Response to the report of

the National Institute of Public Health Québec (INSPQ)

on

Multiple Chemical Sensitivity (MCS)

Summary

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The INSPQ report has collected and evaluated an extensive number of published studies.

However, there are gaps in the concepts required to understand environmental health and links to chronic disease.

Furthermore, studies demonstrating multiple chemical sensitivities are missing.

Review of concepts that are evidence-based in environmental health that are missing:

- Air pollution is one of the top five factors to develop noncommunicable chronic diseases (NCDs)
    - Their etiology (the cause of disease) is complex and the result of a combination of genetic, physiological, environmental and behavioural factors.
    - The common pathophysiological (disturbed or abnormal function in an individual or an organ) mechanisms include oxidative stress (oxidative stress is the connection between pollution exposures and the eventual resulting damage to cells leading to disease*)* and systemic inflammation (chemical messengers promoting the immune system to respond are found widespread, which can cause inflammation).
    - There are multiple risk factors, a long latency period, a prolonged course of illness, and functional impairment or disability.
        - This includes neurological disease, including neurodevelopmental, and neurodegeneration,
- Air pollution is also linked to psychiatric illness, such as anxiety and depression.
- 90% of our time exposed to air pollution is indoors.
- Chemical exposures are worse indoors.
- Common exposures are volatile and semi-volatile organic compounds (VOCs and SVOCs) which are released from commonly used products used for personal, cleaning, furnishings, building, renovation and maintenance purposes, and also from furniture and other household items.

- The most common route of exposure is through inhalation:
    - Because most VOCs are lipophilic (oil soluble); they are easily absorbed from the lungs.
- VOCs are transported by the arterial blood to tissues throughout the body.

- Lipophilic VOCs can quickly accumulate in the brain and can affect function.
- The impact of VOCs may be significantly affected by variables like age, sex, genetics, physiological condition, or lifestyle.

Toxicology concepts have evolved:

- It has been generally accepted that once detectable, the response of an organism to a toxicant increases proportionally with the level of exposure until reaching an upper-limit or maximal-effect level.
    - the paradigm of toxicology is changing and is no longer limited to Paracelsus' principle of toxicology, that "*the dose makes the poison*" (this is known as a monotonic response, which means, a greater response is observed as the dose increases)
    - Nonmonotonic responses (a response may also occur at lower doses as well as at higher doses) also occur (e.g., endocrine disruptors) and one of the mechanisms is to impact on receptor (structure on the surface of a cell (or inside a cell) that receives and binds a specific substance that causes the cell to respond) function
- In signal toxicity, a foreign chemical only has to bind to a receptor on the cell membrane or inside the cell.
- Many chemicals can bind to receptors and cause abnormal cell signaling or responses, and changes cell function.
- Oxidative stress:
    - an imbalance in detoxification leading to an accumulation of reactive oxygen species (can also provoke damage to multiple cellular organelles and processes, which can ultimately disrupt normal physiology) and other free radicals in cells, leading to molecular damage
    - induced by VOCs even at levels typically found in the indoor air.
    - associated with indoor air pollutants and "sick buildings".
    - demonstrated in individuals complaining of poor indoor air quality associated with sick building syndrome.
    - always associated with systemic inflammation.
- Genetic phenotypes for detoxification are associated with cardiovascular, respiratory and neurological effects of air pollution.
- Given the compositional complexity of the cocktail of pollutant gases and particles we breathe from both ambient and indoor sources, there is scientific consensus that oxidative stress is an integrative biological pathway that bridges the causal gap between cause (the initial molecular trigger) and effect (adverse health outcome). What this means is that oxidative stress helps to explain how pollution exposures, which eventually result in

damage to cells, contribute to the development of environmentally linked diseases, including MCS.

TRP receptors were barely acknowledged and inadequately considered

Receptors are usually specific, responding to one particular molecular structure (unimodal), but TRP receptors are polymodal. They function as cellular sensors and can detect a wide spectrum of potentially harmful physical stimuli, such as temperature and mechanical or osmotic stress. More relevantly, they respond to biochemical stimuli, including mediators of inflammation and oxidative stress. In particular, TRPV1 and TRPA1 receptors are fundamentally involved in the molecular physiology (biological process essential to maintain the normal function of cells) of chemical perception. They sense and react to more than 130 different anthropogenic (mostly environmental pollution and pollutants from human activity) chemicals known to date.

- They are highly expressed in the olfactory and trigeminal nerve ending
- They are usually co-expressed and can sensitize each other. (Expression means that they are present; co-expression means the receptors exist together on the cell surface).
- When activated simultaneously, the effect can be synergistic. (When activated together, each receptor makes the other more reactive).
- They are upregulated by oxidative stress and systemic inflammation. (Oxidative stress and systemic inflammation increase the number of TRPV1 and TRPA1 receptors on the cell surface).
- Repeated, chronic activation following repetitive noxious stimuli, oxidative stress or inflammation can lead to upregulation and sensitization. (The more these receptors are activated, the more they are found on cell surfaces, and they become more sensitive).
- They are widely expressed **in the brain**, including such areas as the substantia nigra, hippocampus, hypothalamus, locus coeruleus, amygdala, limbic system and cortex.
    - involved in fear and avoidance behaviour, anxiety and depression.
    - upregulated TRPA1 and TRPV1 receptors are involved in the pathogenesis or pathophysiology of psychiatric disorders including anxiety and altered mood.

Studies on MCS missing from the INSPQ report

Almost half of MCS patients have comorbid migraines, up to 70% are asthmatic, and almost 90% report adverse effects from exposure to fragranced consumer products. This is significant because:

- up to 60% of asthmatics report that odors of perfumes and cleaning sprays provoke asthma symptoms

- 70% of migraine patients report that headaches are triggered by the odors of perfume, paints and gasoline.
- Having migraine headaches increases the likelihood of being an asthmatic, and vice versa, and one common denominator for this bidirectional association is the sensitivity to chemical odors.
- Both conditions are also impacted by air pollutants and TRPV1 and TRPA1 channels are implicated in their triggering mechanisms.

Genetic polymorphisms different genes within a population) predisposing to less efficient metabolism and excretion of commonly encountered environmental chemicals are more common in people who meet the criteria for MCS. These findings have not been completely consistent; however, a regression analysis published in 2019 reinforces the concept that a genetic risk related to phase I and II liver enzymes involved in xenobiotic detoxification can play a role in the pathophysiological route towards sensitization to chemical compounds in MCS. (If you don't detoxify well, then there is more damage, i.e., oxidative stress, which can sensitize the receptors that respond to chemical compounds).

- The INSPQ used the Bradford Hill criteria to rule out detoxification genotypes as a causation for MCS, but this does not rule out the significance of association and risk.
    - Significant association means that conditions are more likely than chance to occur together, which means shared mechanisms and risk factors.
- This is similar to the multiple studies in the literature showing an association with the genotype for detoxification and the risk for developing common noncommunicable diseases (NCDs), that are also associated with air pollution exposures.

Nevertheless, even in the absence of an abnormality among detoxification polymorphisms, oxidative stress and systemic inflammation are universally observed in MCS patients.
There is also evidence suggesting that the blood brain barrier (BBB) may be dysfunctional in MCS, which would enable greater chemical exposures in the central nervous system (CNS).

Onset of MCS

According to the INSPQ report, the proportion of subjects able to specifically identify a chemical exposure episode as a trigger for their MCS is rarely higher than 30%. It is not clear where this statistic was obtained, and it is not consistent with clinical experience.

- Many published papers report the onset of MCS following recognized or well-defined chemical exposures including indoor air contaminants caused by new construction or renovation of a home or office (63.2%), exposure to various solvents and cleaners (54%), indoor air contaminants (45%), followed by exposure to pesticides or agricultural chemicals (27.4%), and exposure to chemicals at work or engaged in hobbies (26.3%).

- This is an important point in the evaluation of causation according to the Bradford Hill criteria.

TRPV1 and TRPA1 sensitization has been consistently and repeatedly demonstrated in MCS.

TRPV1 receptors are heat sensitive and respond to capsaicin, the pungent ingredient in hot chili peppers that produces the sensation of heat. Capsaicin is also a well-known cough-inducing agent when inhaled because it provokes cough in a safe, reliable and dose-dependent manner by stimulating the TRPV1 receptors. The more sensitive the receptors on the sensory neurons lining the bronchial tubes, the more easily coughing can be provoked with capsaicin inhalation. Capsaicin inhalation challenge is a reliable clinical research tool with good short- and long-term reproducibility and has been used in clinical research for more than three decades.

Multiple papers have been published consistently demonstrating respiratory hyperreactivity in those who also meet the criteria for MCS, even when asthma has been ruled out by methacholine challenge. These patients demonstrate respiratory sensory hyperreactivity due to the sensitization of TRPV1 receptors. Follow-up after five and ten years later showed no reduction in sensitivity to inhaled capsaicin. Findings of capsaicin inhalation hypersensitivity in patients meeting the criteria for MCS have been published by centres in Sweden, Denmark and Japan.

There is one single-blind inhalant challenge study in MCS patients using acrolein that also demonstrated greater cough sensitivity than in controls, suggesting that TRPA1 receptor sensitization may be contributing to chemical hypersensitivity as well. TRPA1 receptors almost always are co-expressed with TRPV1 receptors and they interact with each other.

The INSPQ report reviews hypotheses regarding altered neural plasticity, mechanisms that lead to disturbances that affect the state of individuals and cause mood disorders, mediators of change and the hippocampus, but fail to review the literature demonstrating the role of pollution exposure, oxidative stress, systemic inflammation and the TRPV1 and TRPA1 receptors in synaptic plasticity and brain excitability. The authors did not mention that these receptors exist in the structures involved in neural plasticity. They also did not review the association of TRPV1 receptors with fear, anxiety or stress. These are the same receptors that have been shown to be sensitized in MCS.

Misinterpretation of functional brain scan imaging

Multiple studies employing functional brain scan imaging provide measurable evidence that patients with MCS process odors differently compared with normal, healthy controls, including the finding of prolonged recovery time after exposure. It is noteworthy that when challenged with chemical exposures, compared to controls**,** MCS patients demonstrate a stronger signal-

intensity reaction in magnetic resonance imaging (MRI) of the limbic system, and particularly in odor-processing areas such as the hippocampus, amygdala, and thalamus.

- These brain areas also express TRPV1 and TRPA1 receptors.

Functional MRI has also demonstrated that MCS patients do not habituate, i.e., adjust and get used to repeated sensory stimulation when compared to healthy controls, but instead show evidence of sensitization, as evidenced by increased reactivity to repeated, consistent stimulation.
A 2018 systematic review found consistent evidence that MCS patients have altered processing of ascending sensory pathways with overactivation in the limbic system, and olfactory and cognitive manifestations.
A 2019 systematic review identified nine studies that used functional imaging to assess cerebral responses to several different odorous stimuli and all demonstrated that odors are processed differently by MCS patients compared with controls.
A 2020 systematic review stated that the conclusions were not homogeneous (of the same kind, or alike) and are still uncertain and controversial. They did state that there was "a greater involvement of the activity of the limbic system and of the autonomic nervous system at the expense of cortical areas." What this means is that the more basic functioning parts of the brain were more active due to higher functioning areas of the brain.

- The majority of odors used in these functional imaging studies to stimulate a response are recognized agonists (stimulants) of TRPV1 and/or TRPA1 receptors.

Given the involvement of TRPV1 and TRPA1 receptors and evidence for sensitization, it is reductionist (arrive at simple conclusions) to conclude that, that the cause of MCS is psychogenic because the cortex is involved.

Central sensitization has also been evidenced in MCS, which is not surprising given that central sensitization involves the action of TRPV1 receptors. This may help to explain why fibromyalgia and MCS are frequently comorbid. Interestingly, increased hyperalgesia (an increased sensitivity to feeling pain and responding to painful stimulation) and temporal summation of pain can be observed in MCS patients, even without other comorbid disorders.

Association does not mean causation: Bradford Hill criteria for causation

Whether oxidative stress is the cause or consequence remains elusive, but mounting clinical and preclinical evidence now indicates that oxidative stress may be a major component of anxiety pathology. Therefore, it is not surprising to find that biomarkers of inflammation are reliably elevated in a significant proportion of patients with major depression disorder, bipolar disorder, anxiety disorders and post traumatic stress disorder (PTSD), and may be a causal factor driving behavioral symptoms. However, the current literature suggests that air pollution may be a risk factor for depression, anxiety, and suicide. Furthermore, a systematic review and meta-analysis

found an association between long-term exposures to PM2.5 (defined as fine particulate matter that are 2.5 microns or less in diameter) and depression and anxiety.

A statistical association between two variables merely implies that they are more likely than chance to be related or linked in some way. It does not necessarily imply that one ***causes*** the other.

The INSPQ report used the Bradford Hill criteria for causation to rule out detoxification genetics as the cause of MCS and concluded that the cause is psychiatric. Given that the most significant identifying characteristic of MCS is chemical sensitization, the Bradford Hill criteria should be applied to determine:

a) whether sensitization to chemicals is a cause for MCS
b) whether the association of psychiatric conditions meets the Bradford Hill criteria for causation.

Temporality (the state of existing within or having some relationship with time) is perhaps the only criterion which epidemiologists universally agree is essential to causal inference. The cause cannot follow the resulting condition, which means the disease cannot begin before the cause. It is therefore important to note that the INSPQ report failed to look at the epidemiological evidence for the association of psychiatric conditions and MCS. Not all MCS patients have a current psychiatric disorder and not all published research finds an association between chemical intolerance and mental illness. Also, reports as to whether psychiatric disorders pre-exist the onset of MCS are not consistent. In fact, the development of MCS can precede the onset of mental health symptoms.

The position of the INSPQ that VOCs do not enter the brain is wrong. The absence of any significant literature review of the TRPV1 and TRPA1 receptors well-known to be stimulated and potentially sensitized by chemicals has contributed to biased conclusions.

Establishing causation (the act or process of causing something to happen or exist) is critical because it influences the delivery of good medical care. A finding of causation influences decisions related to diagnosis, treatment and prognosis and it may have medical-legal ramifications, regarding personal injury, human rights claims for accommodation and third-party disability claims.

As a result, the conclusion of the INSPQ that the etiology of MCS is psychogenic is wrong and potentially detrimental to patient care, professional and public education and appropriately guided research.