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International Journal of Hygiene and Environmental Health 229 (2020) 113544

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Reply to the letter to the editor by Tuuminen et al. (2020), "Indoor air nontoxicity should be proven with special techniques prior claiming that it may cause a variety of mental disorders."

Dear Editor,

I have taken part of the letter to the editor by Tuuminen et al. (2020) with great interest, and I am thankful for the opportunity to reply to the letter. This enables clarification of key aspects of my article as I address issues raised by these authors based on a large number of misinterpretations and some inaccuracies on their behalf.

1. A psychobiological rather than a biomedical perspective

Non-specific building-related symptoms (NBRS) and chemical intolerance (CI) are commonly referred to as idiopathic environmental intolerances since there is no clear link with organ pathology or dysfunction (Van den Bergh et al., 2017). Whereas a biomedical perspective assumes a clear link of that kind, a psychobiological perspective does not. The latter perspective is open to the possibility of psychological factors (e.g., cognitions, emotions and everyday behaviors) playing an intervening role in the adverse response to the exposure. A psychobiological perspective does not in principle exclude any type of exposure, and can indeed account for the impact of, for example, bacteria, dust, fungi and their secondary metabolites. Rather than having a toxic effect, the levels at which the exposures typically are present in NBRS and CI are more likely to evoke one or several of the body's defense mechanisms described in the article (Nordin, 2020). Hence, chemical and biological compounds as well as psychological and social exposures may act as stressors if interpreted by the body/mind as potentially hazardous, and evoke a defense that we refer to as symptoms. In this context, chemical/biological compounds and psychological/social exposures may interact and thus intensify the response.

Tuuminen et al. (2020) question the choice of viewing symptoms only from the psychological perspective. In fact, all described mechanisms in the article (Nordin, 2020) are biological and psychological in nature. From my biopsychosocial perspective, it is not meaningful to separate biological and psychological processes in health and disease since they constantly interact and guide each other – a perspective that has been around for close to half a century (Engel, 1977). Tuuminen et al. (2020) mention the work of Martin Pall. According to his model on oxidative stress, short-term stressors may increase nitric oxide levels and initiate illness such as CI, chronic fatigue syndrome, fibromyalgia and posttraumatic stress disorder. These stressors, due to the nitric oxide product, peroxynitrite, initiate a complex vicious cycle mechanism that is responsible for chronic illness (Pall, 2007). This is a good example of yet another psychobiological mechanism of relevance for NBRS and CI, since oxidative stress can interact with various types of stressors, including mental stressors (Münzel and Daiber, 2017). The reason for not including the model of oxidative stress in my review article (Nordin, 2020) is that there still is limited empirical support for it regarding NBRS and CI. However, hopefully, studies will be conducted to carefully test this interesting model in these intolerances.

2. Protective defense mechanisms rather than toxicity

We all possess various types of protective mechanisms to defend us from exposures that can be identified by the body/mind as potentially harmful, irrespective of whether they, per se, are harmful (e.g., covid-19) or not (e.g., pollen in allergy). Acting as a stressor, these exposures evoke protective responses that we refer to as adverse symptoms. This will take place irrespective of whether the exposure reaches toxic levels or not. Tuuminen et al. (2020) state in their letter to the editor that "Occupants become ill in water-damaged houses infested with toxin producing microbes". Although it is well documented that water-damaged houses infested with microbes constitute a risk factor for NBRS (Mendell et al., 2011), one should be careful in claiming that is due to an underlying toxic mechanism. Everything around us is potentially toxic (including microbes), but, importantly, it is a *matter of dose.* Claiming that a certain exposure is toxic just because its substance can have a toxic impact at a high dose is meaningless unless it is demonstrated that the dose at hand is actually toxic. In a similar vein, Tuuminen et al. (2020) oppose a statement in which I claim that there is no scientific support for electromagnetic fields from everyday electrical devices having an impact on health, and that there instead is support for expectations (nocebo) underlying symptoms attributed to these exposures (Rubin et al., 2010). Again, it is a *matter of dose.* Without doubt, long-term exposure to high level of electromagnetic fields is hazardous. However, persons who attribute symptoms to everyday electrical devices are not typically exposed to such doses.

Organism such as bacteria and fungi as well as chemical emissions from indoor material should be kept at a minimum in indoor environments, perhaps in schools in particular, since they are associated with health symptoms. However, rather than toxicity, the symptoms are in most cases likely to be explained by our defense mechanisms such as neurogenic inflammation (including neurogenic switching, activation of the autonomic nervous system, axon reflex, and interaction effects between various stressors), sensitization, classical conditioning, symptom misattribution, somatosensory amplification and nocebo. Empirical and theoretical support for these mechanisms is provided in the article (Nordin, 2020).

It is important to point out that mechanism of toxicity can take place in indoor environments, but until there is convincing support that such a mechanisms is the common cause in NBRS and CI, it may be better to take a psychobiological perspective for which there is support. Declaring the exposure as toxic if such a dose is not reached is, in fact, highly irresponsible since the worries it will trigger may initiate a nocebo effect, which, in turn may initiate neurogenic inflammation, sensitization, etc (Nordin, 2020). Nevertheless, if there is good reason to suspect that the exposure dose is sufficiently high to cause a toxic effect,

https://doi.org/10.1016/j.ijheh.2020.113544
Received 14 April 2020; Accepted 16 April 2020
Available online 23 April 2020

the techniques proposed by Tuuminen et al. (2020) for assessing exposure level of potential toxins and toxic impact may well be applied. I am thankful to Tuuminen et al. (2020) for their update on conditions in which the level of indoor microbes, such as Stachybotrys, emit substances as liquid vesicles with concentrations of potential toxicity. In such conditions, a careful toxic investigation can be motivated.

As an argument of toxicity in NBRS and CI, Tuuminen et al. (2020) bring up substances (e.g., phthalates) that after long-term exposure may cause reproductive toxicity in the next generation to come. Although toxic exposure of this kind is a serious concern, it cannot explain symptoms of NBRS and CI, which are evoked, more or less, immediately after exposure.

3. Not a case of mental disorder

It was early recognized that that an outbreak of the common cold and exacerbation of an allergic response are more likely to occur in conditions of mental distress (Cohen et al., 1991; Nagata et al., 1999). Thus, psychobiological processes underlie these conditions. Notably, it is my personal experience that persons with NBRS and CI commonly report that their problems started when being in a condition of distress, and that their problems terminated or decreased considerably when being relieved of distress. Although various stress-related conditions of mental ill-health (e.g., burnout, anxiety and depression) have been shown to be risk factors for NBRS and CI (e.g., Palmquist, 2017), it is important to point out that NBRS and CI are not mental disorders or cases of pathologic personality. It is also important to differentiate risk factors from causes. The defense mechanisms that we all have access to, described in my article (Nordin, 2020), are not more of a sign of mental disorder than are cases of the common cold or allergy. Rather, when being in distress our defense mechanisms are more prone to become activated. The associations between distress and NBRS/CI may well be bidirectional due to the adverse impact these intolerances can have on quality of life (Söderholm et al., 2011, 2016), and may well result in a negative spiral.

4. Avoidance of exposure or self-controlled exposure?

If we experience symptoms in a certain environment, we will as a natural response avoid such an environment. In severe cases of NBRS and CI in which the intolerance has generalized to various odorous and pungent substances, the avoidance will have considerable impact on the ability to participate in society (Söderholm et al., 2011, 2016). However, this dilemma for the individual with severe NBRS/CI is more complex than so. Whereas avoidance may have the positive short-term effect of no symptoms being evoked, it may in severe cases contribute to permanent the adverse reactions to the exposure, and possibly generalize to other exposures. Persons with mild NBRS/CI may recover spontaneously if the exposure is removed, for example at work, at home or at school. However, the situation is different for the patient with severe NBRS/CI. Assuming that the exposure evoking the symptoms does not reach a level of toxicity, total avoidance may, in fact, strengthen the exposure–symptom association; a strengthened non-exposure–non-symptom association will also strengthen an exposure–symptom association. However, as a starting point, it is important to *eliminate the biological or chemical substances* that evoke the symptoms. Thus, exposure to these substances that the afflicted person cannot control him-/herself will continue to evoke symptoms. This includes not only anaphylactic reactions, but all types of adverse reactions. If the afflicted individual with severe NBRS/CI will have a chance to recover from the intolerance in the long-term, the person must relearn the exposure–symptom association to an exposure–non-symptom association ("re-wire" these neural networks), preferably with professional help. A parallel to this is immunotherapy in allergy (Jutel et al., 2015).

5. Long-term cortisol release as a factor of health problems

Tuuminen et al. (2020) note that corticosteroids are used in clinical medicine to reduce inflammation, implying that corticosteroids are beneficiary also in NBRS/CI. However, this negative feedback loop of corticosteroids, predominantly cortisol, is only one of its roles. Cortisol plays an import role also in consequences of chronic stress. It is released as an end product of the hypothalamic–pituitary–adrenal axis. In chronic stress, hypothalamic activation of the pituitary gland changes from corticotropin-releasing hormone-dominant to arginine vasopressin-dominant, and cortisol levels remain raised due at least in part to decreased cortisol metabolism. Hence, chronic exposure to stress results in long-term cortisol exposure becoming maladaptive, which is known to lead to a broad range of health problems (Russell and Lightman, 2019). To quote Tuuminen et al. (2020) in this context, "this general knowledge seems to be at odds with the view of the authors".

6. Concluding remark

Using many of their own words, the authors of the letter to the Editor (Tuuminen et al., 2020) seem to downplay the collected evidence on the interplay between psychological and biological factors regarding moldy (and various other) environments. This biased attitude and denial inevitably endangers the health of the patients and kicks us back towards the strict biomedical times when asthma was considered as a hysteria.

Declaration of competing interest

Declaration of interest: none.

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