

Mold and Human Health: a Reality Check

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Abstract There are possibly millions of mold species on earth. The vast majority of these mold spores live in harmony with humans, rarely causing disease. The rare species that does cause disease does so by triggering allergies or asthma, or may be involved in hypersensitivity diseases such as allergic bronchopulmonary aspergillosis or allergic fungal sinusitis. Other hypersensitivity diseases include those related to occupational or domiciliary exposures to certain mold species, as in the case of Pigeon Breeder's disease, Farmer's lung, or humidifier fever. The final proven category of fungal diseases is through infection, as in the case of onchomycosis or coccidiomycosis. These diseases can be treated using anti-fungal agents. Molds and fungi can also be particularly important in infections that occur in immunocompromised patients. Systemic candidiasis does not occur unless the individual is immunodeficient. Previous reports of "toxic mold syndrome" or "toxic black mold" have been shown to be no more than media hype and mass hysteria, partly stemming from the misinterpreted concept of the "sick building syndrome." There is no scientific evidence that exposure to visible black mold in apartments and buildings can lead to the vague and subjective symptoms of memory loss, inability to focus, fatigue, and headaches that were reported by people who erroneously believed that they were suffering from "mycotoxicosis." Similarly, a causal relationship between cases of infant pulmonary hemorrhage and exposure to "black mold" has never been proven. Finally, there is no evidence of a link between autoimmune disease and mold exposure.

Keywords Fungi · Hypersensitivity pneumonitis · Asthma · Allergic rhinitis · Allergic bronchopulmonary aspergillosis · Allergic fungal sinusitis · Mycotoxins · Mycotoxicosis · Sick building syndrome

Introduction

Mold is a common name for a visible group of fungi that grow as multicellular filaments or hyphae, which then aggregate into web-like structures or mycelia. To date, approximately 100,000 fungi have been described, but true fungal diversity is likely to be at least 7- to 10-fold greater. According to other estimates, as many as 5 million fungal species may await study, description, and classification [1], but the true figure is likely to be somewhere in between [2]. Fungi living in the soil and on plants have vital roles in decomposing organic matter thereby making essential nutrients such as nitrogen and phosphorus available to other organisms. Indeed, the majority of plants would not survive without mycorrhiza, i.e., the symbiotic relationship between the mycelium of a fungus with the roots of the plant, which helps in supplying the plant with water and other necessary nutrients. For humans, yeasts (unicellular fungi) and molds are invaluable in the production of various foods (breads, certain cheeses) and beverages (e.g., beer and wine) and as sources of medications (e.g., antibiotics, immunosuppressants, and statins). Both outdoor and indoor environments contain highly diverse and somewhat different mycobiomes, even if the distribution of species and their levels indoor are greatly influenced by their outdoor counterparts. This means that molds and other fungi are ubiquitous. Indeed, they even live in and on every human being; the human mouth alone may harbor >20 of the >100 species of fungi that have been detected in the oral cavity. In those patients who do have problems attributable to mold, there are well-

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established biophysiological mechanisms through which disease can occur, namely by inducing hypersensitivity reactions and infection in susceptible individuals. Some examples of this would be the uncommon diseases such as farmer's lung and pigeon breeder's disease, patients characterized by fever, dramatic swelling of lymph nodes, and infiltrates in the lung. If untreated, they will likely die. There is also the possibility of a systemic infection and this would be found in individuals who are immunocompromised, e.g., patients with HIV or patients born with a deficient immune system. There is also the potential for allergy to mold, and in those individuals with asthma (who are allergic to mold), there is the potential for asthma exacerbation during exposure. These exacerbations are, however, completely reversible and do not cause any lasting problems. It should be noted that there is a long list of poorly defined health effects that some have complained are secondary to mold exposure, but these observations are flawed, they lack controls, and are non-specific and lack credible medical plausibility. In this review, we will discuss in detail the concept and the relationship between mold and human health.

Methods for Assessing Fungal Concentrations

There are a great number of methods that measure the concentrations of total molds or individual mold species in indoor and outdoor environments. One method for assessing the levels of airborne fungi is to collect a sample over several hours (at least 8 h are recommended) and count spores microscopically to estimate total fungal spores. Another approach is to use fungal cell wall constituents such as ergosterol or (1-3, 1-6)- β -D-glucans as markers of total fungal biomass, but this does not even allow the determination of spore counts and none of these methods provide information on the genera and species present. To identify fungal species, the classical method is based on culturing spores collected from the air or dust. Fungi are ubiquitous and airborne-viable fungal spores are detectable in nearly all indoor environments, though with considerable variation both over short- and long-term observation periods and between geographic areas [3]. Outdoor levels of total culturable fungi range from nearly undetectable to 10^5 colony-forming units (CFU)/m³. In unselected homes, indoor air concentrations generally vary from below the detection limit to $>2 \times 10^3$ CFU/m³ [4–7] and similar ranges have been reported for non-residential environments [3, 8].

The culture-based quantification of airborne fungi has some major drawbacks. The duration of sampling has to be very short (generally <5 min) in order to prevent sampler overload. Fungal spores differ in their cultivability and culture requirements; hence, only a few species grow on the commonly used culture media. In addition, non-viable spores and other fungal materials (fragments) can contribute to allergen [9], mycotoxin [10], and polysaccharide exposure [11], but are

not captured by culture-based methods. Not surprisingly, the number of CFU per square meter of air obtained by culture methods is at least 10-fold lower than the corresponding fungal spore counts [3].

More recently, quantitative polymerase chain reaction (qPCR) has been used to measure indoor fungal concentrations. This is a very sensitive method that is much faster than culture, does not require great expertise in identifying fungal genera or species, and assesses both viable and non-viable fungal material. In direct comparisons with culture-based results, the levels of cell equivalents obtained with qPCR for individual species or assay groups are generally two to three orders of magnitude higher compared to the CFU values both in air [12] and in dust [13]. If sufficient numbers of fungal species are targeted, qPCR can reveal a much greater diversity of the indoor fungal biome in terms of the number of detected species compared to fungal culture. However, the requirement of pre-selecting the targeted fungi means that the results of qPCR-based studies can rarely be compared directly because they frequently target different numbers of species or assay groups. This requirement also makes qPCR unsuitable for appreciating the true diversity of the fungal biome in a given environment. For this purpose, other culture-independent methods relying on internal transcribed spacer region sequencing are more appropriate. Though less sensitive than qPCR, they have nonetheless revealed the indoor mycobiome to be much more diverse than previously appreciated in terms of the number of detected species [14, 15].

Health Effects of Fungi

Allergy

Sensitization

According to the WHO/International Union of Immunological Societies (IUIS) Allergen Nomenclature subcommittee, there are 111 officially approved fungal allergens from 22 species of *Ascomycota* (86 allergens), 6 species of *Basidiomycota* (23 allergens), and 1 species of *Zygomycota* (2 allergens) (see www.allergen.org). However, the actual list of fungal allergens is far longer, particularly when only partially characterized ones are included [16, 17] and is likely to grow further once the true diversity of the indoor and outdoor fungal populations and the allergenicity of the newly recognized species becomes more fully appreciated [1, 18] (see Table 1 for sensitization rates to some infrequently tested fungal antigens). Currently, the most widely acknowledged allergenic mold species are members of the genera *Alternaria* and *Cladosporium* among those considered to be outdoor molds, and *Aspergillus* and *Penicillium* among those considered to be indoor molds.

Table 1 Sensitization to molds commonly found indoors

	BUA/Germany [19]	West Virginia [18]
Method	Serum-specific IgE with ImmunoCAP	SPT
Number	1538–1575	112
Subjects	Children	Atopic children and adults
Age	3–14	8–78
<i>Acremonium strictum</i>		6.0
<i>Alternaria alternata</i>	4.8	11.8
<i>Aspergillus fumigatus</i>	2.6	6.9
<i>Aspergillus versicolor</i>	2.3	
<i>Cladosporium herbarum</i>	2.1	
<i>C. sphaerospermum</i>		6.9
<i>Chaetomium globosum</i>		4.0/7.0 ^a
<i>Epicoccum nigrum</i>		4.9
<i>Eurotium</i> spp.	1.6	
<i>Paecilomyces variotii</i>		7.0
<i>Penicillium chrysogenum</i>	5.0	4.0
<i>P. notatum</i>		6.9
<i>Pullaria</i> spp.		3.9
<i>Rhizopus</i> spp.		3.9
<i>Stachybotrys chartarum</i>		3.0
<i>Trichoderma viride</i>		4.0/8.0 ^a
<i>Wallemia sebi</i>	0.2	
Total indoor molds (excluding <i>alternaria</i>)	8.30%	

^a Depending on the manufacturer of the commercial extract

In the general population, the frequency of sensitization to *Alternaria* ranges from 0.2–14.4%; the corresponding figures for *Cladosporium* are 0–11.9% [20, 21]. The overall sensitization rate to fungal allergens was estimated to be 8.3% in a population-based study of German children, but is considerably higher in atopic subjects, particularly in patients with severe asthma [16]. The true sensitization rate remains unknown not only because many indoor fungal species remain to be identified [14, 15] but also because few fungal extracts are commercially available and these are not standardized and vary widely in their antigen contents and IgE-binding capacity [22]. This in turn is attributable to the complex growth habits of fungi, the variability in allergen expression between different strains of the same species, the shifts in the protein expression profile between different growth stages and in response to different substrates and nutrient availability, and the extensive cross-reactivity of fungal antigens, all of which make the development of standardized reference extracts difficult if not impossible. It is important to note that allergens differ in their potency. For example, at the same dose, exposure to peanut alone is much more likely to induce anaphylaxis than exposure to multiple pollens in individuals with allergies to both peanut and olive tree pollens. The most potent allergens are those found in food, followed by cat, then house dust, and the

very end of the list is mold. In other words, exposure to mold is much less likely at the equivalent dose to induce a clinically significant allergic reaction than other allergens.

Asthma and Rhinitis

In numerous epidemiological studies, sensitization to fungi and subsequent exposure to outdoor airborne fungal allergens, in particular *Alternaria alternata* and *Cladosporium herbarum*, is associated with the development of asthma, its persistence from childhood into early adulthood, and the severity of its symptoms. Interestingly, there is no evidence that this extends to indoor mold exposure. Sensitization to fungal allergens has also been demonstrated in patients with allergic rhinitis and atopic dermatitis, but it has not been conclusively proven that exposure to airborne mold, whether indoors or outdoors, is responsible for their clinical manifestations. The relative lack of influence of indoor mold on the induction and sensitization is very likely due to the overwhelming outdoor exposure that all individuals will have throughout their life spans. This is illustrated by the observations that there are no significant differences in allergies and asthma in patients who live in humid environments versus those

that live in a dry environment; all, at some point or another, have continual exposure to the ubiquitous fungal allergens found in air.

Allergic Bronchopulmonary Aspergillosis and Allergic Fungal Rhinosinusitis

One of the most severe, if rare, fungus-induced allergic diseases is allergic bronchopulmonary aspergillosis (ABPA). It is caused by hypersensitivity to *Aspergillus fumigatus* and occurs in patients with asthma, cystic fibrosis, or chronic obstructive pulmonary disease (COPD). Several other fungi, mainly *Candida*, *Bipolaris* spp., *Schizophyllum commune*, and *Curvularia* spp. are capable of causing a clinical entity similar to ABPA, which is then called allergic bronchopulmonary mycosis (ABPM) [23]. It appears to be associated with asthma much less frequently than ABPA.

Since germination of conidia into mycelium is associated with greater production and release of allergens [24], colonization with *Aspergillus* is thought to be required for sensitization and the generation of *Aspergillus*-specific IgE as well as IgG antibodies [25]. In keeping with the presence of both classes of antibodies, type I as well as type III hypersensitivity reactions contributes to the pathogenesis of ABPA. It is the tissue dysfunction induced by pre-existing airway damage, mucus hypersecretion, and defective clearance that allows the germination of fungal spores within the lung and, thus, colonization and chronic exposure to fungal allergens. This makes ABPA an allergic rather than an infectious disease, even if it is occasionally listed with the infectious fungal diseases [26].

Allergic fungal sinusitis or rhinosinusitis (AFRS) is a localized hypersensitivity reaction similar to that seen in ABPA and first described in patients with ABPA [27]. It can occur when fungi colonize the sinuses of subjects with underlying allergic disease and impaired tissue drainage. While *A. fumigatus* continues to be the most frequently isolated mold species, it has since been recognized that other *Aspergillus* species, dematiaceous fungi (dark pigmented fungi, such as members of the genera *Bipolaris*, *Exserohilum*, *Curvularia*, and *Alternaria*), and various other fungal species can cause AFRS [28].

Of particular note, fungal colonization of the lungs is common in patients with asthma, cystic fibrosis, or COPD, and fungal colonization in the sinuses is seen even in the vast majority of healthy subjects; yet only some of them develop ABPA or AFRS. The reasons for this are currently unclear, but genetic as well as other predisposing factors are likely to play a major role [25]. Also note that *A. fumigatus* is a common outdoor mold, even if it has been associated with building moisture in some studies. Likewise, most of the molds and yeasts implicated in ABPM and AFRS are found primarily

outdoors or detected with near equal frequency in outdoor and indoor environments. There is nothing to conclusively link indoor mold exposure to the development of ABPA, ABPM, or AFRS.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is an interstitial granulomatous lung disease that occurs in susceptible individuals who have become sensitized to a triggering antigen as a result of repeated inhalation exposure to organic dust [29]. Prolonged and/or high-dose exposure is required for sensitization to occur and symptoms to develop. The presentation of HP is traditionally subdivided into acute, subacute, and chronic, but considerable overlap between these forms of presentation is increasingly recognized. A CT scan can be utilized to identify these forms, as acute HP may show pulmonary edema, while subacute HP may show a ground glass appearance. Chronic HP usually demonstrates bronchiectasis or signs of pulmonary fibrosis such as reticulation on CT scan [30].

It is very important to recognize this disease in its earliest stages, when antigen removal is often sufficient for recovery. If antigen exposure continues, chronic HP with irreversible pulmonary fibrosis can develop. Hypersensitivity pneumonitis is most frequently caused by bird proteins (pigeon breeders' disease or bird fancier's HP) and bacteria. For example, one of the most frequent causes of farmer's lung, another designation of HP, are thermophilic actinomycetes. However, a variety of fungal antigens also have been implicated in various forms of occupational HP, including *A. alternata*, *Aspergillus* spp., and *Penicillium* spp. along with other molds and mushrooms [29, 31].

Patients with HP usually have high levels of antigen-specific IgG antibodies, preferably detected as precipitins in double diffusion tests. Whether these IgG antibodies merely represent a marker of exposure or actively participate in the pathogenesis of the disease remains uncertain, but it is generally believed that HP involves a combination of types III and IV hypersensitivity reactions. In the settings where HP occurs, many people may be exposed to the same levels of the causative antigens and some of those may actually become sensitized, as indicated by the presence of specific IgG antibodies in their serum. Yet, only a few of these individuals actually develop HP. This strongly suggests that genetic susceptibility or gene-environment interactions play a major role.

It had long been felt that exposure levels commonly encountered in the home or white-collar work environment would be unlikely to cause HP. One well-known exception has been a seasonal form of HP that occurs mainly in Japan and is caused by members of the genus *Trichosporon*. Each summer after the rainy season, this summer-type HP affects some residents of homes south of latitude of 40° north.

However, there is an increasing number of reports linking other types of household or office mold exposure to the development of HP [32, 33]. These include cases of humidifier lung, which may involve fungi, ameba, thermophilic bacteria, or mixtures of all three, as are found on humidifiers, dehumidifiers, or contaminated air conditioners. Fungal species implicated in HP due to home or office exposures include *Cladosporium cladosporioides*, *C. herbarum* [34], *A. fumigatus* [35], *Bjerkandera adusta* [36], and *Fusarium vasinfectum* [37]. A fatal outcome of HP after “home exposure” to mold has been reported [38], but the exposure level was unusually high because the patient did the renovation of his severely mold-damaged mobile home. *F. vasinfectum* was isolated from wall scrapings in his home, suggesting that the patient had been chronically exposed to this mold, followed by very high levels of exposure during the renovation, which led to an acute exacerbation of his symptoms. Death is believed to have resulted from a complication of an open lung biopsy performed in the context of continuously declining lung function.

Fungal Infections

Infections constitute another well-established way in which fungi can affect human health. It has been estimated that approximately 300–600 fungal species can be pathogenic to humans, but only about 30 of those are responsible for the vast majority of fungal infections. In healthy, immunocompetent individuals, fungal infections mostly remain superficial, i.e., affect the skin (tinea), nails (onychomycosis), or mucosal surfaces (thrush). A limited number of fungal pathogens can cause more serious disease in healthy subjects. These include several dimorphic fungi, meaning fungi that generally grow as yeasts at body temperature, but as molds at room temperature. Four types of these pathogenic dimorphic fungi are endemic in the USA, namely *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, and *Cryptococcus gattii* (see also Table 2 for the diseases they cause and their areas of endemicity). It is noteworthy that infection with any one of these endemic species does not invariably cause symptomatic disease (see also Table 2), indicating that individual susceptibility is a decisive factor. Chronic pulmonary aspergillosis may not only occur in the context of an intact immune system but also in patients who have pre-existing lung disease, such as tuberculosis, non-tuberculous mycobacterial disease, asthma, COPD, pneumothorax, or sarcoidosis.

Other invasive fungal infections are caused by opportunistic fungal pathogens, i.e., fungi that are commensals or are ubiquitous in the environment, do not cause disease in healthy individuals, but have the ability to cause severe, frequently fatal, disease in subjects who are in some way immunocompromised. For example, several species of the yeast *Candida*, in particular *Candida albicans*, are ubiquitous commensal

organisms that live on human mucosal surfaces, but account for about 80% of major systemic fungal infections in immunocompromised patients. Unlike mucosal candida infections, “systemic candidiasis” is a condition that only occurs in people with specific risk factors, such as HIV, immunosuppressed individuals, hospitalized individuals, or the presence of a central line or other invasive foreign body. Unfortunately, many healthy individuals often claim to have systemic candidiasis without any evidence of positive cultures, or identification of the presence of candida by DNA analysis.

Cryptococcus neoformans is a yeast with a worldwide distribution found in the soil and trees, but also associated with bird guano. It most commonly infects the central nervous system, lung, or skin and affects patients with immune deficiencies, in particular those with HIV infection or AIDS. In addition to yeasts, molds can also cause serious infections. Foremost among these is, once again, *A. fumigatus*, the primary cause of invasive aspergillosis, although other species of *Aspergillus* have been implicated as well [39]. This invasive fungal infection used to occur mainly in neutropenic hosts, but is now increasingly diagnosed in non-neutropenic hosts—i.e., subjects who are immunocompromised because of corticosteroid use, chemotherapy, or immunosuppressive therapy after hematopoietic stem cell transplants or solid organ transplants. A variety of *Fusarium* species can also cause invasive and disseminated disease in immunocompromised hosts, with the greatest risk of dissemination in patients with acute leukemia, severe neutropenia, and recipients of hematopoietic stem cell transplants [40]. It must be underscored that fungi, including the potentially pathogenic yeasts and molds are ubiquitous, and this makes it virtually impossible to prevent immunocompromised patients from being exposed to them.

Toxicity

Certain fungal genera can produce mycotoxins, defined as secondary metabolites that can cause a toxic response in vertebrates when ingested in sufficient doses [41, 42]. When such toxins harm bacteria, we choose to call them antibiotics. As secondary metabolites, mycotoxins are not required for primary growth or reproduction, and their precise role remains to be elucidated. Several hundred mycotoxins have been identified to date. Only a limited number of mycotoxins impact global agriculture by reducing crop yield and endangering food security. These are mainly produced by members of the genera *Aspergillus*, *Penicillium*, and *Fusarium* and include the major aflatoxins, namely aflatoxin (AF) B1, AFB2, AFG1, and AFG2; ochratoxin A (OTA); certain trichothecenes such as deoxynivalenol (DON), nivalenol, T-2 toxin and HT-2 toxin; the fumonisins B1 (FB1) and FB2; and zearalenone (see also Table 3 for a selected list of mycotoxins and some of their major producers). Mycotoxicosis in humans and animals is due to the ingestion of contaminated food and feed.

Table 2 Mycoses

Name of disease	Causative agent	In	Area of endemicity	Incubation period	Primary symptoms
Blastomycosis	<i>Blastomyces dermatitidis</i>	In moist soil and decomposing matter	Central and southeastern USA	3 weeks–3 months, but only ~half of all infected people ever develop symptoms	Cough, hemoptysis, fever, dyspnea, muscle aches or joint pain, weight loss, chest pain, fatigue
Coccidiomycosis	<i>Coccidioides immitis</i>	In soil	Southwestern USA	1–3 weeks, but many infected people never develop symptoms	Cough, hemoptysis, fever, dyspnea, muscle ache or joint pain, and weight loss
Histoplasmosis	<i>Histoplasma capsulatum</i>	In soil and bird and bat droppings	Midwestern and southeastern USA, notably Ohio, and Mississippi River valleys	3–17 days, but most people who are infected will not develop symptoms	Fever, chills, headache, muscle aches, dry cough, chest discomfort
Cryptococcosis	<i>Cryptococcus gattii</i>	In soil and in association with certain trees	Northwestern USA	2–13 months	Lung: cough, dyspnea, chest pain, fever Brain: (meningitis) headache, fever, neck pain, nausea, vomiting, sensitivity to light, behavioral changes

Therefore, the maximum concentration of the major mycotoxins in the most frequently affected foodstuffs is regulated in the majority of countries, and acceptable dietary intake levels have been established. As a result, acute toxicoses are rare even in developing countries, but an example is the outbreak of aflatoxicosis in Kenya in 2004 during which 317 cases of acute liver failure occurred and at least 125 people eventually died [43]. Even in industrialized countries, chronic mycotoxicosis may not be completely preventable in certain groups with high consumption of specific dietary items. Humans exhibit substantial differences in susceptibility due to genetic differences in the enzymatic pathways involved in the bioactivation and metabolism of mycotoxins and differential influences of age, sex, weight, dietary factors, nutritional status, presence of chronic infections, and possibly other lifestyle and environmental aspects [41]. Such differences in susceptibility are also seen between and within animal species. Overall, mycotoxins can affect essentially every organ and tissue in the body [42]. Yet, individual mycotoxins show some specificity in the mechanisms of toxicity and also in the tissues they affect, even if these may differ between species. Many mycotoxins are genotoxic and carcinogenic in animals, and chronic mycotoxicosis in humans may also manifest as cancer [41, 42]. The International Agency for Research on Cancer (IARC) has classified the major aflatoxins (AFB1, AFB2, AFG1, AFG2 and the metabolite AFM1) as human carcinogens. As Table 3 shows, several other mycotoxins are considered potential human carcinogens, and yet others cannot currently be classified as to their carcinogenicity.

The only plausible basis for mycotoxicosis would be from ingestion. Although there have been inhalation cases reported,

they are very poorly documented and not plausible [44–46]. Organic dust toxic syndrome (ODTS) represents a toxicosis resulting from massive exposure to highly diverse mixtures of fungi, bacteria, and their toxins and other constituents [27, 47, 48]. Exposure levels exceeding 1×10^7 CFU/m³ or and likely even $\geq 1 \times 10^{10}$ spores/m³ seem to be required for the occurrence of ODTS [47, 48].

Does Dampness Mean Mold?

Associations between Dampness/Mold and Respiratory Health

Respiratory symptoms are the most frequent symptoms reported by occupants of certain buildings with poor indoor air quality and subsumed under the designation of “Sick building syndrome” (SBS), which also includes eye, nose, or throat irritation, cough, dry or itchy skin, nausea, headaches, dizziness, difficulties concentrating, and fatigue. This term is a misnomer since the building is not sick, but its occupants report feeling sick while in the building. In addition, the symptoms it encompasses do not fulfill the definition of a syndrome; hence, a better term would be non-specific building-related symptoms. Investigators generally are unable to find any specific cause for the reported symptoms and a medical diagnosis is equally difficult. However, a large variety of physical causes and psychosocial factors have been linked to such non-specific building-related symptoms; one should consider insufficient ventilation, certain chemical emissions, and dampness or evidence of moisture damage.

Table 3 Selected Mycotoxins and some of the Fungal Species Producing Them [42]

Mycotoxin		Acronym	Species	IARC class ^a
Aflatoxins	Aflatoxin B1	AFB1	<i>Aspergillus</i> section <i>Flavi</i>	1
	Aflatoxin B2	AFB2		
	Aflatoxin G1	AFG1		
	Aflatoxin G2	AFG2		
Ergot alkaloids		EA	<i>Claviceps purpurea</i>	
			<i>C. fusiformis</i>	
			<i>C. africana</i>	
			<i>Neotyphodium</i> spp.	
Fumonisin	Fumonisin B1	FB1	<i>Fusarium</i> section <i>Liseola</i>	2B
	Fumonisin B2	FB2		2B
Ochratoxin A	Ochratoxin A	OTA	<i>Aspergillus</i> section <i>Circumdati</i>	2B
			<i>A.</i> section <i>Nigri</i>	
			<i>Penicillium verrucosum</i>	
			<i>P. nordicum</i>	
Sterigmatocystin	Sterigmatocystin	Various species of - <i>Aspergillus</i> - <i>Penicillium</i> - <i>Chaetomium</i>		2B
Trichothecenes Type A:	T-2 toxin	T-2	<i>Fusarium acuminatum</i>	3
	HT-2 toxin	HT-2	<i>F. poae</i>	
			<i>F. sporotrichoides</i>	
			<i>F. langsethia</i>	
Type B:	Deoxynivalenol	DON	<i>Fusarium graminearum</i>	3
			<i>F. culmorum</i>	
			<i>F. cerealis</i>	
			<i>Fusarium</i> spp	
Type D (macrocyclic trichothecenes)	Nivalenol		<i>Stachybotrys chartarum</i>	3
	Satratoxin G		<i>S. chartarum</i>	
	Satratoxin H			
	Roridin			
Zearalenone	Zearalenone	ZEN	<i>Fusarium graminearum</i>	3
			<i>F. culmorum</i>	
			<i>F. equiseti</i>	
			<i>F. cerealis</i>	
			<i>F. verticillioides</i>	
			<i>F. incarnatum</i>	

^a IARC classes:

1 carcinogenic to humans, 2A probably carcinogenic to humans, 2B possibly carcinogenic to humans, 3 not classifiable as to its carcinogenicity to humans

As reviewed by several scientific bodies, including the Institute of Medicine (IOM) and the WHO [24, 49–53], a long list of studies from a variety of geographic areas quite consistently show signs of building dampness or mold to be associated with a variety of adverse health effects. These associations are seen both in domestic and public building environments and they are present whether the signs of dampness/mold are reported by the occupants or assessed by an inspector. They are particularly detected in allergic individuals, but also in non-atopic subjects. There have been far fewer attempts to link exposure to

dampness or mold to symptoms typically associated with the so-called sick building syndrome, i.e., irritation of eyes, skin, mucous membranes, fatigue, nausea, headache, insomnia, and difficulty concentrating. The results have been quite inconsistent and in the majority of cases, no significant associations could be detected [49].

It needs to be underscored that the agents responsible for the statistical associations between indicators of building dampness and respiratory symptoms have not been identified. The assessment of “dampness or mold” most commonly relies

on answers of the building occupants to questions that may cover anything from condensation on the windowpanes to visible mold or mold odor. The fact that these descriptors often yield similar risk estimates for many types of respiratory symptoms has been taken as an indication that indoor molds could be responsible. So far, this has proven impossible to conclusively demonstrate. With a few exceptions [6, 54–57], indicators of dampness or mold are not associated with total viable fungi in air [4, 13, 15, 58–61] or dust [4, 13, 15, 61]. The associations may even differ between two rooms within the same household [5], suggesting that they are chance findings—in part due to the lack of correction for multiple comparisons. Correlations between signs and dampness and other potential measures of fungal exposure, such as total fungal cell equivalents obtained by qPCR [15], ergosterol, or β -glucans also are mostly weak or entirely absent [61–63]. When attempts are made to link specific fungal genera, species or assay groups identified via qPCR analyses to moisture damage the results differ not only from those obtained by culture-based methods in the same study [13], but also from those of other investigations [15, 64–66]. Furthermore, the various measures of fungal exposure rarely correlate with each other [4, 15], including airborne and dustborne levels of total viable fungi [4, 5]. Even using qPCR and a sampling time of 6–8 h for air samples, no correlation could be detected between dustborne and airborne concentrations of 36 mold species and the few exceptions showed correlation estimates of ≤ 0.34 [64].

Most importantly, studies that attempted to correlate specific measures of microbial exposures to health outcomes have yielded inconsistent and, at times, contradictory results [53]. Among the most recent investigations, there is at least one report of an association between airborne-viable mold levels ≥ 300 CFU/m³ in schools and an increased risk of dry cough at night, persistent cough, and rhinitis [8]. Importantly, however, studies failed to reveal any significant correlations between viable airborne mold and asthma or allergy in children [58, 67], “SBS” symptoms in adults [54], or respiratory health in the elderly [68]. A similar lack of association was noted between dustborne concentrations of culturable mold, ergosterol, β -glucans, or fungal DNA cell equivalents (by qPCR) in homes, schools, or both and allergic disease, asthma, respiratory symptoms, or lung function in children [61, 69–72]. Finally, others detected a protective effect of total viable airborne fungi on throat and respiratory symptoms and a similar protective effect was seen for the genus *Cladosporium*, while *Penicillium* was inversely associated with skin symptoms [73]. The presence of significant correlations appears to depend quite strongly on the precise nature of the sample. [7, 8, 73, 74]. This is illustrated by a series of publications arising from the same dataset obtained by analyzing different types of dust samples from Malaysian schools [75–77]. Wheeze and daytime attacks of breathlessness were found to correlate with *Aspergillus versicolor* DNA concentrations in dust collected in Petri dishes kept on top of book shelves

over a period of 7 days, but not with *A. versicolor* DNA in dust samples swabbed from the top of the classroom blackboard [75]. Similarly, *Streptomyces* DNA from Petri dishes, but not from swab samples, was associated with doctor-diagnosed asthma. Total as well as specific fungal DNA measured in settled dust (vacuumed from the floor and other higher surfaces) was essentially not related with self-reported weekly symptoms of rhinitis or various types of SBS symptoms (i.e., ocular, throat, dermal symptoms, headache, tiredness) [76]. Yet, when total fungal DNA was measured in swab samples of dust from the top of the blackboard associations with rhinitis, eye and throat symptoms were detected, but not in dust collected in Petri dishes [76].

Are Mold Spores the Relevant Exposure?

Such discrepancies raise the questions of whether (a) molds constitute the relevant exposure and (b) this exposure is assessed in a meaningful way. The first question cannot be answered at this time, in part because the answer to the second question is a resounding “no.” It has been largely ignored that there can be enormous within-day and day-to-day variability in the levels of total culturable fungi in indoor air [78], even if the variation may not to be statistically significant in all regions [79]. In addition, total viable spore counts in indoor air show marked variation over longer periods of time [56], particularly during different seasons [80]. Season has also been identified as an important determinant of airborne fungal levels in cross-sectional studies [5–7, 60, 80]. It has been calculated that 11 samples would have to be obtained on separate days and at different times of the day in order to characterize the true (within the 95% confidence interval) mean airborne-viable fungal concentration of a normal residence, at least in a subarctic climate. Yet, the vast majority of studies that attempted to correlate fungal measurement with reported dampness or mold or with respiratory symptoms relied on one single measurement of airborne fungal levels. Further tape lifts for mold evaluation and quantitation are statistically flawed and not clinically useful.

It is frequently claimed that dust—whether floor dust or airborne settled dust—provides a time-integrated or cumulative measure of fungal exposure [5, 12, 61, 81]. However, there are data suggesting that dustborne fungi represent a unique population and, therefore, are not representative of fungal exposure in the breathing zone [4]. In addition, tape lifts for mold evaluation and quantitation are flawed and do not provide meaningful data. Furthermore, considerable variation over time is also seen in dustborne mold concentrations, whether assessed as total viable fungi [82, 83], total fungal biomass as represented by ergosterol concentrations [62], or as the concentrations of individual fungal genera, species, or assay groups determined by PCR [81]. Most importantly, the variation over time is greater within homes than between homes for both airborne and dustborne mold concentrations

[56, 82]. According to calculations based on the ratio of the within-home to between-home variance, at least nine repeated measurements of dustborne culturable fungal concentrations would be necessary to keep the measurement bias below 20% [56, 82]. Can it really be more than chance, then, if the combined levels of three mold species (among a total of 36 species tested) detected in a single dust sample supposedly predict the development of asthma 6 years later [11]?

In view of the considerable short-term variation in fungal levels, it seems far more likely that the use of a single dust or air sample leads to massive exposure misclassification, particularly if one considers that sampling times as short as 1 min are common for the assessment of airborne viable fungi. This means that, when the concentrations of total indoor fungi or individual fungal species are derived from a single sample, their associations with health effects represent chance findings. It should also be remembered that culturable fungi represent only a small fraction of the total fungal biome and provide little insight into its true diversity and complexity. It is recommended to obtain an outdoor air sample at the same time as the indoor air sample so that the composition of the diversity of the mycobiomes and the rank order and concentrations of individual species in the two compartments can be compared in order to determine whether there is an indoor source for the species under investigation. However, since outdoor mold levels fluctuate to a similar or even greater extent compared to indoor concentrations, multiple measurements, including morning and afternoon samples, will be necessary in order to prevent misclassification [84].

Biomonitoring Is Not a Valid Measure of Mold Exposure

Serum IgG against mold is a much abused test. It is helpful in HP, but otherwise, it is to be expected that all individuals will have IgG antibodies against mold, just as they have IgG antibodies against an enormous number of other microbes. In fact, even in subjects with the same high occupational exposure level to molds, the specific IgG value is highly variable; conversely, even healthy individuals can have high levels of specific IgG [3]. Therefore, group mean concentrations in highly exposed workers constitute a marker of exposure, but the use of individual serum concentrations of specific IgG antibodies is not a validated indicator of exposure. The levels of mold-specific IgG detected in environmentally exposed subjects are at least 10 times lower compared to those found in patients with HP [85] and do not show associations with various measures of indoor mold exposure [86–88] or with symptoms attributed to this exposure [85, 89]. The problems discussed in the context of determining mold-specific IgE antibodies also hold for IgG, i.e., the lack of standardized fungal extracts and the extensive cross-reactivity between molds.

Other Potential Explanation for the Associations between Dampness and Respiratory Health

The vast majority of studies that attempt to link respiratory and other health outcomes to building-related factors, including investigations that encompass other SBS symptoms, are cross-sectional and rely on self-reported measures of both exposures and symptoms or health outcomes. This makes them particularly vulnerable to reporting bias. Indeed, both logistic regression analysis and structural equation analysis of longitudinal data strongly suggest that the direction of the causal pathway between the perceived indoor environment and self-reported symptoms is opposite to what is generally assumed. In other words, perceived health problems may lead to complaints about the indoor environment rather than the reverse [90, 91].

Among the physical factors that could mediate an effect of dampness on health, the exclusive focus on molds is difficult to comprehend given the high complexity of the indoor environment even when there is no excess moisture. In addition to a large variety of molds, there is likely to be a similar variety of bacteria; volatile organic compounds (VOC, which can be of microbial origin or gassed off by building materials, furniture, carpeting, etc.); semivolatile organic compounds (sVOC); and other chemicals; along with allergens given off by pets, house dust mites, and possibly even rodents. In damp indoor environments, the concentrations of many of these substances are likely to be elevated because not only certain fungi require high moisture levels for optimal growth but certain bacteria and even dust mites also thrive and reproduce more rapidly at a higher relative humidity [24]. Yet, the potential effects of dampness on changes in the bacterial biome and the impact of these changes on health outcomes have rarely been investigated and the few existing studies have yielded contradictory results [24, 63, 72]. Of note, the same methodological issues that severely limit the validity of the results from fungal studies also apply to bacterial investigations, including the great diversity and temporal as well as spatial variability of bacterial populations both outdoor [92] and indoor [93].

Even though moisture is expected to increase the number of microbes, microbes do not appear to greatly contribute to the indoor air concentrations of total VOC [94]. Nonetheless, moisture accelerates the process of chemical or biological degradation, thereby resulting in the release of chemicals [24]. In addition, increases in the relative humidity are associated with higher concentrations of VOC, possibly because of competition between the water and the VOC for sites of adsorption on certain materials [95]. The low concentrations at which VOC and most other chemicals individually are present in indoor environments are unlikely to represent a direct health hazard [96, 97]. Yet, it should be kept in mind that even relatively simple mixtures of substances may have more than

additive, possibly synergistic, but also antagonistic, effects [96, 98]. In slightly more complex mixtures, even when substances are used at concentrations below the carefully determined “no observed effect” level, their combinations may have measurable effects [99]. Also note that even simple combinations of a mold, a bacterium, and a protozoon can have pro-inflammatory and cytotoxic effects that go beyond mere additivity [100–102], with the precise nature of the outcome depending on the proportion in which the individual microorganisms are present [103]. Most remarkably, a mixture of fungal and bacterial spores derived from co-cultivation of their respective microorganisms can have different effects compared to co-exposure to the separately cultivated spores [103–105]. This should make it clear that the focus of attention should be widened to include fungi, bacteria, chemicals, and, above all, their interactions, even if that is likely to be a daunting task with the currently available tools. But, instead, the focus has all too often narrowed from molds in general to “toxic mold.”

Toxic Mold

Toxic Mold Syndrome

In the early 1990s, an unusual cluster of cases of pulmonary hemorrhage in infants occurred in Cleveland, OH [106]. Although early reports seemed to suggest a link between these cases and inhalation of mycotoxins produced by *Stachybotrys chartarum*, in particular, satratoxins, later epidemiological studies failed to confirm any causal relationship [107]. By that time, however, the initial reports had triggered widespread media coverage and the coining of the term “toxic mold syndrome.” Patients who present with what they consider mold-induced illness report a variety of non-specific symptoms (including upper and lower respiratory tract symptoms, headache, and fatigue) greatly resembling those subsumed under the term “SBS” [108, 109]. Indeed, “toxic mold syndrome” or simply “toxic mold” are terms that now are frequently used as synonymous with “sick building syndrome.” This implies that all of the non-specific symptoms that some people report in association with exposure to a certain building environment are blamed on mycotoxins, and many people think of mycotoxins as meaning satratoxins produced by *S. chartarum*. This is incorrect.

Toxigenic and Non-toxigenic Strains

In order to show conclusively that mycotoxins in general, or satratoxins in particular, are responsible for any effects on human health, it would have to be demonstrated that they are present and can be absorbed in sufficient amounts within a reasonably short time frame. Inhalation represents the most likely route of exposure to mycotoxins in indoor

environments. The first thing to consider is that, in general, not all strains of a particular mycotoxin-producing species are toxigenic, i.e., have the ability to produce mycotoxins [110–112]. *S. chartarum* is a prime example: only 30–40% of its strains produce macrocyclic trichothecenes, including the highly toxic satratoxins G and H, while the other strains are characterized by atranone production [113, 114]. The two types of strains are classified as chemotypes S and A, respectively. Secondly, even if a strain is capable of producing a particular mycotoxin in vitro, the indoor environment from which the strain was isolated does not necessarily contain detectable levels of this mycotoxin [115]. This reflects that mycotoxin production depends on a large variety of factors, including the growth medium or substrate, the growth stage of the fungus, temperature, water activity, pH, and the presence of other fungi and bacteria [104, 111, 116]. Moisture-damaged buildings invariably contain complex mixtures of fungi and bacteria and these may compete for the same substrates and nutrients or may elaborate substances capable of inhibiting the toxin production of other microbes. This means that the mere presence of a toxigenic fungal species does not prove the presence of mycotoxins.

Airborne Mycotoxins

Mycotoxins are not volatile, but can become airborne on conidia [117, 118]. *S. chartarum* and other fungi are capable of exuding mycotoxins in fluid droplets in a process called guttation [119], but the clinical relevance of this ability remains untested. The conidia of *S. chartarum* are formed inside a sticky polysaccharide matrix and, therefore, not easily aerosolized. As a consequence, the presence of *S. chartarum* in air samples is difficult to demonstrate by culture-dependent or -independent methods, and the reported CFU or cell equivalent values are invariably low [8, 120, 121], even in homes with very heavy mold contamination [122]. Detection frequencies via qPCR in dust samples may be considerably higher, but even then the reported levels are very low [8, 123, 124].

Conidia or spores are not the only means of rendering fungal toxins airborne. Most fungal genera, including *S. chartarum*, also release smaller fragments, and there are data suggesting that these conidial and hyphal fragments can carry mycotoxins [10]. Hardin et al. [125] showed that the volume of 20,000 fragments with a spherical shape and a diameter of 0.3 μm would be required to make up the volume of a single spore. Based on the data available at the time, which showed that fragments outnumbered spores by 320:1 to 500:1, it was not plausible to claim that such fragments made a significant contribution to mycotoxin levels in the air. Since the surface area to volume ratio increases as the size of a sphere decreases, only 100 fragments would have the same surface area as one spore. In a recent field

study, such fungal fragments were measured in moldy houses and found to outnumber spores by a factor of 10^3 to 10^6 to 1^{11} .

Exposure Levels and Risk Assessment

Exposure Levels

As summarized in Table 4, a variety of mycotoxins have been detected in indoor air in picogram per cubic meter concentrations, but with wide variations between studies

and between buildings within studies [126–128], while dust contains levels of <1–43 pg/mg. The only reliable data on the detection of satratoxins in indoor air come from LC-MS/MS analysis and show concentrations of satratoxin G and satratoxin H of 0.25 and 0.43 ng/m³, respectively [126]. Assuming this data is even correct, breathing in such air at a respiratory minute volume of 6 L/min over a period of 8 h would result in the inhalation of only 0.72 ng of satratoxin G and 1.2 ng of satratoxin H; as per discussion above and below this is far less than the quantities humans are exposed to in normal activities, including ingestion of food.

Table 4 Mycotoxin concentrations in air samples

Mycotoxin	Sample type	Analytical method	Concentration	Reference
Satratoxin G	Air from 1 water-damaged dwelling	LC-MS/MS	0.25 ng/m ³	[126]
Satratoxin H			0.43 ng/m ³	
Multi-mycotoxin	Air from 20 homes with visible dry rot (<i>Serpula lacrymans</i>)	HPLC-MS/MS		[127]
Altenariol	4/20 homes		<LOQ to 0.30 ng/filter (= 8.3 ng/m ³)	
Ochratoxin A	1/20 homes		0.15–0.34 ng/filter (= 0.0004–0.0009 ng/L = 0.4–0.9 ng/m ³)	
All others (aflatoxins B1, B2, G1, G2, M1, diacetoxyscirpenol, gliotoxin, mycophenolic acid, neosolaniol, ochratoxin A, T-2 toxin and others)			ND	
Multiple mycotoxins	Air from 7 water-damaged buildings	LC-MS/MS		[128]
Ochratoxin A	3/7 buildings		0.0115–0.228 ng/m ³	
Aflatoxin B1			0.0024–0.1463 ng/m ³	
Aflatoxin B2			0.0003–0.0211	
Roquefortine			0.009–4	
Sterigmatocystin			0.0034–1.7674	
Multiple mycotoxins	Dust from 4 homes with a history of water damage			[129]
Verrucarol		GC-MS/MS	19 and 43 pg/mg dust	
Trichodermol			2.4 and 3.4 pg/mg dust	
Trichodermin			ND	
Satratoxin G		HPLC-MS/MS	ND	[130]
Satratoxin H			ND	
Sterigmatocystin			17 pg/mg dust	
Multiple mycotoxins	Dust from 5 severely mold-contaminated homes in New Orleans after Hurricane Katrina			[123]
Verrucarol		GC-MS/MS	0.6, 0.6, 18 pg/mg dust	
Trichodermol			ND	
Trichodermin			ND	
Satratoxin G		HPLC-MS/MS	ND	
Satratoxin H			ND	
Sterigmatocystin			16, 28 pg/mg dust	

ND = not determined

Biomonitoring

Biomarkers of internal exposure were first developed for AFB1 and more recently for OTA, while such markers are under development or in the process of validation for DON, and FB1 [42, 131]. Serum AFB1-albumin adducts are commonly used as a measure of chronic dietary exposure [42]. Such adduct formation has also been demonstrated after exposure via inhalation (with a possible contribution from dermal absorption) in workers exposed to AFB1 in various highly contaminated occupational settings [44–46, 131–133]. Only the highest exposure levels seem to result in detectable AFB1-albumin adduct concentrations after inhalation. It has been claimed that similar adducts between satratoxin G and albumin were present in serum of three adult subjects who were reportedly exposed to *S. chartarum* in their homes [134]. However, others have already criticized the ELISA employed for the detection of satratoxin as non-specific and unvalidated [125], and the results have not been replicated or independently confirmed since then.

Toxicokinetics

Data on the toxicokinetics of mycotoxins are limited, particularly after inhalation exposure, based on direct and high-dose administration, suggest that airway exposure may result in greater bioavailability and toxicity compared to oral or parenteral routes of administration [135–137], but this is not a consistent finding [138]. The toxicokinetic patterns of essentially all orally administered mycotoxins investigated to date show considerable variation between animal species and between strains within species. This raises the question of whether and to what extent animal data can be extrapolated to humans. In airway exposure studies, the issue is further complicated by the widespread practice of giving experimental animals high doses of pure mycotoxins as a bolus via intratracheal instillation. It seems unlikely that this, in any way, captures the pattern of human exposure, which generally would be expected to consist of chronic low doses of mycotoxins associated with spores or fungal fragments mycotoxins.

Based on all available data on airborne concentrations of mycotoxins in residential and agricultural environments, spore counts in these environments, and levels of mycotoxins per fungal spore, it is predicted that exposure levels to mycotoxins in non-agricultural indoor environments will remain below the “concentration of no toxicological concern,” which was calculated as 30 ng/m³ taking into account additional routes of exposure and assuming complete bioavailability [125]. The concentration of no toxicological concern is based on the concept of “threshold of toxicological concern” originally developed for dietary exposures and extends it to inhaled substances. An earlier modeling study essentially yielded the same conclusion [139].

The Toxicity of *S. chartarum* Spores of Chemotypes A and S

There are some animal studies showing *S. chartarum* spores to have detrimental health effects [3]. However, in all of these studies, *S. chartarum* was administered via intratracheal or intranasal instillation and mostly in very high doses. When similar protocols are used, almost any fungal spore will induce comparable responses. Compared to inhalation exposure, intratracheal and intranasal instillation increases the number of spores that reach the alveolar region. According to an overall comparison of the available animal data, this may give rise to greater inflammatory responses and granuloma formation in the lung and dissemination of the spores to other tissues [3].

Unlike fungal spores of other species, *S. chartarum* at very high doses and given into the airways directly can cause pulmonary hemorrhage, but this is seen with both chemotypes, suggesting that this effect is not, or at least not exclusively, attributable to the satratoxins or other macrocyclic trichothecenes [3]. It also requires spore doses that are not likely to occur in indoor environments [140]. However, because of the problems associated with the use of intratracheal or intranasal instillation, animal models based on these routes of administration should not form the basis for extrapolating dose-response relationships to humans [3]. In experimental animals, clear differences in satratoxin susceptibility exist between species and between strains within a species [141, 142]. At somewhat lower doses than were used in the early experiments, differences between the two chemotypes of *S. chartarum* may become apparent. However, they depend on the duration of the experimental treatment, the spore dose and the outcome measures, and they appear to be of a quantitative or pharmacokinetic rather than of a qualitative nature [141, 143, 144]. Most of the differences between treated and control animals were associated with the instillation of any fungal spores (*S. chartarum* of chemotype A or S or *C. cladosporioides*), with minor contributions from the species and toxigenicity of the spores.

There is no evidence that *S. chartarum* or its satratoxins have inflammatory effects in humans. We note that (1) its presence in the breathing zone is difficult to demonstrate and its detection on building materials is not sufficient, (2) the contribution of other fungi and bacteria in a contaminated building is a major confounder, and (3) there are no validated biomarkers for internal exposure assessment. As a consequence, even when the home or work environment is proven to be contaminated with *S. chartarum*, it is not possible to causally link the presence of this mold to the symptoms experienced by the occupants [89]. It should be pointed out, however, that mold-specific allergy may be the cause of mold-related symptoms in patients using an allergy panel of molds [108]. In others, the symptoms attributed to mold exposure may be due to allergic reactions to other aeroallergens,

including some derived from the patients' own pets [109]. Other pre-existing disorders or conditions may underlie the symptomatology in the majority of the remaining cases [109]. Importantly, a contribution from exposures that were not even considered much less investigated cannot be ruled out in any of these subjects.

Is there a Relationship between Mold and Autoimmunity?

Autoimmunity is a broad category of diseases in which the human body targets its own tissues. The presence of antibodies may be pathogenic, but in many cases may simply be an epiphenomenon [145]. The origin of autoimmune diseases is probably a combination of genetic [146, 147], epigenetic [148–150], and environmental factors [151–157], which interact in some chaotic or stochastic manner to produce these diseases in a way that we do not completely understand.

More recently, the microbiome has been targeted as a possible contributor to the development of autoimmunity [158, 159], but molds generally are not part of such investigations [159]. Even the role of probiotics in autoimmune diseases has been studied [161, 162], but again, there is no link between molds and autoimmunity.

Although it has been suggested that there is a relationship between mold exposure and autoimmunity, most of these reports are unfounded and are not based on solid scientific evidence. Unfortunately, many non-scientific and non-medical websites have been spreading false information about mold and autoimmune diseases such as chronic inflammatory demyelinating polyneuropathy (CIDP). CIDP is a disease that resembles Guillain-Barre syndrome, but there is *no* evidence that mold exposure is even remotely associated with this disease. In fact, a search of PubMed revealed that there are no studies confirming an association between CIDP and mold. There are numerous well-designed studies in recent years on the pathogenesis of autoimmune diseases, ranging from genetic predisposition [146, 147, 163, 164] to environmental triggers [165, 166], and yet none of them remotely suggest that molds can be a contributing factor to autoimmunity. Specific cellular [167] and humoral [168, 169] factors of both the innate [170] and adaptive [171–173] immune systems have been demonstrated to play roles in the development of the various autoimmune diseases. The cytokine milieu and the balance of T cells such as Treg and Th17 cells [167, 174], as well as various other cytokines [175–180] and cellular processes such as autophagy [181, 182] have been attributed to the development of autoimmune diseases, yet molds have never been shown to impact these pathways in a clinical significant manner.

In particular, one publication from 2003 describes a putative correlation between mold exposure and a myriad of inflammatory markers [183]. The study claims to establish a link between mold exposure and immunological dysfunction and

coined the term “mixed mold mycotoxicosis.” However, the study is plagued by poor study design, selection bias, and an inability to establish a cause and effect relationship. Moreover, the clinical symptoms reported are vague and subjective and bear no relationship to autoimmunity with the exception of fibromyalgia [184], illustrating the disconnection between what is observed in the laboratory and what is clinically significant.

The closest anyone has come to uncovering an association between molds and autoimmunity is perhaps a paper describing anti-*Saccharomyces cerevisiae* antibodies in patients with Crohn's disease and other autoimmune diseases. The role, if any, of these autoantibodies in Crohn's disease is not clear. It is postulated that there could be a pathogenic mechanism involving molecular mimicry between yeast mannan and autoantibodies that may play a role in autoimmune diseases, such as anti-U2snRNP B*, although much research has to be done to confirm any cause and effect relationship between the presence of these autoantibodies directed against a molecule that is predominately found in Baker's yeast [185].

Conclusion

Molds and fungi are ubiquitous and generally live in harmony with human beings. Only rare molds have been associated with human disease. The diseases that molds can cause are restricted to allergies, hypersensitivity pneumonitis and infection. There is no validity to the hype of “toxic black mold” and “mycotoxicosis.” Humans are not exposed to enough mycotoxins to develop illness, unless they ingest toxic quantities of mycotoxins or become exposed to intense organic dust storms.

With regard to sick building syndrome, it is highly probable that each building has its own unique microbiome with ever-varying combinations of bacterial, fungal, and chemical compounds that are likely to interact [15]. Sick building syndrome has been proven to be more about mass hysteria than any physiological illness. Fungi alone are almost certainly not responsible for the many health effects attributed to them, much less a single fungal species like *S. chartarum*.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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