Mold and Human Health: Separating the Wheat from the Chaff

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Abstract The term "mold" is utilized to define the ubiquitous fungal species commonly found in household dust and observed as visible multicellular filaments. Several well-defined human diseases are known to be caused or exacerbated by mold or by exposure to their byproducts. Among these, a solid connection has been established with infections, allergic bronchopulmonary aspergillosis, allergic fungal rhinosinusitis, hypersensitivity pneumonitis, and asthma. In the past decades, other less-defined and generally false conditions have also been ascribed to mold. We will herein review and critically discuss the available evidence on the influence of mold on human health.

Keywords Mold · Human diseases · Fungi kingdom

Mold and fungi

The Fungi kingdom is composed of ubiquitous unicellular and multicellular organisms, including single-celled yeasts, microscopic hyphae, aggregates of hyphae called mycelia, and spore-bearing, fruiting mushrooms. The term "mold," also called "mildew," refers to those species which form

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visible multicellular filaments, commonly subdivided in Ascomycota, Deuteromycota, and Zygomycota. Molds do not utilize photosynthesis but metabolize organic compounds by secreting hydrolytic enzymes to obtain energy and thus recycle nutrients within ecosystems. Molds are currently crucial in the production of food (i.e., cheese, bread, sausage, soy sauce, alcoholic beverages) and medications (i.e., penicillin, cyclosporine, lovastatin). Molds are pervasive in nature, and their spores are commonly found in household dust, particularly when favorable humidity conditions are present.

Only for a few mold species has a causative link with human disease been established; in these cases, signs and symptoms are usually pathognomonic. Recently, there has been an expansion in the number of conditions putatively ascribed to mold, thus leading to the concept of "mold toxicity" attributed to mycotoxins or irritants derived from fungi. This is little more than junk science.

Mycotoxins

Mycotoxins are low-molecular-weight, non-volatile, secondary metabolites produced by fungi that manifest an adverse effect on plants, animals, or other microorganisms. Roughly 300 mycotoxins have been identified, and these are not necessary for primary growth or reproduction. Examples of pathogenic mycotoxins include aflatoxins, ochratoxins, fumonisins, trichothecenes (including deoxynivalenol and T-2 mycotoxin), zearanenone, and ergot alkaloids [1]. These may have neurotoxic, carcinogenic, and teratogenic effects, causing disease termed mycotoxicosis (Table 1) well represented by the death of over 100 dogs in 2007 caused by commercial food contaminated with aflatoxins [2, 3]. In addition, ergot alkaloids and T-2 mycotoxin are of historical interest. First, ergot alkaloids cause ergotism, also known in the middle ages as St.

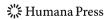


Table 1 List of known mycotoxins (original species) and induced human conditions [1]

Aflatoxins (Aspergillus flavus, Aspergillus parasiticus): hepatotoxicity, carcinogenicity, mutagenicity, teratogenicity, immunosuppression Ergot alkaloids (Claviceps purpurea, Claviceps fusiformis, Claviceps paspali, Neotyphodium coenophialum, Epichloe): convulsive and gangrenous symptoms, nausea, vomiting

Fumonisins (Fusarium verticillioides, Fusarium proliferatum): hepatotoxicity, interference with sphingolipid metabolism, leukoencephalomalacia in equines, pulmonary edema in swine, possible esophageal tumors in humans

Ochratoxin (Aspergillus ochraceus, Penicillium verrucosum): renal toxicity, hepatotoxicity, carcinogen

Trichothecenes

T-2 toxin (Fusarium sporotrichioides): hemorrhage, dermal necrosis and bloody diarrhea

Deoxynivalenol (also known as DON or vomitoxin) (Fusarium graminearum, Fusarium culmorum): vomiting in humans and swine, immunosuppression

Zearalenone (Fusarium graminearum, Fusarium culmorum): potent estrogenic metabolite usually affecting swine

Anthony's Fire, in which *Claviceps purpurea* contaminates rye or wheat and produces the mycotoxin causing convulsions and gangrenous phenomena. Of note, these symptoms were potential causes of the "bewitchments" which later lead to the Salem Witchcraft trials [1]. T-2 mycotoxin, a trichothecene made by *Fusarium*, caused the death of 10% of the population of Orenburg (Russia) due to "alimentary toxic aleukia" in the early 1900's and was later explored as a biological warfare agent [4].

It should be remembered that only specific fungal species produce mycotoxins under particular circumstances and that, for a toxic effect to take place, a particular mycotoxin, a route of exposure, and a sufficient amount of mycotoxin are necessary. This could well occur by ingestion but not by inhalation. Similarly, the effects of mycotoxins do not accumulate; they manifest half-lives ranging from hours to days.

Fungal irritants

Fungi can also produce irritating substances; these are divided into particulates (i.e., fragments, spores) and volatile organic compounds (VOC). The former are nonvolatile, and their contribution to mucosal inflammation remains debated as workplace exposure to 215,000 to 1,460,000 mold spores/m³ in sawmills did not induce respiratory symptoms, as compared to the same stimuli encountered out of the workplace [5]. Nasal lavage fluids from these environments showed similar concentrations of inflammatory mediators (nitric oxide, interleukin (IL)-4, IL-5, and IL-6) [5]. One possible explanation is that ubiquitous airborne fungal particulates that are encountered regularly may not be irritating. On the other hand, VOC are secondary fungal metabolites responsible for the typical musty odor; these include alcohols, aldehydes, carboxylic acids, esters, lactones, nitrogen compounds, terpenes, sulfur compounds, and aliphatic and aromatic hydrocarbons. Generally, VOC measured levels are almost negligible, irritating symptoms are not manifest and VOC concentrations do not change significantly between mold-infested and non-infested indoor environments [6]. Finally, it should be noted that VOC may derive from other biological and chemical sources including cigarette smoke, cooking, compost bins, and plant soil.

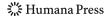
Established mold-associated human diseases

Mold infections

Most common mold infections include dermatological conditions (onychomycosis, tinea, and thrush) found in healthy individuals when mucosal or skin barriers are breeched or resident microflora is disturbed (Table 2). As an example, molds of the Malassezia genus are present on most individuals and often manifest as tinea, dandruff, or seborrhoeic dermatitis at times of uncontrolled growth. In these cases, the diagnosis is often presumed based on clinical presentation, while confirmation can be obtained with direct microscopic examination, fungal culture, or Wood's lamp, and adequate antifungal agents are effective treatments. Less commonly, more aggressive mold infections are observed in occupationally susceptible normal individuals, as in the cases of blastomycosis, coccidioidomycosis, and histoplasmosis. Blastomycosis is more frequently seen in men with outdoor jobs in the midwestern and south central USA and in Canada, while coccidioidomycosis (also coined valley

Table 2 Human diseases with a definite fungal etiology

Infection	Cutaneous
	Systemic
Allergic	Allergic asthma
	Hypersensitivity pneumonitis
	Allergic bronchopulmonary aspergillosis
	Allergic fungal sinusitis
Toxicity	Oral ingestion



fever) is more prevalent in the southwestern USA. Mexico. and Central and South America [7]. Histoplasmosis is often associated with exposure to bird droppings and bat exposure along river valleys in eastern and central USA, eastern Canada, Mexico, Central and South America, southeast Asia, and Africa [7]. Opportunistic fungal infections, including Candidiasis, Aspergillosis, Pneumocysostis, and Cryptococcosis, are frequently observed in individuals with primary or secondary immunodeficiency disorders (mainly human immunodeficiency virus infection or immunosuppressive therapies). These fungi represent a broad range of normally occurring strains which usually do not cause disease in immunocompetent individuals [7]. As expected, the risk of fungal infections in immunocompromised individuals is dependent on the nature and degree of the immunodeficiency, and susceptibility to opportunistic fungal infection is generally secondary to deficiencies in the cellular rather than humoral immune compartment [8]. For both types of fungal infections and opportunistic fungal infections in immunodeficient individuals, the diagnostic workup includes appropriate fungal stain and culture, as well as the search for serum or urine fungal antigens or serum antibody titers while therapy is based on the adequate oral or intravenous antifungal agents.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) manifests with asthma, bronchiectasis, and recurrent pulmonary infiltrates [9] and derives from hypersensitivity to Aspergillus fumigatus [10]. A subgroup of patients with cystic fibrosis (2-15%) or asthma (1-2%) have ABPA, yet prevalence rates depend on the clinical suspicion or systematic screening [10, 11]. The physiological changes in the lungs of individuals with cystic fibrosis or persistent asthma are the primary underlying causes of ABPA in these patients, particularly since A. fumigatus is pervasive, and various other fungi have been found to produce similar clinical manifestations [8]. This observation led to the wider, less universal term of allergic bronchopulmonary mycosis. Cases of pediatric ABPA involving Bipolaris, Candida albicans, Curvularia, Fusarium vasinfectum, and Pseudoallescheria boydii have also been reported [12]. Diagnostic criteria for ABPA include asthma, recurrent pulmonary infiltrates, skin hyperreactivity to Aspergillus, peripheral eosinophilia, serum-specific IgG and IgE specific for Aspergillus, and central bronchiectasis [9, 13]. Ideally, the disease should be diagnosed and treated before the onset of bronchiectasis, as this is associated with worse long-term prognosis. Current management includes treatment with oral corticosteroids and oral itraconazole for recurrent ABPA or glucocorticoiddependent ABPA [9].

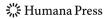


Allergic fungal rhinosinusitis (AFRS) was previously defined as allergic fungal sinusitis and is caused by the non-invasive fungal growth within the sinuses resulting in excess sinus drainage. The underlying pathophysiology is due to a localized hypersensitivity reaction against fungi, similar to ABPA [14–16]. In earlier studies, A. fumigatus was found to be most frequently involved but, more recently, dematicaceous (darkly pigmented) fungi and mitosporic fungi (Bipolaris and Curvularia spp.) have also been found to cause AFRS [16, 17]. Similar to ABPA, type 1 and type 3 hypersensitivity reactions are involved [16]. Diagnostic criteria include eosinophilic mucus without invasive fungi, characteristic CT scan findings, nasal polyposis, type 1 hypersensitivity (based on skin tests, in vitro allergen testing, or history), and positive fungal staining of sinus contents commonly removed with surgery [16, 18]. Medical treatment includes corticosteroids (local or systemic) to reduce the immune hypersensitivity reaction and endoscopic surgery to remove eosinophilic mucus (containing fungal antigen) and obstructive polyps [16]. Fungi have also been implicated in the pathology of some forms of chronic rhinosinusitis (CRS) [19]. Similar to AFRS, an enhanced immune response to ubiquitous fungi has been proposed to explain CRS onset, but substantial evidence to support an immunological mechanism of disease is lacking, and several double-blind, placebocontrolled trials have shown topical and oral antifungal agents have limited effect [19-23].

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HSP), previously coined extrinsic allergic alveolitis or farmer lung, was first observed in farmers at the turn of the century after exposure to moldy straw or hay. Since the first reports in farmers, exposure to multiple other antigens, including birds, moldy wood, humidifiers, and environments high in mold content have been implicated [24, 25]. Primarily, the disease derives from an aberrant immune response to specific organic dust of vegetable, fungal, bacterial, or avian origin. Sensitization and elicitation require prolonged exposure to organic dust, exposure to high concentrations of a particular organic dust, or both stimuli, often related to occupational exposure. Further, chemical compounds (in particular isocyanates) have also been linked to HSP [24-27] acting as haptens, creating antigenic particles when combined with human serum albumin, similar to that observed in autoimmune diseases [28, 29]. HSP aberrant immune response involves both type 3 and type 4 hypersensitivity reactions.

HSP's most used diagnostic criteria include history, physical and pulmonary function tests showing interstitial



lung disease, consistent radiography, exposure to a potential cause, and an antibody titer specific for the suspect agent [24, 30]. Allergen-specific serum IgG may be observed by testing for precipitins in an Ouchterlony double-diffusion assay, while a nonstandardized inhalation challenge may also be useful to reaffirm diagnosis. While avoidance of the initiating organic dust or chemical remains the ideal treatment, oral corticosteroids are beneficial [24] in controlling symptoms but seem not to affect long-term outcome [31]. If inadequately treated, HSP may result in irreversible lung damage, either as emphysema or fibrosis.

Mold and asthma

Exposure to airborne fungal spores in patients with positive IgE antibodies to mold may increase asthma symptoms and the need for therapy in some individuals with asthma [32]. Specifically, *Alternaria alternata* has been associated with the persistence and increased severity of asthma as well as life-threatening exacerbations [33–36]. Several other species of fungi have also been implicated, including *Aspergillus*, *Aureobasidium*, *Cladosporium*, *Epicoccum*, *Helminthosporium*, and *Penicillium* [34, 35, 37–40]. Interestingly, levels of airborne fungal spores have been found to increase during thunderstorms, and this may constitute the causative mechanism of asthma exacerbation in "thunderstorm asthma" [36–41].

Overall, allergic reactions to common outdoor airborne mold is an accepted subtype of allergic asthma, but this link is less established for indoor airborne mold. In this latter case, cough and persistent wheezing in the first year of life in infants at risk for asthma (i.e., with a family history of asthma) have been reported after exposure to high concentrations of indoor mold [42, 43]. These data, however, are biased by coexistence of other airborne allergens and irritants (nitrogen dioxide sources and cockroach antigen) and are not controlled for humidity. Treatment for allergic asthma includes avoidance of known triggers, including the offending mold, and standard of care measures for the bronchial condition. Asthmatic episodes precipitated by mold, in allergic individuals, is of course reversible.

Mold and allergic rhinitis

Mold is considered a cause of allergic rhinitis with *Alternaria*, *Aspergillus*, *Bipolaris*, *Cladosporium*, *Curvularia*, and

Table 3 Symptoms proposed for the toxic mold and sick building syndromes

Respiratory complaints (rhinorrhea, epistaxis, cough, and shortness of breath)

Neurological complaints (shaking, headache, focal weakness, dizziness, restless legs, and memory loss)

Gastrointestinal complaints (abdominal pain, nausea, vomiting, and diarrhea)

Genitourinary complaints (dysuria)

Constitutional complaints (generalized weakness, mood variations, anxiety)

Penicilium more commonly involved [40] through type I hypersensitivity. Indeed, several studies have demonstrated that individuals may be sensitized to particular airborne fungi, by skin testing, and allergen-specific serum IgE testing. Available studies led to conflicting results when attempting to determine a direct relationship between airborne mold exposure (basidiomycetes and Alternaria spp.) and allergic rhinitis symptoms [44–47]. Additionally, studies trying to link indoor mold exposure with allergic rhinitis are questionable due to a lack of standardization of mold exposure [48, 49]. Nevertheless, we should note that sensitization to house dust mites, animal danders, and pollens is significantly more common and more severe compared to sensitization to fungi [8].

Mold and atopic dermatitis

Mold sensitivity has also been reported in children and adults with atopic dermatitis (AD), also known as atopic eczema [50-52], but may be a serendipitous observation. AD is an inflammatory, pruritogenic, chronically relapsing skin disease associated with high titers of allergen-specific and total IgE [53, 54]. Recently, Malassezia spp. have gathered attention in AD pathogenesis, and several studies have demonstrated that patients with AD have more reactive skin testing to Malassezia spp., more reactive to atopy patch testing to Malassezia spp., and have higher titers of Malassezia spp. specific IgE [52, 55-57]. Furthermore, positive skin prick testing against Sacchromyces cerevisiae has also been reported in patients with AD [40]. The fact that AD is a disease characterized by impaired epidermal barriers should be taken into account to determine the impact of these observations as the specific sensitization to Malassezia spp. and S. cerevisiae may occur once the initial skin inflammation is established. For these reasons, the causative link between airborne mold and AD is doubtful.

Mold and autoimmunity

There are a large number of immunological diseases in addition to the type 1 hypersensitivity reactions described herein. These include autoimmunity, an incidence of approximately one in 31 individuals. Autoimmune diseases are commonly divided into organ-specific and organ-nonspecific

Table 4 Mycotoxins produced by Stachybotrys (adapted from [73])

Enzymes (1,3-endoglucanases, b-glucanase, farnesyl-protein transferase)

Macrocyclic trichothecenes (3-acetyl-deosynivalenol, citrinine, deoxynivalenol, diacetoxyscripenol, isosatratoxin (F, G, H, S), kampanols, nivalenol, phenylspirodrimanes, roridin A, satratoxin (F, G, H), T-2-tetraol, T-2 toxin, verrucarin A, verrucarol, vomitoxin

Sesquiterpenes (K-76, K-76 COOH)

SMTP (-3, -4, -5, -6)

Stachybocins (A, B, and C)

Staplabin analogs (SMTP-7, SMTP-8)

Others (stachybotramide, stachybotrin, staplabin, triprenyl phenol metabolites)

diseases. An example of the former is autoimmune thyroiditis, and an example of the latter is systemic lupus erythematosus. There is no evidence nor is there any biologic plausibility for suggesting that exposure to mold would either induce or exacerbate such pathology. Indeed, a review of medical research published in the Journal of Autoimmunity in the last 5 years does not reveal a single example where there is either a viable explanation nor a link between mold exposure and autoimmune disease. Examples of literature which do focus on the mechanisms of autoimmune disease are readily found in recent literature and illustrate the absence of any suggestion of a mold association. In contrast, the mechanisms relate to both a genetic predisposition as well as ultimate loss of tolerance [28, 58–68].

Recently implicated mold-related illnesses

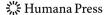
Sick building syndrome, *Stachybotrys*, and toxic mold syndrome

Reports of various syndromes associated with time spent within buildings or near building supplies began to appear in the medical literature in the 1970s but has been largely relegated to junk science. The term sick building syndrome (SBS) was coined to define these syndromes [69–71] and has now been utilized for about 25 years, mostly in groups of office workers [69, 71]. SBS symptoms (Table 3) are commonly numerous and poorly defined, including upper and lower respiratory (nasal congestion and drainage, sneezing, coughing, difficulty breathing, and wheezing), ocular (pruritic and watery eyes), neurological (lack of

concentration, memory loss, and headache), and constitutional (fatigue, malaise and arthalgias) complaints [69]. Several potential causative agents were proposed, including bacterial, fungal, and viral organisms; electrostatic fields; lighting; vibration; and tobacco smoke, yet adequate ventilation does seem to prove beneficial to symptoms [72], but no etiology has ever been demonstrated. In the following decades, likely because there was no obvious cause of SBS, ubiquitous mold became a candidate [69], and the public and media focused on one particular visible mold as a potential cause, Stachybotrys chartarum (also known as Stachybotrys atra and Stachybotrys alternan). Stachybotrys is a greenish-black saprophytic fungus that exists worldwide and is able to produce several mycotoxins (Table 4). The toxic effects of this particular fungus were initially noted in the Ukraine in the 1920s where horses that ingested mold-infested fodder (barley, corn, and wheat) developed agranulocytosis, oral ulcers, respiratory tract inflammation, gastrointestinal hemorrhages and ulcerations, fever, and bleeding diatheses ultimately fatal for thousands of animals [73]. At the same time as the original outbreak, there were also unsubstantiated reports that farmers who handled mold-infested hay or straw developed similar symptoms. However, since the 1940s, no human case has been reported [73], while the systemic disease (after ingestion of contaminated fodder) was observed intermittently in farm animals, including cows, deer, sheep, and swine. As previously mentioned, Stachybotrys reappeared in the 1980s and 1990s as a purported cause of human disease and was sometimes referred to as the "fatal fungus" and the "toxic black mold" [74, 75]. In 1996, a study reported that 53 office workers had suffered allergic or

Table 5 Major settled lawsuits involving mold [4, 69]

Lawsuit	Award
2002: Anderson vs. Allstate Ins. Co	\$18.5 million
2001: Ballard vs. Fire Insurance Exchange	\$32 million (\$12 million punitive in damages, \$8.9 million for legal fees) (reduced on appeal to \$4 million)
1999: New Haverford Partnership, et al.	\$1 million in damages to Stroot vs. Elizabeth Stroot
1997: Doe Homeowners vs. Roe Seller	Case settled for \$1.3 million



immunotoxic illness due to "toxigenic" S. chartarum along with other "atypical" fungi [76]. Multiple flaws reduced the applicability of these data, including the nonrandomized design, the occupational health clinic setting, and the lack of physical examination data. Furthermore, there was a 1998 study on 14 office workers diagnosed with SBS after exposure to S. chartarum and Aspergillus versicolor with similar limitations [77]. Among the flaws, interstitial lung disease was diagnosed by patient-reported symptoms only, no physical exams were performed, and serum-specific IgE and IgG did not correlate with disease. Nevertheless, these and other questionable studies led the worldwide public and media to be convinced of the unproven danger caused by Stachybotrys and other molds. Accordingly, "toxic mold syndrome" (TMS) was coined by the media to refer to a wide range of nonspecific symptoms in individuals exposed to mold [78]. Similar to SBS, these symptoms (Table 3) included respiratory (rhinorrhea, epistaxis, cough, and shortness of breath), neurological (headache, focal weakness and memory loss), gastrointestinal (nausea, vomiting, and diarrhea), and constitutional (generalized weakness and mood variations) complaints [78], as represented by a 2005 study on 65 individuals, self-reported to have TMS [79]. This study concluded that a majority of the symptoms were possibly due to allergic reactions to mold in the environment and proposed the possibility of somatization and secondary gain (either emotional or financial). Most importantly, no evidence has demonstrated that mycotoxins produced by Stachybotrys or another mold are responsible for the diverse and often poorly defined symptoms attributed to "toxic mold syndrome" [69, 70]. The etiology of SBS is more likely psychosocial in origin, as extensively discussed elsewhere [69, 80].

Stachybotrys and infant acute pulmonary hemorrhage

Ten cases of acute pulmonary hemorrhage/hemosiderosis in infants were associated with Stachybotrys between January 1993 and December 1994 in the inner city of Cleveland, OH [81, 82]. Epidemiological evidence suggested water damage and indoor fungal growth, resulting in inhaled mycotoxins from Stachybotrys as causative agents [83], and in the 5 years following the initial report, 128 additional cases of idiopathic pulmonary hemorrhage (with or without hemosiderosis) were reported, 37 of which were from the Cleveland area [84]. As a result, these reports led to major concerns over exposure of infants to Stachybotrys. Yet, when the initial cases were reviewed by the Centers for Disease Control and Prevention, numerous errors were found within the reports, and it was concluded that the association of acute idiopathic pulmonary hemorrhage with exposure to Stachybotrys was unproven [85]. In particular, the features of the reported disease, with acute presentation, narrow age range, and absence of iron deficiency, questioned the diagnosis of idiopathic pulmonary hemosiderosis.

Stachybotrys, TMS, and litigation

SBS and TMS has become a cottage industry (Table 5) with thousands of cases brought to court and many more settled out of court. In 2000, there were 7,000 mold-related claims in Texas which grew to 37,000 in 2001 [86]. In one of the most notable cases, the entertainer Ed McMahon in 2002 sued his insurance company, American Equity Insurance Co., two insurance adjusters, and the environmental cleanup contractors previously hired to clean mold in his home for \$20 million. The claim included personal injuries, damages to his home, and a respiratory illness suffered by his dog [87], and the case was settled out of court for \$7.2 million. Most frequently, when the presence of mold is demonstrated in a house, individual homeowners will claim property damage, personal injuries, or both, and the claim may be presented to either the homeowner's insurance company or the construction company (if a construction defect is suspected). Many insurance companies have responded by adding exclusions for damage and injuries caused by mold in their revised policies.

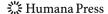
Conclusive remarks

There are numerous human conditions known to be caused by mold, and these manifest specific signs, symptoms, and established etiologies, as in the case of fungal infections, allergic bronchopulmonary aspergillosis, allergic fungal rhinosinusitis, hypersensitivity pneumonitis, and asthma. Despite opposing scientific evidence, there are many who believe that exposure to mold can also cause multiple poorly defined syndromes, and these unfounded beliefs have proven to be profitable for some. As in all fields of science, however, we are convinced that only solid evidence should be considered in all litigation scenarios as well as in the media.

Disclosure M. Eric Gershwin has served as a medical/legal expert for both plaintiff and defense in environmental illness issues.

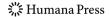
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