

## Health Effects of Mold in Children

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Fungi, ubiquitous unicellular or multicellular organisms of the Kingdom of Fungi, exist in several forms, including single-celled yeasts, microscopic filaments (hyphae), aggregates of these filaments (mycelia), and spore-producing visible fruiting bodies (eg, mushrooms). “Mold” and “mildew” are generic terms used to describe visible aggregates of hyphae that give fungi their fuzzy appearance. Fungi represent about 10% of the earth’s biomass and serve to recycle organic matter. They grow on a wide variety of indoor and outdoor organic substrates, with water (moisture) the most important factor for determining growth for many species. Fungal components (FCs) include spores, hyphae, mycelia, allergenic sites (epitopes), and  $\beta$ -1,3-D-glucan, a principal component of the fungal cell wall. FCs can become airborne under ambient conditions, especially when mold is disturbed physically (eg, by air currents or mechanical disruption). Some molds have the ability to produce mycotoxins and are referred to as “toxigenic.” Mycotoxins can be found in spores and hyphal fragments. Exposure to FCs occurs by inhalation, dermal contact, and ingestion. Mold growth indoors is very common. Respondents in a questionnaire study of white 9- to 11-year-olds in 24 communities across North America reported a prevalence of indoor mold growth of 22% to 57%, exceeding 50% of households in five communities [1].

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Four types of pathogenic mechanisms have been linked to adverse health outcomes (AHOs) caused or exacerbated by molds: (1) immunologic reactions (2) toxicity, (3) infection, and (4) irritation. A fifth category, “indeterminate mechanism,” might be added to account for AHOs, such as fatigue and headache, frequently associated with the presence of damp buildings or ambient mold for which the pathophysiologic mechanisms, if there indeed are any, remain undetermined.

The ability to define or exclude causal relationships between mold exposure and some AHOs is hindered by a number of factors too extensive to discuss in this article and more completely discussed in recent reviews [2–7]. The crux of the challenge is to define relevant FC exposure accurately and to measure the adverse health effects in humans designated for study while excluding confounding variables. Some factors interfering with the ability to elucidate relationships between mold and human morbidity are (1) inadequate knowledge about the health-relevant features of molds (eg, insufficient dose–response data), (2) the greater complexity of human sensitization and morbidity from molds relative to other harmful agents, (3) lack of a standardized methodology for assessing ambient FCs and some AHOs, and (4) inexact, inappropriate, or nonvalidated investigational methodology, (eg, use of nonvalidated self-report questionnaires). Furthermore, as a result of the recent prominence of mold in litigation as an alleged cause of illnesses ranging from asthma to autism, the ability of mold to cause human illness has received intense scrutiny. Despite these controversies and challenges, health care professionals continue to recognize mold as a cause or exacerbating factor in specific disorders and continue to evaluate and treat mold-induced illnesses using widely accepted clinical paradigms.

### **Adverse health outcomes—immunologic reactions**

Three immunopathologic mechanisms have been identified as playing a role in the pathogenesis of hypersensitivity reactions caused by molds: (1) production of mold-specific serum IgE (immediate hypersensitivity), (2) antigen-specific antibody (IgG, IgM) forming immune complexes and activating inflammatory pathways in tissue, and (3) delayed hypersensitivity. A fourth mechanism, inflammation resulting from activation of the innate immune system by FCs, remains intriguing but as yet unproven in humans. Immediate hypersensitivity mechanisms are involved most frequently in the pathogenesis of asthma, rhinitis, eczema, and urticaria. In addition to the role of immediate hypersensitivity, nonimmunologic mechanisms (eg, viral infection and irritants in asthma) frequently contribute to AHOs for a given child who has one or more of these atopic diagnoses. [Table 1](#) provides classical findings differentiating various hypersensitivity disorders. Deviation from these findings is common for many of these disorders.

The overall prevalence of fungal immunologic sensitization (the presence of specific IgE as opposed to atopic disease), ranging from 3% to 91% in the

general population [8] and from 7% to 50% in children who have asthma [9–12], is complicated by varying study methodologies and the significant variability in the composition of mold extract allergens. In the general population of the United States the prevalence of *Alternaria* sensitization was reported to be 12.9% [13]. The antigenic epitopes of several molds, such as *Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium*, have been characterized to varying degrees, and their role in the pathogenesis of allergic respiratory disease has been studied [14,15]. As with other allergens, mold sensitization develops in genetically predisposed individuals in response to recurrent or chronic environmental exposure [16]. Consistent with other classes of allergens, molds demonstrate cross-reactivity [8] (ie, the sharing of similar or identical antigenic sites [epitopes]) with other molds, for example, the enolases of *Cladosporium herbarum*, *Alternaria alternata*, *Saccharomyces cerevisiae*, *Candida albicans*, and *Aspergillus fumigatus* with some nonfungal allergens, such as latex.

Since the possibility was first proposed by Blackley [17] in 1873, scientists have suspected mold as one of several classes of inhaled allergens capable of causing or exacerbating asthma and other allergic respiratory disorders. The medical evaluation and treatment for mold-induced immediate hypersensitivity illnesses follows the methodology pursued for other allergens—a careful medical history to obtain symptom, exposure, and genetic information; a physical examination searching for signs of atopic disorders (eg, asthma, rhinitis, and eczema); skin or laboratory testing to determine allergic sensitization; and a treatment regimen consisting of reduced exposure, pharmacotherapy, and immunotherapy, when indicated. Cantani and Ciaschi [18], studying a population of 6840 atopic 1- to 9-year-old children living in Rome, Italy who had asthma and/or allergic rhinitis, found *A. alternata* sensitization in 3.3%, but monosensitization (no sensitization to the remainder of nonfungal allergens tested) in only 1.3% of the children. Based on the high prevalence of asthma in the 89 monosensitized children, the authors concluded *A. alternata* sensitization posed a significant independent risk factor for pediatric asthma. A prospective longitudinal study of nearly 1000 children in a semiarid climate found *A. alternata* sensitization at age 6 years was the only allergen independently associated with an increased risk of asthma at both age 6 years (odds ratio = 2.3) and 11 years (odds ratio = 2.7) [10]. In a large, multicenter, cross-sectional study of 1041 children who had mild-to-moderate asthma, 88% demonstrated at least one positive skin prick test (SPT) to a panel of inhalant allergens, including 37% to *A. alternata*, 24% to *Penicillium* mix, and 22% to *Aspergillus* mix. The authors found the strongest associations of increased bronchial hyperreactivity (PC<sub>20</sub> with methacholine challenge) with allergic sensitization to dog ( $P = .003$ ), *Alternaria* ( $P = .01$ ), and cat ( $P = .05$ ). The investigators concluded that their findings support the important role sensitization to these allergens plays in modulating bronchial responsiveness [19]. A number of other reports have found sensitization to *Alternaria* to be a significant independent risk factor

Table 1  
Mold-induced hypersensitivity disorders: comparison of findings

Condition	Asthma	Total IgE	Mold-specific IgE	Specific IgG	Peripheral eosinophilia	Lung Function	Imaging	Other findings
Allergic rhinitis	+ or -	↑ or wnl	↑	Irrelevant	+ or -	wnl		
Allergic asthma	+	↑ or wnl	↑	Irrelevant	+ or -	Normal or large or small airway obstruction	Chest radiograph: hyperaeration or wnl	
Nonatopic asthma	+	↑ or wnl	-	Irrelevant	+ or -	Normal or large or small airway obstruction	Chest radiograph: hyperaeration or wnl	
Acute allergic bronchopulmonary mycosis/allergic bronchopulmonary aspergillosis	+	↑↑(> 1000 IU/mL)	↑	Precipitins	+	1. Airway obstruction 2. Restrictive defect (if lung fibrosis)	Chest radiograph: infiltrates Chest CT: usually central bronchiectasis	Aspergillus hyphae in sputum
Allergic fungal sinusitis		Usually ↑-↑↑	+ by skin testing - in serum	↑ but no serum precipitins	-	wnl	Sinus CT: 1. Mucosal hypertrophy 2. Hyperattenuation of sinus contents often present 3. In children: more often unilateral and asymmetric, and bony abnormalities	1. Extramucosal allergic mucin 2. Scattered fungal hyphae or fungal culture + 3. Eosinophilic-lymphocytic sinus mucosal inflammation 4. No tissue invasion 5. Nasal polyps

Hypersensitivity pneumonitis	—	wnl	—	Precipitins, often multiple. Infrequently —	—	<ol style="list-style-type: none"> <li>1. Restrictive defect</li> <li>2. Airway obstruction (sometimes)</li> <li>3. ↓ DLCO</li> </ol>	Chest radiograph: diffuse micronodular infiltrates Chest high-resolution CT: <ol style="list-style-type: none"> <li>1. Ground-glass opacities and/or centrilobular nodules</li> <li>2. Fibrosis (later stage)</li> </ol>	BAL: Lymphocytosis Histopathology: Smaller non-caseating granulomas, loosely arranged and less well defined, peri-alveolar
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*Abbreviations:* BAL: bronchoalveolar lavage; DLCO, diffusing capacity of lung for carbon monoxide; wnl, within normal limits; —, negative; +, positive; ↑, elevated; ↓, decreased.

for the development or persistence of asthma in children [14,20,21] and for respiratory arrest in asthmatic children and young adults [22]. In a prospective study in Norway, Nilsson and Aas [23] identified 53 atopic asthmatic children age 6 to 15 years with positive bronchoprovocation tests to mold extracts of *C. herbarum*. In this study SPTs predicted allergic asthma from *Cladosporium* sensitivity in 83% to 96% of cases compared with 74% to 83% for the radio-allergosorbent assay test. Similar increased adverse health effects on asthma in adults have been described for indoor mold growth [24].

Although antigen-specific immunotherapy has been used to treat mold allergy for years, only a few studies have evaluated its efficacy. Desensitization with standardized *Cladosporium* extracts in polysensitized adults and children has been shown to reduce bronchial or conjunctival challenge reactivity in *Cladosporium*-sensitive asthma or rhinoconjunctivitis, but demonstration of improvement in symptom-medication scores was questionable [25–27]. In a double-blind, placebo-controlled immunotherapy study with 20 adult and pediatric patients having allergic rhinitis (42% of whom also had asthma) monosensitized to *Alternaria*, Horst and colleagues were able to show statistically significant improvement in several parameters following active treatment: patient self-assessment of efficacy, global symptom-medication scores, rhinitis scores, reduced skin test and nasal challenge reactivity [28]. The authors noted the difficulty in finding monosensitized patients to evaluate. Additional studies of desensitization in *Alternaria*-sensitive respiratory tract disease have shown benefit [29,30].

Studies of documented mold-sensitive asthmatics provide evidence-based support for the role of mold sensitivity in allergic disease of the upper airways and conjunctiva, because many children who have asthma have concomitant allergic rhinoconjunctivitis [14,18,28]. Few studies have targeted children who have allergic rhinoconjunctivitis and mold sensitivity. Nineteen percent of 202 children ages 2 to 14 years who had allergic rhinitis living in a tropical environment were SPT positive to one or more molds in a standard testing battery of various types of inhalant allergens. Mold sensitization was significantly more prevalent in houses without air conditioning (odds ratio = 9.4) and usually presented with polysensitization to three or more molds [31]. *Alternaria* sensitivity was associated with increased amounts of leukotriene C4 (LTC<sub>4</sub>), an inflammatory mediator of phospholipids metabolism, in the nasopharyngeal secretions of children with ragweed sensitivity during the ragweed pollen season. Increased levels of LTC<sub>4</sub> continued after the end of the ragweed season, coincident with peaks of mold spore counts [32], supporting a role for mold exposure in allergic inflammation. Stark and colleagues [33] reported infants with a positive family history for atopy exposed to high levels of dust-borne fungi are at increased risk of developing allergic rhinitis by 5 years of age. Mold sensitivity also may be an important risk factor for the development of adenoidal hypertrophy [34] or sinusitis [35] in children who have allergic rhinitis. If not well controlled, the discomfort, frustration, and fatigue that may be

caused by symptoms from allergic hypersensitivity disorders from any allergen, including mold, can result in cognitive impairment (eg, decreased vigilance, slowed mental processing) and reduced quality of life by interfering with sleep (sedation), causing distraction, and inducing or aggravating mood disorders [36–39].

Scientific validation of the role of molds in the pathophysiology of atopic dermatitis (atopic eczema) and urticaria is sparse. In one study, 15 of 30 children who had atopic dermatitis (AD) but only 2 of 30 children who had respiratory allergy but no AD developed eczematous lesions upon patch testing with a mold mix [40]. Clark and Adinoff [41] found patients who had AD, but not controls who had allergic rhinitis, demonstrated patch test–positive delayed cutaneous reactions to various inhalant allergens, including molds, for which they were SPT positive. They concluded aeroallergen contact plays an important role in select patients who have AD. Sampson [42], reviewing the role of allergy in AD, cautioned that, although a few studies provide strong evidence for an etiologic role for mold in AD, further studies are needed to evaluate clinical significance. Two case reports have suggested inhalation or ingestion of *Aspergillus* [43] or *Boletus edulis* (an edible basidiomycete) [44] to which subjects were sensitized resulted in IgE-mediated anaphylactic reactions. Maibach [45] reported the development of contact urticaria from mold exposure.

Allergic bronchopulmonary mycosis (ABPM) is a pulmonary disorder caused by IgE- and immune complex–mediated mold hypersensitivity characterized by asthma, fleeting pulmonary infiltrates, pulmonary and peripheral blood eosinophilia, saprophytic fungal growth in the lower airways without invasion, and a good clinical response to systemic corticosteroids [46–48]. High-resolution CT scans of the chest usually identify central (proximal) bronchiectasis in later stages of the disease. Patients who have ABPM are immunocompetent and almost uniformly demonstrate highly elevated total serum IgE (usually >600 IU/ml), increased amounts of mold-specific IgE by skin testing or in vitro testing, and mold-specific IgG precipitins in serum and/or lung. Allergic bronchopulmonary aspergillosis is the predominant form of ABPM. Allergic bronchopulmonary aspergillosis (ABPA), however, represents only a small subset of *A. fumigatus*–sensitive patients who have asthma (1%–2%) or cystic fibrosis (7%–9%) [49–51]. ABPA is not rare in children and has even been reported in infants [46,52]. All of the classical criteria may be absent in some patients who have ABPM [46]. Pediatric cases of ABPM attributable to other fungi have been described for *Bipolaris*, *C. albicans*, *Curvularia*, *Pseudoallescheria boydii*, and *Fusarium vasinfectum* [53,54]. Treatment consists of allergen avoidance, treatment of asthma, and courses of oral corticosteroids for refractory lung disease.

Allergic fungal sinusitis shares several histopathologic, laboratory, and clinical features with ABPM. First described by Katzenstein and colleagues [55], allergic fungal sinusitis presents with hypertrophic unilateral or bilateral chronic sinusitis that usually is resistant to treatment with

antihistamine/decongestants, antibiotics, and topical anti-inflammatory agents. Classic features include nasal obstruction, nasal polyps, saprophytic fungal growth without tissue invasion, and thick, eosinophil-laden, peanut butter-like sinus masses and nasal casts of allergic mucin. Accumulation of the allergic mucin sometimes results in destruction of bony elements by mass expansion into the orbit or cranial fossae in the absence of fungal tissue invasion. The allergic mucin has a characteristic heterogeneous or attenuating appearance as sinus opacification on CT scanning, and the sinus contents demonstrate positive fungal staining or culture. As in ABPM, total serum IgE often is quite high with demonstrable levels of specific IgE by skin testing but less frequently in serum. Usually, specific IgG for the offending mold is present, although precipitins usually are absent [56–60]. More commonly than in adults, children who have allergic fungal sinusitis are male (ratio of 2.1 versus 0.7 in adults), present with facial dysmorphism (42% versus 10%), unilateral disease (70% versus 37%), asymmetrical disease (88% versus 58%), and sensitivity to fungi other than *Aspergillus* (0% versus 13%) [61]. *Bipolaris* species has been most commonly identified, particularly in the Southwest and inland parts of the United States, with *Curvularia* predominating in the Southeast [57]. *Aspergillus* was the only mold identified in a series from India [62]. Treatment usually consists of endoscopic evacuation of sinus contents with débridement of the affected tissue, may include irrigation with an antifungal antibiotic in saline, and, postoperatively, close follow-up, further débridement as needed, topical and judicious use of oral corticosteroids for an extended period of time, and treatment of underlying allergic disease [59,63].

Hypersensitivity pneumonitis (HP), also termed “extrinsic allergic alveolitis,” is an uncommon but underdiagnosed disorder characterized by (1) exposure to organic dust antigens or certain low molecular weight chemical compounds, (2) a characteristic clinical presentation including abnormalities in lung function and imaging, and (3) laboratory evidence of immune complex and delayed-type hypersensitivity [64]. Children can present with the acute onset of fever, dry cough, malaise, chills, and dyspnea after antigen exposure (acute form). These symptoms generally resolve over 12 to 48 hours after removal from the offending antigen. The chronic form usually is characterized by a slow insidious progression of dyspnea, weight loss, fever, and cough over a period of years. Subacute and subacute chronic forms exist with some characteristics of both acute and chronic forms of the disease [65]. Physical examination may be normal, but often bibasilar crackles are heard over the lung fields, and clubbing may be present with the chronic form. Pulmonary function testing usually demonstrates a restrictive deficit, sometimes with an airway obstruction component. Diffusing capacity is reduced, often with resulting hypoxemia, especially with exercise. Abnormalities in dynamic lung compliance and diffusing capacity can persist for months following removal from the offending antigen(s) [66]. Pulmonary hypertension may develop with



longstanding disease, but in children can reverse completely with successful treatment. Radiographic findings may be absent or show fleeting fine, reticular infiltrates or evidence of end-stage fibrosis. High-resolution CT scan of the chest provides the most accurate diagnostic radiographic assessment, showing micronodules predominantly in the upper and middle lung field and widespread ground-glass appearance. Laboratory findings in adults usually include the presence of precipitating IgG antibody (precipitins) against one or more antigens detectable by agar double-diffusion assay and T-lymphocytosis with decreased CD4+/CD8+ ratio in bronchoalveolar lavage (BAL) fluid. Lung biopsy demonstrates predominantly mononuclear cell infiltration of small airways and pulmonary parenchyma, often with poorly formed granulomas. Although precipitins can be found in as many as 50% of individuals exposed to high levels of the antigen, only a small proportion with this finding (eg, 5% in pigeon breeders) develops disease [67]. Conversely, precipitins were found in only 89% of children who had the diagnosis of HP [64]. Ratjen and colleagues [68] reported finding lymphocytosis with normal CD4+/CD8+ ratios in BAL fluid in nine children aged 6 to 15 years old who had HP; molds were the inciting antigens in four of these children. Failure to make the diagnosis and to eliminate exposure to the offending antigen(s) often results in progression to end-stage interstitial and intra-alveolar fibrosis. The predominant allergens causing HP have been avian proteins, particularly from pigeons, but fungi (eg, *Aspergillus* [66,68–70], *Penicillium*, *Alternaria*, *Cryptosporium*, *Pullularia*, *Rhodotorula* [65], *Cladosporium* [71], *Epicoccum* [72], *Fusarium* [73], and *Trichosporon cutaneum* [74,75]) have been associated with development of this disorder.

Hypersensitivity disorders are created by dysfunction of adaptive immunity, that is, antigen-specific immune responses. Another arm of the immune system, innate immunity, responds nonspecifically to pathogen-associated molecular patterns common to a range of external threats (eg,  $\beta$ -1,3-D-glucan). These foreign pathology-associated molecular patterns (PAMPs) can induce immediate inflammatory responses from the innate immune system and also can activate mechanisms of adaptive immunity downstream [76–78].  $\beta$ -1,3-D-glucan, a polyglucose structural component in the cell walls of molds, can affect mononuclear cell cytokine production and induce inflammation in mice and guinea pigs [79–82]. Holt [82] hypothesized that the binding of  $\beta$ -1,3-D-glucan to receptors on antigen-presenting cells, such as monocytes and dendritic cells, could modulate cytokine production by these cells and skew T-lymphocyte function toward a T-helper cell type 2 (atopic) predominance. Evaluations of changes in secretion of inflammatory mediators by peripheral blood monocytes after  $\beta$ -1,3-D-glucan inhalation in healthy individuals and people living in damp buildings with high or low levels of airborne  $\beta$ -1,3-D-glucan have demonstrated variable and inconsistent responses [83–85]. Hirvonen and colleagues [86] found bacterial strains from moldy buildings were more potent inducers of inflammation than molds, although

Fogelmark and colleagues [81] found equivalent responses to inhaled solubilized  $\beta$ -1,3-D-glucan in guinea pigs. A recent review of the scientific evidence concluded that the data suggest some association between  $\beta$ -1,3-D-glucan exposure, airway inflammation, and symptoms [87], but larger observational studies using validated environmental assessment assays for  $\beta$ -1,3-D-glucan exposure are necessary to determine the nature and strength of any association. Fungal allergens from molds such as *Aspergillus* and *Alternaria* contain proteases with inflammatory modulatory effects in animals and in vitro [88,89], but their relevance to human disease remains unclear. Other fungi-associated molecular patterns with potential relevance to human inflammation and disease include several mannoproteins and zymosan [76,77].

### Adverse health effects—toxicity

Mycotoxins are fungal intermediary metabolic products secreted extracellularly to provide a competitive growth advantage against other microbes. Higher organisms, including humans, can develop toxicity from some of these compounds. There are hundreds of mycotoxins with diverse chemical structures that can be produced by different fungal species. Genetic and environmental factors affecting synthesis include moisture, temperature, substrate, presence of competing organisms, and growth cycle. Mycotoxin production varies within species: not all strains of fungal species produce mycotoxins. Fungi having the potential to produce mycotoxins are assigned the label “toxigenic.”

Mycotoxin exposure is ubiquitous in human populations. Mycotoxins are regularly found in grains, cereals, nuts, and animal products, including meat, eggs, and milk. Mycotoxins found in foods include trichothecenes, fumonisins, ochratoxin A, aflatoxins, and zearalones. Mycotoxins have produced human disease for centuries. The term “mycotoxicosis” refers to a disease caused by mycotoxin exposure. Examples of food-borne outbreaks include alimentary toxic aleukia and ergotism from ingestion of bread made of rye infested with *Claviceps purpurea*. Alimentary toxic aleukia is a radiation-like illness that developed in the 1930s from ingestion of T2 mycotoxin elaborated by *Fusarium* in over-wintered grain among impoverished Eastern Europeans. Food-related mycotoxin illnesses occur primarily in Third World countries. Mycotoxins found in toxic mushrooms can produce serious illness and death, and children may inadvertently ingest them. Mushroom mycotoxins of clinical concern include cyclopeptides, orellanine, muscarine, hallucinogenic indoles, monomethylhydrazine, and isoxazoles.

There has been considerable controversy concerning whether mycotoxins from building exposures produce disease [6]. Some of this controversy can be attributed to the dearth of currently available data addressing the issue of causation and the difficulties with methodology. Fungi associated with damp buildings having the potential to produce mycotoxins include certain *Penicillium* and *Aspergillus* species, *Stachybotrys chartarum*, *Trichoderma*,

and *Chaetomium* species. Toxic health outcomes attributed to building-related exposures include respiratory, immune, and neurologic effects [90,91]. The evidence for building-related mycotoxic illness, however, is limited to anecdotal case reports or limited epidemiologic studies that have many deficiencies [4,92]. Although a few publications have attributed human disease to inhalation or absorption (through skin) of mycotoxins [93], reviews of the medical literature concerning building-associated mycotoxic illness generally reveal an overall consensus that, at this time, credible scientific evidence for non-food-borne mycotoxin-induced human disease is lacking [6,7,92,94–97]. Other factors supporting the lack of effect include the limited doses that can be received by persons from a building-related exposure [98]. Furthermore, mycotoxins that contaminate animal feeds or are produced in laboratory settings are rarely, if ever, found in indoor environments [99].

Building-associated mycotoxin exposure was reported to be the cause of an outbreak of acute idiopathic pulmonary hemorrhage in African American infants. Cases initially were attributed to mycotoxin exposure from growth of *S. chartarum* in water-damaged homes in Cleveland, Ohio [100,101]. In a reassessment of the original study findings, however, the Centers for Disease Control identified several shortcomings in the methodology and the data interpretation employed to reach the initial causal conclusion. Consequently, the Centers for Disease Control retracted its initial conclusion, stating the association between acute idiopathic pulmonary hemorrhage and *S. chartarum* was not proven. The cause or causes of this unusual cluster remains undetermined. Despite a lack of reasonable scientific evidence to support *Stachybotrys*-induced human disease, proponents continue to cite anecdotal evidence as proof of a likely causal link, especially for pulmonary hemorrhage in infants [102–104]. Subsequent animal studies investigating the pulmonary toxicity effects [105,106] of *Stachybotrys* spores suffer from a number of limitations, making analogy with potential human illness tenuous [92,107].

A practical methodology to assess environmental levels of mycotoxins is needed. Environmental test results measuring mycotoxin in materials found in bulk samples collected from buildings correlate poorly with exposure [108]. Methodologies to measure human exposure, such as antibody tests to measure mycotoxin-specific antibody levels of various immunoglobulin classes in serum, have not been validated and are not indicated for clinical use [108,109]. Studies involving measurement of mycotoxins in blood and urine are being assessed to evaluate potential mycotoxin exposure and dose [110,111]. Development of biologic assays for mycotoxins in humans and environmental media that are indicative of exposure potential are key factors in understanding better the relationships between mycotoxic effects and environmental exposures. The complex process of describing the events from environmental contaminant source, including mycotoxins, to human response is illustrated in Table 2.

“Organic dust toxic syndrome” is a term used to describe an acute febrile illness characterized by flulike symptoms including chills, malaise, myalgia,

Table 2  
A generalization of the aerobiologic pathway leading to inhalation exposure

Source factors	→	Aerosol factors	→	Exposure factors	→	Response factors
The organisms		Composition of aerosols		Time spent in aerosol		Dose reaching appropriate organ
Populations, their interactions and dynamics		Particle size distribution		Breathing rate		Dose needed for effect
Chemistry, physiology, biology of the organisms		Dispersion		Particle deposition sites		Metabolism of toxin
		Biologic decay		Clearance rates		
		Physical decay		Metabolic destruction of toxin		Human susceptibility factors
Particle release factors		Patterns of aerosol concentration				

*From* Burge HA. Fungi: toxic killers or unavoidable nuisances? *Ann Allergy Asthma Immunol* 2001;87(6 Suppl 3):52–6; with permission.

cough, and dyspnea following large exposures to organic dusts contaminated with micro-organisms, including molds and bacteria [112]. Pneumonia does not occur, and the condition resolves without sequelae. It occurs primarily following large organic dust exposures, especially moldy grain, hay, straw, and wood chips [113]. One report related exposure to dense airborne dust from a hay-covered floor at a college party resulted in the development of organic dust toxic syndrome [114]. A high attack rate is observed in persons with heavy exposure. Sensitization to an antigen is not required. Several causal agents have been implicated including endotoxin and  $\beta$ -1,3-D-glucan. Although organic dust toxic syndrome generally occurs in occupational agricultural settings where sufficiently large amounts of organic dust are present, this diagnosis should be considered in individuals experiencing these symptoms in highly contaminated indoor environments [6].

**Adverse health effects—infection**

Extensive reviews of fungal infections are available in the literature and are not covered in the print version of this article [108,115–121].

**Adverse health effects—irritation**

The fourth mechanism of mold-induced injury, irritation, has been less well studied than the first three. The olfactory (CN I), trigeminal (CN V), glossopharyngeal (CN IX), and vagal (CN X) nerves provide sensory afferents to the upper respiratory tract. C- and A $\delta$ -nociceptive fibers make up the terminal branches of the trigeminal nerve endings in conjunctival and airway mucosa [122–125]. Volatile organic compounds (VOCs; MVOCs when from microbial sources) have been identified as possible causes of some of the AHOs attributed to mold exposure, presumably mediated

through these irritant receptors. The evidence implicating MVOCs is sparse, however. Nilsson and colleagues [126] identified VOCs known to be produced by the molds *Aspergillus*, *Penicillium*, and *Cladosporium* adsorbed to airborne dust particles in both dry and damp residences. None of the occupants had health complaints, however, and no differences were noted between damp and dry residences in VOCs or mold spore concentrations per gram of dust. Another study investigating the role of home dampness and VOC concentrations on occupants' sick building syndrome (SBS) symptoms [127] found significantly increased odds ratios for the presence of dampness, several individual VOCs, and total VOCs for various types of symptoms referable to skin, eyes, the upper respiratory tract, and general symptoms (eg, fatigue, headache, dizziness). Problems with the study design included assessment of both building dampness and symptoms by questionnaire completed by occupants, which potentially would bias toward the positive any relationship between dampness and symptoms. Additionally, as the authors point out, the levels of VOCs they found were relatively low. There are other confounding factors in the evaluation of VOCs:

1. The conditions that promote mold growth (ie, excessive moisture and organic nutrient sources) promote the growth of other micro-organisms, such as bacteria and dust mites, each having its own potential for producing AHOs.
2. Dampness and VOCs produced by water-damaged building materials also may contribute to the development of AHOs.

Future studies of AHOs in larger groups of subjects with measurable exposure to MVOCs of fungal origin and careful characterization of the fungal flora of the contaminated space will be required to establish any causal relationships for MVOCs

### **Possible adverse health effects—indeterminate mechanisms**

SBS consists of a constellation of mainly subjective health complaints such as headache, mucous membrane irritation, cognitive complaints (eg, memory loss, difficulty concentrating), and fatigue attributed to factors in a building that cannot be related to an established, scientifically valid diagnosis [128]. SBS has been described most commonly in adult office workers; reports of SBS affecting children are rare. Mold is one of a number of agents or conditions suggested as a possible cause of SBS, including cognitive impairment. Reports of mold exposure associated with complaints of SBS [129–131] and cognitive impairment [132] have been deficient in a number of areas (eg, failing to provide details of the prevalence and nature of health complaints, poor characterization of mold exposure, and failure to consider or investigate other possible causes of AHOs such as endotoxin [especially at zoological sites], dust mites, and VOCs). Psychogenic factors may contribute to the pathogenesis or exacerbation of AHOs in mold-contaminated

buildings [133–135]. No scientifically sound data support a role for mold in the pathogenesis of SBS, the causes for which remain elusive and probably are multifactorial.

Dampness in buildings facilitates mold growth but also facilitates the growth of other microbial agents with AHO potential, such as bacteria and dust mites. Moisture can degrade building materials and furnishings, releasing VOCs with the potential to cause irritant responses and, if excessive, can cause physical discomfort. Criteria used to deem a residence damp or moldy vary among studies. The reported prevalence of “damp or moldy” dwellings in studies has ranged from 14.1% to 64%, and the reported prevalence of “mold growth” has ranged from 20% to 57% [1,136–139]. Numerous reports have found associations between dampness and/or mold and AHOs. Some of these reports have attempted to differentiate the effects of dampness from other possible dampness-related causes, such as mold and dust mite (Box 1) [6].

Methodologic and technological problems, too extensive for this article and discussed elsewhere in the literature, sometimes have hindered reliable accurate measurement of the responsivity of building occupants or the adequate characterization of exposure levels to mold and fungal components in the environment. These difficulties have, to varying degrees, confounded the determination of causal relationships [2,4–7,140]. Investigators often have not identified offending agents or explained the pathogenic mechanism(s) for conditions demonstrating statistically significant associations with AHOs (eg, dampness and lower respiratory tract symptoms). Despite these obstacles, it seems that dampness and/or mold exposure in some, as yet, undefined manner can exacerbate or might cause AHOs such as cough, phlegm, wheeze, dyspnea, pneumonia, bronchitis, sore throat, asthma, allergic rhinitis, and acute otitis media. Odds ratios for the risk of the development of upper or lower respiratory tract complaints (doctor diagnosed or self reported) associated with dampness and/or mold exposure range greatly, from insignificant to highly statistically significant, depending on the outcomes measured and the study design [6,127,136,141–147]. Peat and colleagues [146], in a review of the literature, reported an odds ratio ranging from 1.5 to 3.5 for wheeze or chronic cough in children living in damp or moldy homes, with larger sample sizes more likely to be statistically significant. In a study of 165 children 7 to 8 years of age in Edinburgh, Scotland, Strachan and Elton [144] discovered statistically significant associations for nocturnal cough, wheezing, family history of wheezing, and school absence from chest problems with mold and/or dampness in the home. They also remarked about possible reporting bias in the records of the children’s general practitioners, in which this highly significant relationship was not found. Spengler and colleagues [1] concluded it was “highly probable” the presence of mold and damp conditions in homes contributed to the statistically significant increase in lower respiratory tract symptoms in their study population from a questionnaire-based study of white children 9

**Box 1. Summary of findings regarding the association between health outcomes and exposure to damp indoor environments<sup>1</sup>***Sufficient evidence of a causal relationship*

No outcomes met this definition

*Sufficient evidence of an association*

Upper respiratory tract (nasal and throat) symptoms

Cough

Wheeze

Asthma symptoms in sensitized asthmatic persons

*Limited or suggestive evidence of an association*

Dyspnea (shortness of breath)

Lower respiratory illness in otherwise healthy children

Asthma development

*Inadequate or insufficient evidence to determine whether an association exists*

Airflow obstruction (in otherwise-healthy persons)

Mucous membrane irritation syndrome

Chronic obstructive pulmonary disease

Inhalation fevers (nonoccupational exposures)

Lower respiratory illness in otherwise-healthy adults

Acute idiopathic pulmonary hemorrhage in infants

Skin symptoms

Gastrointestinal tract problems

Fatigue

Neuropsychiatric symptoms

Cancer

Reproductive effects

Rheumatologic and other immune diseases

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<sup>1</sup> These conclusions are not applicable to immunocompromised persons, who are at increased risk for fungal colonization or opportunistic infections.

Data from The Institute of Medicine of the National Academies. Damp indoor spaces and health. Washington, DC: The National Academies Press; 2004.

to 11 years of age in 24 communities across North America. They cautioned about the importance of reducing the risk of responder bias in this type of study by comparing self-reported symptoms with a set of objective measures. Some of these studies have also found associations between dampness or mold and various nonrespiratory symptoms such as fatigue, headache,

nausea, dizziness, fever, and difficulty concentrating [127,136]. Some of these studies have reported dose-response relationships between damp/mold exposure and AHOs [136,147]. Objective measurements of lung function, however, have not correlated well with the presence of dampness or mold [138,148]. Bornehag and colleagues [149] reported that their evaluation of 61 epidemiologic peer-reviewed articles supported (1) a causal association between indoor “dampness” and lower respiratory tract symptoms (eg, cough, wheeze, and asthma), and (2) a more tenuous association between dampness and general symptoms (eg, fatigue, headache) despite an undetermined pathogenesis. The Institute of Medicine’s [6] most recent report arrived at the conclusion of an “associational” but not “causal” relationship between dampness and both lower and upper respiratory tract symptoms (Box 1).

Damp or mold-contaminated conditions at schools present a potentially significant public health problem for children and employees [150]. Children at such schools generally are not free simply to pick up and move to another school; they must remain in the school environment. Excessive moisture or mold growth in schools has been associated with a statistically significant increased risk of asthma, upper and lower respiratory tract symptoms, and infections [9,151–154]. Atopy to inhalant allergens other than molds may be an additional risk factor for increased coughing in children in mold-contaminated schools [151]. Conversely, mold exposure in elementary schools has been suggested as a possible factor in increasing IgE sensitization to non-fungal inhalant allergens as well as the development of newly reported allergic disease [155]. Other building-related symptoms (ie, eye and throat irritation, headache, and dizziness) have been significantly associated with total viable mold concentrations in floor dust from schools in adolescent children [156], but not in postmenarchal girls [157]. Scheel and colleagues [158] attributed the presence of “SBS symptoms” in students and staff to *Stachybotrys* growth at a school with indoor water damage. Description of specific symptoms, characterization of exposure, and response to removal from exposure were lacking, however. Adding to the complexity of determining valid causal relationships is the need for scientific investigation to consider the potential for seasonal variations in the concentrations and proportional representation of mold genera [159]. This factor can affect indoor and outdoor mold concentrations in schools in the absence of evidence of visible mold growth or excessive moisture. To assist with identifying and correcting these problems, the Environmental Protection Agency has published “Mold Remediation in Schools and Commercial Buildings,” available at [http://www.epa.gov/mold/mold\\_remediation.html](http://www.epa.gov/mold/mold_remediation.html).

## Summary

Mold is ubiquitous. Children are exposed to mold spores and other FCs every day, whether they are outdoors or indoors. Consequently, depending



on a child's genotype and underlying health status, mold exposure, regardless of source, has the potential to produce AHOs. Certain states of health, notably pre-existing hypersensitivity and immunosuppression, place the child at increased risk of developing illness as a result of mold exposure. The four types of mechanisms by which molds can produce human illness are immunologic reactions, toxicity, infection, and irritation. Several recent reviews of the literature have concluded insufficient valid scientific data exist to establish epidemiologically a causal relationship between inhaled mold exposure and human illness in indoor environments, although associational relationships exist for some AHOs. For some types of illness, the term "insufficient" may mean that, although the data support such a conclusion, there are not enough data for the reviewers to reach a conclusion of "cause" or "association" for a particular AHO. Variations in study design and methodology, the complexity of molds and their FCs, a lack of standardized procedures for environmental assessments of mold and moisture, and other factors complicate the identification of potential relationships between mold exposure and AHOs. When methodologic confounders have been addressed more adequately, studies have been able more often to demonstrate strong relationships for some associations, such as the causal relationship of *Alternaria* to asthma. As in the case of hypersensitivity mechanisms, medical practitioners, including allergists, often operationally treat children who have illnesses that may be "associated" with or "caused" by mold exposure as if the relationship were causal, in the absence of an established "causal" relationship by strict epidemiologic criteria. Such is the case for most hypersensitivity disorders and most molds. As allergens, molds seem to act like other allergens in the diseases they cause, the medical evaluation they require for diagnosis, and the treatment that is effective.

It is clear that, to date, little evidence exists to support the conclusion that mold is responsible for some AHOs for which it is alleged to be the cause. Among the associations for which there is little evidence are toxic injuries from inhalation of mycotoxins in nonoccupational settings, systemic infection with *Candida* in immunocompetent hosts causing multiorgan system disease, and hypersensitivity to mold causing a rapid-onset cascade of neurocognitive symptoms. The relationships, or lack thereof, of cause and effect or association between mold and specific AHOs should become more evident with future investigations. That possibility exists only if the confounding factors noted previously are addressed adequately (eg, by larger subject populations and additional longitudinal studies).

There is the category of "indeterminate mechanisms." Even though it is not known exactly how dampness or mold produces some AHOs, there seems to be at least sufficient evidence for an association (Box 2) [6].

As discussed in this article, excessive moisture facilitates the growth or accumulation of various nonfungal microbial agents, insects, and rodents, all of which can result in AHOs similar to those from mold. The literature supporting other mold-related components, such as MVOCs and  $\beta$ -1,

**Box 2. Summary of findings regarding the association between health outcomes and the presence of mold or other agents in damp indoor environments<sup>1</sup>**

*Sufficient evidence of a causal relationship*

No outcomes met this definition

*Sufficient evidence of an association*

Upper respiratory tract (nasal and throat) symptoms

Asthma symptoms in sensitized asthmatic persons

Hypersensitivity pneumonitis in susceptible persons<sup>2</sup>

Wheeze

Cough

*Limited or suggestive evidence of an association*

Lower respiratory illness in otherwise-healthy children

*Inadequate or insufficient evidence to determine whether an association exists*

Dyspnea (shortness of breath)

Airflow obstruction (in otherwise-healthy persons)

Mucous membrane irritation syndrome

Chronic obstructive pulmonary disease

Inhalation fevers (nonoccupational exposures)

Lower respiratory illness in otherwise-healthy adults

Rheumatologic and other immune diseases

Acute idiopathic pulmonary hemorrhage in infants

Skin symptoms

Asthma development

Gastrointestinal tract problems

Fatigue

Neuropsychiatric symptoms

Cancer

Reproductive effects

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<sup>1</sup> These conclusions are not applicable to immunocompromised persons, who are at increased risk for fungal colonization or opportunistic infections.

<sup>2</sup> For mold or bacteria in damp indoor environments.

*Data from* The Institute of Medicine of the National Academies. Damp indoor spaces and health. Washington, DC: The National Academies Press; 2004. p. 10.

3-D-glucan, as capable of producing AHOs is presently insufficient for the assignation of cause or even association. Nonmicrobial VOCs, however, have been shown to cause irritant effects by activating irritant receptors in the conjunctivae and airways.

Reservoirs of fungal growth can be found outdoors and, frequently, indoors. Exposure requires the FCs to get from the reservoir to the individual, and the amount of exposure depends on concentration and duration of exposure. A high priority always should be assigned to the removal of reservoirs of mold in locations where a child might be exposed, even in the absence of any mold-related health problems. The required next step is to address and, if possible, eliminate the sources of excessive moisture producing those reservoirs. The interpretation of environmental data with a critical and knowing eye and the evaluation and treatment of children who have health problems that could be related to mold exposure are complex. A clinician who is unsure of the data, what to do with the data, or how to evaluate or treat a child who has a possible mold-related health problem should seek assistance from someone who has expertise in this type of environmental assessment or in the relevant pathophysiologic mechanisms of mold-induced injury.

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