PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multiple Chemical Sensitivity Scoping Review Protocol: Overview of Research and MCS Construct
AUTHORS	Hempel, Susanne; Danz, Margie; Robinson, Karen; Bolshakova, Maria; Rodriguez, Jesus; Mears, Alanna; Pham, Cindy; Yagyu, Sachi; Motala, Aneesa; Tolentino, Danica; Akbari, Omid; Johnston, Jill

VERSION 1 – REVIEW

REVIEWER	Jan Vilis Haanes University Hospital of North Norway
REVIEW RETURNED	22-Mar-2023

GENERAL COMMENTS	Multiple Chemical Sensitivity Scoping Review Protocol Review by Jan Haanes, 22.03.23, Tromsø/Norway After 30 years in the field of IEI/SAEF (symptoms associated with environmental factors), I encourage this effort to perform a scoping review on the conditions attributed to chemicals, often referred to as MCS. As a clinician (M.D.), and following and contributing to the literature on the topic, I find it appropriate to widen the scope in order to better understand these conditions. I hope the efforts planned will succeed in this important mission. Hopefully, a discussion on some of the aspects of the paper can be of help. During these 30 years in the field, I have ended up realizing that "traditional models" probably only to a limited degree are able/ useful to explain conditions like IEI/SAEF, including MCS. "Traditional models" may include the biomedical model (i.e. something wrong in the body leads to experiencing symptoms), the culturally well-based schism physical-psychological and the idea that medical conditions must have a (biomedical) cause (that often is from external causes). Most of the literature on IEI/SAEF (incl. MCS) are based on the mentioned traditional models. In sum, the literature has not been able to prove robust causal relationships between the exposure (itself) perceived to cause symptoms and biological mechanisms explaining the symptoms. Instead, a huge amount of hypothesis and constructs have been made – to a large extent based on culturally based applications of the "traditional models". Scientifically, such constructs may be regarded as descriptions of a phenomenon. Appropriate phenomenon descriptions may very well be of value as such, but should not be confused with the actual biological processes taking place in the body that lies behind the phenomena. Models like predictive coding may be more fruitful when it comes to understanding the actual biological processes (i.e. in bringing in, for this topic, a more relevant biomedical model) underlying phenomena like IEI/SAEF (incl. MCS). For further elaboration on the topics discussed her, I refer to papers like

	https://doi.org/10.1016/j.jpsychores.2020.109955, https://doi.org/10.1177/2167702617693327 and a base for this papers: https://doi.org/10.1016/j.neubiorev.2017.01.015. What may this indicate for the 5 review questions? GQ1: Phenomenon description vs. diagnosis – the first is "just" a description while the second preferably should include a likely biomedical causal relation between exposure and health (symptoms). GQ2: In principle there should not be a problem to report prevalence/incidence of a phenomenon – however, such numbers are only valid for the in each case chosen definition of the phenomenon. GQ3/4: I refer to the discussion above – e.g. regarding the assumptions in "… including defining characteristics and the underlying nature of the condition as toxigenic or psychogenic" and in "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, needs to be widened.", and the limitations of the list of examples in "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)". GQ5: Hopefully this will be covered wide enough. My intention and hope are that my discussion, may be of some help in the stated aim of the proposed review, to "cast a wide net". The references of the paper planned and the search terms may be seen as biased towards "traditional models", e.g. phrases like chemicals, intolerance, TILT and total allergy syndrome. However, this may very well be relevant for a scoping review. On the other hand, I assume that literature like the references I gave above may also be "caught" in the "net" using the proposed search strategy. I do not propose any specific changes in the search strategy, but suggest that the authors consider whether there is a need for it based on my discussion. More detailed comments: In keywords you may substitute "Idiopathic Environmental Illness" with "Idiopathic Environmental Intolerance" – see your ref. #2. "More recently, the condition has been described as an idiopathic environmental intolerance" – In my view, 1996 is not "more recently" and ref. #1 is given, should be #2. In addition, you may consider to include the "more recently" description, given in the SAEF-paper mentioned above. "In addition, our review will be informed by existing comprehensive reviews on the topic" is liked to ref. #4 and #45 – I do not see why these two papers are chosen, e.g. ref #20 and the first Van den Bergh paper mentioned above may be more relevant. "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": If the part in italic means that papers that deals with IEI as such, e.g. mechanisms common for IEI, are excluded, I think that the net is not wide enough for the scoping review. The same comment goes for the next bullet point on GQ3 and 4. In the next bullet point I find "diagnosed" rather inappropriate for a condition lacking a (formal/ widely accepted) diagnosis/ definition of it. To me the protocol itself seems to follow a sound and stringent plan – I have no specific comments. However, I have to add that I have limited experience regarding creating such a protocol. It seems to be

	quite a big challenge that is planned! I look forward to the results of the challenge that Hempel et. al. are planning to perform and wish you good luck! Best regards, Jan Haanes

REVIEWER	Giovanni Damiani Case Western Reserve University, Dermatology
REVIEW RETURNED	24-Apr-2023

GENERAL COMMENTS	I read with great interest this scoping review protocol by Hempel and colleagues. Since the MCS evidence are scattering I would like to see in the introduction a rapid discussion toward the guidelines and the mandatory multidisciplinarity that was recently structured in harmony with other speciality scientific societies in the Italian guidelines [10.3390/ijerph182111294]

REVIEWER	John Spengler Harvard School of Public Health
REVIEW RETURNED	24-Apr-2023

GENERAL COMMENTS	The proposed methodology for conducting a systematic review of the MCS literature is thorough and will be an important contribution to our understanding and the uncertainties of MCS. The timing is relevant in light of the constellation of persistent symptoms reported in association with Long COVID. The expert advisors guiding the review are appropriate. A suggestion to the authors/experts would be to explicitly consider including the literature related to the aftermath of the first Gulf War, World Trade Center workers and now burn pit exposures.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Jan Vilis Haanes, University Hospital of North Norway

Comments to the Author:

After 30 years in the field of IEI/SAEF (symptoms associated with environmental factors), I encourage this effort to perform a scoping review on the conditions attributed to chemicals, often referred to as MCS. As a clinician (M.D.), and following and contributing to the literature on the topic, I find it appropriate to widen the scope in order to better understand these conditions. I hope the efforts planned will succeed in this important mission.

Hopefully, a discussion on some of the aspects of the paper can be of help. During these 30 years in the field, I have ended up realizing that "traditional models" probably only to a limited degree are able/ useful to explain conditions like IEI/SAEF, including MCS. "Traditional models" may include the biomedical model (i.e. something wrong in the body leads to experiencing symptoms), the culturally well-based schism physical-psychological and the idea that medical conditions must have a (biomedical) cause (that often is from external causes). Most of the literature on IEI/SAEF (incl. MCS) are based on the mentioned traditional models. In sum, the literature has not been able to prove robust causal relationships between the exposure (itself) perceived to cause symptoms and biological mechanisms explaining the symptoms. Instead, a huge amount of hypothesis and constructs have been made – to a large extent based on culturally based applications of the "traditional models". Scientifically, such constructs may be regarded as descriptions of a phenomenon. Appropriate phenomenon descriptions may very well be of value as such, but should not be confused with the actual biological processes taking place in the body that lies behind the phenomena. Models like predictive coding may be more fruitful when it comes to understanding the actual biological processes (i.e. in bringing in, for this topic, a more relevant biomedical model) underlying phenomena like IEI/SAEF (incl. MCS). For further elaboration on the topics

> discussed her, I refer to papers like https://doi.org/10.1016/j.jpsychores.2020.109955, https://doi.org/10.1177/2167702617693327 and a base for this papers: https://doi.org/10.1016/j.neubiorev.2017.01.015.

Thank you for your insightful comments. We have added discussion about the paradigm shift and the SAEF term to the introduction.

> What may this indicate for the 5 review questions? GQ1: Phenomenon description vs. diagnosis – the first is "just" a description while the second preferably should include a likely biomedical causal relation between exposure and health (symptoms). GQ2: In principle there should not be a problem to report prevalence/incidence of a phenomenon – however, such numbers are only valid for the in each case chosen definition of the phenomenon.

We agree with your concerns and have consequently revised GQ1 from “How is Multiple Chemical Sensitivity (MCS) defined and how is it diagnosed?” to the more neutral: “How is Multiple chemical Sensitivity (MCS) defined and which diagnostic criteria have been proposed?”

> GQ3/4: I refer to the discussion above – e.g. regarding the assumptions in "… including defining characteristics and the underlying nature of the condition as toxigenic or psychogenic"

We have revised the paragraph addressing the defining characteristics to address this comment.

> and in "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, needs to be widened.", and the limitations of the list of examples in "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)". GQ5: Hopefully this will be covered wide enough.

Thank you for your important comments on the guiding questions. We have revised the categorization approach for GQ4 to address this comment but nonetheless believe it is important to characterize the proposed mechanisms of action in this scoping review.

> My intention and hope are that my discussion, may be of some help in the stated aim of the proposed review, to "cast a wide net". The references of the paper planned and the search terms may be seen as biased towards "traditional models", e.g. phrases like chemicals, intolerance, TILT and total allergy syndrome. However, this may very well be relevant for a scoping review. On the other hand, I assume that literature like the references I gave above may also be "caught" in the "net" using the proposed search strategy. I do not propose any specific changes in the search strategy, but suggest that the authors consider whether there is a need for it based on my discussion.

Thank you for your thoughtful response and providing this insightful perspective. Although the articles you’ve cited came up in our search, we have added the term “symptoms associated with environmental factors” to our search strategy.

> More detailed comments: In keywords you may substitute "Idiopathic Environmental Illness" with "Idiopathic Environmental Intolerance"

Thank you for spotting this, revised!

> – see your ref. #2. "More recently, the condition has been described as an idiopathic environmental intolerance" – In my view, 1996 is not "more recently" and ref. #1 is given, should be #2. In addition, you may consider to include the "more recently" description, given in the SAEF-paper mentioned above.

We have revised the paragraph to address this point.

> "In addition, our review will be informed by existing comprehensive reviews on the topic" is liked to ref. #4 and #45 – I do not see why these two papers are chosen, e.g. ref #20 and the first Van den Bergh paper mentioned above may be more relevant.

These papers stood out to us when preparing this manuscript, but we have added other examples, including reviews using systematic review methodology and those that provide a broad overview.

"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*": If the part in italic means that papers that deals with IEI as such, e.g. mechanisms common for IEI, are excluded, I think that the net is not wide enough for the scoping review.

The main intention was here to exclude concepts that were not of interest for this review such as electromagnetic sensitivities. We will not exclude studies that do not use the term chemical as a term or that do not reference a possible mechanism of action, but we do want to restrict to studies where symptoms are associated with chemical agents, solvents, odorants, air pollutants, or materials rather than addressing the full spectrum of environmental factors. We have revised the sentence for clarity.

The same comment goes for the next bullet point on GQ3 and 4. In the next bullet point I find "diagnosed" rather inappropriate for a condition lacking a (formal/ widely accepted) diagnosis/ definition of it.

We agree and have changed the term diagnosed to *characterized*.

To me the protocol itself seems to follow a sound and stringent plan – I have no specific comments. However, I have to add that I have limited experience regarding creating such a protocol. It seems to be quite a big challenge that is planned!
I look forward to the results of the challenge that Hempel et. al. are planning to perform and wish you good luck!

We appreciate the good wishes and thank the reviewer for the thoughtful comments.

Reviewer: 2
Dr. Giovanni Damiani, Case Western Reserve University
Comments to the Author:
I read with great interest this scoping review protocol by Hempel and colleagues.
Since the MCS evidence are scattering I would like to see in the introduction a rapid discussion toward the guidelines and the mandatory multidisciplinarity that was recently structured in harmony with other speciality scientific societies in the Italian guidelines [10.3390/ijerph182111294]

Thank you for this comment and we have added a reference to this important guideline.

Reviewer: 3
Prof. John Spengler, Harvard School of Public Health
Comments to the Author:
The proposed methodology for conducting a systematic review of the MCS literature is thorough and will be an important contribution to our understanding and the uncertainties of MCS. The timing is relevant in light of the constellation of persistent symptoms reported in association with Long COVID. The expert advisors guiding the review are appropriate. A suggestion to the authors/experts would be to explicitly consider including the literature related to the aftermath of the first Gulf War, World Trade Center workers and now burn pit exposures.

Thank you for these encouraging comments. We agree with the importance of these populations. Given the growing list of conditions, including most recently long COVID, we have critically reviewed our search strategy again. Following further discussions with content experts, we decided to use a broad search strategy without reference to developing or established conditions such as Gulf War illness and sick building syndrome (SBS) to keep the strategy as open as possible. Where authors make the connection, papers will still be found, but we avoid including papers in the scoping review where we would make an assumption that may go beyond the authors' intent. But we will critically review all identified publications for overlapping symptoms and similar mechanistic underpinnings regardless of the terminology given the lack of established nomenclature.