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Mold exposure and respiratory health in damp indoor environments

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1. ABSTRACT

Almost all modern buildings experience at least minor, and sometimes serious, water damage during their life span. Excess moisture in buildings becomes a critical factor for mold (fungal) proliferation in nutrient-rich environments. As a result, building occupants may be exposed to increased levels of microbial agents such as fungal spores, cell fragments, cell wall components, or toxins. Such exposures may result in various diseases and symptoms, both respiratory and non-respiratory. Respiratory health complaints are common in damp buildings and have been more thoroughly studied than non-respiratory complaints. Respiratory diseases and symptoms which may be produced by exposure to indoor fungi include asthma development, exacerbation of asthma, hypersensitivity pneumonitis, cough, wheeze, dyspnea (shortness of breath), nasal and throat symptoms, and respiratory infections. In addition to these illnesses, rhinosinusitis and sarcoidosis in water-damaged building occupants are also drawing more scientific attention. In this article, we explore the evidence for adverse effects of fungal exposure on respiratory health in damp indoor environments and potential disease mechanisms related to the exposure.

2. INTRODUCTION

Fungi are eukaryotic organisms and do not have chlorophyll for photosynthesis. Thus, they depend on dead/decaying organic matter or living organisms (heterotrophic) for their survival and growth (1). Fungi are ubiquitous and reproduce by sexual spores, asexual spores, and mycelial fragmentation, and proliferate in damp environments. The number of fungal species on earth has been conservatively estimated as 1.5 million, yet the number of known fungal species (including all orphaned species) are only 120,000 (2). This indicates that fungal taxonomy still needs more research. In particular, there is little available data on the number of fungal species that proliferate in damp indoor environments. Work has shown that *Penicillium*, *Alternaria*, *Aspergillus*, and *Cladosporium* are common indoor fungal genera for which a wide range of species have been reported (3). In the field of indoor environmental quality, the term "mold" is often used interchangeably with the term "fungi" (4). We will follow this convention in our discussion of health effects from exposure to fungi in indoor environments.

Due to the ubiquitous nature of fungi, it is inevitable that human beings are exposed to certain

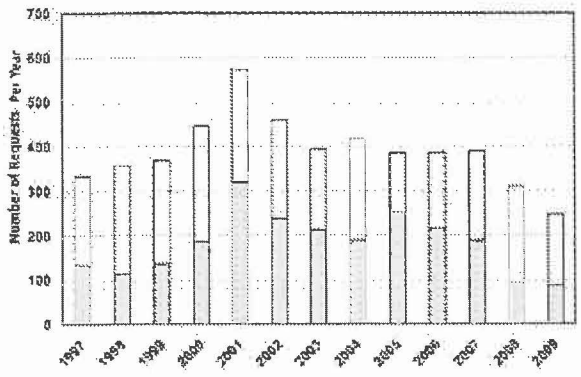

Figure 1. The number of Health Hazard Evaluation requests at the National Institute for Occupational Safety and Health since 1997. Gray and white bars represent indoor environmental quality (IEQ)- and non-IEQ-related requests, respectively.

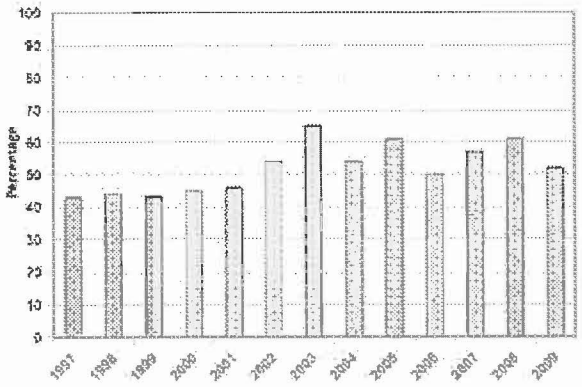

Figure 2. Percentage of mold-exposure related requests in IEQ-related Health Hazard Evaluations requests at the National Institute for Occupational Safety and Health since 1997.

amounts of fungal spores or other fungal structures, including fungal fragments, in everyday life. This is why the human body, especially the lung, has developed mechanisms to tightly regulate immunologic response, develop tolerance, and thus protect from the exposure. Unfortunately, how much exposure to fungal spores or other fungal structures is tolerable for humans is not known and seems to vary among individuals. However, exposure to fungi in damp/water-damaged buildings has been recently acknowledged as a serious public health hazard by authoritative entities (4-6), which was supported by a robust body of toxicological, clinical, and epidemiological findings.

The presence of excess moisture in indoor environments results from external or internal water leaks, or humid weather. Excess moisture on building materials, such as carpets, dry wall, or ceiling tiles, will promote proliferation of fungi and other microorganisms, since these materials contain plenty of organic food sources. In these contaminated environments, fungal spores, hyphal fragments, mycotoxins, fungal cell wall components [such as (1→3)-β-D-glucan, extracellular polysaccharides], and microbial volatile organic compounds (MVOC) can be released into the occupied spaces of a building. Occupants will be mainly exposed to these microbial contaminants through inhalation, although other routes of exposures, such as ingestion and skin exposure, are also possible.

Mold exposure can occur in the home, at the workplace, and outdoors. In the industrialized world, people spend up to 90% of their time in indoor environments, thus a healthy indoor environment is critically important (7). Public interest in indoor environmental quality (IEQ) increased in the 1970s after the energy crisis and subsequent increase of airtight buildings in the U.S. when sick building syndrome (SBS) was first described. SBS symptoms typically occur in workers when they are in the building, and then improve upon leaving the building. Symptoms include headache, mucous membrane irritation, and difficulty concentrating. Since the 1990s, reports of building-related chest symptoms have increased (8). This increase has been linked to several indoor environmental factors (8), and of these, damp/water-damaged building environments seem to be one of the most important contributors (6, 9, 10). The proportion of IEQ-related Health Hazard Evaluation requests to the National Institute for Occupational Safety and Health (NIOSH) in the U.S. has gradually increased since the late 1970s, and since 2000, 50% or more of the total requests have been related to indoor environments (Figure 1). Of these IEQ-related requests, more than half concerned indoor mold exposure in damp/water-damaged buildings (Figure 2). These data suggest that there has been greater public interest in mold exposure and the health effects of damp building environments in recent years. A commonplace source of IEQ problems is water damage, which potentially leads to fungal contamination and exposure (6).

In a nationwide study of 100 buildings not known to have indoor air quality complaints, current water damage was documented in 43% (11). Although the prevalence of indoor dampness is variable depending on the country, continent, and climate zone, the World Health Organization (WHO) estimated that from 10% to 50% of indoor environments are affected by damp conditions in Europe, North America, Australia, India, and Japan (12). Not only is the prevalence of dampness high, but the health effects attributed to poor IEQ is significant. An estimated 20-30% of the indoor workforce has health symptoms that they attribute to IEQ (13), resulting in an estimated $122 billion impact on the U.S. economy each year (9, 14). It was reported that the estimated annual cost of asthma attributable to dampness and mold exposure was $3.5 billion (10), and that the estimated cost of rhinosinusitis in 2003 was $2-5 billion in the U.S. (15).

Specific causal mechanisms between mold exposure and health effects are not yet understood. One of the reasons is that mold exposure may be accompanied by simultaneous exposure to other microbial and chemical agents in indoor environments, which may lead to more complicated disease mechanisms (16, 17). The mixed exposures may involve all or some of the following agents:

fungal components; bacterial cell wall components such as endotoxin (cell wall component of gram negative bacteria) and peptidoglycan (cell wall component of gram positive and negative bacteria); pollens; dust mite, cockroach, and other allergens; volatile organic compounds from cleaning agents; and the off-gassing from building materials. Fungal components of interest include fungal allergens, proteases, (1→3)-β-D-glucan, mycotoxins, MVOCs, and other fungal cell wall components. Nonetheless, ample epidemiologic and toxicological evidence supports the association between mold exposures and various respiratory health effects in indoor environments, which was recognized and published in thorough literature reviews by the WHO (6) and the U.S. Institute of Medicine (IOM) of the National Academy of Sciences (4). The health outcomes with sufficient evidence of an association include asthma development, current asthma, exacerbation of asthma, hypersensitivity pneumonitis, cough, wheeze, dyspnea (shortness of breath), upper respiratory tract symptoms, and respiratory infections. In addition to these illnesses and symptoms, sarcoidosis, allergic rhinitis, and non-respiratory illnesses such as headache, lack of concentration, and neurologic effects in relation to mold exposure have gained scientific and public attention.

In contrast to the research on damp indoor environments where exposure to indoor mold in both children and adults can lead to the development and exacerbation of asthma as well as to lower respiratory symptoms, some studies on early exposure to microbial agents in infants have shown a protective effect for both development of asthma and wheezing (18-20). The duality of response in infants and children to microbial exposures has been a topic of much discussion in the literature since the effects of unhygienic conditions in relation to the development of allergic illnesses were first published (21). A recent review article expands on what has been termed the "hygiene hypothesis" concerning the complexities of exposure characteristics and genetic factors that may influence health outcomes (22).

3. SCOPE OF THE ARTICLE

The main focus of this article is to review respiratory illnesses due to exposure to mold in damp indoor environments. Discussion of these illnesses will include respiratory symptoms since they may be evidence of sub-clinical or non-diagnosed illness. We include discussion of clinical studies and laboratory experiments where they may provide evidence of possible exposure effects or suggest potential mechanisms of disease. However, we do not cover neurologic or systemic illnesses.

In the United States, an IOM committee on Damp Indoor Spaces and Health thoroughly reviewed the literature related to indoor dampness and health effects published up to late 2003, and the final report was published in 2004. In Europe, the WHO used recent major reviews, combined with a new assessment of literature published up to July 2007, and published "WHO Guidelines for Indoor Air Quality: Dampness and Mould" in 2009. In this article, we will summarize and discuss these two organizations' conclusions as well as additional evidence from some important recent epidemiologic studies.

4. RESPIRATORY ILLNESSES IN DAMP/MOLDY INDOOR ENVIRONMENTS

4.1. Asthma

Asthma is a common disease with both environmental etiologies and genetic predisposition. It is a complex chronic disorder of the airways characterized by chronic inflammation involving many cell types, airway obstruction, bronchial hyperresponsiveness, and variable and recurring symptoms (23, 24). Episodic asthma symptoms often include wheezing, shortness of breath, chest tightness, and coughing. These symptoms may occur at any time of the day but are more common at night. People with severe asthma may experience being awakened by difficulty breathing at night. The persistence of chronic inflammation of the airways may result in irreversible airway remodeling. Apter and colleagues reported that about 10% of adults in the U.S. had asthma at some point in their lifetime and that more than half of them (6%) had currently active asthma in 2002 (25, 26). Furthermore, Mudarri and Fisk estimated that 21% of current asthma in the U.S. is attributable to dampness and mold exposure (10). Two different phenotypes of asthma have been reported: Th2 cytokine-driven (allergic or eosinophilic asthma) or non-Th2-driven (non-allergic or non-eosinophilic asthma) (27). Both types of asthma may occur in occupants of damp buildings.

Understanding new-onset asthma in damp indoor environments is complicated by a number of issues. First, asthma is not always simple to diagnose and definitions of asthma differ between studies. Second, it is difficult to study the causal relationship between mold exposure and asthma development due to the potential for multiple causal factors, synergistic effects among exposures, and the occurrence of mixed exposures in the indoor environments. Furthermore, lack of reliable methods for exposure assessment of mold for these epidemiologic studies, as well as a lack of studies on indoor fungal diversity, produces additional challenges. Large temporal and spatial variation of airborne fungi has hampered development of reliable exposure assessment methods. Third, prospective cohort studies or population-based case-control studies which can provide valuable information on causal relationships are resource intensive. Even with these impediments, there has been significant progress in this field of epidemiology since the IOM did not find sufficient evidence of an association between mold exposure and asthma development in 2004 (4).

The WHO concluded in the 2009 guidelines that there is sufficient evidence of an association between development of asthma and mold exposure using additional studies (6). Newer studies which helped inform this conclusion are as follows. In a population-based prospective cohort study in Finland, researchers found that exposure to mold odor in homes increased the risk for development of asthma in children by 2.4 times in 6 years

after the exposure, compared to non-exposed children (28). Another prospective study on European Community Respiratory Health Survey participants in Melbourne, Australia found that increased exposure to airborne *Cladosporium* in homes increased the risk for development of adult asthma by 1.5 times (29). A Finish population-based incident case-control study on adults also reported that exposure to indoor workplace mold increased the risk for new onset asthma by 4.6 times (30). Another Finish retrospective case-control study of children found a 2.6-fold higher risk for new diagnosis of asthma due to living in homes with visible mold (31).

In the U.S., NIOSH research found that post-occupancy physician-diagnosed asthma was strongly associated with exposure to mold (especially, water-loving molds: yeasts, *Phoma herbarum*, *Chaetomium globosum*, *Mucor plumbeus*, *Rhizopus stolonifer*, and *Stachybotrys chartarum*) in a linear exposure-dependent manner among occupants of a water-damaged building (32). The building occupants reported asthma onset at estimated rates that were 7.5 times higher after starting work than before starting work in the building, implying a temporal association between exposure to the moldy building and onset of asthma (33). A recently published NIOSH cross-sectional study on respiratory health in 1171 of 1834 employees in two hospitals found that post-hire onset asthma was positively associated with exposure to dampness (34).

Most recently, since the WHO review, Karvala and colleagues in Finland reported that dampness and mold exposure can lead to the development of adult asthma (35). The researchers clinically examined 694 patients with suspicion of occupational asthma (OA) referred between 1995 and 2004 by occupational health physicians or pulmonologists nationwide for lung function, specific serum IgE, and atopic status using skin prick tests (SPT) with 29 mold mix and common environmental allergens. Their OA status was evaluated based on the examination and grouped into probable OA, possible OA, and unlikely OA. The onset of asthma symptoms in all patients was temporally associated with water damage at their places of work. Patients' exposure to mold was retrospectively evaluated and grouped into low, medium, and high, based on reports by indoor air researchers and occupational safety and health personnel which included workplace water damage, microbial growth, and material and air sample results of mold. In this study, they found significantly higher mold exposure in the probable OA group than in the unlikely OA group. Interestingly, only 33.1% of the probable OA patients were atopic (at least one positive SPT to common environmental allergens) and only 20% of the probable OA patients were sensitized (positive SPT) to mold allergens. However, they found a significantly higher proportion of mold sensitization in the probable OA group than other OA groups.

In summary, there is currently a strong body of new information on the association between exposure to mold in damp indoor environments and the development of asthma since the publication of the IOM report in 2004, which did not find sufficient evidence of this association. These new data suggest that mold exposure may be causally associated with the development of asthma among occupants in damp buildings (6).

In 2004, the IOM committee stated that sufficient epidemiologic evidence supports an association between the exacerbation of asthma in sensitized people and mold exposure in damp indoor environments (4). The 2009 WHO guidelines included evidence from a number of additional studies and also concluded that there is an association between dampness-related agents and the exacerbation of asthma (36). The conclusion of both organizations indicates that people with existing asthma may have onset or worsening of chest symptoms when they are exposed to mold. The increase of asthma symptoms in sensitized asthmatic people has been clearly demonstrated by the occurrence of asthma epidemics in certain seasons. The increase of severe life-threatening asthma, asthma deaths, and hospital admissions for asthma has been linked to high fungal spore seasons (37-39) and the occurrence of thunderstorms (40-43) when concentrations of intact spores, fragments of spores, or mycelia of *Alternaria*, *Cladosporium*, *Didymella*, or *Sporobolomyces* spp. have been reported to be increased (39, 44). These fungi represent some of the major outdoor fungal genera; however, they are also commonly found in high concentrations in damp indoor environments (32). Thus, the data suggest that exposure to these fungi in water-damaged buildings can also produce the same exacerbation of asthma in building occupants. In a randomized control trial published by Burr and colleagues, they recruited 182 asthma patients who lived in moldy homes and randomly assigned them to two groups- an intervention group in which mold contamination was removed and a control group in which mold remediation was delayed for 12 months (45). They evaluated peak expiratory flow (PEF), and respiratory symptoms and medication use through questionnaire at baseline, 6 months, and 12 months. They found that asthma patients in the intervention group significantly improved in perceived symptoms and decreased medication (asthma preventing medicine and daily bronchodilator) use compared to the asthmatics in the control group although they found no significant changes in PEF. Unfortunately, it is not possible for the participants not to know their intervention status in this type of study. However, the authors argued that significant decline in daily bronchodilator and other mediation use, consistent intervention effects observed at both 6 and 12 months, and significant intervention effects on rhinitis and rhinoconjunctivitis consistent with findings in the literature suggest minimal "placebo effects."

Immunologic mechanisms of exacerbation or development of asthma are currently not fully understood. However, for atopic asthma patients with mold exposure, the Th2 type inflammatory response seems to be an important mechanism. Fungal spores have long been known as microbial agents causing allergy and there are more than 80 fungal genera reported to be associated with type I allergies in susceptible people (46, 47). Most of the fungal allergens that have been isolated are proteins or

glycoproteins and many (but not all) of them play an enzymatic role. In particular, proteolytic enzymes have been suggested to have the capability to enhance the allergenicity of fungal allergens (48, 49). An immunologic study using human eosinophils exposed to the cell-free extract of *Alternaria alternata* suggested that aspartate proteases produced by the fungus were recognized by the protease-activated receptor 2 (that is also activated by serine proteases) which in turn activated human eosinophils and degranulation (50). However, Chapman and Wünschmann reported that proteolytic activity is not a requirement for allergic response due to exposure to fungal proteins (48). More research on the characterization of fungal allergens is needed since allergenic proteins have been isolated from only 23 of the more than 80 fungal genera which are currently associated with type I allergies. Approximately 150 individual fungal allergens from those 23 genera have so far been identified (47).

Using a rat model of chronic asthma, Gao and colleagues demonstrated that chronic exposure to *Aspergillus fumigatus* induced a Th2 type inflammatory response in airways, airway remodeling, and increased bronchial hyperresponsiveness (51). *Alternaria* is one of the fungi most commonly found in damp buildings as well as outdoors and allergenic effects have been well documented (52-54). Severe asthma was strongly associated with *Alternaria* sensitivity (53, 55-58). Exposure to high concentrations of *Alternaria* and subsequent sensitization may potentially trigger the development of childhood asthma (52, 57, 59, 60). This fungus produces strong Th2 type adjuvant effects in the airways. Using a naïve mouse model, Kobayashi and colleagues showed that co-exposure of other allergens (ovalbumin or ragweed pollen) with *Alternaria* extract induced Th2 type cytokine production while exposure to ovalbumin or ragweed allergen alone produced only minimal sensitization (61). They discussed that the allergenicity of the fungus may be induced by unidentified proteins such as proteases or by carbohydrate structures such as chitin, and suggested that the allergenic activity of dendritic cells exposed to the fungus down-regulated IL-12, which then polarized the T cell response towards Th2 type inflammation. Similar findings have also been reported by other researchers (62, 63). Another recent study using a mouse model suggested that chronic intranasal exposure to a single allergen (dust mite, ragweed, or *Aspergillus*) for 8 weeks induced tolerance, while mixed exposure to multiple allergens (triple allergens) synergistically increased eosinophilic inflammation in the airways (17). These studies suggest that the synergistically increased allergic response was likely to be induced by adjuvant-like activities of the allergens such as proteases over and above the antigenic activity of proteins (17, 64). These findings imply that the effects and mechanisms of mixed exposures are complex but understanding them is crucial to understand exposure-disease relationships.

A proportion of asthma cases are characterized by a non-eosinophilic phenotype, not related to an allergic type response (65-67). In non-eosinophilic asthma there is an absence of raised levels of eosinophils, but rather a proliferation of neutrophils, elevated levels of the neutrophil chemoattractant IL-8, and increases in the expression of the Toll-like receptor (TLR: transmembrane proteins playing a key role in the innate immune system) 2, TLR4 and CD14, indicating an innate immune response (68-70). Non-eosinophilic and eosinophilic asthma are associated with different gene expression profiles, indicating that these phenotypes of asthma involve different molecular mechanisms of disease development (71).

There is evidence that some asthma in mold-exposed people may be non-eosinophilic or non-allergic in nature. In a study of occupants of a water-damaged building, pre-occupancy onset asthma was associated with atopy, as anticipated, but post-occupancy onset asthma cases had much lower prevalences of IgE-mediated allergen skin-test positivity to common aeroallergens as well as to indoor and outdoor mold (33). In Finland, investigation of a series of 694 patients presenting with lower respiratory symptoms in relation to mold exposure included specific inhalation challenge testing and SPT, or serum IgE testing with mold extracts. Among the 156 patients designated as having probable OA, 85% had a positive reaction in the specific inhalation challenge tests with mold extracts, but only 20% showed mold sensitization. The authors concluded "IgE mediation is a rare mechanism, whereas other mechanisms are unknown" (35).

4.2. Lower respiratory symptoms

Many people who have asthma-like symptoms such as cough, wheezing, shortness of breath, chest tightness, or being awakened by difficulty breathing at night may not be diagnosed as having asthma. For example, Siersted and colleagues reported that in a population-based study of adolescents about one third of all asthma they identified was undiagnosed (72). In this study, cough was the most common symptom in undiagnosed asthmatic subjects. Studies of the health effects of damp indoor environments often report on both building-related symptoms and diagnosed illnesses reflecting the underlying fact that these health effects occur together in populations of building occupants. This suggests that some proportion of symptomatic occupants of water-damaged buildings may have sub-clinical or undiagnosed asthma.

Both the IOM and the WHO found sufficient evidence for an increased risk of cough and wheeze due to exposure to indoor mold or dampness. Additionally, the WHO concluded that there is an increased risk for shortness of breath (dyspnea) due to exposure. A recent NIOSH study of two hospital buildings (one of them had severe water damage over several years) found that exposure to fungi in the buildings significantly increased building-related asthma symptoms (defined as asthma symptoms which improved when away from the building) occurring once or more every week in the last 4 weeks (34). Another NIOSH study of a water-damaged office building also reported that increased risk of asthma, which was defined based on asthma symptoms or physician diagnosis, was significantly associated with increased exposure to mold, measured as the mold concentration in floor or chair

dust collected in the building (32). In a two-year follow-up birth-cohort study of infants with a maternal history of asthma, Rosenbaum and colleagues found a six-fold increased risk of wheeze during the first year of life in infants exposed to higher concentrations (> 120 cfu/m^3) of *Penicillium* compared to infants in the non-exposure group (fungal concentration below the limit of detection) (73). Similarly, a Finish prospective birth-cohort study of 396 children found that engineer-reported visible mold in the living room and child's bedroom at 2 months of age significantly increased the risk of parent-reported wheezing in the first 18 months of life (74). Iossifova and colleagues reported that children living in homes with high visible mold during infancy were at a 7-fold higher risk for development of asthma than those in homes with no visible mold (75). A meta-analysis of 33 peer-reviewed epidemiologic studies on asthma symptoms and exposure to home dampness/mold estimated a 1.5- or 1.8-fold increased risk of cough and a 1.4- or 1.5-fold increased risk of wheeze and showed that the risk was generally higher in children than adults (76).

4.3 Rhinitis/rhinosinusitis

Rhinitis is a highly prevalent disease which is characterized by runny nose, nasal obstruction, nasal itching, and sneezing. There are two different types of rhinitis recognized- allergic and non-allergic. Allergic rhinitis is diagnosed by characteristic symptoms and a positive SPT or specific serum IgE to aeroallergens, while non-allergic rhinitis is diagnosed by nasal symptoms, no known cause of allergy, negative SPT, and no specific serum IgE (77, 78). Non-allergic rhinitis also has been known by several other terms- non-infective, perennial, intrinsic, and idiopathic rhinitis (77). Rhinitis affects about 20-40% of people in western countries (77) and about 20% of the U.S. population have allergic rhinitis (79, 80). Sinusitis is an inflammation of the paranasal sinuses, which concurrently occurs with nasal airway inflammation for most cases and is preceded by rhinitis symptoms (81). Thus, a new term, rhinosinusitis, has been defined as an inflammatory disorder in the mucosa of the nose and paranasal sinuses and is interchangeably used with sinusitis (82). Depending on symptom duration, rhinosinusitis is subdivided into acute (< 4weeks), subacute (4-12 weeks), and chronic (>12 weeks) (83). Allergic fungal sinusitis is a type of chronic rhinosinusitis (CRS) (84). In the United States, there are more than 30 million rhinosinusitis cases diagnosed annually (81).

The 2009 WHO guidelines found suggestive epidemiologic evidence of an association between allergic rhinitis and mold exposure, although they also found clinical evidence of an association of CRS and allergic fungal sinusitis with mold exposure. However, both the IOM and WHO concluded that there is sufficient evidence of an association between nasal symptoms with mold exposure. In a prospective birth cohort study using infants enrolled in the Cincinnati Childhood Allergen and Air pollution Study, Biagini and colleagues found that the risk for allergic rhinitis (defined as having rhinitis symptoms in the past 4 weeks and SPT positive at age 1) was about three times higher in infants living in homes with high visible mold than in those living in homes with no mold (85). The risk was not statistically significant, but the study had low power which resulted from the small number of infants (n=23) in the high mold exposure group. In another prospective birth cohort study of 405 children of parents with asthma or allergies, Stark and colleagues found that home exposure to high levels of fungi within the first 3 months of life was a significant predictor of physician-diagnosed allergic rhinitis in the first 5 years of life (86). The fungi found to be associated with a 2- to 3-fold increase in allergic rhinitis risk included *Aspergillus*, *Alternaria*, *Aureobasidium*, non-sporulating fungi, and yeasts. A few cross-sectional studies published in the 1990s also reported that exposure to dampness or mold at home significantly increased the risk for allergic rhinitis in children 1.4 to 3.5 times (87-90). A recently published cross-sectional study investigated risk factors for allergic rhinitis in 616 Costa Rican children with asthma and reported that exposure to mold at homes was an independent risk factor for physician-diagnosed allergic rhinitis (91). A similar result of increased risk for rhinitis and rhinoconjuctivitis (rhinitis and inflammation of the conjunctiva of the eyes) symptoms due to exposure to visible mold in homes was reported from a cross-sectional study of 4,759 children from randomly selected daycare centers in Singapore (92).

Among adults working in moldy/damp buildings, more than half of the building population may suffer from nasal or sinus symptoms due to mold exposure (34, 93-95). Park and colleagues reported that 60 to 80% of water-damaged office building occupants experienced nasal or sinus symptoms in the past 12 months and that at least half of them reported improvement of their symptoms when away from the building (building-related symptoms) (94). Similar prevalences were also reported in occupants of hospital and community college buildings with water damage (34, 93). Park and colleagues also demonstrated a monotonically increasing exposure-response relationship between mold/dampness exposure index and building-related nasal symptoms in college workers, showing about a three-fold increased risk in the highest exposure group (93). Similar findings were also reported in hospital and office building workers (34, 94). Damp building occupants experiencing building-related rhinitis symptoms may have undiagnosed rhinitis due to indoor mold exposure.

Rhinitis is often concurrent with asthma, sinusitis, or otitis media with effusion (96). The majority of occupational asthma cases or occupants with asthma symptoms in damp buildings may also have work-related rhinitis or rhinitis symptoms. In the occupational setting of increased building-related asthma risk, physicians have described that rhinosinusitis frequently precedes development of asthma with a building-related pattern (97). In the past decade, rhinitis or rhinosinusitis have been suggested as independent risk factors for the development of asthma (98-101). A recent concept of a "unified airway model" suggests a close communication between upper and lower respiratory tracts through concurrent inflammatory processes in both portions of the airways (100, 102). However, there is little information about the degree of risk

of longitudinal progression of building-related rhinosinusitis to building-related asthma. More research on the association of objective measures of disease with mold exposure as well as on the longitudinal progression of rhinosinusitis to lower respiratory diseases among damp building occupants is warranted.

Allergic rhinitis is a type I hypersensitivity response to allergens. Inhaled fungal allergen is processed by antigen presenting cells, which activate Th2 cells and produces Th2 type cytokines such as IL-4 and IL-5 (77, 103). IL-4 stimulates B cells to produce specific IgE binding to mast cells and basophils which then migrate to the nasal mucosa, reflecting sensitization to the specific fungal allergens (104). IL-5 enhances proliferation and differentiation of eosinophil precursors, and prolongs survival of eosinophils and mast cells (105). Activated eosinophils release cytotoxic proteins such as major basic protein and eosinophilic cationic protein which damage the airway epithelium. IL-5 has been causally associated with allergic rhinitis (106). This allergic mechanism ensures that chronic exposure to fungal allergens can induce allergic rhinitis. On the other hand, etiologic mechanisms for non-allergic rhinitis are not well understood although neurogenic and inflammatory mechanisms have been proposed. However, multiple causes may trigger nonallergic rhinitis through different mechanisms which are not yet known.

One of the first etiologic mechanisms proposed for CRS involves eosinophils and T lymphocytes induced by exposure to *Alternaria* or other fungi as a primary pathogenic trigger. Eosinophils migrate from the nasal tissues to nasal mucus, degranulate and release major basic protein onto inhaled fungal agents, and damage epithelium by releasing eosinophilic and cytotoxic mucin (107). This mechanism has been called the 'fungal hypothesis' (82, 99). A second proposed mechanism for CRS is the 'superantigen hypothesis', which involves B cell and T cell responses to superantigenic toxin secreted by *Staphylococcus aureus*. These two hypotheses have been proposed and supported by a finding of a response of CRS patients' peripheral blood mononuclear cells, and T and B cells to two common intranasal microorganisms- *Alternaria* and *Staphylococcus aureus*; however, these microorganisms' etiologic role in CRS has not yet been clearly understood. A recent hypothesis for the etiology of CRS which focuses on host susceptibility is the 'immune barrier hypothesis.' Mechanical and innate immune defense mechanisms in the nasal mucosa protect the body from foreign invaders and control activation of the acquired immune system. Dysfunction of this defense mechanism due to genetic or acquired defects may result in the chronic inflammation of CRS (108-110). Chronic inflammation can be polarized either to Th1 or Th2 type cytokines depending on genetic variation or environmental factors. Impairment of the epithelial tight junction seems to play a primary role in dysfunction of the mechanical defense mechanism in the sinonasal mucosa. High exposure to fungal proteases may result in excessive stimulation of protease-activated receptors in the epithelium and lead to epithelial damage, entry of foreign proteins, and increase of inflammatory and acquired immune responses (82, 111). Furthermore, people who have deficient endogenous protease inhibitors may be even more susceptible to exposures to environmental proteases (112). Dysfunction of the innate immune response in sinonasal epithelial cells such as impairment in secretion of antimicrobial proteins and TLR signaling may also play an important role in development of CRS (82).

4.4. Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is an interstitial granulomatous lung disease caused by repeated inhalation exposure to a sensitizing antigen in susceptible people, and characterized by recurrent symptoms of fever, chills, sweating, fatigue, cough, and dyspnea (113, 114). In HP, characteristics of the antigens, individual susceptibility, and gene-environment interactions are all important factors working together (113). Since not all inhaled antigens induce HP, potential HP-provoking antigens may have certain characteristics such as specific sizes, solubilities, and capability to produce an inflammatory response as well as a cellular immune response. Although a larger portion of exposed subjects may be sensitized (either humoral or cellular) to the HP-provoking antigens, only 5-15% of subjects exposed to them develop HP. This pattern implies that genetic susceptibility is also an important factor. Acute and subacute clinical forms of HP may progress to chronic HP with continued exposure, although prolonged low level exposure may also directly result in the chronic form of the disease (113, 115). Recurrent attacks of acute HP and chronic HP may produce lung fibrosis or emphysema, and chronic HP is characterized by progressive shortness of breath on exertion, increasing cough, fatigue, and weight loss. Since the subacute and chronic forms of the disease may imitate any interstitial lung disease, the subacute form of HP may be misdiagnosed as sarcoidosis, tuberculosis or histoplasmosis, and the chronic form of HP may be misdiagnosed as idiopathic pulmonary fibrosis (116). Currently, relationships of duration and intensity of exposure to different clinical forms of HP are not understood. In addition, the progression of the disease as well as the initiation can be much more complex than as described above, depending on the interaction between the exposure and host response (113, 114).

Both the WHO and the IOM reported that there is sufficient evidence of an association between HP in susceptible subjects and exposure to mold in damp indoor environments. Incidence of HP in the general population is rare; however, the disease has been recognized for decades among occupants of residential and office buildings with contaminated heated-water reservoirs, humidifiers, cool-mist vaporizers, wooden water buckets, water flume slides, and water-damaged carpeting (117-123). More recent publications have implicated exposure to mold or other microbial agents in damp indoor environments as causes of HP. Buildings with long-standing water damage from roof leaks, other water infiltration through the building envelope, plumbing leaks, and below grade water intrusion have had reported clusters of hypersensitivity pneumonitis (33, 97, 124). Since it is well established in agricultural workers that HP can be caused by exposure to various

molds or bacteria in organic dust (124), it can be also assumed that exposure to microbial (including fungal) antigens may cause HP in susceptible occupants of mold-contaminated buildings.

Seuri and colleagues reported a respiratory disease outbreak including one HP case, in workers of a water/mold-damaged military hospital building. Exposure to *Sporobolomyces salmonicolor* was implicated to be causally associated with the HP (124). Apostolakos and colleagues also reported a case of HP who was a resident of a home contaminated with fungi found in water-damaged carpet and fiberglass insulation materials (125). Implicated fungi associated with the HP in the study included *Aureobasidium pullulans* and *Sacharopolyspora rectivirgula*. Trout *et al.* also reported restrictive lung disease suspected as chronic HP in a water-damaged hotel building dominantly contaminated with *Penicillium*, *Aspergillus*, and *Stachybotrys* species (126). In a more recent study of an office building with a long-history of water damage, Cox-Ganser and colleagues reported eight physician-diagnosed HP cases, five of which had post-occupancy onset. Although suspected causal antigens were not reported in the study, the authors discussed that the rarity of HP in the general population suggested a building-related etiology for this cluster (33). A more recent case report in Japan described one HP patient with asthma caused by exposure to *Bjerkandera adusta* identified from the living room and bedroom of the patient's home (127). Other fungi implicated as having etiologic antigens for HP from various occupational environments are as follows: *Absidia corymbifera*, *Aspergillus fumigatus*, *A. clavatus*, *Alternaria* species, *Aureobasidium* species including *Aureobasidium* (*Pullularia*) *pullulans*, *Cladosporium* species, *Cryptostroma corticale*, *Monocillium* species, *Penicillium verrucosum* (*casei*), *P. frequentans*, *P. citreonigrum*, *Rhizopus* (*Mucor*) *stolonifer*, and *Trichosporon cutaneum* (var. *cutaneum*) (128). Because HP is a rare disease in the general population, even one case with building-related symptoms consistent with HP justifies a public health investigation. In the presence of a building-related HP case, there is usually a spectrum of other building-related respiratory symptoms and diseases among coworkers. In addition, HP often co-exists with asthma in damp buildings (129-131).

HP is an antigen-mediated disease, but the immunologic mechanisms are not fully elucidated. However, both type III and type IV hypersensitivity reactions appear to be involved in disease mechanisms. Immune complexes of inhaled antigen and specific IgG may activate the complement cascade reaction (type III hypersensitivity response), resulting in inflammatory responses through macrophage activation, release of inflammatory mediators and cytokines, and recruitment of neutrophils and macrophages in 4-6 hours after the exposure. HP is characterized by bronchoalveolar lavage lymphocytosis abundant with T cells (> 50%), suggesting type IV hypersensitivity (T cell-mediated) response (132). The phenotype of inflammatory T lymphocytes (CD4+/CD8+ ratio) in HP patients appeared to be determined by several factors: the offending antigens, the disease stage, and the intensity and duration of exposure. However, HP is a heterogeneous disease and the involved immunologic mechanisms may be significantly different among various clinical forms of the diseases (133).

4.5. Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown cause involving multiple organs, including the lung, which is the most commonly affected organ. It is characterized by non-caseating granulomas which consist of epithelioid cells, Langerhans giant cells, lymphocytes, monocytes, and fibroblasts (134, 135). Currently, there is no precise and consistent definition of sarcoidosis and no definitive medical tests that establish a diagnosis of sarcoidosis. The prevalence of sarcoidosis in the general population is as low as <1-40 cases/100,000 and annual incidence is 35.5 cases/100,000 African American and 10.9 cases/100,000 Caucasians (134, 136). A recent study on sarcoidosis prevalence in the state of Vermont in the U.S. reported 66.1 cases/100,000 which is much higher than previous estimates for the general population (137). The peak incidence occurs between age of 30 and 39 years, and the disease mostly develops before the age of 50 years in the U.S., although the incidence varies widely worldwide.

The IOM and the WHO did not evaluate sarcoidosis as a potential health outcome of indoor mold exposure. The National Institutes of Health launched 'A Case Control Etiologic Study of Sarcoidosis (ACCESS)' in 1992 to generate hypotheses about etiologic agents for sarcoidosis (135). Although the study was not able to identify definite etiologic agents for the disease, it found multiple exposures and occupations associated with sarcoidosis. The identified exposures include insecticides at work, bird handling, use of home central air conditioners, and workplace mold/mildew (135, 138). Exposure to musty odors at work significantly increased the risk for sarcoidosis 1.6 times in the ACCESS study. In another study of occupational risk factors for sarcoidosis in African-American siblings in the metropolitan Detroit area, Kucera and colleagues also found that indoor exposure for more than a year to high humidity, water damage, or musty odor significantly increased the risk for sarcoidosis 1.5 to 1.8 times (139). In some damp buildings, clusters of sarcoidosis have occurred. A recent epidemiologic study of a large office building with 1,327 occupants identified a cluster of 6 physician-diagnosed sarcoidosis cases including 3 cases with post-occupancy onset (33). The building had ongoing water leaks at the time of the survey with a long history of water damage. Most recently, Laney and colleagues also reported 6 physician-diagnosed sarcoidosis cases from a cross-sectional study of a persistently water-damaged office building with 136 occupants (140). Of the six sarcoidosis cases, two had pulmonary involvement, one had lymph node involvement, and three had multiorgan involvement. All of them had received the diagnosis after they started to work at the water-damaged building. To date, epidemiologic evidence of an association between sarcoidosis and mold exposure is scarce. However, even with possible underdiagnosis or misdiagnosis, all of the above findings suggest that sarcoidosis may occur in water-damaged building

occupants due to persistent exposure to mold or other microbial agents and that the disease in such populations deserves more attention from physicians, health professionals, toxicologists, and epidemiologists.

4.6. OTHER RESPIRATORY ILLNESSES

4.6.1. Infections

It has been our experience that occupants of damp/moldy environments often complain of increased infections including bronchitis, the common cold, ear infections, and nasal and sinus infections. The IOM report discussed little about respiratory infections in relation to dampness or mold, but pointed out that immune-compromised persons are at increased risk for fungal colonization or opportunistic infections. The 2009 WHO report found sufficient evidence for an association between dampness or mold and respiratory infections. Seven studies of children found odds ratios ranging from 0.65 to 5.10. There was also limited evidence for an association between indoor dampness/mold and bronchitis.

There are two theories as to how components of mold may increase susceptibility to respiratory infections: by suppression of the immune system; or by causing membrane inflammation, which in turn can lead to increased permeability to infective organisms. More research is needed to substantiate these theories. In a rat model, a one-time high dose of fungal cell wall (1→3)-β-D-glucan enhanced the lung immune response by activating alveolar macrophages prior to infection, and stimulating T cells involved in the adaptive immune response early after infection with the bacteria *Listeria monocytogenes* (141). Yet in a following study, a similar total dose of zymosan divided into four smaller repeated doses suppressed the host defense against *Listeria monocytogenes* by down-regulating the innate response (142).

4.6.2. Pulmonary hemorrhage in infants

Indoor exposure to mycotoxins from *Stachybotrys chartarum* was suggested to be associated with acute pulmonary hemorrhage in a cluster of 10 babies in Cleveland (143). However, these findings were later retracted (144). Dearborn and colleagues published an update on 30 infants, mainly describing the clinical profile of the cases, but also tabulated that 89% of these infants lived in water-damaged houses with exposure to toxigenic fungi (145). Currently, the role of *Stachybotrys chartarum* is still controversial. In 2004, the IOM concluded that there was insufficient information to determine whether an association exists between acute pulmonary hemorrhage and the presence of *Stachybotrys chartarum* or exposure to damp indoor environments in general.

5. CONCLUSIONS

The presence of patients with mucosal irritation, recurrent rhinitis/rhinosinusitis, or recurrent hoarseness among damp building occupants may point to a potential for development of building-related asthma, exacerbation of asthma, hypersensitivity pneumonitis, sarcoidosis, and interstitial lung disease in the future (97). In this article, we have presented abundant evidence of associations of various respiratory health outcomes with mold exposure and some potential disease mechanisms. Thus, even if we do not fully understand specific causal agents or mechanisms for mold-related illnesses yet, it is very sensible for physicians, environmental professionals, and building managers to recognize potential risk of exposure to mold and support proactive measures for remediation of water-damage and mold contamination to protect occupants' health. The major driving force for mold and other microbial growth in indoor environments is moisture. Thus, identification and repair of the sources of excess moisture such as humid air, or water intrusion or leaks, prompt and complete repair or replacement of water-damaged materials, and thorough cleaning of all indoor surfaces after remediation are essential to minimize mold exposure and decrease mold exposure-related respiratory illnesses. The problem of water damage and mold contamination in indoor environments and related health effects is now a global issue, as is evident from reports from several countries, and thus, needs to be taken much more seriously.

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Abbreviations: ACCESS: A Case Control Etiologic Study of Sarcoidosis, CD: cluster of differentiation, CRS: chronic rhinosinusitis, HP: hypersensitivity pneumonitis, IEQ: Indoor environmental quality, IgE: Immunoglobulin E, IgG: Immunoglobulin G, IL: interleukin, IOM: Institute of Medicine, MVOC: microbial volatile organic compound, NIOSH: National Institute for Occupational Safety and Health, OA: occupational asthma, PEF: peak expiratory flow, SBS: sick building syndrome, SPT: skin prick test, TLR: toll-like receptor, WHO: World Health Organization.

Key Words: Mold, Fungi, Dampness, Building-Related Illness, Asthma, Hypersensitivity Pneumonitis, Sarcoidosis, Rhinitis, Rhinosinusitis, Review

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