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Review

Immunological and toxicological effects of bad indoor air to cause Dampness and Mold Hypersensitivity Syndrome

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Abstract: Water damage in buildings is a universe problem. Long-lasting or cumulative stay in water damaged buildings is a serious health hazard. Exposure to fungal and bacterial toxins, nanoparticles from dampness microbiota as well as decay products from construction materials together with biocides used for cleaning will first cause irritation of the mucosa and later chronic inflammation with stimulation or inhibition of the compartments of the innate and/or adaptive immunity. Mold-related disease has been called Dampness and Mold Hypersensitive Syndrome (DMHS) because hypersensitivity is the cornerstone feature of the disease. The background of hypersensitivity is both immunologic processes and hyperactivation of sensory receptors, neurogenic inflammation and central sensitisation. Immunologic hypersensitivity can occur either through the production of mold specific IgE-class antibodies, which is rare, or through sensitisation and proliferation of T and B specific lymphocyte clones. Immunological switch to Th2/Th17 arm of adaptive immunity often occurs. DMHS is a systemic and multi-organ disease where involvement of mucosa of pulmonary or gastrointestinal tract is central to the pathology. Symptoms include recurrent infections, chronic rhinosinusitis, swelling of the sinuses, irritation of the eyes and skin, voice problems, chronic non-productive cough, neurological symptoms, joint and muscle symptoms, irritable bowel syndrome and cognitive problems. Underdiagnosed or neglected continuous insidious inflammation may lead to Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS) especially when trigged by new infections or even vaccination. Multiple Chemical Sensitivity (MCS) may also develop, however in the later stages of the disease. Chronic cough is sometimes diagnosed as asthma if the criteria for asthma are met. Non-productive cough may also

manifest allergic alveolitis, which is often overlooked. Avoidance of new exposure to dampness microbiota is crucial for recovery. We review the underlying toxicological and immunological mechanisms that are central in the pathology of DMHS.

Keywords: dampness microbiota; asthma; allergic alveolitis; Dampness and Mold Hypersensitivy Syndrome; inflammation; mucosa

1. Water damaged buildings: Why is the problem?

Nearly 45 years ago, the energy crisis forced the Western world to think about energy-saving solutions. As a result, bottle-like buildings with linings made of plastic materials as vapour barriers were constructed. At the same time, natural air replacement has been changed for mechanical ventilation to recycle and filter indoor air and return warm air back. In the 1970s new and poorly studied building materials, adhesives, glues, etc. have been introduced by building industry.

For example, in Finland, in the 70's, building contractor training has been pushed down and buildings were designed to be poorly adapted to the harsh climate conditions. Buildings were built i.e. with flat roofs and cast plinths; the control of the constructions has been inadequate, and schedules were unrealistically tough to make the concrete dry completely. The use of air conditioning machines that may cause accumulation of water condensation along with the irregular filter replacement may cause over the years the growth of a moisture microbiota in homes and public buildings [1]. Already in the 1950s, moisture damage has been reported particularly in the base of the building that was caused by poor design and construction [2]. Climate change and abundant rainfalls may also contribute to increasing moisture damage problems [3].

In Norway, it has been found that up to 30% of residential buildings can be moisture damaged [3]. Similar estimates have also been published by the WHO highlighting that moisture damage is more common in poor residential areas [4]. In the United States it has been found that older homes without air conditioning are more likely to be moisture damaged [5]. Also, in public buildings and workplaces moisture damage is prevalent, but the extent of the damage is difficult to estimate [4]. In Finland, moisture damage occurs in at least 25% of school buildings [1] and even in 50–80% of small houses [2]. Dampness microbiota (DM) are not demanding for nutrients as virtually all organic matter is apt to be an energy source. Wood, plasterboard cardboard, wallpaper and other cellulose materials, and even ordinary room dust is apt nutrient for many microbes. For example, concrete, brick, lightweight barge and building boards may have microbial growth if there is dust or other dirt on the surface [6]. One should also consider the storage and preheating of home by mold-contaminated fire woods that is stored inside the building [7].

2. Clinical presentations of Dampness and Mold Hypersensitivity Syndrome

Mold-related disease is multifaceted and has variable terminology. The term "Sick Building Syndrome" [8] is widely used in the context with DM. In a comprehensive review, the terms used for indoor air illness are summarized as follows: Mycotoxicosis, Mixed Mold Mycotoxicosis, Indoor Mold Sensitivity, Toxicity, Toxicity Induced Loss of Tolerance (TILT) [9], Chronic Inflammatory

Response Syndrome due to Water Damaged Buildings (CIRS WDB or CIRS) (Global Indoor Health Network (GIHN, [10]). In Finland it was called Dampness and Mold Hypersensitivity Syndrome (DMHS), and the clinical criteria have been laid [11]. In this review, we focus on the etiopathogenesis of DMHS trigged by biotoxins and structural components of DM. We will consider more deeply pulmonary manifestations of DMHS because immunological and toxicological effects of DM on mucosa of respiratory tract are studied the best.

The susceptibility to disease may be genetic [12] or even epigenetic. In addition, cumulative exposure and the duration of the exposure is also relevant for morbidity [11]. Deficiency in some micronutrients such as vitamins and/or microelements as the factors predisposing to DMHS, have not yet been thoroughly studied.

It is well known that stay in a water-damaged building can cause variable symptoms such e.g. as eye, ear and skin irritation, respiratory symptoms, increased infection sensitivity, pulmonary function changes, asthma, allergic alveolitis [3,4,8,10,13–18]. At the beginning exposure to DM typically leads to mild irritation symptoms that are reversible. At early stages persons can experience severe fatigue that does not improve with sleep. Avoiding exposure usually corrects the situation. If exposure occurs, for example, at work, the weekend relieves the symptoms, and the condition is called SBS. As exposure continues, the symptoms worsen and for example, the weekends become too short for recovery. Treatment of chronic disease is difficult because the person may experience the breakdown of the tolerance. Persons start to react towards many factors they could tolerate earlier. The symptoms of hypersensitivity may be symptom exacerbation during rainy and humid seasons [15,19].

Neurologic symptoms are common; joint and muscle pain and even overt rheumatoid arthritis is possible [10,20,21]. Development of autoimmune conditions and cancer has been reported [21]. Underdiagnosed or neglected continuous insidious inflammation may lead to ME/CFS especially when trigged by new infections or even vaccination [22]. MCS and Hypersensitivity to Electromagnetic field may also develop, however in the later stages of the disease [11]. Domestic animals and pets may also acquire disease in a mouldy environment [23].

3. Pulmonary manifestations are very common in Dampness and Mold Hypersensitivity Syndrome

3.1. Upper respiratory system

Chronic rhinitis is a symptom that lasts more than 12 weeks [12,24]. In vasomotor rhinitis, the mucosa reacts to various physical or chemical stimuli with sneezing, nasal discharge and congestion [24] and/or itching [12]. In DMHS allergic rhinitis may occur when an allergen, such substances from DM [15] reacts with specific IgE-class antibodies forming immunocomplexes on the surface of mast cells and basophils. When the person gets sensitized (s)he may react also to outdoor molds. Often, the symptoms present as rhinoconjuctivitis. The majority of asthmatics have also chronic rhinitis. Allergic rhinitis increases the risk for asthma [25].

Exposure to DM may associate with nasal polyposis [26]. Formation of biofilms on mucosa of sinus cavities has been considered as a major pathological hurdle [26]. Biofilm formation maintains chronic inflammation with an output of pro-inflammatory cytokines, the interleukin-17 in the first place [27]. Often, chronic rhinitis is unilateral, serous or purulent. Post nasal drip symptoms may last for years even after interruption of the exposure (T. Tuuminen, unpublished data).

3.2. Recurrent upper airway infections

Rrecurrent or unusual infections and especially infections of respiratory tract are pathognomonic for DMHS [4,11,13,15–17,28]. Recurrent infections are considered those that occur more than 3/year and require medical treatment. In small children recurrent otitis media and sinusitis in adults are diagnosed in a great majority of exposed individuals. Bronchitis are also common [11,29]. When recurrent infections occur, health providers should get an alert of the possible infestation with DM at homes, nursing homes, schools or workplaces.

3.3. Lower respiratory system

Asthma is a chronic lung disease involving bronchial mucosal inflammation and smooth muscle hyperactivity which leads to bronchoconstriction sensitivity. Common symptoms include cough, mucous discharge, dyspnoea and wheezing [30]. Asthma is characterized by the accumulation of inflammatory cells such as mast cells, eosinophils, neutrophils, macrophages and T-helper cells on the mucous membrane and the underlying tissue. Pathophysiology of asthma is heterogeneous [30]. Cytokines and chemokines play an important role in pathogenesis. High serum IL-17A concentrations correlate with asthma severity and steroid resistance [31]. Asthma tends to be inherited by many factors. Diagnosis is based on auscultation, Peak Expiratory Flow (PEF), spirometry with bronchodilation and response to glucocorticoid therapy. Differential diagnosis requires X-ray imaging of the lungs and blood tests.

Exposure to DM is known to cause elevated risk for asthma exacerbation and new asthma [4,13,15–17,28]. The newborn's exposure to DM increases the risk of asthma in a child [32]. Increased admission of elderly people to hospital care due to asthma may associate with mouldy environment at homes [33]. With regard to asthma, a causal relationship between DM exposure and morbidity has been recently reviewed [34]. When asthma is caused by the exposure to DM, the symptoms may exacerbate at high outdoor mold content i.e. in late summer and autumn [15]. Symptoms are aggravated by rainy episodes and after the rainy days [15].

Poor indoor air may cause allergic alveolitis [4,12,17,35–38]. This condition is also called hypersensitivity pneumonitis. Similar condition caused by massive exposure to outdoor molds in so-called farmer's disease was called Extrinsic Allergic Bronchiolo- Pneumonitis [39]. This condition has much in common with allergic alveolitis caused by indoor DM, although in the latter the person is exposed to biotoxins in addition to organic compounds. In our opinion hypersensitivity pneumonitis is better to call panbronchopneumonitis to highlight the involvement of all the pulmonary components such as bronchi and small bronchioli, parenchyma and interstitium. This condition refers predominantly to cell mediated lung disease that may be caused by inhalation of nanoparticles of organic content. As consequence of the exposure to DM the damage occurs to alveoli, terminal bronchi or interstitium. Inflammatory reaction will follow the exposure, but serum IgE levels are often normal [40]. Bronchoalveolar lavage (BAL) samples reveal elevated cytokine IL-8 production. CD4+ and CD8+ T lymphocyte counts are generally increased [40,41]. The cause of the disease is variable, often with fever, shortness of breath and cough [41].

Allergic Bronchopulmonary Aspergillosis (ABPA) is a given diagnosis often used instead of DMHS. ABPA is considered as an immunological pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus* which is a common species within DM, however not the only. The disease is

manifested as poorly controlled asthma, recurrent pulmonary infiltrates and bronchiectasis [42]. For ABPA, no agreement of the criteria nor treatment modalities are yet achieved within American Academy of Allergy, Asthma & Immunology [43]. It is however evident that the presence of IgE-class antibodies should be detected to set the diagnosis of ABPA, but in our experience, this is a rare finding in DMHS. To emphasise that the etiology is broader this condition has been later called Allergic Bronchopulmonary Mucosis, ABPM [44]. By contrast, DMHS is a broader definition than ABPA/ABPM. DMHS may associate with other co-morbidities, such as e.g. neurologic, rheumatologic or g-i tract disorders, especially when DMHS goes chronic.

ODTS (Organic Dust Toxic Syndrome) resembles allergic alveolitis and always manifests with fever. Common symptoms of over half of the patients are cough, laryngitis, tiredness, muscle and joint pain, headache, eye irritation, shortness of breath, nasal congestion, laryngeal irritation, itching and flushing, spasms and sometimes wheezing. Symptoms usually occur 4–8 hours after the exposure. Symptoms in ODTS are usually milder than those of allergic alveolitis. Symptoms may occur even from a single exposure. Unlike allergic alveolitis, the symptoms of ODTS disappear within 1 to 3 days and do not leave fibrosis or permanent changes in lung activity [45]. Diagnosis involves largely the same approaches as for allergic alveolitis. Radiological changes and lung function test abnormalities are not observed. In BAL, an increase in polymorphonuclear leucocyte and macrophage counts is observed, but there is no lymphocytosis indicative for immunoactivation [45]. ODTS occurs seldom in DMHS and is mentioned here for differential diagnosis.

4. Dampness microbiota

Dampness microbiota (DM) comprise molds, yeasts, Gram-positive and Gram-negative bacteria species. The following genera and species are often found: *Aspergillus, Penicillium, Fusarium, Stachybotrys chartarum* ("toxic black mold"), etc. Gram-positive bacteria may include *Actinomycetes, Nocardia, Mycobacteria* and *Bacilli*. DM is a so-called ecological community where species may vary over time depending on the microbial unrestricted competition for the availability of nutrition factors [4]. When humidity increases, microbial growth destroys building materials, resulting in volatile organic compounds (VOCs). DM itself emit into the air its own metabolism products (mVOC, microbial). Structural mold components, e.g. (1,3)-D-β-glucan [46] and galactomannans are modulators of the immunological system. Gram-negative bacteria produce lipopolysaccharide (LPS), a powerful activator of the immunological system. Molds secret exotoxins that split organic molecules, such as starch, cellulose and lignin. Exotoxins are strong allergens because they are proteins. They are active also when the soaked surface become dry [10]. DM may cause activation or deprivation of the immunological system, microbial colonization or sometimes even invasive infections [4,8,10,47–51]. There are thousands of studies on this topic; only GIHN [10] cites more than 400 peer-reviewed publications.

The fragments of mold spores are small, about 2–10 μm. Aerodynamically, they can land on the small airway epithelium or penetrate even deeper into the lungs. On arrival at alveoli, the particles and toxins may reach the circulation system and thus be distributed to other organs [52,53].

In a moisture damaged building, a person is exposed to mycotoxins and other volatile components through the skin, mucosa or inhalation. Mycotoxins are in aerosol [54,55]. Air conditioning and heating enhance the aerosol particle movement [10]. Inhalation exposure, i.e. exposure through the respiratory tract is more dangerous than oral exposure because inhaled toxins

avoid the enterohepatic circulation where they may be detoxified by liver. Mycotoxins can alter the blood brain barrier (BBB) and enter the brain directly via *Nervus olfactorius* [56].

Many mycotoxins are lipophilic and are stored in adipocytes and in the brain, which is composed of various neurolipids. When the body's capacity to acquire lipophilic toxins is saturated, it starts to react to hydrophilic substances [10]. Mycotoxins are small molecules, secondary metabolites of molds that can cause adverse effects on animal and human cells at very low concentrations [4,15,57]. Several mold genera such as *Aspergillus, Penicillium, Fusarium, Alternaria and Stachybotrys* produce mycotoxins [8,15]. Mycotoxins can up- or downregulate several genes, can inhibit DNA and RNA and protein synthesis, cause oxidative stress, some mycotoxins are vasoactive, some have cardiovascular effects, and many affect the immunological and (neuro)endocrine system [10]. Mycotoxins activate NLRP3 inflammasome [58]. Their effects on cellular levels are comparable to the effects of ricin, tobacco and asbestos [59] and can be used as biological weapon.

Cytotoxic and immune-modifying effects are dependent on toxin concentrations [4,8,15,48,60] Toxins can potentiate the effects of each other [4,48]. Although respiratory effects of dampness microbiota were regarded as mycotoxicosis [8,48] a broader definition should be used. The term mycotoxicosis should be replaced by biotoxicosis [10] because bacterial toxins play also a big role.

Trichothecenes and gliotoxin are probably the strongest known toxins [15]. Inhaled, toxic effects occur at a lower concentration than at oral administration [15]. T-2 and deoxynivalenol (vomitoxin) belonging to trichothecenes impair the immune response to respiratory infections [61]. T-2 toxin, patulin, penicillinic acid, aflatoxin, satratoxins have been shown to affect macrophage function and are cytotoxic [54]. Trichothecenes cause immunosuppression of lymphocytes and stimulate macrophages to produce IL-1β. These toxins inhibit protein synthesis in ribosomes, impair mitochondrial function, activate MAP kinase (MAPK) and induce apoptosis [59]. *S. chartarum* spores have been shown to affect apoptosis (programmed cell death) [56,62,63] while *S. californicus* spores cause cell cycle arrest [64].

The expression of genes was studied in the nasal mucosal epithelial cells and peripheral blood mononuclear cells from symptomatic and non-symptomatic individuals. It has been found that in symptomatic individuals there was increased expression of a few genes affecting calcium trafficking and MAPK signal transduction [65], neutrophil influx, production of TNFα cytokine, and immunosuppression [66].

Bleaching used for remediation, e.g. chlorine-containing biocides makes dampness microbiota more toxic and mutagenic because mycotoxins become better soluble in fat and therefore better penetrate the skin and stored in the adipose tissue and in the brain [10].

5. Immunologic responses to DM

The immunological effects of the components of dampness microbiota are multilevel and partly even contradictory because they may inhibit and stimulate the innate and adaptive arms of immunity system [48,51,67,68]. The net effect depends on the composition of mycotoxins and on the growing species in the building. In different buildings, the ecological system is different. Therefore, the principles of serology applied from infectious diseases are generally not suitable for the diagnosis of a disease caused by dampness microbiota. Antibodies detected to mold species may only be indicative for the contact but do not have diagnostic value. In other words, increased antibody levels

poorly correlate with the occurrence and severity of the disease. Immunological response caused by dampness microbiota is very different from that of infections, since the presentation of antigens by dendritic cells to T lymphocytes is defective [10]. Generally, immunological responses to dampness microbiota is either of the type I (immediate reaction, e.g. IgE-mediated asthma, allergic rhinitis, Gell and Coombs classification) or the IV type, delayed, cell mediated response (allergic alveolitis). Importantly, the shift of Th1 immunological arm to Th17 immunity is associated with tissue damage [41]. Immunocomplexes are also found (Type III) with clinical signs of vasculitis (T. Tuuminen, unpublished data).

Atopic individuals are more susceptible to develop asthma through IgE mediated response. However, only a small proportion of the patients develop allergy to the molds [4,11]. In one study, IgE class antibodies to different species were found in 30% of asthmatics [69]. In other studies, IgE antibody positivity was reported in only 10% [70]. The development of asthma has traditionally been studied on the basis of the mechanism mediated by allergens. However, there are strong indications that dampness microbiota can trigger pulmonary problems by allergen independent mechanisms [71,72].

Respiratory epithelial cells are an important protective barrier against stimuli. The epithelium acts as a mechanical protection and the cells secrete the mucus that removes foreign particles. These cells also secrete antimicrobial peptides and proteases that neutralize harmful agents [59]. The spermatotoxic effects of toxins have been described [73,74]. The tubular structure of the mammalian sperm tails and of the ciliated cells is identical [75], so the effects of myxotoxins on the spermatozoid cells can be extrapolated from the ciliated cells [76,77].

After the inhalation, the components of dampness microbiota (DM) activate several Pattern Recognition Receptors (PRR) on epithelial, macrophage and dendritic cells [78]. The most important of these are TLR2, TLR4 and TRL9 (Toll Like Receptors) [78,79]. As a result of this activation, an inflammatory process is initiated, whereby the cells produce immune mediators such as TNFα, interleukin-1β, chemokines and adhesion molecules [59]. Continuous overproduction of these pro-inflammatory molecules will damage the surrounding tissues and maintain chronic inflammation [80].

Many toxins are cytotoxic and may interfere with the opsonization of xenobiotics and inhibit phagocytosis by macrophages [81]. Because of this, macrophages may not be as efficient as in infections. For example, the *Aspergillus fumigatus* inhibits the action of dendritic cells [82].

Mannose binding lectin (MBL) is an important PRR structure. It is activated by the binding of β-glucans and galactomannans [46,83]. When this activation starts, its control is problematic. The maker of activation of innate immunity is the activation of the complement cascade with the elevated C4a concentrations as a fingerprint [84]. Macrophages produce transforming growth factor (TGF)-1β, matrix metalloproteinase-9 (MMP9). Neutrophils release proteolytic enzymes, such as serine proteases, and MMP9 that acts on the destruction of the alveoli, leading to chronic pulmonary fibrosis [46,59,79,82,83]. Pro-inflammatory cytokines also activate basophils and mast cells that release components of asurophilic granules such as histamine and bradykinin. The release of these bioactive amines can either be IgE mediated or without IgE. The most important feature of the pathogenesis is silent chronic inflammation, as well as oxidative and nitrosative stress reactions leading to cellular hypoxia and to the dysfunction of ion channels [47,51,67,79,85].

Interleukins and chemokines trigger adaptive immune response, e.g. proliferation of T- and B lymphocytes and memory cell formation. T lymphocytes differentiate into the Th17 subset.

Interleukin-17 produced by these cells together with TNFα attracts white blood cells to the inflammation site. The Th17 subset associates with autoimmunity and maintains inflammation [86].

Significant changes have also been observed in the impairment in B cell profiles [48]. Isolated mononuclear cells in upper respiratory tract of patients exposed to DM produce more IL-17, IL-10, TGF-β and MIP-1β molecules [87]. A particularly interesting finding of epidemiological and experimental models is that β-glucans exacerbated allergic asthma and promoted the Th2/Th17 immunological shift leading to steroid resistance [79].

6. Morphologic findings

Studies of BAL fluid in rodents exposed to *Stachybotrys* spores demonstrated inflammatory changes in bronchioles and alveoli [88] and elevated counts of macrophages, neutrophils and lymphocytes, as well as increased levels of inflammatory cytokines [89]. Exposure of experimental animals to DM increased protein and lactate dehydrogenase levels in BAL and in the lung lesions [4].

In humans, histopathological changes resulting from DM exposure have been meticulously described [39] but these findings seem neglected by medical community. The pathology of hypersensitivity pneumonitis, or panbronchopneumonitis, or extrinsic allergic bronchilo-alveolitis (as has been named by the authors) was described. The authors performed electron microscopy in open lung biopsies of 13 patients with the so-called farmer's lung and other mold exposure. "Eleven of the patients had farmer's lung and two had been exposed to other mouldy dust. Numerous lymphocytes, macrophages and giant cells were present both in the alveolar and bronchiolar lumina. Bronchiolar changes included loss of microvilli on the ciliated cells, granulomas, detachment of basal cells from each other, as well as disintegration of the basement membrane. In the alveolus, hyperplasia and hypertrophy of type II (granular) pneumocytes often loosely connected with the basement membrane were frequently demonstrated. Disintegration of the basement membrane accompanied by detachment of the pneumocytes. In the interstitium lymphocytes, mast cells and plasma cells predominated. The size and shape of lymphocytes were variable. In addition, some lymphocytes with pseudopods were detected both in alveolar lumen and in the interstitium. Mast cells were found in close connection with plasma cells. In two patients there were granulomas consisting of mast, plasma and giant cells. Foreign material resembling hyphal fragments was found in the giant cells of two patients" (cited with minor abbreviations). The authors concluded that the presence of numerous plasma cells in the lung parenchyma suggested the possibility of local antibody response caused by exposure to inhaled antigens.

Another study described a post-mortem examination of a bagpipe player who died from acute respiratory distress syndrome, hypersensitivity pneumonitis with diffuse alveolar injury and fibrosis of the interstitia. *Paecilomyces variotti, Fusarium oxysporum*, *Penicillium* species, *Rhodotorula mucilaginosa and Trichosporon mucoides* were isolated from the instrument. but microbial growth was not detected in the lung tissue [90].

In patients exposed to DM analysis of BAL revealed lymphocytosis and decreased CD19+ leukocyte counts in the peripheral blood sample [91]. In the BAL sample of patients with AA, a decreased CD4+/CD8+ ratio was found [91].

7. Practical considerations

Importantly, because mycotoxins are often cytotoxic, the lymphocyte count in BAL may be much lower than in other allergic alveolitis presentations, e.g. due to the exposure to other organic matter. In allergic alveolitis caused by DM imaging criteria may not be met either [18]. Changes in CD4+/CD8+ T lymphocytes, elevated IL-17 [87,91] and delayed cell-mediated hypersensitivity [92] are typical findings in the pulmonary pathology. The worst case scenario is that chronic inflammation turns to irreversible fibrosis [90].

Respiratory manifestations and rhinosinusitis may be long-lasting and difficult to treat [18]. The gold standard for treatment is avoidance of a new exposure [40]. It has been shown on a cellular level that the disease exacerbates with a continued exposure [40]. Remediation of a workplace prevents new workers from getting respiratory diseases, but the person once sensitized might not tolerate the air in the remediated building. Persons exposed to DM with chronic rhinosinusitis or respiratory problems are recommended to be placed in another workspace instead of just remediated building [18]. Noteworthy, movables contaminated with biotoxins can maintain symptoms [17].

Workplace PEF is still a diagnostic method for occupational asthma, at least in Finland. However, there are important ethical considerations to continue with this investigation. In the case of a workplace DM exposure the person will be deliberately exposed to biotoxins that will exacerbate the disease. Importantly, the safety of workplace PEF has been never demonstrated. Furthermore, workplace PEF is not suitable to diagnose allergic alveolitis. The authors of this article recommend workplace PEF should be abandoned in the context with DM [92]. Only safe methods should be used even at the expense of completeness of information. Work-related illness should be diagnosed from the patient's medical history and documented SBS. In the future, new biomarkers will help diagnosis. Biopsy from a patient's bronchi, for example, is an invasive investigation that should be discouraged for routine use. Instead, analysis of tissue samples taken in any case for research purposes is ethically sustainable.

Patients exposed to DM at homes or workplace often experience medical misconduct. The casualty between the exposure and the symptoms is often questioned, neglected and misinterpreted as a "nosebo effect" or purely as a "functional impairment". Psychiatric and psychological factors as the background of the symptoms are apparently overestimated [10]. On the basis of presented immunological and toxicological evidence, it is high time to accept DMHS as a separate clinical entity and provide multidisciplinary care with appropriate social benefits.

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Conflict of interest

The authors declare no conflict of interests in relation to presented material.

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