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Multiple Chemical Sensitivity Scoping Review Protocol

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ABSTRACT

Introduction: Multiple Chemical Sensitivity (MCS) is characterized by reported adverse responses to environmental exposures of common chemical agents (e.g., perfumes, paint, cleaning products, and other inhaled or ingested agents) in low doses considered non-toxic for the general population. There is currently no consensus on whether MCS can be established as a distinct disorder.

Methods and analysis: The scoping review of the literature will be guided by five questions: How is MCS defined and how is it diagnosed? What methods are used to report prevalence and incidence estimates of MCS? What are the characteristics of the body of scientific evidence that addresses whether MCS is a distinct disorder or syndrome? What underlying mechanisms for MCS have been proposed in the scientific literature? Which treatment and management approaches for MCS have been evaluated in empirical research studies? We will conduct a comprehensive search in 14 research databases. Citation screening will be supported by machine learning algorithms. Two independent reviewers will assess eligibility of full text publications against prespecified criteria. Data abstraction will support concise evidence tables. A formal consultation exercise will elicit input from experts and stakeholders regarding the review results and presentation. The existing evidence about MCS will be documented in a user-friendly visualization in the format of an evidence map.

Ethics and dissemination: Determined to be exempt from review (UP-22-00516). Results will be disseminated through a journal manuscript and data will be publicly accessible through an online data repository.

Registration: The protocol is registered in Open Science Framework (osf.io/4a3wu).

(249 words)

Keywords

Multiple Chemical Sensitivity, Idiopathic Environmental Illness, Chemical Intolerance, Scoping Review, Evidence Map

Strengths and Limitations

- The scoping review of the literature will be guided by five questions: How is MCS defined and how is it diagnosed? What methods are used to report prevalence and incidence estimates of MCS? What are the characteristics of the body of scientific evidence that addresses whether MCS is a distinct disorder or syndrome? What underlying mechanisms for MCS have been proposed in the scientific literature? Which treatment and management approaches for MCS have been evaluated in empirical research studies?
- We will conduct a comprehensive search in 14 multi-disciplinary research databases. Citation screening will be supported by machine learning algorithms. Two independent reviewers will assess eligibility of full text publications against prespecified criteria.
- Data abstraction will support concise evidence tables. A formal consultation exercise will elicit input from experts and stakeholders regarding the review results and presentation.

The existing evidence about MCS will be documented in a user-friendly visualization in the format of an evidence map.

Introduction

Multiple Chemical Sensitivity (MCS) is characterized by reported adverse responses to environmental exposures of common chemical agents in low doses considered non-toxic for the general population. These may be solvents such as paint and cleaning products, odorants such as perfume and scented soaps, air pollutants such as cigarette smoke and smog, or materials such as new furnishings or new carpets. Symptoms are nonspecific, involve multiple organ systems, and may include nausea, dizziness, headache, abdominal pain, fatigue, and depression, among others.[1-3] Responses generalize from individual to sets of often unrelated chemical agents and limit social and occupational functioning.[2 4-8] More recently, the condition has been described as an idiopathic environmental intolerance.[1 9-11]

To date, tens of thousands of publications have addressed MCS in the international lay and scientific literature.[12] However, little consensus exists regarding MCS, including defining characteristics and the underlying nature of the condition as toxigenic or psychogenic.[13-15] Prevalence estimates vary considerably, suggesting differences in operationalizations of the definition and diagnostic criteria for MCS.[16-19] Individual symptoms reported by patients are not unique to MCS and the lack of consensus, including whether MCS should be considered a distinct disorder, hinders the identification and differential diagnosis of MCS in clinical practice.[20-22] A large number of potentially underlying mechanisms of action for MCS have been described that span immune system dysregulation, neural sensitization and hyperresponsivity, neurogenic inflammation, limbic system dysfunction, oxidative stress hypothesis, genetic theories, and classical conditioning [4]. Regardless of the challenges in operationalizing definitions and establishing its etiology, MCS is an international phenomenon that has been

described in different formats and terms for decades [4]. It is a distressing and puzzling condition for patients as well as their healthcare providers.[23-25] Some mechanism of action considerations have resulted in interventions for patients; however, no comprehensive review of the evaluated treatment and management options exists that currently successfully supports patients describing MCS symptoms.[26 27] Surveys describe multiple, often not evidence-based treatment approaches tried by patients, and the lack of clinical guidance leaves healthcare practitioners guessing how to best address MCS in their patients.[8 27-29]

Despite the large number of publications addressing MCS, there is a lack of research syntheses providing an overview of the existing evidence base on MCS. However, we believe that the existing evidence base needs to be mapped as a first step in order to advance research and practice in this complex field. Before trying to establish the most salient definition of MCS or most plausible mechanism of action leading to MCS in a systematic review, a scoping review should systematically identify, explore, and characterize the existing research literature. The proposed work will be based on a scoping review of the literature. Scoping reviews are systematic literature review approaches that explore research fields to systematically capture the volume and content of scientific literature that is relevant to guiding questions for the review.[30-32] To address the complexity of the topic, it is critical that a comprehensive review casts a wide net, incorporating research from different disciplines and conceptual positions. Our planned scoping review will use extensive literature searches to map the existing literature. The review will provide an overview of definitions and diagnostic criteria of MCS, identify prevalence and incidence research, document the body of evidence addressing the question of whether MCS is a distinct disorder, compile a compendium of suggested mechanisms of MCS, and provide an overview of the literature on MCS treatment and management that has been published to date.

This scoping review was prospectively registered and will be conducted according to established procedures to provide a systematic and transparent exploration of the literature.[33] The findings of the scoping review will be presented as an evidence map. Evidence maps are an evidence synthesis tool that provide a visualization of a large evidence base to provide readers with a concise overview.[34 35] Evidence maps allow a visual and user friendly research overview suitable for a large and diverse research field, effectively mapping the existing evidence.[34 36-43] The evidence map will document the presence and absence of research on MCS for the five questions guiding the review in a user-friendly format.

Guiding Questions

The following review questions will guide the scoping review:

- GQ1: How is Multiple Chemical Sensitivity (MCS) defined and how is it diagnosed?
- GQ2: What methods are used to report prevalence and incidence estimates of MCS?
- GQ3: What are the characteristics of the body of scientific evidence that addresses whether MCS is a distinct disorder or syndrome?
- GQ4: What underlying mechanisms for MCS have been proposed in the scientific literature?
- GQ5: Which treatment and management approaches for MCS have been evaluated in empirical research studies?

Review Aim

The review will answer the guiding questions with the identified scientific literature in a user-friendly format. A systematic evidence map will provide a visualization of the existing evidence and research gaps.

Methods and Analysis

The review is registered in the Open Science Framework (OSF).[12] The scoping review will follow the steps for scoping reviews outlined by Arksey and Malloy: Stage 1: identifying the research question; Stage 2: identifying relevant studies; Stage 3: study selection; Stage 4: charting the data; Stage 5: collating, summarizing and reporting the results. In addition, a consultation exercise to inform and validate findings from the scoping review will be conducted. The following outlines the steps in detail. The reporting will follow established guidelines.[31 44]

Search Strategy

We will search the international literature on MCS using different taxonomy and nomenclature. Literature searches will be designed, executed, and documented by an experienced evidence review center librarian. The scoping review addresses multiple aspects of MCS and the search strategy covers multiple databases to ensure that all scientific literature relevant to MCS will be identified. The use of multiple sources is a key method to minimize selection bias being introduced into the review. We plan on searching the following databases to obtain a diverse set of citations potentially relevant to MCS from different disciplines:

- PubMed (biomedical)
- CINAHL (nursing)
- Embase (biomedical)
- Web of Science (general scientific database)
- Scopus (health sciences)

- PsycINFO (behavioral and social sciences)
- Healthcare Administration Database (public health administration)
- Current Contents Connect (multidisciplinary)
- BIOSIS Citation Index (life sciences)
- Environment Index (environmental research)
- Environmental Science Database
- HERO (Health & Environmental Research Online)
- SciFinder (chemical literature)
- Agricultural & Environmental Science Collection (includes AGRICOLA, environmental research)

The search strategy is shown in the appendix. Content experts provided input regarding individual search terms and databases.

In addition, our review will be informed by existing comprehensive reviews on the topic.[4 45] Reviews will be systematically identified through the systematic review filter in PubMed and the Cochrane Database of Systematic Review (SDSR). We will screen the international registry PROSPERO for ongoing efforts that could inform this project during the update search period; currently, the registry includes only two ongoing efforts that address selected aspects of MCS.[46 47]

For individual guiding questions, we will search additional sources, including selected and pre-specified grey literature sources. For definitions and diagnostic criteria (GQ1), we will search the website of global organizations such as the World Health Organization (WHO). Searches for prevalence research (GQ2) will reference-mine existing reviews.[5] We will review reports identified in PubMed Health regarding consensus statements on MCS as a distinct

disorder (GQ3) and regarding published suggested mechanisms of action (GQ4). For intervention studies (GQ5), we will search repositories of practice guidelines including G-I-N[48] and the ECRI-maintained guideline database.[49] In addition, we will search the U.S. trial registry clinicaltrials.gov[50] and the International Clinical Trials Registry Platform maintained by the WHO.[51]

In addition, we will reference-mine relevant reviews and included studies and consult with content experts to ensure that all relevant literature has been captured.

Eligibility Criteria and Screening

We will use a PICOTSO (population, intervention/exposure, comparator, outcome, timing, setting, and other limiter) framework to structure the eligibility criteria. For each guiding question, we will determine detailed inclusion and exclusion criteria. The criteria, thus far, are as follows:

- Population:
    - Publications reporting definitions GQ1) and studies reporting on the prevalence and incidence (GQ2) of MCS will be limited to those that explicitly state *multiple chemical sensitivity*, *chemical intolerance*, or *idiopathic environmental intolerance* with a reference to chemical sensitivities. Publications reporting exclusively on the prevalence of individual sick building syndrome symptoms will be excluded.
    - Eligible populations for GQ3 and GQ4 will include those that either state *multiple chemical sensitivity* or those that are characterized by symptoms of idiopathic environmental intolerance with a reference to chemical sensitivity. Populations will not be restricted to human participants diagnosed with MCS, and will instead

include a wide range of research that may contribute to establishing MCS as a diagnosis and exploring relevant mechanisms.

  - GQ5 will be limited to samples of human participants where a majority (75% or more) is diagnosed with MCS, idiopathic environmental intolerance for chemicals, the equivalent of the ICD-10-CM Code F45.9 (somatoform disorder, unspecified), or studies that report on a subgroup of the patients of interest.

- Intervention/exposure/independent variable:
  - We will accept definitions of MCS and descriptions that include diagnostic criteria (GQ1).
  - Prevalence and incidence measures need to state the criteria of MCS clearly to be eligible (GQ2).
  - GQ3 studies assessing whether MCS is a distinct disorder (i.e., distinct from other "physical" disorders or "psychiatric" disorders) need to provide empirical evidence of discriminatory power to support the authors' conclusions or need to be based on formal expert consensus methods. Opinions of individual authors will not be eligible.
  - Eligible publications suggesting underlying mechanisms (GQ4) may include evidence for the onset of MCS or the course of the disease, including TILT (toxicant-induced loss of tolerance describing an initiation and a triggering stage).
  - Studies evaluating interventions (GQ5) to prevent, manage, or treat MCS will be eligible. Interventions will not be restricted by the content or treatment approach, and may include interventions aiming to avoid triggers, focusing on coping with MCS symptoms, desensitization, or addressing the causes of MCS. In addition,

interventions in patients diagnosed with MCS will be eligible regardless of the intervention focus (patient-centered rather than intervention-centered approach). Case studies of individual patients will be included if focused on intervention rather than the natural course of the condition and the description is published in a peer-reviewed scientific journal.

- Comparator: Studies will be eligible regardless of the presence of a comparator.
- Outcome: GQ1 publications will need to provide sufficiently detailed descriptions that can be operationalized as a definition or diagnostic criteria. GQ2 studies will need to report a numerical estimate of the prevalence or incidence of MCS. GQ3 and GQ4 will not be limited by reported outcomes. GQ5 studies may report on patient health (self or clinician report), physiological or psychosocial measures assessing the effect of the intervention (effectiveness as well as safety indicators); quantitative and qualitative data will be eligible. Studies reporting only on treatment uptake, patient or provider acceptability of treatments, or treatment costs will be excluded.
- Timing: GQ1 studies will be included regardless of the publication year (e.g., definitions from the 1980s are eligible). GQ2 studies will be eligible regardless of the timing of the exposure or assessment (e.g., childhood exposure, symptoms tested in adults); however, only prevalence and incidence estimate elicited in the last ten years will be eligible (historic estimates will be excluded). GQ3 and GQ4 studies will not be restricted by time of exposure or follow-up, and retrospective, concurrent, and prospective studies will be eligible. GQ5 studies will be included regardless of the intervention duration and follow up.

- Setting: Studies will not be restricted by setting and will be drawn from the international literature.
- Other limiters: English-language publications disseminated to a wide audience through a scientific journal will be eligible. Studies published in abbreviated form (e.g., conference abstracts) will not be eligible for inclusion.

Systematic reviews and relevant narrative reviews will be retained for reference-mining. Multiple publications on the same study (i.e., studies defined by the included participants) will be consolidated into one study record to ensure that a given study is not counted multiple times regardless of the number of publications reported on the study. The literature flow will be transparently documented in a citation management program.

Inclusion Screening Process

We will use an online database (DistillerSR) designed for literature reviews to screen the search output. The team will design detailed citation and full text screening forms to ensure a transparent, consistent, and unambiguous approach. Citations found to be potentially relevant by at least one reviewer will be obtained as full text. Citations screening will be supported by machine learning algorithms to reduce reviewer errors and bias. All citations excluded by a human reviewer will be screened for relevance by the machine learning algorithm to ensure that no potentially relevant study has been missed.

Full text screening will apply the detailed eligibility criteria. Training will ensure a shared understanding of all inclusion and exclusion criteria across reviewers. Full text publications will be screened by two independent reviewers and any discrepancies will be resolved through discussion in the review team. Dual screening reduces reviewer bias and errors and is critical for this complex topic. The screening decisions and reasons for exclusion of studies will be tracked

in the online database and citation management software. This allows us to reconstruct a detailed literature flow and facilitates the documentation of included and excluded publications. Reasons for exclusion will match the exclusion criteria dimensions to orient the reader. The literature flow will be documented in a flow diagram.

Studies excluded at full text will be documented in the appendix of the review together with a reason for exclusion. We will retain background papers, i.e., papers to cite or reviews to reference-mine. We will report the number of included studies and the number of publications reporting on each study across the review and for each guiding question.

Data Abstraction

The data abstraction will provide a concise overview of the evidence.

For **GQ1** (definitions and diagnostic criteria), we will document the suggested definitions and the approach to establish it. We will document published diagnostic criteria of MCS and for diagnostic accuracy studies, the type (e.g., self report questionnaire, objective test such as exposure chamber and challenge test) and name of the test will be recorded.

For **GQ2** (prevalence and incidence), we will document the data type (e.g., prevalence or incidence), the method of assessment (e.g., self report, medical record), and the operationalization of MCS (definition, criteria). We will distinguish general, unselected populations (e.g., students) from targeted samples with potentially increased risk (e.g., Gulf War veterans). For each study, we will record the country, sample size, and year of estimate, and identify any published prospective studies.

For **GQ3** (MCS as a distinct disorder), we will document the aim of the study, the employed study design, and the analytic approach to evaluate MCS as a distinct disorder. We will record the type of research approach used to determine whether MCS should or should not be considered a

distinct disorder or syndrome (e.g., establishing a unique biomarker, analyzing symptom clusters, documenting explained variance)[22] and differentiate the use of direct, mechanistic, and parallel evidence by the authors.[52-54] We will abstract the authors' conclusion regarding their conceptual agreement with MCS as a distinct disorder with a differential clinical diagnosis.

For **GQ4** (underlying mechanisms), we will broadly categorize the study type and approach to indicate whether the study addresses the etiology or pathogenic development and whether the approach assumes a biological or psychological hypothesis. For each study, we will categorize the suggested mechanisms (e.g., immune system dysregulation, neural sensitization and hyperresponsivity, neurogenic inflammation, limbic system dysfunction, oxidative stress hypothesis, genetic theories, or classical conditioning).[5] This will involve collating and reviewing all identified mechanisms and establishing a categorization system based on the published literature and identified approaches. We will also establish a compendium of frameworks and diagrams reported by the authors. For this, figures published under the Creative Commons will be included in the compendium; for all others, the publisher will be contacted to request permission to use the figure.

GQ5 (therapy and management for MCS) will collate all identified interventions and broadly categorizing interventions as prevention, management, or treatment. We will document the focus of the intervention (e.g., aiming to alter the course of the condition, coping strategies) together with the broad therapeutic approach (removing triggers from environment, diet, supplements, masks, devices, [off-label] medication, psychological approaches). The categorization system will built on existing reviews and the identified empirical research.[22] We will also abstract the author group, publication year, and country.

Data will be abstracted by one reviewer and checked by an experienced literature review methodologist. We will export data into tables and figures or data files for further analysis.

Consultation Exercise

The last step of the scoping review process will be a consultation exercise. We will ask multi-disciplinary technical experts and stakeholders in MCS research, practice, and advocacy to review the results of the scoping review. These reviewers will not have been involved in the review process and will assess the review *de novo*. Previous experiences have shown that this last step of stakeholder involvement provides invaluable input and adds to the usefulness and validity of the end product.[33 55 56] The consultation exercise will be conducted as an online survey sent to participants together with the review to elicit structured feedback on the content and presentation of the review. The input will contribute to the presentation of the scoping review results.

Patient and Public Involvement

The planned review was presented at a stakeholder meeting organized by the funding agency that included a patient representative. Several stakeholders are also part of the scientific steering committee that reviewed this protocol (see acknowledgement section). The results of the review will be distributed to stakeholders in a formal consultation exercise as outlined above. This step will be instrumental in ensuring a user-friendly presentation of results that is useful to patients and the public.

Result Presentation

Characteristics of all studies meeting inclusion criteria will be documented in concise evidence tables to provide a broad documentation of the underlying evidence base. Findings across studies will be documented in an evidence map. This visual and user friendly research overview will map the existing evidence on MCS.

The evidence map will use a bubble plot format with a limited number of dimensions to display the existing research. Each bubble in the plot will represent a study and the size of the bubble will represent the size of the study. The plot will use the x-axis to display existing types of research studies to characterize the evidence base further. The y-axis can be used to characterize the guiding question addressed by the research. In addition, the shape of the bubble and/or shading may represent different study designs and methodological characteristics. The optimal display will be selected based on input from the consultation exercise.

The tables and figures will be accompanied by a narrative that summarizes the identified evidence base. This scoping review and evidence map will provide a broad overview of the existing research on MCS. It also aims to facilitate a future systematic review of the literature that will answer definitive research questions (e.g., what is the prevalence of MCS and the effectiveness of treatments for MCS). Scoping and mapping has become increasingly useful to prepare more definitive systematic reviews that answer closed questions, in particular for large and controversial topics.[34 35 40 44 57 58] The scoping review will provide context and information on which topic areas are to date amenable to a formal systematic review of the literature. The future systematic review will address a narrower scope of approaches that have been identified in this

scoping review, assess the quality of evidence for distinct topics of interest, and synthesize the evidence.

In addition to documenting the existing evidence base, we will clearly outline gaps in the literature identified in this scoping review. The gap presentation will use the scoping review's eligibility framework to transparently document existing gaps and future research needs. The gap analysis will make concrete recommendations to facilitate future research.

Ethics and Dissemination and Data Availability

The scoping review was determined to be exempt from further review by the University of Southern California Institutional Review Board (IRB) review in July 2022 (ID UP-22-00516). The results of the review will be disseminated through a journal manuscript. Data of the scoping review will be publicly available through an online data repository (SRDR+).

Author Contributions

SH obtained funding; SH, MD, KR, OA, JJ designed the study, SH, MD, MB, JR, AlM, CP screened literature to prepare this manuscript; AnM and DT manage the data; SY conducted the literature searches; all authors contributed conceptually to the work and edited this manuscript.

Competing Interests

None of the authors have any conflicts of interest to declare.

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Appendix: Search Strategies

Multiple Chemical Sensitivity Scoping Review Protocol

PubMed

"multiple chemical sensitivity"[MeSH Terms] OR ("multiple"[Title/Abstract] AND "chemical"[Title/Abstract] AND "sensitivity"[Title/Abstract]) OR "multiple chemical sensitivity"[Title/Abstract] OR ("multiple"[Title/Abstract] AND "chemical"[Title/Abstract] AND "sensitivities"[Title/Abstract]) OR "multiple chemical sensitivities"[Title/Abstract] OR "MCS syndrome"[Title/Abstract] OR "chemical intolerance"[Title/Abstract] OR "chemically intolerant"[Title/Abstract] OR "chemical hypersensitivity"[Title/Abstract] OR "chemical AIDS"[Title/Abstract] OR "chemical sensitivity disorder"[Title/Abstract] OR "chemical sensitivity syndromes"[Title/Abstract] OR "chemophobia"[Title/Abstract] OR "environmental chemical odor intolerance"[Title/Abstract] OR "sensitivity to environmental chemicals"[Title/Abstract] OR ("chemical"[Title/Abstract] AND "environmental illness"[Title/Abstract]) OR "chemically induced environmental illnesses"[Title/Abstract] OR "total allergy syndrome"[Title/Abstract] OR "twentieth century disease"[Title/Abstract] OR "20th century disease"[Title/Abstract] OR “sick building syndrome"[Title/Abstract] OR "building-related illness"[Title/Abstract]

OR "toxicant induced loss of tolerance"[Title/Abstract] OR "Toxicant-Induced Loss of Tolerance"[Title/Abstract] OR "mast cell activation syndrome"[Title/Abstract]

OR "idiopathic environmental intolerance"[Title/Abstract] OR "idiopathic environmental intolerances"[Title/Abstract] OR "idiopathic environmental illness"[Title/Abstract]

Limit: English language

Agricultural & Environmental Science Collection

(noft("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome") OR noft("chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia") OR noft("environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses") OR noft("total allergy syndrome") OR noft("twentieth century disease" OR "20th century disease" OR "sick building syndrome" OR "building-related illness") OR noft("toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance") OR noft("mast cell activation syndrome") OR noft("idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness"))

AND

(stype.exact("Scholarly Journals" OR "Other Sources" OR "Reports")

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BIOSIS

"multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" (Topic) or "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" (Topic) or "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically

induced environmental illnesses" (Topic) or "total allergy syndrome" (Topic) or “twentieth century disease” OR “20th century disease” OR “sick building syndrome” OR “building-related illness” (Topic) or "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" (Topic) or "mast cell activation syndrome" (Topic) or "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" (Topic)

AND Article (Document Types)

AND English (Languages)

CINAHL

TI ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “sick building syndrome” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness") OR SU ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR

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AND

English language

Current Contents

"multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR

"chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “sick building syndrome” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" (Topic)

and

English (Language)

and

Article or Review Article or Correction (Document Types)

EMBASE

('multiple chemical sensitivity':ti,ab,kw OR 'multiple chemical sensitivities':ti,ab,kw OR 'mcs syndrome':ti,ab,kw OR 'chemical intolerance':ti,ab,kw OR 'chemically intolerant':ti,ab,kw OR 'chemical hypersensitivity':ti,ab,kw OR 'chemical aids':ti,ab,kw OR 'chemical sensitivity disorder':ti,ab,kw OR 'chemical sensitivity syndromes':ti,ab,kw OR 'chemophobia':ti,ab,kw OR 'environmental chemical odor intolerance':ti,ab,kw OR 'sensitivity to environmental chemicals':ti,ab,kw OR ('chemical':ti,ab,kw AND 'environmental illness':ti,ab,kw) OR 'chemically induced environmental illnesses':ti,ab,kw OR 'total allergy syndrome':ti,ab,kw OR 'twentieth century disease':ti,ab,kw OR '20th century disease':ti,ab,kw OR 'sick building syndrome':ti,ab,kw OR 'building-related illness':ti,ab,kw OR 'toxicant induced loss of tolerance':ti,ab,kw OR 'toxicant-induced loss of tolerance':ti,ab,kw OR 'mast cell activation

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Environment Index

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Environmental Science

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Source Type: Reports, Scholarly Journals, Working Papers

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Healthcare Administration

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Source type: Reports, Scholarly Journals

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Language: English

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AND

Language: English

PsycINFO

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environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses") OR noft("total allergy syndrome") OR noft("twentieth century disease" OR "20th century disease" OR "sick building syndrome" OR "building-related illness") OR noft("toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance") OR noft("mast cell activation syndrome") OR noft("idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness"))

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SciFinder

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AND

English language

AND

Exclude: Patent, Book, Commentary, Conference, Dissertation, Editorial, Letter

SCOPUS

(TITLE-ABS-KEY ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR "twentieth century disease" OR "20th century disease" OR "sick building syndrome" OR "building-related illness" OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness")

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Web of Science

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AND

English (Language)

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Article or Review Article (Document Types)

BMJ Open

Multiple Chemical Sensitivity Scoping Review Protocol: Overview of Research and MCS Construct

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-072098.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Aug-2023
Complete List of Authors:	Hempel, Susanne; University of Southern California Danz, Margie; University of Southern California Robinson, Karen; Johns Hopkins Medicine, Division of Health Sciences Informatics Bolshakova, Maria; University of Southern California, Preventive Medicine Rodriguez, Jesus; University of Southern California Mears, Alanna; University of Southern California Pham, Cindy; University of Southern California Yagyu, Sachi; University of Southern California, Preventive Medicine Motala, Aneesa; University of Southern California, Southern California Evidence Review Center Tolentino, Danica; University of Southern California Akbari, Omid; University of Southern California, Molecular Microbiology and Immunology Johnston , Jill; USC Keck School of Medicine
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Epidemiology
Keywords:	INTERNAL MEDICINE, Systematic Review, GENERAL MEDICINE (see Internal Medicine)

Multiple Chemical Sensitivity Scoping Review Protocol: Overview of Research and MCS Construct

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Word count: 3,511

ABSTRACT

Introduction: Multiple Chemical Sensitivity (MCS) has been characterized by reported adverse responses to environmental exposures of common chemical agents (e.g., perfumes, paint, cleaning products, and other inhaled or ingested agents) in low doses considered non-toxic for the general population. There is currently no consensus on whether MCS can be established as a distinct disorder.

Methods and analysis: The scoping review of the literature will be guided by five questions: How is MCS defined and which diagnostic criteria have been proposed? What methods are used to report prevalence and incidence estimates of MCS? What are the characteristics of the body of scientific evidence that addresses whether MCS is a distinct disorder or syndrome? What underlying mechanisms for MCS have been proposed in the scientific literature? Which treatment and management approaches for MCS have been evaluated in empirical research studies? We will conduct a comprehensive search in 14 research databases. Citation screening will be supported by machine learning algorithms. Two independent reviewers will assess eligibility of full text publications against prespecified criteria. Data abstraction will support concise evidence tables. A formal consultation exercise will elicit input from experts and stakeholders regarding the review results and presentation. The existing evidence about MCS will be documented in a user-friendly visualization in the format of an evidence map.

Ethics and dissemination: Determined to be exempt from review (UP-22-00516). Results will be disseminated through a journal manuscript and data will be publicly accessible through an online data repository.

Registration: The protocol is registered in Open Science Framework (osf.io/4a3wu).

(249 words)

Keywords

Multiple Chemical Sensitivity, Idiopathic Environmental Intolerance, Chemical Intolerance, Scoping Review, Evidence Map

Strengths and Limitations

- This scoping review will cast a wide net capturing multiple important aspects of the complex construct multiple chemical sensitivity (MCS).
- A formal consultation exercise will provide input from experts and stakeholders.
- The existing research on MCS will be documented in a user-friendly visualization in the format of an evidence map.
- A scoping review can only provide a broad overview of the existing research.
- The lack of standardized terminology for the MCS construct makes identifying and documenting relevant research challenging.

Introduction

Multiple Chemical Sensitivity (MCS) has been characterized by reported adverse responses to environmental exposures of common chemical agents in low doses considered non-toxic for the general population. These may be solvents such as paint and cleaning products, odorants such as perfume and scented soaps, air pollutants such as cigarette smoke and smog, or materials such as new furnishings or new carpets. Symptoms are nonspecific, involve multiple organ systems, and may include nausea, dizziness, headache, abdominal pain, fatigue, and depression, among others [1-3]. Responses generalize from individual to sets of often unrelated chemical agents and limit social and occupational functioning [2, 4-8]. Terminology varies and some authors describe the condition more broadly as an idiopathic environmental intolerance [2, 9, 10]. Other researchers have called for a paradigm shift, moving away from terms that characterize the symptoms ("sensitivities") to a more neutral description as *symptoms associated with environmental factors* (SAEF) [11 12].

To date, tens of thousands of publications have addressed MCS in the international lay and scientific literature [13]. However, little consensus exists regarding MCS, including its defining characteristics [14-19]. Prevalence estimates vary considerably, suggesting differences in operationalizations of the definition and diagnostic criteria for MCS [20-23]. Individual symptoms reported by patients are not unique to MCS and the lack of consensus, including whether MCS should be considered a distinct disorder, hinders the identification and differential diagnosis of MCS in clinical practice [24-26]. Much debate centers around the underlying nature of the condition as toxigenic or psychogenic [27-29]. A large number of potentially underlying mechanisms of action for MCS have been described (e.g., immune system dysregulation, neural

sensitization and hyperresponsivity, neurogenic inflammation, limbic system dysfunction, oxidative stress hypothesis, genetic theories, and classical conditioning) [5]. Regardless of the challenges in operationalizing definitions and establishing its etiology, MCS is an internationally recognized phenomenon that has been described in different formats and terms for decades [5]. It is a distressing and puzzling condition for patients as well as their healthcare providers [30-32]. Some hypotheses about mechanisms of action have resulted in proposed interventions for patients; however, no comprehensive review of the evaluated treatment and management options exists that currently successfully supports patients describing MCS symptoms [33, 34]. Few attempts have been made to establish consensus on how patients presenting with MCS should be assessed or treated in clinical practice and new guidelines highlight the need for a complex multidisciplinary approach [35]. Surveys describe multiple, often not evidence-based treatment approaches that have been tried by patients, and the lack of clinical guidance leaves healthcare practitioners guessing how to best address MCS in their patients [8, 34, 36, 37].

Despite the large number of publications addressing MCS, there is a lack of research syntheses that provide an overview of the existing evidence base on the condition. We believe that the existing evidence base needs to be mapped as a first step in order to advance research and practice in this complex field. Before trying to establish the most salient case definition of MCS or the most plausible underlying mechanism(s) leading to MCS in a systematic review, a scoping review should systematically identify, explore, and characterize the existing research literature. The proposed work will be based on this type of review. Scoping reviews are systematic literature review approaches that explore research fields to capture the volume and content of scientific literature that is relevant to guiding questions for the review [38-40]. To address the complexity of the topic, it is critical that a comprehensive review cast a wide net,

incorporating research from different disciplines and conceptual positions. Our planned scoping review will use extensive literature searches to map the existing literature. The review will provide an overview of proposed definitions of and diagnostic criteria for MCS, identify prevalence and incidence research, document the body of evidence addressing the question of whether MCS is a distinct disorder, compile a compendium of suggested underlying mechanisms of MCS etiology and processes, and provide an overview of the literature on MCS treatment and management that has been published to date.

This scoping review was prospectively registered and will be conducted according to established procedures to provide a systematic and transparent exploration of the literature [41]. The findings of the scoping review will be presented as an evidence map. Evidence maps are an evidence synthesis tool that provide a visualization of a large evidence base to provide readers with a concise overview [42 43]. They allow a visual and user friendly research overview suitable for a large and diverse research field, effectively mapping the existing evidence [42, 44-51]. The evidence map will document the presence and absence of research on MCS for the five questions guiding the review in a user-friendly format.

Guiding Questions

The following review questions will guide the scoping review:

- GQ1: How is Multiple Chemical Sensitivity (MCS) defined and which diagnostic criteria have been proposed?
- GQ2: What methods are used to report prevalence and incidence estimates of MCS?
- GQ3: What are the characteristics of the body of scientific evidence that addresses whether MCS is a distinct disorder or syndrome?

- GQ4: What underlying mechanisms for MCS have been proposed in the scientific literature?
- GQ5: Which treatment and management approaches for MCS have been evaluated in empirical research studies?

Review Aim

The review will answer the guiding questions with the identified scientific literature in a user-friendly format. A systematic evidence map will provide a visualization of the existing evidence and research gaps.

Methods and Analysis

The review is registered in the Open Science Framework (OSF) [13]. The scoping review will follow the steps for scoping reviews outlined by Arksey and Malloy: Stage 1: identifying the research question; Stage 2: identifying relevant studies; Stage 3: study selection; Stage 4: charting the data; Stage 5: collating, summarizing and reporting the results. In addition, a consultation exercise to inform and validate findings from the scoping review will be conducted. The planned duration is April 2022 to December 2023. The following outlines the steps in detail. The reporting will follow established guidelines [39, 52].

Search Strategy

We will search the international literature on MCS using different taxonomy and nomenclature. Literature searches will be designed, executed, and documented by an experienced evidence review center librarian. The scoping review addresses multiple aspects of MCS, and the search

strategy covers multiple databases to ensure that all scientific literature relevant to MCS will be identified. The use of multiple sources is a key method to minimize selection bias being introduced into the review. We plan on searching the following databases to obtain a diverse set of citations potentially relevant to MCS from different disciplines:

- PubMed (biomedical)
- CINAHL (nursing)
- Embase (biomedical)
- Web of Science (general scientific database)
- Scopus (health sciences)
- PsycINFO (behavioral and social sciences)
- Healthcare Administration Database (public health administration)
- Current Contents Connect (multidisciplinary)
- BIOSIS Citation Index (life sciences)
- Environment Index (environmental research)
- Environmental Science Database
- HERO (Health & Environmental Research Online)
- SciFinder (chemical literature)
- Agricultural & Environmental Science Collection (includes AGRICOLA, environmental research)

The search strategy is shown in the appendix. Content experts provided input regarding individual search terms and databases.

In addition, our review will be informed by existing comprehensive reviews on the topic [4, 12, 16, 17, 24, 35, 53-61]. Reviews will be systematically identified through the systematic

review filter in PubMed and the Cochrane Database of Systematic Review (SDSR). We will screen the international registry PROSPERO for ongoing efforts that could inform this project during the update search period; currently, the registry includes only two ongoing efforts that address selected aspects of MCS [62, 63].

For individual guiding questions, we will search additional sources, including selected and pre-specified grey literature sources. For definitions and diagnostic criteria (GQ1), we will search the website of global organizations such as the World Health Organization (WHO). Searches for prevalence research (GQ2) will reference-mine existing reviews [5]. We will review reports identified in PubMed Health regarding consensus statements on MCS as a distinct disorder (GQ3) and regarding published suggested underlying mechanisms (GQ4). For intervention studies (GQ5), we will search repositories of practice guidelines including G-I-N [64] and the ECRI-maintained guideline database.[65] In addition, we will search the U.S. trial registry clinicaltrials.gov [66] and the International Clinical Trials Registry Platform maintained by the WHO [67].

In addition, we will reference-mine relevant reviews and included studies and consult with content experts to ensure that all relevant literature has been captured.

Eligibility Criteria and Screening

We will use a PICOTSO (population, intervention/exposure, comparator, outcome, timing, setting, and other limiter) framework to structure the eligibility criteria. For each guiding question, we will determine detailed inclusion and exclusion criteria. The criteria, thus far, are as follows:

- Population:

- Publications reporting definitions (GQ1) and studies reporting on the prevalence and incidence (GQ2) of MCS will be limited to those that explicitly state *multiple chemical sensitivity*, *chemical intolerance*, or *idiopathic environmental intolerance* with a reference to *chemical* sensitivities (rather than electromagnetic sensitivity or other conditions not associated with perceived exposure to chemical agents, solvents, odorants, air pollutants, or materials). Publications reporting exclusively on the prevalence of individual sick building syndrome symptoms or electromagnetic hypersensitivity will be excluded.
- Eligible populations for GQ3 and GQ4 will include those that either state *multiple chemical sensitivity* or those that are characterized by symptoms of idiopathic environmental intolerance or exposure to environmental factors with a reference to chemical agents, solvents, odorants, air pollutants, or materials . Populations will not be restricted to human participants diagnosed with MCS, and will instead include a wide range of research that may contribute to establishing MCS as a diagnosis and exploring relevant underlying mechanisms.
- GQ5 will be limited to samples of human participants where some participants are characterized by MCS, idiopathic environmental intolerance for chemicals, the equivalent of the ICD-10-CM Code F45.9 (somatoform disorder, unspecified), or studies that report on a subgroup of the patients of interest.

- Intervention/exposure/independent variable:
  - We will accept definitions of MCS and descriptions that include diagnostic criteria (GQ1).

- Prevalence and incidence measures need to state the criteria of MCS clearly to be eligible (GQ2).
- GQ3 studies assessing whether MCS is a distinct disorder (i.e., distinct from other "physical" disorders or "psychiatric" disorders) need to provide empirical evidence of discriminatory power to support the authors' conclusions or need to be based on formal expert consensus methods. Opinions of individual authors will not be eligible.
- Eligible publications suggesting underlying mechanisms (GQ4) may include evidence for the onset of MCS or the course of the disease, including TILT (toxicant-induced loss of tolerance describing an initiation and a triggering stage).
- Studies evaluating interventions (GQ5) to prevent, manage, or treat MCS will be eligible. Interventions will not be restricted by the content or treatment approach and may include interventions aiming to avoid triggers, focusing on coping with MCS symptoms, desensitization, or addressing the causes of MCS. In addition, interventions in patients diagnosed with MCS will be eligible regardless of the intervention focus (patient-centered rather than intervention-centered approach). Case studies of individual patients will be included if focused on intervention rather than the natural course of the condition and the description is published in a peer-reviewed scientific journal.

- Comparator: Studies will be eligible regardless of the presence of a comparator.
- Outcome: GQ1 publications will need to provide sufficiently detailed descriptions that can be operationalized as a definition or diagnostic criteria. GQ2 studies will need to report a numerical estimate of the prevalence or incidence of MCS. GQ3 and GQ4 will

not be limited by reported outcomes. GQ5 studies may report on patient health (self or clinician report), physiological or psychosocial measures assessing the effect of the intervention (effectiveness as well as safety indicators); quantitative and qualitative data will be eligible. Studies reporting only on treatment uptake, patient or provider acceptability of treatments, or treatment costs will be excluded.

- Timing: GQ1 studies will be included regardless of the publication year (e.g., definitions from the 1980s are eligible). GQ2 studies will be eligible regardless of the timing of the exposure or assessment (e.g., childhood exposure, symptoms tested in adults). GQ3 and GQ4 studies will not be restricted by time of exposure or follow-up, and retrospective, concurrent, and prospective studies will be eligible. GQ5 studies will be included regardless of the intervention duration and follow up.
- Setting: Studies will not be restricted by setting and will be drawn from the international literature.
- Other limiters: English-language publications disseminated to a wide audience through a scientific journal will be eligible. Studies published in abbreviated form (e.g., conference abstracts) will not be eligible for inclusion.

Systematic reviews and relevant narrative reviews will be retained for reference-mining. Multiple publications on the same study (i.e., studies defined by the included participants) will be consolidated into one study record to ensure that a given study is not counted multiple times regardless of the number of publications reported on the study. The literature flow will be transparently documented in a citation management program.

Inclusion Screening Process

We will use an online database (DistillerSR) designed for literature reviews to screen the search output. The team will design detailed citation and full text screening forms to ensure a transparent, consistent, and unambiguous approach. Citations found to be potentially relevant by at least one reviewer will be obtained as full text. Citations screening will be supported by machine learning algorithms to reduce reviewer errors and bias. All citations excluded by a human reviewer will be screened for relevance by the machine learning algorithm to ensure that no potentially relevant publication has been missed.

Full text screening will apply the detailed eligibility criteria. Training will ensure a shared understanding of all inclusion and exclusion criteria across reviewers. Full text publications will be screened by two independent reviewers and any discrepancies will be resolved through discussion in the review team. Dual screening reduces reviewer bias and errors and is critical for this complex topic. The screening decisions and reasons for exclusion of studies will be tracked in the online database and citation management software. This allows us to reconstruct a detailed literature flow and facilitates the documentation of included and excluded publications. Reasons for exclusion will match the exclusion criteria dimensions to orient the reader. The literature flow will be documented in a flow diagram.

Studies excluded at full text will be documented in the appendix of the review together with a reason for exclusion. We will retain background papers, i.e., papers to cite or reviews to reference-mine. We will report the number of included studies and the number of publications reporting on each study across the review and for each guiding question.

Data Abstraction

The data abstraction will provide a concise overview of the evidence.

For **GQ1** (definitions and diagnostic criteria), we will document the suggested definitions and the approach to establish it. We will document published diagnostic criteria of MCS and for diagnostic accuracy studies, the type (e.g., self-report questionnaire, objective test such as exposure chamber and challenge test) and name of the test will be recorded.

For **GQ2** (prevalence and incidence), we will document the data type (e.g., prevalence or incidence), the method of assessment (e.g., self-report, medical record), and the operationalization of MCS (definition, criteria). We will distinguish general, unselected populations (e.g., students) from targeted samples with potentially increased risk (e.g., Gulf War veterans). For each study, we will record the country, sample size, and year of estimate, and identify any published prospective studies.

For **GQ3** (MCS as a distinct disorder), we will document the aim of the study, the employed study design, and the analytic approach to evaluate MCS as a distinct disorder. We will record the type of research approach used to determine whether MCS should or should not be considered a distinct disorder or syndrome (e.g., establishing a unique biomarker, analyzing symptom clusters, documenting explained variance) [26] and differentiate the use of direct, mechanistic, and parallel evidence by the authors [68-70]. We will abstract the authors' conclusion regarding their conceptual agreement with MCS as a distinct disorder with a differential clinical diagnosis.

For **GQ4** (underlying mechanisms), we will broadly categorize the study type and approach to indicate which aspect of the condition the study addresses (e.g., the general etiology or a specific process such as the mechanism of generalizing across agents) and whether the approach assumes a biological, psychological, or other (e.g., multiple processes) hypothesis. For each study, we will

categorize the suggested mechanisms (e.g., immune system dysregulation, neural sensitization and hyperresponsivity, neurogenic inflammation, limbic system dysfunction, oxidative stress hypothesis, genetic theories, or classical conditioning) [5]. This will involve collating and reviewing all identified mechanisms and establishing a categorization system based on the published literature and identified approaches. We will also establish a compendium of frameworks and diagrams reported by the authors. For this, figures published under a Creative Commons license will be included in the compendium; for all others, the publisher will be contacted to request permission to use the figure.

GQ5 (therapy and management for MCS) will collate all identified interventions and broadly categorizing interventions as prevention, management, or treatment. We will document the focus of the intervention (e.g., aiming to alter the course of the condition, coping strategies) together with the broad therapeutic approach (removing triggers from environment, diet, supplements, masks, devices, [off-label] medication, psychological approaches). The categorization system will built on existing reviews and the identified empirical research [26]. We will also abstract the author group, publication year, and country.

Data will be abstracted by one reviewer and checked by an experienced literature review methodologist. We will export data into tables and figures or data files for further analysis.

Consultation Exercise

The last step of the scoping review process will be a consultation exercise. We will ask multi-disciplinary technical experts and stakeholders in MCS research, practice, and advocacy to review the results of the scoping review. These reviewers will not have been involved in the review process and will assess the review *de novo*. Previous experiences have shown that this last step of stakeholder involvement provides invaluable input and adds to the usefulness and

validity of the end product [41, 71, 72]. The consultation exercise will be conducted as an online survey sent to participants together with the review to elicit structured feedback on the content and presentation of the review. The input will contribute to the presentation of the scoping review results.

Patient and Public Involvement

The planned review was presented at a stakeholder meeting organized by the funding agency that included a patient representative. Several stakeholders are also part of the scientific steering committee that reviewed this protocol (see acknowledgement section). The results of the review will be distributed to stakeholders in a formal consultation exercise as outlined above. This step will be instrumental in ensuring a user-friendly presentation of results that is useful to patients and the public.

Result Presentation

Characteristics of all studies meeting inclusion criteria will be documented in concise evidence tables to provide a broad documentation of the underlying evidence base. Findings across studies will be documented in an evidence map. This visual and user friendly research overview will map the existing evidence on MCS.

The evidence map will use a limited number of dimensions to display the existing research. Displaying the evidence as a bubble plot, each bubble in the plot will represent a study and the size of the bubble will represent the size of the study. The plot will use the x-axis to display existing types of research studies to characterize the evidence base further. The y-axis

can be used to characterize the guiding question addressed by the research. In addition, the shape of the bubble and/or shading may represent different study designs and methodological characteristics. The optimal display will be selected based on input from the consultation exercise.

The tables and figures will be accompanied by a narrative that summarizes the identified evidence base. This scoping review and evidence map will provide a broad overview of the existing research on MCS. It also aims to facilitate a future systematic review of the literature that will answer definitive research questions (e.g., what is the prevalence of MCS and the effectiveness of treatments for MCS). Scoping and mapping has become increasingly useful to prepare more definitive systematic reviews that answer closed questions, in particular for large and controversial topics [42, 43, 48, 52, 73, 74]. The scoping review will provide context and information on which topic areas are to date amenable to a formal systematic review of the literature. The future systematic review will address a narrower scope of approaches that have been identified in this scoping review, assess the quality of evidence for distinct topics of interest, and synthesize the evidence.

In addition to documenting the existing evidence base, we will clearly outline gaps in the literature identified in this scoping review. The gap presentation will use the scoping review's eligibility framework to transparently document existing gaps and future research needs. The gap analysis will make concrete recommendations to facilitate future research.

Ethics and Dissemination and Data Availability

The scoping review was determined to be exempt from further review by the University of Southern California Institutional Review Board (IRB) review in July 2022 (ID UP-22-00516). The results of the review will be disseminated through a journal manuscript. Data of the scoping review will be publicly available through an online data repository (SRDR+).

Author Contributions

SH obtained funding; SH, MD, KR, OA, JJ designed the study, SH, MD, MB, JR, AlM, CP screened literature to prepare this manuscript; AnM and DT manage the data; SY conducted the literature searches; all authors contributed conceptually to the work and edited this manuscript.

Competing Interests

None of the authors have any conflicts of interest to declare.

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Appendix: Search Strategies

Multiple Chemical Sensitivity Scoping Review Protocol

PubMed

"multiple chemical sensitivity"[MeSH Terms] OR ("multiple"[Title/Abstract] AND "chemical"[Title/Abstract] AND "sensitivity"[Title/Abstract]) OR "multiple chemical sensitivity"[Title/Abstract] OR ("multiple"[Title/Abstract] AND "chemical"[Title/Abstract] AND "sensitivities"[Title/Abstract]) OR "multiple chemical sensitivities"[Title/Abstract] OR "MCS syndrome"[Title/Abstract] OR "chemical intolerance"[Title/Abstract] OR "chemically intolerant"[Title/Abstract] OR "chemical hypersensitivity"[Title/Abstract] OR "chemical AIDS"[Title/Abstract] OR "chemical sensitivity disorder"[Title/Abstract] OR "chemical sensitivity syndromes"[Title/Abstract] OR "chemophobia"[Title/Abstract] OR "environmental chemical odor intolerance"[Title/Abstract] OR "sensitivity to environmental chemicals"[Title/Abstract] OR ("chemical"[Title/Abstract] AND "environmental illness"[Title/Abstract]) OR "chemically induced environmental illnesses"[Title/Abstract] OR "total allergy syndrome"[Title/Abstract] OR "twentieth century disease"[Title/Abstract] OR "20th century disease"[Title/Abstract] OR "building-related illness"[Title/Abstract] OR "toxicant induced loss of tolerance"[Title/Abstract] OR "Toxicant-Induced Loss of Tolerance"[Title/Abstract] OR "mast cell activation syndrome"[Title/Abstract] OR "idiopathic environmental intolerance"[Title/Abstract] OR "idiopathic environmental intolerances"[Title/Abstract] OR "idiopathic environmental illness"[Title/Abstract] OR “symptoms associated with environmental factors”[Title/Abstract]

Limit: English language

Agricultural & Environmental Science Collection

(noft("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome") OR noft("chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia") OR noft("environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses") OR noft("total allergy syndrome") OR noft("twentieth century disease" OR "20th century disease" OR "building-related illness") OR noft("toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance") OR noft("mast cell activation syndrome") OR noft("idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”))

AND

(stype.exact("Scholarly Journals" OR "Other Sources" OR "Reports")

AND

la.exact("ENG"))

BIOSIS

"multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" (Topic) or "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" (Topic) or "environmental chemical odor intolerance" OR "sensitivity to

environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" (Topic) OR "total allergy syndrome" (Topic) OR “twentieth century disease” OR “20th century disease” OR “building-related illness” (Topic) or "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" (Topic) OR "mast cell activation syndrome" (Topic) OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" (Topic) OR “symptoms associated with environmental factors” (Topic)

AND Article (Document Types)

AND English (Languages)

CINAHL

TI ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness") OR SU ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR

"chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness") OR AB ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”)

AND

English language

Current Contents

"multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR

"chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" (Topic) OR “symptoms associated with environmental factors” (Topic)

and

English (Language)

and

Article or Review Article or Correction (Document Types)

EMBASE

('multiple chemical sensitivity':ti,ab,kw OR 'multiple chemical sensitivities':ti,ab,kw OR 'mcs syndrome':ti,ab,kw OR 'chemical intolerance':ti,ab,kw OR 'chemically intolerant':ti,ab,kw OR 'chemical hypersensitivity':ti,ab,kw OR 'chemical aids':ti,ab,kw OR 'chemical sensitivity disorder':ti,ab,kw OR 'chemical sensitivity syndromes':ti,ab,kw OR 'chemophobia':ti,ab,kw OR 'environmental chemical odor intolerance':ti,ab,kw OR 'sensitivity to environmental chemicals':ti,ab,kw OR ('chemical':ti,ab,kw AND 'environmental illness':ti,ab,kw) OR 'chemically induced environmental illnesses':ti,ab,kw OR 'total allergy syndrome':ti,ab,kw OR 'twentieth century disease':ti,ab,kw OR '20th century disease':ti,ab,kw OR 'building-related illness':ti,ab,kw OR 'toxicant induced loss of tolerance':ti,ab,kw OR 'toxicant-induced loss of

tolerance':ti,ab,kw OR 'mast cell activation syndrome':ti,ab,kw OR 'idiopathic environmental intolerance':ti,ab,kw OR 'idiopathic environmental intolerances':ti,ab,kw OR 'idiopathic environmental illness':ti,ab,kw OR symptoms associated with environmental factors':ti,ab,kw)

AND

english:la

AND

('article'/it OR 'review'/it)

Environment Index

TI ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness") OR SU ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental

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AND

English language

Environmental Science

(noft("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental

chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR "twentieth century disease" OR "20th century disease" OR "building-related illness" OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”) AND stype.exact("Reports" OR "Working Papers" OR "Scholarly Journals") AND la.exact("English")) AND stype.exact("Reports" OR "Working Papers" OR "Scholarly Journals")

And

Source Type: Reports, Scholarly Journals, Working Papers

AND

Language: English

Healthcare Administration

noft("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic

environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”)Limits applied

AND

Source type: Reports, Scholarly Journals

AND

Language: English

HERO

"multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR OR “building-related illness” OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”

AND

Language: English

PsycINFO

(noft("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome") OR noft("chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR

"chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia") OR noft("environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses") OR noft("total allergy syndrome") OR noft("twentieth century disease" OR "20th century disease" OR "building-related illness") OR noft("toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance") OR noft("mast cell activation syndrome") OR noft("idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”))

AND

(la.exact("ENG")

AND

stype.exact("Scholarly Journals"))

SciFinder

“multiple chemical sensitivity” OR “multiple chemical sensitivities” OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR

"idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”

AND

English language

AND

Exclude: Patent, Book, Commentary, Conference, Dissertation, Editorial, Letter

SCOPUS

(TITLE-ABS-KEY ("multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR "twentieth century disease" OR "20th century disease" OR "building-related illness" OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors”)

AND

(LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re"))

AND

(LIMIT-TO (LANGUAGE, "English"))

Web of Science

"multiple chemical sensitivity" OR "multiple chemical sensitivities" OR "MCS syndrome" OR "chemical intolerance" OR "chemically intolerant" OR "chemical hypersensitivity" OR "chemical AIDS" OR "chemical sensitivity disorder" OR "chemical sensitivity syndromes" OR "chemophobia" OR "environmental chemical odor intolerance" OR "sensitivity to environmental chemicals" OR ("chemical" AND "environmental illness") OR "chemically induced environmental illnesses" OR "total allergy syndrome" OR “twentieth century disease” OR “20th century disease” OR “building-related illness” OR "toxicant induced loss of tolerance" OR "Toxicant-Induced Loss of Tolerance" OR "mast cell activation syndrome" OR "idiopathic environmental intolerance" OR "idiopathic environmental intolerances" OR "idiopathic environmental illness" OR “symptoms associated with environmental factors” (Topic)

AND

English (Language)

AND

Article or Review Article (Document Types)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (p 1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (p 1)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (p 7)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (p 1, system)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (p 17- 18)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review (p 18)
Sponsor	5b	Provide name for the review funder and/or sponsor (p 18)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (p. 18)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (p 3)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (p 7)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (p 9-12)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (p 7-9)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (appendix)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (p 12-13)

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (p 12)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (p 15)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (p 13-15)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (p 13-15)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (N/A)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (p 16-17)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (p 16-17)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (N/A)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (p 16-17)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (N/A)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (N/A)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.