of subjects per group, (See Table 16). Within this Table, studies that found statistically significant differences for MCS patients are indicated by a (+) and green shading and studies with no statistically significant differences for MCS patients are noted with a (-) and light blue shading. Studies involving patients with self-reported MCS are summarized in Appendix C. All the studies reviewed used a prospective, experimental study design; however, more than three diagnostic frameworks were used, and some studies involved chamber and other nose-only exposures. These differences may have contributed to the observed variability in the results. Additional studies were identified that involved self-diagnosed MCS patients (summarized in Appendix C). It is apparent that larger studies of subjects with clearly diagnosed MCS are needed to further elucidate the role of sensory processing and neurogenic inflammation.

The finding that sensory neuron stimulation may contribute to secondary pain symptoms in MCS was unique; however, only one study evaluated this (Holst et al., 2011a). Of the studies evaluating capsaicin-challenge, the results were somewhat conflicting with respect to respiratory sensory hypersensitivity (i.e. Ternesten-Hasseus et al. (2002) and Nogami et al. (2005) compared with Holst et al. (2010)) but generally suggest an involvement of an increased sensitivity to stimuli in MCS patients. Differences in nasal flow, respiratory and neural symptoms following inhalation of capsaicin or chemicals within controlled environments were observed. While some studies considered inflammatory mechanisms, others focused on neuronal processing.

The **consistency** of the evidence related to neurological sensitization or neurogenic inflammation is **Moderate** for cough reflex, increased irritant symptoms and hyperalgesia. Although the studies do not have unanimous findings, in general, the evidence is in the same direction. However, this cannot be said for changes in ventilatory function. The overall **utility** of the evidence is rated as **Moderate**, due to the inclusion of several experimental studies, but also in recognition of result of the smaller sample sizes used in the studies.

Table 16: Summary of Findings Regarding Diagnosed MCS, Neurological Sensitization Neurogenic Sensitization

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[3]
Capsaicin Studies						
Holst et al. (2010)	16 MCS 15 eczema 29 controls	Experimental	Yes	Cullen 1987	-	No difference in cough reflex with capsaicin (-)
Holst et al. (2011a)	16 MCS 15 eczema 29 controls	Experimental	Yes	Cullen 1987	-	Increased pain intensity and secondary hyperalgesia with capsaicin (+)
Holst et al. (2011b)	16 MCS 15 eczema 29 controls	Experimental	Yes	Cullen 1987	-	No increases in skin wheal with capsaicin (-)
Nogami et al. (2004)	15 MCS 29 chronic cough 29 controls	Experimental	Yes	Cullen 1987	-	More sensitive cough reflex to capsaicin (+) No differences in ventilatory function tests after capsaicin (-)
Ternesten-Hasseus et al. (2002)	12 MCS 12 controls	Experimental	Yes	Cullen 1987	-	Increased cough reflex and symptoms with capsaicin (+)
Tran et al. (2013)	15 MCS 15 controls	Experimental	Yes	Lacour et al. 2005	ECRHS, SCL-92, SSAS	Increased secondary punctate hyperalgesia, punctate pain ratings (+) No differences in pressure pain, heat pain, temporal summation, pain ratings or conditioning pain modulation (-)
Non-Capsaicin Studies						
Dantoft et al. (2017)	18 MCS 17 controls	Experimental	Yes	Bartha et al. (1999) and Lacour et al. (2005)	-	No differences in gene expression for substance P or nerve growth factor (-)
Österberg et al. (2003)	10 MCS 10 controls	Experimental	Yes	Bartha et al., (1999), Nethercott et al. (1993), NRC (1992), WHO IPCS (1996)	-	Increased mucous membrane irritation and fatigue, worsening of reaction time with VOCs (+)

Acronyms:, ECRS: European Community Respiratory Health Survey, , SCL-92: Symptom Checklist 92, SSAS: Somatosensory Amplification Scale

[1] Defined and published diagnostic criteria were required for a study to receive a 'yes' and be considered to have relied upon diagnostic criteria. The use of questionnaires as a diagnostic tool was counted as a screening questionnaire, rather than a diagnostic framework, as the questionnaires rely upon self-reporting, while a clinical diagnosis relies on both self-reporting an assessment by a practitioner.

[2] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[3] 'Other' is noted when a standardized questionnaire was used, but is not named or specified

[4] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue. Due to a lack of a reference group, the significance of results was difficult to determine in some studies, and findings are presented in grey.

4.5.2 Background Information for Neurologic Sensitization and Neurogenic Inflammation

Both the upper and lower airways contain sensory neurons from the parasympathetic and sympathetic nervous systems (CoA, 2010). In the upper airways, the olfactory and trigeminal nerves mediate the detection of chemicals (Claeson and Andersson, 2017). Many of these nerves express ion channel proteins belonging to the transient receptor potential (TRP) superfamily that can act as sensors to various stimuli, including the presence of chemicals, temperature changes, oxidation, and pH variation. When TRP channels are activated, they depolarize cells and produce an action potential and sensory nerve activation that can trigger several responses. In mammals, six sub-families of TRP have been identified that have a common amino acid sequence, with one group being the TRP vanilloid (TRPV) family. The TRPV1 ion channel (which is discussed in some of the studies presented within this section) is activated by high temperatures and a range of both endogenous and exogenous chemicals, including the hot-pepper derivative capsaicin. Other TRP channels that have been reported to be involved in the perception of inhaled irritants include TRPA1 and acid sensing ion channel receptor 3 (ASIC3) (Omar et al., 2017). Acrolein is a stimulant of TRPA1 in airways (Claeson and Andersson, 2017). TRPV1, TRPA1 and ASICS3 are all known to be upregulated by hypoxia and respiratory viruses (Omar et al., 2017).

The primary type of nerve fibres involved in the cough reflex have been identified as the C-fibres (un-myelinated, chemosensitive, slow conducting) and Aδ fibres (myelinated, mechanosensitive, fast conducting) (Bonvini and Belvisi, 2017). TRPV1 has been demonstrated to activate both C-fibre and Aδ fibres in animal studies (Bonvini and Belvisi, 2017). TRPV1 has been found to be expressed in certain ganglia neurons, and in neurons within the dorsal root and trigeminal ganglia, as well as in non-neuronal cells. Stimulation of the trigeminal nerve can result in the sensations of irritation and pain, while stimulation of the olfactory nerve results in the detection of odours (Claeson and Andersson, 2017).

4.5.3 Capsaicin Studies

Several studies were identified that involved the use of capsaicin to induce a cough-reflex.

The cough reflex in diagnosed MCS patients following capsaicin exposure was compared with patients with eczema and also healthy controls (all female) by Holst et al. (2010). All subjects were exposed to aerosolized saline or increasing serial dilutions of capsaicin via a nebulizer, and coughs were counted starting 10-seconds after exposure. A high degree of variation was observed in the incidence of respiratory symptoms and cough reflex across all groups. Only the eczema group demonstrated a significantly enhanced cough reflex relative to controls (all observed differences for the MCS group did not reach statistical significance, $p < 0.05$). No influence on the results was observed by asthma or age. However, a positive and significant association ($p < 0.05$) was observed in relation to capsaicin concentration and lower airway symptoms, regardless of the study group. The authors determined that capsaicin-challenge may not be a reliable indicator of MCS respiratory hyperreactivity.

Contrasting results were observed in the capsaicin cough-reflex studies involving MCS patients by Terneston-Hasseus et al. (2002) and Nogami et al. (2004). In Terneston-Hasseus et al. (2002), diagnosed MCS subjects (12) and matched controls (12) were exposed to saline or three increasing doses of capsaicin. A significantly enhanced cough-reflex was observed in the MCS group relative to controls ($p < 0.05$) at the lowest dose of capsaicin, and ($p < 0.005$) at the two higher doses. In addition, a significant difference in the number and severity of symptoms reported by the MCS group was identified relative to the controls, with the most common symptoms reported in the MCS group being throat irritation, hoarseness, heavy breathing, runny nose, eye irritation, phlegm and sweating. Nogami et al. (2004) compared the responses to increasing doses of inhaled capsaicin (via mouth only breathing) on the cough reflex in patients with diagnosed MCS (15), chronic cough (29), and healthy controls (29). The cough reflex was observed to be more sensitive in the MCS group compared to control group, but not to the chronic cough group), and Nogami et al. (2004) suggested that the capsaicin response may be a useful clinical diagnostic tool for MCS. It was proposed by Nogami et al. (2004) that MCS is a sensory hypersensitivity disorder, and that MCS sufferers may have an increased density of C-fibre neurons in some organ systems, although physiological confirmation of this is lacking. Ternesten-Hasseus et al. (2002) suggested that the MCS subjects had an upregulated sensory nervous system response within the respiratory tract, possibly involving the stimulation of c-fibres within the sensory nervous system via stimulation of vanilloid receptor (VR1).

Holst et al. (2011a; b) evaluated neurogenic inflammation in the skin through the evaluation of erythema and visual flare following dermal capsaicin injection. Holst et al. (2011a) evaluated both the dermal response to capsaicin injection as well as secondary pain (hyperalgesia). A statistically significant difference ($p < 0.05$) between the diagnosed MCS group (16 subjects) and controls was observed in pain intensity and in the area of skin affected by hyperalgesia. In MCS subjects who also had diagnosed fibromyalgia, chronic fatigue or chronic pain, the effect of the injection was experienced as pain for a longer-duration when compared to control subjects (29). When individuals with MCS (16) and eczema (15) were compared, no significant differences were observed between the two groups or controls (Holst et al., 2011b). Capsaicin-injection responses were also compared between diagnosed MCS subjects (15) and age-matched healthy controls (15) by Tran et al. (2013). Specifically, aspects of central hyperexcitability and central sensory processing were evaluated, including pain response and hyperalgesia. A larger area of secondary punctate hyperalgesia was observed in MCS patients compared to controls up to 1-hour post-injection ($p = 0.01$) in addition to higher pain ratings in response to punctate mechanical stimuli ($p < 0.001$) and in conditioning pain modulation tests ($p = 0.002$). However, no significant differences in pressure or heat pain thresholds, or capsaicin or tonic pain ratings were observed. Tran et al. (2013) suggested that facilitated central sensitization may be involved in MCS.

4.5.4 Non-Capsaicin Studies

The studies of sensitization that did not involve capsaicin were more varied in their study design and endpoints.

While not specific to MCS, the review by Bonvini et al. (2017) noted that one theory to explain the origin of chronic idiopathic cough (a chronic cough that is of unexplained origin and not related to an underlying disease) is the abnormal functioning of neuronal pathways that control the cough reflex. This reflex may involve TRPV1 and other ion channels. However, the role of ion channels and their expression abnormalities associated with the cough reflex is still under examination (Bonvini et al. 2017).

The incidence of membrane irritation in MCS was discussed by Österberg et al. (2003), who compared respiratory responses to increasing concentrations of both n-butyl acetate and toluene in women with diagnosed MCS (10) and matched controls (10). All exposures took place within a controlled exposure chamber and ranged from 10 to 20 minutes. Significant differences in the rate and severity of mucous membrane irritation and fatigue, as indicated by the steepness of the symptom- chemical- concentration curves, were observed for the MCS group relative to controls ($p < 0.05$). A worsening of reaction time was observed in the MCS group over consecutive chamber exposures. No differences in reported odour intensity were noted between groups or chemicals, and no evidence of panic, abnormal behaviours, or expectancy or anticipation reactions were observed in either group at any time during the study, but as Österberg et al. (2003) noted, this could be a function of the stringent inclusion criteria.

The expression of genes associated with the substance P receptor, and nerve growth factor was compared between individuals with diagnosed MCS and controls in Dantoft et al. (2017), both before and after n-butanol exposure.

The reviews completed by CoA (2010), Marshall et al. (2010) and Sears (2007) all noted that respiratory sensory hypersensitivity is potentially involved in MCS, possibly via vanilloid sensitive receptor stimulation within the bronchi (i.e. TRPV1), as demonstrated by various studies involving capsaicin-challenge. However, many of the studies cited as evidence for this did not necessarily involve MCS specifically or did not meet the inclusion criteria for the present review. Sears (2007) also proposed that gamma-aminobutryic acid (GABA) receptors may be involved in hypersensitivity; however, limited information was provided in support of this.

Additional studies of self-diagnosed MCS are summarized in Appendix C.

4.6 Neurological Dysfunction

Several studies of neurological dysfunction in MCS patients were identified. For diagnosed MCS patients, the available information is presented in Sections 4.6.1 to 4.6.4. The studies for self-diagnosed MCS patients are summarized within Appendix C.

4.6.1 Summary of Findings for Neurological Dysfunction

There is consistent evidence of differences in the activation patterns between MCS and controls following odorant exposure (Table 17). Within this Table, studies that found statistically significant differences for MCS patients are indicated by a (+) and green shading and studies with no statistically significant differences for MCS patients are noted with a (-) and light blue shading. Several of the imaging studies included the use of both hemodynamic and metabolic markers, and these markers indicated that the brain regions involved in olfactory processing exhibited various activation/deactivation patterns in MCS subjects. However, many of these studies were completed by the same research team. The imaging studies suggested that areas within the prefrontal cortex that are involved in odour processing eventually become deactivated or take longer to recover from odour exposures (Azuma et al. ,2016), and that this may be how people with MCS become eventually intolerant of odours (Azuma et al., 2013). Along with differences in the activation patterns, differences in the deactivation patterns were evident as well (e.g. within the inhibitory node, rostral anterior cingulate) (Andersson et al., 2014, 2017).

The olfactory studies involved small subject numbers, a variety of study designs, and the use of different methods of administering odorant substances to subjects (ranging from scratch and sniff tests, to nasal olfactometers to chamber exposures). The majority of the studies evaluated were of case-control or experimental design and involved the use of a diagnostic framework –

all attributes of stronger study designs. However, the group sizes were generally smaller (less than 10 to over 50). Dose-response information was generally lacking. Generally, the studies were single-blinded at a technical level, but at a practical level, the odours would have been detectable without masking agents (which were not commonly used). Consideration must also be given to the variability in the resolution of the imaging equipment used when comparing the results across studies. Several studies examined the more qualitative aspects of odour identification, recognition and response, and generally found that the ability to detect and identify odours was the same in MCS subjects as for controls. However, it is possible that individuals with severe MCS did not participate in or complete the study, thereby potentially impacted the results of the various studies. The reviewed literature indicated that individuals with MCS were more likely to report more enhanced (positive or negative) responses to odours, and that responses to odour likely involved, to some degree, responses to the emotional connotations of pleasant vs. unpleasant odours, potentially due to memories.

Despite all of the challenges identified in relation to olfactory studies, the overall weight of evidence regarding olfaction in MCS subjects is suggestive of both physiological and psychological/emotional differences in MCS subjects with respect to how odours affect the brain and was assigned a **consistency** ranking of **Moderate-High** based on the overall consistency of the information from imaging and non-imaging studies, using an assortment of techniques. A utility rating of **Moderate** was assigned based on the number of experimental case-control studies involving diagnosed MCS patients. It is noted that several studies of patients with self-reported MCS (Appendix C) also found significant evidence of the involvement of olfaction in studies with and without the use of imaging.

While there is evidence of potential vestibular and auditory abnormalities in MCS patients, all of the work was completed by the same research team. The studies are impacted by relatively small subject numbers and the precision and accuracy of the methods used. These vestibular effects seem to be secondary to the development of MCS, rather than being related to the cause of MCS. The vestibular and auditory processing line of evidence was assigned a consistency rating of **Low-Moderate** due to the existence of only a few studies on this topic, and a utility rating of **Low**, due to the limited number of studies, and the generally small number of subjects examined.

There was a large amount of variability in the results of studies investigating the involvement of the Autonomic Nervous System ANS) in the physiological response to odours in MCS and controls subjects. It is possible that the physiological response to odour involves an interaction between the sympathetic and the parasympathetic nervous system. Differences in reaction time and hemodynamic parameters in response to postural shift have also been observed, but the studies have not been reproduced. The other neurological effects were assigned a **Low** consistency rating and a **Low** utility rating.

Table 17: Summary of Findings - Diagnosed MCS and Neurological Dysfunction

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[4]
Imaging Studies						
Alessandrini et al. (2016)	26 MCS 11 controls	Experimental	Yes	Bartha et al. (1999); Lacour et al. (2005)	-	Increased glucose metabolism and hyperactivation of olfactory structures (+)
Azuma et al. (2013)	12 MCS 11 controls	Experimental	Yes	Bartha et al. (1999)	DSM-IV, QEESI©	Changes in cerebral blood flow in prefrontal cortex, and impairment in odour processing with repetition (+)
Azuma et al. (2015)	6 MCS 6 controls	Experimental	Yes	Bartha et al. (1999)	DSM-IV, QEESI©	Changes in cerebral blood flow in prefrontal cortex, delayed recovery (+)
Azuma et al. (2016)	12 MCS 7 controls	Experimental	Yes	Bartha et al. (1999)	DSM-IV, QEESI©	Changes in cerebral blood flow in prefrontal cortex, delayed recovery (+)
Belpomme et al., 2015	52 MCS 521 EHS 154 EHS and MCS No control	Cohort	Yes	Bartha et al. (1999)	-	No statistical analysis details provided, but subjective evidence of altered blood flow in temporal lobe
Chiaravalloti et al. (2015)	26 MCS 11 controls	Experimental	Yes	Cullen (1987)	MMSE	Deactivation of glucose metabolism in frontal cortex (+)
Hillert et al. (2013)	12 MCS 11 controls	Experimental	Yes	Bartha et al. (1999)	-	Abnormal activation patters, increased activity in anterior cingulate cortex and cuneus precuneus and less activation in odour processing regions. Significantly lower $5HT_{1A}$ binding within amygdala and anterior cingulate cortex (+) No differences in odour detection, familiarity or symptoms, no association of $5H_{T1A}$ binding with psychological profiles (-)
Orriols et al. (2009)	8 MCS 8 controls	Experimental	Yes	Bartha et al. (1999)	OTI	Decreased activity in frontal cortex and altered activation patterns within various brain regions (+)
Non-Imaging Studies						
Andersson et al. (2016)	18 MCS 18 controls	Experimental	Yes	Bartha et al. (1999), Lacour et al. (2005)	Other	Altered autonomic response to odour, increased symptoms (+)
Eis et al. (2008)	45 MCS 208 controls	Case-Control	Yes	Cullen (1987)	DSM-IV, CIDI, EMQ	No differences in olfactory performance (-)
Georgellis et al. (2003)	14 MCS 15 controls	Experimental	Yes	Cullen (1987)	-	Decreased plasma prolactin levels following odorant exposure (+)

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[4]
						No differences in reports of odour sensations (-)
						No trend in heart rate variability with VOC exposure (-)
Ojima et al. (2002)	25 MCS 50 controls	Experimental	Yes	Cullen (1987)	UPSIT, CCSIT	Enhanced positive and negative responses to odours (+)
Papo et al. (2006)	23 MCS 21 odour sensitive 23 controls	Experimental	Yes	Bartha et al. (1999)	Other	No differences in olfactory function, chemosensory or cognitive olfactory information processing (-)
Vestibular and Auditory Dysfunction						
Micarelli et al. (2016a)	18 MCS 20 controls	Case-Control	Yes	Bartha et al. (1999), Lacour et al. (2005)	MMSE, DSM IV	Different patterns in vestibular processing (+)
Micarelli et al. (2016b)	18 MCS 20 controls	Case-Control	Yes	Bartha et al. (1999), Lacour et al. (2005)	MMSE, DSM IV	Different patterns in vestibular processing and dizziness (+)
Micarelli et al. (2016c)	18 MCS 20 controls	Case-Control	Yes	Bartha et al. (1999), Lacour et al. (2005)	-	Reduced transient evoked otoacoustic emission responses, indicative of reduced medial olivocochlear reflex (+)
Other Neurological Factors						
McFetridge-Durdle et al. (2009)	17 MCS Baseline controls	Case-Control	Yes	Bartha et al. (1999)	-	Changes in hemodynamic parameters with postural shift (+)
Bornschein et al. (2007)	264 patients	Cross-Sectional	Yes	WHO IPCS (1996)	SCID, DSM-IV	No statistical analysis available
Österberg et al. (2002)	24 MCS 31 TE with neuropscyh. 26 TE no neuropsych	Case-Cohort	Yes	Cullen (1987)	-	Significant reductions in reaction time (+)
						No evidence of brain impairment (other than reaction time) (-)

Acronyms: CIDI: Composite International Diagnostic Interview, CCSIT: Cross-Cultural Smell Identification Test, DSM-IV: Diagnosis and Statistical Manual of Mental Disorders, Version IV, EMQ: Environmental Medicine Questionnaire, MMSE: Mini Mental State Examination, , OTI: odour tolerance index, QEESI©: Quick Environmental Exposure and Sensitivity Invent, SCID: Structured Clinical Interview, STAI: State-Trait-Anxiety-Inventory UPSIT: University of Pennsylvania Smell Identification Test

[1] Defined and published diagnostic criteria were required for a study to receive a 'yes' and be considered to have relied upon diagnostic criteria. The use of questionnaires as a diagnostic tool was counted as a screening questionnaire, rather than a diagnostic framework, as the questionnaires rely upon self-reporting, while a clinical diagnosis relies on both self-reporting an assessment by a practitioner.

[2]Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[3] "other' was noted when was not evident that a formally standardized questionnaire was used

[4] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue. Due to a lack of a reference group, the significance of results was difficult to determine in some studies, and findings are presented in grey.

4.6.2 Olfactory Processing Dysfunction

Previously, the term "limbic kindling" was used to refer to several olfactory processing endpoints (CoA, 2010). However, given that investigations into changes within the brain and nervous system in response to odorants were identified, the term "limbic kindling" was not used as it has been integrated with other evidence under the heading "olfactory processing dysfunction".

Alberta Health (2017) recently completed a comprehensive literature review regarding odours and human health. This review concluded that the relationship between odours and health effects is complex, and that the physiological responses to odours are influenced not only by odour characteristics (pleasantness, intensity, familiarity) but also individual factors (e.g., past experiences associated with specific experiences, cognitive bias, etc.). Several limitations were identified in the olfactory literature reviewed by Alberta Health (2017), including the use of subjective measures of odour, variations and quality in exposure assessment methods, lack of standardization, lack of study-blinding, among others. The literature presented within this section is intended to be complimentary to the Alberta Health (2017) document. Accordingly, the focus of the information presented below is on the literature identified relating to how the nervous system responds to odour in MCS patients, and general information regarding odour and general physiological responses to odour are intentionally not reviewed.

The review by Alberta Health (2017) noted that 24 distinct regions of the brain are activated during odour perception, 13 different regions are involved in the determination of odour hedonicity (pleasant vs. unpleasant), and approximately 23 regions are involved in olfactory tasks, such as hedonicity judgement, intensity judgement, odour discrimination and identification.

The three means of studying hemodynamics within the brain as a measure of olfactory function used in some of the MCS studies identified were functional MRI (fMRI,) positron emission tomography (PET), and near-infrared spectroscopy (NIRS). fMRI is used to measure oxygen metabolism relative to cerebral blood flow, specifically evaluating blood oxygen level dependent (BOLD) contrasts. fMRI is non-radioactive, considered to have better temporal resolution than PET. PET involves the injection of a radioactive tracer and involves the measurement of radioactivity emitted from various brain regions, providing an indicating of changes in regional blood blow. NIRS is used to assess changes in oxyhemoglobin, deoxyhemoglobin and total hemoglobin as measures of blood flow, with higher oxygenated hemoglobin indicating increased activity (Alberta Health, 2017).

Due to the number of studies, the case-control studies have been divided into two groups based on the use of imaging equipment (fMRI, PET or NIRs) and studies without the use of imaging.

Imaging Studies

One preliminary prospective cohort study (Belpomme et al., 2015) was identified that evaluated changes in the brain in MCS patients, as well as a suite of biochemical and physiological tests. The study population included individuals with electrohypersensitivity (EHS), diagnosed MCS, and individuals with both EHS and MCS. Using percentages, it is suggested by Belpomme et

al. (2015) that the MCS group had signs indicative of oxidative stress, altered blood brain barrier function, chronic inflammation, deficits in melatonin metabolism, and altered blood flow within the temporal lobe (assessed using ultrasonic cerebral tomosphygmography (UCTS)). In the introduction, the authors note that the results are preliminary, and no description or data regarding statistics are included in the published document. Additional details are necessary regarding analysis before this study can be given further examination.

Changes in cerebral blood flow were examined using NIRS by Azuma et al. (2013) in 12 diagnosed MCS subjects and 11 controls following olfactory stimulation using a standardized test kit. Questionnaires and several assessment scales were used to evaluate physical and psychological parameters. Significantly increased cerebral blood flow ($p < 0.001$) was observed in MCS patients following exposure to 8 out of 10 of the selected odorants. For one of the two odorants where stability was observed in cerebral blood flow following exposure (mandarin orange), subsequent repetitions of the exposure resulted in activation within the prefrontal cortex within the MCS group ($p < 0.001$), suggesting that odour processing eventually became impaired for this stimulant. The reported symptoms using two unique questionnaires were also higher for the MCS group compared to controls ($p < 0.001$). Azuma et al. (2013) suggested that in MCS patients, prefrontal information processing was activated through emotional responses based memories of past exposures to a stimulus. In the subsequent repetitions of the stimuli, this processing system became overwhelmed and could not respond.

A smaller group of diagnosed MCS patients (6) and matched controls (6) were evaluated in a later study (Azuma et al., 2015a) using the same study methodology as Azuma et al. (2013), employing NIRS and repeated testing using a standardized odour kit, except for the addition of a 30-second rest and recovery period, where imaging and symptom questionnaires were repeated. Azuma et al. (2015a) had similar findings with respect to odour processing and increased cerebral blood flow in MCS subjects ($p < 0.05$). In addition, Azuma et al. (2015a) observed that the recovery period following activation was delayed in the MCS subjects relative to controls ($p < 0.05$), and that this may contribute to the eventual development of odour intolerance over time.

Another study by the same group (Azuma et al., 2016) examined cerebral blood blow, odour detection thresholds and subjective odour assessments in 12 diagnosed MCS subjects and 7 controls following exposure to fresh air, a sweet or a pungent odorant at three concentration levels. Questionnaires were used to collect information regarding physical and psychological parameters. Several established scales were used to evaluate these parameters. No differences in the odour recognition or threshold were observed between the groups. However, significantly increased cerebral blood flow was observed in the prefrontal cortex and the OFC following stimulation by both categories of odours (sweet and pungent), and these differences remained significant for up to 20 to 30-seconds post-exposure. The scores from the QEESI®, CSS-SHR, Autonomic Perception Questionnaire (APQ) and Toronto Alexthymia Scale (TAS-20) were significantly higher for the MCS group relative to controls. Azuma et al. (2016) suggested that MCS patients do not necessarily detect odours at lower levels but that the odour results in a different level of activation in the brain, which takes time to return to baseline. This odour processing may be the result of previous experiences with odorants and associated memories, which may influence physiological responses, as was demonstrated by the significantly increased symptom scores in the MCS group compared to controls ($p < 0.05$).

Another type of imaging, single photon emission computed tomography (SPECT), was utilized by Orriols et al. (2009) to evaluate diagnosed MCS patients (8) and controls (8) following exposure to several odorants. Notable and statistically significant differences ($p < 0.01$) were observed in the pattern of hypoperfusion within the frontal cortex in the scans of cases and

controls. In addition, higher cluster activation patterns ($p = 0.012$) were observed in controls. Orriols et al. (2009) noted that the parietotemporal cortex and frontal-subcortical circuits are likely involved in the neurological effects reported in MCS. The MCS subjects also reported deficits in neurocognitive function and in quality of life.

As a means of evaluating olfactory stimulation, changes in blood glucose consumption within the brain during olfactory stimulation were examined by Chiaravalloti et al. (2015). Chiaravallotti et al. (2015) compared diagnosed MCS (26) and control (11) subjects exposed to neutral and olfactory stimulants by using a 18F-2-fluoro-2-deoxy-D-glucose (FDG)-PET scanner. It was observed that based on blood glucose consumption, metabolism in the brain following olfactory stimulation is significantly different between MCS subjects and healthy controls, and MCS subjects were found to have intensive deactivation within the frontal cortex, whereas healthy controls did not exhibit a distinct glucose consumption pattern (Chiaravalloti et al., 2015). The same team of researchers also completed a similar study (Alessandrini et al., 2016), which examined brain activity during olfactory stimulation via the use of a (FDG)-PET device in diagnosed MCS cases (26) and controls (11) exposed to saline or vanillin via a face mask. A significantly increased ($p < 0.05$) levels of glucose metabolism and relative hyperactivation in the olfactory structures of the brain were observed during exposure and after rest, and symptom scores ($p < 0.05$) were higher in the MCS group relative controls during olfactory stimulation. Controls reported the vanillin odour as being more pleasant than the MCS group ($p < 0.05$).

The anterior cingulate cortex (ACC), along with the media prefrontal cortex and amygdala are involved in the modulation of emotional stimuli. The amygdala and ACC have both been reported to have high densities serotonin 5-HT_{1A} receptor (5-HT_{1A}) which has been observed to be reduced in anxiety, depression and harm-avoidance conditions. Further, 5-HT_{1A} binding has an inhibitory response on glutaminergic and GABA neurons within the frontal cortex, and as a result, 5-HT_{1A} binding can influence the firing of both of these neuron types in both the frontal cortex and amygdala (Hillert et al., 2013). Significant differences in odour-processing brain regions were also observed by Hillert et al. (2013) in a PET imaging study involving multiple odorant stimuli and the assessment of regional cerebral blood flow and 5-HT_{1A} binding. Diagnosed MCS subjects (12) and matched controls (12) were examined to determine if MCS subjects have an increased odour-signal response within odour-processing neuronal circuitry Baseline patterns were determined to be comparable between the groups. After odorant exposure, abnormal activation patterns were observed in the MCS group ($p < 0.05$) with MCS patients having less activation within the odour-processing regions observed at baseline and in controls following odorant exposure ($p < 0.05$). In addition, increased activity in the activation of the anterior cingulate cortex and cuneus-precuneus was observed in the MCS group compared to controls ($p < 0.05$). No significant differences in the detection, familiarity or experiences of the various odorants were noted between the groups, and no evidence of neuronal hypersensitivity was apparent. The MCS group had a significantly lower extent of 5-HT_{1A} receptor binding within the amygdala ($p = 0.029$) and anterior cingulate cortex ($p = 0.005$), as well as non-statistically significant 5-HT_{1A} binding in other parts of the brain. Significant differences between the MCS group and controls were reported with respect to the regions of the brain with changes in 5-HT_{1A} binding ($p = 0.025$). The response to startle tests was more evident in the MCS group than controls ($p = 0.006$), and the MCS subjects had higher levels of anxiety and harm avoidance, and more negative ratings of pictures ($p = 0.03$) than controls. However, no association between the psychological profiles for the two groups and 5-HT_{1A} binding was observed (Hillert et al., 2013).

Non-Imaging Studies

The olfactory studies that did not include the use of imaging technologies were more varied in their design and the endpoints evaluated.

Andersson et al. (2016) compared odour responses (perceived odour intensities), reported symptoms and pulse rate variability in both diagnosed MCS subjects (18) and controls (18) exposed to n-butanol or fresh air for 10-minutes within a controlled chamber. The MCS group was observed to have a higher pulse rate than controls ($p < 0.001$) with significantly lower pulse rate variability than controls ($p = 0.009$), suggesting differences in autonomic responses. In addition, the MCS group reported more symptoms for both n-butanol and the blank, with symptoms increasing over the exposure period.

The familiarity of an odour may influence how it is processed by the brain, and the potential interactions between emotions and past psychological associations with odours and physiological responses have been explored by several researchers. The incidence of symptoms and psychological effects were compared between male painters with self-reported MCS (14) and controls (painters without MCS, 15) exposed to furfuryl mercaptan, acetone, and mixture of 21 VOCs. No significant differences with respect to odour sensations were observed. However, the subjective reports of irritation were higher in the MCS group. Plasma prolactin levels were lower in the MCS group following exposure than controls ($p < 0.01$), suggesting that olfaction in these individuals resulted in dopaminergic activation, resulting in an inhibition of prolactin release, or a degree of psychological stress (Georgellis et al., 2003).

Ojima et al. (2002) compared the responses of diagnosed MCS subjects with matched controls following exposure to several odours. While no differences in odour detection thresholds were identified, a higher number of unpleasant reactions to more of the odours were reported in the MCS group ($p < 0.05$). In addition, more pleasant reactions to menthol and gingerbread were reported by MCS than controls ($p < 0.05$). Ojima et al. (2002) postulated then emotional associations with the odours may contribute to the differences between the groups

Papo et al. (2006) compared chemosensory or cognitive olfactory information processing in diagnosed MCS subjects (23), 21 subjects with self-reported odour sensitivities, and healthy controls (23). Chemosensory potential was assessed using electroencephalogram (EEG) recordings, as were psychological tests and surveys, and trigeminal provocation tests, were conducted before and after odour exposures via a standardized test kit. No significant differences in olfactory processing were observed.

A standardized olfactory function test was performed by Eis et al. (2008) on 45 MCS subjects from a sub-set of a larger multi-centre study population, and compared with previously published reference controls. In a subsample of subjects that included MCS subjects and healthy controls, the ability for the subjects to identify and discriminate between different odours following exposure to “Sniffin Sticks”, and their response to odours (assessed by olfactory evoked potentials and the presence of inflammatory mediators within nasal lavage samples). No significant differences in olfactory performance were found for any of the MCS sub-categories examined in this study, including clinical and self-diagnosed MCS. The only difference between the MCS group and controls was in the identification of distinct odours, where the MCS group identified only one odour more than the control group.

4.6.3 Vestibular and Auditory Dysfunction

A small number of studies was identified that examined the potential for the vestibular system, which includes parts of the inner ear and brain that control balance, posture and eye movement. A research team led by Micarelli in Italy has published three studies evaluating the role of vestibular impairment in MCS (Micarelli et al. 2016a,b,c). Two of these studies evaluated the potential for vestibular decay to occur in MCS subjects, with the hypothesis that abnormalities in the otoneurological functions may contribute to some of the symptoms attribute to MCS, such as dizziness. It is also proposed by Micarelli that this vestibular decay may be the result of pathophysiological changes in the nervous system over time in these individuals.

In the first study (Micarelli et al. 2016a), 18 diagnosed MCS subjects and 20 controls underwent clinical otoneurological examinations and assessments of limb coordination, gait and stance. Following this several tests of balance, coordination, sensory-motor control and alignment were completed. Analysis of the result patterns in the tests revealed that there were significant differences in central and peripheral vestibular processing in the MCS group compared to the controls.

In Micarelli et al. (2016b), 18 diagnosed MCS subjects and 20 healthy controls were compared with respect to otoneurological variables. A significantly higher prevalence of defective vestibular processing was identified in the MCS group ($p < 0.01$) as well as an increased number of dizziness-related symptoms during the testing. MCS subjects also were determined to be more visually-dependent (as assessed by several parameters related to visual dependency) than controls. Micarelli et al. (2016b) hypothesize that this may be attributable to sensory “re-weighting” in response to stimuli over time.

The third study (Micarelli et al. 2016c) considered the role of otoacoustic processing and the functionality of the medial olivocochlear (MOC) reflex. Transient-evoked otoacoustic emission (TEOAE) testing was completed on 18 diagnosed MCS subjects and 20 controls to assess the medial olivocochlear (MOC) reflex, which is involved in the perception of speech (particularly within environments with background noise) and in the protection of auditory organs from loud sounds. A significant reduction in the TEOAE testing results was recorded for the MCS group in comparison with controls ($p < 0.01$). At some of the sound frequencies studied, the MOC reflex was reduced in the MCS group ($p < 0.01$) and was correlated to various symptoms from the QEESI® data collected as part of the study. Micarelli et al. (2016c) proposed that the MOC could be involved in the aspects of the CNS abnormalities associated with MCS.

4.6.4 Other Neurological Factors

A small number of studies were identified during the literature search that did not fall into the categories of olfactory or vestibular/auditory functions and involved a variety of study designs

Impedance cardiography was used to examine the hemodynamic responses to postural shift in women with diagnosed MCS as a means of comparing ANS function (McFetridge-Durdle et al., 2009). No controls were included in this study, as the authors noted it to be observational in nature; however, pre-assessment measurements were collected for comparison. With postural change, increased heart rate ($p < 0.0001$), decreased stroke volume ($p = 0.002$), increased systemic vascular resistance ($p = 0.002$) and increased diastolic blood pressure ($p = 0.01$) were observed compared to baseline. The authors noted that the results were potentially impacted by several factors, including age, body mass index, and activity levels. Several individuals were reported to also have overlapping medical conditions, including CFS and fibromyalgia.

PET scans were used to examine IEI subjects and controls during the administration of a battery of neuropsychological tests evaluating verbal skills, learning and memory in a study by Bornschein et al. (2007). Unlike the Chiaravalloti et al. (2015) study, olfactory stimulants were not included. No significant differences in cerebral glucose metabolism were apparent. Although many of the IEI subjects reported difficulties with concentration and memory, slight impairment of verbal learning and memory was observed in the neuropsychological tests for the IEI patients. No statistics for the results were provided, making further interpretation of this study challenging.

Several neuropsychological tests were performed by Österberg et al. (2002) to compare the responses of individuals with diagnosed MCS cases (17) and matched controls (34). A total of six tests evaluating various aspects of brain impairment were completed, that included a total of 17 test variables. Only one significant difference in the test results was observed for the MCS group (mean reaction time, $p < 0.002$), and no differences were apparent in the other 16 variables used to evaluate potential brain impairment, including executive functioning, vocabulary, knowledge, memory retention, auditory processing, sustained attention, perception and fine motor skills.

4.7 Behavioural and Psychological Factors

While MCS has been associated with odours, it is important to note the statement from the recent Alberta Health (2017) review of odours and human health: "*the relationship between odours and physiological or psychological health is extremely complex and influenced by a wide variety of odour characteristics… and odours appear to have their own cognitive and mood profiles*". Further complicating this are the observations that unique, individual responses to odours with respect to neurological studies can occur, likely due to the involvement of memory and emotion as well as altered neurological processing (discussed in Sections 4.5 and 4.6.1 of this report). The responses associated with MCS can result in an aversion of potential triggers.

The co-morbidity of MCS with various psychiatric conditions has been assessed extensively in the scientific literature, with some individuals having developed the conditions before experiencing MCS symptoms, and many not having a diagnosable psychiatric condition until after an MCS diagnosis (CoA, 2010). Other researchers have concluded that MCS is purely a somatoform disorder related to depression, post-traumatic stress syndrome (PTSD) or panic disorder (CoA, 2010).

It is not currently evident if mental health disorders or having experienced a traumatic experience pre-dispose some individuals to MCS, or if MCS may be triggered by other factors, (e.g. chemical exposure incident) and produce behavioural and psychological sequelae. However, as described by the 2010 Australian review (CoA, 2010), "*psychological/psychiatric factors in MCS individuals have been seen either as the cause of MCS, and effect of having MCS, a pre-disposing factor in the development of MCS, or a co-morbid occurrence with MCS*". The Australian review also noted that "the lack of evidence for a physiological cause for MCS should not be interpreted as indicating support for a primarily psychiatric explanation".

Several studies examining behavioural and psychological features in MCS patients were identified during the literature search. The studies of diagnosed MCS patients are presented in Sections 4.7.1 to 4.7.4, and the studies for self-diagnosed MCS patients are discussed in Appendix C.

The literature collected for diagnosed MCS patients with respect to psychological and psychiatric factors has been divided into two topic areas based on common themes that emerged: i)behavioural and psychological responses to stimuli, and ii) MCS symptoms and

comorbid conditions. An additional section regarding psychological diagnostic tools was added to aid in the interpretation of the MCS study findings.

4.7.1 Summary of Findings for Behavioural and Psychological Factors

It is difficult to understand from the overall weight of evidence for psychological outcomes, whether the observed symptoms and disorders in MCS populations make individuals more susceptible to developing MCS, or that several side effects associated with MCS (once established) are psychological and may lead to the development of psychological or psychiatric conditions. Several studies were identified that involved diagnosed MCS patients, however, over half (17 out of 31) of identified studies involved self-reported MCS subjects as opposed to diagnosed MCS subjects (these are presented in Appendix C). The studies of diagnosed MCS involved a mixture of different study designs (cross-sectional, experimental, observational, presented in Table 18). Within Table 18, studies that found statistically significant differences for MCS patients are indicated by a (+) and green shading and studies with no statistically significant differences for MCS patients are noted with a (-) and light blue shading. Overall, the database of MCS studies that include the evaluation of psychological and psychiatric symptoms and conditions is associated with higher degrees of bias and uncertainty than some of the other lines of research discussed within this review.

The MMPI-2 and other diagnostic tools were examined in a multi-experiment study by Davidoff et al. (2000). The authors concluded that the use of psychometric tests in populations already suffering from a disease for the purposes of evaluating the psychogenic origin of the disease is misleading. The testing strategy is not well suited to distinguishing between pathology that may have pre-existed before the onset of MCS and changes in pathology arising from MCS. Davidoff et al. (2000) also concluded that the observed degree of psychopathology observed in the study was consistent with what might be expected for a healthy person developing MCS or a syndrome like MCS. Thus, some degree of caution should be given to the results of studies of psychological effects in individuals who have been diagnosed with a medical condition (such as MCS).

The review by the CoA (2010) provides summaries of some studies published before 2000 where it has been observed that MCS subjects (not clear if diagnosed or self-reported) were observed to have a conditioned response to strong-smelling and irritant stimuli. Other than the CoA (2010) review, the documents identified in the grey or recent review literature (e.g. Sears, 2007; Marshall et al., 2010; Busby, 2017; Rossi and Pitidis, 2017) do not provide additional context for psychological factors in MCS.

The studies that evaluated responses to stimuli generally found significant effects regarding psychological responses, with enhanced psychological symptoms relative to controls being reported, a greater number of symptoms, avoidance behaviours or evidence of attenuation bias. Five studies in this category involved the use of a diagnostic framework, and the studies were predominantly experimental in design, with some observational studies. The consistency of the studies within this category are rated as **Low-Moderate**, based on the observed trend of enhanced or more severe psychological symptoms in response to stimuli. A full rating of moderate is not applied due to the mixture of endpoints evaluated. The utility of the information is rated as **Low-Moderate**, due to the group sizes and the mixture of experimental and observational study designs. Two of the studies within this group used a less commonly used diagnostic framework, and three others used a combination of frameworks. These approaches may have contributed some variability to the findings.

With respect to MCS and the development of psychological symptoms (without specified stimuli), most studies relied on self-diagnosed MCS patients and cross-sectional designs.

The disorders that were found to be co-morbid in the MCS populations included: anxiety, depression, somatization disorders and panic disorder. In general, the information was fairly consistent with respect to these findings. Only a few studies with diagnosed MCS patients were identified, and these involved relatively small populations and study designs. The ratings for **consistency** and **utility** of the information regarding comorbid psychological conditions with MCS are both **Low.** In most instances, it was not clear whether the comorbid conditions that were found to be associated with MCS came before or after MCS symptoms.

Table 18 Summary of Findings Regarding Psychological Factors and Diagnosed MCS

Study	Number of Subjects	Design Type	Diagnosed[1]	Diagnostic Criteria[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[4]
Behavioural and Psychological Responses to Stimuli						
Papo et al. (2006)	23 MCS 21 odour sensitive 23 controls	Experimental	Yes	Bartha et al. (1999)	Other[3]	Increased number and severity of symptoms and a higher state of anxiety in response to odorants (+)
Poonai et al. (2001)	36 IEI 37 controls	Experimental	Yes	Simon et al. (1993)	DSM-IV SCID	Significant increase in symptoms of panic, anxiety, stress, depression and agoraphobia (+)
Poonai et al. (2000)	31 IEI 31 controls	Experimental	Yes	Simon et al. (1993)	DSM-IV SCID	Increased panic symptoms in response to CO_2 (+)
Witthöft et al. (2006)	54 IEI 44 SFD 54 controls	Experimental	Yes	Combination	COSS, DSM-IV SCID	Increased reactions to trigger words, dysfunctional believes regarding health, elevated symptoms of chemical sensitivity (+)
Witthöft et al. (2008)	54 IEI 44 SFD 54 controls	Experimental	Yes	Combination	COSS, DSM-IV SCID	Higher rates of absorption and reports of medically unexplained symptoms; unique from somatoform disorder group (+)
Witthöft et al. (2009)	49 IEI 43 SFD 54 controls	Experimental	Yes	Combination	COSS, DSM-IV, SCID	Increased reactions to trigger words, increased emotional intrusion from symptom words, significant relationship between reactions to trigger words and emotional intrusion from symptom words (+)
Comorbidity with Various Psychological/Psychiatric Conditions with MCS						
Binder et al. (2006)	14 MCS 14 epileptic seizures 14 Non-epileptic seizures	Observational	Yes	Bartha et al. (1999)	Other	Increased scores for hypochondriasis, depression and hysteria higher in MCS group compared to either seizure group (+)
Bailer et al. (2004)	35 moderate sensitive 35 high sensitive 36 controls	Cross-Sectional	Yes	Nimnuan et al. (2001)	COSS, DSM-IV,	Higher scores on self-reported depression and somatoform disorders, tendency to focus on autonomic sensation, general environmental sensitivity (+)

Bornschein et al. (2002)	264 subjects	Cross-Sectional	Yes	WHO IPCS, (1996)	SCID, DSM-IV	High proportion of individuals with psychiatric disorders in a population with MCS (+)
Caccappolo-van Vliet et al. (2002)	30 MCS 19 asthmatics 31 controls	Case-Control	Yes	Cullen (1987)	COII	Increased proportion of lifetime anxiety disorders and current depressive symptoms, difficulties with memory and attention (+)
Eis et al. (2008)	251 subjects	Cross-Sectional	Yes	Cullen (1987)	DSM-IV, CIDI, EMQ,	Somatoform disorders most common in MCS patients, and preceded MCS disease in 80% of patients (+)
Hausteiner et al. (2006)	54 IEI 251 controls	Case-control	Yes	WHO IPCS (1996)	DSM-IV, SCID	Relatively high prevalence of psychotic disorders in IEI group (+)
Tonori et al. (2001)	46 MCS 46 controls	Case-Control	Yes	Cullen (1987)	STAI, SRDS. HRSD	Increased and sustained symptoms of anxiety and depression (+)
Weiss et al. (2017)	25 IEI 26 psychiatric disorder 19 schizo-affective disorder	Cross-Sectional	Yes	Bartha et al. (1999)	QEESI© modified for the German population, DSM-	Higher scores for chemical intolerance, neurotoxic symptoms, and general health problems (+) IEI symptom profile is different than what is reported for major depression and schizophrenia/schizoaffective disorder (-)

Acronyms: ASI: Anxiety Sensitivity Index, CCHS: Canadian Community Health Survey, CCII Chemical Odour Intolerance Index, COSS: Chemical Odour Sensitivity Scale, DMT: defence mechanism test, DSM-IV, EMQ: environmental medicine questionnaire, HRSD: Hamilton Rating Scale for Depression, IBS: irritable bowel syndrome, NEM/PEM: Negative and Positive Emotionality Measure; Positive and Negative Affect Schedule PHQ: Patient Health Questionnaire, SCID: Structured Clinical Interview, STAI: State Trait Anxiety Inventory, SRDS: Self-rating Depression Scale

[1] Defined and published diagnostic criteria were required for a study to receive a 'yes' and be considered to have relied upon diagnostic criteria. The use of questionnaires as a diagnostic tool was counted as a screening questionnaire, rather than a diagnostic framework, as the questionnaires rely upon self-reporting, while a clinical diagnosis relies on both self-reporting an assessment by a practitioner.

[2] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[3] 'Other' is noted when a standardized questionnaire was used, but is not named or specified

[4] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue. Due to a lack of a reference group, the significance of results was difficult to determine in some studies, and findings are presented in grey.

*indicates that criteria were applied but the source of these criteria was not clear

4.7.2 Background Information for Behavioural and Psychological Factors

Several diagnostic tools from within the realm of human behavioural studies were included within the studies identified in relation to psychological and psychiatric factors in MCS.

Two of the most-common tests used in the assessment of psychological effects and psychiatric conditions were the Multi-Phasic Personality Inventory (MMPI-2) and the Diagnostic and Statistical Manual (DSM-IV). The MMPI-2 scales have been developed by the University of Minnesota for the evaluation of various behavioural and psychiatric conditions. T he MMP-2 consists of several qualitative scores that are applied to patients by trained professionals in a number of categories (UMP, 2018). Another means of diagnosing psychiatric conditions is the Structured Clinical Interview for the DSM (SCID), a process developed by the American

Psychiatric Association (APA) for the standardized diagnosis of mental diseases. Both the MMPI-2 and DSM-IV qualitatively describe various psychiatric conditions, but do not assess causation. The Karolinska Scales of Personality (KSP) is an inventory used to evaluated personality through the use of qualitative subscales that evaluate various aspects of personality and the PRIME-MD system for the evaluation of depression anxiety disorders was also used in some studies. Other tests involved checklists of symptoms (i.e. Symptom Checklist-90 or Symptom Checklist-92).

4.7.3 Behavioural and Psychological Responses to Stimuli

The review by the CoA (2010) described several studies completed that have proposed that MCS involves an element of conditioning or psychobiological learning, where a stimulatory experience (such as an odour) may evolve into the ability of the stimulus to induce a non-deliberate conditioned behavioural response (CoA, 2010). A comparable phenomenon noted by the CoA (2010) is odour and taste aversion, where exposures can result in a conditioned response as a result of the memory of the previous experience with a food or smell (CoA, 2010). Interestingly, conditioning has been noted in association with irritating or unpleasant odours, but not pleasant odours, suggesting the involvement of the olfactory processing system with memory and behaviour (CoA, 2010). The involvement of emotion in the response to odours and how reactions may be learned (and beyond conscious control) were discussed in the studies by) within the olfactory processing section of this review (Section 4.6.1 and Appendix C). It is possible that there is a degree of overlap between the reactions of the thalamus and limbic system to odours and psychological responses and learning processes.

Another behaviour that has been examined in relation to MCS individuals is the tendency to avoid or block stimuli (chemical or physical) upon re-exposure to stimuli.

The involvement of altered psychological profile in association with MCS was explored by an Papo et al. (2006). This study compared chemosensory or cognitive olfactory information processing in diagnosed MCS subjects (23), 21 subjects with self-reported odour sensitivities, and healthy controls (23). Chemosensory potential was assessed using electroencephalogram (EEG) recordings, as were psychological tests and surveys, and trigeminal provocation tests, were conducted before and after odour exposures via a standardized test kit. A higher level of adverse responses to odours were reported in all psychometric tests ($p < 0.05$) and a higher stated of anxiety was observed in the MCS group relative to the other two groups ($p < 0.05$). All MCS patients had significantly higher scores for adversity in the psychometric evaluations completed as parts of the study. Papo et al. (2006) suggest that the sensitization of limbic structures and neural networks within the brain may result in avoidance behaviours and enhance anxiety symptoms in individuals with MCS.

Poonai et al. (2001) have suggested that the psychological morbidity of IEI subjects lies between that of the general population and a clinical psychiatric population. In this study, groups of diagnosed IEI subjects (36) and controls (37), all of whom did not have pre-existing psychiatric conditions were compared with respect to the results of self-reporting psychological questionnaires evaluating anxiety, depression, stress and agoraphobia after exposure to clean air or CO_2. The IEI group had significantly higher scores on the assessments of agoraphobia cognition, depression, anxiety and stress ($p < 0.05$ for all) compared to controls. Within the IEI group, 22 out of the 31 subjects fulfilled criteria for having experienced a panic attack in response to CO_2, and this subset of individuals also achieved higher scores for depression and on one criterion for agoraphobia than the rest of the IEI group ($p = 0.01$ and 0.03).

The relationship between IEI and panic disorder was evaluated in a blinded experimental study by Poonai et al. (2000). The behavioural responses to clean air or CO_2 (administered via a flow spirometer) were compared between diagnosed IEI subjects (31) and controls (31). The DSM IV (SCID IV) was used to evaluate the presence of psychiatric disorders, in addition to other behavioural survey instruments. A significantly higher proportion of people in the IEI group (71%) qualified as meeting panic criteria following CO_2 inhalation ($p < 0.001$) relative to controls. The number and severity of panic symptoms was found to be higher in the IEI group. Both IEI and control subjects exhibited higher breathing rates after CO_2 inhalation, but no significant difference was found. Poonai et al. (2000) postulated that IEI and panic disorder may share some common features, and that psychological assessment is of value in IEI studies.

Several related cross-sectional studies on the same study population were completed by Witthöft et al. (2006, 2008, 2009) to examine the differences in psychological patterns between diagnosed IEI patients (54), individuals with diagnosed somatoform disorder (44) and healthy controls (54). The results of Witthöft et al. (2006) focused on selective attention, memory and symptom perception. Strong similarities in symptom patterns and overlapping psychological factors were comparable for the IEI and somatoform groups in relation to each other, but different than controls ($p < 0.01$). "Trigger" words (not specified) were remembered more accurately and associated with elevated symptoms of chemical sensitivity by the IEI group compared to the other groups ($p < 0.01$). In response to the trigger words, IEI subjects reported more somatic symptoms and dysfunctional beliefs regarding health, indicative of selective attention and selective recognition ($p < 0.01$). No evidence of a shift away from or avoidance from the trigger words or symptoms were noted in any of the three groups. Witthöft et al. (2006) suggested that IEI might involve a "cognitive-behavioural formulation of somatization as the result of a complex and vicious circle of increased symptom-focused attention, catastrophizing and symptom amplification", with differences in elaborative and attribution related cognitive processes contributing to differences in the clinical conditions of IEI and somatoform disorder.

Witthöft et al. (2009) assessed cognitive-emotional processing within the same population through the evaluation of test performances and responses to IEI "trigger words" and "symptom words". The IEI group demonstrated significantly higher negative association effects than both the other groups in response to IEI "trigger words" ($p = 0.01$), and both the IEI and somatoform groups were significantly ($p < 0.01$) more severe with respect to emotional intrusion effects of "symptom words" (but not IEI trigger words). In addition, a significant association with negative reactions to "trigger words" were associated with greater emotional intrusion effects for "symptom words". The cognitive theory surrounding functional somatic complaints is proposed to be related to the amount of attention given to previous experiences and cognitive symptom representations that were formed as a result of physiological disorders or trauma), causing individuals to have a decreased threshold for experiencing symptoms in response to stimuli. The symptoms are experienced as being real by the individual, but could be the result of dysfunctions within cognitive-processing (Mobini, 2015; Witthöft et al., 2009).

4.7.4 MCS Symptoms and Comorbid Psychological and Psychiatric Conditions with MCS

Several studies were identified that examined the incidence of psychological symptoms following the development of MCS symptoms but did not examine the co-morbidity of MCS with psychological or psychiatric conditions specifically.

The psychological profiles (measured by MMPI-2) of individuals with MCS from a single clinic in relation to legal matters stemming from a common chemical exposure incident, were compared

to individuals with diagnosed epileptic seizures (ES, 14) and medically-unexplained, non-epileptic seizures (NES) by Binder et al. (2006). No control group of individuals without a seizure disorder was included. The MMPI-2 assessments using the scales for hypochondriasis, depression and hysteria were found to be significantly different between the groups, with the MCS group having the highest scores categories ($p < 0.001$, $p < 0.002$ and $p < 0.002$, respectively) compared to the NES group, and the ES group ($p < 0.001$ for all three categories). There were no other significant differences for other aspects of the MMPI-2 scales.

As noted in Section 3.6, several medical conditions are suspected to overlap with MCS, including psychological or psychiatric disorders.

A large multi-centre study in Germany was completed by Eis et al. (2008) where four categories of MCS were evaluated (clinically-estimated MCS, self-reported MCS, and F1 MCS and F2 MCS – differentiated on the lack or addition of physician comments in the computer-facilitated diagnosis of MCS). Of the 251 patients that participated in this portion of the study, 84% of the participants reported having at least one psychological disorder compared to 50% of the German general population. The most common disorders reported in the MCS group were somatoform disorder, specifically “undifferentiated somatoform disorder”, “subthreshold somatoform disorder”, “persistent somatoform pain disorder” and “severe depressive episode without psychotic syndrome”. The MCS subjects reported a significantly higher number of somatoform disorders than controls. To determine if these somatoform disorders were the result of MCS, or preceded MCS, analyses examining the time of onset and environmental complaints were conducted. For 80% of the patients included in the analysis (251 of 291 environmental health patients, approximately 86% of the study population), the mental disorder had been present longer than the symptoms, while only 18% reported that the symptoms were experienced for longer than the mental disorder. The mean duration of difference between the onset of the mental disorder and the environmental symptoms was estimated to be 15-17 years based on the data reviewed.

Cognitive function, and experience with both lifetime and current psychiatric disorders were compared between groups of patients with diagnosed MCS (30), diagnosed asthma (19), and healthy controls (31) (Caccappolo - van Vliet al., 2002). Asthmatic subjects were included, as they represent individuals with a chronic health condition that can worsen in response to environmental triggers. Both the MCS and asthmatic groups were reported to have a greater proportion of lifetime anxiety disorders, but not other lifetime psychiatric disorders. A higher rate of depression was noted for MCS patients in the analysis of current disorders (reported in the last 12-months) compared to both asthmatics and controls. A significantly larger proportion of the MCS group met the criteria for somatization disorder than the other groups. Both MCS and asthmatics reported more memory problems, attention and prospective memory than controls. Caccappolo-van Vliet et al. (2002) suggested that both anxiety and depression have roles in the physical and cognitive symptoms reported in association with MCS.

The psychological characteristics of individuals with diagnosed MCS (high MCS and low-MCS, as determined by questionnaire responses) and age- and sex-matched controls were examined by Bailer et al. (2004) within a cross-sectional study. A total of 59 recruited individuals were selected to participate in the study at a University using an 11-item self-reporting Chemical Odor Sensitivity Scale (COSS), followed by a clinical interview. Using questionnaires and interviews, chemical odour sensitivity, the presence of somatoform disorders (diagnosed using the DSM-IV), self-reported allergy and environmental sensitivities, and sociodemographic information were collected. Using these data, subjects were divided into three groups – control, low-MCS and high, diagnosed MCS. The high MCS group was found to have significantly higher scores on self-report scale for depression ($p < 0.05$) and somatoform disorders ($p < 0.01$). Statistically

significant associations (all $p < 0.001$) between the high-MCS group and the other groups with respect to scores regarding environmental threats, anxiety, autonomic sensations and general environmental sensitivity. Bailer et al. (2004) proposed that differences in cognitive-perceptual style and trait anxiety may have contributed to the symptoms reported by MCS subjects in response to perceived environmental threats.

Anxiety and depression symptoms were compared between 46 diagnosed MCS patients and 46 controls using several tests and scales. Both groups were comprised of new patients to a Japanese clinic and follow-up patients to the same clinic. The MCS patients in the follow-up group were found to have higher anxiety scores than the new MCS patients and the controls ($p < 0.01$ to 0.05). The anxiety at subsequent clinic visits remained high for both the new and follow-up MCS patients, while any anxiety scores reported in the control group decreased with follow-up visits. The MCS patients in the follow-up group had higher scores for depressive symptoms than either the new-patient group or controls. Tonori et al. (2001) suggested that patients with MCS are in a state of continued depression and anxiety.

Bornschein et al. (2002) compared the rates of psychiatric morbidity in a population of 264 out-patients of a University Environmental Medicine clinic. All subjects were examined and interviewed and completed various questionnaires, and the DSM-IV was used for the assessment of morbidity. Once all subjects with symptoms with identifiable causes were eliminated, only 36 out of the original 199 subjects (18%) remained. In 75% of the population, at least one or more psychiatric disorder was diagnosed, with the largest diagnostic category being somatoform disorders, followed by affective and anxiety disorders. Bornschein et al. (2002) also attempted to relate the reported symptoms to the most plausible factors, and in 23% of the patients (59) somatic disease was identified as the likely cause of the symptoms, and in 39% of the patients, a psychiatric disorder was determined to be the cause of the symptoms. For 36 patients (14%) no clear psychiatric, somatic or toxicological factor was identified as the cause of the symptoms. Only 5 out-patients were identified as having chemical exposures as a likely cause of the reported symptoms. These exposures were attributable to occupational exposures to cadmium, organic solvents or general exposure to cigarette smoke.

A total of 305 subjects were recruited from an environmental health clinic in Germany (Hausteiner et al., 2006). Of these, 54 individuals were diagnosed with IEI and the other 251 were identified as controls. Structured clinical interviews including an evaluation of medical history and psychological status (using the DSM-IV) were completed. A relatively high prevalence of psychotic disorders (primarily delusional disorders) was identified compared to controls ($p < 0.05$) in the IEI group. Various somatoform disorders (somatization, affective and anxiety disorders) were reported in both the IEI group and controls, and were similar in incidence (Hausteiner et al., 2006).

Weiss et al. (2017) compared the incidence of psychological and somatic symptoms in diagnosed IEI patients (25) and two groups of patients with diagnosed psychiatric disorder: major depression (26) and schizophrenia/schizoaffective disorder (19). The IEI group had higher scores for chemical intolerance and neurotoxicity, more general health problems (with low energy and pain being the most common) than the other group. Overall, the symptom profiles of the IEI patients were significantly different from subjects with major depression or schizophrenia. Weiss et al. (2017) notes that the study results support the theory of somatosensory amplification in the propagation of IEI symptoms, as proposed by Skovbjerg et al (2010a).

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4.8 Overall Weight of Evidence

The overall WOE was classified with criteria developed by the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission (SCENIHR, 2012). However, as the SCENIHR (2012) approach is intended for the assessment of individual chemicals that may have human, animal and mechanistic data, the approach had to be simplified based on the nature of the database for MCS and the boundaries set for the scope of this review (i.e., human-only data for a disease condition that is not consistently defined).

- **Strong overall WOE**: coherent evidence for one or more line of evidence in the absence of conflicting evidence;
- **Moderate overall WOE:** generally good evidence from one line of research, but evidence missing from others;
- **Weak overall WOE:** consistently weak evidence from the various lines of research;
- **Uncertain WOE:** due to conflicting evidence from the various lines of research that cannot be explained; and,
- **WOE** cannot be assessed due to lack of information.

To achieve this, the ratings for consistency and utility and the overall information presented in the various Summary tables within Sections 4.1 to 4.7 were considered all together. A “heat-map” chart is presented in Table 19, with the darker colours and text. None of the lines of research, or their sub-parts were assigned ratings of high for either consistency or utility, primarily due to the impact of the uncertainty inherent in the diagnosis of MCS. Even the use of diagnosed MCS subjects in studies (which was given credit in the rating) does not eliminate the potential variability in the study results that could arise from the use of several sets of diagnostic criteria, the variability in diagnoses using the same set of criteria between practitioners and treatment centres/clinics/research facilities.

When plotted in a chart (Utility vs. Consistency, Figure 2), it is evident that two lines of research stand out as having a greater overall weight of evidence compared to the others:

1. Olfactory processing dysfunction in diagnosed MCS; and
2. Neurologic sensitization and neurogenic inflammation in diagnosed MCS.

Table 19: Integration of Consistency and Utility Ratings for All Lines of Research

Lines of Research	Consistency Rating	Utility Rating
TILT	Very low	Very Low
Immunological Dysfunction	Low	**Low-Moderate**
Genetic Factors (all)	Low	**Low-Moderate**
NMDA receptor, nitric oxide/peroxynitrate	Very low	Very Low
Neurologic Sensitization and Neurogenic Inflammation	**Moderate**	**Moderate**
Neurological Dysfunction		
Olfactory Processing Dysfunction	**Moderate-High**	**Moderate**
Vestibular Dysfunction	**Low - Moderate**	Low
Other Neurological Factors	Low	Low
Psychological and Psychiatric Factors		
Behavioural and Psychologica Responses to Stimuli	**Low-Moderate**	**Low-Moderate**
MCS Symptoms, Effects and Comorbidity	Low	Low

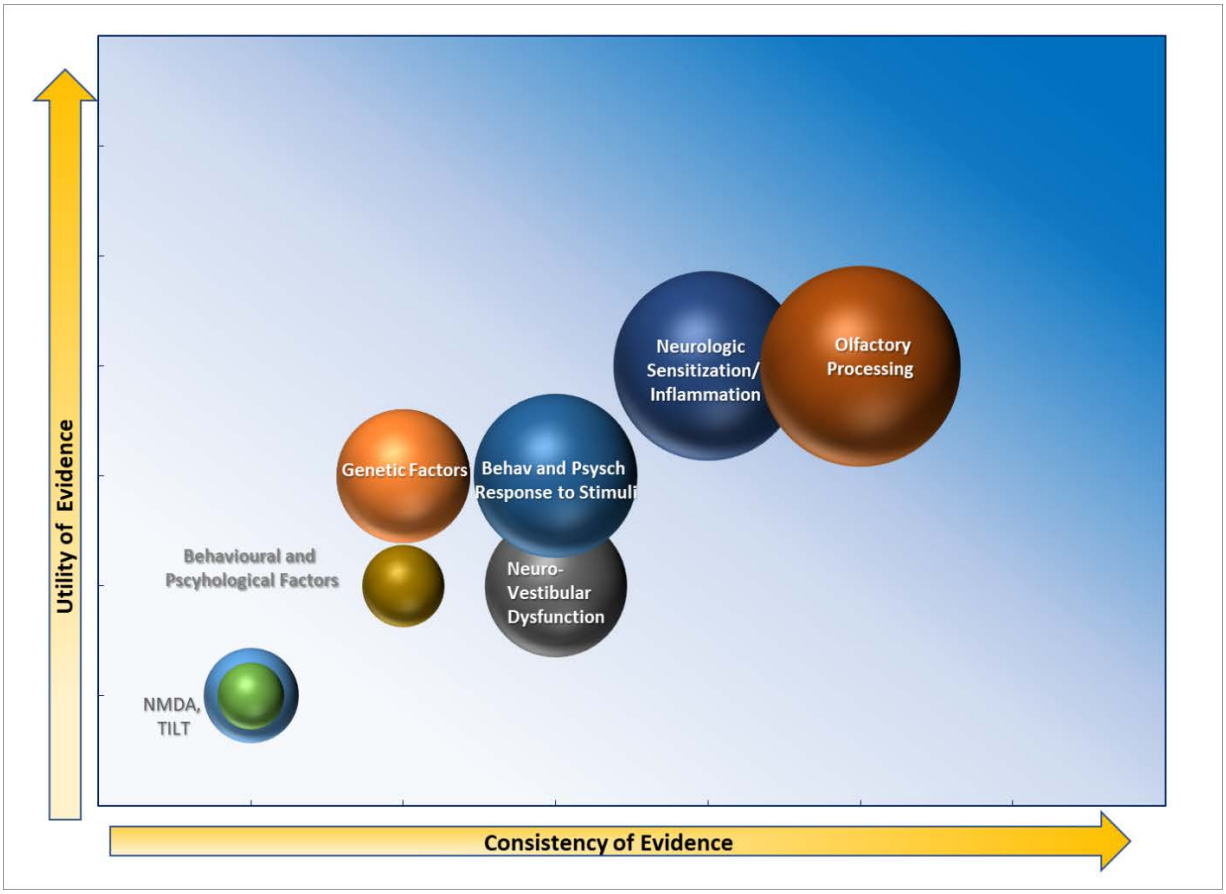

Figure 2: Graphical Plot of Weight of Evidence for MCS Lines of Research

A summary of the significant effects associated with these lines of research, filtering the data for studies that used diagnosed MCS subjects and results significantly associated with MCS, is presented in Table 20. At this time, the overall WOE is rated as **Moderate: generally good evidence from one line of evidence but evidence missing from others.**

Consideration should be given to the possibility that the biological processes examined within the olfactory processing, neurological sensitization and neurogenic inflammation are all related in MCS. These areas all involve the nervous system and the reaction of the brain to stimuli (irritant and olfactory) as evidenced by regional changes in blood flow and glucose metabolism. Further, the available studies that support the WOE for these research areas note the involvement of emotion, memory, learning behaviours and both physical and associations with behavioural effects. Some of the most commonly reported symptoms in Table 6 included: increased odour intensity, irritant responses of the eyes and upper respiratory tract, increased cough reflex, all of which could be related to the involvement of the olfactory and other regions of the brain, and the nervous system. The next most highly ranked lines of research, behavioural and psychological responses to stimuli and neurological dysfunction (specifically, vestibular and auditory dysfunction) could be associated with some other symptoms frequently reported in studies reported in Table 6, such as dizziness, anxiety, depression, irritability, somatic symptoms, joint and muscle pain.

Further study of the various aspects of MCS in the years to come will likely continue to enhance the state of knowledge, which will likely contribute to advances in the management of MCS.

Table 20: Comparison of Results for Neurological Sensitization/Neurogenic Inflammation and Olfactory Processing Dysfunction and with Focus on Diagnosed MCS Cases and Results Significantly Associated with MCS

Study	Number of Subjects	Design Type	Diagnostic Criteria[1]	Statistically Significant (Positive Association) Findings Regarding MCS[3]
Neurological Sensitization and Neurogenic Inflammation				
Holst et al. (2011a)	16 MCS,15 eczema, 29 controls	Experimental	Cullen (1987)	Increased pain intensity and secondary hyperalgesia with capsaicin (+)
Nogami et al. (2004)	15 MCS, 29 chronic cough, 29 controls	Experimental	Cullen (1987)	More sensitive cough reflex to capsaicin (+)
Ternesten-Hasseus et al., (2002)	12 MCS, 12 controls	Experimental	Cullen (1987)	Increased cough reflex and symptoms with capsaicin (+)
Tran et al. (2013)	15 MCS, 15 controls	Experimental	Lacour et al. (2005)	Increased secondary punctate hyperalgesia, punctate pain ratings (+)
Österberg et al. (2003)	10 MCS, 10 controls	Experimental	Bartha et al. (1999), Nethercott et al. (1993), NRC (1992), WHO IPCS (1996)	Increased mucous membrane irritation and fatigue, worsening of reaction time with VOCs (+)
Olfactory Processing Dysfunction				
Alessandrini et al. (2016)	26 MCS 11 controls	Experimental	Bartha et al. (1999); Lacour et al. (2005)	Increased glucose metabolism and hyperactivation of olfactory structures (+)
Andersson et al. (2016)	18 MCS, 18 controls	Experimental	Bartha et al. (1999); Lacour et al. (2005)	Altered autonomic response to odour, increased symptoms (+)
Azuma et al. (2013)	12 MCS, 11 controls	Experimental	Bartha et al. (1999)	Changes in cerebral blood flow in prefrontal cortex, and impairment in odour processing with repetition (+)
Azuma et al. (2015a)	6 MCS, 6 controls	Experimental	Bartha et al. (1999)	Changes in cerebral blood flow in prefrontal cortex, delayed recovery (+)
Azuma et al. (2016)	12 MCS 7 controls	Experimental	Bartha et al. (1999)	Changes in cerebral blood flow in prefrontal cortex, delayed recovery (+)
Chiaravalloti et al. (2015)	26 MCS, 11 controls	Experimental	Cullen (1987)	Deactivation of glucose metabolism in frontal cortex (+)
Georgellis et al. (2003)	14 MCS, 15 controls	Experimental	Cullen (1987)	Decreased plasma prolactin levels following odorant exposure (+)
Hillert et al. (2013)	12 MCS, 11 controls	Experimental	Bartha et al. (1999)	Abnormal activation patters, increased activity in anterior cingulate cortex and cuneus precuneus and less activation in odour processing regions (+)
Orriols et al. (2009)	8 MCS, 8 controls	Experimental	Bartha et al. (1999)	Decreased activity in frontal cortex and altered activation patterns within various brain regions (+)
Ojima et al. (2002)	25 MCS, 50 controls	Experimental	Cullen (1987)	Enhanced positive and negative responses to odours (+)

5.0 PUBLIC HEALTH MANAGEMENT OF MCS

As identified in the SOW for this project, Alberta Health has an interest in the management of MCS from a public health perspective. Several documents from the peer-reviewed scientific and grey literature were identified as being potentially useful in the literature search and screening process outlined in Section 2.0.

Although clinical management of MCS was initially included in the SOW, this aspect has been given less emphasis in this report, as this topic is better examined by experienced clinicians, given the variation in diagnostic practices, the overall complexity and evolving database of literature regarding MCS. A list of the identified clinical studies is provided within the annotated bibliography (Tables A1 and A2).

5.1 Summary of Findings

The management of MCS from a public and occupational health perspective varies between jurisdictions and organizations. The available management strategies focus on the minimization or avoidance of exposure. However, the success of these strategies depends on the general level of awareness of MCS in workplaces. Similar to what was noted throughout Section 4, the lack of a single, clear set of diagnostic criteria for MCS has a profound impact on the understanding of the condition. In addition, there seem to be challenges with respect to medical terminology and documentation between practitioners.

The literature reviewed indicates that many individuals with MCS can find it difficult to receive quality care, and experience adverse effects on quality of life as a result. From a public health and occupational health perspective, the published information is primarily focused on avoidance-based practices within indoor environments (e.g., public health facilities, offices). However, such practices rely not only on the involvement and commitment of the property owner/operator, but also all on the other individuals within it (other patients, practitioners, contractors, workers, visitors, etc.) , their use of scented or odourous substances, and their compliance with any policies or practices (e.g. scent-free spaces) put in place by the building operator or workplace management.

5.2 Current Issues and Challenges

Several issues and challenges associated with MCS within a public health and occupational context were identified in the peer-reviewed research studies and grey literature and are summarized in subsequent subsections.

5.2.1 Terminology and Acknowledgement

As discussed within Section 3.0, there is a lack of clear consensus with respect to the case definition, diagnostic criteria and symptoms for MCS. This in turn has affected the management of MCS with respect to management at both a clinical and public health level. In addition, a lack of consistency in the terminology used in the assessment of MCS subjects, and communication practices by health practitioners and public health organizations have been noted as a complicating factor in the management of MCS by Sampalli et al. (2011).

An assessment by Sampalli et al. (2011) proposed the development of standardized, controlled clinical vocabulary terminologies so that clinicians can share the knowledge of various diseases and concepts in a collaborative way for care management while also expanding the base knowledge of the illnesses. Physicians have several resources that serve as references for

diagnoses and disease management. The Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT®) is a computer system that has comprehensive coverage of diseases and clinical findings, is multilingual, and has standardized vocabulary used for a number of diseases (Sampalli et al., 2010). The intellectual property rights were transferred to SNOMED® Standards Development Organization in the formal creation of the International Health Terminology Standards Development Organization.

In the work conducted by Sampalli et al. (2010), SNOMED CT® was tested in its ability to cover MCS health concepts and symptoms. Sampalli et al. identified the frequently occurring terms and health concepts in 100 MCS patient profiles and matched them to the terms and synonyms of the terms on SNOMED CT® through the use of string-based mapping techniques. Sampalli et al. (2010) noted that there were important terms (i.e. "multiple chemical sensitivity") which were not in SNOMED CT® and thus recommended that more work is required to improve the coverage that SNOMED CT® has for MCS. The results determined that SNOMED CT® had captured nearly 82% of the multidisciplinary health concepts for MCS. However, it is not clear how often a system like SNOMED CT® (or something similar) is used within health care settings in Alberta or Canada, or how it is used with respect to the management of MCS.

In addition to the use of improved and more consistent terminology, it has been noted that there is a need for healthcare providers to more openly provide acknowledgement of the symptoms presented by the patients in the form of required referrals and treatment options (CoA, 2010; Gibson et al., 2016). The legitimization of the illness through a diagnosis or through the acknowledgement of the presence of symptoms has been identified as being of importance to individuals suffering from MCS, as it allows them to seek out effective services for their treatment (Gibson et al., 2016; Koch et al., 2006). Swoboda (2008) surveyed 445 physicians to examine the tendency for diagnosing illnesses such as MCS. The survey identified that physicians that diagnose MCS utilize several diagnostic tools, including the use of therapeutic applications, and the completion of psychological evaluation tests in collaboration with patients when compared to non-diagnosing physicians. Swoboda (2008) remarks that in diagnosing MCS, clinicians are contributing to legitimizing the illness.

Gibson and Lindberg (2011) conducted a survey on ninety physicians in the state of Virginia USA; found that 97% of the respondents had patients who reported chemical sensitivities, but only 6% had a treatment protocol. The study noted that 48% of the respondents were "somewhat familiar", 36% were "somewhat unfamiliar", 9% "very unfamiliar" and 8% were "very familiar" with MCS. The study revealed that various sources were used to learn about MCS and that 51% of the physicians learned about MCS from other healthcare providers whereas only 30% had received training in medical school. In addition, more than half of the participating physicians perceived MCS as a combination of a medical and psychological condition, and that it was due to "multiple low level chemical exposures over time" (Gibson and Lindberg, 2011). However, as noted by the CoA (2010) "the lack of evidence for a physiological cause for MCS should not be interpreted as indicating support for a primarily psychiatric explanation".

A survey of 60 individuals with MCS by Gibson et al. (2016) found that counselling was the reason most individuals approach mental health providers. When visiting the mental health care providers, it was reported that some practitioners provided for the accommodations that individuals requested for (e.g. meeting in a fragrance-free, chemical-free space), while others did not. Gibson et al. (2016) indicated that many of the survey respondents reported to have felt that their mental health providers were not knowledgeable about MCS, with over 83.3% of the respondents considering their mental health care provider as somewhat or not experienced.

5.2.2 Cost of Care and Income Instability

Another challenge that was identified in a number of studies associated with MCS management is financial, where treatment costs, and income instability or loss of income are reported to be a notable concern for individuals with MCS (CoA, 2010; Fox et al., 2007; Gibson and Lindberg, 2007; Halapy and Parlor, 2013).

Studies have shown that individuals with MCS have a higher rate of physician consultations, misdiagnosis and increased health care cost (Fox et al., 2007). The 2014 CCHS revealed that 16% of individuals with chronic fatigue syndrome, fibromyalgia and MCS went to at least 10 consultation appointments with a general practitioner in the past year compared to the 5% of individuals without one of the 3 illnesses (Park and Gilmour, 2017). According to work completed by Gibson and Lindberg (2007), medical care costs became substantial for many individuals.

A study conducted at the Nova Scotia Environmental Health Centre (NSEHC) investigated how a multidisciplinary facility providing holistic care would affect health care utilization and the associated costs for individuals with MCS (Fox et al., 2007). Many patients at NSEHC were reported to have taken a variety of pharmaceuticals and/or natural products but have experienced limited effectivity. At NSEHC, holistic management of symptoms through individualized consultations and treatment regimens were prescribed to patients. The results from the study indicated that there was a relative decrease in health care utilization and healthcare and associated costs for the three cohorts. Fox et al. (2007) noted that the decrease in health care utilization and costs does not necessarily mean an improvement in the health status of the patients but does encourage further research on health care utilization cost for individuals with MCS.

In regards to income loss and instability, approximately 11% of people with MCS/ES were reported to have household income less than $15,000, as determined through the 2010 Statistics Canada for the CCHS (Halapy and Parlor, 2013). The CCHS suggested that the reasons for low income for individuals with MCS could include reduced employment income, inability to work as a result of the limitations of MCS, and having difficulties in obtaining and retaining long-term disability leave (Halapy and Parlor, 2013). More recent statistics for Canadian or other relevant jurisdictions were not identified.

Despite the above noted challenges, some progress has been made by governmental organizations with respect to accommodating individuals with MCS in the workplace (see Sections 5.2.1 and 5.2.2).

5.2.3 Barriers for Individuals with MCS

Gibson (2010) reported that individuals with environmental sensitivities (including MCS) have rarely, if ever, had true access to common community resources such communities of worship, grocery stores, health food stores, community meetings, public libraries, the homes of extended family members and friends, offices of dentists and medical doctors, public parks, and classes at their local universities. Gibson (2010) identified that, the two most common barriers that have been reported in public spaces are fragrance/perfumes and cleaning products, both of which are barriers that can be relatively easy to remove.

Similar findings were reported by Koch et al. (2006), who reported that it can be difficult for MCS patients to properly manage their symptoms because they may be exposed to environmental

triggers from numerous situations and in a wide range of environmental settings. In a number of studies, social isolation due to poor access to community resources is reported to be a result of MCS (Gibson, 2010; Gibson and Lindberg, 2011; Koch et al., 2006). Koch et al. (2006) also noted that skepticism from friends, family and co-workers furthered the sense of isolation for those with MCS as other people did not understand the extent of impact that the environment had on the health of those with MCS. In order to reduce the sense of isolation, Koch et al. (2006) recommended that services such as outreach, disability awareness training, health referrals, employment assistance and improved help at home be provided to individuals with MCS.

Barriers within workplace environments have also been identified by individuals with MCS. A study by Gibson and Lindberg (2007) observed that challenges associated with triggers or fear of triggers can often result in financial loss and isolation for the individual with MCS. In addition, Gibson and Lindberg (2007) also reported that workplace harassment was identified as a common experience for individuals with MCS and this may be due to lack of education provided to employees about disabling sensitivities that co-workers may have. Similarly, Koch et al. (2006), identify that co-workers may ostracize individuals with MCS and see complaints as being psychosomatic or attention-seeking. In addition, some literature showed that there is a lack of acceptance of MCS as a legitimate disabling condition and a lack of support which can lead to people with MCS to experience psychosocial isolation (Koch et al., 2006; Lipson and Doiron, 2006).

However, as outlined in sections 5.2.1 and 5.2.2, advances have been made by governmental organizations with respect to accommodations for individuals with MCS.

5.3 Public Health Approaches and Strategies for MCS Management

Several documents from grey and peer-reviewed scientific literature described current and proposed approaches and strategies taken by governments, hospitals and other public buildings, and workplaces for the management of MCS. Existing policies protective of individuals with MCS and proposed approaches are presented in the subsequent sections, if identified during the literature review.

5.3.1 Governments

A report by the Environmental Health Clinic at the Women's College Hospital in Toronto (Marshall et al., 2010) noted that there are a number of advances, through government involvement, in understanding and managing MCS including: having the consensus case criteria validated and funded by Ontario Ministry of Health, the establishment of referral clinics in Ontario and Nova Scotia which are funded by the Ministry of Health, establishment of the Paediatric Environmental Health Speciality Unit in Alberta, initiation of prevalence studies through Statistics Canada CCHS, and recognizing MCS as a disability requiring accommodation under the Ontario and Canadian Human Rights Commissions.

A review completed by Wilkie and Baker (2007) suggested that within a Canadian and Australian context, in the *Canadian Human Rights Act*[10] and the *Australian Disability Discrimination Act* [11]respectively, environmental sensitivities are characterized as disabilities under broad definitions, and that individuals with MCS do not need to prove the validity of their

[10] *Canadian Human Rights Act* R.S.C., 1985, c -6. Last Amended July 12, 2019. https://laws-lois.justice.gc.ca/eng/acts/h-6/
[11] Australian Disability Discrimination Act. No. 135, 1992. Last Amended April 12, 2018. https://www.legislation.gov.au/Details/C2018C00125

condition in order to receive accommodations in the workplace or from other service providers. Although somewhat dated (and thus may not be completely indicative of current legislative status), Wilkie and Baker (2007) recommended that one of the ways governments across Canada can address the issues revolving around accessibility and accommodations for individuals with disabilities is through the review of building codes since building codes, air quality and ventilation can be barriers for individuals with sensitivities. Wilkie and Baker (2007) noted that since Canadian building codes do not provide accommodation for environmental sensitivities, they are lagging behind United States and Australia building codes. Sears (2007) suggested that the Canadian building standards are not protective of individuals with environmental sensitivities. It was noted that Canadian building codes do not address measuring indoor environmental quality, through assessing the building materials used in the building and ensuring that buildings have been degassed prior to occupancy (Sears, 2007).

As part of a review of various existing public health approaches by the CoA, several governments and non-governmental organizations were contacted to provide information on the status and current treatments of MCS (CoA, 2010). At the Federal level, the review referred to the amendment of the Department of Health Act (Bill C-416) that allowed for research in environmental illnesses, including MCS, and initiated conveyance of MCS information to the general public (CoA, 2010). On a Provincial basis, the government of Nova Scotia was provided as an example. The Nova Scotia Environmental Health Centre was established to provide treatment for individuals with chemical sensitivities. At the municipal scale, the review noted that there are by-laws in place in a number of municipalities which prohibit the use of pesticides and fertilizers (CoA, 2010).

The review by Sears (2007) for the Canadian Human Rights Commission (CHRC) noted that public policy and regulation can play a role in protecting individuals from various triggers of sensitivities (i.e. tobacco smoke, pesticides, fragrance). Sears (2007) recommended that in addition to restriction on pesticide use through pesticide bylaws, anti-idling bylaws should be implemented at the municipal level. Provincially, Sears (2007) noted that clear strategies set forth by government agencies may aid in the availability and use of education and funding of health care programs. The Sears (2007) review for CHRC also recommended that where possible, the least-toxic materials and practices for construction, maintenance, pest control and infrastructure be used to create healthier indoor spaces to help accommodate sensitive individuals and prevent sensitivities from developing.

Two studies proposed the use of the precautionary principle and suggested that a way governments can manage exposures is by creating a framework which regulates the types of chemicals that are made available while also requiring products to have sufficient evidence of its effects on the general population (Eaton et al., 2000; Lipson and Doiron, 2006). It was suggested by Eaton et al. (2000) that governments can also play a role by increasing awareness of the general public about MCS.

5.3.2 Management within Public Health Settings

As discussed in Section 6.1.3, Gibson (2010) noted that public environments where exposures to incitants may occur include libraries, medical offices, grocery stores, community meetings spaces, and many other public spaces. In order to reduce reactions to chemicals for MCS patients, there are a number of approaches that have been presented in the available literature (CoA, 2010; Martini et al., 2013; Public Service Alliance of Canada, 2003; Sears, 2007; Wilkie and Baker, 2007). The strategies and accommodations that were recommended for making public spaces more comfortable for sensitive individuals included the following (CoA, 2010;

Martini et al., 2013; Public Service Alliance of Canada, 2003; Sears, 2007; Wilkie and Baker, 2007):

- The selection and use of cleaning and maintenance products that are not as likely to lead to reactions[12];
- Provision of adequate notice to sensitive individuals within public spaces prior to renovations or other events (*i.e.,* painting, pesticide applications, and cleaning carpets);
- Carpet-free environments;
- Presence of windows that can open;
- Development of a scent free environment, through the avoidance or by minimizing the use of air fresheners, and having scent-free policies;
- The existence of adequate ventilation for buildings to ensure incoming air is clear of possible contamination (*i.e.,* exhaust fumes);
- Availability of portable air cleaners with additional air filter (HEPA and/or charcoal filters);
- Flexible work options, including telecommuting; and,
- The establishment of no-idling policies, where applicable.

Commonwealth of Australia note that hospitals and other health service settings have a responsibility as healthcare provides to provide environments that are considerate of individuals with MCS (2010).

The Canberra Hospital and Health Services have created a regulatory procedure document that outline the standard operating procedures (SOPs) required for their hospital staff and visitors. Individuals, ranging from administrative staff, medical staff, food services and cleaning staff, as well as visitors, have a role in creating an environment that reduces exposures to incitants for patients that require treatment at hospitals (CHHS, 2012). The SOPs that were outlined in the document for admitting individuals with MCS include the use of low irritant cleaning products (*i.e.,* sodium bicarbonate), fragrance free hand wash, cleaning products, and cloths, signs that caution patients of potential exposures (CHHS, 2012). Environments that were determined to be unsuitable for MCS patients included areas under renovation, high traffic areas, and areas with chemical storage (CHHS, 2012). Health care providers are expected to not wear or be exposed to perfumed hygiene products prior to their shifts, not wear new clothing or clothing that has been freshly dry-cleaned as it may still have chemical residue, and not to have cigarette smoke lingering (CHHS, 2012). General care procedures such as those outlined above in the SOPs, give attention to the quality of the patients' experience at hospitals and may improve patients' general wellbeing by reducing their risks of exposure to incitants (CHHS, 2012).

[12] It is important to note that people may react differently to consumer products, and only the affected individual can determine if a they are reactive or not to a particular agent.

5.3.3 Management within Occupational Settings

A number of documents in peer-reviewed and grey literature indicated that MCS can be debilitating in its symptoms and can negatively impact the overall quality of life for individuals with MCS (Government of South Australia, 2010; Lipson and Doiron, 2006; Martini et al., 2013). Gibson and Lindberg (2007) noted that workplace barriers can cause significant disability for individuals with MCS which may lead to financial instability and isolation in addition to their symptoms.

In an ethnographic study conducted by Lipson and Doiron (2006), 35 women with MCS, recognized to be due to workplace exposures, were interviewed. It was addressed in the study that workplace accommodations were difficult to acquire as MCS is a hidden disability and individuals with MCS generally appear to be in good health (Lipson and Doiron, 2006). The participants from the study often reported negative scenarios in which there was a lack of support for individuals with MCS (Lipson and Doiron, 2006).

Lipson and Doiron (2006) also noted that due to the lack of or inadequacy of workplace accommodations, the majority of the participants were terminated or had quit their jobs. In addition, the participants described applying for workers' compensation as being a difficult and lengthy process which often denied their claims due to the lack of legitimacy given to the illness (Lipson and Doiron, 2006). According to Gibson and Lindberg (2007), requests for workplace accommodations are often resisted by employers due to the misconception that accommodations are too difficult or costly. Gibson and Lindberg conducted a survey on 100 individuals with self-identified MCS and it was noted that from the employed group of 58 respondents, 46 individuals had some accommodation from their employer and of those individuals 44% had difficulty acquiring them (2007). Gibson and Lindberg (2007) also noted that individuals that received workplace accommodations showed higher mean life satisfaction scores on the Satisfaction with Life Scale (with possible scores on the scale ranging from 5 to 35) which compared individuals with accommodation (mean life satisfaction of 17.64) and those that did not receive accommodation (mean life satisfaction of 11.2).

The content of many requests for accommodation are often simple changes that may require little effort and expense from the employer (Gibson and Lindberg, 2007; Koch et al., 2006). Documents from primary and grey literature showed that the accommodations that are often requested by workers with MCS are the following (Gibson and Lindberg, 2007; Koch et al., 2006):

- Fragrance-related;
- Area-related (e.g., working from home);
- Cleaning and renovation-related; and
- Ventilation-related.

Although based on information from 12-years ago, Gibson and Lindberg (2007) mentioned that employers often resist requests for accommodations. Marshall et al. (2010) identified that MCS has been recognized as a disability requiring accommodation by both the Ontario Human Rights Commission and the Canadian Human Rights Commission (Marshall et al., 2010). In addition, the Newfoundland and Labrador Human Rights Commission has a document which provides guidelines for accommodation for environmental sensitivities, including MCS (NL Human Rights Commission, 2011). The guidelines provided by the Newfoundland and Labrador Human

Rights Commission discussed a number of topics including discrimination, duty to accommodate, and the challenges associated with accommodation in the workplace (NL Human Rights Commission, 2011). *The Canadian Human Rights Act* requires that where it is determined that an individual or class of individuals has a *bona fide* occupational requirement for accommodation, that accommodation must be provided up to the point of incurring 'undue hardship' upon the individual or organization who would have to accommodate those needs.

The degree to which exposures to triggers impact and limit individuals with MCS varies among individuals. The Job Accommodation Network recommended that employers consider the following questions when determining accommodations for their employees (Saab, 2013):

- What limitations are experienced by employees with MCS?
- How do the limitations impact job performance?
- What tasks/duties are problematic due to the limitations?
- What accommodations can be made available to reduce or remove the limitations? Have there been discussions with employees with MCS.
- Do co-workers require training regarding MCS?

The Job Accommodation Network acknowledged that although there are a wide array of possible accommodations, considering these questions may assist in determining the accommodation methods best suited for the individual suffering with MCS and the workplace (Saab, 2013).

However, it has been also acknowledged that accommodating individuals with MCS may be more challenging than accommodating for some other disabilities (Martini et al., 2013; NL Human Rights Commission, 2011; Saab, 2013). The establishment of policies, such as a scent-free policy that the successful implementation of requires the cooperation from other individuals at the workplace, has been noted posing a potential challenge in the workplace (Martini et al., 2013). Other studies have concluded that more education is required in the workplace to increase awareness about MCS, which may help improve awareness and compliance (Gibson and Lindberg, 2007; Lipson and Doiron, 2006; Wilkie and Baker, 2007). It was also noted by Wilkie and Baker (2007) that if accommodation requests are refused, employers should ensure that the reason for rejection is not due to the lack of clear medical evidence since the knowledge of MCS is still developing.

6.0 LIMITATIONS, UNCERTAINTIES AND DATA GAPS

The limitations, uncertainties and data gaps related to MCS are described in this section.

- The most significant data gap identified in the review is the lack of clear case definition and diagnostic criteria for which there is consensus among international experts and organizations. This deficiency recurred throughout the entire review. The last remarkable revision to the MCS diagnostic criteria was in 2005 by Lacour. Since this time, scientific research focusing on MCS has continued, and a variety of diagnostic criteria have been used in the selection of study participants (if any are used at all). This deficiency affects everything from the development of a concise clinical profile, the consistent diagnosis of patients within and between centres, the design of research studies, to effective health-care management.

- There was a lack of objective information regarding the effects of MCS. The assessment of the condition relied heavily on subjective, self-reported symptoms and in some instances, self-identified causation attribution. It is possible that publication bias may contribute to the type of studies available in the post-2000 literature. The lack of a clearly defined set of diagnostic criteria and widespread recognition of MCS may also affect how studies of MCS are funded and published. For example, studies with less funding may not be as robustly designed and as a result, not be published. Studies with negative findings may also not be published.

- The focus of the assessment, based on the Scope of Work, budget and timeline provided by Alberta Health, was necessarily on the peer-reviewed literature, with the exclusion of review articles and opinion pieces. The purpose in doing this was to identify studies that involved documented methodologies and statistical approaches, and to exclude studies that represent the viewpoints of a few individuals (e.g., case studies) or anecdotal reports to reduce the introduction of bias. It is acknowledged that review documents and other items such as textbook chapters or books written by experienced clinicians and experts in the field may provide additional, helpful scientific information regarding MCS.

- The emphasis on documents published after the year 2000 was completed for practical reasons to help meet the objective of providing a “state of the science” review, with the focus on more recently published information. In the selection of this date, it was considered that science is often iterative in nature, and through the capture of almost two decades of research, an adequate sample of recently published literature had been selected with the identified inclusion criteria. A complete historical review of the entire MCS literature database was not within the intended scope of this review. Further, the literature search was focused specifically on MCS, rather than the various terminologies or conditions that have been identified as being similar to MCS or overlapping with MCS. It is acknowledged that the study of MCS and potentially overlapping conditions dates back several decades. As a result, some of the historical context and potentially useful documents may have been excluded as a result of the structure of the search methdology.

- No Alberta-specific public health information regarding the prevalence, diagnosis or management of MCS was identified during the review. However, a detailed search beyond what was included within the overall search strategy was not completed (e.g., public health officials and organizations were not actively surveyed for information). While some Canadian prevalence data were identified through the CCHS, the actual CCHS information was not easy to access or review. Most of the Canadian information discussed within this report was from the peer-reviewed literature, with some from the grey literature. It is also not clear what, if any, diagnostic criteria or strategies are employed by Alberta and Canadian healthcare practitioners or how consistently these approaches are between provinces or practitioners.

- A large variability in study design was evident.. Some studies reviewed involved less than 10 subjects, while others had hundreds. Several study designs have been used in the literature (case-control, cross-sectional with or without nested case-control, experimental), and each have their pros and cons with respect to the potential for bias and error. There is a very limited amount of longitudinal study data, and no

cohort studies were identified. This is a significant gap, as such studies are useful in assessing the causal influences on disease states.

- Studies that evaluated self-reported MCS (e.g., MCS diagnosed by study participants themselves and not confirmed by a medical professional) were included in the initial literature search and review but are not included within the analysis completed in the main body of the report. However, many of the self-reported MCS studies were well-designed and provide insight into MCS, and summaries are included within an Appendix C to this report.

- It is not clear whether MCS is of relevance to children and adolescents, given the limited amount of information identified during this review for these age groups.

- There is a lack of experimental studies that evaluate multiple doses (e.g., 3 or more) of irritants or odorous VOCs. As a result, it is not clear if there is a dose-response relationship apparent for MCS, particularly in relation to olfactory processing and neurological sensitization/neurogenic inflammation. However, it is recognized that these types of studies could be challenging to complete in sensitive individuals.

- For any studies where chemicals are administered, additional efforts regarding single-or double-blinding the studies may add reliability to the data. For odorants, this might involve the use of masking agents (although it is theoretically possible that an MCS individual could react even to a masking agent as well as the chemical under study). Most of the experimental studies examined in this review were single-blinded and did not involve masking. Some studies had randomized block-type designs, to prevent the individuals from expecting/anticipating exposure to the chemical at any given point during an experiment.

- There is a limited amount of information involving MCS and controlled exposure to chemical mixtures. The challenge studies included typically evaluated exposure to one chemical at a time. However, chemicals are present within indoor and outdoor environments as mixtures. It is not known if the observed responses in the MCS subjects (or lack of responses) would change when another chemical is added to the mix? What would the nature of this effect be - additive, synergistic, less-than-additive and why? These are dilemmas which impact conventional toxicological risk assessments and are also applicable to MCS.

- For the olfactory and neurological sensitization studies, there were notable differences in the mode of delivery of odorants or chemicals to subjects. Some studies involved nasal mask, a nasal olfactometer, chamber studies (with and without nose plugs), scratch and sniff or “Sniffin Sticks’ tests, and aerosolized vapours. There were also no clear, objective measures of exposure consistently used in the studies. This lack of consistency in administration contributes to the overall gap of knowledge regarding dose-response. For these studies, it was also not always clear as to which of the observed effects were physical or psychological.

- As a result of the various study designs, there is some variability in how long study subjects were permitted to become acclimatized or adapted to their study environment, and how their individual sensitivities were managed before, during and after the study. This variation could have affected study outcomes.

- There is a lack of clarity and consistency with respect to comorbidity with other conditions and medication use. As discussed in Section 3.6, several overlapping conditions have been identified for MCS. While many studies did adjust for such variables, due to the vague nature of some of the diagnoses for these conditions, it is not clear how accurate these adjustments have been and how they could have influenced the MCS study data across endpoints.

- The atopic or allergy status of subjects was not always determined consistently in the studies. Until the relationship (if any) of allergy and immune dysfunction and MCS is more refined, the variability that could result in the data as a result of people both with and without allergies or atopic conditions being included in study populations is not known.

- The potential role of memories of previous exposures to odours and the determination of familiar vs. novel, sweet vs. pungent or foul and emotions attached to these sensations may contribute variability to symptom profiles of MCS. It is likely that individuals would vary greatly with respect to emotions attached to odours, and thus their responses would also vary. Within a clinical study context, these factors (memory, emotional responses) are likely challenging to manage and document.

- For the most part, the studies evaluated within Section 4 all were focused on one area (e.g., immune effects, genotype, phenotype, olfactory processing, etc.), perhaps with psychological symptom scoring also being considered. There is a lack of MCS studies that evaluate more than one biological mechanism at a time. The research value in monitoring immunological and genetic endpoints in subjects included in olfactory studies may be something to be considered in future studies.

- There is an apparent gap in the recent literature regarding the potential for autoimmune-like responses to be involved in MCS. Currently, potential overlap between the study of MCS and chemical sensitization is not well elucidated, and further examination is needed.

7.0 SUMMARY AND RECOMMENDATIONS

A detailed review of seven potential lines of research using a modified and qualitative WOE approach for MCS suggest there are two lines of research reveal the greatest weight of evidence based on the consistency and utility of the data. It is possible that biological processes related to olfactory processing, neurologic sensitization/neurogenic inflammation are involved in either the clinical presentation of MCS or contribute to its development. Some of the most commonly reported symptoms in diagnosed MCS involve physiological responses to stimuli (primarily in the brain) and mucosal irritation. The next two most highly ranked areas in the WOE analysis, neurologic dysfunction (specifically, vestibular and auditory dysfunction), and behavioural and psychological factors also may be related to other commonly reported symptoms in diagnosed MCS patients, including dizziness, somatic symptoms, and psychological effects.

Several factors were taken into consideration in the evaluation of the studies, and overall, there was a high degree of variability in the numbers of subjects included in the studies, the inherent uncertainty associated with the diagnosis of MCS, the predominance of case-control and cross-sectional studies with potential inherent bias, variations in statistical analysis, study design and effect measurement, and contradictory results across studies. Taking all this into

account, the overall weight of evidence based on all the information together is considered to be **Moderate: generally good evidence from at least one line of evidence but evidence missing from others.** The study of MCS appears to be continually evolving and over time, the current WOE will likely shift as new information becomes available.

Several areas for future research are noted based on the findings of this review:

1. There is an urgent need for the diagnostic criteria for MCS to be reviewed, updated and harmonized to help ensure proper and consistent diagnosis. The last notable update in the literature was by Lacour et al. (2005), however, the majority of the studies (if they used diagnostic criteria at all during subject recruitment) used the Cullen criteria from 1987 or the 1999 Consensus (Bartha et al., 1999; Graveling et al., 1999). This improvement will likely benefit the individuals with MCS directly but will also eventually lead to a more concise literature database with studies with results that are more directly comparable than what currently exists. At this time, the lack of diagnostic criteria is an inherent gap in the overall quality and weight of evidence for MCS, and also limits the management of MCS as a condition as a result.

2. There is evidence that MCS is a multi-factorial adverse physiological condition that has been reported to affect about 2-3% of the Canadian population and can exhibit itself with both physiological and psychological responses. There is a wide range of symptoms and triggers for MCS reported in the literature, but a clear causal relationship has not been identified. It is also not clear from the scientific literature if there are underlying susceptibilities that potentially pre-dispose some individuals to developing MCS symptoms and not others.

3. The baseline status of MCS patients, the amount of time allowed during studies of the condition and the management of potential sensitivities during the course of studies may affect study outcomes. It may be worthwhile for clinicians to develop an agreed upon approach for the study of MCS patients, potentially involving more defined adaptation periods, exposure protocols and the use of environmentally controlled medical units[13].

4. The results of this review suggest that there is a lack of Alberta-specific public health information regarding the prevalence, diagnosis or management of MCS. There is also a limited amount of available Canadian information regarding MCS diagnosis and management. Improved availability of this information may provide an up-to-date indication of how MCS is diagnosed and managed in Alberta and the other Provinces and promote collaboration and harmonization.

5. Most studies included in this review were of case-control, cross-sectional or experimental design and were necessarily of shorter duration. The completion of

[13] An environmentally-controlled medical unit (EMU) is a section of a hospital of medical facility that allows patients to be accommodated for several days in advance of a study, in an environment that is pristine with minimal emissions of airborne chemicals from building materials or furnishings, with no use of disinfectants, fragrances, pesticides, etc. permitted. Such units should include the use of filters (HEPA or charcoal) to reduce the presence of air contaminants. In addition, it is recommended that pure water and organic foods with an elimination diet or fasting be applied as appropriate to obtain a baseline assessment in a non-triggered state, but after a period of time (4 to 7 days) where any withdrawal symptoms may occur in the absence of environmental triggers. in the patient before a study is commenced. Additional information is available at:
https://tiltresearch.org/provider-resources/environmental-medical-unit/

longitudinal studies including patients with diagnosed MCS to evaluate the development of MCS over time would be of value, particularly with respect to the identification of risk factors and the biological processes involved in MCS.

6. The findings of this review overlap to some extent with the findings of the comprehensive review regarding odours and health (Alberta Health, 2017), with the exception that they are more specific to individuals with MCS. One key difference is that there are no differences in response thresholds for odours between MCS and non-MCS individuals. However, the MCS individuals have a greater degree of physiological and psychological effects, and may have an enhanced ability to identify odours (potentially due to the association of olfactory processing with emotions and differences in the brain regions involved in olfactory processing in individuals with MCS).

7. It may be of value for researchers in the MCS area to collaborate with toxicologists and epidemiologists with respect to study designs and data-sharing relating to the "exposome". The exposome is an assessment of all exposures that an individual might have over a lifetime (starting before birth) and how these exposures relate to health, including the future development of disease (CDC, 2018)[14]. Such tests may be beneficial with respect to the more quantitative physiological features of MCS and understanding what pre-disposes or causes MCS in some individuals but not others, and how MCS progresses as a disease state. It would also be of value for psychological assessments to be incorporated into such studies. The evaluation of epigenetic modifications in MCS may be another interesting area to evaluate.

8. While it is understood that there are certainly ethical considerations with respect to MCS individuals to be mindful of, low dose studies with thorough exposure characterization would be of value in understanding the mechanics of MCS, potentially involving techniques such as imaging or toxicogenomics (to evaluate low-dose gene expression) or computational toxicology tools (e.g., the Comparative Toxicogenomics Database15 or the Integrated Chemical Environment (ICE) Integrator from the National Toxicology Program (NTP)16, among others.

[14] CDC (Centers for Disease Control and Prevention). Exposome and Exposomics. National Institute for Occupational Safety and Health (NIOSH). Available at: https://www.cdc.gov/niosh/topics/exposome/default.html
[15] Comparative Toxicogenomics Database. Available at: http://ctdbase.org/.
[16] NTP (National Toxicology Program). Integrated Chemical Environment (ICE). Available at: https://ice.ntp.niehs.nih.gov/

8.0 REFERENCES

Alobid, I., Nogué, S., Izquierdo-Dominguez, A., Centellas, S., Bernal-Sprekelsen, M., and J. Mullol (2014). Multiple Chemical Sensitivity Worsens Quality of Life and Cognitive and Sensorial Features of Sense of Smell. *European Archives of Oto-Rhino-Laryngology* [online] 271(12), pp. 3203–3208. Available at: https://doi.org/10.1007/s00405-014-3015-5

Andersson, L., Claeson, A.-S., Nyberg, L., Stenberg, B., and Nordin, S. (2014). Brain Responses to Olfactory and Trigeminal Exposure in Idiopathic Environmental Illness (IEI) Attributed to Smells - An fMRI study. *Journal of Psychosomatic Research*, 77(5), pp. 401–408. Available at: https://doi.org/10.1016/j.jpsychores.2014.09.014

Andersson, L., Johansson, A., Millqvist, E., Nordin, S., and Bende, M. (2008). Prevalence and Risk Factors for Chemical Sensitivity and Sensory Hyperreactivity in Teenagers. *International Journal of Hygiene and Environmental Health*, 211(5), pp. 690–697. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1438463908000199?via%3Dihub

Azuma, K., Uchiyama, I., Katoh, T., Ogata, H., Arashidani, K., and Kunugita, N. (2015). Prevalence and Characteristics of Chemical Intolerance: a Japanese population-based study. *Archives of Environmental and Occupational Health,* 70(6), pp. 341–353. Available at: 10.1080/19338244.2014.926855

Azuma, K., Uchiyama, I., Takano, H., Tanigawa, M., Azuma, M., Bamba, I., and Yoshikawa, T. (2013). Changes in Cerebral Blood Flow during Olfactory Stimulation in Patients with Multiple Chemical Sensitivity: A Multi-Channel Near-Infrared Spectroscopic Study. *Plos One*, 8(11), e80567. Available at: https://doi.org/10.1371/journal.pone.0080567

Azuma, K., Uchiyama, I., Tanigawa, M., Bamba, I., Azuma, M., Takano, H., and Sakabe, K. (2015). Assessment of Cerebral Blood Flow in Patients with Multiple Chemical Sensitivity Using Near-Infrared Spectroscopy-Recovery After Olfactory Stimulation: A Case-Control Study. *Environmental Health and Preventive Medicine,* 20(3), pp.185–194. Available at: https://doi.org/10.1007/s12199-015-0448-4

Azuma, K., Uchiyama, I., Tanigawa, M., Bamba, I., Azuma, M., Takano, H., and Sakabe, K. (2016). Association of Odor Thresholds and Responses in Cerebral Blood Flow of the Prefrontal Area during Olfactory Stimulation in Patients with Multiple Chemical Sensitivity. *Plos One*, 11(12), e0168006. Available at: https://doi.org/10.1371/journal.pone.0168006

Bailer, J., Rist, F., Witthöft, M., Paul, C., and Bayerl, C. (2004). Symptom Patterns, and Perceptual and Cognitive Styles in Subjects with Multiple Chemical Sensitivity (MCS). *Journal of Environmental Psychology*, 24(4), pp. 517–525. Available at: https://doi.org/10.1016/j.jenvp.2004.08.002

Bailer, J., Witthöft, M., and Rist, F. (2006). The Chemical Odor Sensitivity Scale: Reliability and Validity of a Screening Instrument for Idiopathic Environmental Intolerance. *Journal of Psychosomatic Research*, 61(1), pp. 71–79. Available at: https://doi.org/10.1016/j.jpsychores.2005.11.005

Baines, C. J., McKeown-Eyssen, G. E., Riley, N., Cole, D. E. C., Marshall, L., Loescher, B., and Jazmaji, V. (2004). Case-Control Study of Multiple Chemical Sensitivity, Comparing Haematology, Biochemistry, Vitamins and Serum Volatile Organic Compound Measures. *Occupational Medicine-Oxford*, 54(6), pp. 408–418. Available at: https://doi.org/10.1093/occmed/kqh083

Bartha, L., Baumzweiger, W., S. Buscher, D., Callender, T., Dahl, K. A., Davidoff, A., and Ziem, G. (1999). Multiple Chemical Sensitivity: A 1999 Consensus. *Archives of Environmental Health*, 54, pp.147–149. Available at: https://doi.org/10.1080/00039899909602251

Becker, R. A., Dellarco, V., Seed, J., Kronenberg, J. M., Meek, B., Foreman, J., Palermo, C., Kirman, C., Linkov, I., Schoeny, R., Dourson, M., Pottenger, L.H., and Manibusan, M. K. (2017). Quantitative Weight of Evidence to Assess Confidence in Potential Modes of Action. *Regulatory Toxicology and Pharmacology,* 86, pp. 205–220. Available at: https://doi.org/10.1016/j.yrtph.2017.02.017

Belpomme, D., Campagnac, C., and Irigaray, P. (2015). Reliable Disease Biomarkers Characterizing and Identifying Electrohypersensitivity and Multiple Chemical Sensitivity as Two Etiopathogenic Aspects of a Unique Pathological Disorder. *Reviews on Environmental Health*, 30(4), pp. 251–271. Available at: https://doi.org/10.1515/reveh-2015-0027

Berg, N. D., Berg Rasmussen, H., Linneberg, A., Brasch-Andersen, C., Fenger, M., Dirksen, A., Vesterhaue, S., Werge, T. and Elberling, J. (2010). Genetic Susceptibility Factors for Multiple Chemical Sensitivity Tevisited. *International Journal of Hygiene and Environmental Health*, 213(2), pp.131–139. Available at: https://doi.org/10.1016/j.ijheh.2010.02.001

Binder, L. M., Storzbach, D., and Salinsky, M. C. (2006). MMPI-2 Profiles of Persons with Multiple Chemical Sensitivity. *Clinical Neuropsychologist*, 20(4), pp. 848–857. Available at: https://doi.org/10.1080/13854040500246927

Binkley, K., King, N., Poonai, N., Seeman, P., Ulpian, C., & Kennedy, J. (2001). Idiopathic Environmental Intolerance: Increased Prevalence of Panic Disorder-Associated Cholecystokinin B Receptor Allele 7. *Journal of Allergy and Clinical Immunology*, 107(5), pp. 887–890. Available at: https://doi.org/10.1067/mai.2001.114798

Bischoff, E., Soetekouw, P., De Vries, M., Scheepers, P. T. J., Bleijenberg, G., and van der Meer, J. W. M. (2003). Chemical Sensitivity in Symptomatic Cambodia Veterans. *Archives of Environmental Health*, 58(12), 740–745. Available at: https://doi.org/10.3200/AEOH.58.12.740-745

Black, D. W., Doebbeling, B. N., Voelker, M. D., Clarke, W. R., Woolson, R. F., Barrett, D. H., and Schwartz, D. A. (2000). Multiple Chemical Sensitivity Syndrome - Symptom Prevalence and Risk Factors in a Military Population. *Archives of Internal Medicine*, 160(8), pp, 1169–1176. Available at: https://doi.org/10.1001/archinte.160.8.1169

Black, D. W., Okiishi, C., and Schlosser, S. (2000). A Nine-Year Follow-Up of People Diagnosed with Multiple Chemical Sensitivities. *Psychosomatics*, 41(3), pp. 253–261. Available at: https://doi.org/10.1176/appi.psy.41.3.253

Black, D. W., Okiishi, C., and Schlosser, S. (2001). The Iowa Follow-up of Chemically Sensitive Persons. *Annals of the New York Academy of Sciences*, 933(1), pp. 48–56. Available at: https://doi.org/10.1111/j.1749-6632.2001.tb05813.x

Bonvini, S. J., and Belvisi, M. G. (2017). Cough and Airway Disease: The Role of Ion Channels. *Pulmonary Pharmacology and Therapeutics*, 47, pp. 21–28. Available at : https://doi.org/10.1016/j.pupt.2017.06.009

Bornschein, S., Hausteiner, C., Drzezga, A., Theml, T., Heldmann, B., Grimmer, T., Perneczky, R., Jahn, T., Schwaiger, M., Zilker, T., and Foerstl, H. (2007). Neuropsychological and Positron Emission Tomography Correlates in Idiopathic Environmental Intolerances. *Scandinavian Journal of Work Environment and Health*, 33(6), pp. 447–453. Available at: https://doi.org/10.5271/sjweh.1164

Bornschein, S., Hausteiner, C., Pohl, C., Jahn, T., Angerer, J., Forstl, H., and Zilker, T. (2008). Pest Controllers: A High-Risk Group for Multiple Chemical Sensitivity (MCS)? *Clinical Toxicology*, 46(3), pp. 193–200. Available at: https://doi.org/10.1080/15563650601185126

Bornschein, S., Hausteiner, C., Zilker, T., and Forstl, H. (2002). Psychiatric and Somatic Disorders and Multiple Chemical Sensitivity (MCS) in 264 "Environmental Patients*." Psychological Medicine*, 32(8), pp. 1387–1394. Available at: https://doi.org/10.1017/S0033291702006554

Busby, L. D. (2017). A Comparison of Multiple Chemical Sensitivity with Other Hypersensitivity Illnesses Suggests Evidence and a Path to Answers. *Ecopsychology*, 9(2). Available at: https://doi.org/10.1089/eco.2017.0003

Brülls, C., Niggemann, H., Weibbach, W., Dott, W., Fischer, M., Blömeke, Merk, H.G., Isselstein, J., Ilgner, J., Westhofen, M. and Wiesmüller, G.A. (2006) Living Conditions at Home of Patients with Self-Reported Multiple Chemical Sensitivity (sMCS), Fragrance Allergies or Nasal Polyps*. HB-2006* Healthy Buildings: Creating a Healthy Indoor Environment for People. pp. 165-168. 9789899506718 (ISBN).

Caccamo, D., Cesareo, E., Mariani, S., Raskovic, D., Ientile, R., Curro, M., Korkina, L, and De Luca, C. (2013). Xenobiotic Sensor- and Metabolism-Related Gene Variants in Environmental Sensitivity-Related Illnesses: A Survey on the Italian Population. *Oxidative Medicine and Cellular Longevity*, Article ID 831969. Available at: https://doi.org/10.1155/2013/831969

Caccappolo-van Vliet, E., Kelly-McNeil, K., Natelson, B., Kipen, H., and Fiedler, N. (2002). Anxiety Sensitivity and Depression in Multiple Chemical Sensitivities and Asthma. *Journal of Occupational and Environmental Medicine*, 44(10), pp. 890–901. Available at: https://doi.org/10.1097/01.jom.0000026646.83602.bb

Caress, S. M., Steinemann, A. C., and Waddick, C. (2002). Symptomatology and Etiology of Multiple Chemical Sensitivities in the Southeastern United States. *Archives of Environmental Health: An International Journal*, 57(5), pp. 429–436. Available at: https://doi.org/10.1080/00039890209601433

Canberra Hospital and Health Services (CHHS). (2012). Canberra Hospital and Health Services Standard Operating Procedure: Multiple Chemical Sensitivities (MCS) - Care of Patients (No. CHHS12/168). ACT Government Health. Available at: https://www.health.act.gov.au/sites/default/files/2019-02/Multiple%20Chemical%20Sensitivities%20Procedure.docx

Chiaravalloti, A., Pagani, M., Micarelli, A., Di, P., Genovesi, G., Alessandrini, M., and Schillaci, O. (2015). Cortical Activity During Olfactory Stimulation in Multiple Chemical Sensitivity: a 18F-FDG PET/CT study. *European Journal of Nuclear Medicine and Molecular Imaging*, 42(5), pp. 733–740. Available at: https://doi.org/10.1007/s00259-014-2969-2

Chun, C., Kim, E., Park, J., and Sung, K. (2006). MCS/IEI and Personal Exposures of VOCs by Job Groups in Construction Worker. VOL. I-Indoor Air Quality (IAQ), Building Related Diseases and Human Response, pp. 225.

Chun, C., Sung, K., Kim, E., and Park, J. (2010). Self-reported multiple chemical sensitivity symptoms and personal volatile organic compounds exposure concentrations in construction workers. *Building and Environment*, 45(4), pp. 901–906. Available at: https://doi.org/10.1016/j.buildenv.2009.09.008

Claeson, A.-S., and Andersson, L. (2017). Symptoms from Masked Acrolein Exposure Suggest Altered Trigeminal Reactivity in Chemical Intolerance. *Neurotoxicology*, 60, pp. 92–98. Available at: https://doi.org/10.1016/j.neuro.2017.03.007

Commonwealth of Australia (CoA). (2010). A Scientific Review of Multiple Chemical Sensitivity: Identifying Key Research Needs. National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and the Office of Chemical Safety and Environmental Health (OCSEH). Available at: http://www.sacfs.asn.au/news/2010/12/12_06_nicnas_mcs_report_final_report_and_submissions.htm

Cullen, M. R. (1987). The Worker with Multiple Chemical Sensitivities: An Overview. *Occupational Medicine*, 2(4), pp. 655–661.

Dantoft, T. M., Elberling, J., Brix, S., Szecsi, P. B., Vesterhauge, S., and Skovbjerg, S. (2014). An Elevated Pro-Inflammatory Cytokine Profile in Multiple Chemical Sensitivity. *Psychoneuroendocrinology*, 40, pp. 140-150. Available at: https://doi.org/10.1016/j.psyneuen.2013.11.012

Dantoft, T. M., Skovbjerg, S., Andersson, L., Claeson, A.-S., Engkilde, K., Lind, N., Nordin, S., Hellgren, L. I. (2017). Gene Expression Profiling in Persons with Multiple Chemical Sensitivity Before and After a Controlled n-butanol Exposure Session. *BMH Open*, 7(2), e013879. Available at: https://doi.org/10.1136/bmjopen-2016-013879

Dantoft, T. M., Skovbjerg, S., Andersson, L., Claeson, A.-S., Lind, N., Nordin, S., and Brix, S. (2015). Inflammatory Mediator Profiling of n-butanol Exposed Upper Airways in Individuals with Multiple Chemical Sensitivity. *Plos One*, 10(11), e0143534. Available at: https://doi.org/10.1371/journal.pone.0143534

Davidoff, A. L., Fogarty, L., and Keyl, P. M. (2000). Psychiatric Inferences from Data on Psychologic/Psychiatric Symptoms in Multiple Chemical Sensitivities Syndrome. *Archives of Environmental Health*, 55(3), pp. 165–175. Available at: https://doi.org/10.1080/00039890009603402

De Luca, C., Gugliandolo, A., Calabro, C., Curro, M., Ientile, R., Raskovic, D., Korkina, L. Caccamo, D. (2015). Role of Polymorphisms of Inducible Nitric Oxide Synthase and Endothelial Nitric Oxide Synthase in Idiopathic Environmental Intolerances. *Mediators of Inflammation*, UNSP 245308. Available at: https://doi.org/10.1155/2015/245308

De Luca, C., Scordo, M. G., Cesareo, E., Pastore, S., Mariani, S., Maiani, G., Stancato, A., Loreti, B., Valacchi, G., Lubrano, C., Rascovic, D., De Padova, L., Genovesi, G., and Korkina, L. G. (2010). Biological Definition of Multiple Chemical Sensitivity from Redox State and Cytokine Profiling and Not From Polymorphisms of Xenobiotic-Metabolizing Enzymes. *Toxicology and Applied Pharmacology*, 248(3), pp. 285–292. Available at: https://doi.org/10.1016/j.taap.2010.04.017

Eaton, K. K., Anthony, H. M., Birtwistle, S., Downing, D., Freed, D. L. J., Howard, J. M., Maberly, D.J., Mansfield J.R., Myhill, S. and Radcliffe, M. J. (2000). Multiple Chemical Sensitivity: Recognition and Management. A Document on the Health Effects of Everyday Chemical Exposures and Their Implications. *Journal of Nutritional and Environmental Medicine*, 10(1), pp. 39–84. Available at: https://doi.org/10.1080/13590840050000889

Eis, D., Helm, D., Muehlinghaus, T., Birkner, N., Dietel, A., Eikmann, T., Gieler, U., Herr, C., Lacour, M., Nowak, D., Pedrosa, G.F., Podoll, K., Renner, B., Wiesmüller, G., and Worm, M. (2008). The German Multicentre Study on Multiple Chemical Sensitivity (MCS). *International Journal of Hygiene and Environmental Health*, 211(5–6), pp. 658–681. Available at https://doi.org/10.1016/j.ijheh.2008.03.002

Fox, R. A., Joffres, M. R., Sampalli, T., and Casey, J. (2007). The Impact of a Multidisciplinary, Holistic Approach to Management of Patients Diagnosed With Multiple Chemical Sensitivity on

Health Care Utilization Costs: An Observational Study. *Journal of Alternative and Complementary Medicine*, 13(2), pp. 223–229. Available at: https://doi.org/10.1089/acm.2006.6011

García-Sierra, R., and Álvarez-Moleiro, M. (2014). Evaluation of Suffering in Individuals with Multiple Chemical Sensitivity. *Clinica y Salud*, 25(2), pp. 95–103. Available at: https://doi.org/10.1016/j.clysa.2014.06.006

Genuis, S. J. (2013). Chemical Sensitivity: Pathophysiology or Pathopsychology? *Clinical Therapeutics*, 35(5), 572–577. Available at: https://doi.org/10.1016/j.clinthera.2013.04.003

Genuis, S. J., and Kyrillos, E. (2017). The Chemical Disruption of Human Metabolism. *Toxicology Mechanisms and Methods*, 27(7), pp. 477–500. Available at: https://doi.org/10.1080/15376516.2017.1323986

Genuis, S. J., and Tymchak, M. G. (2014). Approach to Patients with Unexplained Multimorbidity with Sensitivities. *Canadian Family Physician*, 60(6), pp. 533–538. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4055318/pdf/0600533.pdf

Georgellis, A., Lindelof, B., Lundin, A., Arnetz, B., and Hillert, L. (2003). Multiple Chemical Sensitivity in Male Painters; A Controlled Provocation Study. *International Journal of Hygiene and Environmental Health*, 206(6), pp. 531–538. Available at: https://doi.org/10.1078/1438-4639-00253

Gibson, P. R. (2010). Of the world but not in it: Barriers to Community Access and Education for Persons with Environmental Sensitivities. Health Care for Women International, 31(1), pp. 3-16. Available at: https://doi.org/10.1080/07399330903042823

Gibson, P. R., and Lindberg, A. (2007). Work Accommodation for People with Multiple Chemical Sensitivity. *Disability and Society*, 22(7), pp. 717–732. Available at: https://doi.org/10.1080/09687590701659576

Gibson, P. R., and Lindberg, A. (2011). Physicians' Perceptions and Practices Regarding Patient Reports of Multiple Chemical Sensitivity. *ISRN Nursing,* 2011. Available at: https://doi.org/10.5402/2011/838930

Gibson, P. R., Lockaby, S. D., and Bryant, J. M. (2016). Experiences of Persons with Multiple Chemical Sensitivity with Mental Health Providers. *Journal of Multidisciplinary Healthcare*, p. 9. Available at: https://doi.org/10.2147/JMDH.S100688

Gibson, P. R., and Vogel, V. M. (2009). Sickness-Related Dysfunction in Persons with Self-Reported Multiple Chemical Sensitivity at Four Levels of Severity. *Journal of Clinical Nursing*, 18(1), pp. 72–81. Available at: https://doi.org/10.1111/j.1365-2702.2008.02439.x

Government of Alberta (2017). Odours and Human Health [PDF, ISBN 978-1-4601-3153-4]. Edmonton, Alberta: Environmental Public Health Science Unit, Health Protection Branch, Public Health and Compliance Division, Alberta Health. Available at: https://open.alberta.ca/dataset/04b23f8e-eec1-48bb-b69c-2625ab6a2a08/resource/b87aeb58-f1f7-4c70-a07e-6440f0b1d613/download/odours-and-human-health-2017-final.pdf

Government of South Australia. (2010). A Review of the Multiple Chemical Sensitivity (MCS) Guidelines for South Australian Hospitals 2010. Government of South Australia. Available at: https://www.sahealth.sa.gov.au/wps/wcm/connect/ff826a004f0e15b79823fe9ea2e2f365/MCS+hosp+Guideline+Review+report+2016.FINAL.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-ff826a004f0e15b79823fe9ea2e2f365-mN5FSXQ

Graveling, R. A., Pilkington, A., George, J. P., Butler, M. P., and Tannahill, S. N. (1999). A Review of Multiple Chemical Sensitivity. *Occupational and Environmental Medicine*, 56(2), pp. 73–85. Available at: https://oem.bmj.com/content/56/2/73

Halapy, E., and Parlor, M. (2013). The Quantitative Data: Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS), Fibromyalgia (FM), Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Ontario Ministry of Health and Long-term Care, Ontario Trillium Foundation.

Hausteiner, C., Bornschein, S., Hansen, J., Zilker, T., and Förstl, H. (2005). Self-Reported Chemical Sensitivity in Germany: A Population-Based Survey. *International Journal of Hygiene and Environmental Health*, 208(4), pp. 271–278. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1438463905000684?via%3Dihub

Hausteiner, C., Mergeay, A., Bornschein, S., Zilker, T., and Forstl, H. (2006). New Aspects of Psychiatric Morbidity in Idiopathic Environmental Intolerances. *Journal of Occupational and Environmental Medicine*, 48(1), pp. 76–82. Available: https://doi.org/10.1097/01.jom.0000182207.68987.d7

Hillert, L., Jovanovic, H., Ahs, F., and Savic, I. (2013). Women with Multiple Chemical Sensitivity Have Increased Harm Avoidance and Reduced 5-HT1A Receptor Binding Potential in the Anterior Cingulate and Amygdala. *Plos One*, 8(1), e54781. Available at: https://doi.org/10.1371/journal.pone.0054781

Hillert, L., Musabasic, V., Berglund, H., Ciumas, C.,and Savic, I. (2007). Odor Processing in Multiple Chemical Sensitivity. *Human Brain Mapping*, 28, pp. 172–82. Available at: https://doi.org/10.1002/hbm.20266

Hojo, S., Kumano, H., Ishikawa, S., Miyata, M., Matsui, T., and Sakabe, K. (2007). Indoor Air Contaminants as the Most Common Onset Factor of Multiple Chemical Sensitivity in Japan. Available at: https://waseda.pure.elsevier.com/en/publications/indoor-air-contaminants-as-the-most-common-onset-factor-of-multip

Hojo, S., Kumano, H., Yoshino, H., Kakuta, K., and Ishikawa, S. (2003). Application of Quick Environment Exposure Sensitivity Inventory (QEESI (c)) for Japanese population: study of reliability and validity of the questionnaire. *Toxicology and Industrial Health*, 19(2–6), pp. 41-49. Available at: https://doi.org/10.1191/0748233703th180oa

Hojo, S., Sakabe, K., Ishikawa, S., Miyata, M., and Kumano, H. (2009). Evaluation of Subjective Symptoms of Japanese Patients with Multiple Chemical Sensitivity using QEESI (c). *Environmental Health and Preventive Medicine*, 14(5), pp. 267–275. Available at: https://doi.org/10.1007/s12199-009-0095-8

Hojo, S., Yoshino, H., Kumano, H., Kakuta, K., Miyata, M., Sakabe, K., Matsui, T., Ikeda, K., Nozaki, A., and Ishikawa, S. (2005). Use of QEESI (c) Questionnaire for a Screening Study in Japan. *Toxicology and Industrial Health*, 21(5–6), pp. 113–124. Available at: https://doi.org/10.1191/0748233705th219oa

Holst, H., Arendt-Nielsen, L., Mosbech, H., and Elberling, J. (2011). Increased Capsaicin-induced Secondary Hyperalgesia in Patients With Multiple Chemical Sensitivity. *Clinical Journal of Pain*, 27(2), pp. 156-162. Available at: https://doi.org/10.1097/AJP.0b013e3181f9d60c

Holst, H., Arendt-Nielsen, L., Mosbech, H., Serup, J., and Elberling, J. (2011). Capsaicin-Induced Neurogenic Inflammation in the Skin in Patients with Symptoms Induced by Odorous Chemicals. *Skin Research and Technology*, 17(1), pp. 82–90. Available at: https://doi.org/10.1111/j.1600-0846.2010.00470.x

Holst, H., Arendt-Nielsen, L., Mosbech, H., Vesterhauge, S., and Elberling, J. (2010). The Capsaicin Cough Reflex in Patients with Symptoms Elicited by Odorous Chemicals. *International Journal of Hygiene and Environmental Health*, 213(1), pp. 66-71. Available at: https://doi.org/10.1016/j.ijheh.2009.08.005

Hüppe, M., Ohnsorge, P., Krauß, B., and Schmucker, P. (2000). Der MCSFragebogen: erste Befunde eines neuen Verfahrens zur Beschreibung MCS-auslösender Stoffe und Symptome. Umweltmed. Forsch. Prax.

Jeong, I., Kim, I., Park, H. J., Roh, J., Park, J.-W., and Lee, J.H. (2014). Allergic Diseases and Multiple Chemical Sensitivity in Korean Adults. Allergy Asthma and Immunology *Research*, 6(5), pp. 409-414. Available at: https://doi.org/10.4168/aair.2014.6.5.409

Joffres, M. R., Williams, T., Sabo, B., and Fox, R. A. (2001). Environmental Sensitivities: Prevalence of Major Symptoms in a Referral Center: the Nova Scotia Environmental Sensitivities Research Center Study. *Environmental Health Perspectives*, 109(2), pp. 161-165. Available at: https://dx.doi.org/10.1289%2Fehp.01109161

Klaassen, C. D. (2018). Casarett & Doulls Toxicology The Basic Science of Poisons (9th edition). McGraw-Hill Education / Medical.

Koch, L., Vierstra, C., and Penix, K. (2006). A Qualitative Investigation of the Psychosocial Impact of Multiple Chemical Sensitivity. *Journal of Applied Rehabilitation Counseling*, 37, pp. 33-40. Available at: doi: 10.1891/0047-2220.37.3.33

Kutsogiannis, D. J., and Davidoff, A. L. (2001). A Multiple Center Study of Multiple Chemical Sensitivity Syndrome. *Archives of Environmental Health*, 56(3), pp. 196-207. Available at: https://doi.org/10.1080/00039890109604443

Labarge, A. S., and McCaffrey, R. J. (2000). Multiple Chemical Sensitivity: A Review of the Theoretical and Research Literature. *Neuropsychology Review*, 10(4), pp. 183-211. Available at: https://doi.org/10.1023/A:1026460726965

Lacour, M., Zunder, T., Schmidtke, K., Vaith, P., and Scheidt, C. (2005). Multiple Chemical Sensitivity Syndrome (MCS)—Suggestions for an Extension of the US MCS Case Definition. International Journal of Hygiene and Environmental Health, 208(3), pp. 141-151. Available at: https://doi.org/10.1016/j.ijheh.2005.01.017

Lavergne, M. R., Cole, D. C., Kerr, K., and Marshall, L. M. (2010). Functional Impairment in Chronic Fatigue Syndrome, Fibromyalgia, and Multiple Chemical Sensitivity. *Canadian Family Physician*, 56(2), pp. E57-E65. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821254/pdf/0560e57.pdf

Lipson, J. G., and Doiron, N. (2006). Environmental Issues and Work: Women With Multiple Chemical Sensitivities. *Health Care for Women International*, 27(7), pp. 571–584. Available at: https://doi.org/10.1080/07399330600803709

Marshall, L., Bested, A., Molot, J., Kerr, K., and Bray, R. (2010). Environmental Sensitivities-Multiple Chemical Sensitivities Status Report: Advances in Knowledge, and Current Service Gaps. Women's College Hospital. Available at: https://www.ohchr.org/Documents/HRBodies/CRPD/GC/EnvironmentalHealthClinicWomensCollegeArt.9EN.pdf

Martini, A., Iavicoli, S., and Corso, L. (2013). Multiple Chemical Sensitivity and the Workplace: Current Position and Need for an Occupational Health Surveillance Protocol. *Oxidative*

Medicine and Cellular Longevity, PMCID 351457. Available at: https://doi.org/10.1155/2013/351457

McFetridge-Durdle, J. A., Routledge, F. S., Sampalli, T., Fox, R., Livingston, H., and Adams, B. (2009). Hemodynamic Response to Postural Shift in Women with Multiple Chemical Sensitivities. *Biological Research for Nursing*, 10(3), pp. 267–273. Available at: https://doi.org/10.1177/1099800408324251

McKeown-Eyssen, G., Baines, C., Cole, D. E., Riley, N., Tyndale, R. F., Marshall, L., and Jazmaji, V. (2004). Case-Control study of Genotypes in Multiple Chemical Sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. *International Journal of Epidemiology*, 33(5), pp. 971–978. Available at: https://doi.org/10.1093/ije/dyh251

McKeown-Eyssen, G. E., Sokoloff, E. R., Jazmaji, V., Marshall, L. M., and Baines, C. J. (2000). Reproducibility of the University of Toronto Self-Administered Questionnaire Used to Assess Environmental Sensitivity. *American Journal of Epidemiology*, 151(12), pp. 1216-1222. Available at: https://doi.org/10.1093/oxfordjournals.aje.a010172

Micarelli, A., Viziano, A., Bruno, E., Micarelli, E., and Alessandrini, M. (2016). Vestibular Impairment in Multiple Chemical Sensitivity: Component Analysis Findings. *Journal of Vestibular Research*, 26(5-6), pp. 459-468. Available at: https://doi.org/10.3233/VES-160594

Micarelli, A., Viziano, A., Genovesi, G., Bruno, E., Ottaviani, F., and Alessandrini, M. (2016). Lack of Contralateral Suppression in Transient-Evoked Otoacoustic Emissions in Multiple Chemical Sensitivity: A Clinical Correlation Study. *Noise and Health,* 18(82), pp. 143-149. Available at: https://doi.org/10.4103/1463-1741.181997

Micarelli, A., Viziano, A., Micarelli, E., Genovesi, G., Bruno, E., and Alessandrini, M. (2016). Deranged Dimensionality of Vestibular Re-Weighting in Multiple Chemical Sensitivity. *Applied Sciences-Basel*, 6(11), p. 330. Available at: https://doi.org/10.3390/app6110330

Miller, C. (1998). Quick Environmental Exposure and Sensitivity Inventory (QEESI©). Available at: http://drclaudiamiller.com/wp-content/uploads/2012/01/qeesi.pdf.

Miller, C. S., and Prihoda, T. J. (1999). The Environmental Exposure and Sensitivity Inventory (EESI): a Standardized Approach for Measuring Chemical Intolerances for Research and Clinical Applications. *Toxicology and Industrial Health*, 15(3-4), pp. 370–385. Available at: https://doi.org/10.1177/074823379901500311

Mobini, S. (2015). Psychology of Medically Unexplained Symptoms: A Practical Review. *Cogent Psychology*, 2(1), 1033876. Available at: https://doi.org/10.1080/23311908.2015.1033876

Nethercott, J. R., Davidoff, L. L., Curbow, B., and Abbey, H. (1993). Multiple Chemical Sensitivities Syndrome: Toward a Working Case Definition. *Archives of Environmental Health*, 48(1), pp. 19-26. Available at: https://doi.org/10.1080/00039896.1993.9938389

NL Human Rights Commission. (2011). Guidelines for Accommodation of Environmental Sensitivities.

Nogami, H., Odajima, H., Shoji, S., Shimoda, T., and Nishima, S. (2004). Capsaicin Provocation Test as a Diagnostic Method for Determining Multiple Chemical Sensitivity. *Allergology International*, 53(2), pp, 153-157. Available at: https://doi.org/10.1111/j.1440-1592.2004.00317.x

Nordin. S, Millqvist, E., Löwhagen, and Bende, M. (2004). A Short Chemical Sensitivity Scale for Assessment of Airway Sensory Hyperreactivity. *International Archives of Occupational and Environmental Health*, 77(4), pp. 249-254. Available at: https://doi.org/10.1007/s00420-004-0504-7

National Research Council (NRC). (1992). Multiple Chemical Sensitivities: Addendum to Biologic Markers in Immunotoxicology. Available at: https://doi.org/10.17226/1988

Ojima, M., Tonori, H., Sato, T., Sakabe, K., Miyata, M., Ishikawa, S., and Aizawa, Y. (2002). Odor Perception in Patients with Multiple Chemical Sensitivity. *Tohoku Journal of Experimental Medicine*, 198(3), pp. 163-173. Available at: https://doi.org/10.1620/tjem.198.163

Omar, S., Clarke, R., Abdullah, H., Brady, C., Corry, J., Winter, H., Touzelet, O., Power, U.F., Lundy, F., McGarvey, L.P.A., Cosby, S. L. (2017). Respiratory Virus Infection Up-regulates TRPV1, TRPA1 and ASICS3 Receptors on Airway Cells. *PloS One*, 12(2), e0171681. Available at: https://doi.org/10.1371/journal.pone.0171681

Orriols, R., Costa, R., Cuberas, G., Jacas, C., Castell, J., and Sunyer, J. (2009). Brain Dysfunction in Multiple Chemical Sensitivity. *Journal of the Neurological Sciences*, 287(1-2), pp. 72–78. Available at: https://doi.org/10.1016/j.jns.2009.09.003

Österberg, K., Karlson, B., and Orbaek, P. (2002). Personality, Mental Distress, and Risk Perception in Subjects with Multiple Chemical Sensitivity and Toxic Encephalopathy. *Scandinavian Journal of Psychology*, 43(2), pp. 169–175. Available at: https://doi.org/10.1111/1467-9450.00283

Österberg, K., Ørbæk, P., and Karlson, B. (2002). Neuropsychological Test Performance of Swedish Multiple Chemical Sensitivity Patients - An exploratory study. *Applied Neuropsychology*, 9(3), pp. 139–147. https://doi.org/10.1207/S15324826AN0903_2

Österberg, K., Orbaek, P., Karlson, B., Akesson, B., and Bergendorf, U. (2003). Annoyance and Performance During the Experimental Chemical Challenge of Subjects with Multiple Chemical Sensitivity. *Scandinavian Journal of Work Environment and Health*, 29(1), pp. 40–50. Available at: https://doi.org/10.1207/S15324826AN0903_2

Pall, M. L. (2001). Common Etiology of Posttraumatic Stress disorder, Fibromyalgia, Chronic Fatigue Syndrome and Multiple Chemical Sensitivity via Elevated Nitric Oxide/Peroxynitrite. *Medical Hypotheses,* 57(2), pp. 139-145. Available at: https://doi.org/10.1054/mehy.2001.1325

Papo, D., Eberlein-Konig, B., Berresheim, H. W., Huss-Marp, J., Grimm, V., Ring, J., Behrendt, H., and Winneke, G. (2006). Chemosensory Function and Psychological Profile in Patients with Multiple Chemical Sensitivity: Comparison with Odor-Sensitive and Asymptomatic Controls. *Journal of Psychosomatic Research*, 60(2), pp. 199-209. Available at: https://doi.org/10.1016/j.jpsychores.2005.06.075

Park, J., and Gilmour, H. (2017). Medically Unexplained Physical Symptoms (MUPS) Among Adults in Canada: Comorbidity, Health Care Use and Employment. *Health Reports*, 28(3), pp. 3-8.Available at: https://www150.statcan.gc.ca/n1/pub/82-003-x/2017003/article/14780-eng.pdf

Pigatto, P. D., Minoia, C., Ronchi, A., Brambilla, L., Ferrucci, S. M., Spadari, F., Passoni, M., Somalvico, F., Bombeccari, G.P., and Guzzi, G. (2013). Allergological and Toxicological Aspects in a Multiple Chemical Sensitivity Cohort. *Oxidative Medicine and Cellular Longevity,* UNSP 356235. Available at: https://doi.org/10.1155/2013/356235

Poonai, N., Antony, M., Binkley, K., Stenn, P., Swinson, R., Corey, P., Silverman, F. and Tarlo, S. (2000). Carbon Dioxide Inhalation Challenges in Idiopathic Environmental Intolerances. *Journal of Allergy and Clinical Immunology*, 105(1), pp. S128–S128. Available at: https://doi.org/10.1016/S0091-6749(00)90811-X

Poonai, N. P., Antony, M. M., Binkley, K. E., Stenn, P., Swinson, R. P., Corey, P. Silverman, F.S., and Tarlo, S. M. (2001). Psychological Features of Subjects With Idiopathic Environmental

Intolerance. *Journal of Psychosomatic Research*, 51(3), pp. 537–541. https://doi.org/10.1016/S0022-3999(01)00250-1

Public Service Alliance of Canada (PSAC). (2003). Multiple Chemical Sensitivity at Work: Guide for PSAC Members. Available at: http://psac-ncr.com/guide/multiple-chemical-sensitivity-work-guide-psac-members

Reid, S., Hotopf, M., Hull, L., Ismail, K., Unwin, C., and Wessely, S. (2001). Multiple Chemical Sensitivity and Chronic Fatigue Syndrome in British Gulf War veterans. *American Journal of Epidemiology*, 153(6), pp. 604–609. Available at: https://doi.org/10.1093/aje/153.6.604

Rossi, S., and Pitidis, A. (2017). Multiple Chemical Sensitivity: Review of the State of the Art in Epidemiology, Diagnosis and Future Perspectives. *Journal of Occupational and Environmental Medicine.* Available at: https://doi.org/10.1097/JOM.0000000000001215

Saab, T. D. (2013). Accommodation and Compliance Series: Employees with Multiple Chemical Sensitivity (MCS) and Environmental Illness (EI). U.S. Department of Labor's Office of Disability Employment Policy. Available at: https://askjan.org/media/MCS.html

Saito, M., Kumano, H., Yoshiuchi, K., Kokubo, N., Ohashi, K., Yamamoto, Y., Shinohara, N., Yanagisawa, Y., Sakabe, K., Miyata, M., Ishikawa, S., and Kuboti, T. (2005). Symptom Profile of Multiple Chemical Sensitivity in Actual Life. *Psychosomatic Medicine*, 67(2), pp. 318–325. Available at: 10.1097/01.psy.0000155676.69030.28.

Sampalli, T., Shepherd, M., and Duffy, J. (2011). Clinical Vocabulary as a Boundary Object in Multidisciplinary Care Management of Multiple Chemical Sensitivity, A Complex and Chronic Condition. *Journal of Multidisciplinary Healthcare*, 4, pp. 91–102. Available at: https://doi.org/10.2147/JMDH.S17564

Sampalli, T., Shepherd, M., Duffy, J., and Fox, R. (2010). An Evaluation of SNOMED CT® in the Domain of Complex Chronic Conditions. *International Journal of Integrated Care*, 10(e038). Available at: https://doi.org/10.5334/ijic.514

Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). (2012). Memorandum on The Use of the Scientific Literature for Human Health Risk Assessment Purposes – Weighing of Evidence and Expression of Uncertainty. Available at: https://www.ices-emfsafety.org/wp-content/uploads/2014/11/scenihr.pdf

Sears, M. (2007). The Medical Perspective on Environmental Sensitivities. Canadian Human Rights Comission. Available at: https://www.chrc-ccdp.gc.ca/eng/content/medical-perspective-environmental-sensitivities

Shinohara, N., Mizukoshi, A., and Yanagisawa, Y. (2004). Identification of Responsible Volatile Chemicals that Induce Hypersensitive Reactions to Multiple Chemical Sensitivity Patients. *Journal of Exposure Analysis and Environmental Epidemiology*, 14(1), pp. 84–91. https://doi.org/10.1038/sj.jea.7500303

Skovbjerg, S., Brorson, S., Rasmussen, A., Johansen, J. D., and Elberling, J. (2009). Impact of self-reported multiple chemical sensitivity on everyday life: a qualitative study. *Scandinavian Journal of Social Medicine*, 37(6), 621–626. Available at: https://doi.org/10.1177/1403494809105430

Skovbjerg, S., Johansen, J. D., Rasmussen, A., Thorsen, H., and Elberling, J. (2009). General Practitioners' Experiences with Provision of Healthcare to Patients with Self-Reported Multiple Chemical Sensitivity. *Scandinavian Journal of Primary Health Care*, 27(3), pp. 148–152. Available at: https://doi.org/10.1080/02813430902888355

Statistics Canada. (2016). Canadian Community Health Survey - Annual Component (CCHS). Retrieved January 24, 2018, from http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3226

Swoboda, D. A. (2008). Negotiating the Diagnostic Uncertainty of Contested Illnesses: Physician Practices and Paradigms. Health, 12(4), pp. 453–478. Available at: https://doi.org/10.1177/1363459308094420

Ternesten-Hasseus, E., Bende, M., and Millqvist, E. (2002). Increased Capsaicin Cough Sensitivity in Patients with Multiple Chemical Sensitivity. *Journal of Occupational and Environmental Medicine*, 44(11), pp. 1012–1017. Available at: https://doi.org/10.1097/01.jom.0000034349.94005.3d

Tonori, H., Aizawa, Y., Ojima, M., Miyata, M., Ishikawa, S., and Sakabe, K. (2001). Anxiety and Depressive States in Multiple Chemical Sensitivity. *Tohoku Journal of Experimental Medicine*, 193(2), pp. 115–126. Available at: https://doi.org/10.1620/tjem.193.115

Tran, M. T. D., Arendt-Nielsen, L., Kupers, R., and Elberling, J. (2013). Multiple chemical sensitivity: On the Scent of Central Sensitization. *International Journal of Hygiene and Environmental Health*, 216(2), pp. 202–210. Available at: https://doi.org/10.1016/j.ijheh.2012.02.010

Viziano, A., Micarelli, A., and Alessandrini, M. (2017). Noise Sensitivity and Hyperacusis in Patients Affected by Multiple Chemical Sensitivity*. International Archives of Occupational and Environmental Health*, 90(2), pp. 189–196. Available at: doi: 10.1007/s00420-016-1185-8

Weiss, E.M., Singewald, E., Baldus, C., Hofer, E., Marksteiner, J., Nasrouei, S., Ruepp, B., Kapfhammer, H.P., Fitz, W., Mai, C., Bauer, A., Papousek, I., and Holzer, P. (2017). Differences in Psychological and Somatic Symptom Cluster Score Profiles Between Subjects with Idiopathic Environmental Intolerance, Major Depression and Schizophrenia. *Psychiatry Research*, 249, pp. 187–194. Available at: https://doi.org/10.1016/j.psychres.2016.12.057

World Health Organization, International Programme on Chemical Safety (WHO IPCS). (1996). Report of the Workshop on Multiple Chemical Sensitivities (MCS), Berlin, Germany, 21-23 February 1996. Available at: http://www.who.int/iris/handle/10665/63109254.

Wilkie, C., and Baker, D. (2007). Accommodation for Environmental Sensitivities: Legal Perspective. Canadian Human Rights Commission. Available at: https://www.chrc-ccdp.gc.ca/eng/content/accommodation-environmental-sensitivities-legal-perspective

Witthöft, M., Gerlach, A. L., and Bailer, J. (2006). Selective Attention, Memory Bias, and Symptom Perception in Idiopathic Environmental Intolerance and Somatoform Disorders. *Journal of Abnormal Psychology*, 115(3), pp. 397–407. Available at: https://doi.org/10.1037/0021-843X.115.3.397

Witthöft, M., Rist, F., and Bailer, J. (2008). Evidence for a Specific Link Between the Personality Trait of Absorption and Idiopathic Environmental Intolerance. *Journal of Toxicology and Environmental Health-Part A Current Issues*, 71(11–12), pp. 795–802. Available at: https://doi.org/10.1080/15287390801985687

Witthöft, M., Rist, F., and Bailer, J. (2009). Abnormalities in cognitive-emotional information processing in idiopathic environmental intolerance and somatoform disorders. *Journal of Behavior Therapy and Experimental Psychiatry*, 40(1), pp. 70–84. Available at: https://doi.org/10.1016/j.jbtep.2008.04.002

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Diagnosis, Symptoms and Prevalence of MCS				
Alobid, I.; Noguue, S.; Izquierdo-Dominguez, A.; Centellas, S.; Bernal-Sprekelsen, M.; Mullol, J.	Multiple chemical sensitivity worsens quality of life and cognitive and sensorial features of sense of smell	Alobid, I., Nogué, S., Izquierdo-Dominguez, A., Centellas, S., Bernal-Sprekelsen, M., & Mullol, J. (2014). Multiple chemical sensitivity worsens quality of life and cognitive and sensorial features of sense of smell. *European Archives of Oto-Rhino-Laryngology*, *271*(12), 3203–3208.	In the case-control study, 58 diagnosed female MCS patients and 60 controls underwent the Barcelona Smell Test 24, and the QEESI© to measure the sense of smell and quality of life. The results found that compared to the controls, MCS subjects showed significant impairment in smell identification but not in detection. MCS subjects demonstrated nasal hypersensitivity and reported smells as more intense and irritating. Significantly higher impacts on quality of life were also noted for MCS subjects. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Andersson, L.; Johansson, A.; Millqvist, E.; Nordin, S.; Bende, M.	Prevalence and risk factors for chemical sensitivity and sensory hyperreactivity in teenagers	Andersson, L., Johansson, A., Millqvist, E., Nordin, S., & Bende, M. (2008). Prevalence and risk factors for chemical sensitivity and sensory hyperreactivity in teenagers. *International Journal of Hygiene and Environmental Health*, *211*(5), 690–697.	In the cross-sectional study, 401 randomly-selected adolescents answered questionnaires to assess chemical and noise sensitivity, anxiety and depression, while a subgroup of 85 teenagers underwent a capsaicin inhalation test to determine the prevalence of chemical sensitivity and sensory hyperactivity in adolescents. The prevalence of self-reported chemical sensitivity was determined to be 15.6% and 3.7% for chemical sensitivity with behavioural effects. The authors suggest that chemical sensitivities develop later in life. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Andersson, M.J.E.; Andersson, L.; Bende, M.; Millqvist, E.; Nordin, S.	The idiopathic environmental intolerance symptom inventory: Development, evaluation, and application	Andersson, M. J., Andersson, L., Bende, M., Millqvist, E., & Nordin, S. (2009). The idiopathic environmental intolerance symptom inventory: development, evaluation, and application. *Journal of Occupational and Environmental Medicine*, *51*(7), 838–847.	A questionnaire called the IEISI was developed to evaluate symptoms in IEI. A total of 207 self-reported sensitive individuals completed the IEISI in the first round, and only 193 went through a re-test. Participants responded to 82 candidate symptoms and completed 3 subscales of QEESI© for two testing occasions. Five symptom categories were created and based on the 27 commonly reported symptoms. The results showed that the IEISI is a reliable and valid tool to study symptom prevalence in IEI. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Azuma, K.; Uchiyama, I.; Katoh, T.; Ogata, H.; Arashidani, K.; Kunugita, N.	Prevalence and Characteristics of Chemical Intolerance: A Japanese Population-Based Study	Azuma, K., Uchiyama, I., Katoh, T., Ogata, H., Arashidani, K., & Kunugita, N. (2015). Prevalence and characteristics of chemical intolerance: a Japanese population-based study. *Archives of Environmental & Occupational Health*, *70*(6), 341–353.	In the population-based cross-sectional study, 7,245 individuals completed a survey to estimate the prevalence of self-reported chemical intolerance and to examine the demographic characteristics, housing environment, medical history and psychosomatic states in the general Japanese adult population. The results suggest that there are several characteristics associated with chemical intolerances. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms and prevalence.	
Bailer, J.; Witthoft, M.; Rist, F.	The Chemical Odor Sensitivity Scale: Reliability and validity of a screening	Bailer, J., Witthoft, M., & Rist, F. (2006). The Chemical Odor Sensitivity Scale: Reliability and validity of a screening instrument for idiopathic environmental intolerance. *Journal of Psychosomatic Research*, *61*(1),	In the cross-sectional study, the COSS was applied to four different groups (n=1660, n=1300, n=2759, n=166) consisting of students, IEI subjects, and controls to	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
	instrument for idiopathic environmental intolerance	71–79. https://doi.org/10.1016/j.jpsychores.2005.11.005	measure the psychometric qualities for IEI by measures of environmental sensitivity, IEI and symptom scales. The results showed that the COSS was consistent with good factorial, convergent, and discriminant validity for the samples. The COSS and other IEI features were stable across time in a longitudinal sample. The COSS can be a tool to assess self-reported chemical odor sensitivity and to screen for IEI. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms	
Bischoff, E.W.M.A.; Soetekouw, P.M.M.B.; De Vries, M.; Scheepers, P.T.J.; Bleijenberg, G.; Van Der Meer, J.W.M.	Chemical sensitivity in symptomatic Cambodia veterans	Bischoff, E., Soetekouw, P., De Vries, M., Scheepers, P. T. J., Bleijenberg, G., & van der Meer, J. W. M. (2003). Chemical sensitivity in symptomatic Cambodia veterans. *Archives of Environmental Health*, *58*(12), 740–745. https://doi.org/10.3200/AEOH.58.12.740-745	In the cross-sectional study, 76 veterans with diagnosed MCS syndrome and 32 were compared with respect to time spent in service in Cambodia, and self-reported previous exposure to chemicals while in service and upon return. The number of symptomatic veterans which reported having used insect repellant with DEET was higher than the asymptomatic veterans. The study did not support that the symptoms in the total group of veterans could be related to MCS. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms	symptoms
Black, D. W.; Doebbeling, B. N.; Voelker, M. D.; Clarke, W. R.; Woolson, R. F.; Barrett, D. H.;	Multiple chemical sensitivity syndrome - Symptom prevalence and risk factors in a military population	Black, D. W., Doebbeling, B. N., Voelker, M. D., Clarke, W. R., Woolson, R. F., Barrett, D. H., & Schwartz, D. A. (2000). Multiple chemical sensitivity syndrome - Symptom prevalence and risk factors in a military population. *Archives of Internal Medicine*, *160*(8), 1169–1176. https://doi.org/10.1001/archinte.160.8.1169	In a cross-sectional telephone interview, military personnel were surveyed and study participates were randomly drawn. 3695 study participates completed the telephone survey and indicated MCS/IEI prevalence of 3.4%. The conclusions of showed that	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Schwartz, D. A.			self-reported symptoms of MCS are prevalent in the military population, particularly in Gulf War veterans. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of prevalence and symptoms	
Black, D.W.; Okiishi, C.; Schlosser, S.	The Iowa follow-up of chemically sensitive persons	Black, D. W., Okiishi, C., & Schlosser, S. (2001). The Iowa Follow-up of Chemically Sensitive Persons. *Annals of the New York Academy of Sciences*, *933*(1), 48–56. https://doi.org/10.1111/j.1749-6632.2001.tb05813.x	The clinical symptoms and health status was reported from a 9-year follow-up study are discussed. Of the 26 originally surveyed individuals (with diagnosed MCS), 18 were interviewed and completed self-report questionnaires for the follow up in 1997. Compared to the 1988 data for Illness Behavior Questionnaire and SCL-90, there was little change in the follow up data. The results indicated that headache, memory loss, forgetfulness, sore throat, joint aches, trouble thinking, shortness of breath, back pain, muscle aches and nausea were the 10 most frequent complaints. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Bornschein, S.; Hausteiner, C.; Pohl, C.; Jahn, T.; Angerer, J.; Foerstl, H.; Zilker, T.	Pest controllers: A high-risk group for Multiple Chemical Sensitivity (MCS)?	Bornschein, S., Hausteiner, C., Pohl, C., Jahn, T., Angerer, J., Forstl, H., & Zilker, T. (2008). Pest controllers: A high-risk group for multiple chemical sensitivity (MCS)? *Clinical Toxicology*, *46*(3), 193–200. https://doi.org/10.1080/15563650601185126	A sample of 45 pest controllers underwent a physical and laboratory examination with urine screening for pyrethroid metabolites, a psychiatric interview, a neuropsychological test battery, and a chemical sensitivity. The results indicated that neuropsychological testing results were normal, with a few exceptions. The results did not support the hypothesis that work-related pesticide exposure promotes	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			chemical sensitivity. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of tolerance-related MOA	
Brülls, Ch.; Niggemann, H.; Weibach, W.; Dott, W.; Fischer, M.; Blomeke, B.; Merk, H.F.; Isselstein, J.; Ilgner, J.; Westhofen, M.; Wiesmüller, G.A.	Living conditions at home of patients with self-reported multiple chemical sensitivity (SMCS), fragrance allergies or nasal polyps	Brülls, C., Niggemann, H., Wei\s sbach, W., Dott, W., Fischer, M., Blömeke, B., … others. (2006). Living Conditions at Home of Patients with self-reported Multiple Chemical Sensitivity (sMCS), Fragrance Allergies or Nasal Polyps. *VOL. I-Indoor Air Quality (IAQ), Building Related Diseases and Human Response*, 165.	In this cross-sectional study, the relation of self-reported MCS cases, fragrance allergies and nasal polyps to home conditions were statistically analyzed through the use of a questionnaire. The self-reported MCS group consisted of 14 men and 45 women, the fragrance allergy group consisted of 19 men and 25 women and the nasal polyps group consisted of 42 men and 27 women. The MCS group was found to have a higher rate of odour avoidance, reported sensitivities, and time spent indoors. The authors suggest that the responses of the fragrance group may be psychological. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included in discussion of symptoms	
Caress, S.M.; Steinemann, A.C.; Waddick, C.	Symptomatology and etiology of multiple chemical sensitivities in the Southeastern United States	Caress, S. M., Steinemann, A. C., & Waddick, C. (2002). Symptomatology and etiology of multiple chemical sensitivities in the southeastern United States. *Archives of Environmental Health: An International Journal*, *57*(5), 429–436.	A two-phase study of 1,579 randomly selected individuals a telephone-based questionnaire that self-reported chemical hypersensitivity, investigated symptoms, factors that may trigger reactions, associated lifestyle modifications, and the relationship with other illnesses. The second phase was a follow-up to the first questionnaire and focused on the were 221 individuals who reported a hypersensitivity to common chemicals in Phase I, and these individuals were called back for a	Symptoms; there is information perhaps of relevance to behaviour

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			follow-up examination of symptomatology, etiology, potential triggering agents, linkages to other disorders, and lifestyle modifications. The results from the cross-sectional study indicated that the triggers of symptoms included cleaning products, tobacco smoke, perfume, pesticides and car exhaust. In addition, a majority of the subjects experienced "severe" or "somewhat severe" symptoms. In general, physical symptoms emerged first, followed by emotional symptoms in a sub-set of the hypersensitive individuals. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Chun, C.; Kim, E.; Park, J.; Sung, K.	MCS/IEI and personal exposures of VOCS by job groups in construction worker	Chun, C., Kim, E., Park, J., & Sung, K. (2006). MCS/IEI and Personal Exposures of VOCs by Job Groups in Construction Worker. *VOL. I-Indoor Air Quality (IAQ), Building Related Diseases and Human Response*, 225.	Self-reported symptom surveys and personal exposure concentration monitoring were conducted on 3 job groups (exterior worker, interior worker, and office worker) in the construction business. A total of 305 workers responded to a survey, and a randomly selected subset of 15 individuals underwent an assessment of personal VOC (e.g. BTEX) exposures via passive sampling. The results of this study suggested that showed that the interior workers were the most exposed to VOC concentrations, followed by the office worker and then the exterior worker, and that the frequency of self-reported MCS/IEI symptoms were high in all groups. **Quality of study:** ** **Relevant to Objectives:** Yes, will be	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			included under discussion of symptoms.	
Chun, C.; Sung, K.; Kim, E.; Park, J.	Self-reported multiple chemical sensitivity symptoms and personal volatile organic compounds exposure concentrations in construction workers	Chun, C., Sung, K., Kim, E., & Park, J. (2010). Self-reported multiple chemical sensitivity symptoms and personal volatile organic compounds exposure concentrations in construction workers. *Building and Environment*, *45*(4), 901–906.	In this cross-sectional study of a total of 305 interior workers, office workers and exterior workers in the construction business underwent self-reported symptom surveys regarding chemical exposures and hypersensitivity. A total of 5 workers from each group also had personal exposure monitoring completed to assess VOC exposures (e.g. BTEX and styrene). Of the three groups, the interior workers had greatest exposure to VOCs, followed by the office workers and the exterior workers. The self-reported symptom surveys indicated that office workers experienced a relatively high frequency of MCS. To provide context to the results, university students and office workers outside of the construction business were surveyed as a comparison group. The similarity of increased risk for MCS was seen in the office workers outside of the construction business but not as pronounced when the construction workers were compared to the university students. Personal VOC exposures for the interior workers group were described as 'remarkably high' compared to the office worker and exterior groups. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Garcia-Sierra, R.; Ã□lvarez-Moleiro, M.	Evaluation of suffering in individuals with	García-Sierra, R., & Álvarez-Moleiro, M. (2014). Evaluation of suffering in individuals with multiple chemical sensitivity. *Clinica y Salud*, *25*(2), 95–103.	In the correlational study, 125 subjects completed a survey including 3 scales for assessing the impact of MCS and 3 scales	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
	multiple chemical sensitivity	https://doi.org/10.1016/j.clysa.2014.06.006	for assessing suffering. The results show that MCS affects mostly women and the QEESI©, showed high correlation between the QEESI© and suffering scales. MCS generates physical, psychological and existential suffering, where severity of symptoms is what generates most suffering. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms	
Georgellis, A.; Lindelof, B.; Lundin, A.; Arnetz, B.; Hillert, L.	Multiple chemical sensitivity in male painters; a controlled provocation study	Georgellis, A., Lindelof, B., Lundin, A., Arnetz, B., & Hillert, L. (2003). Multiple chemical sensitivity in male painters; a controlled provocation study. *International Journal of Hygiene and Environmental Health*, *206*(6), 531–538. https://doi.org/10.1078/1438-4639-00253	In this controlled provocation study, 14 male painters with self-reported MCS and 15 controls were exposed to various odorous chemicals within an exposure chamber to examine if there are differences in the rating of respiratory and other symptoms and sensations, changes in serum prolactin and cortisol levels and changes in nasal cavity and eye redness. In addition, the mental well-being was also assessed. No significant differences between MCS and control group in the controlled chamber challenges for the sensations of smell or development of CNS related symptoms. The subjective rating of symptoms for irritations was higher for MCS subjects. Serum prolactin levels declined in the MCS group. No definitive conclusions were drawn from the results of the study. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms and neurological factors.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Gibson, P. R.; Placek, E.; Lane, J.; Brohimer, S. O.; Lovelace, A. C. E.	Disability-induced identity changes in persons with multiple chemical sensitivity	Gibson, P. R., Placek, E., Lane, J., Brohimer, S. O., & Lovelace, A. C. E. (2005). Disability-induced identity changes in persons with multiple chemical sensitivity. *Qualitative Health Research*, *15*(4), 502–524. https://doi.org/10.1177/1049732304271960	In the qualitative study, self-reported MCS subjects responded to surveys how the condition affected their identities, and examined the responses for emergent themes. The themes where a loss of a stable, familiar personality, loss of self-positioning, emotional suppression to meet others' expectations, redesigning the planned life, forced growth, struggling with support, discovering the spiritual self, and identity reconsolidation. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms	
Gibson, P.R.; Vogel, V.M.	Sickness-related dysfunction in persons with self-reported multiple chemical sensitivity at four levels of severity	Gibson, P. R., & Vogel, V. M. (2009). Sickness-related dysfunction in persons with self-reported multiple chemical sensitivity at four levels of severity. *Journal of Clinical Nursing*, *18*(1), 72–81.	A survey was conducted on 254 individuals with self-reported MCS to examine symptom inducing chemicals, symptoms and the related behavioral dysfunctions measured by a Sickness Impact Profile. Results indicated the chemicals/products that caused the most symptoms were pesticide, formaldehyde, fresh paint, new carpet, diesel exhaust, perfume and air fresheners. The top 5 rated symptoms were tiredness/lethargy, difficulty concentrating, muscle aches, memory difficulties and long-term fatigue. The results showed that MCS includes serious dysfunction through the Sickness Impact Profile scores. Communication with individuals affected by MCS is needed to further understand the condition and treatment options for the chemical sensitivities. **Quality of study:** **	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Relevant to Objectives: Yes, will be included under discussion of symptoms and management.	
Hausteiner, C.; Bornschein, S.; Hansen, J.; Zilker, T.; Forstl, H.	Self-reported chemical sensitivity in Germany: A population-based survey	Hausteiner, C., Bornschein, S., Hansen, J., Zilker, T., & Förstl, H. (2005). Self-reported chemical sensitivity in Germany: a population-based survey. *International Journal of Hygiene and Environmental Health*, *208*(4), 271–278.	A population-based survey was conducted for 2032 individuals to obtain information about symptoms, environmental triggers, the frequency of self-reported chemical sensitivity, and of the diagnosis of MCS in Germany. Of the respondents, 9% represented self-reported chemical sensitivity and 0.5% diagnosed MCS. The results revealed that headache, fatigue, sleep disturbances, joint pain, mood changes and nervousness were the most common complaints. The prevalence of subjective sensitivity towards chemicals is similar to rates reported from other countries. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Hojo, S.; Kumano, H.; Yoshino, H.; Kakuta, K.; Ishikawa, S.	Application of Quick Environment Exposure Sensitivity Inventory (QEESI©) for Japanese population: study of reliability and validity of the questionnaire	Hojo, S., Kumano, H., Yoshino, H., Kakuta, K., & Ishikawa, S. (2003). Application of Quick Environment Exposure Sensitivity Inventory (QEESI©) for Japanese population: study of reliability and validity of the questionnaire. *Toxicology and Industrial Health*, *19* (2–6), 41–49. https://doi.org/10.1191/0748233703th180oa	In this study, 498 subjects from the general population in Japan underwent the Japanese version of the QEESI© to investigate the reliability and validity of the assessment. The mean scores on 3 subscales were also compared for 131 self-reported MCS patients and 131 controls. Results showed that the sMCS group had scores higher than those for the controls in all subscales. The findings show that the 30 items from the subscales in the QEESI© can be used for surveys, diagnostic assessment and for comparative studies between patients.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Quality of study: ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Hojo, S.; Yoshino, H.; Kumano, H.; Kakuta, K.; Miyata, M.; Sakabe, K.; Matsui, T.; Ikeda, K.; Nozaki, A.; Ishikawa, S.	Use of QEESI© questionnaire for a screening study in Japan	Hojo, S., Yoshino, H., Kumano, H., Kakuta, K., Miyata, M., Sakabe, K., Ishikawa, S. (2005). Use of QEESI© questionnaire for a screening study in Japan. *Toxicology and Industrial Health*, *21*(5–6), 113–124. https://doi.org/10.1191/0748233705th219oa	In the screening study, the QEESI© was applied to 498 subjects who had not been diagnosed with MCS or sick building syndrome but reported symptoms consistent with those conditions. A total 17 patients with valid completed questionnaire were classified as having symptoms suggestive of MCS. Of the 17 subjects, 7 subjects underwent a medical check and an indoor air quality monitoring program, while an additional 6 subjects participated in the air quality monitoring program, and 4 subjects did not participate in either. The subjects that underwent the medical check were clinically diagnosed as having MCS. The results from the indoor air monitoring program showed to have indoor air concentrations of acetaldehyde, formaldehyde, total VOCs, and paradichlorobenzene above the guidelines. This suggests that indoor air pollutants particularly those associated with new built or remodeled homes, may contribute to MCS symptoms. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms and triggers	
Hojo, S.; Ishikawa, S.; Kumano, H.; Miyata, M.; Sakabe, K.	Clinical characteristics of physician-diagnosed patients with multiple chemical sensitivity in	Hojo, S.; Ishikawa, S.; Kumano, H.; Miyata, M.; Sakabe, K. (2008). Clinical characteristics of physician-diagnosed patients with multiple chemical sensitivity in Japan. *Int J Hyg Environ Health* 211: 682-689.	In this retrospective study, clinical patient medical records were studied by using the QEESI© in 106 physician-diagnosed MCS patients according to the 1999 Consensus and to the Japanese diagnostic criteria for	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
	Japan		MCS. The patients QEESI© scores were compared to the symptoms and intolerances previously reported for self-reported patients. The results indicated that the majority of the patients were females with the ages ranging from 10 to 65 years compared to the male patients which were found to be in their 30s. The diagnosed MCS patient group in this study had lower mean QEESI© score than the 4 self-reported patient groups. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Hojo, S.; Sakabe, K.; Ishikawa, S.; Miyata, M.; Kumano, H.	Evaluation of subjective symptoms of Japanese patients with multiple chemical sensitivity using QEESI©	Hojo, S., Sakabe, K., Ishikawa, S., Miyata, M., & Kumano, H. (2009). Evaluation of subjective symptoms of Japanese patients with multiple chemical sensitivity using QEESI© *Environmental Health and Preventive Medicine*, *14*(5), 267–275. https://doi.org/10.1007/s12199-009-0095-8	A study of 103 diagnosed MCS patients and 309 age and sex-matched controls underwent neuroophthalmologic examinations, various questionnaires including the QEESI© and a qualitative chemical intolerance ranking. Results from the groups were compared using logistic regression analysis, receiver operating characteristic analysis, and the Mann-Whitney test. The authors developed Japanese 'cutoff' values for MCS using the QEESI© for the following subscales of chemical intolerance, symptom severity, and life impact were 40, 20, and 10, respectively. If scores exceeded the cutoff values in 2 out of the 3 subscales, the patient can be determined to be suffering from MCS. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Jeong, I.; Kim, I.; Park, H.J.; Roh, J.; Park, J.-W.; Lee, J.-H.	Allergic diseases and multiple chemical sensitivity in Korean adults	Jeong, I., Kim, I., Park, H. J., Roh, J., Park, J.-W., & Lee, J.-H. (2014). Allergic Diseases and Multiple Chemical Sensitivity in Korean Adults. *Allergy Asthma & Immunology Research*, *6*(5), 409–414. https://doi.org/10.4168/aair.2014.6.5.409	Using the QEESI© the prevalence and related factors of MCS was evaluated. 379 participants from the Severance Hospital completed a questionnaire interview on sociodemographic factors, occupational and environmental factors, allergic diseases, and the QEESI©. The results estimated that MCS prevalence was higher in allergic patients than non-allergic patients, and that people with the experience of living in a new house and atopic dermatitis were more at risk of being intolerant to chemicals. **Quality of study: **** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Joffres, M.R.; Williams, T.; Sabo, B.; Fox, R.A.	Environmental sensitivities: Prevalence of major symptoms in a referral center: The Nova Scotia environmental sensitivities research center study	Joffres, M. R., Williams, T., Sabo, B., & Fox, R. A. (2001). Environmental sensitivities: prevalence of major symptoms in a referral center: the Nova Scotia Environmental Sensitivities Research Center Study. *Environmental Health Perspectives*, *109*(2), 161.	Through a questionnaire, 385 individuals with diagnosed MCS were surveyed Results showed that the participants were mostly women, middle-aged individuals. The general symptoms reported included difficulty concentrating, fatigue, forgetfulness, and irritability while symptoms related to irritation were reported to be most common after an exposure to an irritant. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Kutsogiannis, D J; Davidoff, Ann L	A multiple center study of multiple chemical sensitivity syndrome	Kutsogiannis, D. J., & Davidoff, A. L. (2001). A multiple center study of Multiple Chemical Sensitivity syndrome. *Archives of Environmental Health*, *56*(3), 196–207.	The psychometric properties of 2 sets of clinical/epidemiologic criteria for MCS syndrome was evaluated through a multiple center cross-sectional survey of 1,116 patients who had visited	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			occupational, otolaryngology, allergy or clinical ecological clinics. A patient-completed questionnaire assessed medical, psychosocial, and psychological status of self-reported MCS patients to allow for the formulation of 6 domains that were the commonly observed characteristics of MCS. The results showed that the less-stringent 4-domain definition had higher prevalence estimates when compared to the 6-domain definition. The authors recommend the use of both formats for diagnosis of MCS. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms and prevalence	
Lavergne, M.R.; Cole, D.C.; Kerr, K.; Marshall, L.M.	Functional impairment in chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity	Lavergne, M. R., Cole, D. C., Kerr, K., & Marshall, L. M. (2010). Functional impairment in chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. *Canadian Family Physician*, *56*(2), E57–+.	A chart review and clinical information review was conducted to characterize patients with MCS, CFS, or FM. The demographic and socioeconomic characteristics, comorbid diagnoses, duration of illness, health services usage, life stresses, helpful therapeutic strategies and functional impairments were assessed from the 128 patients diagnosed with one or more of MCS, CFS, FM through the Short Form-36. Results showed that the patients showed functional impairment that was consistent with their reported difficulties in daily life. to further etiologic and prognostic research, more education and information resources are required for public and health care providers. **Quality of study:** ***	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Relevant to Objectives: Yes, will be included under discussion of management	
McKeown-Eyssen, G.E.; Sokoloff, E.R.; Jazmaji, V.; Marshall, L.M.; Baines, C.J.	Reproducibility of the University of Toronto self-administered questionnaire used to assess environmental sensitivity	McKeown-Eyssen, G. E., Sokoloff, E. R., Jazmaji, V., Marshall, L. M., & Baines, C. J. (2000). Reproducibility of the University of Toronto self-administered questionnaire used to assess environmental sensitivity. *American Journal of Epidemiology*, *151*(12), 1216–1222.	The reproducibility of the University of Toronto Health Survey was assessed by having 134 respondents who attended several types of medical practices in 1994 completed a second questionnaire, 5 to 7 months after the first one. The questionnaire asks participants to report general health and demographic characteristics, including symptoms that are linked to exposures. The results showed that the survey achieved good reproducibility for self-reporting of MCS symptoms. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
McKeown-Eyssen, G.E.; Baines, C.J.; Marshall, L.M.; Jazmaji, V.; Sokoloff, E.R.	Multiple chemical sensitivity: Discriminant validity of case definitions	McKeown-Eyssen, G. E., Baines, C. J., Marshall, L. M., Jazmaji, V., & Sokoloff, E. R. (2001). Multiple chemical sensitivity: discriminant validity of case definitions. *Archives of Environmental Health: An International Journal*, *56*(5), 406–412.	The University of Toronto's Health Survey self-administered questionnaire was used to determine the validity of MCS definitions. Approximately 61.7% of 4,126 questionnaires were completed and matched to the existing case definitions. The results indicated that environmental health practice had the highest prevalence of reported symptoms when compared to general practices and occupational health and allergy practices. The University of Toronto Health Survey achieved good discrimination and identified patients with higher likelihood of MCS. **Quality of study:** ** **Relevant to Objectives:** Yes, will be	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			included under discussion of symptoms.	
Reid, S.; Hotopf, M.; Hull, L.; Ismail, K.; Unwin, C.; Wessely, S.	Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans	Reid, S., Hotopf, M., Hull, L., Ismail, K., Unwin, C., & Wessely, S. (2001). Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans. *American Journal of Epidemiology*, *153*(6), 604–609. https://doi.org/10.1093/aje/153.6.604	In the cross-sectional survey) of the prevalence of self-reported MCS and CFS was assessed. of 3 cohorts of military personnel, Gulf veterans (n = 3,531), those who had served in Bosnia (n = 2,050), and those serving during the Gulf War but not deployed there (n = 2,614). A survey of chemical exposures was also completed. Results showed that both syndromes were associated with high psychologic morbidity, and that symptoms of CFS and MCS may explain some of the unexplained illness reported by veterans. A potential association between reported pesticide exposure and MCS was identified. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Saito, M.; Kumano, H.; Yoshiuchi, K.; Kokubo, N.; Ohashi, K.; Yamamoto, Y.; Shinohara, N.; Yanagisawa, Y.; Sakabe, K.; Miyata, M.; Ishikawa, S.; Kuboki, T.	Symptom profile of multiple chemical sensitivity in actual life	Saito, M., Kumano, H., Yoshiuchi, K., Kokubo, N., Ohashi, K., Yamamoto, Y. (2005). Symptom profile of multiple chemical sensitivity in actual life. *Psychosomatic Medicine*, *67*(2), 318–325.	In this case-control study, the Ecological Momentary Assessment was used to measure symptoms and active and passive sampling methods. In the study, 18 diagnosed MCS patients and 12 controls were compared with respect to physical and psychological symptoms and the level of chemical exposure via passive sample monitors carried for 1-week. The results indicated that there were some common chemical exposure chemicals, such as formaldehyde, acetaldehyde, and toluene for many of the patients. **Quality of study:** *** **Relevant to Objectives:** Yes, will be	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			included under discussion of symptoms	
Shinohara, N.; Mizukoshi, A.; Yanagisawa, Y.	Identification of responsible volatile chemicals that induce hypersensitive reactions to multiple chemical sensitivity patients	Shinohara, N., Mizukoshi, A., & Yanagisawa, Y. (2004). Identification of responsible volatile chemicals that induce hypersensitive reactions to multiple chemical sensitivity patients. *Journal of Exposure Analysis and Environmental Epidemiology*, *14*(1), 84–91. https://doi.org/10.1038/sj.jea.7500303	In the case-control study, active and passive sampling methods were used to measure carbonyls and VOC exposure to 15 MCS patients and controls. The results showed that the chemicals which induce hypersensitive reactions varied from patient to patient and that the concentrations for some of the MCS patients were far below the WHO and Japanese indoor guidelines. This indicates that MCS patients try keep away from exposures that cause symptoms. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms and triggers	
Skovbjerg, S.; Elberling, J.; Brorson, S.; Rasmussen, A.; Johansen, J.D.	Impact of self-reported multiple chemical sensitivity on everyday life: A qualitative study	Skovbjerg, S., Brorson, S., Rasmussen, A., Johansen, J. D., & Elberling, J. (2009). Impact of self-reported multiple chemical sensitivity on everyday life: a qualitative study. *Scandinavian Journal of Social Medicine*, *37*(6), 621–626.	In a focus group study, 6 women and 6 men with a duration of diagnosed MCS for at least 1 year, and with different occupational conditions were assessed to describe the impact that MCS has on everyday life, the different strategies for management of the condition and the experience with healthcare management. The results found that MCS impacts social relations, lifestyle and occupational conditions and access to health care. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms	
Viziano, A.; Micarelli, A.; Alessandrini, M.	Noise sensitivity and hyperacusis in patients affected by multiple chemical	Viziano, A., Micarelli, A., & Alessandrini, M. (2017). Noise sensitivity and hyperacusis in patients affected by multiple chemical sensitivity. *International Archives of Occupational and Environmental Health*, *90*(2), 189–	In the cross-sectional study, a questionnaire-based survey conducted on 18 diagnosed MCS patients and 20 healthy	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
	sensitivity	196.	age- and gender matched controls to investigate the presence of noise sensitivity and hyperacusis in patients with MCS. The Weinstein Noise Sensitivity Questionnaire and Khalfa Hyperacusis Questionnaire results were compared to the QEESI©. Through an analysis of variance, the MCS patients had higher scores in WNS, HQ and QEESI© when compared to the controls. There is a strong association between WNS, HQ results and MCS symptoms and it suggests that MCS patients have decreased sound tolerance compared to healthy individuals. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included in evaluation of symptoms in the context of noise sensitivity	
Mode of Action – Immunological				
Baines, C. J.; McKeown-Eyssen, G. E.; Riley, N.; Cole, D. E. C.; Marshall, L.; Loescher, B.; Jazmaji, V.	Case-control study of multiple chemical sensitivity, comparing haematology, biochemistry, vitamins and serum volatile organic compound measures	Baines, C. J., McKeown-Eyssen, G. E., Riley, N., Cole, D. E. C., Marshall, L., Loescher, B., & Jazmaji, V. (2004). Case-control study of multiple chemical sensitivity, comparing haematology, biochemistry, vitamins and serum volatile organic compound measures. *Occupational Medicine-Oxford*, *54*(6), 408–418. https://doi.org/10.1093/occmed/kqh083	In this case-control study, the 223 MCS cases and 194 controls underwent routine testing of serum levels of volatile organic compounds (VOCs) to examine the possibility of causality between exposures and dose-response relationships. Results indicated that MCS was negatively associated with lymphocyte counts and total plasma homocysteine, positively associated with mean cell hemoglobin concentration, alanine aminotransferase and serum vitamin B_6; and not associated with thyroid stimulating hormone, folate or serum vitamin B_{12}. MCS cases had higher concentrations of chloroform but lower means of detectable serum levels of	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			ethylbenzene, m&p-xylene, 3-methylpentane and hexane, and of 1,3,5- and 1,2,3-trimethylbenzene, 2- and 3-methylpentane, and m&p-xylene. The findings suggest that MCS is not associated with vitamin deficiency or thyroid dysfunction. The association of lower lymphocyte counts with an increased likelihood of MCS is consistent with the theories of immune dysfunction in MCS. **Quality of study:** *** **Relevant to Objectives:** Yes, study will be included under discussion of immune dysfunction	
Berg, N.D.; Linneberg, A.; Thyssen, J.P.; Dirksen, A.; Elberling, J.	Non-allergic cutaneous reactions in airborne chemical sensitivity - A population-based study	Non-allergic cutaneous reactions in airborne chemical sensitivity – A population-based study - ScienceDirect. (2011). Retrieved October 5, 2017, from http://www.sciencedirect.com/science/article/pii/S1438463911000046	The relationship between cutaneous reactions from patch testing and self-reported chemical sensitivity was investigated through a population-based study with 3,460 individuals, which were sub-divided into four levels of sensitivity. The results suggested that increased non-allergic cutaneous reactions are significantly associated with severely affected individuals. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	immune
Dantoft, T. M.; Elberling, J.; Brix, S.; Szecsi, P. B.; Vesterhauge, S.; Skovbjerg, S.	An elevated pro-inflammatory cytokine profile in multiple chemical sensitivity	Dantoft, T. M., Elberling, J., Brix, S., Szecsi, P. B., Vesterhauge, S., & Skovbjerg, S. (2014). An elevated pro-inflammatory cytokine profile in multiple chemical sensitivity. *Psychoneuroendocrinology*, *40*, 140–150. https://doi.org/10.1016/j.psyneuen.2013.11.012	In this case-control study, blood samples were collected from 150 MCS individuals and 148 healthy controls. The plasma concentrations of 14 cytokines, chemokines, and growth and allergen-specific IgE were measured. A questionnaire about MCS, psychological	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			distress, morbidities and medication used at the time of the study was also completed. The results report a different immunological profile in MCS individuals, with increased levels of pro-inflammatory cytokines and an enhanced IL-4/IL-13 ratio. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of immunological dysfunction	
Dantoft, T.M.; Skovbjerg, S.; Andersson, L.; Claeson, A.-S.; Lind, N.; Nordin, S.; Brix, S.	Inflammatory mediator profiling of n-butanol exposed upper airways in individuals with multiple chemical sensitivity	Dantoft, T. M., Skovbjerg, S., Andersson, L., Claeson, A.-S., Lind, N., Nordin, S., & Brix, S. (2015). Inflammatory Mediator Profiling of n-butanol Exposed Upper Airways in Individuals with Multiple Chemical Sensitivity. *Plos One*, *10*(11), e0143534. https://doi.org/10.1371/journal.pone.0143534	In this case-control study, 18 MCS subjects and 18 healthy controls had their epithelial lining fluid collected from the nasal cavity three times: baseline, within 15 minutes of being exposed to 3.7 ppm *n*-butanol and four hours after the exposure stopped. Results suggest that a MCS symptom-eliciting exposure through the odorant *n*-butanol does not trigger upper air inflammatory response based on cytokine and chemokine profiles. The systemic response to the exposure is thought to not be influenced by upper airway inflammation, so it is unlikely that the previous blood plasma cytokine levels in unexposed MCS subjects is caused by exaggerated upper airway inflammatory responses. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of immunological dysfunction	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Dantoft, T.M.; Skovbjerg, S.; Andersson, L.; Claeson, A.-S.; Engkilde, K.; Lind, N.; Nordin, S.; Hellgren, L.I.	Gene expression profiling in persons with multiple chemical sensitivity before and after a controlled n-butanol exposure session	Dantoft, T. M., Skovbjerg, S., Andersson, L., Claeson, A.-S., Engkilde, K., Lind, N., Hellgren, L. I. (2017). Gene expression profiling in persons with multiple chemical sensitivity before and after a controlled n-butanol exposure session. *Bmj Open*, *7*(2), e013879. https://doi.org/10.1136/bmjopen-2016-013879	Gene expression in MCS participants (18) and healthy controls (18) were compared before a chemical exposure in this case-control study, 15 minutes after being exposed and 4 hours after a chemical exposure of *n*-butanol (.3.7 ppm). Blood samples were collected at baseline and after exposure, and the transcription of 17 different potential MCS-related genes was evaluated. Results showed that MCS participants and controls have similar gene expression levels at baseline and after exposure, but that individuals with MCS had an overall transcription rate greater than the controls. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion immune and metabolic MOA.	
Eis, D.; Helm, D.; Muehlinghaus, T.; Birkner, N.; Dietel, A.; Eikmann, T.; Gieler, U.; Herr, C.; Lacour, M.; Nowak, D.; Pedrosa Gil, F.; Podoll, K.; Renner, B.; Andreas Wiesmueller, G.; Worm, M.	The German Multicentre Study on Multiple Chemical Sensitivity (MCS)	Eis, D., Helm, D., Muehlinghaus, T., Birkner, N., Dietel, A., Eikmann, T., … Worm, M. (2008). The German Multicentre Study on Multiple Chemical Sensitivity (MCS). *International Journal of Hygiene and Environmental Health*, *211*(5–6), 658–681. https://doi.org/10.1016/j.ijheh.2008.03.002	In the cross-sectional study with an integrated case-control comparison, 291 environmental medicine outpatients were examined in centres throughout Germany. The study population was later divided into MCS and non-MCS groups. All patients completed environmental questionnaires, psychosocial questionnaires, the German version of the CIDI, a medical baseline, and examination for genetic susceptibility markers. The study showed that was no systematic connection observed between complaints and triggers, and there was no evidence for genetic predisposition. The results showed there were indicators for the relevance of behavioural	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			accentuations, psychic alterations or psychosomatic impairments in the EM-outpatients with subjective "environmental illness". The assumption of toxicogenic-somatic bases of MCS was not supported. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of several headings	
Eberlein-Konig, B.; Przybilla, B.; Kuhnl, P.; Golling, G.; Gebefugi, I.; Ring, J.	Multiple chemical sensitivity (MCS) and others: Allergological, environmental and psychological investigations in individuals with indoor air related complaints	Eberlein-Konig, B., Przybilla, B., Kuhnl, P., Golling, G., Gebefugi, I., & Ring, J. (2002). Multiple chemical sensitivity (MCS) and others: Allergological, environmental and psychological investigations in individuals with indoor air related complaints. *International Journal of Hygiene and Environmental Health*, *205*(3), 213–220. https://doi.org/10.1078/1438-4639-00150	The study evaluated individuals that complain of hypersensitivity to indoor pollution through allergological and psychological investigations. Interviews and allergological tests were used to select a total of 65 individuals were selected through a public campaign after exclusion criteria being applied. All individuals completed a questionnaire regarding their symptoms, and living and work places, underwent skin prick tests, and participated in an unstructured psychological interview. Indoor air testing was completed for some subjects. 65% of the patients revealed a sensitization to common allergens, 58% showed a psychosomatic or psychotic disorder. **Quality of study:** ** **Relevant to Objectives:** Yes. Although no controls were included in the study and subjects had self-reported symptoms, the potential relationship between MCS and allergy/hypersensitivity as a mechanism is relevant.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Pigatto, P.D.; Minoia, C.; Ronchi, A.; Brambilla, L.; Ferrucci, S.M.; Spadari, F.; Passoni, M.; Somalvico, F.; Bombeccari, G.P.; Guzzi, G.	Allergological and toxicological aspects in a multiple chemical sensitivity cohort	Pigatto, P. D., Minoia, C., Ronchi, A., Brambilla, L., Ferrucci, S. M., Spadari, F., … Guzzi, G. (2013). Allergological and Toxicological Aspects in a Multiple Chemical Sensitivity Cohort. *Oxidative Medicine and Cellular Longevity*, UNSP 356235. https://doi.org/10.1155/2013/356235	This retrospective case-control study looked at the medical records of 41 patients with MCS. Patch testing for dental components (n=21) and lymphocyte transformation test (n=18) for 20 metal allergens were also performed to investigate the association of mercury and MCS cases. Compared to 8 controls, elevated mercury levels in 22 MCS patients were associated with mercury amalgams. Data indicated that there was an increased prevalence of metal allergy and elevation of mercury levels among the patients with MCS, whereas a higher level of mercury in biological matrices is associated with the presence of mercury-containing dental amalgam fillings. Exposure to mercury may contribute to the observed MCS symptoms as the study shows an association between increased mercury concentrations in biological indicator media and the risk of MCS. **Quality of study:** ** **Relevant to Objectives:** Yes. Although the study did not include controls, the role of delayed hypersensitivity in clinically defined MCS cases was investigated and many aspects of study were well-designed.	Some information within may of relevance to the symptoms and prevalence of MCS
Mode of Action –Genetic Factors				
Berg, N.D.; Berg Rasmussen, H.; Linneberg, A.; Brasch-Andersen,	Genetic susceptibility factors for multiple chemical sensitivity revisited	Berg, N. D., Berg Rasmussen, H., Linneberg, A., Brasch-Andersen, C., Fenger, M., Dirksen, A., … Elberling, J. (2010). Genetic susceptibility factors for multiple chemical sensitivity revisited. *International*	The effect of metabolic gene variants was assessed in 96 MCS patients diagnosed according to Cullen's criteria and 1207 controls from a general population. The	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
C.; Fenger, M.; Dirksen, A.; Vesterhauge, S.; Werge, T.; Elberling, J.		*Journal of Hygiene and Environmental Health*, *213*(2), 131–139. https://doi.org/10.1016/j.ijheh.2010.02.001	participants were divided into four severity groups of chemical sensitivity, and were genotyped for the variants in the genes encoding for CYP2D6, NAT2, PON 1, MTHFR and CCK2R. Questionnaires inquiring about the common airborne chemicals that elicit symptoms, and the character and consequences of the symptoms were completed. The questionnaire genotype data from the population sample was assessed as a cross-sectional study, whereas the patient sample was analyzed as a case-control study. Results suggest that variants in the genes examined are of less importance to MCS than previously reported. It is hypothesized that gene-environment interactions arising from chemical exposures or genetic heterogeneity could have impacted the study results. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included in discussion of genetic factors	
Binkley, K.; King, N.; Poonai, N.; Seeman, P.; Ulpian, C.; Kennedy, J.	Idiopathic environmental intolerance: Increased prevalence of panic disorder-associated cholecystokinin B receptor allele 7	Binkley, K., King, N., Poonai, N., Seeman, P., Ulpian, C., & Kennedy, J. (2001). Idiopathic environmental intolerance: Increased prevalence of panic disorder-associated cholecystokinin B receptor allele 7. *Journal of Allergy and Clinical Immunology*, *107*(5), 887–890.	In this case-control study, the DNA from peripheral blood samples of 11 diagnosed IEI patients and controls were examined for panic disorder-associated CCK-B receptor alleles and for personality trait-associated dopamine D4 receptor polymorphisms. The results showed a higher prevalence of the panic disorder –associated CCK-B receptor allele 7 in IEI patients when compared to controls. There was no difference in the polymorphisms of dopamine D4 receptor. The authors note that IEI and panic disorder may share a neurogenetic basis,	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			which may help shape management strategies. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of genetic factors	
Caccamo, D.; Cesareo, E.; Mariani, S.; Raskovic, D.; Ientile, R.; Curro, M.; Korkina, L.; De Luca, C.	Xenobiotic sensor- and metabolism-related gene variants in environmental sensitivity-related illnesses: A survey on the Italian population	Caccamo, D., Cesareo, E., Mariani, S., Raskovic, D., Ientile, R., Curro, M., De Luca, C. (2013). Xenobiotic Sensor- and Metabolism-Related Gene Variants in Environmental Sensitivity-Related Illnesses: A Survey on the Italian Population. *Oxidative Medicine and Cellular Longevity*, UNSP 831969. https://doi.org/10.1155/2013/831969	The frequency of gene polymorphisms of selected cytochrome P450 (CYP) metabolising enzymes and the xenobiotic sensor Aryl hydrocarbon receptor in 3 cohorts: 156 diagnosed MCS, 94 suspected MCS, and 80 fibromyalgia/chronic fatigue syndrome patients versus 113 healthy controls were compared. Results indicated that there are genetic variants which can serve as diagnostic markers for several environmental-borne, sensitivity-related illnesses. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of genetic factors	
Cui, X.; Lu, X.; Hiura, M.; Oda, M.; Miyazaki, W.; Katoh, T.	Evaluation of Genetic Polymorphisms in Patients with Multiple Chemical Sensitivity	Cui, X., Lu, X., Hiura, M., Oda, M., Miyazaki, W., & Katoh, T. (2013). Evaluation of Genetic Polymorphisms in Patients with Multiple Chemical Sensitivity. *Plos One*, *8*(8), UNSP e73708. https://doi.org/10.1371/journal.pone.0073708	The effect of genetic polymorphisms was investigated in a case-control study of people chemical sensitivities by a QEESI© questionnaire and DNA analysis. DNA samples from 324 Japanese male workers were collected and select genes (CYP, GST, NAT, ALDH2, SOD) were analyzed to determine their predisposition to CSP. Results from the case control study indicated that high chemical sensitive individuals, diagnosed by Japanese criteria	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			as MCS patients, were significantly more associated with SOD2 polymorphisms. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of genetic factors	
De Luca, C.; Scordo, M.G.; Cesareo, E.; Pastore, S.; Mariani, S.; Maiani, G.; Stancato, A.; Loreti, B.; Valacchi, G.; Lubrano, C.; Raskovic, D.; De Padova, L.; Genovesi, G.; Korkina, L.G.	Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes	De Luca, C., Scordo, M. G., Cesareo, E., Pastore, S., Mariani, S., Maiani, G., … Korkina, L. G. (2010). Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. *Toxicology and Applied Pharmacology*, *248*(3), 285–292. https://doi.org/10.1016/j.taap.2010.04.017	MCS patients and healthy controls were genotyped for a number of genetic, immunological and metabolic markers in the case-control study. A total of diagnosed 226 participants were in the MCS case group, and 218 healthy controls. In the MCS patients, the results which were indicating altered redox and cytokine patterns suggest the inhibition of metabolizing and antioxidant enzymes. In the diagnosis of MCS, metabolic parameters which indicate accelerated lipid oxidation, increased nitric oxide production and glutathione depletion with increased plasma inflammatory cytokines should be considered. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of genetic factors	
Fujimori, S.; Hiura, M.; Yi, C.X.; Xi, L.; Katoh, T.	Factors in genetic susceptibility in a chemical sensitive population using QEESI©	Fujimori, S., Hiura, M., Yi, C. X., Xi, L., & Katoh, T. (2012). Factors in genetic susceptibility in a chemical sensitive population using QEESI©. *Environmental Health and Preventive Medicine*, *17*(5), 357–363. https://doi.org/10.1007/s12199-011-0260-8	The cross-sectional study evaluated sensitivity to chemicals using QEESI© questionnaires, and the collection of blood samples to determine if there are any differences in the gene expression of specific enzymes (GSTM1, GSTT1, ALDH2, PON1) in peripheral leukocytes. 1084 employees of various Japanese	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			companies were surveyed and common genotypes (*i.e.* GST, ALDH2, PON1) were analyzed. Based on the QEESI© subscales, participants were divided into 4 levels, in addition to being differentiated into CSP cases and controls by using the MCS criteria by Hojo. The results indicated there were no significant differences in the allelic distribution of genetic polymorphism in GST, ALDH2 or PON1 between cases and controls. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of genetic factors	
McKeown-Eyssen, G.; Baines, C.; Cole, D. E.; Riley, N.; Tyndale, R. F.; Marshall, L.; Jazmaji, V.	Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR	McKeown-Eyssen, G., Baines, C., Cole, D. E., Riley, N., Tyndale, R. F., Marshall, L., & Jazmaji, V. (2004). Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. *International Journal of Epidemiology*, *33*(5), 971–978. https://doi.org/10.1093/ije/dyh251	In this case-control study, common polymorphisms were genotyped to determine if the drug-metabolizing enzymes in MCS cases had different genetic polymorphisms compared to the controls. In the study, 203 MCS cases and 162 controls participated, and the results indicated that there are significant differences in the genotype distributions for CYP2D6 and NAT2. It is speculated that the CYP2D6 and NAT2 enzymes may interact on exogenous chemicals or endogenous pathways and may substantially elevate the risk for MCS beyond what would be expected for each gene alone. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of genetic factors	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Wiesmüller, G.A.; Niggemann, H.; Weissbach, W.; Riley, F.; Maarouf, Z.; Dott, W.; Kunert, H.-J.; Zerres, K.; Eggermann, T.; Bloemeke, B.	Sequence variations in subjects with self-reported multiple chemical sensitivity (sMCS): A case-control study	Wiesmüller, G.A.; Niggemann, H.; Weissbach, W.; Riley, F.; Maarouf, Z.; Dott, W.; Kunert, H.-J.; Zerres, K.; Eggermann, T.; Bloemeke, B. (2008). Sequence Variations in Subjects with Self-Reported Multiple Chemical Sensitivity (sMCS): A Case-Control Study. Retrieved September 11, 2017, from https://ncbi.nlm.nih.gov/labs/articles/18569577/	This case-control study evaluated the association between polymorphisms in the genes of 5HTT (SLC6A4), NAT1, NAT2, PON1, PON2, and SOD2 (MnSOD) and MCS by studying 59 sMCS cases and 40 controls. Participants were characterized by utilizing a MCS questionnaire from Hüppe et.al (2000) and a living conditions and living factors questionnaire. Allele frequencies of genomic variations for a number of genes were also determined. Results showed that the sMCS cases had lower exposures, and worse social conditions compared to the controls. Allelic distribution had no significant differences in the genes assessed between the cases and controls. The Hüppe et. Al. (2000) questionnaire helped to differentiate the sMCS cases from the controls but it was not strong enough to discriminate based on the sequence variations in the enzymes playing a role in xenobiotic metabolism. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of genetic factors.	There might be useful information regarding symptoms and the diagnosis of MCS in the Hüppe et al. 2000 paper.
MOA – Neurological Dysfunction				
Alessandrini, M.; Micarelli, A.; Chiaravalloti, A.; Bruno, E.; Danieli, R.; Pierantozzi, M.; Genovesi, G.;	Involvement of Subcortical Brain Structures During Olfactory Stimulation in Multiple Chemical Sensitivity	Alessandrini, M., Micarelli, A., Chiaravalloti, A., Bruno, E., Danieli, R., Pierantozzi, M., … Schillaci, O. (2016). Involvement of Subcortical Brain Structures During Olfactory Stimulation in Multiple Chemical Sensitivity. *Brain Topography*, *29*(2), 243–252. https://doi.org/10.1007/s10548-015-0453-3	The case-control study tested 26 MCS patients and 11 controls by analyzing sub-cortical metabolic changes during a neutral and pure olfactory stimulation through 18F-2-FDG-PET procedure and applying a battery of clinical tests. When comparing	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Oberg, J.; Pagani, M.; Schillaci, O.			both neutral and pure olfactory stimulation, the within-subjects ANOVA showed a decrease in metabolism in the bilateral putamen and hippocampus and an increase in metabolism in the bilateral amygdala, OLF, caudate and pallidum in both groups. The between-group ANOVA showed a higher metabolism in bilateral OLF in the neutral olfactory stimulation in MCS. The study found a higher metabolism increase in OLF in MCS subjects. The metabolic index of behavioral and neurological aspects of MCS complaints were described in the study. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA.	
Andersson, L.; Bende, M.; Millqvist, E.; Nordin, S.	Attention bias and sensitization in chemical sensitivity	Andersson, L., Bende, M., Millqvist, E., & Nordin, S. (2009). Attention bias and sensitization in chemical sensitivity. *Journal of Psychosomatic Research*, *66*(5), 407–416. https://doi.org/10.1016/j.jpsychores.2008.11.005	In this case-control study, 21 self-reported chemical sensitivity cases and 17 controls underwent a series of chemosomatosensory, olfactory, and auditory event-related potentials to investigate if self-reported chemical sensitivity individuals have an attention bias and enhanced sensitization to chemical exposures. Results indicated that the cases had faster reaction times, perceived intensities that did not decrease over time. In addition, the chemical sensitive cases had difficulties in ignoring the chemical exposures. This indicates that there is an attention bias and enhanced sensitization in self-reported chemical sensitivity individuals, suggesting that there are alternations in the cognitive responses	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			to the chemical exposure. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA.	
Andersson, L.; Claeson, A.-S.; Nyberg, L.; Stenberg, B.; Nordin, S.	Brain responses to olfactory and trigeminal exposure in idiopathic environmental illness (IEI) attributed to smells - An fMRI study	Andersson, L., Claeson, A.-S., Nyberg, L., Stenberg, B., & Nordin, S. (2014). Brain responses to olfactory and trigeminal exposure in idiopathic environmental illness (IEI) attributed to smells - An fMRI study. *Journal of Psychosomatic Research*, *77*(5), 401–408. https://doi.org/10.1016/j.jpsychores.2014.09.014	In this case-control study, the brain responses of 25 women with IEI and 26 controls to intranasal exposure to isoamyl acetate and carbon dioxide were investigated. Results showed that the case group had higher BOLD signal than the controls in the thalamus and several parietal areas, and lower BOLD signal in the superior frontal gyrus. The case group did not rate the exposures as more intense than the control and there were no BOLD signal differences in the piriform cortex or the olfactory regions. Evidence of hyper-responsiveness in sensory areas of the brain were not observed, and it is suggested that the results relate to limbic hyperreactivity and potentially a lack of inhibition of external stimuli. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Andersson, L.; Claeson, A.-S.; Dantoft, T.M.; Skovbjerg, S.; Lind, N.; Nordin, S.	Chemosensory perception, symptoms and autonomic responses during chemical exposure in multiple chemical sensitivity	Andersson, L., Claeson, A.-S., Dantoft, T. M., Skovbjerg, S., Lind, N., & Nordin, S. (2016). Chemosensory perception, symptoms and autonomic responses during chemical exposure in multiple chemical sensitivity. *International Archives of Occupational and Environmental Health*, *89*(1), 79–88. https://doi.org/10.1007/s00420-015-1053-y	The case-control study with 18 MCS participants and 18 controls, involved exposure to low concentration of *n*-butanol (11.5 mg/m^3) and investigating the expressions of the individuals. MCS participants reported greater intensities and more unpleasantness to the exposure. And	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			had a higher pulse rate and lower pulse rate variability than controls. MCS participants were concluded to have different autonomic responses, symptoms and chemosensory perception during chemical exposure. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Andersson, L.; Claeson, A.-S.; Nyberg, L.; Nordin, S.	Short-term olfactory sensitization involves brain networks relevant for pain, and indicates chemical intolerance	Andersson, L., Claeson, A.-S., Nyberg, L., & Nordin, S. (2017). Short-term olfactory sensitization involves brain networks relevant for pain, and indicates chemical intolerance. *International Journal of Hygiene and Environmental Health*, *220*(2), 503–509. https://doi.org/10.1016/j.ijheh.2017.02.002	In this case-control study, 58 females with and without self-reported CI, and without anosmia were exposed to 20 consecutive amyl acetate at 5 mg/m^3 and 20 consecutive CO_2 stimulations of 30 s in duration (with 30 s baseline) to investigate whether sensitization and habituation to odours involve the same brain regions as those in pain modulation, and if there is an association with self-reported CI. The author's hypotheses were that that individuals who sensitize to repeated olfactory stimulation, compared to those habituated would express lower BOLD response in inhibitory areas like the raCC, have higher signal in pain detection regions, primary and secondary olfactory projection areas and olfactory sensitization; and that olfactory sensitization would be associated with greater self-reported CI. Results confirmed the hypotheses where olfactory sensitizers compared to individuals who were habituated had displayed lower BOLD response. **Quality of study:** **	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Relevant to Objectives: Yes, will be included under discussion of neurological MOA	
Azuma, K.; Uchiyama, I.; Takano, H.; Tanigawa, M.; Azuma, M.; Bamba, I.; Yoshikawa, T.	Changes in cerebral blood flow during olfactory stimulation in patients with multiple chemical sensitivity: A multi-channel near-infrared spectroscopic study	Azuma, K., Uchiyama, I., Takano, H., Tanigawa, M., Azuma, M., Bamba, I., & Yoshikawa, T. (2013). Changes in Cerebral Blood Flow during Olfactory Stimulation in Patients with Multiple Chemical Sensitivity: A Multi-Channel Near-Infrared Spectroscopic Study. *Plos One*, *8*(11), e80567. https://doi.org/10.1371/journal.pone.0080567	In this case-control study, chances in rCBF in the PFC were investigated following olfactory stimulation with different odorants on a card-type olfactory test kit. NIRS imaging was used on 12 MCS patients and 11 controls, along with the completion of a physical and psychological assessment. QEESI© questionnaires were used in the selection of subjects. Blood samples were collected and evaluated for several clinical chemical parameters. Results showed that significant changes in rCBF were observed in MCS patients with poorer autonomic perception and negative affectivity when compared to controls. It is suggested that the prefrontal odor processing and memory processes from past chemical exposures play significant roles in pathology of the disorder. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Azuma, K.; Uchiyama, Iwao; Tanigawa, Mari; Bamba, Ikuko; Azuma, Michiyo; Takano, Hirohisa; Yoshikawa, Toshikazu; Sakabe, Kou	Assessment of cerebral blood flow in patients with multiple chemical sensitivity using near-infrared spectroscopy--recovery after olfactory stimulation: a case-control study	Azuma, K., Uchiyama, I., Tanigawa, M., Bamba, I., Azuma, M., Takano, H., … Sakabe, K. (2015). Assessment of cerebral blood flow in patients with multiple chemical sensitivity using near-infrared spectroscopy-recovery after olfactory stimulation: a case-control study. *Environmental Health and Preventive Medicine*, *20*(3), 185–194. https://doi.org/10.1007/s12199-015-0448-4	In this case-control study, the recovery process of rCBF after olfactory stimulation using standardized test kits in patients with MCS was examined. NIRS imaging was conducted on 6 MCS patients and 6 controls, along with an assessment of the physical and psychological status of the perception of the odors. Baseline and rest periods were 30 s in duration, and odorant	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			exposure periods were 10 s. The results indicated that there were significant activations in the PFC of MCS patients on both sides, with strong activations in the OFC compared to the controls. MCS patients had poorer autonomic perception and feelings identification. The OFC activations suggest that a past strong chemical exposure activates the PFC during olfactory stimuli in MCS patients, and a strong activation in the PFC remains in the OFC after the stimuli. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Azuma, K.; Uchiyama, I.; Tanigawa, M.; Bamba, I.; Azuma, M.; Takano, H.; Yoshikawa, T.; Sakabe, K.	Association of odor thresholds and responses in cerebral blood flow of the prefrontal area during olfactory stimulation in patients with multiple chemical sensitivity	Azuma, K., Uchiyama, I., Tanigawa, M., Bamba, I., Azuma, M., Takano, H., … Sakabe, K. (2016). Association of Odor Thresholds and Responses in Cerebral Blood Flow of the Prefrontal Area during Olfactory Stimulation in Patients with Multiple Chemical Sensitivity. *Plos One*, *11*(12), e0168006. https://doi.org/10.1371/journal.pone.0168006	This case-control study investigated the association of the odor thresholds and changes in the rCBF during olfactory stimulation by utilizing NIRS imaging and a T&T olfactometer. 10 MCS patients and 6 controls were exposed to two odorants using a standardized test at three concentrations (zero, odor recognition threshold, and normal perceived odor level). Baseline and recovery periods were 30 s in duration, and exposure periods were 10 s. Results showed the brain responses at the recognition threshold and normal perceived levels were stronger in patients with MCS than in controls, but odor detection, recognition thresholds, and odor intensity score did not show a significant difference between the two groups.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Quality of study: ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Belpomme, D.; Campagnac, C.; Irigaray, P.	Reliable disease biomarkers characterizing and identifying electrohypersensitivity and multiple chemical sensitivity as two etiopathogenic aspects of a unique pathological disorder	Belpomme, D., Campagnac, C., & Irigaray, P. (2015). Reliable disease biomarkers characterizing and identifying electrohypersensitivity and multiple chemical sensitivity as two etiopathogenic aspects of a unique pathological disorder. *Reviews on Environmental Health*, *30*(4), 251–271. https://doi.org/10.1515/reveh-2015-0027	The clinical criteria and objective biomarkers for electrohypersensitivity (EHS) and MCS were investigated by examining 521 diagnosed EHS subjects, 52 diagnosed MCS subjects, and 154 subjects with both diagnosed EHS and MCS. No controls were recruited to the study, but control data is discussed. Blood and urine samples were collected from all subjects, and brain blood flow was assessed in the temporal lobes. Both EHS and MCS are suggested to pose a risk of chronic neurodegenerative disease as they appear to be involved in inflammation-related hyper-histaminemia, oxidative stress, autoimmune response, capsulothalamic hypoperfusion and BBB opening, and a deficit in melatonin metabolic availability Cerebral pulsatility in the EHS and/or MCS subjects was decreased or eliminated in one or both temporal lobes, similar to neurodegenerative diseases. The authors suggest that there may be a common mechanism between EHS and MCS involving an inflammatory and oxidative response that affects the brain. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Bornschein, S.; Hausteiner, C.; Drzega, A.; Theml, T.; Heldmann, B.; Grimmer, T.; Perneczky, R.; Jahn, T.; Schwaiger, M.; Zilker, T.; Forstl, H.	Neuropsychological and positron emission tomography correlates in idiopathic environmental intolerances	Bornschein, S., Hausteiner, C., Drzezga, A., Theml, T., Heldmann, B., Grimmer, T., … Foerstl, H. (2007). Neuropsychological and positron emission tomography correlates in idiopathic environmental intolerances. *Scandinavian Journal of Work Environment & Health*, *33*(6), 447–453.	In this case-control study, 12 diagnosed IEI patients and 17 controls underwent F-18 FDG-PET scans in order to identify any changes due to neuronal damage. The results showed that 6 patients displayed deficits in verbal learning and memory, while 3 patients had reduced information processing speed. Normal cerebral glucose metabolism was seen in 11 patients. There was no consistent pathological cognitive performance and functional imaging pattern found in this study in IEI patients compared to controls. The authors note that cerebral F-18 FDG-PET should not be used to rule out or corroborate IEI as it appears that claiming specific neuropsychological or neuroimaging findings characteristic of IEI is premature. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Caccappolo, E.; Kipen, H.; Kelly-McNeil, K.; Knasko, S.; Hamer, R.M.; Natelson, B.; Fiedler, N.	Odor perception: Multiple chemical sensitivities, chronic fatigue, and asthma	Caccappolo, E., Kipen, H., Kelly-McNeil, K., Knasko, S., Hamer, R. M., Natelson, B., & Fiedler, N. (2000). Odor perception: Multiple chemical sensitivities, chronic fatigue, and asthma. *Journal of Occupational and Environmental Medicine*, *42*(6), 629–638. https://doi.org/10.1097/00043764-200006000-00012	In the case-control study, 33 diagnosed MCS subjects, 13 diagnosed chronic fatigue syndrome subjects, 16 asthmatic subjects, and 27 healthy controls underwent odor detection threshold testing to PEA and PYR, and odor identification through the UPSIT, and rate suprathreshold levels of PEA and PYR. Results showed that both odor detection and identification ability were equivalent for all groups with MCS subjects. MCS subjects were differentiated from the other groups by their symptomatic and esthetic	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			ratings of PEA but not PYR and overall, they did not demonstrate lower olfactory threshold sensitivity or enhanced ability for odor identification. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Chiaravalloti, A.; Pagani, M.; Micarelli, A.; Di Pietro, B.; Genovesi, G.; Alessandrini, M.; Schillaci, O.	Cortical activity during olfactory stimulation in multiple chemical sensitivity: a 18F-FDG PET/CT study	Chiaravalloti, A., Pagani, M., Micarelli, A., Di, P., Genovesi, G., Alessandrini, M., & Schillaci, O. (2015). Cortical activity during olfactory stimulation in multiple chemical sensitivity: a 18F-FDG PET/CT study. *European Journal of Nuclear Medicine and Molecular Imaging*, *42*(5), 733–740. https://doi.org/10.1007/s00259-014-2969-2	This study investigated the differences in brain glucose consumption during olfactory stimulation (OS) between 26 MCS patients and 11 controls by using PET/CT scans. Results in this study showed that OS led to increase in glucose consumption in BA 18 and 19 and a reduction in glucose metabolism in BA 10, 11, 32, 47 in controls. In MCS patients, OS led to increase in glucose consumption in BA 20,23,18 and 37 and a reduction in glucose metabolism in BA 8,9, and 10. This suggests that the cortical activity in MCS patients differs from the controls following OS. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Haumann, K.; Kiesswetter, E.; Van Thriel, C.; Blaszkewicz, M.; Seeber, A.	Psychophysiological functions of subjects with self-reported multiple chemical sensitivity (sMCS) during experimental solvent exposure	Haumann, K., Kiesswetter, E., van Thriel, C., Blaszkewicz, M., & Seeber, A. (2002). Psychophysiological functions of subjects with self-reported multiple chemical sensitivity (sMCS) during experimental solvent exposure. *International Journal of Hygiene and Environmental Health*, *204*(5–6), 371–373. https://doi.org/10.1078/1438-4639-00113	In the case control study, 12 self-reported MCS subjects and 12 controls were exposed to solvents for 4 hours on four different days. At the beginning and end of the exposure, heart rate and breathing rate were evaluated for 30 minutes each. Control subjects demonstrated relatively	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			constant breathing rate with a small increase in heart rate where sMCS subjects had both functions elevated at the beginning of testing period with a tendency to decrease over the 30 minutes period. The mean of the breathing rate for sMCS was generally higher compared to control, but no specific reactions to the type or level of chemical exposures were observed. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Haumann, K.; Kiesswetter, E.; Van Thriel, C.; Blaszkewicz, M.; Golka, K.; Seeber, A.	Breathing and heart rate during experimental solvent exposure of young adults with self-reported multiple chemical sensitivity (sMCS)	Haumann, K., Kiesswetter, E., van Thriel, C., Blaszkewicz, M., Golka, K., & Seeber, A. (2003). Breathing and heart rate during experimental solvent exposure of young adults with self-reported multiple chemical sensitivity (sMCS). *Neurotoxicology*, *24*(2), 179–186. https://doi.org/10.1016/S0161-813X(02)00213-9	In this paper, two independent experiments were carried out with 12 sMCS subjects and 12 controls in both experiments to investigate the assumption that young adults with sMCS have heightened sensitivity of autonomic functions during experimental solvent exposure. The first experiment used two concentrations of ethyl benzene (10 and 98 ppm) and 2-butanone (10 and 189 ppm). The second experiment used 2-proponal (35 and 190 ppm) and 1-octanol (0.1 and 6.4 ppm). Under each condition, the exposure duration was 4 hours at a random sequence including intervals of 2 days without exposure. Breathing rate and heart rate were recorded during the exposure. Neither experiment had significant specific reactions to the type or level of the exposure. **Quality of study:** ** **Relevant to Objectives:** Yes, will be	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			included under discussion of neurological MOA	
Hillert, L.; Jovanovic, H.; Ahs, F.; Savic, I.	Women with Multiple Chemical Sensitivity Have Increased Harm Avoidance and Reduced 5-HT1A Receptor Binding Potential in the Anterior Cingulate and Amygdala	Hillert, L., Jovanovic, H., Ahs, F., & Savic, I. (2013). Women with Multiple Chemical Sensitivity Have Increased Harm Avoidance and Reduced 5-HT1A Receptor Binding Potential in the Anterior Cingulate and Amygdala. *Plos One*, *8*(1), e54781. https://doi.org/10.1371/journal.pone.0054781	In this follow up case-control study (follow up to Hillert et al. 2007), 12 diagnosed MCS patients and 11 controls underwent a PET study were the 5-HT1A receptor BP was assessed after the bolus injection of [^{11}C]WAY100635, and psychological profiles were assessed. In addition, participants were tested for emotional startle modulation through an acoustic startle test. Compared to controls, the MCS patients showed increased harm avoidance and anxiety. MCS patients had reduced 5-HT1A receptor BP in amygdala, ACC, and insular cortex while also showing an inverse correlation between degree of anxiety and BP. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
McFetridge-Durdle, J.A.; Routledge, F.S.; Sampalli, T.; Fox, R.; Livingston, H.; Adams, B.	Hemodynamic response to postural shift in women with multiple chemical sensitivities	McFetridge-Durdle, J. A., Routledge, F. S., Sampalli, T., Fox, R., Livingston, H., & Adams, B. (2009). Hemodynamic Response to Postural Shift in Women with Multiple Chemical Sensitivities. *Biological Research for Nursing*, *10*(3), 267–273. https://doi.org/10.1177/1099800408324251	This observational study evaluated the hemodynamic response to postural shift (e.g. sit to stand, used as a marker of ANS function) in 17 women diagnosed with MCS was assessed, and of the 17 participants, 3 had FM and MCS, 5 had CFS and MCS, and 9 had only MCS. Individuals served as their own controls. Hemodynamic measures were taken while sitting and immediately standing. Results showed increased heart rate, decreased stroke volume, decreased left ventricular ejection	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			time, increased diastolic blood pressure, and increased systemic vascular resistance. The hemodynamic responses observed were determined to be normal, but the magnitude of changes was less than what was observed in healthy participants in previous studies. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Micarelli, A.; Viziano, A.; Genovesi, G.; Bruno, E.; Ottaviani, F.; Alessandrini, M.	Lack of contralateral suppression in transient-evoked otoacoustic emissions in multiple chemical sensitivity: A clinical correlation study	Micarelli, A., Viziano, A., Genovesi, G., Bruno, E., Ottaviani, F., & Alessandrini, M. (2016). Lack of contralateral suppression in transient-evoked otoacoustic emissions in multiple chemical sensitivity: A clinical correlation study. *Noise and Health*, *18*(82), 143–149. https://doi.org/10.4103/1463-1741.181997	To evaluate potential changes in auditory function, 18 MCS patients and 20 controls underwent TEOAE testing with and without contralateral suppression, and a QEESI© questionnaire was completed. MCS patients showed significant impairment of the MOC reflex. The results suggest that changes of the MOC reflex and subclinical alterations of auditory function may be occurring in MCS subjects. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Micarelli, A.; Viziano, A.; Micarelli, E.; Genovesi, G.; Bruno, E.; Alessandrini, M.	Deranged dimensionality of vestibular re-weighting in multiple chemical sensitivity	Micarelli, A., Viziano, A., Micarelli, E., Genovesi, G., Bruno, E., & Alessandrini, M. (2016). Deranged Dimensionality of Vestibular Re-Weighting in Multiple Chemical Sensitivity. *Applied Sciences-Basel*, *6*(11), 330. https://doi.org/10.3390/app6110330	In this case-control study, the potential role of vestibular impairment in MCS patients (18) were compared with 20 healthy subjects who underwent otoneurologic testing, inferential statistic and principal component analysis. All subjects filled in a dizziness and environment exposure inventory and underwent the Rod and Disc and Rod and Frame Test, vHIT and SPT	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			with FFT. Results identified defective vestibular processing in the MCS patients via a significant increase in SPT and FFT parameters, increase in VD behavior, and a decrease in vHIT scores. The authors note that the results support a hypothesis that, in MCS, physiopathological cascades might contribute to vestibular decay, possibly contributing to the dizziness symptoms reported by MCS patients. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Micarelli, A.; Viziano, A.; Bruno, E.; Micarelli, E.; Alessandrini, M.	Vestibular impairment in Multiple Chemical Sensitivity: Component analysis findings	Micarelli, A., Viziano, A., Bruno, E., Micarelli, E., & Alessandrini, M. (2016). Vestibular impairment in multiple chemical sensitivity: component analysis findings. *Journal of Vestibular Research*, *26*(5–6), 459–468.	In the case-control study, 18 right-handed MCS patients and 20 healthy controls underwent a battery of otoneurological tests to examine the clinical/subclinical aspects of vestibular impairment related to MCS symptoms. In MCS patients, deranged dimensionality in near-optimal re-weighting within otoneurological variables was found compared to controls. The study suggests that the physiopathology of MCS is associated with peripheral and vestibular decay. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Mizukoshi, A.; Kumagai, K.; Yamamoto, N.; Noguchi, M.; Yoshiuchi, K.;	In-situ real-time monitoring of volatile organic compound exposure and heart rate variability for	Mizukoshi, A., Kumagai, K., Yamamoto, N., Noguchi, M., Yoshiuchi, K., Kumano, H., … Yanagisawa, Y. (2015). In-situ Real-Time Monitoring of Volatile Organic Compound Exposure and Heart Rate Variability for Patients with Multiple Chemical	In the retrospective case-control study, VOC exposure and both high and low frequency signals (to evaluate parasympathetic and sympathetic activity) were conducted for 8 MCS patients using a	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Kumano, H.; Sakabe, K.; Yanagisawa, Y.	patients with multiple chemical sensitivity	Sensitivity. *International Journal of Environmental Research and Public Health*, *12*(10), 12446–12465. https://doi.org/10.3390/ijerph121012446	VOC monitor, an ECG r, and a time-activity questionnaire, for a study period of 24 hours. The results were compared with 7 controls from a previous study. Significant negative correlations for four MCS subjects were observed between HF exposure and VOC change. The authors note that the findings are suggestive of potential changes in parasympathetic/sympathetic neural activity in MCS patients upon VOC exposure and a potential relationship between exposure and symptoms. **Quality of study:** ** **Relevant to Objectives:** Yes, although there are a limited number of subjects, the study is well designed otherwise and examines a novel mechanism	
Ojima, M.; Tonori, H.; Sato, T.; Sakabe, K.; Miyata, M.; Ishikawa, S.; Aizawa, Y.	Odor perception in patients with multiple chemical sensitivity	Ojima, M., Tonori, H., Sato, T., Sakabe, K., Miyata, M., Ishikawa, S., & Aizawa, Y. (2002). Odor perception in patients with multiple chemical sensitivity. *Tohoku Journal of Experimental Medicine*, *198*(3), 163–173. https://doi.org/10.1620/tjem.198.163	This case-control study evaluated odour recognition and emotional reaction in 25 diagnosed MCS subjects and 50 control subjects. All subjects underwent standardized odour tests, along with completing an odor identifiability assessment. The mean CC-SIT odor per person with pleasant feeling was lower in MCS subjects and the mean odor per person creating an unpleasant sensation was higher than the controls. 9/40 UPSIT odors were felt as unpleasant by MCS subjects more than controls. The results indicate that MCS subjects were identify the odors comparable to controls, but were more likely to identify odours as being unpleasant. The authors note that this may be attributable to sensory changes in olfactory or trigeminal nerves in the airway,	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			sensitization, limbic kindling, toxicity, or psychological factors. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Orriols, R.; Costa, R.; Cuberas, G.; Jacas, C.; Castell, J.; Sunyer, J.	Brain dysfunction in multiple chemical sensitivity	Orriols, R., Costa, R., Cuberas, G., Jacas, C., Castell, J., & Sunyer, J. (2009). Brain dysfunction in multiple chemical sensitivity. *Journal of the Neurological Sciences*, *287*(1–2), 72–78. https://doi.org/10.1016/j.jns.2009.09.003	To determine if MCS patient's present dysfunction within odour-processing areas of the brain, SPECT and psychometric scale changes after a chemical challenge were compared between 8 MCS patients and 8 healthy controls. The chemical exposure consisted of an exposure to plastic-based paint odours or glutaraldehyde within an exposure chamber until the MCS subject experienced symptoms, and then the exposure for the patient and matched control ended. Exposure durations ranged from 3-35 min Neurocognitive deficits were observed in MCS patients relative to controls. Brain dysfunction as measured by SPECT was apparent in the MCS subjects but not controls. Results are suggestive of a neurogenic mechanism for MCS. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA, although there is a small number of subjects.	
Österberg, K.; Orbaek, P.; Karlson, B.	Neuropsychological test performance of Swedish multiple	Österberg, K., Ørbæk, P., & Karlson, B. (2002). Neuropsychological test performance of Swedish multiple chemical sensitivity patients - An exploratory	A neuropsychological battery consisting of 8 tests were given to 17 MCS patients and 34 controls in the case-control study to	mechanism - neural

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
	chemical sensitivity patients--an exploratory study.	study. *Applied Neuropsychology*, *9*(3), 139–147.	address the hypothesis of brain dysfunction as a component of the MCS syndrome. Results showed that MCS group performed poorer in a complex reaction time across 6 tests that are used as indicators of brain impairment. Test results were in most cases within normal limits and brain impairment was not evidenced but further research with larger MCS cases is required. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Papo, D.; Eberlein-Konig, B.; Berresheim, H. W.; Huss-Marp, J.; Grimm, V.; Ring, J.; Behrendt, H.; Winneke, G.	Chemosensory function and psychological profile in patients with multiple chemical sensitivity: Comparison with odor-sensitive and asymptomatic controls	Papo, D., Eberlein-Konig, B., Berresheim, H. W., Huss-Marp, J., Grimm, V., Ring, J., … Winneke, G. (2006). Chemosensory function and psychological profile in patients with multiple chemical sensitivity: Comparison with odor-sensitive and asymptomatic controls. *Journal of Psychosomatic Research*, *60*(2), 199–209. https://doi.org/10.1016/j.jpsychores.2005.06.075	The case-control study examined 23 MCS patients, 21 subjects with self-reported odor sensitivity, and 23 controls using electrophysiological and psychophysical olfactometric tests to investigate if the MCS patients differ from the self-reported odor sensitive group and the controls in chemosensory, cognitive, and clinical psychological endpoints. Standardized odour tests were administered. Results revealed that there were no significant differences between the groups with respect to olfactory function or processing or chemosensory processing. The results support findings that MCS patients have altered psychological profile and moderate psychopathology as they had higher scores on negative mood states following odorant exposure, on health complaints, global indices, and the somatization subscale of the Symptom Check List, trait and state anxiety and symptoms, and triggering	This study also has information related to psychology

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			matters of the MCS questionnaire. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurological MOA	
Sucker, K.; Berresheim, H.; Ramcke-Krull, H.; Schulze, P.; Bruning, T.; Bunger, J.	Approach to characterize a sub-group susceptible to odour annoyance	Sucker, K., Berresheim, H., Ramcke-Kruell, H., Schulze, P., Bruening, T., & Buenger, J. (2010). Approach to characterize a sub-group susceptible to odour annoyance. In R. DelRosso (Ed.), *Nose 2010: International Conference on Environmental Odour Monitoring and Control* (Vol. 23, pp. 99–104). Milano: Aidic Servizi Srl.	A total of 322 visitors to a tradeshow in Germany were recruited and assessed. Subjects were determined to be self-reporting as having MCS (59) or not (225) Standardized odour tests and information regarding lifestyles were collected. Results of the tests indicated sMCS subjects gave lower ratings of PEA intensity and higher unpleasant ratings of PEA hedonic tone compared to non-sMCS subjects. This result from the cross-sectional study suggests that sMCS and rating of hedonic tone and intensity of PEA can be used to characterize people that are susceptible to environmental odours. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of symptoms	
Van Thriel, C.; Haumann, K.; Kiesswetter, E.; Blaszkewicz, M.; Seeber, A.	Time courses of sensory irritations due to 2-butanone and ethyl benzene exposure: Influences of self-reported multiple chemical sensitivity (sMCS)	Van Thriel, C., Haumann, K., Klesswetter, E., Blaszkewicz, M., & Seeber, A. (2002). Time courses of sensory irritations due to 2-butanone and ethyl benzene exposure: Influences of self-reported multiple chemical sensitivity (sMCS). *International Journal of Hygiene and Environmental Health*, *204*(5–6), 367–369.	In the case-control study, 12 self-reported MCS subjects and 12 healthy subjects were exposed to 2-butanone and ethyl benzene at different levels (low, higher) for 4-hours within an exposure laboratory, and measures of sensory irritation were assessed prior, during and after the 4 hours of exposure through the use of the CGES. Exposures were separated by periods of 2-days. sMCS patients had significantly higher symptom scores than	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			controls, and reported low to moderate irritation. sMCS subjects showed increasing symptom scores when compared to controls and more rapidly with respect to time. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion olfactory and neurological effects.	
Van Thriel, C.; Kiesswetter, E.; Schaeper, M.; Juran, S.A.; Blaszkewicz, M.; Kleinbeck, S.	Odor annoyance of environmental chemicals: Sensory and cognitive influences	Van Thriel, C., Kiesswetter, E., Schaeper, M., Juran, S. A., Blaszkewicz, M., & Kleinbeck, S. (2008). Odor annoyance of environmental chemicals: Sensory and cognitive influences. *Journal of Toxicology and Environmental Health-Part a-Current Issues*, *71*(11–12), 776–785. https://doi.org/10.1080/15287390801985596	This cross-sectional study addressed the influences of the different types of modulators, including olfactory functioning on chemosensory perceptions. A total of 44 subjects (who were later administered questionnaires to determine self-reported MCS status) were examined in a psychophysical scaling experiment involving a standardized odour test. The subjects rated four olfactory and nine trigeminal perceptions after the application of nine concentrations of six chemicals by flow-olfactometry. Results showed that subjects with self-reported higher sensitivity reported stronger odour perceptions. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under the discussion olfactory and neurological effects.	
MOA – NMDA/NO/ONOO-				
De Luca, C.; Gugliandolo, A.; Calabro, C.; Curro, M.; Ientile,	Role of polymorphisms of inducible nitric oxide synthase and endothelial nitric oxide	De Luca, C., Gugliandolo, A., Calabro, C., Curro, M., Lentile, R., Raskovic, D., … Caccamo, D. (2015). Role of Polymorphisms of Inducible Nitric Oxide Synthase and Endothelial Nitric Oxide Synthase in Idiopathic	The case-control study investigated the distribution of NOS gene polymorphisms and the correlation with nitrite/nitrate levels in 170 diagnosed MCS patients, 108	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
R.; Raskovic, D.; Korkina, L.; Caccamo, D.	synthase in idiopathic environmental intolerances	Environmental Intolerances. *Mediators of Inflammation*, UNSP 245308. https://doi.org/10.1155/2015/245308	suspected MCS subjects, 89 diagnosed FM/CFS subjects, and 196 controls. One genotype was associated with increased nitrite/nitrate levels only in MCS, FM/CFS subjects. Results also showed that NOS2A -2.5 kb (CCTTT), a NOS allele, represents a genetic determinant for FM/CFS, and that it discriminates diagnosable MCS from sMCS patients. The (CCTTT) allele reduces the risks of MCS, sMCS, and FM/CFS but 3, 6, and 10 folds, respectively. The higher number of (CCTTT) repeats associates with higher concentrations of nitrites/nitrates. The polymorphism NOS2A -2.5 kb (CCTTT) may be useful for the diagnoses of various IEI. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of NMDA oxidation	
Pall, M. L.	Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite.	Pall, M. L. (2001). Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. *Medical Hypotheses*, *57*(2), 139–145. https://doi.org/10.1054/mehy.2001.1325	Four conditions, CFS, FM, MCS, and PTSD share common symptoms. These disorders are often induced by a relatively short-term stress with the mechanism of having elevated levels of nitric oxide and peroxynitrite. Six positive feedback loops were proposed to act when peroxynitrite levels are elevated. Evidence of the role of elevated nitric oxide/peroxynitrite is summarized for the four conditions. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of NDMA oxidation.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
MOA –Psychological and Psychiatric Factors				
Bailer, J.; Rist, F.; Witthoft, M.; Paul, C.; Bayerl, C.	Symptom patterns, and perceptual and cognitive styles in subjects with multiple chemical sensitivity (MCS)	Bailer, J., Rist, F., Witthoft, M., Paul, C., & Bayerl, C. (2004). Symptom patterns, and perceptual and cognitive styles in subjects with multiple chemical sensitivity (MCS). *Journal of Environmental Psychology*, *24*(4), 517–525. https://doi.org/10.1016/j.jenvp.2004.08.002	In the study, 35 diagnosed subjects with moderate MCS intensity and 35 diagnosed subjects with high MCS intensity were compared to 36 controls in psychological questionnaires and structured interviews for depression and somatoform disorders. The subjects with high MCS intensity scored higher than the other groups on the scales for somatoform symptoms and depression, and was were strongly associated with the diagnosis of somatoform disorder and depression. The authors note that the results support a hypothesis that trait negativity and symptom perception amplification contribute to the enhanced symptom reports for the MCS subjects. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Bailer, J.; Witthoft, M.; Bayerl, C.; Rist, F.	Syndrome stability and psychological predictors of symptom severity in idiopathic environmental intolerance and somatoform disorders	Bailer, J., Witthoeft, M., Bayerl, C., & Rist, F. (2007a). Syndrome stability and psychological predictors of symptom severity in idiopathic environmental intolerance and somatoform disorders. *Psychological Medicine*, *37*(2), 271–281. https://doi.org/10.1017/S0033291706009354	In the prospective cohort study, the 1-year stability of somatic symptoms and IEI features in 49 diagnosed IEI subjects, 43 diagnosed SFD subjects, and 54 controls was examined. The results showed that the SFD and IEI groups scored higher on all measures of somatic symptoms and on the questionnaires assessing psychological predictors for somatization compared to the controls. Negative affectivity trait and the processes of symptoms perception, interpretation and attribution appeared to contribute to the persistence of SFD and	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			IEI symptoms. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Bailer, J.; Witthoft, M.; Bayerl, C.; Rist, F.	Trauma experience in individuals with idiopathic environmental intolerance and individuals with somatoform disorders	Bailer, J., Witthoeft, M., Bayerl, C., & Rist, F. (2007b). Trauma experience in individuals with idiopathic environmental intolerance and individuals with somatoform disorders. *Journal of Psychosomatic Research*, *63*(6), 657–661. https://doi.org/10.1016/j.jpsychores.2007.03.012	The cross-sectional study examined various lifetime traumas, diagnosed IEI and SFD by comparing 54 IEI subjects, 44 SFD subjects, and 54 controls free from IEI and SFD. At least one potential traumatic event was reported frequently in both groups, but there were no significant group differences in the proportion of subjects with neither any trauma, nor traumas that met DSM-IV criteria, or multipole traumas. No clear evidence was found for increased trauma experience in IEI and SFD. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Binder, L.M.; Storzbach, D.; Salinsky, M.C.	MMPI-2 profiles of persons with multiple chemical sensitivity	Binder, L. M., Storzbach, D., & Salinsky, M. C. (2006). MMPI-2 profiles of persons with multiple chemical sensitivity. *Clinical Neuropsychologist*, *20*(4), 848–857. https://doi.org/10.1080/13854040500246927	The MMPI-2 profiles of subjects with diagnosed MCS were compared to groups with diagnosed seizure conditions (ES and NES). There were 14 MCS patients who were matched on gender, age and education with patients with either ES or NES. Results indicated on the MMPI-2 Hs, D, and Hy scales, the MCS group had higher means than the ES or NES groups. The MMPI-2 data suggests that there is a strong psychological component to MCS symptoms. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Black, D.W.; Okiishi, C.; Schlosser, S.	A nine-year follow-up of people diagnosed with multiple chemical sensitivities	Black, D. W., Okiishi, C., & Schlosser, S. (2000b). A nine-year follow-up of people diagnosed with multiple chemical sensitivities. *Psychosomatics*, *41*(3), 253–261.	In this cohort study, the self-reported health status and clinical symptoms in individuals with MCS was assessed over at a 9-year follow-up interview in 69% (89 people) of the original sample using structured and semi-structured instruments and self-report questionnaires. Results showed that 83%, 56% and 56% of the subjects met the DSM-IV criteria for lifetime mood disorder, anxiety disorder, and somatoform disorder, respectively. The SCL-90 and Illness Behavior Questionnaire results showed little change from the original 1988 data. Many individuals with MCS remain symptomatic with ongoing lifestyle changes. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms, and psychological factors.	
Bloch, R.M.; Meggs, W.J.	Comorbidity patterns of self-reported chemical sensitivity, allergy, and other medical illnesses with anxiety and depression	Bloch, R. M., & Meggs, W. J. (2007). Comorbidity patterns of self-reported chemical sensitivity, allergy, and other medical illnesses with anxiety and depression. *Journal of Nutritional and Environmental Medicine*, *16*(2), 136–148. https://doi.org/10.1080/13590840701352823	Through a random dialing telephone survey, the relationship between self-reported chemical sensitivity, allergy, and medical illnesses, to anxiety and depression was assessed. 1027 households completed the survey and results showed that positive PRIME-MD screens for anxiety was significantly associated with increased risk of reporting chemical sensitivity and allergy. The study suggests that anxiety and depression have strong associations with varying illnesses, including chemical sensitivity and that there may be a psychosomatic component that influences symptom onset and duration.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Quality of study: ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Bornschein, S.; Hausteiner, C.; Zilker, T.; Forstl, H.	Psychiatric and somatic disorders and multiple chemical sensitivity (MCS) in 264 'environmental patients'	Bornschein, S., Hausteiner, C., Zilker, T., & Forstl, H. (2002). Psychiatric and somatic disorders and multiple chemical sensitivity (MCS) in 264 “environmental patients.” *Psychological Medicine*, *32*(8), 1387–1394. https://doi.org/10.1017/S0033291702006554	In this retrospective cohort study, 264 diagnosed MCS/IEI patients underwent routine medical examination, toxicological analysis, and clinical interview for DSM-IV psychiatric disorders within a 2-year period. The results indicated that 75% of the patients met the DSM-IV criteria for at least one psychiatric disorder, 35% of the patients suffered from somatoform disorders, and other frequent diagnoses were affective and anxiety, and dependence or substance abuse. The study confirms previous findings that MCS is a type of subgroup of somatoform disorders. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Bornschein, S; Hausteiner, C; Roemmelt, H; Nowak, D; Foerstl, H; Zilker, T	Double-blind placebo-controlled provocation study in patients with subjective Multiple Chemical Sensitivity (MCS) and matched control subjects	Bornschein, S., Hausteiner, C., Roemmelt, H., Nowak, D., Foerstl, H., & Zilker, T. (2008). Double-blind placebo-controlled provocation study in patients with subjective Multiple Chemical Sensitivity (MCS) and matched control subjects. *Clinical Toxicology*, *46*(5), 443–449. https://doi.org/10.1080/15563650701742438	In the double-blind placebo-controlled study, two hypotheses were tested: MCS patients can distinguish reliably between solvents and placebo, and that there are significant differences in biological and neuropsychological parameters between solvent and placebo exposures. 20 diagnosed MCS patients and 17 controls underwent 6 exposure sessions (solvent mixture and clean air in random order, double-blind). Blood samples were collected. Results showed that there were no differences between the groups in sensitivity, specificity, accuracy, and	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			cognitive performance. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Caccappolo-van Vliet, E.C.-V.; Kelly-McNeil, K.; Natelson, B.; Kipen, H.; Fiedler, N.	Anxiety sensitivity and depression in multiple chemical sensitivities and asthma	Caccappolo-van Vliet, E., Kelly-McNeil, K., Natelson, B., Kipen, H., & Fiedler, N. (2002). Anxiety sensitivity and depression in multiple chemical sensitivities and asthma. *Journal of Occupational and Environmental Medicine*, *44*(10), 890–901. https://doi.org/10.1097/01.jom.0000026646.83602.bb	In the case-control study, 30 MCS patients, 19 asthmatics, and 31 controls underwent assessment for lifetime and current psychiatric disorders, personality traits associated with symptom reporting, and tests of cognitive function. Results showed that MCS patients and asthmatics scored higher on chemical odor intolerance and anxiety sensitivity. MCS patients with comorbid depression performed worse on verbal memory test relative to asthmatics but not the controls. The authors suggest that anxiety and depression are significant to MCS physical and cognitive symptoms. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Cui, X.; Lu, X.; Hisada, A.; Fujiwara, Y.; Katoh, T.	The correlation between mental health and multiple chemical sensitivity: a survey study in Japanese workers	Cui, X., Lu, X., Hisada, A., Fujiwara, Y., & Katoh, T. (2015). The correlation between mental health and multiple chemical sensitivity: a survey study in Japanese workers. *Environmental Health and Preventive Medicine*, *20*(2), 123–129. https://doi.org/10.1007/s12199-014-0434-2	The cross-sectional study assessed the correlation between mental health and MCS from the use of 565 QEESI© questionnaires on workers for two large companies exposed to chemicals. A structural regression path was composed using structural equation analysis to determine if chemical exposure had an impact on mental health. A significant causal relationship was found between MCS and mental health. **Quality of study:** ** **Relevant to Objectives:** Yes, will be	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			included under discussion of psychology	
Davidoff, A.L.; Fogarty, L.; Keyl, P.M.	Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome	Davidoff, A. L., Fogarty, L., & Keyl, P. M. (2000). Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. *Archives of Environmental Health*, *55*(3), 165–175.	This paper describes three studies evaluating the possibility of non-psychiatric explanations of the psychologic/psychiatric symptom data in MCS. The first study applied the MMPI-2 to 56 diagnosed MCS patients to determine what changed after they developed MCS. Study two involved professionals to predict the types of changes reported and study 3 involved a second sample of 100 diagnosed MCS patients to complete the MMPI-2 and other questionnaires. The data from the first study suggested that MCS might result in a psychopathological MMPI-2 profile with abnormal hypochondriasis and hysteria scores. The prediction from study 2 showed a consensus about the changes seen from the syndrome including elevated hypochondriasis, hysteria, psychasthenia, depression, and schizophrenia scale scores. The third study showed elevations on the hypochondriasis, hysteria, depression in female patients, and schizophrenia scales. The authors concluded that the study data support a hypothesis that MCS patients do not show abnormal psychopathology different than a healthy person with a chronic illness. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychological factors.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Devriese, S.; Winters, W.; Stegen, K.; Van Diest, I.; Veulemans, H.; Nemery, B.; Eelen, P.; Van de Woestijne, K.; Van den Bergh, O.	Generalization of acquired somatic symptoms in response to odors: A Pavlovian perspective on multiple chemical sensitivity	Devriese, S., Winters, W., Stegen, K., Van Diest, I., Veulemans, H., Nemery, B., … Van den Bergh, O. (2000). Generalization of acquired somatic symptoms in response to odors: A Pavlovian perspective on multiple chemical sensitivity. *Psychosomatic Medicine*, *62*(6), 751–759.	In the semi-randomized study, 56 individuals underwent testing which involved exposure to one odor (ammonia or niaouli) mixed with 7.4% CO_2-enriched air during 2-minute trails (CS+ trial) and other odor with air (CS- trial). 3 CS+ and 3 CS- trials were conducted. Where the test phase involved one CS+-only (CS+ without CO_2) and one CS-test trial, followed by three trials using new odors (butyric acid, acetic acid, and citric aroma). Half of the subjects were tested immediately, with the other half tested after a week. Results showed that participants had more symptoms in the CS+ only exposures when ammonia was used as the CS+. Conclusions drawn from the study was that symptoms that occur due to odors can be learned and generalized to new substances, especially with people with high negative affectivity, suggesting a Pavlovian like mechanism. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Eek, F.; Karlson, B.; Österberg, K.; Ostergren, P.-O.	Factors associated with prospective development of environmental annoyance	Eek, F., Karlson, B., Österberg, K., & Ostergren, P.-O. (2010). Factors associated with prospective development of environmental annoyance. *Journal of Psychosomatic Research*, *69*(1), 9–15. https://doi.org/10.1016/j.jpsychores.2009.12.001	In the prospective panel study design, 10,275 were recruited by a postal survey, that included 5 questions about annoyance from environmental factors as a baseline and for a follow-up 5 years later. Results indicated that participants having developed environmental annoyance in between the baseline and follow-up had elevated subjective health complaints, high stress in daily life and a strained work	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			situation. The authors suggest a link between environmental factors and subjective health issues. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Fuller-Thomson, E.; Sulman, J.; Brennenstuhl, S.; Merchant, M.	Functional somatic syndromes and childhood physical abuse in women: Data from a representative community-based sample	Fuller-Thomson, E., Sulman, J., Brennenstuhl, S., & Merchant, M. (2011). Functional somatic syndromes and childhood physical abuse in women: Data from a representative community-based sample. *Journal of Aggression, Maltreatment and Trauma*, *20*(4), 445–469. https://doi.org/10.1080/10926771.2011.566035	The retrospective cross-sectional study investigated if childhood physical abuse was associated with functional somatic syndromes. A community based subsample of 7,342 women from the 2005 Canadian Health Survey reported if they have been diagnosed with CFS, FM, IBS, or MCS. The results showed that 749 individuals reported being physically abused in their youth and when the confounding factors were controlled, childhood physical abuse was significantly associated with CFS, FM, and MCS. For future research, longitudinal research is required along with a more objective assessment of FSS. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Hausteiner, C.; Mergeay, A.; Bornschein, S.; Zilker, T.; Forstl, H.	New aspects of psychiatric morbidity in idiopathic environmental intolerances	Hausteiner, C., Mergeay, A., Bornschein, S., Zilker, T., & Forstl, H. (2006). New aspects of psychiatric morbidity in idiopathic environmental intolerances. *Journal of Occupational and Environmental Medicine*, *48*(1), 76–82. https://doi.org/10.1097/01.jom.0000182207.68987.d7	A standardized interview was applied to 305 environmental patients, who were further differentiated as having been diagnosed IEI (54) or not (control, 251) following medical assessment. The results indicated that the most frequent diagnoses are of somatoform, affective and anxiety disorders. Psychotic disorders were found at a higher prevalence in IEI patients.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Quality of study: ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Henningsson, M.; Sundbom, E.	Conversion disorder and multiple chemical sensitivity: A comparative study of psychological defense strategies	Henningsson, M., & Sundbom, E. (2000). Conversion disorder and multiple chemical sensitivity: A comparative study of psychological defense strategies. *Perceptual and Motor Skills*, *91*(3), 803–818. https://doi.org/10.2466/PMS.91.7.803-818	The perceptual Defense Mechanism Test (anxiety-provoking stimulus) was used to compare the psychological defense strategies for 10 patients with diagnosed MCS, 10 patients with conversion disorder, and controls. Results showed that the clinical groups were distinct from each other and from controls. MCS patients demonstrated an inability to verbalize emotions, the defensive strategy for the MCS group was blocking from consciousness maneuvers, and for the conversion disorder group it was distortion of content. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychological factors.	
Meulders, A.; Fannes, S.; Van Diest, I.; De Peuter, S.; Vansteenwegen, D.; Van den Bergh, O.	Resistance to extinction in an odor-20% CO_2 inhalation paradigm: Further evidence for a symptom learning account of multiple chemical sensitivity	Meulders, A., Fannes, S., Van Diest, I., De Peuter, S., Vansteenwegen, D., & Van den Bergh, O. (2010). Resistance to extinction in an odor–20% CO_2 inhalation paradigm: Further evidence for a symptom learning account of multiple chemical sensitivity. *Journal of Psychosomatic Research*, *68*(1), 47–56.	In the randomized study, healthy participants underwent a learning phase and a test phase to test a laboratory model of MCS by symptom learning. Participants underwent a learning phase in which 3 breathing trials of BA mixed with CO_2 and 3 trials of AM mixed with regular air or the reverse combination. In the test phase the same trials were administered without CO_2. The AM and BA were the conditioned stimuli (CSs) and after odor onset, anxiety and expectancy to experience symptoms was rated. Self-reported symptoms were addressed after each trail while the	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			respiratory behavior was tracked throughout the experiment. Results indicated that those participant that anticipated symptoms in the learning phase correctly, reported elevated symptoms in response to the test phase. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Österberg, K.; Karlson, B.; Orbaek, P.	Personality, mental distress, and risk perception in subjects with multiple chemical sensitivity and toxic encephalopathy	Österberg, K., Karlson, B., & Orbaek, P. (2002). Personality, mental distress, and risk perception in subjects with multiple chemical sensitivity and toxic encephalopathy. *Scandinavian Journal of Psychology*, *43*(2), 169–175. https://doi.org/10.1111/1467-9450.00283	To evaluate the potential for increased vulnerability to neural sensitization, four groups of individuals were considered: 17 diagnosed MCS subjects (male and female), male subjects with toxic encephalopathy (TE) (2 groups, 31 and 26 subjects respectively), and a control group (n=200). Several tests and scales were applied to subjects, including: SCL-90, and Meta Contrast Technique test. Some evidence of mental distress was evident in the MCS group relative to controls, but not as pronounced as was observed in the TE groups. The authors speculate a limbic sensitization mechanism rather than a somatic-immunological or psychiatric mechanism. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Poonai, N.; Antony, M. M.; Binkley, K. E.; Stenn, P.; Swinson, R. P.;	Carbon dioxide inhalation challenges in idiopathic environmental intolerance	Poonai, N., Antony, M., Binkley, K., Stenn, P., Swinson, R., Corey, P., … Tarlo, S. (2000). Carbon dioxide inhalation challenges in idiopathic environmental intolerances. *Journal of Allergy and Clinical Immunology*, *105*(1), S128–S128.	The case-control, single blind study was conducted on 36 diagnosed IEI patients and 37 controls to test the hypothesis that patients with symptoms suggesting IEI exhibit features of panic disorders to	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Corey, P.; Silverman, F. S.; Tarlo, S. M.		https://doi.org/10.1016/S0091-6749(00)90811-X	environmental stimuli (single breath inhalation to air with 35% CO_2 for 5s via a flow spirometer). Subjects were also exposed to fresh air, with 10-min resting phases between. Results showed that IEI patients scored higher on the Anxiety Sensitivity Index than the controls and more IEI patients fulfilled the diagnostic criteria several mood and anxiety disorders after CO_2, as IEI patients had a higher anxiety sensitivity and response to CO_2 inhalation. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Poonai, N.P.; Antony, M.M.; Binkley, K.E.; Stenn, P.; Swinson, R.P.; Corey, P.; Silverman, F.S.; Tarlo, S.M.	Psychological features of subjects with idiopathic environmental intolerance	Poonai, N. P., Antony, M. M., Binkley, K. E., Stenn, P., Swinson, R. P., Corey, P., … Tarlo, S. M. (2001). Psychological features of subjects with idiopathic environmental intolerance. *Journal of Psychosomatic Research*, *51*(3), 537–541. https://doi.org/10.1016/S0022-3999(01)00250-1	In this retrospective case-control study, 36 diagnosed IEI patients (from Poonai et al. 2000) and 37 controls were compared by a self-report psychological questionnaire to assess depression, stress, anxiety, and agoraphobic symptoms. The results indicated that IEI subjects scored higher in the ACQ, DASS, and MI when compared to controls. IEI patients have higher morbidity than control population but less than what would be expected for clinical psychiatric population. The authors suggest possible value in psychological intervention as a management strategy. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	This study also makes recommendations regarding management.

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Rethage, T.; Eis, D.; Gieler, U.; Nowak, D.; Wiesmüller, G.A.; Lacour, M.; Hodapp, V.; Stilianakis, N.; Eikmann, T.F.; W. Herr, C.E.	Assessment of environmental worry in health-related settings: Re-evaluation and modification of an environmental worry scale	Rethage, T., Eis, D., Gieler, U., Nowak, D., Wiesmueller, G. A., Lacour, M., … Herr, C. E. W. (2008). Assessment of environmental worry in health-related settings: Re-evaluation and modification of an environmental worry scale. *International Journal of Hygiene and Environmental Health*, *211*(1–2), 105–113. https://doi.org/10.1016/j.ijheh.2007.01.030	In order to re-evaluate and modify the EWS, 227 patients suffering from an environmental disease were examined in the cross-sectional study. The participants were subdivided into patients with self-reported MCS and patients without sMCS and completed the EWS and a worry scale. For a reference group, 161 healthy interview participants from a previous epidemiological study were used. The analysis of the data differentiated two components of worry: “personal” and “general” environmental worry. The two components lead to a new evaluation method. The new evaluation method was then applied to 227 patients with or without self-reported MCS. The results indicated that new developed evaluation with a ratio of “personal” and “general” worry can be calculated. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Skovbjerg, S.; Rasmussen, A.; Zachariae, R.; Schmidt, L.; Lund, R.; Elberling, J.	The association between idiopathic environmental intolerance and psychological distress, and the influence of social support and recent major life events	Skovbjerg, S., Rasmussen, A., Zachariae, R., Schmidt, L., Lund, R., & Elberling, J. (2012). The association between idiopathic environmental intolerance and psychological distress, and the influence of social support and recent major life events. *Environmental Health and Preventive Medicine*, *17*(1), 2–9. https://doi.org/10.1007/s12199-011-0210-5	In the ecological study, 101 individuals who contacted the Danish Research Centre for Chemical Sensitivities and 136 individuals who had been diagnosed with environmental intolerance underwent questionnaires to study the association between psychological distress and IEI and symptoms of psychological distress. The study confirmed positive and significant associations between psychological distress and IEI, and that the association cannot be explained by known risk factors.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			The authors suggest that distress may be a risk factor for IEI or a symptom of more severe IEI. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Skovbjerg, S.; Zachariae, R.; Rasmussen, A.; Johansen, J.D.; Elberling, J.	Repressive coping and alexithymia in idiopathic environmental intolerance	Skovbjerg, S., Zachariae, R., Rasmussen, A., Johansen, J. D., & Elberling, J. (2010). Repressive coping and alexithymia in idiopathic environmental intolerance. *Environmental Health and Preventive Medicine*, *15*(5), 299–310. https://doi.org/10.1007/s12199-010-0143-4	A total 787 individuals who previously reported symptoms of environmental intolerance, and 237 diagnosed IEI patients, completed questionnaires assessing IEI by completing the MCSDS, TMAS, TAD-20, and NAS. Hierarchical linear regression analyses were conducted, and the results provided no evidence of repressive coping skills in IEI subjects. The influence of emotional reactions in IEI can be explored as the results showed strong association between IEI and negative emotional reactions, defensiveness and difficulties identifying feelings. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology, although the lack of control group may limit the results.	
Skovbjerg, S.; Zachariae, R.; Rasmussen, A.; Johansen, J.D.; Jesper Elberling	Attention to bodily sensations and symptom perception in individuals with idiopathic environmental intolerance	Skovbjerg, S., Zachariae, R., Rasmussen, A., Johansen, J. D., & Jesper, E. (2010). Attention to bodily sensations and symptom perception in individuals with idiopathic environmental intolerance. *Environmental Health and Preventive Medicine*, *15*(3), 141–150. https://doi.org/10.1007/s12199-009-0120-y	In this cross-sectional study, a total of 732 individuals from the general population, including self-reported IEI individuals and clinically diagnosed IEI patients were compared. Subjects completed questionnaires including the SSAS, APQ, TAS, NAS to investigate if measures of somato-sensory amplification, autonomic perception and absorption are associated	mechanism - psychology

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			with IEI. The results through hierarchical linear regression analyses showed there are positive associations between SSAS, APQ, and IEI, and a small inverse association was seen between TAS and IEI. The association with SSAS and APQ suggests that to understand the disorder, perceptual personality characteristics are important. The authors note that the study provides evidence of an association between somato-sensory amplification, autonomic perception, and number of symptom reports. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology. No control group was included.	
Tonori, H.; Aizawa, Y.; Ojima, M.; Miyata, M.; Ishikawa, S.; Sakabe, K.	Anxiety and depressive states in multiple chemical sensitivity	Tonori, H., Aizawa, Y., Ojima, M., Miyata, M., Ishikawa, S., & Sakabe, K. (2001). Anxiety and depressive states in multiple chemical sensitivity. *Tohoku Journal of Experimental Medicine*, *193*(2), 115–126. https://doi.org/10.1620/tjem.193.115	In the case-control study, 48 diagnosed MCS subjects and 48 controls (patients visiting ophthalmologists with other diseases) underwent evaluation of anxiety and depressive state using the Japanese version of the State-Trait Anxiety Inventory, SDS, and the Hamilton Rating Scale for Depression. MCS was found to be characterized by continuous high anxiety level and by the continuance of depressive state at a “neurotic level” category by the SDS. In MCS patients, anxiety and a depressive state remained at a continuous high level until subsequent examination while controls decreased to the normal level. **Quality of study:** *** **Relevant to Objectives:** Yes, will be	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			included under discussion of psychology	
Weiss, E.M.; Singewald, E.; Baldus, C.; Hofer, E.; Marksteiner, J.; Nasrouei, S.; Ruepp, B.; Kapfhammer, H.-P.; Fitz, W.; Mai, C.; Bauer, A.; Papousek, I.; Holzer, P.	Differences in psychological and somatic symptom cluster score profiles between subjects with Idiopathic environmental intolerance, major depression and schizophrenia	Weiss, E. M., Singewald, E., Baldus, C., Hofer, E., Marksteiner, J., Nasrouei, S., … Holzer, P. (2017). Differences in psychological and somatic symptom cluster score profiles between subjects with Idiopathic environmental intolerance, major depression and schizophrenia. *Psychiatry Research*, *249*, 187–194. https://doi.org/10.1016/j.psychres.2016.12.057	The cross-sectional study examined 25 diagnosed IEI patients, 26 patients with major depression and 19 patients with schizophrenia for overlapping psychological and somatic symptoms as well as differences. The IEI patients reported higher physical symptoms, schizophrenia patients showed higher levels in self-experienced disturbances, and patients with depression showed highest ratings for anxiety and depression. These results suggest that IEI patients can be distinguished from subjects with depression and schizophrenia, and that specific domains of psychological and somatic symptoms are seen for specific diagnostic groups. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Witthoeft, M.; Rist, F.; Bailer, J.	Evidence for a specific link between the personality trait of absorption and idiopathic environmental intolerance	Witthoeft, M., Rist, F., & Bailer, J. (2008). Evidence for a specific link between the personality trait of absorption and idiopathic environmental intolerance. *Journal of Toxicology and Environmental Health-Part a-Current Issues*, *71*(11–12), 795–802. https://doi.org/10.1080/15287390801985687	This longitudinal study investigated if diagnosed IEI was related to absorption (predisposition to be immersed in sensory or mystical experiences) by comparing 54 diagnosed IEI subjects, 44 subjects with SFD (without IEI) and 54 controls utilizing self-report measures of somatic symptoms, severity of IEI and the level of absorption at first examination and 32 months later. Results showed that IEI was associated with the tendency to experience self-altering states of consciousness. The	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			authors suggest that absorption might contribute to IEI by enhancing the susceptibility for IEI-specific conviction or by conditioning processes of medically unexplained symptoms by enhanced cognitive-imaginative representations of assumed IEI triggers. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Witthoeft, Michael; Rist, Fred; Bailer, Josef	Abnormalities in cognitive-emotional information processing in idiopathic environmental intolerance and somatoform disorders	Witthoeft, M., Rist, F., & Bailer, J. (2009). Abnormalities in cognitive-emotional information processing in idiopathic environmental intolerance and somatoform disorders. *Journal of Behavior Therapy and Experimental Psychiatry*, *40*(1), 70–84. https://doi.org/10.1016/j.jbtep.2008.04.002	In this case-control study, 49 diagnosed IEI subjects, 43 diagnosed somatoform disorder subjects, and 54 controls were compared based on the Simon task to investigate cognitive-emotional abnormalities. Results demonstrated negative association effects toward IEI-trigger words were strongest for IEI subjects compared to the other two groups, whereas emotional intrusion effects of symptom words were larger than IEI and SFD subjects relative to controls. Results support cognitive models of IEI. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
Witthoft, M.; Gerlach, A.L.; Bailer, J.	Selective attention, memory bias, and symptom perception in idiopathic environmental intolerance and somatoform disorders	Witthoeft, M., Gerlach, A. L., & Bailer, J. (2006). Selective attention, memory bias, and symptom perception in idiopathic environmental intolerance and somatoform disorders. *Journal of Abnormal Psychology*, *115*(3), 397–407. https://doi.org/10.1037/0021-843X.115.3.397	In this case-control study, 54 diagnosed IEI subjects, 44 diagnosed somatoform disorder subjects, and 54 controls underwent a series of tasks for attention and memory for somatic symptom and IEI-trigger words. In a dot-probe task, the groups did not differ. There was a bias in the IEI and SFD groups towards symptom	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			words by not toward IEI-trigger words in an emotional Stroop task. The IEI group rated the trigger words as more unpleasant and more arousing while also remembering them better in a recognition task. The authors suggest that both implicit and explicit cognitive processes are related to IEI. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of psychology	
MOA – Neurogenic inflammation and sensitization				
Claeson, A.-S.; Andersson, L.	Symptoms from masked acrolein exposure suggest altered trigeminal reactivity in chemical intolerance	Claeson, A.-S., & Andersson, L. (2017). Symptoms from masked acrolein exposure suggest altered trigeminal reactivity in chemical intolerance. *Neurotoxicology*, *60*, 92–98. https://doi.org/10.1016/j.neuro.2017.03.007	In this blind case-control study, 18 individuals with CI and 19 controls were exposed to acrolein, heptane or clean air within an exposure chamber to investigate if individuals with self-reported CI report more sensory irritation during acrolein exposure compared to controls without CI. Participants were exposed to two conditions, where the first was being exposed to the masking compound heptane and the second being heptane and acrolein at concentrations below the reported sensory irritation thresholds for an exposure time of 60 minutes. Individuals with CI reported greater sensory irritation in eyes, nose and throat when exposed masked acrolein when compared to the controls, but no difference was seen in exposure to heptane only. The authors suggest that there is altered trigeminal reactivity in individuals with CI compared to	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			controls. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of symptoms.	
Elberling, J.; Lerbaek, A.; Kyvik, K. O.; Hjelmborg, J.	A twin study of perfume-related respiratory symptoms	Elberling, J., Lerbaek, A., Kyvik, K. O., & Hjelmborg, J. (2009). A twin study of perfume-related respiratory symptoms. *International Journal of Hygiene and Environmental Health*, *212*(6), 670–678. https://doi.org/10.1016/j.ijheh.2009.05.001	A total of 570 pairs of identical twins and 817 fraternal twins were included in a study examining the heritability of perfume-related respiratory symptoms and see if the co-occurrences of the symptoms in asthma, atopic dermatitis, hand eczema or contact allergy are influenced by environmental or genetic factors common with these diseases. About 40% of the observed correlation between atopic dermatitis symptoms and respiratory symptoms in response to perfume exposure were attributable to genetic factors (e.g. genes for the protein filaggrin). However, the co-occurrence of symptoms of hand eczema, contact allergy and asthma were not attributable to genetic factors or shared environments during childhood. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of respiratory	
Holst, H.; Arendt-Nielsen, L.; Mosbech, H.; Serup, J.; Elberling, J.	Capsaicin-induced neurogenic inflammation in the skin in patients with symptoms induced by odorous chemicals	Holst, H., Arendt-Nielsen, L., Mosbech, H., Serup, J., & Elberling, J. (2011). Capsaicin-induced neurogenic inflammation in the skin in patients with symptoms induced by odorous chemicals. *Skin Research and Technology*, *17*(1), 82–90. https://doi.org/10.1111/j.1600-0846.2010.00470.x	In this case-control study, 16 MCS patients, 15 eczema patients, and 29 controls were administered 2 intradermal injections of capsaicin to compare the capsaicin-induced neurogenic inflammation and erythema intensity. Erythema intensity and flare area did not differ between patients and controls and they were not	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			correlated. There was a dose-dependent increase for erythema intensity and flare area. Both erythema intensity and visual flare were normal for MCS and EC patients. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization.	
Holst, H.; Arendt-Nielsen, L.; Mosbech, H.; Vesterhauge, S.; Elberling, J.	The capsaicin cough reflex in patients with symptoms elicited by odorous chemicals	Holst, H., Arendt-Nielsen, L., Mosbech, H., Vesterhauge, S., & Elberling, J. (2010). The capsaicin cough reflex in patients with symptoms elicited by odorous chemicals. *International Journal of Hygiene and Environmental Health*, *213*(1), 66–71. https://doi.org/10.1016/j.ijheh.2009.08.005	The case-control study, 16 MCS patients, 15 eczema patients with airway symptoms and 29 controls underwent the tidal breathing method to test if capsaicin induced cough reflex was similar to patients with symptoms related to odorous chemicals and what extent the lower airway symptoms influence the cough reflex. Results showed that there was no difference between the groups in age, body mass index, or pulmonary function. The lower airway symptoms were correlated to increased cough reflex. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization.	
Holst, H.; Arendt-Nielsen, L.; Mosbech, H.; Elberling, J.	Increased capsaicin-induced secondary hyperalgesia in patients with multiple chemical sensitivity	Holst, H., Arendt-Nielsen, L., Mosbech, H., & Elberling, J. (2011). Increased Capsaicin-induced Secondary Hyperalgesia in Patients With Multiple Chemical Sensitivity. *Clinical Journal of Pain*, *27*(2), 156–162. https://doi.org/10.1097/AJP.0b013e3181f9d60c	In the randomized control study, the exhaled breath content was measured under a control condition and under exposure to n-propanol, an olfactory stressor, in 10 health volunteers. The results indicated that recording system that was used was able to detect and differentiate the breath content during the two conditions. The results suggest that	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			chronic hypoxia could be involved in MCS disorder. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization.	
Österberg, K.; Orbaek, P.; Karlson, B.; Akesson, B.; Bergendorf, U.	Annoyance and performance during the experimental chemical challenge of subjects with multiple chemical sensitivity	Österberg, K., Orbaek, P., Karlson, B., Akesson, B., & Bergendorf, U. (2003). Annoyance and performance during the experimental chemical challenge of subjects with multiple chemical sensitivity. *Scandinavian Journal of Work Environment & Health*, *29*(1), 40–50.	In the case-control study, 10 individuals with MCS symptoms and 20 controls were challenged in an exposure chamber for 2 separate 2-hour sessions with exposure to toluene and n-butyl acetate. Subjects rated annoyance and the smell intensity while also completing a neurobehavioral test performance. Results showed that there was an increase in the annoyance ratings and a decrease in the test performance for both groups in the initial unexposed chamber phase and the first phase of the chemical exposure. The MCS group showed a reduction in test performance and had a steeper increase for the ratings of mucous membrane irritation and fatigue. The MCS group showed stronger build-up of fatigue, mucous membrane irritation and a reduced test performance during the exposure. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization	
Kiesswetter, E.; van Thriel, C.; Schaper, M.; Blaszkewicz, M.;	Eye blinks as indicator for sensory irritation during constant and peak exposures to 2-	Kiesswetter, E., van Thriel, C., Schaper, M., Blaszkewicz, M., & Seeber, A. (2005). Eye blinks as indicator for sensory irritation during constant and peak exposures to 2-ethylhexanol. *Environmental Toxicology and Pharmacology*, *19*(3), 531–541.	The case-control study tested the sensory irritating properties of 2-ethylhexanolin relation to dose and time by recording electromyographic eye blinks as an indicator of sensory irritation. Self-reported	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Seeber, A.	ethylhexanol	https://doi.org/10.1016/j.etap.2004.12.056	MCS subjects (12) and controls (12) were exposed to 20ethylhexanol at 1.5, 10, and 20 ppm in either constant or variable 4-hour exposures. There were 12 non-sMCS and 12 MCS subjects that were investigated under the variable conditions, and 12 non-sMCs and 8 sMCS subjects that were investigated under the constant exposure conditions. The results showed strong dose-response relationships between airborne solvent and blink rates. Blink rates for sMCS subjects were not significantly higher than control. Results indicate that the irritative potential of the chemical is higher than expected. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization.	
Kimata, H.	Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity	Kimata, H. (2004). Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity. *International Journal of Hygiene and Environmental Health*, *207*(2), 159–163. https://doi.org/10.1078/1438-4639-00262	In the cross-over randomized controlled trial, plasma levels of SP, VIP, and NGF in before and after VOC exposure from fresh-paint (8% solvents) were studied in 25 normal subjects, 25 AEDS patients, and 25 self-reported MCS patients. In addition, plasma histamine levels and skin wheal responses were also studied. The study was designed with 3 groups, where subjects were randomly assigned to the first, second and third group. Medical checkups were conducted every 5 minutes and after 15 minutes of exposure, and SP, VIP, and NGF were measured as well. Plasma levels of SP, VIP and NGF parameters in sMCS subjects increased when exposed to VOCs but had no effects	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			on AEDs subjects or controls. The results also showed that VOC exposure may enhance neurogenic inflammation with the enhancement of histamine-induced responses in MCS. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization.	
Nogami, H.; Odajima, H.; Shoji, S.; Shimoda, T.; Nishima, S.	Capsaicin provocation test as a diagnostic method for determining multiple chemical sensitivity	Nogami, H., Odajima, H., Shoji, S., Shimoda, T., & Nishima, S. (2004). Capsaicin Provocation Test as a Diagnostic Method for Determining Multiple Chemical Sensitivity. *Allergology International*, *53*(2), 153–157. https://doi.org/10.1111/j.1440-1592.2004.00317.x	The sensitivity of the cough reflex in relation to neurogenic inflammatory mechanism was evaluated in 15 MCS patients, 29 patients, and 29 control subjects, Subjects inhaled incremental concentrations of capsaicin for 15 seconds for inhalation intervals of 45 seconds. Ventilatory functions and the number of coughs per minute were measured. The results indicated no significant differences were observed in the ventilatory function test. The log concentration of capsaicin causing five or more coughs was significantly lower in MCS patients than in patients with chronic cough or control subjects. The authors note that the results are suggestive of a role of non-myelinated C-fiber neurons within the sensory nervous system in MCS. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation.	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Ternesten-Hasseus, E.; Bende, M.; Millqvist, E.	Increased capsaicin cough sensitivity in patients with multiple chemical sensitivity	Ternesten-Hasseus, E., Bende, M., & Millqvist, E. (2002). Increased capsaicin cough sensitivity in patients with multiple chemical sensitivity. *Journal of Occupational and Environmental Medicine*, *44*(11), 1012–1017. https://doi.org/10.1097/01.jom.0000034349.94005.3d	In the double-blind case-control study, 12 diagnosed MCS patients with chemically induced airway symptoms and 12 controls underwent randomized exposure to saline and or 2 increments of inhaled capsaicin via a mouthpiece for 6-minutes, separated by 4-minute rest periods. MCS patients demonstrated a significantly higher capsaicin cough sensitivity than controls. The authors hypothesize that neurogenic inflammation may be the mechanism involved. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization.	
Tran, M.T.D.; Arendt-Nielsen, L.; Kupers, R.; Elberling, J.	Multiple chemical sensitivity: On the scent of central sensitization	Tran, M. T. D., Arendt-Nielsen, L., Kupers, R., & Elberling, J. (2013). Multiple chemical sensitivity: On the scent of central sensitization. *International Journal of Hygiene and Environmental Health*, *216*(2), 202–210. https://doi.org/10.1016/j.ijheh.2012.02.010	This study used quantitative sensory testing to evaluate and compare hyperexcitability and aspects of the central sensory processing in 15 diagnosed MCS patients and 15 controls. Response to pain was assessed through: capsaicin-induced secondary punctate hyperalgesia, SRF to punctate mechanical stimuli before and after capsaicin injection, temporal summation to punctate stimuli post capsaicin injection, pressure pain thresholds, heat pain thresholds, tonic heat stimulation and CPM. Results showed that capsaicin-induced secondary punctate hyperalgesia was significantly more in MCS patients when compared to the controls suggesting facilitated central sensitization and hyperexcitability in MCS patients, above and beyond olfactory	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			processing changes. MCS patients also had higher pain ratings in the CPM test. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation	
Wiesmüller; G.A., Christoph Van Thriel; Steup, Achim; Bachert, Claus; et al	Nasal function in self-reported chemically intolerant individuals	Wiesmüller, G. A., Van Thriel, C., Steup, A., Bachert, C., Blaszkewicz, M., Golka, K., … Seeber, A. (2002). Nasal function in self-reported chemically intolerant individuals. *Archives of Environmental Health*, *57*(3), 247–254.	To investigate nasal functions in self-reported MCS individuals, anterior rhinomanometry and acoustic rhinometry were conducted on 12 sMCS individuals and 12 controls in the case-control study. Subjects were exposed to ethylbenzene and 2-butanone in sessions of 4-6 hours in duration, with four exposures separated by 2-days via a half-mask. Regardless of the chemical or exposure concentration sMCS individuals had a significantly decreased flow in the anterior rhinomanometry relative to controls. However, no corresponding effect was observed for acoustic rhinometry. The authors suggest a possible somatic /neurological component. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of neurogenic inflammation and sensitization.	
Management – Public Health				
Fox, R.A.; Joffres, M.R.; Sampalli, T.; Casey, J.	The impact of a multidisciplinary, holistic approach to management of patients diagnosed	Fox, R. A., Joffres, M. R., Sampalli, T., & Casey, J. (2007). The impact of a multidisciplinary, holistic approach to management of patients diagnosed with multiple chemical sensitivity on health care utilization costs: An observational study. *Journal of Alternative*	In the cohort study, a total of 563 diagnosed MCS patients formed 3 cohorts (145 in 1998; 181 in 1999; and 237 in 2000) to compare health care utilization in Nova Scotia, pre- and post-management of	Management – public health

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
	with multiple chemical sensitivity on health care utilization costs: An observational study	*and Complementary Medicine*, *13*(2), 223–229. https://doi.org/10.1089/acm.2006.6011	individuals with MCS by applying a detailed-symptoms questionnaire and undergoing research activities. The results indicated there was a relative decrease in the years after the consultation at NSEHC for physicians' visits by general practitioner and by specialists, emergency and hospital separations, and the associated costs of these visit. The patients with high symptom scores had highest decrease in physician visits. The paper presents the preliminary utilization costs in the management of MCS patients. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	
Gibson, P.R.	Of the world but not in it: Barriers to community access and education for persons with environmental sensitivities	Gibson, P. R. (2010). Of the world but not in it: Barriers to community access and education for persons with environmental sensitivities. *Health Care for Women International*, *31*(1), 3–16. https://doi.org/10.1080/07399330903042823	The cross-sectional study evaluated100 individuals with self-reported MCS about their level of community access, and barriers that prevent them from having access to these resources. Quantitative and qualitative data were analyzed and the results demonstrated that respondents with chemical and electrical sensitivities had tentative access for common community resources such communities of worship, grocery stores, health food stores, community meetings, public libraries, the homes of extended family members and friends, offices of dentists and medical doctors, public parks, and classes at their local universities. The two most common barriers to public buildings were reported to be: fragrance/perfume and cleaning products, and thus potential mitigation strategies include limiting fragrance use	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			and employ less toxic cleaners. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	
Gibson, P.R.; Elms, A.N.-M.; Ruding, L.A.	Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity	Gibson, P. R., Elms, A. N. M., & Ruding, L. A. (2003). Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. *Environmental Health Perspectives*, *111*(12), 1498–1504. https://doi.org/10.1289/ehp.5936	In this cross-sectional study, 917 subjects with self-reported MCS participated in a mail survey that examined health care use and the self-reported efficacy of 108 treatments that are commonly used for MCS. These treatments included environmental techniques, holistic therapies, and others. The results showed that subjects had consulted an average of 12 health care providers and spent over a third of their yearly salary. The paper discusses financial impacts and attitudes towards the possibility of healing from MCS. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	Management – clinical. This study also provides interesting information regarding symptom triggers
Gibson, P.R.; Lindberg, A.	Work accommodation for people with multiple chemical sensitivity	Gibson, P. R., & Lindberg, A. (2007). Work accommodation for people with multiple chemical sensitivity. *Disability & Society*, *22*(7), 717–732. https://doi.org/10.1080/09687590701659576	This study examined various work accommodations and experiences for 100 self-reported MCS individuals and the relation to life satisfaction. Participants answered questions about their demographics, work experiences, accommodations that have been introduced into their workplaces, and any workplace harassment that they have experienced. Unemployed persons were also included in the study. The most frequently received accommodations out of all that had been requested by patients	Management – public health

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			were: fragrance-free areas, the use of less toxic cleaners and insect control products. Work was described as being a struggle for most of the working participants, with harassment being a common experience in the workplace. **Quality of study:** ** **Relevant to Objectives:** Yes, the information regarding interventions will be included under discussion of public health management	
Gibson, P.R.; Sledd, L.G.; Mcenroe, W.H.; Vos, A.P.	Isolation and lack of access in multiple chemical sensitivity: A qualitative study	Gibson, P. R., Sledd, L. G., McEnroe, W. H., & Vos, A. P. (2011). Isolation and lack of access in multiple chemical sensitivity: A qualitative study. *Nursing & Health Sciences*, *13*(3), 232–237. https://doi.org/10.1111/j.1442-2018.2011.00606.x	A phenomenological perspective was used to focus on the impact of MCS on relationships through a qualitative interview study of 26 self-reported MCS individuals. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of management	Management – public health
Gibson P.R; Lindberg, A.	Physicians' Perceptions and Practices Regarding Patient Reports of Multiple Chemical Sensitivity	Gibson, P. R., & Lindberg, A. (2011). Physicians' Perceptions and Practices Regarding Patient Reports of Multiple Chemical Sensitivity. *ISRN Nursing*, *2011*. https://doi.org/10.5402/2011/838930	A mail survey was completed by 90 physicians to evaluate demographics, familiarity with MCS etiology, overlapping conditions, accommodations made for patients, treatment, and referrals. The results showed that under a third of the group received medical training for MCS, although a little over half were familiar with it. The interventions recommended included chemical avoidance, changes in diet and home environment, the use of air filters and referrals to specialists. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	Management – public health

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Gibson, P.R.; Lockaby, S.D.; Bryant, J.M.	Experiences of persons with multiple chemical sensitivity with mental health providers	Gibson, P. R., Lockaby, S. D., & Bryant, J. M. (2016). Experiences of persons with multiple chemical sensitivity with mental health providers. *Journal of Multidisciplinary Healthcare*, *9*. https://doi.org/10.2147/JMDH.S100688	Through an online survey of 60 individuals with self-reported chemical intolerance or MCS who sought help from health care providers, respondents reported their most recent contact with a health care provider, the reason for contact, and the accommodations requested and received and any suggestions for how the experience can be more helpful. Results showed that some clients did not receive any accommodation. The importance of providers being more aware of MCS is also discussed. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of management	Management – public health
Herr, C.E.W.; Kopka, I.; Mach, J.; Runkel, B.; Schill, W.-B.; Gieler, U.; Eikmann, T.F.	Interdisciplinary diagnostics in environmental medicine - Findings and follow-up in patients with chronic medically unexplained health complaints	Herr, C. E. W., Kopka, I., Mach, J., Runkel, B., Schill, W. B., Gieler, U., & Eikmann, T. F. (2004). Interdisciplinary diagnostics in environmental medicine - findings and follow-up in patients with chronic medically unexplained health complaints. *International Journal of Hygiene and Environmental Health*, *207*(1), 31–44. https://doi.org/10.1078/1438-4639-00263	This prospective study of people who had been suffering from self-reported long-term environmental symptoms involved a telephone survey followed by an in-person assessment at a clinic, where they were seen by multiple specialists. Co-morbid health conditions were also assessed. Of the 51 patients evaluated, 63% of the cases had symptoms lasting for more than 3 years, and 70% attributed it to more than one environmental case. Following discussions with the specialists, approximately half of the subjects were able to consider other explanations for their symptoms than environmental causes. Approximately 50% of the subjects were found to not have a psychosomatic disorder. **Quality of study:** ***	Management – public health

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Relevant to Objectives: Yes, will be included under discussion of management	
Koch, Lynn; Vierstra, Courtney; Penix, Ken	A Qualitative Investigation of the Psychosocial Impact of Multiple Chemical Sensitivity.	Koch, L., Vierstra, C., & Penix, K. (2006). A qualitative investigation of the psychosocial impact of multiple chemical sensitivity. *J. Appl. Rehabil. Counseling.*, *37*, 33–40.	Semi-structured telephone interviews were conducted on 10 individuals with self-reported MCS and the resulting data was organized into 9 preliminary categories to study the psychosocial impact of MCS. Results indicated that there are reoccurring themes observed that are key to the rehabilitation of people with MCS: including: on-going struggle to live in a chemical society, negative consequences of living with a condition that is invalidated, the result of psychosocial isolation, and the reliance of people with MCS on alternative coping and symptoms. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	Management – public health
Lipson, J.; Doiron, N.	Environmental issues and work: Women with multiple chemical sensitivities	Lipson, J. G., & Doiron, N. (2006). Environmental Issues and Work: Women With Multiple Chemical Sensitivities. Health Care for Women International, 27(7), 571–584. https://doi.org/10.1080/07399330600803709	The article is based on an ethnographic study of MCS in the United States and Canada. The article describes the issues associated with work as described by women. The encompassed 33 semi-structured interviews with people with self-reported MCS (most also had previously diagnosed MCS). Suggestions including MCS education to help increase accommodations were presented. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of management	

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Martini, A.; Iavicoli, S.; Corso, L.	Multiple chemical sensitivity and the workplace: Current position and need for an occupational health surveillance protocol	Martini, A., Iavicoli, S., & Corso, L. (2013). Multiple Chemical Sensitivity and the Workplace: Current Position and Need for an Occupational Health Surveillance Protocol. *Oxidative Medicine and Cellular Longevity*, *2013*, 351457. https://doi.org/10.1155/2013/351457	The article discusses various MCS diagnostic approaches and proposes an approach and flow-chart that physicians who are required to diagnose MCS may have a tool to use. **Quality of study:** ** **Relevant to Objectives:** Yes, will be included under discussion of management	
Sampalli, Tara; Shepherd, Michael; Duffy, Jack; Fox, Roy	An evaluation of SNOMED CT (R) in the domain of complex chronic conditions	Sampalli, T., Shepherd, M., Duffy, J., & Fox, R. (2010). An evaluation of SNOMED CT (R) in the domain of complex chronic conditions. *International Journal of Integrated Care*, *10*.	In the retrospective review of patient charts and feedback from multidisciplinary clinicians, the evaluation of the coverage of health factors in the concept-based clinical vocabulary system SNOMED CT (R) for MCS is conducted on 100 patient charts and 9 clinicians. Conclusions show that the SNOMED CT (R) has coverage that is relevant to MCS, but a few terms were not available in SNOMED CT indicating that there is room to expand the terminology within the system. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	Management – public health
Sampalli, T.; Shepherd, M.; Duffy, J.	Clinical vocabulary as a boundary object in multidisciplinary care management of multiple chemical sensitivity, a complex and chronic condition	Sampalli, T., Shepherd, M., & Duffy, J. (2011). Clinical vocabulary as a boundary object in multidisciplinary care management of multiple chemical sensitivity, a complex and chronic condition. *Journal of Multidisciplinary Healthcare*, *4*, 91–102. https://doi.org/10.2147/JMDH.S17564	In this study of 100 diagnosed MCS patients, 9 multidisciplinary clinicians that are involved in MCS patient care, and 36 community clinicians took part in developing a standardized, controlled clinical vocabulary as a boundary object to improve communication. This study identified that over 65% of the clinicians evaluated found the standardized vocabulary useful. **Quality of study:** **	Management – public health

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			Relevant to Objectives: Yes, will be included under discussion of management	
Skovbjerg, S.; Johansen, J.D.; Rasmussen, A.; Thorsen, H.; Elberling, J.	General practitioners' experiences with provision of healthcare to patients with self-reported multiple chemical sensitivity	Skovbjerg, S., Johansen, J. D., Rasmussen, A., Thorsen, H., & Elberling, J. (2009). General practitioners' experiences with provision of healthcare to patients with self-reported multiple chemical sensitivity. *Scandinavian Journal of Primary Health Care*, *27*(3), 148–152. https://doi.org/10.1080/02813430902888355	Through a cross-sectional survey, 671 general practitioners (GPs) who had directly managed patients with MCS completed structured questionnaires to evaluate evaluation and management strategies used for these patients. The majority of the GPs agreed that MCS has a multi-factorial etiology, and tt was determined that many GPs found it difficult to meet patient's expectations for healthcare and thus GPs requested more guidance for the management of MCS patients. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	Management – public health
Swoboda, D.A.	Negotiating the diagnostic uncertainty of contested illnesses: Physician practices and paradigms	Swoboda, D. A. (2008). Negotiating the diagnostic uncertainty of contested illnesses: physician practices and paradigms. *Health*, *12*(4), 453–478. https://doi.org/10.1177/1363459308094420	The study examined the tendency for physicians to diagnose CFS, MCS, and GWS through a survey. A total of 445 physicians responded to the survey, and results indicate that a considerable number of physicians are diagnosing CFS, MCS, and GWS and thus contributing to legitimizing the illness. The commonly used approaches to diagnosing MCS included medical history evaluation, empirical tests, and evaluation of exposure history. With respect to the cause of MCS, most doctors rejected psychological explanations but appear to disagree on etiology. Results also suggest that patients may benefit with working with physicians that use diagnostic	Management – public health

APPENDIX A

Table A-1 Annotated Bibliography of Studies to be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
			strategies such as including consulting ancillary information sources, conducting analytically informed tests and considering physiological explanations of causation. **Quality of study:** *** **Relevant to Objectives:** Yes, will be included under discussion of management	

Appendix A
Table A-2 Studies that Will Not be Carried Forward Into Literature Review

Author	*Title*	*Citation*	*Annotation*	*Notes*
Management – Clinical (Not included in literature review)				
Alessandrini, M.; Micarelli, A.; Bruno, E.; Ottaviani, F.; Conetta, M.; Cormano, A.; Genovesi, G.	Intranasal administration of hyaluronan as a further resource in olfactory performance in Multiple Chemical Sensitivity Syndrome	Alessandrini, M., Micarelli, A., Bruno, E., Ottaviani, F., Conetta, M., Cormano, A., & Genovesi, G. (2013). Intranasal Administration of Hyaluronan as a Further Resource in Olfactory Performance in Multiple Chemical Sensitivity Syndrome. *International Journal of Immunopathology and Pharmacology*, *26*(4), 1019–1025.	Intranasal administration of hyaluronan was evaluated for its modifying effect on odour threshold and quality of life in MCS syndrome was examined in 59 MCS patients. Using a double-blind randomized trial, the patients were randomized into two groups (nasal spray treatment or physiological solution) and exposed to various standardized tests for odour and anxiety. Results from the paired t-test analysis found a reduction in odor threshold and an improvement in QOD and SAS between the pre- and post-treatments results for the group with nasal spray treatment. There were also positive correlations found between the OT reduction, SAS and QOD improvement. HA can be suggested as a well-tolerated resource in alleviating MCS olfactory discomfort. **Quality of study:** *** **Relevant to Objectives:** Yes, but will not be carried forward into review, at the direction of Alberta Health.	

Araki, A.; Watanabe, K.; Eitaki, Y.; Kawai, T.; Kishi, R.	The feasibility of aromatherapy massage to reduce symptoms of Idiopathic Environmental Intolerance: A pilot study	Araki, A., Watanabe, K., Eitaki, Y., Kawai, T., & Kishi, R. (2012). The feasibility of aromatherapy massage to reduce symptoms of Idiopathic Environmental Intolerance: A pilot study. Complementary Therapies in Medicine, 20(6), 400–408. https://doi.org/10.1016/j.ctim.2012.07.005	The non-blinded crossover trail looked at the feasibility of aromatherapy massage for individuals with IEI. 16 participants received 4 one-hour aromatherapy massage sessions every two weeks and during the control period, the participants did not receive any massages. The scores on the IEI-scales trigger checklist, symptoms, life impact and the State Anxiety Inventory were assessed before and after each period. In addition, exposure monitoring of patients' homes was conducted and various aldehydes, acetone, and VOCS were monitored, and levels were general comparable to other population studies, with the exception of two homes that had acetone and p-dichlorobenzene concentrations about safe thresholds. Overall the results showed that aromatherapy was well tolerated by subjects with IEI other than complaints about the odours of the oils, but did not observe significant benefits in mitigation symptoms. **Quality of study:** *** **Relevant to Objectives:** Yes, but will not be carried forward into review, at the direction of Alberta Health.	

Fisher, M. McD; Rose, M.	Anaesthesia for patients with idiopathic environmental intolerance and chronic fatigue syndrome	Fisher, M. M., & Rose, M. (2008). Anaesthesia for patients with idiopathic environmental intolerance and chronic fatigue syndrome. *British Journal of Anaesthesia*, *101*(4), 486–491. https://doi.org/10.1093/bja/aen242	In the study, 27 patients were referred to an anaesthetic allergy clinic because of a perceived risk of or history of IEI, CFS, or both. Out of the 27 patients, 25 were studied by intradermal testing for drugs used in general anaesthesia. In addition, literature and web searches were performed on anaesthesia and these illnesses. The patients had adverse events related to anaesthesia that were not allergic in nature, self-limiting and occurred postoperatively. It is suggested that anaesthetist may use the technique that they would use for non- CFS and non-IEI patients, but to avoid the drugs that have history of adverse response. Further recommendations are provided for the safe conduct of anesthesia in CFS and IEI patients. **Quality of study:** *** **Relevant to Objectives:** Yes, but will not be carried forward into review, at the direction of Alberta Health.	

Fox, R. A.; Sampalli, T.	Adaptation to low levels of chemical exposure in individuals with multiple chemical sensitivity in a controlled indoor environment	Fox, R. A., & Sampalli, T. (2015). Adaptation to low levels of chemical exposure in individuals with multiple chemical sensitivity in a controlled indoor environment. *Indoor and Built Environment*, *24*(5), 713–721. https://doi.org/10.1177/1420326X14534094	In this double-blind randomized study, 90 diagnosed MCS subjects underwent exposure to low chemical concentrations in a controlled environment to determine if the findings will be consistent with a previous pilot study and if MCS individuals can adapt to the presences of “safe” household products. The test substances used in the study were scented dryer sheets or clean air, delivered to the controlled exposure booths within a steel box, with exposures separated by a week. Information regarding symptoms experienced, respiratory and hear rate, and skin conductance response tests (via surface electromyography, and are indicative of eccrine sweating and ANS function) were completed. The results confirmed physiological reactivity to the test substance in 60% of the female and 40% of the male subjects. Changes in skin conductance were determined to be the most consistent indicator of reactivity. **Quality of study:** *** **Relevant to Objectives:** Yes, but will not be carried forward into review, at the direction of Alberta Health.	

Hauge, C.R.; Rasmussen, A.; Piet, J.; Bonde, J.P.; Jensen, C.; Sumbundu, A.; Skovbjerg, S.	Mindfulness-based cognitive therapy (MBCT) for multiple chemical sensitivity (MCS): Results from a randomized controlled trial with 1-year follow-up	Hauge, C. R., Rasmussen, A., Piet, J., Bonde, J. P., Jensen, C., Sumbundu, A., & Skovbjerg, S. (2015). Mindfulness-based cognitive therapy (MBCT) for multiple chemical sensitivity (MCS): Results from a randomized controlled trial with 1-year follow-up. *Journal of Psychosomatic Research*, *79*(6), 628–634. https://doi.org/10.1016/j.jpsychores.2015.06.010	In the randomized control trial, the effects of mindfulness-based cognitive therapy (MBCT) were studied in individuals with MCS. A total of 69 individuals were randomized into the MBCT group or treatment as usual and completed the QEESI© and SCL-92. Participants were assessed at baseline, post treatment and at follow-ups at 6 and 12 months. Results indicated that there was no effect of MBCT on the QEESI© and on depression or anxiety. However, there were positive changes in illness perceptions. The MCBT did not change the illness status but does positively change the emotional and cognitive representations. **Quality of study:** *** **Relevant to Objectives:** Yes, but will not be carried forward into review, at the direction of Alberta Health.	
Skovbjerg, S.; Hauge, C.R.; Rasmussen, A.; Winkel, P.; Elberling, J.	Mindfulness-based cognitive therapy to treat multiple chemical sensitivities: A randomized pilot trial	Skovbjerg, S., Hauge, C. R., Rasmussen, A., Winkel, P., & Elberling, J. (2012). Mindfulness-based cognitive therapy to treat multiple chemical sensitivities: A randomized pilot trial. *Scandinavian Journal of Psychology*, *53*(3), 233–238. https://doi.org/10.1111/j.1467-9450.2012.00950.x	The randomized clinical trial was conducted on 37 adults to assess the feasibility of an 8-week mindfulness cognitive therapy program and to evaluate the effects it may have on the psychological distress and illness perception. The participants were randomized into treatment as usual (TAU) or MBCT and underwent assessment at baseline, 4 weeks, 8 weeks and a follow up at 3 months. Results showed that there were no significant differences in the measures between the groups. The participants that completed the MBCT program did report benefiting in coping strategies and sleep quality. **Quality of study:** *** **Relevant to Objectives:** Yes, but will not be carried forward into review, at the direction of Alberta Health.	

Tran, M.T.D.; Skovbjerg, S.; Arendt-Nielsen, L.; Christensen, K.B.; Elberling, J.	A randomised, placebo-controlled trial of transcranial pulsed electromagnetic fields in patients with multiple chemical sensitivity	Tran, M. T. D., Skovbjerg, S., Arendt-Nielsen, L., Christensen, K. B., & Elberling, J. (2016). *A randomised, placebo-controlled trial of transcranial pulsed electromagnetic fields in patients with multiple chemical sensitivity*. Article in Press. https://doi.org/10.1017/neu.2016.51	In the double-blind and placebo-controlled study, the efficacy of transcranially applied pulsed magnetic fields (PEMF) on functional impairments and symptom severity in MCS patients was evaluated. 39 participants received either PEMF or placebo for 6 weeks, and underwent the Life Impact, Symptom Severity and Chemical Intolerance portions of the QEESI©. The results showed that there was a significant decrease on the SSS within and between groups. Though the 6 weeks of PEMF treatment showed no significant effect on functional impairments in MCS, although a significant decrease in symptom severity was observed. **Quality of study:** *** **Relevant to Objectives:** Yes, but will not be carried forward into review, at the direction of Alberta Health.	
Studies Rejected During Full Text Review				
Bornschein, S.; Hausteiner, C.; Drzezga, A.; Bartenstein, P.; Schwaiger, M.; Forstl, H.; Zilker, Th	PET in patients with clear-cut multiple chemical sensitivity (MCS).	Bornschein, S., Hausteiner, C., Drzezga, A., Bartenstein, P., Schwaiger, M., Forstl, H., & Zilker, T. (2002). PET in patients with clear-cut multiple chemical sensitivity (MCS). *Nuklearmedizin-Nuclear Medicine*, *41*(6), 233–239.	It has been suggested that MCS leads to neurotoxic damage or neuroimmunological alteration in the brain that could be detected by PET and SPECT. This study scanned 12 MCS patients with PET and results showed that, in comparison with normal controls, MCS patients showed no significant brain changes. **Quality of study:** ** **Relevant to Objectives:** No, although the abstract is in English, the entire text of the paper is in German, and thus meets the exclusion criteria.	
Bornschein, S; Hausteiner, C; Roemmelt, H; Foerstl, H; Nowak, D; Zilker, T	Double-blind chemical exposure experiment in patients with MCS	Bornschein, S., Hausteiner, C., Roemmelt, H., Foerstl, H., Nowak, D., & Zilker, T. (2005). Double-blind chemical exposure experiment in patients with MCS. *Journal of Toxicology: Clinical Toxicology*, *43*(5), 436.	In the double-blind experiment, 20 MCS patients and 17 controls underwent 6 consecutive 15-minute exposure sessions (3 solvent and 3 placebo, i.e. clean air, exposures in random order, double-blind) followed by a 15-minute break. The mixture of solvents included toluene, xylene,	

			ethylacetate, heptane, decane, undecane at a concentration which was below odor threshold (800 mu g/m). There was continuous recording of the EEG, repeated monitoring of blood pressure, HR, and cognitive performance speed that was measured with ZVT. Significant group differences were not found. **Quality of study:** ** **Relevant to Objectives:** No, full text of this document cannot be found as this abstract with within a series of published abstracts related to the European Association of Poisons Centres and Clinical Toxicologists XXV International Congress.	
Brown, M.M.; Jason, L.A.	Functioning in individuals with chronic fatigue syndrome: Increased impairment with co-occurring multiple chemical sensitivity and fibromyalgia	Brown, M. M., & Jason, L. A. (2007). Functioning in individuals with chronic fatigue syndrome: increased impairment with co-occurring multiple chemical sensitivity and fibromyalgia. *Dynamic Medicine*, *6*, 6. https://doi.org/10.1186/1476-5918-6-6	In the cross-sectional study, 114 participants that met the criteria for CFS underwent physical examination for diagnosing FM, and a questionnaire to assess MCS to differentiate the diagnoses by comparing psychiatric comorbidity, coping style, and in vivo physical measures. The participants were divided into four groups: CFS alone, CFS-MCS, CFS-FM, and CFS-MCS-FM. Results indicated that the individuals that had CFS alone were the highest functioning group in several domains and the individuals with all 3 diagnoses had the greatest amount of disability. **Quality of study:** ** **Relevant to Objectives:** No, this study examined MCS prevalence within a population of individuals with diagnosed CFS, thus the conditions overlapped with the focus being on CFS	
Ciccone, D. S.; Natelson, B. H.	Comorbid illness in women with chronic fatigue syndrome: A test of the single syndrome hypothesis	Ciccone, D. S., & Natelson, B. H. (2003). Comorbid illness in women with chronic fatigue syndrome: A test of the single syndrome hypothesis. *Psychosomatic Medicine*, *65*(2), 268–275. https://doi.org/10.1097/01.PSY.0000033125.08272.A9	In the retrospective study, 163 females with diagnosed illnesses were assigned to one of four groups: CFS only, CFS/FM, CFS/MCS, and CFS/FM/MCS. The results showed that additional unexplained	

			symptoms were present within the sample group (37% for FM and 33% for MCS) and that there were few differences between the CFS only and CFS with comorbid illness groups. The study concluded that the support for the single syndrome hypothesis is apparent through the prevalence of comorbid illness in the CFS sample and the inability to find differences in symptom severity. Increasing comorbidity was associated with increased risk of major depression. **Quality of study:** ** **Relevant to Objectives:** No, MCS is only assessed as a co-morbid illness with CFS and FM.	
Dimitriadis, E. A.; Anagnostopoulos, I.	Multiple Chemical Sensitivities or Idiopathic Environmental Intolerances & Related Syndromes	Dimitriadis, E. A., & Anagnostopoulos, I. (2008). *Multiple Chemical Sensitivities or Idiopathic Environmental Intolerances & Related Syndroms*. (S. J. Baloyannis, Ed.). 40128 Bologna: Medimond S R L.	In editorial, the neurological and neurotoxic aspects of MCS problems are described. **Quality of study:** * **Relevant to Objectives:** No, will not be included because it is an editorial piece from a book and not a peer reviewed paper.	
Dumit, J.	Illnesses you have to fight to get: Facts as forces in uncertain, emergent illnesses	Dumit, J. (2006). Illnesses you have to fight to get: Facts as forces in uncertain, emergent illnesses. *Social Science & Medicine*, *62*(3), 577–590. https://doi.org/10.1016/j.socscimed.2005.06.018	The article discusses struggles of CFS and MCS patients and discusses how the illnesses are talked about in the US. It finds that CFS and MCS sufferers have experienced being denied healthcare. In addition, collective patient action can develop counter-tactics for these exclusions. **Quality of study:** * **Relevant to Objectives:** No, the data for this study was collected via internet newsgroups over a number of years	
Gilbert, M.E.	Does the kindling model of epilepsy contribute to our understanding of multiple chemical	Gilbert, M. E. (2001). Does the kindling model of epilepsy contribute to our understanding of multiple chemical sensitivity? *Annals of the New York Academy of Sciences*, *933*, 68–91.	Kindling is a model of synaptic plasticity where repeated low-level electrical stimulation brain sites leads to permanent increases in seizure susceptibility. Over time, stimulation that would initially be	

	sensitivity?		subthreshold for subclinical seizure provocation outcomes can cause full-blown motor seizures. MCS symptoms suggest that CNS limbic pathways involved in anxiety are altered in MCS patients and it is the limbic structures are the most susceptible to kindling-induced seizures in humans. Since there are a number of parallels between kindling and MCS, it is speculated that MCS may occur *via* kindling-like mechanism. The kindling model may serve for the enhanced chemical responsiveness characteristic of MCS and as a tool to selectively increase sensitivity in subcomponents of the neural fear circuit to address the role of anxiety in MCS patients. **Quality of study:** ** **Relevant to Objectives:** No, this is a review document, thus meets the exclusion criteria	
Gibson, P.R.	Chemical and electromagnetic exposures as disability barriers: Environmental sensitivity	Gibson, P. R. (2009). Chemical and electromagnetic exposures as disability barriers: environmental sensitivity. *Disability & Society*, *24*(2), 187–199. https://doi.org/10.1080/09687590802652454	The paper proposes that barriers should be integrated into the understanding of the disability. To move forward in legitimizing environmental sensitivities, a 3-part approach to action is presented. **Quality of study:** ** **Relevant to Objectives:** No, is an opinion piece and review, and thus meets exclusion criteria.	
Guthlin, C.; Anton, A.; Kruse, J.; Walach, H.	Subjective concepts of chronically ill patients using distant healing	Guethlin, C., Anton, A., Kruse, J., & Walach, H. (2012). Subjective Concepts of Chronically Ill Patients Using Distant Healing. *Qualitative Health Research*, *22*(3), 320–331. https://doi.org/10.1177/1049732311421914	During a four-armed randomized controlled trial, the subjective concepts of distant healing (e.g. actions with benevolent intentions, such as prayer) were studied in 17 patients with self-reported CFS and/or MCS. A two-by two factorial design was chosen, where two arms received deferred treatment (after 6 months) and two arms were treated immediately. In addition, the SF-36 was also conducted to measure quality of life in the patients. Reconstructive interview analysis was applied when	

			reviewing results. **Quality of study:** * **Relevant to Objectives:** No, this study will not be included as despite the strong study design, the nature of the intervention is non-physical, non-standardized difficult to quantify and subject to interpretive differences.	
Guerrero, Alejandro; Ramirez, Laura; Orpella, Xavier; Prat, Noemi; Gonzalez, Josep Anton	P289 Multiple chemical sensitivity syndrome: analysis of cases visited in our occupational health unit from 2011 to 2015	Guerrero, A., Ramírez, L., Orpella, X., Prat, N., & González, J. A. (2016). P289 Multiple chemical sensitivity syndrome: analysis of cases visited in our occupational health unit from 2011 to 2015. *Occup Environ Med*, *73*(Suppl 1), A218–A218. https://doi.org/10.1136/oemed-2016-103951.604	In a retrospective study, 17 medical records were reviewed of patients that visited a specialty care services and occupational medical services unit. The results indicate that the most common causative agent is cleaning products and that all cases have at least two groups of symptoms: respiratory and neurological. MCS can cause disability in patients and affect everyday life. Thus, it is important to study possible biomarkers that allow for early diagnosis and study the possible treatments. **Quality of study:** *** **Relevant to Objectives:** No, only an abstract summary of this document is available.	
Hauge, C.R.; Bonde, P.J.E.; Rasmussen, A.; Skovbjerg, S.	Mindfulness-based cognitive therapy for multiple chemical sensitivity: A study protocol for a randomized controlled trial	Hauge, C. R., Bonde, J. P. E., Rasmussen, A., & Skovbjerg, S. (2012). Mindfulness-based cognitive therapy for multiple chemical sensitivity: a study protocol for a randomized controlled trial. *Trials*, *13*, 179. https://doi.org/10.1186/1745-6215-13-179	In a randomized controlled design, the mindfulness based cognitive (MBCT) program was compared to treatment as usual (TAU), where the MBCT program included 8 weekly 2.5-hour sessions and 45 minutes of mindfulness home practice 6 days each week. By randomization, 82 participants were assigned to the MBCT program or to TAU. In addition, participants also underwent questionnaires at baseline, post-treatment, and at 6 and 12 months' follow-up. **Quality of study:** * **Relevant to Objectives:** No, this article describes a proposed study, and not one that has not actually been completed, or	

			results.	
Hojo, S.; Kumano, H.; Ishikawa, S.; Miyata, M.; Matsui, T.; Sakabe, K.	Indoor air contaminants as the most common onset factor of multiple chemical sensitivity in Japan	Hojo, S., Kumano, H., Ishikawa, S., Miyata, M., Matsui, T., & Sakabe, K. (2007). Indoor air contaminants as the most common onset factor of multiple chemical sensitivity in Japan. Presented at the 6th International Conference on Indoor Air Quality, Ventilation and Energy Conservation in Buildings: Sustainable Built Environment, IAQVEC 2007. Retrieved from https://waseda.pure.elsevier.com/en/publications/indoor-air-contaminants-as-the-most-common-onset-factor-of-multip	The retrospective study looked at the medical records of 106 MCS patients according to the 1999 Consensus and the Japanese diagnostic criteria for MCS. The demographic characteristics, onset factors and co-morbid allergic diseases were analyzed by using the QEESI© and compared to 4 self-reported patient groups in the U.S. Females had a wider age distribution when compared to males. The most common MCs onset included indoor air contaminants through the construction and renovation of home and or work areas. The results also showed that for 84% of the patients, co-morbid allergic disease was also present. **Quality of study:** ** **Relevant to Objectives:** No, is a conference proceeding and could not be obtained.	
Ishibashi, M.; Tonori, H.; Miki, T.; Miyajima, E.; Kudo, Y.; Tsunoda, M.; Sakabe, K.; Aizawa, Y.	Classification of patients complaining of sick house syndrome and/or multiple chemical sensitivity	Ishibashi, M., Tonori, H., Miki, T., Miyajima, E., Kudo, Y., Tsunoda, M., … Aizawa, Y. (2007). Classification of patients complaining of sick house syndrome and/or multiple chemical sensitivity. *The Tohoku Journal of Experimental Medicine*, *211*(3), 223–233.	A new classification of Sick House Syndrome was established, and diagnostic criteria defined. A total of 214 patients with diagnosed SHS MCS were classified into one of four types: type 1 (symptoms of chemical intoxication), type 2 (symptoms developed possibly due to chemical exposure), type 3 (symptoms developed not because of chemical exposure but rather because of psychological or mental factors), and type 4 (symptoms developed due to allergies or other diseases). The new classification was suggested to be accurate as there was 77.1% agreement made by the clinical ecologists and general physicians. The cases classified as SHS type 4 were shown to have allergic past histories compared to other types. It was also noted that among male patients, the	

			MCS cases were higher in SHS types 1 and 2 when compared to other types. **Quality of study:** ** **Relevant to Objectives:** No, the focus of this study is on SHS and not MCS, although they are examined as overlapping conditions in a sub-group of SHS.	
Jason, L. A.; Taylor, R. R.; Kennedy, C. L.	Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms.	Jason, L. A., Taylor, R. R., Kennedy, C. L., & others. (2000). Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. *Psychosomatic Medicine*, *62*(5), 655–663.	Cross-sectional screening telephone interviews were conducted on 18,675 Chicago, Illinois residents to identify the rate of comorbidity in addition to the characteristics related to the severity of fatigue, disability and psychiatric comorbidity of CFS, FM, and MCS. Of those with positive findings of CFS in the screening interview, a structured psychiatric interview was administered. A medical examination was conducted on a control group and on individuals with chronic fatigue that showed at least four minor CFS symptoms. Of the 32 individuals with CFS, 40.65 met the MCS criteria and 15.6% met the criteria for FM. The results indicated that individuals with MCS or those with comorbidity reported greater mental fatigue and greater disability than those with no diagnosis. Individuals with CFS, FM or MCS have significant disability in regards to physical, occupational and social functioning. **Quality of study:** ** **Relevant to Objectives:** No, this study focuses on the overlap of symptoms between three conditions	
Joffres, M.R.; Sampalli, T.; Fox, R.A.	Physiologic and symptomatic responses to low-level substances in individuals with and without chemical sensitivities: A randomized controlled	Joffres, M. R., Sampalli, T., & Fox, R. A. (2005). Physiologic and symptomatic responses to low-level substances in individuals with and without chemical sensitivities: A randomized controlled blinded pilot booth study. *Environmental Health Perspectives*, *113*(9), 1178–1183. https://doi.org/10.1289/chp.7198	The randomized, single-blind, placebo-controlled investigated the length of adaptation period to obtain stable readings, evaluate responses to different substances and measure the level and type of symptomatic and physiologic reactions to low-level exposures in 10 individuals with diagnosed chemical sensitivities and 7	

	blinded pilot booth study		controls. Results showed that individuals with chemical sensitivities took longer to adapt to baseline protocols and showed significant responses in the tonic electrodermal response to the test substances when compared to the controls. No other patterns were seen in other measures. The study shows importance in using an adaptation period for individuals with chemical sensitivities. **Quality of study:** * **Relevant to Objectives:** No, will not be included as it represented a pilot study of exposure conditions with a small number of subjects.	
Koch, L.; Rumrill, P.; Hennessey, M.; Viestra, C.; Roessler, R.T.	An ecological approach to facilitate successful employment outcomes among people with multiple chemical sensitivity	Koch, L., Rumrill, P., Hennessey, M., Viestra, C., & Roessler, R. T. (2007). An ecological approach to facilitate successful employment outcomes among people with multiple chemical sensitivity. *Work*, *29*(4), 341–349.	The paper explores the constructs and processes that have the most impact on the career development for individuals with MCS and discusses the implications for rehabilitation planning. **Quality of study:** ** **Relevant to Objectives:** No, is a review/opinion piece, and thus meets exclusion criteria	t
Lee, H.-S.; Hong, S.-Y.; Hong, Z.-R.; Gil, H.-O.; Yang, J.-O.; Lee, E.-Y.; Han, M.-J.; Jang, N.-W.; Hong, S.-Y.	Pesticide-initiated idiopathic environmental intolerance in south Korean farmers	Lee, H.-S., Hong, S.-Y., Hong, Z.-R., Gil, H.-O., Yang, J.-O., Lee, E.-Y., … Hong, S.-Y. (2007). Pesticide-initiated idiopathic environmental intolerance in south Korean farmers. *Inhalation Toxicology*, *19*(6–7), 577–585. https://doi.org/10.1080/08958370701271522	The study looked at diagnosed 10 subjects with pesticide intolerance and MCS. The subjects underwent a series of tests such as: complete blood cell count, urinalysis, and blood chemistry as routine tests; esophogastroduodenoscopy and abdomen ultrasonography for the gastrointestinal symptoms; chest x-ray, pulmonary function tests, and electrocardiography for the respiratory and/or cardiac symptoms; nerve conduction velocity and brain magnetic resonance imaging (MRI) for peripheral and central nerve system symptoms; and K-WAIS, Rey-Kim memory test, Rorschach, MMSE, and MMPI for psychoanalysis. Two cases were caused by maxillary sinusitis; two cases showed typical MCS, and the 6 out of 10 showed	

			symptoms which did not meet the criteria for MCS. Psychoanalysis and clinical tests should be used for diagnosis to help verify causes of MCS or IEI. **Quality of study:** * **Relevant to Objectives:** No, will not be included under discussion of psychology due to limited sample size and lack of controls.	
Leer, A.; Smeets, M.A.M.; Bulsing, P.J.; Van Den Hout, M.A.	Odors eliciting fear: A conditioning approach to Idiopathic Environmental Intolerances	Leer, A., Smeets, M. A. M., Bulsing, P. J., & van den Hout, M. A. (2011). Odors eliciting fear: A conditioning approach to Idiopathic Environmental Intolerances. *Journal of Behavior Therapy and Experimental Psychiatry*, *42*(2), 240–249. https://doi.org/10.1016/j.jbtep.2010.12.007	The randomized study included 53 healthy individuals that were randomly divided over two conditions. No subjects were diagnosed as having MCS. The conditioned stimuli (CSs) were dimethyl sulfide (unpleasant) and peach (pleasant), and the unconditioned stimuli (US) is an electrical shock. For fear acquisition, one odour was followed by shock, while other odour was not. Fear extinction was tested by presenting both odours without US. The electrodermal response results showed successful fear conditioning, and that the acquired fear did not extinguish, but there was no evidence for evaluative conditioning. The study suggests that fear conditioning is only partially satisfactory. **Quality of study:** * **Relevant to Objectives:** No, while the mechanism studied is relevant to MCS, this study did not include an IEI or MCS group for comparison with the healthy individuals.	
Leznoff, A.; Binkley, K.E.	Idiopathic environmental intolerances: Results of challenge studies	Leznoff, A., & Binkley, K. E. (2000). Idiopathic environmental intolerances: Results of challenge studies. *Occupational Medicine-State of the Art Reviews*, *15*(3), 529–537.	Reported challenge studies with self-identified triggers in IEI patients are consistent with the etiology of panic disorder. The results of the panicogenic stimuli with intravenous sodium lactate and 35% CO_2 inhalation reproduce IEI symptoms for IEI patients but not in controls. The reported challenge studies are consistent with the etiology of the disorder.	

			Quality of study: * **Relevant to Objectives:** No, is a summary of other study results, thus meets the exclusion criteria as being a review.	
Lipson, J.G.	Multiple chemical sensitivities: Stigma and social experiences	Lipson, J. G. (2004). Multiple chemical sensitivities: Stigma and social experiences. Medical Anthropologyrly Quarterly 2(18): 200-213.	This document is a review of the stigma and social experiences reported in a previously published ethnographic study. **Quality of study:** ** **Relevant to Objectives:** No, this is a review/opinion piece, does not explore interventions, and thus meets the exclusion criteria	
Lipson, J.G.	We are the canaries: Self-care in multiple chemical sensitivity sufferers	Lipson, J. G. (2001). We are the canaries: self-care in multiple chemical sensitivity sufferers. Qualitative Health Research, 11(1), 103–116.	The ethnographic study investigates the experiences of MCS sufferers by conducting semi-structured interviews with 33 individuals with MCS. Along with the discussion of the methodological issues associated with conducting peer research, the article also describes self-care for symptom management. The study shows that being alert to bodily cues makes a difference between short-lived reactions and strong reactions that can disable an individual for longer periods of time. **Quality of study:** * **Relevant to Objectives:** No, while the article provides some insight into the experiences of MCS sufferers, specific mitigation measures are not explored beyond a survey level.	
McIntyre, R.S.; Konarski, J.Z.; Soczynska, J.K.; Wilkins, K.; Panjwani, G.; Bouffard, B.; Bottas, A.; Kennedy, S.H.	Medical comorbidity in bipolar disorder: Implications for functional outcomes and health service utilization	McIntyre, R. S., Konarski, J. Z., Soczynska, J. K., Wilkins, K., Panjwani, G., Bouffard, B., … Kennedy, S. H. (2006). Medical comorbidity in bipolar disorder: Implications for functional outcomes and health service utilization. *Psychiatric Services*, *57*(8), 1140–1144. https://doi.org/10.1176/appi.ps.57.8.1140	The ecological study extracted data from the Canadian Community Health Survey (n-36,984) and analyses to determine the prevalence and implications of pre-determined comorbid disorders among those who screened positive for lifetime manic episodes were conducted as manic episodes are a diagnosis of bipolar disorder. Comorbid medical disorders in bipolar disorder are associated with harmful dysfunction, decrements in	

			functional outcomes, and increased utilization of medical services. **Quality of study:** * **Relevant to Objectives:** No, the focus of this study was on bipolar disorder and examine co-morbidity with other conditions.	
Nogue, S; Fernandez-Sola, J; Rovira, E; Montori, E; Fernandez-Huerta, J M; Munne, P; Montero, M; Salmeron, J M	Multiple Chemical Sensitivity: Analysis of 52 Cases	Nogué, S., Fernández-Solá, J., Rovira, E., Montori, E., Fernández-Huerta, J. M., & Munné, P. (2007). Multiple chemical sensitivity: study of 52 cases. *Medicina clinica*, *129*(3), 96–8; quiz 99. https://doi.org/10.1157/13107370	In the cohort study, 52 patients that were seen by the Clinical Toxicology and Chronic Fatigue Units completed the QEESI© questionnaire and were followed up for a minimum of 12 months. The results suggested that the origin of the syndrome was related to occupational exposure or an association with CFS. MCS patients' quality of life is seriously affected. **Quality of study:** *** **Relevant to Objectives:** No, the document (other than the abstract) is entirely in Spanish and thus meets the exclusion criteria	
Österberg, K.; Persson, R.; Karlson, B.; Carlsson Eek, F.; Orbaek, P.	Personality, mental distress, and subjective health complaints among persons with environmental annoyance	Österberg, K., Persson, R., Karlson, B., Eek, F. C., & Orbaek, P. (2007). Personality, mental distress, and subjective health complaints among persons with environmental annoyance. *Human & Experimental Toxicology*, *26*(3), 231–241. https://doi.org/10.1177/0960327107070575	To assess possible early determinants of idiopathic environmental intolerance (IEI), 84 participants from the general population that attributed annoyance to smells (n=29), electrical equipment (n=16), both (n=39), and 54 referents completed questionnaires concerning personality traits, current mental distress, subjective health complaints, work load and satisfaction, and options for recovery. The results suggest that anxiety may facilitate the acquisition of attribution of health complaints to environmental factors and that it is at prodromal stages of IEI. **Quality of study:** * **Relevant to Objectives:** No, this study did not examine diagnosed MCS or IEI specifically	
Mazzatenta, A.; Pokorski, M.; Cozzutto, S.;	Non-invasive assessment of exhaled breath pattern	Mazzatenta, A., Pokorski, M., Cozzutto, S., Barbieri, P., Veratti, V., & Di Giulio, C. (2013). Non-invasive Assessment of Exhaled Breath Pattern in Patients with	In this randomized control study, the exhaled breath content of 10 healthy volunteers exposed to n-propanol or fresh	

Barbieri, P.; Verratti, V.; Giulio, C.D.	in patients with multiple chemical sensibility disorder	Multiple Chemical Sensibility Disorder. In M. Pokorski (Ed.), *Respiratory Regulation - the Molecular Approach* (Vol. 756, pp. 179–188). Dordrecht: Springer.	air were analyzed using a metal oxide semiconductor (MOS) capable of detecting various VOCs. The MOS detector was able to detect and differentiate the breath content during the two conditions. The results suggest that chronic hypoxia could be involved in MCS disorder. **Quality of study:** * **Relevant to Objectives:** No, MCS subjects were not included in the study – only healthy controls to explore the use of the technology.	
Mellish, C.E.	Multiple chemical sensitivity - An extreme case of a universal condition	Mellish, C. E. (2001). Multiple chemical sensitivity - An extreme case of a universal condition. *Journal of Nutritional and Environmental Medicine*, *11*(1), 63–67. https://doi.org/10.1080/13590840020030276	It is proposed that exposures below the threshold level give rise to MCS with the condition being described as the complement of allergy. This theory could lead to new approaches to the treatment. **Quality of study:** * **Relevant to Objectives:** No, will not be included as it is a review/hypothesis paper, and meets exclusion criteria.	
Mellish, C.E.	Multiple chemical sensitivity - An elevation of enzyme induction thresholds	Mellish, C. E. (2002). Multiple Chemical Sensitivity–An Elevation of Enzyme Induction Thresholds. *Journal of Nutritional & Environmental Medicine*, *12*(4), 337–342.	This paper proposed that the basic parameters that give rise to MCS symptoms are from the elevation of induction thresholds above the normal levels for enzymes that mediate biotransformation of xenobiotics. Support from experimental and theoretical evidence is noted along with the characteristics of MCS that would be expected to follow the proposed argument. **Quality of study:** * **Relevant to Objectives:** No, will not be included as it is a review paper.	
Micovic, V.; Bulog, A.; Mrakovcic-Sutic, I.	The role of chronic exposure to gasoline and diesel on cell mediated immunity of people situated near gasoline industry	Micovic, V., Bulog, A., & Mrakovcic-Sutic, I. (2007). *The role of chronic exposure to gasoline and diesel on cell mediated immunity of people situated near gasoline industry*. (J. Kalil, E. CunhaNeto, & L. V. Rizzo, Eds.). 40128 Bologna: Medimond S R L.	This case-control studied evaluated changes in cell mediated immunity and the role of cytolytic molecule perforin that is released from cytotoxic T lymphocytes and natural killer cells. Peripheral blood samples were taken from 30 individuals	

			living near gasoline industry locations, and results were compared to samples from 30 healthy donors. Results showed that PBL in all examined groups were perforin positive, where total perforin was significantly lower in exposure than in the control group. **Quality of study:** * **Relevant to Objectives:** No, will not be included in discussion of immune mechanism because the study does not specifically address MCS.	
Niedoszytko, M.; Chelminska, M.; Buss, T.; RoikRook, E.; Jassem, E.	Drug intolerance in patients with idiopathic environmental intolerance syndrome	Niedoszytko, M., Chelminska, M., Buss, T., Roik, E., & Jassem, E. (2006). Drug intolerance in patients with idiopathic environmental intolerance syndrome. *International Journal of Clinical Practice*, *60*(10), 1327–1329. https://doi.org/10.1111/j.1742-1241.2006.00846.x	To evaluate allergic component of IEI in relation to drug intolerance, six patients that were diagnosed with idiopathic environmental intolerance underwent clinical assessment consisting of physical examinations, patch tests, chest X-rays, spirometry. Skin prick tests were also completed for commonly used antibiotics, nonsteroidal anti-inflammatory drugs, myorelaxants, verapamil etc. Results indicated that symptoms related to allergy contributed to making IEI symptoms worse. **Quality of study:** * **Relevant to Objectives:** No, will not be included in review, because of small sample size and the lack of controls in the study.	
Pall, M.L.	Elevated nitric oxide/peroxynitrite theory of multiple chemical sensitivity: Central role of N-methyl-D-aspartate receptors in the sensitivity mechanism	Pall, M. L. (2003). Elevated nitric oxide/peroxynitrite theory of multiple chemical sensitivity: Central role of N-methyl-D-aspartate receptors in the sensitivity mechanism. *Environmental Health Perspectives*, *111*(12), 1461–1464. https://doi.org/10.1289/ehp.5935	MCS is proposed to be centered on the activation of NMDA receptors by organic solvents, leading to elevated nitric oxide/peroxynitrite and increased stimulation and hypersensitivity of NMDA receptors. This may lead to progressive sensitivity to organic solvents. Increased BBB permeability, induced by peroxynitrite, and CYP inhibition by nitric oxide may be accessory mechanisms of sensitivity. **Quality of study:** ** **Relevant to Objectives:** No is a review	

			article and thus meets exclusion criteria,	
Pall, M.L.	NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity	Pall, M. L. (2002). NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. *Faseb Journal*, *16*(11), 1407–1417. https://doi.org/10.1096/fj.01-0861hyp	Four possible sensitization pathways are proposed to act synergistically: Nitric oxide-mediated stimulation of neurotransmitter (glutamate) release; peroxynitrite-mediated ATP depletion and consequent hypersensitivity of NMDA receptors; peroxynitrite-mediated increased BBB permeability, producing increased accessibility of organic chemicals to the CNS; and nitric oxide inhibition of CYP metabolism. **Quality of study:** ** **Relevant to Objectives:** No, is a review article and thus meets exclusion criteria.	
Papo, D; Eberlein-Koenig, B; Berresheim, H; Huss-Marp, J; Grimm, V; Walkowiak, J; Kraemer, U; Ring, J; Winneke, G; Behrendt, H	Comparison of chemosensory function and psychological profile in patients with idiopathic environmental intolerances (IEI)/multiple chemical sensitivity (MCS), odorant sensitive and insensitive controls	Papo, D., Eberlein-Koenig, B., Berresheim, H., Huss-Marp, J., Grimm, V., Walkowiak, J., … Behrendt, H. (2004). Comparison of chemosensory function and psychological profile in patients with idiopathic environmental intolerances (IEI)/multiple chemical sensitivity (MCS), odorant sensitive and insensitive controls. *Journal of Allergy and Clinical Immunology*, *113*(2), S66. https://doi.org/10.1016/j.jaci.2003.12.210	In the case-control study, 23 IEI patients, 21 olfactory sensitive patients, and 23 controls had undergone olfactometric investigations, trigeminal provocation and completed psychometric assessments. Results from the olfactometric investigations found no significant differences between the study groups. The findings of the study show that there are no changes in olfactory performance, central chemosensory and cognitive olfactory information processing in patients with IEI and support previous findings of changes in the psychological profile and clinical psychopathological parameters in IEI. **Quality of study:** * **Relevant to Objectives:** No. Only the abstract (not full text) is available, and the full study cannot be reviewed.	
Ross, P.M.	Chemical sensitivity and fatigue syndromes from hypoxia/hypercapnia	Ross, P. M. (2000). Chemical sensitivity and fatigue syndromes from hypoxia/hypercapnia. *Medical Hypotheses*, *54*(5), 734–738. https://doi.org/10.1054/mehy.1999.0942	MCS and other chronic syndromes are proposed to result from H/H due to disturbed breathing. Reasons for considering the etiologic linkage are explained in terms of sleep apnea. In	

			addition, implications for diagnosis and treatment of MCS are discussed. **Quality of study:** ** **Relevant to Objectives:** No, is a review article and meets the exclusion criteria.	
Staudenmayer, H.; Christopher, K.L.; Repsher, L.; Hill, R.H.	Mass Psychogenic Illness: Psychological Predisposition and Iatrogenic Pseudo-vocal Cord Dysfunction and Pseudo-reactive Airways Disease Syndrome	Staudenmayer, H., Christopher, K. L., Repsher, L., & Hill, R. H. (2011). Mass Psychogenic Illness: Psychological Predisposition and Iatrogenic Pseudo-vocal Cord Dysfunction and Pseudo-reactive Airways Disease Syndrome. *Journal of Medical Toxicology*, *7*(2), 109–117. https://doi.org/10.1007/s13181-011-0136-8	Medical, psychological and industrial hygiene evaluations were conducted on 5 patients who had symptoms described as IEI due to exposure to solvents used in roof repair work. Each case had personality traits associated with at least one personality disorder, and social histories showed premorbid life events and stressors. **Quality of study:** * **Relevant to Objectives:** No, will not be included under discussion of psychology due to sample size and lack of controls. Paper prepared in relation to litigation.	
Staudenmayer, H.; Phillips, S.	MMPI-2 validity, clinical and content scales, and the Fake Bad Scale for personal injury litigants claiming idiopathic environmental intolerance	Staudenmayer, H., & Phillips, S. (2007). MMPI-2 validity, clinical and content scales, and the Fake Bad Scale for personal injury litigants claiming idiopathic environmental intolerance. *Journal of Psychosomatic Research*, *62*(1), 61–72. https://doi.org/10.1016/j.jpsychores.2006.01.013	Utilizing the MMPI-2, 50 females and 20 males with personal injury litigants alleging IEI were evaluated using standardized personality tests. The study authors suggested that the IEI litigants examined are more defensive about expressing psychopathology, expressing distress through somatization, exaggerate health concerns and may exaggerate unauthenticated symptoms. **Quality of study:** * **Relevant to Objectives:** No. This work was prepared in association with litigation and did not include an assessment of controls.	
Tarlo, S.M.; Poonai, N.; Binkley, K.; Antony, M.M.; Swinson, R.P.	Responses to panic induction procedures in subjects with multiple chemical sensitivity/idiopathic environmental	Tarlo, S. M., Poonai, N., Binkley, K., Antony, M. M., & Swinson, R. P. (2002). Responses to panic induction procedures in subjects with multiple chemical sensitivity/idiopathic environmental intolerance: Understanding the relationship with panic disorder. *Environmental Health Perspectives*, *110*, 669–671.	The paper discussed how there is higher prevalence of major depression, mood disorders, anxiety disorders, and somatization disorder in patients with environmental illness compared to controls. In addition, since panic responses are a	

	intolerance: understanding the relationship with panic disorder.		significant proportion of IEI patients, intervention to help reduce panic responses, such as deconditioning of responses and triggers may be available. **Quality of study:** ** **Relevant to Objectives:** No, this paper will not be included, as it is a review and thus meets the exclusion criteria.	
Sampalli, T.; Shepherd, M.; Fox, R.	Boundary objects in the multidisciplinary care management of chronic conditions: Multiple Chemical Sensitivity	Sampalli, T., Shepherd, M., & Fox, R. (2009). Boundary Objects in the Multidisciplinary Care Management of Chronic Conditions: Multiple Chemical Sensitivity. In J. G. McDaniel (Ed.), *Advances in Information Technology and Communication in Health* (Vol. 143, pp. 534–539). Amsterdam: I O S Press.	The article looks at using controlled clinical vocabulary as a boundary object to better manage MCS patients. Boundary objects are physical items such as health records that are the interface between disciplines and practice areas. A methodology to develop a boundary object for MCS is discussed. Creating a standardized vocabulary can act as boundary objects which can help clinicians to share information across disciplines. **Quality of study:** * **Relevant to Objectives:** No, this article summarizes a study in progress and does not present results.	
Sampalli, T.; Shepherd, M.; Duffy, J.	Enabling interoperability through an ontology approach in the heterogeneous domains of complex chronic conditions	Sampalli, T., Shepherd, M., & Duffy, J. (2012). Enabling interoperability through an ontology approach in the heterogeneous domains of complex chronic conditions (pp. 46–52). Presented at the HEALTHINF 2012 - Proceedings of the International Conference on Health Informatics.	In the study, a way to develop, test and evaluate a model and methodology for creating ontologies and enabling interoperability in MCS and chronic pain was assessed. **Quality of study:** * **Relevant to Objectives:** No, is from a conference proceeding rather than a peer-reviewed publication.	
Swoboda, D.A.	The social construction of contested illness legitimacy: A grounded theory analysis	Swoboda, D. A. (2006). The social construction of contested illness legitimacy: A grounded theory analysis. *Qualitative Research in Psychology*, *3*(3), 233–251. https://doi.org/10.1191/1478088706qrp061oa	The study examined 22 individuals who had self-reported MCS, CFS, or GWS to investigate the social influences that shape how individuals come to believe they have the contested illness. The finding indicates that claiming legitimacy for a contested illness is a difficult process. **Quality of study:** **	

			Relevant to Objectives: No, this study evaluates social aspects of MCS rather than identifying management needs or approaches	
Tran, M.T.D.; Skovbjerg, S.; Arendt-Nielsen, L.; Christensen, K.B.; Elberling, J.	Transcranial pulsed electromagnetic fields for multiple chemical sensitivity: Study protocol for a randomized, double-blind, placebo-controlled trial	Tran, M. T. D., Skovbjerg, S., Arendt-Nielsen, L., Christensen, K. B., & Elberling, J. (2013). Transcranial pulsed electromagnetic fields for multiple chemical sensitivity: study protocol for a randomized, double-blind, placebo-controlled trial. *Trials*, *14*, 256. https://doi.org/10.1186/1745-6215-14-256	In a randomized, double-blind, placebo-controlled trail, the effects of PEMF in 40 diagnosed MCS patients. The participants underwent PEMF therapy or placebo for 30 minutes twice a day for 7 days a week over 6 consecutive weeks with measurements for baseline, once weekly during treatment, post-treatment and at 2.5 and 4.5-month follow-ups. **Quality of study:** * **Relevant to Objectives:** No, will not be included, as this paper describes the methods for a study but not the results.	
Vierstra, C.V.; Rumrill, P.D.; Koch, L.C.; McMahon, B.T.	Multiple chemical sensitivity and workplace discrimination: The national EEOC ADA research project	Vierstra, C. V., Rumrill, P. D., Koch, L. C., & McMahon, B. T. (2007). Multiple chemical sensitivity and workplace discrimination: The national EEOC ADA research project. *Work*, *28*(4), 391–402.	In the ecological study, information from the Integrated Mission System of the United States Equal Employment Opportunity Commission was used to determine the employment experiences of individuals with MCS compared to individuals with general disability. The findings showed that individuals with MCS were more likely to allege discrimination and file them against employers than the comparison group. **Quality of study:** ** **Relevant to Objectives:** No, this study does not evaluate clinical or public health management aspects of MCS.	
Walach, H.; Bosch, H.; Haraldsson, E.; Marx, A.; Tomasson, H.; Wiesendanger, H.; Lewith, G.	Efficacy of distant healing--a proposal for a four-armed randomized study (EUHEALS).	Walach, H., Bosch, H., Haraldsson, E., Marx, A., Tomasson, H., Wiesendanger, H., & Lewith, G. (2002). Efficacy of distant healing - a proposal for a four-armed randomized study (EUHEALS). *Forschende Komplementarmedizin Und Klassische Naturheilkunde*, *9*(3), 168–176. https://doi.org/10.1159/000064267	In a four-armed randomized study, 400 patients with self-attributed environmental problems of CFS, or MCS underwent treatment by 3 healers that are specialized general practitioners and environmental clinics. The patients were randomized to one of 4 groups where they receive distant healing or not and if they know or not know this decision. Primary outcome measure	

			will be from the mental health summary scale of the MOS SF-36. **Quality of study:** * **Relevant to Objectives:** No, will not be included under discussion of management as only methods are discussed, not results.	

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
Accommodation for Environmental Sensitivities: Legal Perspective	Canadian Human Rights Commission. (2007). Accommodation for Environmental Sensitivities: Legal Perspective. Prepared by: C. Wilkie and D. Baker.	Review of case law, best practices and accommodations of individuals with environmental sensitivities in Canada, as well as international perspectives. Seven recommendations are made to describe how employers and service providers should accommodate individuals with sensitivities. **Quality of Study: **** **Relevant to Objectives:** Yes. While the information may be somewhat outdated, as it is from 2007, the information with in may be useful with respect to management.
An Integrative Approach to Environmental Intolerances: Multiple Chemical Sensitivity and Related Illnesses.	University of Wisconsin (UW). (2012). An Integrative Approach to Environmental Intolerances: Multiple Chemical Sensitivity and Related Illnesses. University of Wisconsin, School of Medicine and Public Health. UW Integrative Medicine and Department of Family Medicine.	The document provides an overview of MCS and its potential causes, and several potential treatments are discussed in brief detail. This medical organizations proposes a multi-faceted, integrative approach that includes dietary and physical care, trigger avoidance as well as alternative therapies. References are provided, as are a list of other information sources. **Quality of Study**: ** **Relevant to Objectives**: Yes. This document is most useful for evaluating how MCS can potentially be managed as a clinical condition. Is more of a factsheet than a review.
A review of the Multiple Chemical Sensitivity (MCS) Guidelines for South Australian Hospitals 2010	South Australia Health. (2016). A review of the Multiple Chemical Sensitivity	This document is brief overview of MCS and the management of MCS within a clinical setting in relation to a 2010 guideline regarding MCS for South Australia

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
	(MCS) Guidelines for South Australian Hospitals	Health. Although it is noted that a brief literature review of MCS and possible mechanisms was completed, it does not appear to be a comprehensive, critical or systematic review. A survey of clinicians was completed by the study authors to get a sense of how the 2010 MCS guidelines were being implemented in South Australia. Details of the 2010 guidelines are not included in this document. **Quality of Study:** * **Relevant to Objectives:** Yes, may have some information regarding MCS management.
A Scientific Review of Multiple Chemical Sensitivity: Identifying Key Research Needs.	National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and the Office of Chemical Safety and Environmental Health (OCSEH). (2010). A Scientific Review of Multiple Chemical Sensitivity: Identifying Key Research Needs.	The review provided a comprehensive summary of MCS definitions, discussions of potential modes of action, and several approaches to clinical diagnosis and treatment. Several governmental and non-governmental organizations were contacted as part of this review, and information regarding the current status and treatment of MCS is provided from each. This review also highlights several research gaps and areas for future study. **Quality of study:** *** **Relevant to Objectives:** Yes. This document is valuable to the project and represents the most current comprehensive grey literature document regarding mechanisms. Very Relevant.
British Society for Allergy, Environmental and Nutritional Medicine (BSAENM) Report: Multiple Chemical Sensitivity: Recognition and Management. A document on the health effects of everyday chemical exposures and their implications.	Eaton, K.K., Anthony, H.M., Birtwistle, S., Downing, D., Freed, D.L.J., McLaren Howard, Maberly, D.J., Mansfield, J.R., Myhill, S. & M.J. Radcliffe. (2000). BSAENM Report: Multiple Chemical Sensitivity: Recognition and	The BSAENM is a non-profit medical organization that focuses on allergy, environmental and nutritional medicine, and promote the use of ecological medicinal approaches in professional practice. MCS is recognized as a clinical condition by this organization. Various mechanisms including metabolic differences, immune

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
	Management. A document on the health effects of everyday chemical exposures and their implications. *J Nutr Environ Med* 10: 39-84.	sensitization, are discussed. Several research priorities and treatment strategies are also presented. **Quality of Study**: ** **Relevant to Objectives**: Yes. This document could be use useful for providing insight into mechanisms, as well as for research areas and condition management. Not a critical review.
Employees with Multiple Chemical Sensitivity and Environmental Illness	Job Accommodation Network – (JAN) (2013). Employees with Multiple Chemical Sensitivity and Environmental Illness Office of Disability and Employment Policy. United States Department of Labor.	This document provides an overview of MCS, a questionnaire to aid in determining the appropriate workplace accommodations for people with MCS. Various options for accommodation are listed briefly. JAN also has a searchable online resource to allow employers to search accommodation options and seek guidance. **Quality of Study: **** **Relevant to Objectives: Yes.** Document provides an outline as to how American governmental and non-governmental organizations accommodate MCS.
Environmental Sensitivities – Multiple Chemical Sensitivities Status Report. Advances in Knowledge and Current Service Gaps	Women's College Hospital (WCH). (2011). Environmental Sensitivities – Multiple Chemical Sensitivities Status Report. Advances in Knowledge and Current Service Gaps. Environmental Health Clinic, Toronto.	Document provides a summary of MCS diagnostic criteria and potential mechanisms, current management approaches and needs, and various activities that have been conducted by organizations to address MCS in Canada and other countries. Also describes some of the work that is completed at the WCH clinic. **Quality of Study: **** **Relevant to Objectives:** Yes. Provides an annotated, brief high-level summary of MCS, its potential mechanisms. and medical management activities.

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
Guideline for Accommodation of Environmental Sensitivities	Newfoundland and Labrador Human Rights Commission. (2011). Guideline for Accommodation of Environmental Sensitivities. June 15, 2011.	Guidelines provide an overview of environmental sensitivities in terms of being a disability and a protected condition under human rights legislation. A list of potential options to accommodate people with environmental sensitivities is included. **Quality of Study: **** **Relevant to Objectives:** Yes. The document provides a high-level summary of how MCS and related conditions can be managed within a human rights/ accommodation context within the workplace.
Idiopathic Environmental Tolerance	Weinberg, A. (2007). Idiopathic Environmental Tolerance. Discussion Paper Prepared for the Workplace Safety and Insurance Appeals Tribunal of Ontario. University of Ottawa.	Document is a brief position paper from a medical specialist that provides a limited literature review of potential symptoms and mechanisms, and notes that while there is no consensus on etiology, that the most evidence exists for psychological/cognitive etiology. **Quality of Study: **** **Relevant to Objectives**: Yes. The document provides a high-level summary, and is from a Canadian expert/organization. However, the review is limited in scope and depth.
Medically unexplained physical symptoms (MUPS) among adults in Canada: comorbidity, health case use and employment	Statistics Canada. (2017). Medically unexplained physical symptoms (MUPS) among adults in Canada: comorbidity, health case use and employment Prepared by: J. Park and H. Gilmour. Cat. No. 82-003-X. ISSN 1209-1367.	Document summarizes statistics from the 2014 Canadian Community Health Survey and the 2012 Canadian Community Health Survey-Mental Health. The conditions evaluated under the definition of MUPS include MCS as well as fibromyalgia, and chronic fatigue syndrome. **Quality of Study: **** **Relevant to Objectives**: Yes, useful, current information regarding the prevalence of MUPS in Canada and health

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
		case usage. However, the data for MCS is not teased out from the other conditions for all endpoints.
Multiple Chemical Sensitivity.	Danish Environmental Protection Agency. (2005). Danish Ministry of the Environment, Environmental Protection Agency.	This review was focused on literature published between 1999 to 2001, and effort was made to focus only on MCS and not overlapping conditions. A brief description of the history of MCS and its symptoms are provided. Much of the report is focused on a brief overview of how MCS is viewed and managed by certain governments and non-governmental agencies. While there is some discussion of the potential mechanisms of MCS, the information summarized is primarily from the 1990s. **Quality of Study: *** **Relevant to Objectives**: Yes, but will not be included. Information in document is outdated, and limited technical information of value is presented.
Multiple Chemical Sensitivity Disorder. Factsheet.	New South Wales Government.	Provides an overview of the Australian Human Rights Commission and health and safety requirements with respect to minimizing reactions in individuals with MCS. Very limited information regarding MCS as a condition is provided. **Quality of Study**: * **Relevant to Objectives:** Yes, but will not be included as very limited information is provided.
Multiple Chemical Sensitivity at Work	Public Service Alliance of Canada (PSAC). (2003). Multiple Chemical Sensitivity at Work.	This document is a position paper issued by a public service union in Canada representing workers. Several symptoms associated with MCS and environmental illness are reported, but no references are provided.

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
		Several steps are outlined that unions can take to help workers with MCS. Instructions for workers with respect to filing claims, grievances and seeing medical professionals are provided. **Quality of Study:** * **Relevant to Objectives:** Yes, has some information regarding MCS management in a workplace in Canada.
Policy Guideline – Idiopathic Environmental Intolerance or Multiple Chemical Sensitivity Policy Guideline	Government of South Australia. (2016). Policy Guideline – Idiopathic Environmental Intolerance or Multiple Chemical Sensitivity Policy Guideline	Guideline outlines how a patient with idiopathic environmental intolerance (i.e. MCS) should be managed within South Australian hospitals. **Quality of Study: **** **Relevant to Objectives:** Yes. Document is brief, but represents guidance from a health regulator regarding patient management in facilities that could be useful.
Queensland Health Position Statement on Multiple Chemical Sensitivity.	Queensland Health. (2011). Queensland Health Position Statement on Multiple Chemical Sensitivity.	The document provides a brief overview of MCS, as well as data regarding prevalence in Australia. A summary of local and international policies regarding MCS within workplace is provided. **Quality of Study: **** **Relevant to Objectives:** Yes**.** Document contains some information regarding existing policy.
Recognition, Inclusion and Equity, the Time is Now. Perspectives of Ontarians Living with Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS), Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia (FM)	MEAO and Ontario Trillium Foundations. (2013). Recognition, Inclusion and Equity, the Time is Now. Perspectives of Ontarians Living with Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS), Myalgic Encephalomyelitis/Chronic Fatigue	Report consists of multiple sub-parts: summary of key issues faced by Ontarians (collected by stakeholder engagement) affected by the conditions (including MCS) and associated recommendations made by the authors; summaries of the conditions and potential impacts on

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
	Syndrome (ME/CFS) and Fibromyalgia (FM). Appendix to The Ontario Centre of Excellence in Environmental Health Business Case Proposal.	individuals, how services meet patients needs (collected from stakeholder engagement), social impacts **Quality of Study: ***** **Relevant to Objectives: Yes.** Provides a "patient" perspective of challenges associated with living with the condition, including management of the condition.
Standard Operating Procedure – Multiple Chemical Sensitivities (MCS): Care of Patients	Canberra Hospital and Health Services. (2015). Standard Operating Procedure – Multiple Chemical Sensitivities (MCS): Care of Patients. Division Medicine. Doc Number CHHS12/168.	This document is a regulatory procedure document for all hospital staff regarding MCS patients, ranging from administrative staff, medical staff, food services and cleaning staff, as well as visitors. **Quality of Study: **** **Relevant to Objectives:** Yes. Although rationale as to why these measures have been implemented is included, but the document is informative as to how MCS patients can be managed. Appendices include a discussion of MCS and triggers, process charts for medical care
The Quantitative Data – Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS), Fibromyalgia (FM), Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Appendix to: The Ontario Centre of Excellence in Environmental Health Business Case.	MEAO and Ontario Trillium Foundations. (2013). The Quantitative Data – Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS), Fibromyalgia (FM), Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Appendix to: The Ontario Centre of Excellence in Environmental Health Business Case. October 2013.	Report relies upon the Canadian Community Health Survey (CCHS) data collected in 2005 and 2010, with a focus on Ontario with some national data. MCS is one of the conditions evaluated. Information regarding prevalence, health care usage, income instability, **Quality of Study: **** **Relevant to Objectives: Yes.** Document provides some information regarding MCS statistics in Canada, and notes some of the challenges that these individuals face.

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
What You Should Know About Multiple Chemical Sensitivity	Massachusetts Department of Public Health. (No Date).	This document is a trifold brochure that provides a general overview of MCS triggers and symptoms, but no references are provided. **Quality of Study: *** **Relevant to Objectives**: Yes, but will not be included. Information within this document is very limited and not cited.
The Medical Perspective on Environmental Sensitivities	Sears, M.E. The Medical Perspective on Environmental Sensitivities. (2007). Prepared for: Canadian Human Rights Commission.	The document provides an overview of several types of environmental sensitivities, including MCS, electromagnetic fields, fibromyalgia, among others. The acknowledgement and management of environmental sensitivities by various organizations (including government, medical and industry organizations) and regulatory frameworks (e.g. building codes) are briefly summarized. The authors appear to have consulted with various environmental health professionals in the preparation of the draft. Several theories regarding the potential mechanisms of MCS are briefly discussed at a high level. **Quality of Study**: ** **Relevant to Objectives**: Yes. Provides a very general overview of topic, valuable for obtaining perspectives and insights into the management of MCS from a regulatory perspective. This reference is 10 years old, so the regulatory and organizational approaches in relation to MCS may have changed over time.

APPENDIX B

Table B-1 Summaries of Grey Literature to be Included in Literature Review

Title	*Citation*	*Annotation*
Topics – Multiple Chemical Sensitivity	Arizona Technology Access Program. (2008). Topics – Multiple Chemical Sensitivity. Institute for Human Development/Northern Arizona University Program. 2008.	This document is a factsheet on MCS, that provides a reading list but does not cite or list key references. The factsheet provides an overview of MCS symptoms, suspected causes and triggers of MCS, and a discussion of how the medical community and occupational organizations view MCS. **Quality of Study**: * **Relevant to Objectives:** Yes, but will not be included. Document does not represent a scientific review and information sources relied on are not clear.

APPENDIX B

Table B-2 Grey Literature Excluded from Literature Review

Title	*Citation*	*Annotation*
Disparities in Primary Health Care Experiences Among Canadians with Ambulatory Care Sensitive Conditions	Canadian Institute for Health Information (CIHI). (2012). Disparities in Primary Health Care Experiences Among Canadians with Ambulatory Care Sensitive Conditions.	Report relies on 2008 Canadian Survey of Experiences with Primary Health Care for specific conditions: asthma, chronic obstructive pulmonary disease, emphysema, diabetes, hypertension and heart disease. **Quality of Study: *** **Relevant to Objectives:** No. MCS is not specifically discussed.
Environmental Linked Illnesses: A Mainpro Workshop Recap.	Bested, A. Environmental Linked Illnesses: A Mainpro Workshop Recap. (2016). Ontario College of Family Physicians. January 2016.	This reference is a webpage summary of a workshop that took place at an unspecified date, and does not represent policy. **Quality of Study: *** **Relevant to Objectives:** No, is an opinion piece with limited information regarding MCS or management.
Multiple Chemical Sensitivity	Orme, T and P. Benedetti. (2012). Multiple Chemical Sensitivity. Prepared for the American Council on Science and Health (ACSH).	Position paper that provides an overview of MCS and several definitions of the condition, summarizes positions taken by individuals and organizations in the 1980s and 1990s. **Quality of Study:** * **Relevant to Objectives:** Yes, but no weight of evidence or clear discussion of post-2000 science is discussed. All references are from 1980s and 1990s.
Multiple Chemical Sensitivity – What is it?	We are OHS Reps (2015). Multiple Chemical Sensitivity – What is it?	Document is a factsheet with no references that outlines in general terms what MCS is, potential triggers, and how workers can be accommodated. **Quality of Study: ***

APPENDIX B

Table B-2 Grey Literature Excluded from Literature Review

Title	*Citation*	*Annotation*
		Relevant to Objectives: No. Document is a brief, unreferenced factsheet focused on workers rights.
OCFP Case Criteria Checklist.	OCFP. (2013). Case Criteria Checklist. Appendix 5.	Document consists of several checklists cited from various sources for several conditions. But, it is not apparent how these checklists were developed or how they should be used. The document also seems dated. **Quality of Study: *** **Relevant to Objectives:** No. Document seems to be a scattered collection of checklists.
Queensland Health Process for the Management of Patients who Identify Themselves As Suffering From Multiple Chemical Sensitivity	Queensland Health (undated). Queensland Health Process for the Management of Patients who Identify Themselves As Suffering From Multiple Chemical Sensitivity.	Document is a 1-page letter that provides a brief process as to how patients with MCS at Queensland Health facilities in Australia. **Quality of Study: *** **Relevant to Objectives: No.** No relevant information is provided.
Research Insight: Achieving Healthy Indoor Environments: A Review of Canadian Options	Canada Mortgage and Housing Corporation (CMHC). (2002). Research Insight - Achieving Healthy Indoor Environments: A Review of Canadian Options. Technical Series 02-105	Document is a high-level review of indoor air quality monitoring in Canada, and various initiatives that have been used to improve indoor air quality. Thirteen recommendations were formulated as part of this document. **Quality of Study: *** **Relevant to Objectives:** No. MCS is not specifically discussed.

APPENDIX B

Table B-2 Grey Literature Excluded from Literature Review

Title	*Citation*	*Annotation*
Socio-Economic Impacts of Environmental Illness in Canada	Environmental Illness Society of Canada. (2000). Socio-Economic Impacts of Environmental Illness in Canada. November 15, 2000.	Provides an overview of MCS and potential impacts on quality of life and health. **Quality of Study: **** **Relevant to Objectives:** No. Document is not scientific, and was prepared by a marketing and communications firm in consultation with some experts. Many of the resources cited are pre-2000 and are quite outdated.

APPENDIX C

Multiple Chemical Sensitivity – Studies of Self-Reported Multiple Chemical Sensitivity

During the collection and review of literature for MCS, it became apparent that a notable proportion of the published studies relied upon patients who self-identified as having MCS or chemical sensitivities. The key difference between diagnosed and self-reporting MCS patients within the context of this report is the use of published diagnostic criteria by an experienced health-care practitioner.

At the request of Alberta Health, the studies with self-reported MCS that were initially reviewed and included in the main draft of the report have been moved into this Appendix. These studies provide useful information regarding MCS.

C1.0 Prevalence – How Common is MCS?

In Canada, the most recent information available regarding the prevalence of MCS was identified in the 2014 Canadian Community Health Survey (as summarized in Park and Gilmour (2017)); 2.7% of the Canadians surveyed aged 25 or older, approximately 671,500 individuals, were self-reported as having been diagnosed with MCS. However, clinical assessments or the application of one of the available sets of diagnostic criteria were not applied as the survey was completed via telephone or mail. These data are based on the responses of individuals to a series of survey questions, rather than formal medical diagnoses. As a result, there may be variability within the surveyed population as MCS diagnosis. Additional characteristics of the population are presented in Table C1.

Table C 1 Prevalence of Multiple Chemical Sensitivity in Canadians, 25 years and Older, As reported in the Canadian Community Health Survey (Adapted from Park and Gilmour (2017))

Characteristic	Number of Individuals Reported to have MCS (in 1,000s)	Relative Percentage (%)of Canadian Population Surveyed*(23.9 million)	95% Confidence Interval
Total	671.5	2.7	2.5 to 3.0
Sex			
Male	169.6	1.4	1.2 to 1.7
Female	501.9	4.0	3.6 to 4.4
Age Group			
25 to 44	138.4	1.5	1.2 to 1.8
45 to 59	230.0	3.1	2.6 to 3.5
60 to 74	230.7	4.2	3.7 to 4.7
75 or older	72.4	3.5	2.8 to 4.4
Household Education			
Postsecondary	402.3	2.6	2.3 to 2.9
Less than postsecondary	255.3	3.0	2.6 to 3.3
Marital Status			
Married/common law	402.9	2.4	2.1 to 2.6

Widowed, separated, divorced	159.3	4.3	3.7 to 5.1
Never married	108.2	2.8	2.3 to 3.4
Cultural Identity			
White	519.8	2.8	2.6 to 3.1
Non-white	136.7	2.6	2.1 to 3.2

In the 2014 Canadian Community Health Survey, women were found to be more than twice as likely to have MCS then men, with MCS being most commonly reported in middle age (Park and Gilmour, 2017). This observation is consistent with the literature reviewed and summarized within the Australian review (CoA, 2010), where it was noted that MCS subjects are often females between the ages of 30 to 50 years of age. No notable influence of other sociodemographic factors in relation to MCS were apparent. Although information regarding household income was provided in Park and Gilmour (2017), it was difficult to decipher due to a lack of information regarding the household income quintiles. A summary of the 2014 Canadian data is presented in Table C1 for "white" and "non-white" individuals (for which the lack of detail limits the interpretation of the data). However, Park and Gilmour (2017) stated that individuals within the lower household income quintile had the highest prevalence of MCS.

Similar results were reported in the review by Marshall et al. (2010). Here it is was noted that from the 2002 and 2003 Canadian Community Health Surveys, based on self-reporting, 2-3% of Canadians were clinically diagnosed with MCS (Marshall et al., 2010). From the 2005 Canadian Community Health Surveys, 2.5% of adult Ontarians were clinically diagnosed with MCS (Marshall et al., 2010). No information for Alberta was identified in the review.

In the general German adult population, Hausteiner et al. (2005) determined that the prevalence of self-reported MCS and physician-diagnosed MCS was 9% and 0.5%, respectively. Within the Korean adult population, Jeong et al. (2014) determined that the prevalence was 16.4%. It was noted by Jeong et al. (2014) that when participants were grouped as allergic or non-allergic participants, the allergic participants had higher estimated prevalence of MCS (19.5% vs 11.3%).

In Australia, the Commonwealth of Australia (2010) reported that through combining two surveys commissioned by the State Health Department in 2002 and 2004, the prevalence of physician-diagnosed MCS was 0.9% and reported self-diagnosed MCS was 16.4%.

Andersson et al. (2008) estimated the prevalence of self-reported MCS in a random sample of 326 teenagers (ages 13-19 years) from Skövde, Sweden to be 15.6%,.

The prevalence of MCS in occupational settings is also impacted by the lack of use of diagnosed MCS patients.

Reid et al. (2001) determined the prevalence of MCS in three cohorts of British military personnel including Gulf War veterans, Bosnia veterans, and those serving during the Gulf War (but were not deployed), to be 1.3%, 0.03%, and 0.2%, respectively. Based on self-reported exposures to various factors (chemical and non-chemical), the strongest and statistically significant adjusted Odds Ratios (OR) for MCS in relation to chemical exposures identified within the Reid et al. (2001) study included: pesticides on clothing (adjusted OR 12.3, 95% CI: 5.1 – 30), personal pesticides (adjusted OR 10.9, 95%CI: 2.6 – 45.8), smoke from burning rubbish or feces (adjusted OR 5.8, 95% CI 2.0 – 16.7), smoke from oil fires (adjusted OR 4.6,

95% CI: 1.6 – 13.3), chemical or nerve gas attack (adjusted OR 3.2, 95% CI: 1.5- 6.7), and exhaust from heaters (adjusted OR 2.8, 95% CI 1.1 – 7.5). A high level of comorbidity of MCS and CFS with psychiatric disorders was also evident in the British military population studied, and an adjusted OR of 14.6 (95% CI 7.2 – 26.6) was identified for post-traumatic stress (Reid et al., 2001).

Black et al. (2000) studied the prevalence rates of self-reported symptoms suggestive of MCS in individuals that were deployed in the Persian Gulf War relative to military personal who were not deployed and found that individuals who were deployed were twice as likely to report symptoms of MCS (5.4% vs 2.6%). According to Black et al., (2000) the prevalence of symptoms suggestive of MCS in all 3,695 participants was 3.4%. While reported sensitivities to various triggers were noted, no discussion of potential causes of MCS were discussed within Black et al. (2000).

In Chun et al. (2006), differences between the prevalence of self-reported symptoms suggestive of MCS were observed in construction workers who were assigned to one of three job groups: (interior worker (16.8%), office worker (24.5%), and exterior worker (5.1%). Chun et al. (2006) suggested that construction workers doing interior or office work had a higher risk of developing MCS compared to those who did exterior work. Chun et al. (2010) recommended considering ventilation systems during construction as a means to improve work environments as there is high exposure to volatile organic compounds for the interior worker and office worker.

The potential for the “healthy worker effect” to have influenced the results of studies of MCS in occupational populations should be considered. Since healthy individuals are selected for employment, they commonly have lower disease incidence than the general population.

C2.0 What Conditions Overlap with MCS?

Of the population evaluated within the 2014 Canadian Community Health Survey, those who reported as having MCS also reported having one (24.7%), two (22.2%), three or more chronic physical diseases (40.6%), other than conditions that overlap with MCS. Examples of these other chronic conditions include asthma, arthritis (excluding fibromyalgia), heart disease, and cancer, among others. The most commonly reported mental disorders in people who reported as having MCS included mood or anxiety disorders (27.2%), major depressive disorder (12.6%), or general mental disorders (not specific, 18.8%). It has been suggested that such conditions may arise as a result of experiencing unexplained symptoms (Park and Gilmour, 2017).

C3.0 Multiple Chemical Sensitivity - Lines of Research

Factors that may contribute to the development of MCS have been identified and sorted into different categories by lines of research based on the results of the literature search.

Assessments of the various lines of research associated with MCS have been reported in the Australian review CoA (2010) and also in a review by Rossi and Pitidis (2017). The following review is intended to build upon the foundations set by these two documents.

The literature identified in Section 2.0 was evaluated in detail. Based on more comprehensive document reviews, some studies that were ‘binned’ in the annotated bibliography (Appendices A and B) were moved between categories based on relevance. For the purposes of this review, the following headings have been used to organize the available information into key lines of research into MCS::

- Toxicant Induced Loss of Tolerance;

- Immunological Dysregulation
- Genetic Factors:
    - Genes Related to Metabolism;
    - Genes for Immunological Modulators; and
    - Genes for Neurological Mediators.
- N-methyl-D aspartate (NMDA) Receptor Activity and Nitric Oxide/Peroxynitrate;
- Neurological Sensitization and Neurogenic Inflammation;
- Neurological Abnormalities:
    - Olfactory Processing Dysfunction;
    - Vestibular and Auditory Dysfunction; and
    - Other Neurological Factors.
- Behavioural and Psychiatric Factors.

The above-listed categories are intended to organize the information in a manner that facilitates critical review and evaluation. It is also recognized that it is difficult to determine if effects reported in the literature within the various sections are involved in the etiology of MCS or are consequences of MCS.

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The approach to analysing the WOE for this report is in the spirit of or inspired by qualitative and quantitative WOE frameworks available within the scientific literature. By necessity this review evaluates only human studies as no animal model exists for MCS. A common scoring framework could not be established for the review due to the variability in study designs, clinical signs, and symptoms. Furthermore, dose-response data were generally lacking.

C3.1 Toxicant Induced Loss of Tolerance (TILT)

No studies of self-diagnosed MCS that related to the TILT line of research were identified.

C3.2 Immunological Dysregulation

Two studies involving self-diagnosed MCS were identified, and are summarized below and in Table C2.

Table C2 Summary of Findings Regarding MCS and Immune Dysfunction, Self-Reported Literature

Study	Number of Subjects	Design Type	Diagnosed	Screening Questionnaire Type[1]	Statistically Significant Findings Regarding MCS[2]
Berg et al. (2011)	3,460 divided into 4 levels of sensitivity	Cross-Sectional	No	ECRHS, NOSQ, other[3]	Association between increased non-allergic skin reactions and self-reported sensitivity (+)
Eberlein-Konig et al. (2002)	65 sensitive No controls	Cross-Sectional	No	GHCCS	Elevated IgE levels, high proportion of allergy or hypersensitivity disease (+)

Acronyms: ECRHS: European Community Respiratory Health Survey, GHLCS: German Health Locus of Control Scale NOSQ: Nordic Occupational Skin Questionnaire,

[1] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[2] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue

The existence or exacerbation of allergic sensitivity has also been studied in relation to MCS. Eberlein-Konig et al. (2002) evaluated allergic sensitization within a population of 65 individuals who self-reported as having chemical sensitivities (not defined as MCS within the study). No controls were included. The allergy test results revealed that 42 patients (65% of subjects) were sensitized to common allergens, including dust mites, pollen and animal epithelia. An allergic or hypersensitivity-related disease was diagnosed in 71% of the group. Total IgE levels were elevated in 25% of the subjects. Approximately 58% of the group were found to suffer from psychosomatic symptoms following a review of medical history and an interview with a psychologist. Eberlein-Konig et al. (2002) concluded that the results suggest that the potential for hypersensitivity to indoor chemical exposures may alter reactions to common allergens, and suggest that allergic status be explored in individuals with chemical hypersensitivity.

Patch-testing for several contact allergens and allergens via skin prick tests was completed in a cross-sectional study of 3,460 individuals by Berg et al. (2011) for a population randomly recruited from the general population within Denmark. The incidence of both allergic and non-allergic skin reactions following prick tests were determined to be associated with chemical sensitivity (determined by questionnaire responses) when each was adjusted for the other in a regression model ($p < 0.001$). However, when sex and age were also evaluated as co-variates in the regression analysis, only non-allergic cutaneous skin reactions were found to be significantly associated with the most severe skin symptoms (OR: 2.52, $p = 0.003$). No further influence on the OR was identified following adjustment for comorbidity with eczema, atopic dermatitis, asthma, depression and anxiety, smoking and socioeconomic factors. Berg et al. (2011) hypothesized that the skin-reactions are not mediated by IgE, but may involve histaminergic , or a non-specific physiological response that triggers a neurovascular or vascular response following chemical exposure.

Various hypersensitivity conditions are suspected to have a potential autoimmune basis (Busby, 2017). A recent review by Genuis and Kyrillos (2017) hypothesized that while further study is required to better understand the interaction between the immune system and chemicals in the development of autoimmunity, the exposure and retention of some chemicals “following an adverse exposure present differently to an intact immune system, and trigger an autoimmune P primary research articles that specifically evaluate autoimmune-related aspects of MCS were not specifically identified during this review other than the gene-expression study by De Luca et al. (2010).

C3.2 Genetic Factors

Another line of research for MCS is focused on potential differences genetic profiles between individuals with MCS, or in the expression of genes associated with the production of enzymes or endogenous substances (e.g. neuropeptides, immunomodulators) related to various physiological functions (refer to Section 4.2 of report for additional information) in MCS.

Summary

Overall, there is a lack of a clear, consistent genetic profile for MCS in the self-reported literature. The results of the available self-reported studies are presented in Table C3.

Cui et al. (2013) identified an increased prevalence of polymorphisms for SOD2 Ala (+) in sensitive individuals. In contrast, Wiesmüller et al. (2008) did not find evidence of increased gene variants for SO_2 in individuals with self-reported MCS. Neither of these studies involved the use of diagnosed MCS subjects. Although the Cui et al. (2013) study involved a larger study population, it was of cross-sectional design, and potentially influenced by selection bias. It is not clear what the selection criteria were for the 324 subjects for which DNA samples had collected and stored by the pulp and paper facility that was the focus on the investigation.

Table C3 Summary of Findings Regarding Self-Reported MCS and Genetic Factors

Study	Number of Subjects	Design Type	Diagnosed	Screening Questionnaire Type[1]	Statistically Significant Findings Regarding MCS[2]
Genes Related to Metabolism					
Cui et al. (2013)	116 sensitive 208 controls	Cross-Sectional	No	Modified QEESI©	Increased prevalence of polymorphism gene variant SOD2 Ala (+)
Fujimori et al. (2012)	47 sensitive 1,037 controls	Case-Control	No	Modified QEESI©	No difference in gene variants of ALDH2, GSTT1 or GSTM1 or PON1 (-)
Schnakenberg et al. (2007)	521 sensitive (2 groups) No controls	Cross-Sectional	No	QEESI©	Homozygous deletions for GSTM1 and GSTT1, NAT2 slow metabolizers (+) No evident gene variants in GSTP1 (-)
Wiesmüller et al. (2008)	59 MCS 40 controls	Case-Control	No	Hüppe et al. 2000, Q-LL, Q-OEUM	No increased incidence of gene variants of NAT1, NAT2, PON1, PON2, SOD2 (-)
Genes Related to Neurological Mediators					
Wiesmüller et al. (2008)	59 MCS 40 controls	Case-Control	No	Hüppe et al. 2000, Q-LL, Q-OEUM	No increased incidence of *gene variants of* $5H_{TT}$ (-)

Acronyms: , Q-LL: questionnaire of living conditions and living factors, Q-OUEM: Questionnaire of the Outpatient Unit of Environmental Medicine,

[1] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[2]Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue.

C3.2.1 Genes Related to Metabolism

A study by Wiesmüller et al. (2008) did not find any differences in genotype variants of NAT1, NAT2, PON1, PON2, SOD2 in 50 self-reported MCS subjects and controls (40).

A cross-sectional study was conducted by Schnakenberg et al. (2007) evaluated genetic variants of the NAT2, GSTM1, GSTT1 and GSTP1 genes in a group of 521 individuals with self-reported chemical sensitivity via a questionnaire. The subjects were divided into two groups – those who were reported to be highly sensitive to common chemicals and the other with low to moderate sensitivity. A significant difference between the highly sensitive and less sensitive groups in GSTT1 in genotype frequency (OR 2.80, $p < 0.0001$), with the difference being a higher frequency in a homozygous GSTT1 deletion. Similarly, homozygous deletion variants of GSTM1 were observed in the highly sensitive group relative to the less sensitive group (OR 2.08, 95% CI: 1.46-2.96, $p < 0.0001$). Deletion variants would likely result in reduced GSH. A significant difference between the two groups was also observed for NAT2 genotypes in females (but not males), with the incidence of NAT2 slow metabolizers being more prevalent (OR 2.15, 95%CI: 1.65-4.75), and the genotype NAT2*6/*6 being the most notable in the highly sensitive group. However, none of the NAT2 genotype variants were significantly different between groups – the findings were only positive when all slow variants were pooled together. No significant differences in GSTP1 frequencies were observed (Schnakenberg et al., 2007).

No significant differences in ALDH2, GSTT1 or GSTM1 or PON1 variants were observed in a population of Japanese workers (47, subdivided into groups according to QEESI© scores for chemical sensitivity) compared to controls (1,307) (Fujimori et al., 2012).

Significant differences between self-reported MCS subjects (116) and controls (208) were observed by Cui et al. (2013) in the incidence of polymorphisms for the metabolic enzyme superoxide dismutase (SOD2), specifically for a genotype variant that contains alanine (Ala) versus valine (Val) in the high chemical sensitivity group (adjusted OR 4.30, 95% CI, 1.23-15.03, $p = 0.01$). The Ala variant is suspected to allow more efficient movement of SOD2 into the cellular mitochondria and a more active SOD2 enzyme. An additive model was also applied to evaluate the incidence of Ala/Ala vs. Val/Ala vs. Val/Val, and a significant difference between the sensitive group and controls (adjusted OR 4.54, 95%CI, 1.52 to 13.51, $p = 0.01$) SOD2 overexpression can result in increased hydrogen peroxide levels and subsequent oxidative stress and cell damage. Cui et al. (2013) did not observe any significant differences in the distributions of genotypes for CYP2E1, NAT2, GSTP1, ALDH2.

C3.2.2 Genes for Immunological Modulators

No studies of self-reported MCS were identified for this line of research.

C3.2.3 Genes for Neurological Mediators

Wiesmüller et al. (2008) compared allelic frequencies of genomic variants of $5H_{TT}$ (SLC6A4) in a population of self-reported MCS patients recruited following a radio program about MCS. This gene codes for a transporter protein for the neurotransmitter serotonin that transports it from synapses to presynaptic neurons. No significant differences between the MCS group and controls were observed.

C3.3 N-methyl-D-aspartate (NMDA) Receptor Activity and Nitric Oxide/Peroxynitrate

No studies of self-reported MCS were identified for this line of research.

C3.5 Neurogenic Inflammation and Neurological Sensitization

Four studies of self-reported MCS were identified that examined the role of neurogenic inflammation and neurological sensitization, which are summarized below and in Table C4.

Table C4 Summary of Findings Regarding Diagnosed MCS, Neurological Sensitization and Neurogenic Sensitization

Study	Number of Subjects	Design Type	Diagnosed	Screening Questionnaire Type	Statistically Significant Findings Regarding MCS[2]
Claeson and Andersson (2017)	13 chemical intolerance 19 controls	Experimental	No	CSS, PSQ,	Increased sensory irritation of eyes, nose and throat with VOCs (+)
Kiesswetter et al. (2005)	8-12 MCS 12 controls	Experimental	No	Other[1]	No increase in eye blinks with VOCs (-)
Kimata et al. (2004)	25 MCS 25 eczema 25 controls	Experimental	No	-	Elevated neurogenic mediators (substance P, vasoactive intestinal peptide, nerve growth factor) in plasma following VOC exposure (+)
Wiesmüller et al. (2002)	12 MCS 12 controls	Experimental	No	Other[1]	Decreased anterior nasal flow following chemical exposure (+)

Acronyms: CSS: Chemical Sensitivity Scale,
[1]Other' is noted when a standardized questionnaire was used, but is not named or specified
[2] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue.

The use of eye blinks as an indicator for sensory irritation in MCS subjects was explored by Kiesswetter et al. (2005). In this study, experiments were completed in a controlled-chamber with either variable or peak 2-ethylhexanol exposure for 4-hours with subjects with self-reported MCS (8-12 depending on exposure) and healthy controls (12). A general increase in blink frequency was observed in association with both time and exposure concentration; however, no significant difference between the two groups with respect to blink frequencies was observed. No other indicators of eye irritation were assessed and no other potential differences between the groups following exposure to 2-ethylhexanol were observed.

Wiesmüller et al. (2002) compared nasal function following exposure to chemical irritants in self-reported MCS (12) and matched controls (12) to determine if changes in nasal pathophysiology were occurring in the MCS group. Nasal function was assessed via anterior active rhinomanometry (which allows an estimation of air pressure relative to flow in the nasal passages) and acoustic rhinometry (use of acoustic signal to provide cross-sectional assessments of the upper airways). Evaluations were completed before, and after 4-hour exposures to low or high concentrations of ethylbenzene and 2-butanone using facial masks. The MCS group was observed to have a significant decrease ($p < 0.05$) in the measured flow value as measured by the anterior active rhinomanometry relative to the control group, which was independent of the chemical and level of exposures. No significant effects were observed in controls.

Kimata (2004) explored the role of several suspected neurogenic inflammatory mediators (substance P, vasoactive intestinal peptide, nerve growth factor) as well as histamine through the comparison of VOC exposures from a freshly painted room in subjects with self-reported MCS (25), subjects with atopic eczema dermatitis syndrome (25) and control subjects (25). The MCS group was observed to have significantly higher concentrations of all the measured mediators ($p < 0.01$) except for histamine.

The role of TRPA1 ion channel stimulation in MCS was examined by Claeson and Andersson (2017), where 13 subjects with self-reported chemical intolerance were compared with controls (19) with respect to their responses to controlled-chamber exposures to fresh air, heptane, or a mixture of acrolein and heptane for 1-hour. The chemical intolerance group were determined to have significantly greater sensory irritation of the eyes ($p < 0.01$ to $p < 0.001$), nose ($p < 0.01$ to $p< 0.001$) and throat ($p < 0.05$ to $p < 0.001$) when exposed to the acrolein-heptane mixture in comparison with the control group, but no differences were observed following exposures to heptane only.

C3.6 Neurological Dysfunction

Several studies of neurological dysfunction involving self-diagnosed MCS patients were identified. These studies are listed within Table C5 along with their key findings, and brief text summaries are provided following the table.

Table C5 Summary of Findings, Self-Reported MCS and Neurological Dysfunction

Study	Number of Subjects	Design Type	Diagnosed	Screening Questionnaire Type[1]	Statistically Significant Findings Regarding MCS[3]
Imaging Studies					
Andersson et al. (2014)	25 IEI 26 controls	Experimental	No	Other[2]	Increased activity in thalamus and decreased activity in superior frontal gyrus (+)
Andersson et al. (2017)	58 MCS Self-control	Experimental	No	CSS	Increased activation in several brain regions (mid- and anterior insula, precuneus, middle cingulate gyrus, superior parietal lobule, and decreased activation in inhibitory node/ rostral anterior cingulate cortex (+)
Non-Imaging Studies					
Andersson et al. (2009)	21 MCS 17 controls	Experimental	No	CSS-SHR	Faster reaction times and altered latency times following paired olfactory and auditory stimuli (+)
Haumann et al. (2002)	12 MCS 12 controls	Experimental	No	CGES	Significant differences in mean heart and breathing rate patterns with odorant exposure (+)
Haumann et al. (2003)	12 MCS 12 controls	Experimental	No	CGES, STAI	Significant decreases in breathing and heart rate with VOCs (+)
					No changes in breathing or heart rate with 2-propanol or octanol (-)
Mizukoshi et al. (2015)	8 MCS 7 controls	Experimental	No	QEESI© Japanese version	Inhibited parasympathetic activity with VOC exposure (+)
Sucker et al. (2010)	59 MCS 225 controls	Cross-Sectional/ Experimental	No	CGES, OAS	Enhanced response to rose odour (+)
					No differences in odour identification or awareness (-)
Van Thriel et al. (2002)	12 MCS 12 controls	Cross-Sectional/ Experimental	No	CGES	Increasing intensity and frequency of symptoms in response to odorants (+)
Van Thriel et al. (2008)	44 subjects, divided into sMCS and controls	Cross-Sectional/ Experimental	No	CGES	Increasing intensity and frequency of symptoms (+)

Acronyms: CSS: Chemical Sensitivity Scale ' CSS-SHR: Chemical Sensitivity Scale for Sensory Hyperreactivity, CGES: German Questionnaire on Chemical and Environmental Sensitivity; OAS: odour awareness scale

[1]Defined and published diagnostic criteria were required for a study to receive a 'yes' and be considered to have relied upon diagnostic criteria. The use of questionnaires as a diagnostic tool was counted as a screening questionnaire, rather than a diagnostic framework, as the questionnaires rely upon self-reporting, while a clinical diagnosis relies on both self-reporting an assessment by a practitioner.

[2]other' was noted when was not evident that a formally standardized questionnaire was used

[3] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue.

C3.6.1 Imaging Studies

An experimental case-control study of women with self-reported IEI and controls were exposed to isoamyl acetate or carbon dioxide (CO_2) via intranasal administration and examined using fMRI to measured BOLD differences in the various brain regions (Andersson et al. 2014). The IEI group was found to have a higher BOLD signal in the thalamus and lower signal in the superior frontal gyrus during exposure than controls ($p < 0.05$). The authors suggested that the results indicated the involvement of a hyperactive limbic response (the thalamus) and a lack of ability to inhibit salient, arousing stimuli as demonstrated by the reduced activity in the prefrontal cortex, specifically, the superior frontal gyrus.

The assessment of BOLD using fMRI was recently used by Andersson et al. (2017) in the evaluation of short-term olfactory sensitization and brain networks related to the sensation of pain. A total of 58 subjects with self-reported MCS were included in the study, and each served as their own control. Subjects were exposed to amyl acetate (banana-like odour) and CO_2 (pungent-like sensation) for 30-seconds, following a 30-second baseline exposure with no exposure to either agent. Based on reported intensities during the exposure, the subjects were divided into three groups: sensitizers, intermediate or habituaters. The sensitizer group were observed to have a greater BOLD signal during exposure within the left mid- and anterior insula, precuneus, middle cingulate gyrus, superior parietal lobule and in olfactory regions of the orbitofrontal cortex. A lower BOLD signal was apparent within the rostral anterior cingulate cortex (rACC, an inhibitory node within the prefrontal region involved in the habituation to pain). However, no significant differences in BOLD within these regions over time was observed for any group. Andersson et al. (2017) proposed that while additional study is needed to provide further clarity, consideration of the potential for overlap between the pain inhibitory regions of the brain in response to odour may help to explain why some individuals experience pain in response to exposures that were previously tolerated.

C3.6.2 Non-Imaging Studies

Altered chemosomatosensory, olfactory and auditory event related potentials were assessed by Andersson et al. (2009) in individuals with self-reported MCS and controls to determine if there were any differences between the groups indicative enhanced sensitization. An olfactometer was used to expose the subjects to distilled water, amyl acetate (banana odour), or CO_2 via nasal-only inhalation for 10-second increments. Auditory stimuli were administered via headphones at the same time as the olfactometer exposures. The MCS group demonstrated a faster ($p < 0.001$) reaction time to the olfactory-auditory stimulus pairs, and shorter chemosensory and olfactory latencies than controls ($p < 0.05$ for amyl acetate, and $p < 0.01$ for CO_2). Control subjects were observed to habituate to the CO_2 exposure, while the MCS group did not. Andersson et al. (2009) propose that sensitization is a type of learning process that is generally beyond conscious control, contribute to some individuals finding some exposures hard to ignore.

Studies by van Thriel et al. (2002; 2008) compared olfactory function between individuals with self-reported MCS and controls. Stronger various odorants delivered via nasal olfactometer and standardised test kits. Increasing symptoms were reported over time in the MCS group but not in controls. Both concentration and the type of agent influenced the subjects' responses. Van Thriel suggested that the potential differences between the groups related to individual learning processes in the responses to odours. A survey of 332 visitors at an international trade fair for occupational safety and health was completed by Sucker et al. (2010), where questions regarding chemical sensitivity were posed, and odour identification and odour awareness tests were completed using standardized test kits. No significant differences in odour identification or

awareness were observed between the self-reported MCS group and controls. However, the response to one odorant, phenylethylalcohol (PEA, rose odour) was reported as being less intense but more unpleasant than controls.

Some variability in responses of the autonomic nervous system (ANS) has been reported in association with odour exposure. Haumann et al. (2003) compared ANS responses (via changes in breathing and heart rates) between two groups (12 self-reported MCS and 12 matched controls) following 4-hour exposures to various solvents (ethylbenzene, 2-butanone, 2-propanol, and 1-octanol, within a controlled chamber) at levels comparable to olfactory thresholds and at levels approaching occupational health limits. Decreased breathing and heart rate were observed in the MCS group with the ethylbenzene and 2-butanone exposures ($p < 0.001$), but not the other two chemicals. No significant associations with the level of exposure were identified for any of the subjects. Another study by the same research group, Haumann et al. (2002) had similar findings with a similar experimental protocol. Significant differences in the mean breathing rates of the self-reported MCS group (12) and controls (12) were observed ($p = 0.034$), and the groups also were observed to have divergent trends in breathing and heart rate patterns over the course of the exposures ($p = 0.023$ and $p = 0.011$). Haumann et al. (2002, 2003) concluded their results indicate that the involvement of the ANS in the olfactory response to odours is evident, but generally inconclusive. Both studies focused on younger adults, and Haumann et al. (2003) noted that typically, the onset of MCS is generally in middle age, and only male studies were included. Thus, age- and sex-related differences may have influenced the results. Acclimatization responses to the laboratory environment by subjects were also noted as having a potential influence on the data by Haumann et al. (2002).

Temporal changes in ANS function in response to environmental chemicals encountered in daily activities were studied by Mizukoshi et al. (2015) using heart rate variability monitors and portable VOC monitors. A total of 8 diagnosed MCS patients and age- and sex-matched controls (7) were included, who recorded time-activity patterns in logs in 5-minute intervals. No consistent trend in heart rate variability were apparent. Some evidence of inhibited parasympathetic activity was observed, through the real-time electrocardiogram data. These decreases in activity were correlated with increases in measured VOC concentrations. Higher, but not statistically different levels of total VOCs were encountered by the MCS group than the controls. The VOC scan included on the monitors was not comprehensive, and some VOCs that may have triggered MCS symptoms may not have been captured.

C7 Behavioural and Psychiatric Factors

Several studies involving self-diagnosed MCS patients were identified during the literature review that pertained to behavioural and psychological symptoms or conditions. These studies are summarized in Table C6, followed by brief text summaries.

Table C6 Summary of Findings Regarding Psychological Factors and Self-Reported MCS

Study	Number of Subjects	Design Type	Diagnosed[1]	Screening Questionnaire Type[2]	Statistically Significant Findings Regarding MCS[4]
Bailer et al. (2007a)	54 IEI 44 SFD 54 controls	Experimental	No	COSS, PHQ	Evidence of attenuation bias towards symptom words on tests, enhanced awareness (+)

Bailer et al. (2007a)	54 IEI 44 SFD 54 controls	Cross-Sectional	No	COSS, PHQ	High stability of IEI symptoms over 1-year, higher degree of functional impairment and symptom severity, SFD potential risk factor for IEI development (+)
Bailer et al. (2007b)	54 IEI 44 SFD 54 controls	Cross-Sectional	No	COSS, PHQ, SCID-I	Potential behavioural changes resulting from traumatic exposure to life-threatening illness (+)
					No evidence of increased rates of previous trauma or multiple traumas in relation to IEI (-)
Black et al. (2000b)	26 MCS 26 controls	Cross-Sectional	No	-	Persistence of psychological effects over time, high rates of depression and somatization disorder, increasing over time (+)
Bloch and Meggs (2007)	318 sensitive No control	Cross-Sectional	No	PRIME-MD	Prevalence of anxiety and depression in people with sensitivity (+)
					MCS not attributable directly to anxiety (-)
Cui et al. (2015)	565, divided into chemical sensitivity groups	Cross-Sectional	No	QEESI©	Subject scores for chemical sensitivity predictive of adverse health effects using a Path model (+)
DeVriese et al. (2000)	56 divided into groups based on affectivity	Cross-sectional	No	ASI, NEM/PEM, PNAS, Other	Significance of results not clear for MCS
Eek et al. (2010)	10,275 subjects	Cross-Sectional	No	Other[3]	Reduced subjective health associated with development of environmental intolerance (+)
Fuller-Thomson et al. (2011)	7,068 MCS 7072 CFS 7070 FM 7076 IBS	Cross-Sectional	No	CCHS	Significant association with childhood physical abuse (+)
Henningson and Sunbom (2000)	10 MCS 10 conversion disorder 10 controls	Case-control	No	DMT, DSM-IV, Other	Use of blocking manoeuvres to avoid anxiety-provoking stimuli (+)
Johnson and Colman (2017)	21,977 total	Cross-Sectional	No	CCHS	MCS associated with greater odds of having major depressive disorder, severe distress, asthma or CFS (+)
Johnson and Colman (2017)	21,977 total	Cross-Sectional	No	CCHS	Significant association with childhood sexual abuse (+)
					No association with childhood physical abuse (-)
Österberg et al. (2002)	17 MCS 57 TE 200 controls	Observational	No	-	Significant increased psychasthenia scores in MCS group (+)
Rethage et al. (2008)	90 MCS 137 controls 161 historical	Case-Control	No	Other	Increased reporting of “personal worry” but not “general worry” (+)
Skovbjerg et al. (2010a)	161 subjects 571 population	Cross-Sectional	No	Other	Increased negative affectivity, defensiveness and difficulties identifying feelings (+)
					No evidence of repressed coping or alexithymia (-)

Skovbjerg et al. (2010b)	161 subjects 571 population	Cross-Sectional	No	Other	Increased somatosensory amplification, autonomic perception and multiple mucous and CNS symptoms (+)
					No association with personality trait of absorption (-)
Skovbjerg et al. (2012)	161 subjects 571 population	Cross-Sectional	No	Other	Higher scores for CNS and mucousal symptoms, depressive symptoms, chemical hypersensitivity and consequences for social activities (+)

Acronyms: ASI: Anxiety Sensitivity Index, CCHS: Canadian Community Health Survey, CCII Chemical Odour Intolerance Index, COSS: Chemical Odour Sensitivity Scale, DMT: defence mechanism test, DSM-IV, EMQ: environmental medicine questionnaire, IBS: irritable bowel syndrome, NEM/PEM: Negative and Positive Emotionality Measure; Positive and Negative Affect Schedule PHQ: Patient Health Questionnaire, SCID: Structured Clinical Interview, STAI: State Trait Anxiety Inventory,

[1] Includes only questionnaires that were used to screen and evaluate subjects in relation to inclusion and exclusion criteria for the study, and do not include questionnaires used to evaluate or test subjects.

[2] 'Other' is noted when a standardized questionnaire was used, but is not named or specified

[3] Findings that were determined to be statistically significant and indicated a clear difference in the effect for the MCS group are highlighted in green, while findings that were statistically significant but found no difference for the MCS group are in light blue. Due to a lack of a reference group, the significance of results was difficult to determine in some studies, and findings are presented in grey.

Behavioural and Psychological Responses to Stimuli

In a small case-control study by Henningsson and Sundbom (2000), a group of 10 self-reported MCS subjects who reported symptoms associated with dental amalgam fillings, were compared with a group of 10 patients with diagnosed conversion disorder according to DSM-IV and had either pseudoseizures or a loss of voluntary motor function. A separate control group was also included. Several tests were conducted to evaluate psychological defense mechanisms that involved anxiety-provoking imagery. Both the MCS group and the conversion disorder group trended towards distorting or avoiding the stimulus. The MCS group was observed to more frequently avoid the imagery or were unable to perceive the image. Henningsson and Sundbom (2000) suggested that MCS subjects employ 'blocking maneouvers" in attempt to avoid the stimuli, while the conversion disorder group distort. Henningsson and Sundbom (2000) also noted that the results are similar to previous studies in psychosomatic patients who have an inability to verbalize emotions and interpret bodily sensations as symptoms. While statistical analysis was noted as having been completed, the level of significance in the observed differences were not apparent.

DeVriese et al. (2000) developed an experiment to evaluate if Pavlovian conditioning to odours can arise in response to a chemical stimuli. A group of 56 recruited subjects were divided into two groups (low-negative affectivity or high-negative affectivity) based on responses to a health survey and questionnaires regarding emotional responses. The latter group was considered to have generally heightened aversive emotional responses following exposure to chemical stimuli associated with negative physical responses (ammonia), a generalized response to foul odours (ammonia, butyric and acetic acid) was observed ($p < 0.001$) but not for a more positive odour (niaiouli or eucalyptus, citrus). The amount of time between the initial chemical exposure and the subsequent tests did not impact the degree of conditioning – the conditioning response was still evident, regardless of time. The extent of the selective conditioning and reported effects of the exposures were mediated by the low- or high-negative affectivity status of the individual. The results of this study were challenging to interpret with respect to MCS, as while MCS is discussed by DeVriese et al. (2000), the two subject groups in the study were not noted as having either diagnosed MCS or self-reported MCS.

The psychological responses to CO_2 as well as ammonia and butyric acid were compared by Meulders et al. (2010) to evaluate the role of learning in symptom response upon challenge in a group of healthy subjects. Subjects were exposed in a 'learning phase' to three exposures to butyric acid combined with 20% CO_2, or diluted ammonia mixed with air. During the "testing" phase, all subjects were exposed to the same odorants but without CO_2. The odorants were administered in small containers, while the CO_2 was administered via a nasal sampling cannula and mask. In both tests, the subjects rated their anxiety levels as soon as the odours were detected and stated whether or not they could expect symptoms. Respiratory rates were monitored throughout the study, and symptom reports were collected after exposures. Only the subjects who in the first phase learned to anticipate symptoms reported increased symptom scores in the test phase. The results suggest that, following an initial exposure where adverse effects, panic, hyperventilation or a functional psychological syndrome resulted, subsequent exposures to the same chemicals are able to trigger symptoms.

A total of 970 subjects were recruited, interviewed, and underwent a medical and psychology examination by Bailer et al. (2007a), and following exclusions, three subject groups were created: controls (54), diagnosed IEI (54) and diagnosed somatoform disorder (SFD, 44). After 1-year, the baseline tests were repeated on all subjects, to examine changes over time. Evidence of an attenuation bias towards symptom words included in the tests, suggesting that IEI effects could be activated by encountered stimuli (chemical or physical), but also from discussion or reports of symptoms, or an enhanced awareness of physical symptoms (Bailer et al., 2007a).

Comorbidity of Mental Health Symptoms and Conditions with MCS

A large cross-sectional study of 10,275 respondents to a postal survey that included five questions about environmental annoyance and self-reported indications of health, stress and working conditions was completed by Eek et al. (2010). Follow-up with respondents was completed five years later. Significant associations between environmental annoyance and subjective health complaints, higher levels of stress, strain, lack of recovery, lower social support and a general dissatisfaction from their occupational work, were observed. Eek et al. (2010) hypothesized that reduced subjective and mental health precede the development of environmental intolerance. This study did not specifically diagnose subjects as having MCS and may have included individuals with self-diagnosed MCS or IEI as a result.

The research team of Skovbjerg et al. (2012) completed a study of the association between IEI and psychological distress. Three groups were included: diagnosed IEI (136), individuals at an environmental clinic who reported symptoms of chemical intolerance (101), and individuals selected from the general population (787). The results of the diagnosed and undiagnosed sensitivities group were pooled such that the entire group may be considered to have self-reported IEI. Strong correlations were observed for IEI with the results of scales for reported physical symptoms (CNS and mucousal) and consequences for social activities ($p < 0.001$ for all endpoints), as well as symptoms of depression ($p < 0.001$). The results remained statistically valid after adjustment for major life events and social support. Skovbjerg et al. (2012) recommended that further study of IEI include the influence of several factors, including central sensitization processes, changes in the hypothalamic-pituitary-adrenal-axis (HPAA), psychopathological processes and disorders, processes involved in the perception and amplification of symptoms, emotional regulation and socioeconomic factors.

A cross-sectional study of Japanese workers in a pulp and paper producing facility and at an automotive company was completed by Cui et al. (2015) to determine if MCS was an indicator of future mental health issues in workers. A total of 565 subjects were recruited and completed various questionnaires regarding self-reported chemical sensitivity, lifestyle, health symptoms, and sociodemographic endpoints. Using this data, subjects were divided into three groups: controls, "other chemical sensitivity" and "chemical sensitivity" (the authors did not clearly state the difference between the two chemical sensitivity categories apart from QEESI© score). A 'path' model was used to examine the data, and it was determined that the subject scores for chemical sensitivity were predictive (and statistically significant) of adverse health effects associated with exposure to multiple chemicals (Cui et al., 2015). The mental health scores of MCS subjects were significantly higher than controls ($p < 0.001$). The chemical sensitivity scores were found to be positively correlated with symptom severity ($p < 0.01$), life impact ($p < 0.01$) and mental health ($p < 0.01$). Symptom severity and life impact scores were determined to be predictive of mental health effects using the 'path' model. The authors suggested that the occurrence of MCS in workers could be used to predict future mental health issues.

A recent Canadian cross-sectional study (Johnson and Colman, 2017) evaluated 21,911 individuals selected from all ten Canadian provinces to investigate the association between self-reported MCS and certain mental health conditions: major depressive disorder (MDD), generalized anxiety disorder (GAD), comorbidity of MDD and GAD, severe distress and positive mental wellbeing. Data from the 2012 Canadian Community Health Survey (mental health component only) were used. While no significant association between GAD and MCS was noted, the individuals with MCS had significantly greater odds of also having MDD (OR: 2.37, 95% CI: 1.55-3.64), comorbidity of MCS and MDD (3.09, 95%CI: 1.8-5.30) and also severe distress (OR: 2.60, 95% CI: 1.67-4.07). These data also revealed that people with MCS were more likely to also have asthma and CFS. Johnson and Colman (2017) noted that while it appeared MCS and mental disorders could co-exist, it was not clear if one condition preceded the other (i.e. did having a mental illness predispose some individuals to MCS or did having MCS result in a greater risk of having a mental disorder develop, or both).

Bailer et al. (2007a) completed a multi-stage cross-sectional study of subject groups: controls (54), diagnosed IEI (54) and diagnosed somatoform disorder (SFD, 44). After 1-year, the baseline tests were repeated on all subjects, to examine changes over time in IEI and SFD. The symptoms and characteristics of IEI were found to be stable, with 92% of the 54 subjects meeting the IEI diagnostic criteria after 1-year. A significantly higher degree of functional impairment and severity of symptoms was reported in the IEI group both at baseline and after 1-year ($p < 0.05$) than the SFD or control groups. Approximately 10% of the baseline SFD group met the IEI diagnostic criteria after 1-year and presented a significantly increased number of IEI symptoms ($p < 0.05$), suggesting that the presence of an SFD may be a risk factor for the development of IEI over time (Bailer et al., 2007a).

Black et al. (2000b) compared the characteristics of 18 individuals with self-reported MCS over time using various questionnaires and interviews to assess sociodemographic status, mental health during an initial interview in 1988 and a follow-up session in 1997 (9-year period). No control group was included, and the subjects were not randomly selected. The prevalence of lifetime major depression and somatization disorders were observed to increase in the group between the two assessment periods (increases from 30 to 70%, and 17 to 50%, respectively). Black et al. (2000b) note the similarity of the subjects reported reactions to chemicals to panic attacks and agoraphobia.

A study by Bloch and Meggs (2007) examined the prevalence of anxiety and depressive conditions, as well as self-reported allergies, sociodemographics, and the presence of other

health conditions through the use of random telephone interviews. A total of 1,026 households participated. Chemical sensitivity was reported by 31% of the participants, with over 40% of these being women. Chemical sensitivity was identified as being more likely to be reported by individuals with allergies than without (OR: 1.98, 95% CI: 1.50 to 2.63). Depression (23%) and anxiety (31%) were both reported in the study population, with more women being positive for both anxiety (OR: 1.79, 95%CI; 1.36-2.36) and depression than men (OR 1.57, 95% CI: 1.16-2.13). Bloch and Meggs (2007) concluded that there was a clear association between anxiety and chemical sensitivity, and depression and chemical sensitivity. However, the authors did suggest that chemical sensitivity was the result of somatised anxiety, and that all disease states were associated with some degree of anxiety.

Personality Traits

The personality trait of absorption has been noted to be associated with openness to new and unusual experiences and an elevated involvement of imagination and a tendency to experience self-altering states of consciousness. Absorption is theorized as potentially contributing to IEI symptoms through enhancing susceptibility and also through enhanced cognitive imaginative representations of potential IEI triggers (Witthöft et al., 2008). Significantly higher absorption values ($p < 0.001$) were reported in the IEI group compared to the somatoform and control groups, and both the IEI and somatoform disorder group reported higher numbers of medically unexplained symptoms.

In contrast, Skovbjerg et al. (2010a) compared the extent of somatosensory amplification, autonomic perception and absorption in reference population, with a group of individuals with reported sensitivities and a third group with diagnosed IEI. The IEI group was observed to have a higher and statistically significant association for somatosensory amplification ($p < 0.001$), autonomic perception ($p < 0.001$) and reports of multiple symptoms involving the mucous membranes or CNS ($p < 0.001$). However, no significant association was found for the IEI group with respect to the personality trait of absorption (increased reactiveness).

Österberg et al. (2002) compared neurospsychological profiles between 4 groups: 24 individuals with self-reported MCS (17), diagnosed toxic encephalopathy subjects (TE) with and without abnormal neurospsychological profiles (31, and 26 subjects each), and a reference group of 200. Some markers of mental distress were observed to be significantly elevated, to a moderate degree in MCS patients relative to controls but were not as severe as observed for the TE group. No significant differences in the incidence of deviating personality characteristics, irritability and indirect aggression were observed between the MCS and TE groups. None of the four study groups exhibited differences in risk perception, and a significant difference from controls was found only for the assessment pf psychasthenia ($p < 0.017$). In contrast, the TE groups presented higher scores in several subscales of anxiety and aggression and hostility ($p < 0.001$ to 0.007). Österberg et al. (2002) postulated based on the study results, that MCS may be associated with an “asthenic coloring of personality” accompanied by a dysfunctional limbic system and increased susceptibility to sensitivity. Furthermore, the authors suggested that scores from self-rating scales should not be interpreted as evidence of primary psychiatric disease in MCS or that individuals with MCS have an “exaggerated generalized fear of environmental exposures”.

A strong association between negative affectivity, defensiveness and difficulties identifying feelings were observed by Skovbjerg et al. (2010b) for individuals with diagnosed IEI but not controls. In this cross-sectional study, a group of 151 individuals diagnosed with IEI by physicians were compared with 571 individuals from the general Danish population. Questionnaires were used to assess IEI, coping skills, negative affectivity and alexithymia to

explore how emotional regulation may affect the focus of IEI individuals on physiological sensations and the subsequent interpretation of these sensations as disease symptom. No evidence of repressed coping or the incidence of alexithymia were observed between the groups. However, strong associations between the IEI group with negative emotional reactions, defensiveness and difficulties in the identification of feelings were observed.

The study by Rethage et al. (2008) is sub-study of the German multi-centre study described by Eis et al. (2008). This investigation focused on the assessment of environmental worry in subjects with self-reported MCS (90), without self-reported MCS, who were participating in multicentre study (137) compared to a historical reference population (161). A characteristic of reporting MCS by the individuals were higher levels of reports of "personal worry" than controls, but less "general worry". It is suggested by Rethage et al. (2008) that the increase in personal worry may be related to the knowledge of their symptoms by the self-reported MCS group, resulting in increased worry.

Trauma

Physical and psychologic trauma have been discussed as a potential risk-factors for the development of MCS. However, only a few studies that specifically evaluated the relationship between previous trauma and MCS were identified.

Data from the Canadian Community Health Survey (CCHS) from 2012 were used by Johnson and Colman (2017) to examine the characteristics of 21,911 individuals selected from all ten Canadian provinces to investigate the association with self-reported MCS. An association of MCS with history of childhood sexual abuse ($p < 0.001$) was observed, but no association was evidence for childhood physical abuse. The incidence of child abuse experiences in individuals with MCS and other functional somatic syndromes (chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome) was also examined by Fuller-Thomson et al. (2011). A sub-sample of the Canadian Community Health Survey (CCHS) completed in 2005 was utilized in this study, and only data regarding childhood physical abuse were included in this survey (other forms of above were not covered). These data included 7,342 women from Manitoba and Saskatchewan, which included 7,068 women with MCS (although not specified, it is assumed that MCS was self-diagnosed due to small proportion of short clinical interviews and also telephone surveys). As part of the interview, information regarding socioeconomic status, stress, mental health, childhood experiences (retrospective) were collected. Approximately 2.7% of the study population were determined to have MCS (95% CI: 1.9 to 3.5). Childhood physical abuse was associated with significantly increased odds of MCS (OR 3.15, 95% CI: 2.21 to 4.49). Following adjustment for adult lifestyle and mental health factors, the relationship between childhood abuse and the development of MCS remained significant (OR: 2.82, 95% CI 1.90-4.17). The potential mechanism as to how previous traumatic experiences may influence the development of other conditions (such as MCS) was postulated by Fuller-Thomson et al. (2011) to involve the hypothalamus-pituitary-adrenal (HPA) axis, which is involved in the release of cortisol in response to stressful effects and neuroendocrine deregulation.

Although the study populations for both Johnson and Colman (2017) and Fuller-Thomson et al. (2011) evaluated were relatively large, the use of self-reported MCS rather than diagnosed MCS lends considerable variability to the results. Further, both studies were retrospective in nature, and involved adults recalling previous experiences, which may have resulted in either an over or under-estimation of data.

Bailer et al. (2007b) examined the rates of previous trauma experience between the IEI, SFD and control groups. No evidence of increased rates of previous trauma were observed in the IEI or SFD groups relative to controls, with the exception of 'unspecified events' or 'life-threatening illness'. All three groups together (70% of total study population) reported having at least one lifetime traumatic event, and all groups had a proportion of subjects reporting multiple traumatic events, and various types of trauma. It is suggested by Bailer et al. (2007b) that exposure to illnesses in family and friends may result in the development of 'dysfunctional beliefs' that may result in an enhanced awareness of bodily symptoms.

Due to a limited set of information that is cross-sectional in nature, a conclusion regarding the involvement of previous trauma with MCS cannot be reached at this time.