PUTTING THE CHEMICALS BACK IN "MULTIPLE CHEMICAL SENSITIVITY"

preface, highlights, summary

Ontario Environmental Health Advocates Address

Syndrome de sensibilité chimique multiple, une approche intégrative pour identifier les mécanismes physiopathologiques/ Multiple chemical sensitivity syndrome, an integrative approach to identifying the pathophysiological mechanisms

Lead author Varda Burstyn Collaborating author Maureen MacQuarrie
for the Ontario Environmental Health Advocates Group

ontarioadvocates@gmail.com
http://recognitioninclusionandequity.org/inspq-mcs-report-critique/

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CHEMICALS OR ANXIETY: WHAT CAUSES MULTIPLE CHEMICAL SENSITIVITY?

The quote below is from Masri, S., Miller, C. S., Palmer, R. F., and Ashford, N., (2021), "Toxicant-induced loss of tolerance for chemicals, foods, and drugs: assessing patterns of exposure behind a global phenomenon," Environmental Sciences Europe. Background and evolution of chemical intolerance, paragraph 1.

> The sharp growth in reports of TILT ["toxic-induced loss of tolerance," a synonym for MCS], appears to coincide with the post-WWII expansion of the petrochemical industry and widespread growth in the production of petrochemicals such as organophosphate pesticides, solvents, dyes, and fragrances. U.S. production of the so-called "synthetic organics," which had been less than 1 billion pounds per year, soared to over 460 billion pounds per year by 1994 (of note, while the term "synthetic" can be interpreted differently, its use in this paper is in reference to compounds whose chemical structures do not appear in nature). The same pattern can be seen for pesticide use in U.S. agriculture, which grew from 200 million pounds of active ingredient in 1960 to over 600 million pounds by 1980. Assuming that exposure to synthetic pesticides and other chemicals is a function of their production and use in everyday society, it is reasonable to assume that these trends have led to increased human exposure over time. Importantly, given their absence prior to modern history, such chemicals can be considered evolutionarily novel and may present particular challenges as [they] relate to the body's ability to process them through detoxification or elimination pathways. Furthermore, while the human toxicity of pesticides is widely recognized, regulations to safeguard the public are likely insufficient given their focus on the toxicity of individual chemical ingredients . . . as opposed to complex mixtures of multiple chemicals, the latter being more reflective of commercial chemical products and other environmental exposures.

The quote below has been translated from « L'institut national de santé publique du Québec, (2021), Syndrome de sensibilité chimique multiple, une approche intégrative pour identifier les mécanismes physiopathologiques, p. 811.

> The authors of this report conclude that MCS . . . is due to fear conditioning accompanied by chronic anxiety resulting from the constant desire to avoid exposure to odours that cause these people to develop or exacerbate symptoms because they consider this exposure to be threatening to their health.

PUTTING THE CHEMICALS BACK IN "MULTIPLE CHEMICAL SENSITIVITY"

Ontario advocates address *Syndrome de sensibilité chimique multiple, une approche intégrative pour identifier les mécanismes physiopathologiques/ Multiple Chemical Sensitivity Syndrome, an integrative approach to identifying the pathophysiological mechanisms*

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OCTOBER 2022 PREFACE TO THE SECOND EDITION: WHY A SECOND EDITION WAS NEEDED

The first edition of this document, written to dispute and refute the central conclusions of the INSQP's June 2021 report, *Syndrome de sensibilité chimique multiple, une approche intégrative pour identifier les mécanismes physiopathologiques,* was posted online and narrowly distributed at the end of June 2022. A broader distribution was planned to take place later this fall. Given the delay, it seemed an opportune time to clean up textual errors (e.g., spelling), improve clarity, add a few more supporting references and, where possible, minimize repetition, although some is unavoidable in making sure that the main points of our counterargument get carried across from chapter to chapter. The most important of the small changes we have made are listed at the end of this preface, and in no way change the document's substantive content.

With respect to one issue, however, several parts of this second edition do contain new elaborative text. This new text focuses on a May 2022 hypothesis article, "The Pathobiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Case for Neuroglial Failure," published in *Frontiers in Cellular Neuroscience* (Renz-Polster et al., 2022). The article is important as a contribution to ME studies, but what makes it particularly interesting and important to us is that it was co-authored by one of the INSPQ's three principal authors, Marie-Ève Tremblay, along with Herbert Renz-Polster, Dorothee Bienzle and Joachim E. Fischer. **This article appears to lend support to the fundamental disagreement we have with one of the central conclusions of the INSPQ's report: namely that MCS and ME are caused by anxiety and have a psychological origin**. Our counterargument explicates this fundamental disagreement in detail.

The Renz-Polster et al. article suggests that the dysfunction of neuroglia (e.g., astrocytes, microglia – innate immune cells, oligodendrocytes) in the brain plays a dominant role among a host of additional biological processes in ME. It explores various supportive findings and hypotheses for its neuroglial hypothesis, but – and this is key – chronic anxiety is not one of them. (However, the emerging role of mast cells in ME is, an issue we address in this document vis à vis MCS.) In contrast to the INSPQ report, this article contends that exposure to chronic stress – and stress in general, not simply emotional stress – is only one in a long list of possible causative mechanisms for central nervous system inflammation and neuroglial reactivity.

Simply put, this article seems to have much in common with the research we report on and the approach we take to ME, and for that matter to MCS; but to contradict the narrow conclusion of the INSPQ report – that chronic anxiety is central to it. Indeed, we devote our "Part 9: Myalgic Encephalomyelitis (ME) and long COVID – what can we learn?" to a review of current ME research efforts internationally to show just that, that this anxiety causation theory plays no role in these and, further, to warn against the psychologization of long COVID going forward.

Just as importantly – if still to be fully explored – we believe the approach to the understanding of causal factors and mechanisms in Renz-Polster et al. has important implications for how we

understand the causes and mechanisms of MCS. Although glial cells are mentioned in the INSPQ report, primarily in the chapter dealing with the immunological hypothesis, there is no fulsome discussion of possible implications, such as is presented in the Renz-Polster et al. article. This is not a theme we can explore here. However, more broadly in this document, we do address the role of a number of types of brain cells and neuro-receptors, and we show that physical-toxicological stress – not emotional stress – is key in understanding MCS onset and ongoing symptomatology.

Perhaps what appears to us as Tremblay's contradictory stance on ME as between the INSPQ report and the *Frontiers* paper can be explained by an evolution of her understanding of ME since the INSPQ report was written. New research since that time has indeed provided evidence that supports the biophysical paradigms of ME, and also of MCS, as we demonstrate in our commentary. In our discussion of the matter of comprehensiveness of research done for the INSPQ report (Part 2), we point out that the report's conclusions need to stand up not only to work that was omitted or neglected in the literature review process, some of which we detail; but also to new research, published since it was released. The Renz-Polster et al. article, although a hypothesis study, is a very important example of such new research. The INSPQ conclusions do not, in our view, stand up to it.

But, if Tremblay's understanding of ME has shifted, it is highly problematic that she has not moved to recall or correct the INSPQ report. The Association pour la santé environnemental du Québec / Environmental Health Association of Québec (ASEQ-EHAQ), through their health minister, has been asking for the withdrawal of the INSPQ report for some time, and we have supported their call (Appendix 5). At the very least, it is important that problems with that report are identified publicly so that steps in policy or action by authorities wherever the report is read may be based on the new understanding. This, by extension, would also include a questioning of the INSPQ report's characterization of MCS as being caused by chronic anxiety -- the purported mechanism common to both MCS and ME in the INSPQ report, such that they are both explained as psychogenic.

This has implications from societal disease-burden and patient safety perspectives for those already sick with both ME and MCS, and for many people with long COVID (Post Acute sequelae of Covid-19 or PASC) who have dysfunctions clinically indistinguishable from ME (as Renz-Polster et al. note, and as we have done as well.)

Finally, we want to make a timely plea. Now that it has become crystal clear that in long-COVID we are facing a type of complex illness for which our usual medicine does not have answers, it has also become increasingly clear that a) this is not a psychogenic disorder and b) we have to think beyond the single-organ specialization system of medicine that our health ministries have relied on for so long. This is what it will take to find a way for our society to successfully confront this new reality. And so it is now time to acknowledge that in ME and MCS we have had a very similar situation – although one that, through neglect and denial, was not publicly visible like COVID.

It is now time to look to the approaches of the researchers and clinicians who have developed expertise and supported those with these complex diseases to help develop system-wide care capacity that can assist both those newly facing the many challenges of long COVID and those already struggling with MCS and ME. Again, the INSPQ report takes us in the opposite direction from this approach.

Here are the smaller changes of note in this second edition:[1]

- We updated and restructured "Overview and Highlights," (the first part of the Executive Summary) starting on page 19 and added more extracts of translated text from the complete INSPQ report.

- In Part 2.5.4, the first of two sections dealing with mast cell activation we added two graphical examples (Chemical Intolerances by Group and Other Intolerances by Group) from the Miller et al., 2021 paper (pp. 75, 76). This is also where we begin our discussion of the Renz-Polster et al. article (pp. 72-74 and 77).

- In Part 2.7 dealing with biological individuality we provide a reference to the INSPQ report, wherein they acknowledge the wide variety in symptoms and presentation amongst people with MCS (p. 82).

- In Part 4.5.2, the second section on mast cells (p. 117), and in Part 9.3, "Myalgic Encephalomyelitis is widely accepted as a biomedical disease" (pp. 198, 199), we included further discussion of Renz-Polster et al.

- To Part 5.2, page 130 (Heavy metal and toxic chemical body burden), and to Part 5.6, page 134 (Mold and mycotoxin illness), we have added two substantive quotes from Jeanette Hope's 2013 "A Review of the Mechanism of Injury and Treatment Approaches for Illness Resulting from Exposure to Water-Damaged Buildings, Mold, and Mycotoxins." *The Scientific World Journal, 2013*, 767482.

- We updated the citations for references that were in preprint when our 1st edition was prepared and which now are published (Carazo et al., 2022 and Che et al., 2022).

- We added two references on MCS patient experience (Gibson et al., 2015 and 2016).

- We added some further references on long COVID. One supports the possible connection between mast cells and long COVID (Weinstock et al., 2021), another, a news feature

[1] Please note that the page numbers refer to the pages in the full text of the commentary's 2nd edition.

from *Nature*, that reports on research into an intriguing microclot hypothesis that may well be relevant beyond long COVID (Willyard, 2022). We also added an article from the US National Institutes of Health, Covid-19 Research on NIH clinical studies investigating ME and Long COVID (August 8, 2022).

- We provided an updated citation for the prevalence, disease burden and funding of ME in the US (Mirin et al., 2022).

Toronto, October 25, 2022

JUNE 2022 PREFACE: WHY THIS COMMENTARY AND ABOUT ITS SIGNATORIES

The year 2021 was, for the most part, a good year in multiple chemical sensitivity (MCS) studies. Several major research articles that we substantially draw on in this commentary were published. An extensive literature review from Alberta Health was released. In a field so terribly underfunded, these important additions were very welcome.

However, the INSPQ report, *Syndrome de sensibilité chimique multiple, une approche intégrative pour identifier les mécanismes physiopathologiques,* came to our attention in the fall of 2021, and although we looked forward to reading and learning from it, as soon as we began, the alarm bells went off. For we saw that it had taken an approach and arrived at conclusions highly divergent from the other new pieces, and that, it soon became clear, were both wrong and dangerous. The Association pour la santé environnemental du Québec / Environmental Health Association of Québec (ASEQ-EHAQ), similarly concerned about the INSPQ report's conclusions, asked their Minister of Health and Social Services to remove the report from the institute's website and update it. The ASEQ-EHAQ letter of appeal, which we support, is included as an Appendix to our commentary.

Our fears were deepened when, in early 2022, a member of our community, "Sophia" (a pseudonym) ended her unbearable MCS-induced pain and hardship with MAiD (medical assistance in dying). After years of desperately seeking a safe place to live where, on a limited budget, she could be free of the fumes of her neighbours' cleaning products and cigarette smoke, her suffering became unbearable and she chose to end her life. Some of us knew her and had worked directly with her, so her death was particularly difficult. Despite the advocacy of doctors and disability professionals, every level of government refused her help. Except for six units created long ago in Ottawa, no dedicated safe housing units have ever been built for people with MCS, finding an affordable safe residence is extremely difficult and there are no programs to assist people like her to find safer places anywhere. We have learned since that a number of others facing a similarly dire situation have also applied for MAiD.

Our fear is that if the conclusions about the nature and mechanisms of MCS in the INSPQ report attain acceptance by any government or medical association, they will have extremely deleterious consequences. Because these conclusions are wrong, authorities will treat Sophia's physical suffering as a mental illness, deny appropriate medical care, leave disability needs unmet and thereby doom many more people to the same fate. Out of this profound concern, we decided that the erroneous and dangerous conclusions of the INSPQ report had to be disputed and refuted substantively and piece by piece. Thus, this critique and counterargument was born.

Though we find the INSPQ report's conclusions frightening, we used the opportunity that its critique presents to showcase some of the exciting work and top-tier researchers in MCS studies, environmental studies and myalgic encephalomyelitis (ME) studies, not included in the INSPQ report. This is work that policy makers, health providers, those working in the disability field, and

many others really need to know about. It will help to explain what MCS really is, and, to a certain extent, also ME (myalgic encephalomyelitis/chronic fatigue syndrome). This knowledge is critical in assisting these groups to understand and to help modernize health care in general to address complex, environmentally-linked diseases and to develop healthier public policy on chemical use – a modernization that is very badly overdue.

The patient perspective is essential for any illness, and its incorporation has become common practice. It is l needed in any process that seeks to identify any or all of the nature, mechanisms and definitions of MCS, and it is also essential to the creation of clinical programs and sites, disability needs, population health and prevention strategies and research priorities. But it is entirely missing from the INSPQ report. It is a perspective we have used to frame our critique, and included it very explicitly at key junctures within it.

We are an Ontario-based group of advocates who have worked together for the recognition and inclusion of the medical conditions ES/MCS, ME and FM, with which about one million Ontarians live and struggle. These are often devastating and disabling conditions, but have little to zero care and support from our provincial health and social services systems, with ES/MCS the most excluded of the conditions. Our group includes environmental health consultants and educators, writers, health and social policy planners, participants in national research efforts (ME), senior health system administrators, health system change experts, human and disability rights advocates, educators, patient organization leaders, a lawyer and caregivers. Some of us live with one or more of the conditions, some of us do not. More details about us can be found in Appendix 1, "Information about the Signatories."

We have worked along with the Ontario Ministry of Health in leading roles since 2010 – some even earlier than that – towards bringing into existence a centre of excellence in environmental health with dedicated affiliated local clinics and a specially trained cohort of family physicians across the province. In other words, we have worked for a system of care for our groups, and for the kind of policy change that is needed to turn the recognition of these as disabilities into meaningful rights in real life. Foundational to the work has been the understanding that the three conditions are biophysical medical conditions with neurological, immunological and other body system involvement, and not, as the INSPQ report concludes, mental illnesses, psychological or psychiatric in nature.

The Ontario project, involving extensive research and planning, has had three major phases and has produced a number of important documents (linked below), to which we refer in our commentary. The implementation phase, COVID delayed, is still to come; however, we have been assured that it is an active file within the Ministry.

Our commentary is based both on the best of what we know of research to May 2022, and the knowledge we have gathered from and about our communities as advocates. We learn every day about lived experience, including experiences with physicians and the health care system. So, with this perspective, our critique of, and counterargument to the INSPQ report provides:

1. An explanation for how the science reviewed and approved in the report does *not* describe, explain or accord with the real-life experience of people living with MCS. The research that we cite and explicate, much of it more recent, does accord with that experience, and corrects an incomplete and erroneous picture painted by the INSPQ report.

2. Important dimensions of the experience of those living with MCS, which the report is entirely lacking. We evaluated the conclusions of the INSPQ report in the light of the patient experience and the literature and found the conclusions neither credible nor well-supported. We have identified some of the relevant literature and given a voice to the missing patients in a number of ways throughout.

3. Key lessons from the clinical experience, also missing from the report, and also absolutely critical to validate any conclusions and definitions. We introduce a body of clinical work, evolving for decades in state-of-the-art settings of environmental and functional medicine outside of our public health care system, especially but not only in the United States.

4. A set of recommendations for moving forward at both federal and provincial levels. Informed by the 12-year process in Ontario as well as our work in this counterargument, these recommendations hold many useful features for other governments, federal, provincial and territorial.

We hope that this contribution can go some distance to providing what is needed to correct deficiencies and errors of the INSPQ report and averting their potential negative consequences.

Varda Burstyn, Maureen MacQuarrie, Bev Agar, Ted Ball, Mike Ford, John Doherty, Izzat Jiwani, Denise Magi, Scott Simpson and Adrianna Tetley

Toronto, June 27, 2022

The documents from the first phase of the Ontario study can be found at http://recognitioninclusionandequity.org/resources/ .

The second major study process produced two reports: The Interim Report - Time for Leadership: Recognizing and Improving Care for those with ME, FM and ES/MCS and the final report, Care Now: An Action Plan to Improve Health for People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME), Fibromyalgia (FM) and Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS).

The document from the third phase, “Laying the Groundwork” is not yet a public document, but in process at Ontario’s Ministry of Health

EXECUTIVE SUMMARY

PUTTING THE CHEMICALS BACK IN "MULTIPLE CHEMICAL SENSITIVITY"

OVERVIEW AND HIGHLIGHTS

The INSPQ report, *Syndrome de sensibilité chimique multiple, une approche intégrative pour identifier les mécanismes physiopathologiques*, is massive in length – 823 pages – and ambition. Its three principal authors – Gaétan Carrier, Marie-Ève Tremblay and Rollande Allard – state that their objective was "to identify the pathophysiological mechanisms that underlie MCS [for multiple chemical sensitivity] using an approach that considers all the research conducted on the hypotheses put forward to date." (INSPQ, Summary, Objective, p. 3.) This and a few other key quotations from the INSPQ report have, for ease of reference, been collected in a box at the end of this executive summary.

We do not believe these authors have succeeded in their mission; indeed we believe that grave harm to people living with MCS will result if the report's conclusions are accepted and used to guide policy or clinical practice. In our commentary and counterargument we explain why. First, though, to provide the context for our concern, we set out the main points from the INSPQ report.[2]

We contend the INSPQ Report is reductionist and contains erroneous conclusions that would have grave negative implications for clinical, disability, public health and research efforts

The INSPQ authors believe that they have found the sought-after pathophysiological mechanism – note, only one mechanism – "chronic anxiety," triggered by fear conditioning, causing a reaction in the limbic system which sets off a biological cascade of multi-system symptoms. (Summary, Results, p. 3) The authors are so confident that they have settled all outstanding questions related to MCS mechanisms that they propose a new name for MCS: CSMCS (central sensitivity to multiple chemical substances.)[3]

The authors dismiss the role of chemicals in MCS at, in the report's usage, "normal" or "usual" concentrations – a formulation riddled with problems. They even describe these concentrations as "harmless."[4] Further, they write, "there is no evidence to support the hypothesis of a relationship between MCS and the toxicity of chemicals at their usual concentrations in the environment." (Summary, Conclusion, p. 3) In the INSPQ formulation it is not chemicals but the "perception of odours" that is involved in setting off the biological cascade and the resulting neuronal sensitization. They note, in the narrow context of the olfactory hypothesis, that the brain cannot receive and respond to chemical odorants. (Ch.12, Discussion et Conclusion, 12.1.7.6 Chapitre 9 – Hypothèse olfactive, pp. 803, 804 -- see box at end of summary for translated extract). This becomes a foundational position for their larger argument. They do not look beyond the olfactory system in this regard.

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[2] The INSPQ report was produced in French, with a 4-page Summary and Key Messages in English. Where possible we reference and use the words of the officially translated English document in our commentary.

[3] Translated from 'SCSCM' – Sensibilité central aux substances chimiques multiples (Box p. 811, Rapport complet)

[4] Translated from"… des stimuli odorants inoffensifs couramment rencontrés dans l'environnement…" (12.2.4 Résumé des perturbations biologiques observes chez les sujets SCM, Rapport complet) p.811.

Their final conclusion: “People with MCS, therefore, are not hypersensitive to chemical substances.” (Summary, Conclusion, p. 3)

Instead, these authors conclude that “chronic anxiety” causes or “explains” MCS. “Chronic anxiety … [has as] its main feature … the *anticipation of danger,* i.e., feeling a persistent, excessive, and inappropriate concern about one’s day-to-day activities.” (Summary, Results, p. 3.) Thus MCS constitutes an anxiety disorder and somatoform illness – in other words, MCS is a psychogenic condition.

In this construct, what many experienced MCS researchers see as a complex, multi-etiological, multi-mechanism and multi-symptom disease process is radically and erroneously reduced to one anxiety-triggered mechanism in the brain’s limbic system. (We discuss this in Parts 2, 3, 4, 5 and 6 of our commentary), a reductionism that is striking to us in its erroneous approach.

Finally, the INSPQ report claims that its anxiety-causation thesis is also relevant to chronic fatigue syndrome, post-traumatic stress disorder, electromagnetic hypersensitivity, fibromyalgia, chronic anxiety, depression, somatization disorder, phobias, and panic disorder. They write that chronic anxiety is an element common to all these conditions. (Key Messages, p. 2)

We disagree with all these conclusions. In this counterargument we dispute and refute them.

We make a case for multiple xenobiotic etiologies, multiple mechanisms and multiple pathways to sensitization in multiple chemical sensitivity (MCS)

First, methodologically, we show that the claim of the INSPQ report to have considered all relevant literature is false. We support this by referencing research that was omitted or neglected, and further by comparing INSPQ conclusions to the contrary conclusions of new studies, completed since evidence collection ended for the INSPQ process. Both the unengaged older research and that published more recently support the view that MCS is a complex, multi-etiological and multi-mechanism biophysical-toxicological syndrome and disease process, very much linked to chemicals.

We strongly disagree that all questions of etiology and mechanisms are settled. We acknowledge that there is much to be discovered about MCS and that there is a pressing need for further research. However, we argue and show that the evidence of current research lends support to the thesis that it is chemicals (note: not “odours” the terminology used in the INSPQ report) that trigger onset and continuing flares in chronic MCS. (We discuss this in our Parts 2, 4, 5, 6 and 7). Even at low concentrations, and certainly at higher ones, certain chemicals do indeed cause onset and perpetuate chronicity in a particular subset of people – very possibly through impacts on certain parts and cells in the brain and immune system. This document provides examples of research on these hypothesized impacts, explaining how they are thought to be involved in MCS symptoms, both initial and ongoing.

Our commentary explains that the reactivity or intolerance of MCS is a complex reaction and that it involves many more body systems than the limbic system. The INSPQ report opens the door to this line of reasoning but focused, as it was, on one mechanism never fully explored it. We suggest, based on the studies we put forward, that it is very likely that disturbed neurological and immune systems that have been harmed by encounters with particular chemicals have thus become sensitized. Further – and critical, from an etiological point of view – we point out that pathways to such sensitization are often created or encouraged by the presence of other disease factors such as infections, high body burden of chemicals and pharmaceuticals, previous brain injuries, certain genetics and mycotoxin illness. (Discussed in Parts 2 and 5).

Drawing on literature from the field of environmental health as well as MCS studies, we also show that even when they do not trigger MCS reactions, many of the "everyday chemicals" involved in both onset and chronicity in MCS are not "harmless" on a population health basis, even in so-called "normal" or "usual" concentrations, as the INSPQ report declares. (We discuss this in Parts 4, 5, 6 and 7)).

We also enter into the discussion a) a body of clinical experience and b) a literature on patient experience, which were not considered by the INSPQ authors, but which support the biophysical-toxicological paradigm of the disease process. In designated sections we provide key lessons from the clinical experience (in Part 3, 5 and 10), and from the patient experience (in Part 3 and 8 in particular).

The INSPQ report has very little to say about the clinical implications of their conclusions, except to say that MCS is a "real health issue" that should be addressed in dedicated programs. (Key Messages, p. 2) But the INSPQ conclusions contain an implicit clinical agenda, the errors of which are so grave that they would be dangerous to patients and potentially violate the important medical dictum, "first do no harm," were they to guide new clinical services.

Whether completed prior to the end of the INSPQ report's collection period or since, up to May 2022, the research we present confirms these concerns and analysis, and provides the basis for an entirely different understanding of MCS than that of the INSPQ report with respect to both mechanisms and to etiological factors, one that explains that MCS is not psychogenic but biophysical-toxicological in nature. (See Parts 2, 3, 4, 5, 6, 7, 8, 9.)

We make a case that anxiety is a result, not the cause, of MCS

From the perspective of the work we rely on with respect to MCS, a central and crucial issue in the INSPQ report, anxiety is one *result* of MCS reactions; it is not the cause, as the INSPQ report claims. (We take this up in almost every section of this document, but especially in Parts 7 and 8)

When anxiety is experienced as a result of an MCS exposure, it is what we term a "physical" anxiety and it is only one among many in a constellation of triggered neurological symptoms, sometimes referred to (in others' work) as "neuropsychiatric." These neurological symptoms may – often are – also accompanied by other bodily symptoms, all of which are the *effects* of an

exposure, not the cause of the reaction. This “physical” anxiety disappears when the MCS reaction subsides.

There is also “psychosocial anxiety,” or, more accurately in this context, legitimate worry and fear. When concern and even fear are repeatedly experienced with respect to real dangers in life after MCS onset (the psycho-socio-medical factors that cause such fear are discussed in detail in Part 8), these are not imagined dangers, but real. Certainly, the stress of these factors can exacerbate, undermine and retard improvement, as stress does in all disease processes. But again, these concerns and fears are not the cause of MCS, rather the effects of living with it in society at present. This type of worry, concern or fear is not neurotic, and it is not an anxiety disorder.

The same reductionism and erroneous conclusion of anxiety causation applied by the INSPQ report with respect to MCS is also applied to ME (for myalgic encephalomyelitis), which is often referred to as ME/CFS (myalgic encephalomyelitis)/chronic fatigue syndrome), or, as in the outdated language of the INSPQ report, chronic fatigue syndrome. Much more research has been completed on ME than on MCS, and so the evidence (discussed in Part 9) is even more strongly ranged against the “anxiety causation” theory in that condition. Indeed, in May 2022, the article “The Pathobiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Case for Neuroglial Failure,” was published, authored by four researchers including Marie-Ève Tremblay, one of the INSPQ report’s three principal co-authors (Renz-Polster et al. 2022). This article appears to us to directly contradict the method and conclusion of the INSPQ report with respect to ME. In contrast to the anxiety causation thesis, it considers its hypothesized role for neuroglial cells as mutually complementary, rather than exclusive of, a host of etiological and mechanistic factors that do not include chronic anxiety. The approach described in this article has a great deal in common with the approach we take here to analyzing a number of etiological factors and mechanisms in MCS (Parts 2, 4 and 9) as well as in ME.

This divergence between the INSPQ report (2021) and the Renz-Polster et al. article (2022) is very striking and needs to be accounted for. Given the greatly overlapping symptoms and markers between ME and long COVID, a major new disease burden for society added to the considerable, already existing disease burden of ME, it is imperative that the anxiety-causation approach be retired and rapidly so as to identify the real causes and symptoms and so appropriate care can be developed.

A working description of MCS

We provide a working description of MCS in line with our conclusions and the evidence against the INSPQ psychogenic approach. This description, based on multiple sources, is explained in detail in the main text in Part 2.3, supported throughout, and is extracted on the next page. It differs substantially from the definition provided in the INSPQ report, reproduced in part in the extracts at the end of this Executive Summary.

A Working Description of MCS

MCS is a multi-system, recurrent, environmental syndrome and disease process that flares in response to different exposures (i.e., pesticides, solvents, toxic metals, fragrances, cleaning products, cigarette smoke, certain foods, drugs/medicine, mold and other vehicles of exposure) at concentrations that do not provoke such symptoms in other people. It is characterized by neurological, immunological, cutaneous, allergic, gastrointestinal, rheumatological, cardiological and endocrinological signs and symptoms. MCS is a widespread condition and the majority of those who live with it (approximately 70 percent) are women, though a significant minority are men.

Onset, which may happen slowly over time or rapidly, begins on exposure to a particular chemical or mixture of chemicals (including bio and well as synthetic toxicants) that commonly affect the immune system and/or nervous system, such that MCS appears to be primarily a neuroimmune disease process. This chemical exposure interacts with one (or both) of these systems in a way that renders individuals intolerant to subsequent exposures, which are then experienced as triggering or flaring events. After the initial onset, some new triggering events may result in “crashes” - additional worsening to qualitatively greater degrees of severity that are not easily reversible without intervention.

Affected individuals no longer tolerate everyday exposures to a wide range of structurally diverse substances at levels that never bothered them previously, including ingestants, inhalants, implants, and skin contactants. Many previously tolerated foods and drugs may trigger symptoms. At times, onset is not observed or reported immediately, and the phenomenon of "masking" can obscure MCS and delay diagnosis.

MCS ranges in severity. Early, milder stages are often erroneously perceived to be allergies, require adjustments and avoidance, but go undiagnosed. Moderate to severe MCS involves greater intensity and duration of symptoms. Severe MCS brings intense reactions, great physical suffering and can be life-threatening for some people when exposed to some chemicals. Major efforts to avoid triggers are required, making life in the ambient air of chemically-laden everyday environments unsustainable. This is how MCS disables those affected. When co-morbidities are present – often the case – overall health is further compromised, and additional barriers are encountered.

MCS is usually responsive to appropriate measures and treatments, but becomes worse without these.

Our Conclusions

Reducing the causes and mechanisms of the complex syndrome and disease process of MCS to a singular, unproven allegedly causal factor – "anxiety" or "chronic anxiety" – makes it impossible to develop correct analytical accounts of MCS, which in turn makes it impossible to develop a competent and effective clinical response and an accurate assessment of MCS as a disability. It also makes it impossible to devise appropriate public health measures or to develop a productive research agenda. So, the chronic anxiety conclusion of the INSPQ report is very consequential and very dangerous. It could potentially result in the violation of medical responsibilities and disability rights, go in the opposite direction of what is needed on a population health basis vis à vis common chemicals, and suggest a research program that would miss the many marks that must be hit in basic, epidemiological and clinical dimensions.

In our conclusion (Part 10) we offer a set of recommendations for what is needed for these dimensions of MCS, going forward. Having looked in some detail not only at omissions and errors in research in the fields of MCS and environmental health studies, but also at many of the key lessons of the clinical record (Parts 3, 5 and 10), we demonstrate that though we have a long way to go in understanding MCS, there is already sufficient research as well as clinical experience to move ahead on a system of care for people with living with MCS based on a biophysical-toxicological approach. The lessons of the clinical record must be sought out and utilized, not hidden away.

To this end, we include practical recommendations for both Health Canada and for provincial/territorial health care systems, drawing on the 12-year experience in Ontario as well as our broader research. These provide a critical path for how to create a responsive and effective system of care, including tertiary-level centres of excellence, dedicated affiliated local clinics with staff and facilities to provide hands-care and support to local/regional physicians, and a special trained cohort of family physicians in local communities. As well, we advance recommendations for an urgently needed, all-important federal safe housing program.

PART BY PART SUMMARIES

Readers please note: the main text of this report is highly researched and referenced. You will find the research support in the main text, not in this summary.

Part 1: Contextualizing the INSPQ report on Multiple Chemical Sensitivity

With 1.1 million Canadians, or 3.5 percent of the population, diagnosed with MCS, an often severe and disabling condition, and after emerging as a distinct clinical entity as early as the 1950s, MCS remains excluded from Canadian health care. This poses a medical crisis for those who live with it and what should be a moral as well as medical crisis for our health care systems. MCS has been a contested illness, with two diverging schools of thought, or two diverging

paradigms, on its causes and mechanisms: the biophysical-toxicological school, in which patients and MCS clinicians have long located themselves (since the 1960s); and the psychogenic school with founding documents from the 1990s, of which the INSPQ report is the latest iteration.

This divergence, and the historical (and what should now be obsolete) attachment, of many medical associations to the psychogenic paradigm has served as a pretext for provincial health ministries to do nothing about MCS even as its prevalence grows. But by 2010, with numbers affected rapidly growing and with new efforts made by advocacy groups and individuals to seek care, three provincial processes were initiated. Ontario's has been the most extensive by far, with three major phases of study and planning, and an implementation report, delayed by COVID, awaiting the attention of a new health minister. The signatories of this document have all been participants and leaders in this process. All the phases of Ontario's process have been based on the biophysical-toxicological paradigm of MCS.

In 2013, Québec commissioned a literature review as a first step to policy development. Alberta's review of the state of the science was commissioned a year or so later in response to recommendations from the Alberta Energy Regulator regarding health concerns of residents in the Peace River area. Both reviews took place over many years, but were released within a month of each other – May 2021 (Alberta Health) and June 2021 (Québec National Institute of Public Health – INSPQ). The reviews diverged in methodology and conclusion, both reviewed in Part 1.3 of our main text. Alberta's report found the greatest weight of evidence for olfactory dysfunction, neurologic sensitization and neuroinflammation on exposure to chemicals. It found the psychological line of research of low utility, noting it was impossible to determine whether the affective symptoms reported were causes of MCS, or, in fact and more likely, the effects of MCS. The INSPQ report concluded there was no link between MCS symptoms and chemicals, rather that "anxiety" explains MCS.

Last in Part 1 we begin our explanation, taken up again in Parts 5 and 10, of why, despite the long way to go in arriving at definitive answers regarding pathophysiology (true for many diseases and medical conditions), the current state of knowledge (detailed in its main features in Parts 2, 5 and 10 but excluded from the INSPQ report) is indeed sufficient for health and other relevant ministries to proceed with: creating clinical programs; making disability rights meaningful; advancing policy on improved indoor air quality; and, regulating of common chemicals.

Part 2: Missing pieces in basic research and epidemiology

In order to deepen understanding of the differences in the science called on by the two broad schools of thought in MCS studies – the psychogenic and the biophysical-toxicogenic – Part 2 begins with a more detailed history of the ideas and the authors in the respective schools. This clarifies how the INSPQ report is the latest iteration of the former, and why we consider ourselves squarely located in the latter. Then, to illuminate why we have selected key pieces of scientific research that dispute the INSPQ conclusions and, in other chapters, why we draw on scholarship in the wider field of environmental health studies, we provide our working

description of MCS (reproduced in this Executive Summary on page15). In it, we take care to specify what from the patient experience is clear about MCS – especially that is a staged disease process, divisible at least into onset and chronicity. This understanding, key to many research and clinical accounts, is absent from the INSPQ report, and so, conveniently, is the role of chemicals in triggering onset, both strategic and important omissions.

We then proceed to provide our first discussion of the omitted or neglected toxicologically-informed research on potential MCS mechanisms that disputes the INSPQ conclusions. We begin by describing a "unifying theory" based in environmental factors that links all the disorders the INSPQ report ascribes to anxiety: the "cell danger response" theory of physician and researcher Robert Naviaux (Naviaux, 2018), a theory that describes the adverse health effects of documented body burdens of common chemicals that disrupt mitochondrial function. Though we endorse no individual theories – we are advocates, not physicians or scientists – we do advance and support work that is much more plausible than the INSPQ report. This work is harmonious with the science that we consider enlightening, and is grounded in both MCS and environmental health studies.

From this basis, we then discuss two very important lines of research on hypothesized sensitization mechanisms that have been, respectively, neglected and omitted in the report. These provide toxicologically-linked explanations for sensitization: the TRPV1 and TRPA1 receptors is a *neurological* discussion; and mast cell activation and mast cell activation syndrome (MCAS) is an *immunological* discussion. We want in particular to discredit the INSPQ proposition that "low" or "normal" or "usual" concentrations of "odours" (i.e. chemicals) cannot enter the brain or set off the biological triggers responsible for the symptoms of MCS. This is a very important, foundational idea for the INSPQ report that we begin to contest and refute here, and return to specifically in Part 4.

We also review several other fields in MCS studies that, thanks to extremely low funding (a function of the politicization of MCS), have yet to be fully explored, but are very promising with respect to the identification of biological markers – unlikely to be present if MCS were an anxiety disorder. These include the study of what biophysical findings are common to other hypersensitivity illnesses; the presence and role of specific genetic polymorphisms and epigenetic changes, and the information that the application of metabolomics (the study of metabolites) may yield in terms of specific MCS markers. The research in these fields has not emerged anxiety as a factor in any way.

Finally, we introduce the critical concept of biological individuality (and return to it at various junctures). This concept is central to understanding MCS both as a whole, in addressing individual patients, and in rejecting the idea that anxiety is responsible for MCS in all patients all of the time. Again, an exploration of this concept is missing from the INSPQ report.

Part 3: Deficiencies in epidemiological, clinical and socio-political analysis

The problems in the INSPQ report are not only that it is missing science that can account for neurological and immunological mechanisms for sensitization and promising biomarkers, but also that there are a number of other important deficiencies in the overall analysis that must be factored in. To begin with, returning to epidemiology, the report's outdated statistics understate the prevalence of MCS and the rapidity with which numbers are increasing, tending to trivialize the urgency of understanding causes and developing serious, health and societal responses. Further, the preponderance of women (70+ percent) is barely noted, but must be accounted for by any categorical assertion of mechanism. We devote Part 6 entirely to this subject.

Another omission of great importance is the clinical knowledge that has been amassed by environmental health physicians in diagnosing MCS, and whether or not that experience confirms or contradicts the INSPQ conclusions. This is an astounding omission. Perhaps it is explained by the politicization of MCS. We provide a framework and historical account to this, including the early attacks on the "reality" of MCS, and the competence of the medical practitioners who care for MCS patients. This attack was led – we document this – by the chemical industry, which explicitly declared MCS to be a threat to it, beginning in the late 1980s-early 1990s. It was also supported by a number of doctors and scientists whose work became well known thereafter. This politicization has skewed MCS research and impacted clinical publication. Likewise, we find the complete absence of the patient experience from the INSPQ report surprising, very troubling and undermining of its credibility, a discussion we begin in this Part.

Finally, there is no discussion, not even a mention, of MCS in children, or of what factors in childhood can increase risk for MCS in later stages of life. Just as with the missing "onset" discussion, this severs chronic MCS from the real life of individuals prior to and during onset. It also makes MCS children invisible. Finally, it obscures the urgent necessity of reducing the presence of both industrial and consumer chemicals in children's lives – an issue we do discuss, and return to again.

By way of conclusion, for Parts 2 and 3, we underline that a definitional process that omits all these critical items cannot be considered comprehensive, and nor can its conclusions be considered well-substantiated, let alone final. We then move on to look more closely at the dismissed role of chemicals in MCS.

Part 4: Chemicals and MCS

We begin the discussion of the links between chemicals and MCS – a link that is dismissed by the INSPQ report – by explaining why it is a fundamental error to define MCS in relation to "odours" and not to chemicals. In addition to respiration, MCS reactions take place through ingestion, eyes and skin contact and even through internal tissue contact (e.g. via surgical implants) – pathways that have nothing to do with odours, but everything to do with chemicals, and are not accounted for by the INSPQ report. In discussing MCS links to chemicals, we are

particularly interested in neurological impacts, but there are other pathways to sensitization as well, most importantly immunological ones. Accordingly, we begin with a discussion of the many toxic chemicals that comprise today's synthetic fragrances, a topic that has been studied academically but is not well-understood by the general public or medicine, even though many of these chemicals are implicated in a host of other chronic and serious diseases, and are neurotoxic. We then present important recent findings on what we might term "non-fragrant" chemicals, such as pesticides, printer inks, traffic emissions, building materials that equally trigger MCS and equally are implicated in multiple disease processes, including cancer, and are also neurotoxic. We discuss the extent of toxics-related disease on a global basis, and link MCS to this trend.

With these factors in mind, we then extend the discussion of the neurological and immunological mechanism research on TRP channels and mast cell activation we began in Part 2.5. In doing so we deepen our presentation of the science and how it shows the links between chemicals, sensitization and MCS. We proceed to a discussion of the impact of many common chemicals on neurological/mental functions, the role of chemicals in MCS onset, and report on a 2021 empirical study demonstrating the MCS-chemical link.

Part 5: Lessons from the clinical experience

The search for one mechanism is MCS is very likely misguided because there are many pathways to sensitization, a fact that has emerged from the clinical experience. That clinical experience is missing from the INSPQ report, and we briefly review and document some of its most important findings in Part 5.

Very importantly, having a body burden of heavy metals and/or toxic chemicals such as pesticides, all measurable by standard tests, affects the central nervous system and can lead to sensitization and make de-sensitization difficult or even impossible, though modalities of treatment exist that can be helpful. Very importantly, toxic chemicals such as pesticides can also damage gastrointestinal health in several ways and particularly affect the health of the gut, which has a direct relationship with the brain and affective states, which we document. Brain injuries are likewise risk factors for sensitization when chemicals become involved. Fundamentally important from the clinical experience has been the role of serious but chronic and often, due to our inadequate testing, sub-clinical bacterial, viral, fungal and parasitical infections that affect the nervous system in a number of ways, including through the production of biotoxins. In the last decade or so, clinicians have found when Lyme disease is present, sensitization persists. Mold and mycotoxin illness, a common problem, can also act as sensitizers and retardants on recovery. In addition, many patients present with immunological deficiencies related to other immune functions, e.g. immunoglobulin deficiencies.

The overarching point of this catalogue is to underline the specific paths to sensitization, the existence of clinical practice that concerns itself with ameliorating them, and to demonstrate that clinical experience counters the hypothesis of one anxiety-driven causative mechanism.

Part 6: Women and MCS

Women comprise more than 70 per cent of MCS sufferers, internationally, a long and well-established fact. Any account of MCS that does not grapple with this must by definition be incomplete at best, erroneous at worst.

The INSPQ report attributes this preponderance to women's greater propensity to anxiety, and makes no effort to determine whether there are important links between women's biology, their chemical exposures relative to men, and, indeed, how this impacts their neurological/mental health. We do. First, we introduce a number of toxicological factors linked to women's greater share of MCS. We explain how women's special biological makeup puts them at greater risk than men during chemical exposure – a fact proven in the proportionally greater severity of Gulf War illness among women veterans than men. We also delineate the factors in women's social role – in women's workplaces and at home – that expose them to unregulated chemicals, at "normal" but truly unhealthy concentrations. We look at the tragic fact that the chemicals in many beauty products are also toxic, and have added to women's load.

Also, importantly but never addressed by the INSPQ report, is women's much greater medicalization than men, and the massive doses they receive particularly of gut disturbing antibiotics as compared with men, and how this undermines neurological health. We also discuss the gender bias against women that exists in medicine. Physicians are more likely to give women's reports of illness less credibility than men's and much more frequently ascribe symptoms they do not understand to emotional and mental disturbances.

Finally in this section, we introduce the findings of a very important new field of study that has begun to tackle the *synergistic effects of chemical exposures, socio-economic stressors and trauma* with respect to maternal and child health – a field that does not counterpose these factors and create a false choice between them, but shows their respective as well as highly negative synergistic effects. This emerging field should have a great deal to offer MCS studies in the future. We conclude that there is overwhelming evidence for adverse impacts of chemicals on women's mental and neurological health as well as on all other aspects of health, all of which undercut the simple and simplistic "anxiety causation" theory.

Part 7: Understanding chronic stress, anxiety and MCS

In the INSPQ report, chronic stress leads to, or, along with chronic anxiety is seen to cause the biological cascade that provokes MCS symptoms. The relationship of stress to anxiety, and of both to MCS symptoms is formulated differently at different times in the INSPQ report, so we begin Part 7 by attempting to clarify the key terms of this central tenet, and then set about addressing and refuting it via a number of steps.

First, we introduce the distinction between fear and anxiety – an issue we return to at length in Part 8. We use the example of the life and death need for chemically-safe housing to demonstrate that people with MCS have fears of *real dangers*, rather than an anxiety disorder

related to vague and unjustified concerns. At the same time, we explain that these fears do not cause MCS, rather they stem from it. Then, moving to a more theoretical formulation, we address the conceptual error, central to the INSPQ report, of counterposing "biopsychosocial" factors to "toxicological" ones.

We unpack this problem by introducing the types of chronic stress – personal/psychological, social (as in the WHO determinants of health), physical and toxicological –and their relation to individual and population health in general and how these figure in MCS. We discuss the now accepted understanding that personal trauma and psychosocial stress underpin all forms of disease and in so doing draw on the work of Hans Selye, the Adverse Childhood Experiences (ACE) project and the multi-decade Whitehall study to develop this point. This review shows that while psychosocial stresses predispose to ill-health, they are not enough to tip people into MCS; for MCS, a toxicological input is needed. This is a fundamental point that places toxicological insult as a necessary factor in MCS, even if it is usually combined (as in all illness) with other life stressors.

To illustrate this proposition with respect to onset, we turn to the lessons of Gulf War Illness (GWI), which included MCS for a significant subset of veterans. We first point out that GWI is not PTSD, as the INSPQ report erroneously states. We note that GWI need not include PTSD and even when it does, it is much more than that, with a host of debilitating physical symptoms. Drawing on the work of many distinguished researchers, we then analyze the presence and role of chemicals in Gulf War 1, and briefly trace how these came to be acknowledged as the key factors in the development of GWI. We further discuss a recent study showing a genetic component resulting in difficulty in metabolizing certain chemicals (e.g., sarin gas) for those who developed GWI. We then add a discussion of the illness-exacerbating role of high stress – combat stress – augmenting the vulnerability of soldiers to the chemical insults, in aid of understanding both the leading role of chemicals, and the synergistic effects of chemical and non-chemical stressors.

Part 8: Socially determined stress in chronic MCS exacerbates illness

Moving from onset to chronicity, we discuss the causative role of chemicals (*not* anxiety) in initiation, but also in prolongation of chemical intolerance (chronicity) in a subset of breast implant recipients who developed MCS. From there, we move on to identifying the role of multiple types of stressors – personal, socio-economic, physical and toxicological – in enabling disease, as a way to establish this point in examining the life of post-onset MCS patients. For source material for the stressors commonly experienced after MCS sets in (which we analyze at length) we used the findings of a major, qualitative needs-identification study conducted in Ontario for the Ministry of Health from 2011 to 2013. This study queried participants on the WHO social determinants of health because deficits in these are well known to have adverse health impacts. The study showed that, for every determinant, the overall burden of stress skyrockets during the chronic phase of MCS, does not abate over time, and becomes an exacerbating factor in illness, undermining recovery.

We break our discussion of the study results into four main clusters: the determinants of disability, employment, income security, housing, food, clothing and transportation; the determinants of social environments, support networks and healthy child development; the determinants of discrimination, genetics, personal care practices and coping skills; and finally, but massively important, the determinant of access to health services of a decent quality. The study revealed almost unbelievable deficits in all these determinants as a result of the stigmatization of MCS by the medical profession and, in lock step, by society as a whole; by the inescapability of triggering chemicals and enormous difficulties in practicing avoidance; and by the complete vacuum in care and support for people who live with MCS.

The key takeaways of this section are a) it is the unbearable weight of real existential dangers that causes fear and vigilance in MCS, not an anxiety disorder, per the INSPQ report and b) stress reduction for people with MCS can be achieved with the provision of appropriate health and social supports – a social and moral decision to provide which is clearly within reach for our governments if they so choose.

Our final section discusses the psychological and neuro-plasticity derived therapeutic modalities relative to MCS. In the anxiety-causation theory of the INSPQ report, it would be logical that these would be the modalities that would be implemented for MCS patients. We review the dismal record of classical talk therapy, and CBT (cognitive behavioural therapy) in resolving MCS, and note the better success, at least anecdotally, in *some* people, of approaches that seek to "retrain the brain." We also note how these do not work for others, for whom biophysical interventions work better. We conclude that psychoneurological modalities, as well as support counselling, should be offered in clinical settings, but cannot replace the biophysical-toxicological clinical program discussed in Part 5 and again in the conclusion.

Part 9: Myalgic encephalomyelitis (ME) and long COVID: What can we learn?

In Part 9, we take on the erroneous claim that chronic anxiety is what is common to, and causes MCS, but also and in the same way, is causal for a long list of other conditions, "chronic fatigue syndrome" and fibromyalgia among them. We express grave concern that the INSPQ report authors buttress their conclusions on such a faulty basis, for us one of the most fundamental errors in the report's conclusions. In order to make our point, we specifically look at the case of ME (myalgic encephalomyelitis, known formerly as "chronic fatigue syndrome").

We lead our analysis with extracts from a hypothesis article on ME (Renz-Polster et al., 2022) – co-authored by Marie-Ève Tremblay, one of the INSPQ principal authors. The article suggests that a common denominator in ME's multi-faceted nature may be dysfunctional neuroglia, and proposes greater focus on the role of neuroglia in ME and long COVID research. The article builds upon many as yet unsubstantiated hypotheses and disease mechanisms but suggests the evidence for neuroglial dysfunction is strong. Chronic anxiety is not mentioned, although the role of chronic stress is listed as one in a long list of possible causative mechanisms for central nervous system (CNS) inflammation and neuroglial reactivity generally, not specifically for ME. This list includes, among other causes, injury or infection of the brain, vagal dysfunction,

autoimmune reactivity. The INSPQ report, by contrast, in looking at CNS inflammation focuses almost exclusively on chronic anxiety/stress.

We show that research into ME is ongoing and active, with important projects supported by national research efforts, for example, in the US, through the National Institutes of Health, and in Canada, through the Canadian Institutes of Health Research. The research, growing in scope and depth as more funding is brought online, is showing ME to be a complex and multi-system biomedical disease. And more and more, there is an understanding that one single mechanism is unlikely to explain all pathophysiological processes for all people and that subgrouping is needed—not everyone with the condition is the same.

Treatment guidelines deal with ME as a biomedical disease, including those recently released from the UK prepared by the National Institute for Care and Excellence (NICE). ME is marked by many symptoms, with post-exertional malaise being the most characteristic. Anxiety, not amongst the disease's diagnostic criteria, can be present in some cases, but it is not causative, and recommendations for its treatment are similar to those that are given for any medical condition. There are cautions against the use of cognitive behaviour therapy (CBT) and graduated exercise therapy (GET), and in one example, best practices from the US Clinicians Coalition, these treatments are highlighted as an out-dated standard of care.

We also discuss long COVID, which is a newly recognized and yet-to-be understood condition that follows infection by the virus causing COVID-19. Like ME, MCS and FM, its symptoms are multi-system; indeed, many people with long COVID are qualifying for a ME diagnosis. We note that there is an underlying tendency when pathophysiologic mechanisms are not known to assume the condition in question is psychogenic. We caution against this happening with long COVID.

Part 10: Recommendations for moving forward

Our conclusion is devoted to practical conclusions and recommendations, to help advance the discussion from literature reviews to practical steps in establishing – recognizing, including and creating access for – MCS in health care and disability rights, and in population health and research. We agree with the INSPQ that MCS qualifies it as a "real health issue," that "centres of expertise specializing in MCS" should be created, and that MCS should continue to be tracked and researched. But what definition of MCS will guide the clinical programs and facility creation in these proposed dedicated centres of expertise, and what research will be funded and prioritized?

In terms of medical care, working from clear needs identified by patients, physicians and health ministry officials, we recommend a process to establish a case definition and clinical guidelines that could work across the country, including in identifying the appropriate roster of effective diagnostic and treatment services. It makes no sense to have multiple, diverging versions, so we recommend that Health Canada fund a process to bring this about. We urge that for this, expert clinicians practicing state-of-the art environmental medicine with established clinical track

records from Canada and internationally, along with the handful of knowledgeable clinicians in Canada who work within the public system, be recruited, and that expert patient advocates be fully integrated into this process. We emphasize the need for safe air quality – and all that makes it possible – must be indicated for MCS clinical sites, as a fundamental medical need.

With respect to disability rights, we urge that recognition, policy, education and enforcement of MCS accommodation as a disability be enacted to maximize accessibility and maximize equity. We explain the main issues and measures in this respect, including accessibility and equity in inclusion in the many social assistance entitlements and programs now available to other disabled Canadians, including medical device and pharma care subsidies.

MCS-safe housing is both a medical necessity and disability need, so we strongly support the call of the *Association de la santé environnementale du Québec-Environmental Health Association of Québec* (ASEQ-EHAQ) for a national MCS housing program, as well as for safe medical facilities and safe schools. We detail the components of what such a program ought to include.

As well, the federal government can and ought to fund research through the Canadian Institutes of Health Research, create at least two research chairs at major medical schools and jump-start funding to help provincial/territorial governments to create appropriate services along the continuum of care and integrated into our health care systems.

However, provincial/ territorial governments need not wait for federal action and can move forward on most of these fronts on their own. This will mean new diagnostic and treatment services, new ways of practicing medicine and new funding mechanisms. The experience of clinically responsive patients to such specialized treatment shows that it makes more fiscal sense to provide appropriate and effective care than to continue with high costs, wasting tens of millions of dollars annually, for current, but often useless, physician utilization.

We do have the knowledge and we do have the financial resources to deal with MCS, and if we do, everyone wins: people with MCS and their families, the modernized health care system and governments that truly spend less for good care than more for bad.

EXCERPTS FROM THE INSPQ's 'KEY MESSAGES AND SUMMARY' & 'RAPPORT COMPLET'

Multiple Chemical Sensitivity Syndrome, an integrative approach to identifying the pathophysiological mechanisms

EXCERPTS FROM THE INSPQ REPORT'S KEY MESSAGES AND SUMMARY
English language version

The objective of this [INSPQ] report is to identify the pathophysiological mechanisms that underlie MCS using an approach that considers all the research conducted on the hypotheses put forward to date. (Summary, Objective, p. 3)

Considering the chronic polysymptomatic nature of MCS and other related syndromes (chronic fatigue syndrome, post-traumatic stress disorder, electromagnetic hypersensitivity, fibromyalgia, chronic anxiety, depression, somatization disorder, phobias, and panic disorder), the authors of this report hypothesize that recent research on MCS, as well as on other related health conditions, may help to explain the origin of the observed symptoms. (Summary, Objective, p. 3)

Over the past two decades, advances in neuroscience, in particular in psychoneuroimmunology, and the availability of new techniques for measuring biological parameters and performing functional brain imaging have shed light on the pathophysiological mechanisms underlying MCS. These scientific advances confirm that the psychological, biological, and social aspects of this syndrome are inextricably linked. (Key Messages, p. 1, Emphasis added)

Studies have found the following changes in all the syndromes and pathologies studied: a disruption of the hypothalamic-pituitary-adrenal axis, an increase in inflammatory cytokines, a disruption in oxidative homeostasis, a chronic decrease in neuromodulator levels (serotonin, dopamine, norepinephrine). In addition, using brain imaging, alterations in brain function and structure were observed that affect the limbic system circuits (emotions, memory, learning) and the prefrontal cortex (attention, reasoning, strategic thinking, judgment). (Summary, Results, p. 3)

Collectively, these changes help to explain all the acute symptoms (those observed at the time of exposure to odours) and chronic symptoms reported by people with MCS. As a consequence of these alterations, MCS-affected individuals develop neuronal sensitization. This makes them more vulnerable to subsequent episodes of stress triggered by the perception of odours, which they consider a threat to their health. (Summary, Results, p. 3, Emphasis added)

Chronic anxiety is an element common to all the syndromes studied and its main feature is the *anticipation of danger,* i.e., feeling a persistent, excessive, and inappropriate concern about one's day-to-day activities. A number of factors may be involved, e.g., an individual's temperament, personal history, and psychosocial makeup. The severity of the syndrome depends on its duration and the comorbidity that MCS patients frequently experience, i.e.

chronic fatigue syndrome, electromagnetic hypersensitivity, fibromyalgia, and depression, etc. (Summary, Results, p. 3, Emphasis added)

Affected individuals perceive odours as a threat to their health. When they detect odours they experience acute stress symptoms that manifest as ailments that they attribute to chemical products associated with those odours. (Key Messages, p. 2)

What is more, olfactory studies have demonstrated that there is no absorption of odorous substances at the low ambient concentrations to which people with MCS are exposed. These individuals have a normal capacity for detecting odours, while exhibiting reduced, rather than increased, activation in the brain regions that process these signals. This reduced activation points to the suppression of activity in olfactory pathway structures by regions within the neocortex. If, indeed, people with MCS are hypersensitive to odours, one would expect to see increased, not decreased, brain activity when compared with control subjects. (Summary, Results, p. 3)

The authors of this report conclude that, based on the available data, there is no evidence to support the hypothesis of a relationship between MCS and the toxicity of chemicals at their usual concentrations in the environment. People with MCS, therefore, are not hypersensitive to chemical substances. Nonetheless, the chronic biological disturbances observed, the severity of the symptoms experienced, the impact on the social and professional lives of affected individuals, and the high prevalence of MCS in the population qualify it as a real health issue. (Summary, Conclusion, p. 3)

EXCERPTS FROM INSPQ RAPPORT COMPLET – UNOFFICIAL TRANSLATION

Please refer to the original document in the places noted for context and the official text

[Translated, two paragraphs] When an organism is exposed to a stressor, it is first perceived by the limbic system and by various regions of the central nervous system involved in sensory processing, culminating in the paraventricular nucleus of the hypothalamus, which activates the two main hormonal stress response systems: the sympatho-adreno-medullary system and the hypothalamic-pituitary-adrenal system. …The activation of these two complementary systems leads respectively to the release, by the cortex of the adrenal glands, of adrenaline and glucocorticoid hormones (cortisol in humans, corticosterone in rodents)…. Adrenaline can cause the release of neuromodulators like noradrenaline from central projections, especially in areas of the limbic system initially involved in processing the stressful situation. Corticosterone acts at the level of the pituitary gland and the hypothalamus, to normalize the release of stress hormones, in addition to acting on numerous extrahypothalamic regions including the entire limbic system and the prefrontal cortex, particularly on the cells (neurons, microglia, astrocytes, etc.) that express the appropriate receptors, i.e. glucocorticoid receptors.

There are two types of receptors in the body that corticosteroids can bind to, mineralocorticoid receptors (MR) and glucocorticoid (GR) receptors. The balance of receptor-mediated actions is crucial for homeostasis (De Kloet, 2013). In chronic stress, there is an imbalance in the number

of MR and GR receptors on neurons in the structures of the limbic system, the prefrontal cortex and the hypothalamus.(Ch. 5, Neurobiologic Hypothesis, Neuroendocrine response to stress, pp. 204-205)

[Translated] In recent years, with the discovery of bilateral interactions between the immune system, the nervous system (central and peripheral) and the endocrine system, research in the field of activity of neuroinflammation has taken off considerably. This research shows that the CNS [central nervous system] has the ability to produce and modulate inflammatory reactions, not only in response to infections, allergies, trauma or tissue damage, but also in response to psychological stress. They also show that in addition to mediators produced by cells[97] (footnote 97 - Lymphocytes, mast cells, dendritic cells and macrophages) of the immune system (such as histamine-His, tryptase, bradykinins, prostaglandins, various cytokines), neuropeptides produced by neurons of the peripheral nervous system (SP, *vasoactive intestinal peptide* – VIP, *calcitonin gene related peptide* – CGRP, *neurokinin A* – NKA, *neurotensin* – NT, *neuropeptides – corticotrophin-releasing factor* – CRF, *nerve growth factor* – NGF) and neurotransmitters (SE, NA , Ach, His) produced by the neurons of the CNS as well as hormones of the endocrine system (*adrenocorticotropic hormone* – ACTH, cortisol) are jointly involved in the inflammatory reactions exacerbated in several pathologies: …. (Ch. 8, Neuroinflammation Hypothesis, 8.6 Second part: central neuroinflammation, 2nd paragraph, p. 363)

[Translated] At the socio-demographic level, women are more often affected by MCS, for all age groups. This reflects other published data on mental illnesses where the predominance of women for anxiety disorders and certain types of personality disorders was measured. These are all factors considered to be predisposing for the development of MCS. On the other hand, although MCS can occur following initial exposure to odorous chemicals, there is no clear evidence regarding the role of these exposures in the establishment of MCS. (Ch. 10, Psychogenic Hypothesis 10.7 Conclusion,2nd paragraph, p. 645)

[Translated]… [C]onsidering the mechanisms explained in the preceding chapters and all the results presented in this chapter, it must be concluded that these mechanisms support a biopsychosocial model for multiple chemical sensitivity syndrome and not a toxicogenic model related to the toxicity of chemicals (Ch. 10, Psychogenic Hypothesis, 10.7 Conclusion, p. 646)

[Translated] Sexual differences in the amygdala response have been cited by several authors as a potentially important factor that could explain why certain psychological disorders, such as anxiety disorders and depression, have a greater prevalence in women than in men (Davidson et al., 2002 - Chapters 3 and 10 of this document). (Ch. 11, Chronic Anxiety hypothesis, 11.11.7 Differences according to sex, 4th paragraph, p 739)

[Translated] … The syndrome of multiple chemical sensitivity (MCS) is a chronic, acquired disorder characterized by recurring non-specific symptoms associated with multiple organ systems. The symptoms are caused or exacerbated by environmental exposure to multiple chemicals with different molecular structures and toxicological mechanisms, at concentrations close to the odour retention threshold (Hummel et al., 1996), therefore much considered an unexplained syndrome because clinical examination does not reveal any

abnormality in an organ or system that might explain the symptoms. In subjects suffering from this syndrome, the acute symptoms are usually caused by the olfactory detection of any odour. The hypothesis most often advanced by patients is an increased sensitivity to odours as a causal factor in their syndrome. Chemical products incriminated are varied and can include both perfumes and cleaning agents, deodorants, fresh paint, gasoline or other smells. For an exposure to the same odorous molecule, symptoms vary over time in people with the condition and also from person to person. Symptoms are usually caused by chemicals from different molecular structures and toxicological mechanisms. [Ch. 12, Discussion and Conclusion, 12.1.1 Definition of Multiple Chemical Sensitivity (part) 2nd paragraph, p. 779, Emphasis added]

[Translated] It is important to remember how the brain perceives smells….. like all external signals picked up by our other senses, smells are first detected by specific receptors before being converted into nerve impulses and transmitted to the brain by a network of neurons and their axons. Indeed, chemical odorants encountered in the usual environment do not enter the brain, only information in the form of nerve impulses gets to the brain. (Ch.12, Discussion and Conclusion, 12.1.7.6, Chapter 9 – Olfactory Hypothesis, paragraph 12, pp. 803, 804)

[Translated] The biological changes observed in these studies are not unique to MCS. Indeed, they are reported in chronic fatigue [syndrome], post-traumatic stress, electrosensitivity, fibromyalgia, chronic anxiety and depression, somatization, phobic disorders and panic disorder, unrelated to problems of perception of odours. What emerges from the literature in relation to all these chronic health problems, it is that disruption of adaptation mechanisms aimed at maintaining the body's homeostasis plays a decisive role in their development. However, the peculiarity with MCS is the nature of the stimuli that induce fear conditioning is to harmless odorous stimuli commonly encountered in the environment. (Ch. 12, Discussion and Conclusion, 12.2.4 Summary of the Biological Perturbations Observed in People with MCS – last bullet, p. 811, Emphasis added)

[Translated] 1. The authors of this report conclude that MCS subjects have developed central neuronal sensitization associated with chronic dysregulation, mainly of the limbic system, of certain brain functions, the management of emotions, of memory and learning as well as of judgment. This is due to fear conditioning accompanied by chronic anxiety resulting from the constant desire to avoid exposure to odours that cause these people to develop or exacerbate symptoms because they consider this exposure to be threatening to their health. (Ch. 12, Discussion and Conclusion, 12.3 Conclusion p. 811, Emphasis Added)

[Translated] In order to correctly describe the health problem that affects these people, the authors of the present report propose the following name: Central sensitivity to multiple chemical substances (CSMCS) replacing the name MCS. (Chapter 12, Discussion and Conclusion, Box at bottom of page 811)