TECHNICAL REPORT

Spectrum of Noninfectious Health Effects From Molds

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ABSTRACT

Molds are multicellular fungi that are ubiquitous in outdoor and indoor environments. For humans, they are both beneficial (for the production of antimicrobial agents, chemotherapeutic agents, and vitamins) and detrimental. Exposure to mold can occur through inhalation, ingestion, and touching moldy surfaces. Adverse health effects may occur through allergic, infectious, irritant, or toxic processes. The cause-and-effect relationship between mold exposure and allergic and infectious illnesses is well known. Exposures to toxins via the gastrointestinal tract also are well described. However, the cause-and-effect relationship between inhalational exposure to mold toxins and other untoward health effects (eg, acute idiopathic pulmonary hemorrhage in infants and other illnesses and health complaints) is controversial and requires additional investigation. In this report we examine evidence of fungal-related illnesses and the unique aspects of mold exposure to children. Mold-remediation procedures are also discussed.

BACKGROUND

Neither plant nor animal, fungi are a group of eukaryotic (possessing a true nucleus) nonphotosynthetic microorganisms. The almost 100 000 recognized fungal species include mildews, molds, mushrooms, puffballs, rusts, slime molds, smuts, truffles, and yeast. Molds are multicellular fungi that grow as a mass of branching, interlacing filaments (hyphae) known as a mycelium. Although the terms mold and fungi are commonly interchanged, all molds are fungi but not all fungi are molds.

Outdoors, fungi break down organic matter such as fallen leaves and dead trees and are ecologically beneficial. Indoors, molds usually are not a problem unless the spores encounter persistently humid or wet areas, and then colonies begin to grow. Mold flourishes in many household areas such as air conditioners, basements, bathrooms, crawl spaces, ground floors, refrigerator seals, sinks, shower grout, windowsills, and other places where standing water occurs. Leaks in roofs, water-damaged walls, damp basements, plant pots, or even pet urine contribute to mold growth. Carpeting, ceilings, paneled or hollow walls, pillows, and wicker or straw baskets may serve as reservoirs for mold proliferation if there is moisture accumulation.

Exposure to mold varies, reflecting regional differences; the effect of the local climate (humidity and wind); home construction; and use of varying heating and cooling, humidifying, dehumidifying devices, and air-filtering devices. Outdoor factors such as shade, organic debris near the home, and landscape maintenance also influence indoor concentrations. Indoor characteristics such as electrostatic

filters and dust control are associated with lower levels of mold-spore isolation. Because typical urban residents spend more than 90% of their time indoors, there is potential for exposure to mold when homes are contaminated.[1]

The most common outdoor molds are *Cladosporium* species, *Aspergillus* species, *Penicillium* species, *Alternaria* species, *Candida* species, *Botrytis* species, and *Helminthosporium* species. The most prevalent indoor molds in nonproblem homes are *Cladosporium* species, *Penicillium* species, *Alternaria* species, *Streptomyces* species, *Epicoccum* species, and *Aspergillus* species.[2]

In children and adults, molds have the potential to adversely affect health by both immune- and non–immune-related mechanisms (Table 1). The cell walls of fungi are formed of chitin (acetylglucosamine polymers), β-1(1–3)-D-glucans, polysaccharides and mucopolysaccharides, waxes, and pigments. The glucans are endotoxin-like substances that may be irritating and stimulate the immune system. During growth, fungi produce and release new enzymes and secondary metabolites that can be allergenic (eg, enzymes), irritating (eg, volatile metabolites), or toxic for other forms of life (eg, mycotoxins and antimicrobial agents).

Immunologically, molds produce allergens that may lead to sneezing, runny nose, red eyes, and other manifestations. Nonimmune effects include irritation of mucous membranes, infection, and reactions from toxic (mycotoxins) or microbial (endotoxins) byproducts. The scope of toxin-mediated effects is controversial and is being widely studied and debated in medical, scientific, insurance, and legal circles.

The purpose of this technical report is to describe mold-related clinical illness in children and to summarize the evidence of health effects in damp, moldy environments. Assessment of exposures to mold and prevention strategies will be presented. The infectious complications of fungi are beyond the scope of this article.

IMMUNE-MEDIATED HEALTH EFFECTS OF MOLD EXPOSURE

Type I reactions are mediated by immunoglobulin (Ig) E and are the basis of most allergic reactions, including immune responses, to mold exposure. The main types of IgE-mediated responses are allergic rhinitis/conjunctivitis and asthma. Other less common immune-mediated responses are allergic bronchopulmonary aspergillosis (ABPA), allergic fungal sinusitis (AFS), and hypersensitivity pneumonitis.

Allergic Rhinitis

In the pediatric population, as many as 10% of children and 20% to 30% of adolescents have allergic rhinitis, and the prevalence is increasing.[3] The most common adverse health effect associated with mold exposure is allergic rhinitis. Fungi belonging to the group Deuteromycotina (*Fungi imperfecti*), particularly *Alternaria* species and *Cladosporium species*, are the most commonly studied. The second National Health and Nutrition Examination Survey noted that the most prevalent fungal IgE antibody was for *Alternaria* species (7%).[4] Studies suggest that the fungal cell wall component β-D-glucan may play a role in altering the host immune response to antigens leading to development of a T-helper type 2 or proallergenic-type response (interleukins 4 and 5, which preferentially enhance IgE synthesis and eosinophil differentiation) in the host.[5] Mold exposure is a strong irritant factor and worsens symptoms of any preexisting allergic disease in the same manner as other specific irritants such as tobacco smoke, ozone, or cold air.

The Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology has published guidelines for the diagnosis and treatment of allergic rhinitis.[6] The principal symptoms of allergic rhinitis are sneezing, rhinorrhea, and/or nasal blockage. The diagnosis requires the correlation of symptoms with a history of exposure to an allergen and in vitro demonstration of IgE antibodies by allergy skin tests or a radioallergosorbent test (RAST) for specific IgE antibodies in blood. However, the sensitivity and specificity of skin testing with mold antigens is poor. Commercially available fungal extracts are mixtures of soluble materials from spores, mycelia, cellular metabolites, and cytoplasm. Therefore, the panel of fungal allergen extracts available to clinicians may not accurately reflect the true mold-exposure profile in most indoor environments. Furthermore, cross-reactivity between different fungal extracts clearly exists, but to what extent is not known. Determination of mold-specific IgE antibodies (RAST, enzyme-linked immunosorbent assay) is costly. RASTs and related tests have lower sensitivity as well.

Asthma

The National Asthma Education Program's expert panel report defines asthma as "a lung disease with the following characteristics: 1) airway obstruction that is reversible; 2) airway inflammation; and 3) increased airway responsiveness to a variety of stimuli."[7] The panel states that the prevalence of asthma is approximately 10% in

TABLE 1   Noninfectious Health Effects Associated With Exposure to Molds

Immune
  Allergic rhinitis/conjunctivitis
  Asthma
  Hypersensitivity pneumonitis
  ABPA
  AFS
Nonimmune
  Irritant symptoms
  Inhalation fever (humidifier fever, organic dust toxic syndrome)
  AIPH in infants
  Toxin-mediated diseases (primarily associated with ingestions of nuts or grains contaminated with toxigenic molds)

the pediatric population and that it continues to increase. Asthma and allergic rhinitis frequently coexist, and there is evidence of a connection between allergic rhinitis and asthma. A cohort study of college freshmen with and without allergic rhinitis showed that allergic rhinitis almost tripled the risk (10.5% vs 3.6%) for the development of new asthma over the 20-year follow-up period.[8] The National Health and Nutritional Examination Survey report showed that when a skin-test result was positive for *Alternaria* species, the odds ratio (OR) of having asthma was 5.[4]

There is increasing evidence that fungi are an important environmental trigger for asthma exacerbations. High levels of basidiospores in the environment have been associated with asthma exacerbations in New Orleans, Louisiana.[9] Positive bronchial challenges in individuals with positive skin-test results have been noted with *Alternaria* species, *Basidiomycetes* species, *Cladosporium* species, *Penicillium* species, and others.[10,11] A case-control study investigated 11 young patients with asthma who experienced respiratory arrest (2 fatal cases) in seasons when high levels of *Alternaria* spores are present. Of the 11 patients, 10 had positive *Alternaria* skin-test results, compared with 31% of the controls, suggesting that *Alternaria* exposure was a risk factor for respiratory arrest.[12] Epidemiologic studies also suggest an association between dampness and mold in homes and asthma symptoms[13–17]; this association will be discussed further in "Health Risks Associated With Damp Indoor Environments."

In addition to airborne fungi, certain skin organisms (dermatophytes) can cause sensitization and antigen exposure in some patients with asthma. One study reported patients with asthma, chronic fungal skin infection, and immediate hypersensitivity to *Trichophyton* species. Patients demonstrated both upper and lower airway sensitization to dermatophyte antigens after bronchial and nasal challenge.[18] The diagnosis and treatment of asthma are well described in the National Asthma Education Program's expert panel report.[7]

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, is a group of immunologically mediated lung diseases in which the repeated inhalation of certain antigens provokes a hypersensitivity reaction with granulomatous inflammation and fibrosis in the gas-exchanging portion of the lung. Causative agents of hypersensitivity pneumonitis include bacteria (eg, thermophilic actinomycetes), fungi (eg, *Trichosporon cutaneum*), animal proteins (eg, avian), and chemicals (eg, diisocyanates). These antigens are typically less than 3 μm in diameter and are easily inhaled into the distal bronchial tree and alveoli, where they are cleared via the local lymphatic drainage into the hilar nodes, which induces an IgG antibody response. Antibody alone is not sufficient to cause disease; cytotoxic delayed hypersensitivity involving $CD8^+$ cytotoxic lymphocytes is required. A type III reaction is suggested by the presence of precipitating antibody to the offending antigen, immune complex deposition, and activation of the complement cascade, the resulting C5 activates macrophages. A type IV reaction is suggested by an increased percentage of T lymphocytes in bronchoalveolar lavage fluid, with a strong predominance of $CD8^+$ lymphocyte subsets, a low CD4-to-CD8 T-lymphocyte ratio, and the presence of granulomas on lung biopsy. Hypersensitivity pneumonitis must be distinguished from a number of nonallergic, inflammatory reactions such as "inhalation fevers," toxic alveolitis, and organic dust toxic syndrome, which is also associated with the inhalation of high levels of organic dust.

Genetics may play an important role in determining susceptibility to the development of hypersensitivity pneumonitis, because only a small proportion of exposed persons is ultimately affected. Studies have shown an association between HLA types A2 W15 and DQw3 and hypersensitivity pneumonitis.[19,20]

The prevalence of hypersensitivity pneumonitis in children is unknown. In a review of 86 pediatric cases of hypersensitivity pneumonitis, 17% were mold related; the mean age was 10 years, and the youngest patient was 8 months old.[21] Table 2 lists the fungal agents associated with hypersensitivity pneumonitis in childhood.[22]

The 3 stages of hypersensitivity pneumonitis development are acute lymphocytic infiltration, subacute granuloma formation, and chronic fibrosis. Subacute and chronic presentations are more common in children; the acute form is more common in adults.

In the acute form, symptoms of hypersensitivity pneumonitis mimic influenza (fever, myalgias, arthralgias, dyspnea, and cough, occasionally with cyanosis); these symptoms occur a few hours after exposure and resolve in 12 to 24 hours without specific treatment. Physical examination reveals an ill-appearing child with fever, dyspnea, and bibasilar crackles. Chest radiographic findings include poorly defined micronodules found predominantly in the upper and middle lung fields. High-resolution computed tomography (CT) demonstrates ground-glass attenuation of the lung fields.

In the subacute stage of hypersensitivity pneumonitis, there is an insidious onset of exertional dyspnea and fatigue. Cough can occur several days to weeks after exposure. The patient might have a subacute or chronic course, interspersed with acute exacerbations related to intermittent or seasonal exposure to the antigen(s).

The chronic form is characterized by insidious and progressive development of dyspnea and pulmonary fibrosis in a patient who has not experienced acute symptoms. The most common symptoms are exercise intolerance, cough, weight loss, and fever. On physical examination, approximately two thirds of these patients

TABLE 2 Fungal Agents Associated With Hypersensitivity Pneumonitis

Agent	Disease	Source
Thermoactinomyces vulgaris	Farmer's lung	Plant mold
Thermoactinomyces sacchari	Bagassosis	Sugarcane residue
Alternaria species	Woodworker's lung	Wood mold
Aspergillus clavatus	Malt worker's lung	Grain mold
Aspergillus species	Tobacco worker's lung	Tobacco mold
	Greenhouse lung	Greenhouse soil
Aureobasidium pullulans	Sequoiosis	Sequoia dust mold
Botrytis cinerea	Winegrower's lung	Grape mold
Candida albicans	Sax lung	Saxophone mouthpiece
Cephalosporium species	Basement lung	Contaminated basement (sewage/mold)
Cladosporium species	Hot-tub lung	Ceiling mold
Cryptostroma corticale	Maple-bark disease	Maple bark mold
	Greenhouse lung	Greenhouse soil
Epicoccum nigrum	Shower-curtain lung	Shower mold
Penicillium casei	Cheese washer's lung	Cheese mold
Penicillium chrysogenum	Woodworker's lung	Wood dust mold
Penicillium frequentans	Suberosis	Cork mold
Penicillium species	Domiciliary pneumonitis	House mold
Pullularia fungus	Sauna taker's disease	Sauna mold
Stachybotrys species	Domiciliary pneumonitis	House mold
Trichosporon cutaneum[a]	Summer-type hypersensitivity pneumonitis	Mold in Japanese homes
Mixed ameba, fungi, and bacteria	Air-conditioner lung	Cold mist and other humidifiers
	Ventilation pneumonitis	

[a] Association with HLA-DQw3.

have crackles and one third have digital clubbing. Chest radiographs show interstitial infiltrates with varying degrees of fibrosis and possible honeycomb appearance. The following criteria are considered essential for the diagnosis:

1. symptoms compatible with hypersensitivity pneumonitis;

2. evidence of exposure to appropriate antigen by history or detection of antibody in serum and/or bronchoalveolar lavage;

3. findings compatible with hypersensitivity pneumonitis on chest radiograph or high-resolution CT;

4. bronchoalveolar lavage lymphocytosis (40%–80%) with a predominance of CD4 (acute) or CD8 (chronic) T lymphocytes (if bronchoalveolar lavage is performed);

5. pulmonary histologic changes compatible with hypersensitivity pneumonitis (if open or video-assisted lung biopsy has been performed); and

6. positive "natural challenge" (reproduction of symptoms and laboratory abnormalities after exposure to the suspected agent).

Minor criteria include bibasilar crackles, decreased diffusing capacity, and arterial hypoxemia.

Confirmation of the diagnosis requires 4 major and 2 minor criteria and the exclusion of other diseases with similar symptoms and signs.[23] Despite the term "hypersensitivity," hypersensitivity pneumonitis is not associated with increased concentrations of IgE or eosinophils in the blood or lung. However, test results for rheumatoid factor are often positive. Treatment consists of antigen avoidance in all cases and steroid therapy in severe cases. There has been 1 case report of resolution of symptoms after installation of filters in an air-conditioning system, which lowered mold-colony counts.[24,25] The overall prognosis for children with hypersensitivity pneumonitis is excellent. In the 67 pediatric cases of hypersensitivity pneumonitis with reported outcomes, 65 children improved or became asymptomatic, 1 patient worsened, and 1 patient died.[21]

Allergic Bronchopulmonary Aspergillosis

ABPA is an immunologically mediated lung disease that occurs primarily in patients with asthma and cystic fibrosis (CF). *Aspergillus fumigatus* represents the most common etiologic agent, but other causative fungi include *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, *Candida* species, *Curvularia* species, *Dreschlera* species, and *Penicillium* species. The alveolar deposition rate is highest for agents approximately 3 μm in size, such as *Acremonium* species, *Aspergillus* species, and *Penicillium* species. The fungi are not invasive but rather colonize the respiratory tract. The resultant hypersensitivity reactions are both IgE mediated (type I) and IgG mediated (type III). Estimated prevalences of ABPA range from 0.25% to 0.8% in children with asthma and 7% to 11% in children with CF.[26]

Asthma is usually present 5 to 10 years before the diagnosis, and the presence of atopy (allergic skin-test reactivity and hay fever) increases the risk. The clinical

course is characterized by recurrent acute episodes with intervening remission. Symptoms range from acute recurrent asthma exacerbations with wheeze, cough, and chest radiographic infiltrates to generalized systemic features of fever, anorexia, headache, and malaise. Abnormal sputum production occurs in more than half of patients and is characterized by solid chunks of "dirty-green–" to beige-colored sputum plugs. In addition to recurrent wheezing, long-standing illness may lead to digital clubbing and bronchiectasis. Characteristic radiographic patterns for bronchiectasis include the "gloved finger" and "toothpaste" shadows, air fluid levels from dilated central bronchi, and tramline shadows (edematous bronchial walls).[27,28] CT is the most sensitive tool for the detection of bronchiectasis.[29]

The Rosenberg criteria for ABPA are the most widely used and remain the diagnostic standard:

1. asthma or CF with peripheral blood eosinophilia;

2. immediate cutaneous reactivity to *A fumigatus*;

3. precipitating (IgG) antibodies to *A fumigatus*;

4. elevated serum-specific IgE antibodies to *A fumigatus*;

5. elevated total serum IgE (>500 IU/mL);

6. peripheral blood eosinophilia (>1.0 × 10⁹/L);

7. pulmonary infiltrates (or history of) on chest radiographs; or

8. central bronchiectasis.

Not all of the criteria are needed for diagnosis. The first 5 are essential, and having 6 is generally required to confirm the diagnosis. However, continued diagnostic testing may be required for months to years to fulfill all of the criteria. In addition, a positive sputum culture for *A fumigatus* is not essential for the diagnosis, because up to 40% of patients have negative cultures.[30]

Corticosteroids modulate inflammation and immunologic reactivity and are the mainstay of treatment. The use of antifungal agents to decrease the fungal burden arising from colonization remains controversial.[31]

Allergic Fungal Sinusitis

The combination of nasal polyposis, crust formation, and sinus cultures yielding a fungal agent is known as AFS. It is estimated that approximately 5% to 10% of patients with chronic rhinosinusitis have AFS. In a review of 263 cases, 168 yielded positive fungal cultures. Of these, 87% were organisms of dematiaceous genera (*Bipolaris, Curvularia, Exserohilum, Alternaria, Drechslera, Helminthosporium,* and *Fusarium*); only 13% yielded *Aspergillus.*[32] AFS is similar in pathophysiology to ABPA. First, an atopic host is exposed to fungi through normal nasal respiration, thus providing an initial antigenic stimulus. Type I (IgE)– and type III (immune complex)–mediated reactions then trigger an eosinophilic inflammatory re-

sponse. The resulting inflammation leads to obstruction of the sinus ostia, which may be accentuated by anatomic factors such as septal deviation or turbinate hypertrophy, resulting in stasis within the sinuses. The end result is an allergic mucin that fills the involved sinuses. The clinical presentation may be dramatic, giving rise to visual loss, facial dysmorphia, or complete nasal obstruction. Alternatively, patients may present with chronic sinusitis and nasal polyposis with a gradual increase in production of nasal crusts. Pain is uncommon. Physical findings may include exophthalmus, facial dysmorphia, or intracranial extension. The production of allergic mucin is characteristic of AFS. Grossly, allergic fungal mucin is thick, tenacious, and highly viscous in consistency; its color may vary from light tan to brown or dark green. This characteristic appearance has lead to the use of such descriptive terms as "peanut butter" and "axle grease." There is no consensus concerning diagnostic criteria for AFS. Medical treatment of AFS requires long-term immunotherapy and/or corticosteroids and fungistatic antimicrobial agents (oral and/or topical). Surgical removal of all fungal mucin is a crucial component.[33]

NON–IMMUNE-MEDIATED HEALTH EFFECTS

Irritation

Volatile organic compounds (VOCs) produced by fungi can provoke symptoms in susceptible individuals in a manner similar to nonmold irritants such as tobacco smoke, formaldehyde, or ozone. Symptoms of exposure to microbial VOCs (MVOCs) can include eye, nose, and throat irritation; headache; and fatigue. MVOCs are low molecular weight alcohols, aldehydes, and ketones. The principal volatile compound produced by many molds is 1-octen-3-ol, which has a characteristic mushroom odor. The MVOC 2-octen-1-ol may account for the musty odor of many molds; geosmin (1,10 dimethyl-9 decalol), produced by *Aspergillus versicolor*, has a characteristic earthy odor. The human nose is very sensitive to mold odors, often more so than current analytical instruments. Animal data indicate that the median lethal dose of many of these compounds is high,[34] but inhalation may provoke acute respiratory responses that range from a feeling of stuffiness to frank wheezing. The effects of prolonged low-level exposure are not known.

Inhalation Fever (Humidifier Fever and Organic Dust Toxic Syndromes)

Inhalation fever (influenza-like, self-limited syndromes including humidifier fever and organic dust toxic syndromes) have been reported in occupational or agricultural settings after acute exposures to high concentrations of microbial agents including bacteria, fungi, and associated microbial byproducts.[35] Humidifier fever is a flu-like illness occurring a few hours after exposure to aerosols generated from forced air-conditioning and hu-

midifier systems. Symptoms include fever, headache, chills, myalgia, and, less prominently, pulmonary symptoms. It usually subsides within 24 hours without residual effects. The high attack rate and the short-term effects may indicate that toxins or endotoxin-like reactions are involved. The onset occurs after intense exposure in a single day, but tachyphylaxis occurs on frequent repeated exposures. Hence, humidifier fever is sometimes called "Monday fever," because symptoms occur only on the first day back to work despite similar antigen exposure throughout the week. The pathogenesis of humidifier fever is not completely understood but has been related to excessive growth of microorganisms in humidifier reservoirs, air conditioners, and aquaria. Microorganisms implicated include amoebas, bacteria, fungi, and parasites.[36]

Similarly, organic dust toxic syndrome is a self-limited inhalation fever syndrome occurring after the inhalation of organic dusts from moldy or damp silage, hay, or other agricultural dusts or contaminated wood chips from mulching. Clinically, fever, chills, cough, minimal dyspnea, chest tightness, myalgias, malaise, nausea, and headache occur 4 to 12 hours after exposure. Symptoms of eye and mucous membrane irritation and dry cough are often reported during the acute exposure. It is postulated that organic dust toxic syndrome results from endotoxin-like reactions to high doses of microbial byproducts.[35]

More severe acute lung injury after exposure to damp and moldy organic materials in an agricultural setting also has been reported. The syndrome of toxin-related acute lung injury includes prominent respiratory symptoms, radiographic infiltrates on chest radiographs, and hypoxemia. In 1 case report, a patient developed acute pulmonary edema, presumably resulting from a severe organic dust toxic syndrome reaction or other toxin-mediated injury caused by fungal byproducts, after exposure to high levels of *Penicillium* species contaminating moldy oranges in a storehouse.[35]

Mycotoxins and Associated Health Effects of Mycotoxin Exposure

The fungi that produce mycotoxins are called "toxigenic fungi." The amount, if any, and type of mycotoxin produced depends on a complex and poorly understood interaction of factors that include (1) species of fungus, (2) genetic pattern of the particular strain of the species, (3) maturity of the colony, (4) available food source, (5) amount of water available, (6) temperature, (7) light amounts and wavelengths, (8) presence or absence of competition, (9) presence or absence of specific gases, (10) presence or absence of essential metals, and (11) other unknown factors. Thus, it does not necessarily follow from the presence of a toxigenic species that mycotoxins are present.

Mycotoxins are primarily found in spores and have been identified in the spores of *Acremonium* species, *Alternaria* species, *Aspergillus* species, *Cladosporium* species, *Cylindrocarpon* species, *Fusarium* species, *Mycothecium* species, *Penicillium* species, *Pithomyces* species, *Stachybotrys* (*S atra*, *S alternans*, or *S chartarum*), and *Trichoderma* species (see Table 3 for mycotoxin-producing molds and their health effects). Routes of exposure include ingestion, inhalation, and skin contact. Because mycotoxin-producing molds are lipid soluble, they are easily absorbed via the airways or through the skin. By convention, the term "mycotoxin" excludes mushroom toxins; therefore, the hallucinogenic toxins such as lysergic acid will not be discussed.

Toxic effects from the ingestion of moldy foods have been known for centuries. Although "St Anthony's fire" was described in the Middle Ages, it was not until the 19th century that the chemicals responsible for ergot poisoning were isolated. The fungus *Claviceps purpurea*

TABLE 3	Mycotoxin-Producing Molds and Their Health Effects	
Fungus	Mycotoxin	Adverse Health Effect
Alternaria alternate	Tenuazonic acid	Hepatotoxic and nephrotoxic, hemorrhagic
Aspergillus flavus	Aflatoxins	Hepatotoxic, carcinogenic
Aspergillus fumigatus	Fumitremorgens	Tremorgenic
Aspergillus nidulans	Sterigmatocystin	Hepatotoxic, carcinogenic
Aspergillus ochraceus	Ochratoxin A	Hepatotoxic and nephrotoxic, carcinogenic
Cladosporium species	Epicladosporic acid	Immunosuppressive
Fusarium moniliforme	Fumonisins	Neurotoxic, hepatotoxic and nephrotoxic
Fusarium poae	T-2 toxin	Hemorrhagic and immunosuppressive
Fusarium sporotrichioides	Trichothecenes	Causes alimentary tract aleukia (nausea, vomiting)
Penicillium expansum	Patulin	Nephrotoxic and carcinogenic
	Citrinin	
Penicillium griseofulvum	Griseofulvin	Hepatotoxic, carcinogenic, teratogenic
Pithomyces chartarum	Sporidesmin	Hepatotoxic; causes photosensitization, eczema
	Phylloerythrin	
Stachybotrys chartarum	Satratoxins toxins	Immunosuppressive, hematotoxic
	Verrucarins	Inflammatory, immunosuppressive
	Roridins	Causes dermatitis; hematotoxic, hemorrhagic

grows on rye and contains a number of toxic alkaloids (eg, ergotamine and ergonovine), which are used in the treatment of migraine headaches or as uterine stimulants. The epidemic form of ergotamine poisoning attributable to the ingestion of contaminated rye is rarely seen. Ingestion of 1 g of ergot has been fatal; ergotamine has caused gangrene in doses of 10 mg/day. Circulatory changes are attributable both to prolonged vasoconstriction and to intimal hyperplasia and thrombosis. Symptoms of acute or chronic ergotamine poisoning include vomiting, diarrhea, burning abdominal pain, severe muscle pains, ischemic peripheral gangrene, headache, psychotic behavior, muscle tremors, convulsions, and coma. Treatment is based on symptoms and includes the use of vasodilators and analgesic agents.

Because mycotoxins are natural contaminants of food sources, they cannot be totally eliminated before consumption. The following mycotoxins have well-described adverse health effects.[37]

Aflatoxins

Aflatoxins are produced by certain strains of *Aspergillus* species. They were first discovered after an epidemic that killed 100 000 turkeys in the 1960s. The toxin was found in moldy Brazilian peanuts that were included in the feed. Later, these naturally occurring mycotoxins were discovered in barley, corn, other nuts, and wheat. The maximum concentrations of aflatoxins allowed in food are set by the US Food and Drug Administration. The limits for food and milk are 20 and 0.5 parts per billion (ppb), respectively. Levels up to 300 ppb are allowed in feed for livestock and poultry. A recent outbreak of aflatoxin-related jaundice in Kenya resulted from widespread contamination of locally grown maize, which occurred during storage of the maize under damp conditions. Of the 317 cases, the case fatality rate was 39%. The level of toxin in food samples ranged from 20 to 8000 ppb.[38]

Citrinin

Citrinin is found in the *Penicillium* species. It typically contaminates barley, corn, rye, and wheat. Adverse health effects include fatty infiltration and necrosis of the liver and nephrotoxicity. Because this mycotoxin is destroyed by food processing, there are no Food and Drug Administration regulations or guidelines.

Fumonisins

Fumonisins are produced by *Fusarium* species. They are commonly found in corn and are detectable in tortilla flour. They have been implicated in equine leukoencephalomalacia. The mechanism of action involves the inhibition of the sphingolipid synthesis, resulting in disruption of sphingomyelin. In humans, no toxic effects have been described, but there may be an association with the development of esophageal carcinoma. The

Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) recommend a maximum tolerable intake at 2 μg/kg of body weight per day.

Ochratoxins

Ochratoxins have been isolated from *Aspergillus* and *Penicillium* species and are found in barley, cocoa, coffee, corn, soybeans, and wheat. They inhibit protein synthesis and produce most of their adverse affects in the gastrointestinal tract and kidneys. The FAO/WHO recommend a tolerable weekly intake of 100 μg/kg. Suggested tolerance levels for infant cereals and foods are 5 and 1 μg/kg, respectively.

Patulin

Patulin is produced by *Aspergillus* and *Penicillium* species and other mold species that grow in fruits such as apples, grapes, and pears. Because it is carcinogenic in animals, there are concerns about the possibility of carcinogenicity in children who drink large amounts of fruit juice, especially apple juice. There is a recommended limit of 50 μg/kg of patulin in apple juice and cider. Sulfur dioxide, a common food preservative for dry foods and juices, degrades the toxin.

Trichothecenes

Trichothecenes are metabolites that are produced by a number of fungi including *Fusarium*, *Mycothecium*, *Stachybotrys*, *Trichoderma*, and *Cephalosporium* species. There are almost 150 natural trichothecenes, of which at least 40 are mycotoxins. They are found in crops and animal feed (particularly hay and straw) contaminated with *Fusarium* species. Levels in the range of 0.5 to 40 mg/kg of T-2 toxin, 4-deoxynivalenol (DON), and nivalenol are detected in corn, peanuts, rice, and wheat. In commercial foods, such as corn, flour, popcorn, potato, wheat flour, breakfast cereals, and infant food, trichothecene levels are much lower, in the range of 0.03 to 0.5 mg/kg.

There are 4 main groups of trichothecenes. Group A includes the highly toxic T-2 toxin and diacetoxyscirpenol. Group B includes DON and nivalenol. Group C is produced by *Baccharis megapotamica* and is the least common. Group D includes roridins produced by *Mycothecium roridum*, verrucarin produced by *Mycothecium verrucaria*, and satratoxins produced by *S chartarum*. Only group D trichothecenes are produced by *S chartarum*. Setting tolerance levels for trichothecenes is difficult because of the mixtures of toxins with different toxicities. The FAO/WHO Joint Expert Committee recommends a provisional maximum tolerable daily intake of 1 μg/kg for DON and 60 μg/kg for T-2 toxin. *S chartarum* has gained recent media attention as the "toxic mold." *S chartarum* is a shiny, black mold that grows only on water-soaked cellulose. It is unusual to find it indoors because of the chronic waterlogged condition necessary

for its growth. Thus, the black mold commonly found on bathroom tile and grout is not *Stachybotrys*. In addition to the trichothecenes, *S chartarum* isolates can produce a number of other mycotoxins (Table 4).

CLINICAL EFFECTS LINKED TO *Stachybotrys* MYCOTOXINS

The first reported cases of stachybotryotoxicosis in humans occurred in the 1940s. Russians who handled contaminated hay or slept on straw-filled mattresses experienced dermatitis, pain and inflammation of the mucous membranes, burning nasal passages, tightness of the chest, bloody rhinitis, cough, fever, headache, and fatigue. Later studies reported similar symptoms in individuals exposed to *S chartarum*.[39,40] A case-control study by Johanning et al[40] was the first investigation of *Stachybotrys*-associated complaints and building-related illness. Comprehensive testing of immunologic indices using a test battery developed by the National Institute for Occupational Safety and Health to detect immunomodulation from exposure to xenobiotics was used to study the red and white blood cell systems, serum chemistry, immune function, and Ig antibodies. Results showed that the workers with direct contact with moldy materials or working in locations with the highest airborne *Stachybotrys* levels (range: 116 to more than 20 000 colony-forming units [CFU]) required temporary or permanent removal because of severely increased symptoms after return to the building with *Stachybotrys* contamination as compared with unexposed controls. Fingertip skin inflammation in 3 women handling moldy horticulture pots made of recycled paper that had visible black masses

of *Stachybotrys conidia* as well as *Chaetomium perithecia* and other fungi has been reported. The illness, described as painful, inflamed efflorescences at the fingertips, followed by scaling, was attributed to the effects of a mycotoxin. However, no tests were performed to determine the etiologic agent or the mechanism (allergic or irritant contact dermatitis, toxicity, or infection).[41]

Idiopathic Pulmonary Hemorrhage

The first cluster of idiopathic pulmonary hemorrhage in infants was reported from Greece in the 1980s.[42] Other reported clusters of the illness have been reported throughout the United States, but the first report to implicate *S chartarum* was a community-based case-control study in Cleveland, Ohio.[43] Investigators found an association between exposure to water-damaged buildings and *S chartarum* with acute pulmonary hemorrhage/hemosiderosis in infants. The calculated OR was 16.25 (95% confidence interval [CI]: 2.55 to infinity). Case infants were also more likely to have had close relatives with pulmonary hemorrhage (OR: 33.14; 95% CI: 5.10 to infinity). In addition, 50% of the case infants experienced recurrent pulmonary hemorrhage after returning to their homes.[43] Of note, the OR associated with exposure to cigarette smoke in the cases was 7.9. Also of note was that none of the children had been breastfed. A study by Etzel et al[44] revealed a greater than 4-fold increase in all fungi and a more than 10-fold increase in *S chartarum* concentrations in case homes compared with control homes. The high prevalence of *S chartarum* in the Cleveland cluster-area homes (65%) was unusual; other studies in North America have detected it in less than 3% of homes. Other toxin-producing species were identified, including *A versicolor*, *Penicillium aurantiogriseum*, and *Penicillium chrysogenum*, but the differences between case and control homes for these molds were not significant. To test for interaction with environmental tobacco smoke, a multivariate matched analysis assessed the impact of *S chartarum* concentration and exposure to environmental tobacco smoke, finding an OR of 21 (95% CI: 1.07 to 7.5×10^6), for an increase of 10 U in the mean concentration of *S chartarum* in the presence of environmental tobacco smoke.[44,45] Reexamination of these data years later led the Centers for Disease Control and Prevention (CDC) to conclude that "a possible association between acute pulmonary hemorrhage/hemosiderosis in infants and exposure to molds, specifically, *S chartarum*, was not proven."[46] When 1 outlier case was excluded, the OR dropped from 9.8 to 1.5. Although the OR was lower, it remained significant (OR: 1.5; 95% CI: 1.1 to 2.5). Problems with the data collection (oversampling of air samples from case homes) and nonstandardized methods to generate artificial aerosols for sampling (vacuuming carpets and pounding on furnace ducts and furniture) were noted, leaving the hypothesis unproven. However, additional cases from on-

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TABLE 4   *Stachybotrys* Metabolites and Their Actions

Stachybotrys Metabolites	Action
Atranones	Immunotoxic, inflammatory
Cyclosporin	Immunosuppressive
Enzymes	Collagenolytic proteinase
Stachyrase A	
Hemolysin	Hemolytic
Stachyhemolysin	
Macrocyclic trichothecenes	Protein synthesis inhibitors, cytotoxic
Isosatratoxins	
Roridins	
Satratoxins	
Verrucarin	
Microbial VOCs	Irritant
1-butanol	
3-methyl-1-butanol	
3-methyl-2-butanol thujopsene	
Phenylspirodrimanes	Immunosuppressive
Spironolactones	
Spironolactams	
Simple trichothecenes	Not well defined
Trichodermol	
Trichodermin	
Trichoverroid trichothecenes[a]	Not well defined

This table illustrates the many *Stachybotrys* mycotoxins and metabolites that may contribute to toxicity and is not meant to be comprehensive.

[a] Lie along the biosynthetic path between the simple and the macrocyclic trichothecenes.

going surveillance in Cleveland continue to show an association between acute idiopathic pulmonary hemorrhage (AIPH) and water-damaged homes in conjunction with exposure to cigarette smoke.[47] A recent study of toxin production by the fungal isolates in victims' homes was performed. Isolates of *S chartarum* and *Memnoniella echinata* (a fungus closely related to *S chartarum*) were isolated from homes of the case infants and then analyzed both for cytotoxicity and specific toxins. The most common toxins were satratoxin H and roridin, and the results showed that the levels of cytotoxicity correlated with the levels of these trichothecenes. However, there was no relationship between cytotoxicity and the origin of the isolate (a case home or a control home).[48]

Case reports from other cities have also been published.[49,50] A report from Kansas City, Missouri, described a 1-month-old male with pulmonary hemorrhage.[49] Questioning of the family identified a recent water leak in the home after hail damage to the roof. The leak occurred in a closet of the bedroom where the infant slept. The mother also smoked cigarettes. *Stachybotrys* spores were collected from the infant's bedroom, along with several other mold species. High quantities of several potent trichothecenes were detected. The mycotoxins roridin and satratoxins were also identified. It is hypothesized that these toxins interfere with synthesis of type IV collagen and other endothelial basement membrane components, leading to increased capillary fragility and hemorrhage. It is postulated that infants are particularly sensitive to the effects of the toxins because of their rapid lung growth.[49]

S chartarum was first isolated from a patient in a case report by Elidemir et al.[51] The mold was isolated from bronchoalveolar lavage of a 7-year-old boy with a 2-year history of chronic, nonproductive cough accompanied by intermittent low-grade fever, malaise, fatigue, and decreased appetite. His bronchoalveolar lavage showed 26% hemosiderin-laden macrophages and grew *S chartarum*. *S chartarum* was also recovered from the child's water-damaged farm home. Within a month of relocating to his grandmother's house, his cough resolved, his appetite improved, and his weight increased by 2 kg.

Because the relationship among idiopathic pulmonary hemorrhage, pulmonary hemorrhage, and AIPH in infants is not clearly understood in terms of rate, etiology, and risk factors, the CDC formed a working group for the investigation and surveillance of infants with AIPH.[52] The group recommended a case definition for AIPH in infants and a plan for retrospective surveillance for AIPH in infants. The definition of a case of AIPH in an infant uses the term "pulmonary hemosiderosis" as a pathologic finding to denote the possible occurrence of pulmonary hemorrhage and not to describe a clinical syndrome. CDC criteria for a confirmed case of AIPH include pulmonary hemorrhage in a previously healthy infant younger than 1 year with a gestational age of more than 32 weeks, no history of problems that might cause pulmonary hemorrhage, and a condition that meets all of the following 3 criteria:

1. abrupt or sudden onset of overt bleeding or obvious evidence of blood in the airway, including epistaxis, hemoptysis, or frank blood in the airway below the larynx at visualization, not caused by any medical procedure (eg, laryngoscopy or intubation) or identification of hemosiderin-laden macrophages (>20% of pulmonary macrophages containing hemosiderin on bronchoalveolar lavage or biopsy specimen); a source of bleeding from the nose and oropharynx should be ruled out at the time of admission;

2. severe-appearing illness leading to acute respiratory distress or respiratory failure resulting in hospitalization in a PICU or NICU with intubation and mechanical ventilation; and

3. diffuse unilateral or bilateral pulmonary infiltrates visible on radiographs or CT of the chest; chest radiographic or CT findings should be documented within 48 hours of examination of the infant.

A previously healthy infant should:

1. have been discharged from the hospital after birth with an uneventful course before the occurrence of bronchoalveolar hemorrhage;

2. have neither never been previously intubated nor required respiratory support with oxygen;

3. not have evidence of physical abuse;

4. not have any abnormality identified on admission that would explain the bleeding; and

5. not have neonatal medical problems that can cause pulmonary hemorrhage.

Less stringent criteria define probable and suspected cases.

Currently, the CDC is in the process of a retrospective review for AIPH among infants in metropolitan areas in states with the highest death rates and with 100 or more deaths associated with pulmonary hemorrhage among infants from 1979 to the present.

Experimental animal models of *Stachybotrys* mycotoxicosis in mice are limited. In 1 study, intranasal exposure to spores of *S chartarum* containing satratoxins caused severe intraalveolar, bronchiolar, and interstitial inflammation with hemorrhagic exudation.[53]

The Institute of Medicine (IOM) conducted a comprehensive review of the literature on the adverse health effects of mold and dampness in indoor spaces, including the literature on *Stachybotrys* species and pulmonary hemorrhage.[54] They concluded that there was insufficient evidence to determine if mold exposure to *Stachybotrys* species was associated with AIPH, in part because of problems with data collection and lack of available,

standardized tools for exposure assessment. The IOM recommended further surveillance and additional research.

In summary, although the causal association between AIPH in infants has not been firmly established, the Cleveland study, additional case series, case reports from independent sources, and basic scientific studies in animal models have provided some evidence of plausibility. Epidemiologic studies suggest that exposure to second-hand cigarette smoke may be an additional risk factor. Ongoing work in toxicology and epidemiology will provide more insight in the future.

CLINICAL EFFECTS LINKED TO OTHER MYCOTOXINS

Neurologic Toxicity
Ingestion of 3-nitropropionic acid produced by *Arthrinium* species is thought to cause "moldy sugarcane" or "kodua" poisoning. Symptoms include dystonia, convulsion, carpopedal spasm, and coma.[55] Cyclopiazonic acid produced by *Penicillium* species and *Aspergillus* species has also been linked to kodua poisoning. Clinically, patients have somnolence, tremors, and giddiness.[56] Other fungal components, such as VOCs, may produce neurologic effects. There is no evidence of neurologic injury associated with inhalation of mycotoxins. Patients, their parents, and clinicians have raised concerns regarding potential neurotoxicity from mold exposure, and the scant literature has been reviewed.[57]

Gastrointestinal Toxicity
Mold-contaminated food products are known to cause nausea, vomiting, abdominal pain, and diarrhea when ingested. High concentrations of trichothecenes destroy skin layers and cause acute necrosis. The mucosa of the mouth, esophagus, and intestine can be affected, and necrosis and inflammation can occur.[55,58]

Renal Toxicity
Ochratoxins (found in cereals, coffee, bread, and meat) produced by *Penicillium* species and *Aspergillus* species are associated with Balkan endemic nephropathy.[37]

Teratogenic Effects
Zearalenone produced by *Fusarium* species (F-2 toxin) possesses estrogenic activity and causes infertility and fetal malformations in animal models. Human studies have not been performed.

Cancer
Studies performed in Asia and Africa have shown that chronic consumption of aflatoxins in food increases the risk of developing hepatocellular carcinoma. However, coinfection with hepatitis B virus is an important synergistic factor that affects the carcinogenicity of aflatoxins.[59] There is no evidence linking inhaled mycotoxins to human malignancy.

SICK BUILDING SYNDROME
Sick building syndrome (SBS) was originally defined by the WHO as an excess prevalence of work-related irritations of the skin and mucous membranes and other symptoms reported by workers in modern office buildings.[60] Clinical features typically include eye, nose, and throat problems, dermatitis, drowsiness, difficulty in concentrating, headache, and fatigue. Chemical contaminants, bioaerosols, poor ventilation, odor perception, thermal comfort, and psychological factors have been suggested as causal factors. Some have suggested that the term SBS be abandoned for its lack of clarity. "Non-specific building-related illness" as a new term has been proposed by some experts. Although individual symptoms of SBS have been associated with damp, moldy environments, the constellation of symptoms together has not been systematically evaluated in epidemiologic studies.

HEALTH RISKS ASSOCIATED WITH DAMP INDOOR ENVIRONMENTS
In the previous sections we have discussed the clinical spectrum of noninfectious health effects associated with exposures to mold; however, the pediatrician may be asked what the scientific evidence is for health risks associated with living in damp indoor environments. In the past 10 to 20 years, numerous epidemiologic studies have reported on health effects attributed to damp or moldy indoor environments or mycotoxins, and these findings were reviewed.[7,13,14,61]

In one of the first epidemiologic studies, Brunekreef et al[62] found associations between self-reported mold exposures and respiratory symptoms (wheeze, cough, hay fever) in a survey of more than 4600 US children (7–11 years of age). After taking into account other home environmental factors such as environmental tobacco smoke, the adjusted OR for wheeze was 1.79 (95% CI: 1.44 to 2.32). A Canadian survey of more than 13 000 children found associations between wheeze and cough and self-reported dampness or mold (adjusted OR: 1.89; 95% CI: 1.61 to 2.20).[15] Among the more recent studies, in a prospective cohort of 849 infants with a family history of asthma, investigators found associations between measures of mold exposure (reported persistent mold or mildew in previous 12 months or air concentrations of *Penicillium* species and humidifier use) and cough and wheezing.[63,64] In a case-control study of 272 children, there was an increased risk of allergic sensitization among those in homes with a high level of mold spores in the winter (as determined by dust collection), even after adjusting for dust mite levels, especially in children who had lived in the same home since birth.[65] Many of the larger studies were cross-sectional surveys, often with self-reported symptoms and exposures, and could be subject to bias. However, an analysis of a subset that used surveyor assessment of a

damp environment found associations between respiratory systems (eg, cough and wheeze) and the presence of mold.[13] Taken together, Bornehag et al[13] found that large surveys and smaller case-control studies with more objective surveyor assessments found a consistent increase in risk of respiratory symptoms among those who lived in a damp environment.

Dampness can be associated with dust mites and bacterial growth. However, associations between "dampness" and health have been found in areas with little dust mite exposure (eg, in northern Scandinavia) or after taking mite exposure into account in the analysis.[13]

Because of increasing public concern regarding health effects of mold spurred, in part, by reports of cases of pulmonary hemorrhage in infants in Cleveland linked to *Stachybotrys* species and a great deal of attention in the mass media, the CDC asked the IOM to conduct a comprehensive review of the scientific literature regarding the relationship between damp or moldy indoor environments and adverse health effects.

The authors of the IOM report (summarized in Table 5) found sufficient evidence of an association between mold and other agents in damp indoor environments and upper and lower respiratory tract symptoms, as well as asthma symptoms in sensitized persons.[54] There was insufficient information to determine if mold exposure was associated with the development of asthma. Similarly, the IOM reported that there was insufficient evidence to determine if mold exposure to *S chartarum* was

associated with idiopathic infantile pulmonary hemorrhage because of the limitations of previous epidemiologic studies.[43–46] The IOM report also noted that other conditions reported with a damp indoor environment, including constitutional or neuropsychiatric symptoms, skin rashes, and rheumatologic diseases, were poorly studied, and no conclusions could be drawn.

Although inhalation fevers have been reported in occupational or agricultural settings after acute exposures to high concentrations of fungal agents, it would be very unusual to have concentrations of bioaerosols comparable to those experienced in inhalation/humidifier fever in most homes or public buildings. However, the IOM report noted that physicians should consider the syndrome in cases of highly contaminated indoor environments.[54] As noted previously, although individual symptoms of SBS have been associated with damp moldy environments, the constellation of symptoms together has not been systematically evaluated in epidemiologic studies. The authors of another systematic review of the literature reviewed 13 studies on fungi, mycotoxins, and the indoor environment and also concluded that there is inadequate evidence to support a causal relationship between symptoms or illness among building occupants and exposure to mycotoxins.[66]

Similarly, the American College of Occupational and Environmental Medicine review and policy statement on "Adverse Human Health Effects of Molds in the Indoor Environment" concluded that "current scientific evidence does not support the proposition that human health has been adversely affected by inhaled mycotoxins in the home, school, or office environment."[67]

There are few data assessing the health benefits of decreasing exposure to damp environments. A before-and-after intervention study in the Pacific Northwest examined health-related complaints in 37 building occupants before and after relocation from a water-damaged building.[68] The health survey revealed a high prevalence of multiple symptoms, with a predominance of neurobehavioral (fatigue, headache, and difficulty concentrating) and upper respiratory tract complaints. Public health officials were contacted and conducted a walk-through evaluation of the building. They found evidence of moisture incursion throughout the building. Mold odors were detected, and *S chartarum* was isolated from the baseboard of one of the walls. The authors concluded that the toxigenic mold was likely to be present within all the wet walls of the building and that symptoms reported by building occupants were consistent with toxigenic mold exposure. They strongly recommended that the occupants be relocated. Comparison of symptoms before and after relocation showed that most symptoms were significantly less prevalent after relocation ($P < .0001$). The majority (70%) described their overall health as "better" since relocation, and equal proportions (15%) described their overall health as

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TABLE 5   Findings of the IOM Report: Association Between Health Outcomes and the Presence of Mold or Other Agents in Damp Indoor Environments

Sufficient evidence of an association
  Upper respiratory tract symptoms (nasal and throat)
  Wheeze
  Cough
  Asthma symptoms in sensitized persons
  Hypersensitivity pneumonitis in sensitized persons
Limited or suggested evidence of an association
  Lower respiratory tract illness (eg, pneumonia, frequent colds) in children
Inadequate or insufficient evidence to determine whether an association exists
  Dyspnea
  Skin symptoms
  Asthma development
  Gastrointestinal tract problems
  Airflow obstruction (in otherwise healthy persons)
  Fatigue
  Chronic obstructive pulmonary disease
  Neuropsychiatric symptoms
  Inhalation fevers (nonoccupational exposures)
  Cancer
  Lower respiratory illness in otherwise healthy adults
  Reproductive effects
  AIPH in infants
  Rheumatologic and other immune diseases

Source: Institute of Medicine, Board on Health Promotion and Disease Prevention, Committee on Damp Indoor Spaces and Health. *Damp Indoor Spaces and Health*. Washington, DC: National Academies Press; 2004.

"same" and "worse." A causal relationship between the symptoms and the toxigenic fungi is difficult to prove because of the study design and the subjective nature of self-reported symptoms.

ASSESSMENT, REMEDIATION, AND PREVENTION

Assessing Exposures to Indoor Mold

The diagnosis of mold-related illness and issues related to exposure as a cause of disease is problematic. Because of our incomplete knowledge of what agents in damp indoor environments (and what amount of exposure) contribute to health effects, there are no uniformly accepted, valid, quantitative environmental sampling methods or serologic tests to assess exposures to mold and other agents associated with damp indoor environments. Because of uncertainties in the exposure assessments used in health studies, federal and state regulatory agencies have not established health-based guidelines for exposure limits for indoor biological agents (ie, what air concentrations of mold spores are unlikely to cause health risk). Sampling cannot be used to check a building's compliance, because no federal mold guidelines exist. In this section, we summarize the available exposure-assessment methods, discuss their limitations, and provide some practical guidelines for the practicing physician. *Guidance for Clinicians on the Recognition and Management of Health Effects of Mold Exposure and Moisture Indoors* provides an excellent discussion of environmental assessment strategies (see "Resource for Pediatricians").

Environmental Assessment and Sampling

Methods for sampling of indoor fungi were recently reviewed and include visual inspection, bulk or surface sampling (eg, culturing pieces of damp or discolored wallboard), and air sampling.[69] Air sampling may include measurement of total spore concentration (number of spores per m³) or viable (ie, culturable) spore concentration (CFU/m³). Air fungal capturing devices may have a variation of up to 1000-fold between specimens obtained from the same source. Single samples from either the suspected or control area cannot provide scientifically meaningful conclusions because of the lack of statistical and practical significance. Some texts suggest at least 16 samples over 4 time periods.[70,71]

Burge[70] has suggested some rules of thumb as evidence of mold overgrowth in the indoor environment (although proposed levels are not necessarily associated with symptoms): (1) more than 200 CFU/m³ of air or 500 spores per m³*; (2) a CFU count 10 times higher than a noncomplaint environment; (3) CFU counts exceeding those outdoors by order of magnitude (10×);

and (4) a single fungus accounting for more than half of the total. However, the criteria proposed by Burge need additional evaluation.

To date, the majority of population-based epidemiologic studies have used questionnaires regarding signs of dampness (eg, visible mold, recent water damage, musty smell, etc) as measures of exposure or inspections with trained investigators, but these methods are difficult to quantify. Recently, studies have begun to quantify exposures to mold with environmental sampling of air or dust for spores or fungal byproducts, including toxins. There is a clear need for establishing consistent methods for quantifying indoor exposures to mold for use in future health studies. Thus, the Environmental Protection Agency (EPA) and other environmental agencies have not set numeric standards for indoor concentrations of mold or mold spores regarding the levels at which adverse health impacts are associated.

Another inherent limitation of the interpretation of environmental sampling is that the sampling is conducted over a limited period (ie, snapshot of potential exposure), and measurements are often made after the development of illness or symptoms. Because production and release of mold spores and mycotoxins vary substantially, depending on physiologic and environmental factors, exposure measurements may not always track with past exposures.

Another complicating fact is that multiple species of molds are usually found in damp indoor environments; for example, exclusive exposure to *Stachybotrys* species is rare. Many fungi known to produce toxins, allergens, and irritant chemical compounds are usually found in large numbers in buildings with water problems and fungal contamination. Thus, attributing causation to one particular mold species from epidemiologic studies alone may be problematic.

Although results of environmental sampling should be interpreted with caution, the clinical and epidemiologic evidence to date suggests that damp, moldy indoor environments are unhealthy, and we outline a practical approach for assessing mold in the indoor environment in Table 6. Additional clinical evaluation tools for the recognition and management of mold and moisture-related illnesses are available (http://oehc.uchc.edu/clinser/indoor.htm).

Should I Test for Mold? What Tests Should I Order?

In clinical practice, extensive documentation of indoor fungal growth may not be necessary, depending on concerns of the occupants. Visible signs of mold growth (eg, discolored patches or cottony or speckled growth on walls or furniture, evidence of dampness or water damage or an earthy musty odor in a particular area) suggest a damp environment and mold growth. If a child with persistent asthma symptoms is sensitized to mold and there is visible mold growth in the home, efforts should

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*Spores per m³ is the unit of measurement for total spores (both viable and nonviable); CFU/m³ measures viable spores only. Spores per m³ is a better indicator of potential mycotoxin exposure, assuming that mold spores contain mycotoxins.

TABLE 6 Guidelines for Pediatricians Considering Possible Illness Related to Damp, Moldy Indoor Spaces

When to consider indoor mold-related illness[a]
- Chronic respiratory symptoms of unclear etiology
- Poorly controlled asthma, perennial allergic rhinitis, or chronic sinusitis
- Respiratory symptoms or recurrent influenza-like symptoms in a moldy environment
- Suspected or diagnosed hypersensitivity pneumonitis, ABPA, or fungal sinusitis
- Unexplained pulmonary hemorrhage, especially in infants

Assessing exposures to molds: helpful questions
- Have you seen any mold or mildew on walls, floors, ceilings, or carpets, including your basement (evidence of discolored patches or cottony or speckled growth on walls or furniture)?
- Have you noticed a musty or earthy smell indoors?
- Has the home been flooded?
- Is there any water-damaged wood or cardboard in the house?
- Has there been a roof or plumbing leak, standing water in the home or areas with chronic dampness/moisture, including the basement?
- Is there often condensation (fog) on the inside of the windows and/or cold inside surfaces?
- Have humidifiers or air-conditioner drip pans been checked for mold overgrowth?
- Are symptoms better away from the house?
- Describe your basement dwellings and conditions at school or other places where you routinely spend time.

Environmental assessment
- Work with an experienced industrial hygienist or investigator.
- Methods: visual inspection, bulk sampling, and air sampling of visible or culturable fungal spores.
- Serologic testing may be helpful in some settings.[a]

[a] Physicians should also consider and rule out other possible non–mold-related etiologies. For symptoms attributable to mycotoxin ingestion, see text.

be focused on cleanup and addressing the moisture problem to prevent recurrence. Additional documentation of mold exposure with sampling is not necessary.

Environmental inspection and sampling may be useful to identify the source if there is a suspicion of mold (eg, musty odor) but no visible mold growth. In addition, environmental inspection and sampling for mold may be necessary as part of the diagnostic evaluation and treatment plan when certain medical conditions are being considered (eg, hypersensitivity pneumonitis, ABPA, or acute pulmonary hemorrhage in infants). Environmental sampling for mold may also be necessary for insurance purposes or litigation. Consultation with pediatricians who have expertise in pulmonary medicine, allergy/immunology, or environmental health or physicians who have expertise in occupational environmental health may be helpful.

If environmental sampling for mold is done, the study should be performed by professionals, such as industrial hygienists or indoor air-quality consultants, who have expertise in evaluating indoor mold/dampness problems. An industrial hygienist and contractor may work together to identify the moisture problem and conduct sampling. There is currently no formal certification process for mold evaluation; however, guidelines for appropriate evaluation have been outlined.[72,73]

In addition to visual inspection, bulk sampling (culturing materials [eg, wood, particle board suspected of mold contamination]) may be used to document whether materials are contaminated. Surface sampling (cultured swabs of surfaces) may be used to document whether discoloration on surfaces is the result of fungal growth. Reliable air sampling can be expensive and requires expertise and specialized equipment. If air sampling is conducted, an outdoor air sample should be collected at the same time for comparison. In general, the levels and types of fungi found indoors (in nonproblem buildings) should be similar to those found outdoors. Exceptions may occur (eg, when there are extremely low concentrations of mold spores outdoors after a snowfall). Higher concentrations of fungal spores, a predominance of one type of fungal spores, or a difference in types of fungi found in indoor versus outdoor air samples suggest an indoor mold problem.

Other assays to detect fungi, mycotoxins, and MVOCs in environmental samples have been developed. One caveat is that the half-life of the important mycotoxins, such as the trichothecenes, is several hours, and individuals present for medical evaluation long after the acute exposure. Thus, current mycotoxin assays of blood specimens or environmental samples can serve as important tools for researchers studying pathogenesis of disease; however, the tests have not been standardized for clinical use, and it is not clear at which levels health effects are associated.

Laboratory Tests for Human Exposure to Molds or Toxins
Because fungi produce antigenic proteins that can lead to an immunologic response, medical evaluations of people concerned about exposures to mold or fungi may include laboratory testing. Trout et al[74] recently reviewed the role of immunoassay for fungal antibodies in evaluating patients in various clinical settings. The authors concluded that immunoassays are a useful adjunct

to a complete evaluation, but in general, the assays should not be used as the only means of primary assessment. Problems include lack of standardized fungal extracts and cross-reactivity among fungal species. Although the immunoassays are suggestive of exposure to mold or fungi (which are widespread in nature), the current assays cannot specify when the exposure occurred or reliably identify the particular type of mold or fungus involved. Because of these limitations, results of the immunoassays must be interpreted in the context of the clinical setting and other supporting diagnostic tests.

Thus, detection of IgE specific to common outdoor molds by skin testing or serologic testing indicates sensitization and is supportive of fungal allergies or allergy in general. However, a positive test result does not necessarily mean that the agent is the cause of the patient's symptoms. Similarly, detection of antibody by precipitin testing is often used to confirm exposure to a suspected antigen in an evaluation for hypersensitivity pneumonitis. However, asymptomatic farmers and pigeon breeders may have positive precipitin test results.[75] Conversely, some patients with clinically confirmed hypersensitivity pneumonitis will have negative antibody test results, presumably because of poorly standardized antigens, low concentrations of IgG, or incorrect identification of the causative agent.

Currently, no tests can reliably determine if a person was exposed to *S chartarum* mold, its toxins, or other molds commonly found in damp environments. A few physicians have used immunoassays to determine if their patients have been exposed to *S chartarum* mold. However, these immunoassays for *S chartarum* have not been proven to be valid for use in clinical evaluation. For instance, an isotype-specific immunoassay developed for IgE, IgG, and IgA to *S chartarum* is cross-reactive with antibodies to *A fumigatus* and *Alternaria alternata*, 2 common outdoor fungi.[74]

In 1 small study, Barnes et al[76] found IgE and IgG directed against *S chartarum* in a general population in Kansas City, Missouri. Enzyme immunoassay indicated that 65 (49.2%) of 132 serum samples tested contained IgG against *S chartarum*, and 13 (9.4%) of 139 serum samples tested contained IgE against *S chartarum*, suggesting either that *S chartarum* antibodies developed without history of overt clinical disease or that the presence of *S chartarum* may be a false-positive result. Furthermore, persons who become ill after exposure to *S chartarum* may not develop IgG or IgE anti-*Stachybotrys* antibodies.

Presence of antibodies to hemolysin produced by *S chartarum* has been suggested as a biomarker of exposure to *S chartarum*.[77] However, additional studies are needed to determine the sensitivity and specificity of testing for these antibodies.[74] A discussion of the possible misinterpretation of *Stachybotrys* serology is available.[78]

Prevention

It is impossible to keep mold spores out of the house. They come in through windows and doors, and humans and pets bring them in from the outside. The challenge is to keep the spores from colonizing and growing. Therefore, the key to mold control is moisture control. Actions that will help reduce indoor air humidity and prevent condensation include venting appliances that produce moisture (clothes dryers and stoves) to the outside and using a bathroom fan or opening a window when showering or bathing. When there is inadequate bathroom ventilation, using a towel to wipe shower walls and turning a fan or space heater on for a short period of time may diminish excessive moisture accumulation. Dehumidifiers can be used in areas with consistently elevated humidity levels, with a target humidity level of less than 50%. Dehumidifiers reduce ambient humidity but do not significantly reduce growth on surfaces in contact with ground water. To effectively control additional growth on damp surfaces, the water source must be eliminated. Bathrooms and basements should be left uncarpeted, and other indoor organic sources such as plants, wood, and paper products should be eliminated. Outdoors, fallen leaves can harbor mold and should be collected and discarded in a timely fashion. Parents should be aware that playing on or near piles of leaves exposes their children to increased levels of mold spores. This increased exposure could contribute to increased symptoms among children with asthma/allergies.

Actions that will help prevent condensation include reducing humidity; increasing ventilation by opening doors or using fans; covering cold surfaces, such as cold water pipes, with insulation; and increasing the air temperature.

Air Cleaners

People with allergies and asthma may use certain air cleaners such as air-filtration units, electrostatic precipitators, and ozone generators to eliminate bacteria, mold, and chemical contaminants from the air. Filters on central forced-air systems and furnaces should be changed periodically, according to the manufacturers' recommendations. Upgrading to a medium-efficiency filter (rated at 20%–50%) will improve air quality and is economical. Electrostatic filters/precipitators in central furnace and air-conditioning systems may be beneficial for airborne particles but are only effective when turned on. Room high-efficiency particulate air (HEPA) filters may be beneficial. However, they only work in a single room, and the noise generated may not be acceptable.

Ozone generators often advertised as "air purifiers" are touted to cleanse the air of microbes. However, ozone-producing air-cleaning devices may produce indoor concentrations of ozone high enough to reduce lung function. A study conducted by the EPA ran an

ozone generator in a test home at its maximum setting. When the room's air was sampled, ozone levels were found exceeding 0.3 ppm. This level is equal to a stage 1 smog alert, when local air-pollution–control districts advise the public to avoid some outdoor activities. These levels far exceed some states' ambient 1-hour standard for ozone of 0.09 ppm. High ozone effectively destroys microbes in water; however, air levels must reach extremely hazardous levels (50–100 times the outdoor air-quality standards) to be effective. Other electronic air cleaners, such as electrostatic precipitators and ionizers, produce ozone as a byproduct, and certain units generate potentially unhealthy levels. These devices should be cleaned and maintained regularly to minimize ozone emissions.[79]

Air-cleaning devices such as air-filtration units and electrostatic precipitators have the capacity, in theory, to remove airborne spores. However, their effectiveness in decreasing air concentrations of spores in damp indoor spaces and decreasing respiratory symptoms are unproven.

Humidifiers

Many parents use cool-mist humidifiers or vaporizers when children have colds or when the air is dry in winter. A systematic review in the *Cochrane Database of Systematic Reviews* assessed the effects of inhaling heated water vapor in the treatment of the common cold by comparing symptoms, viral shedding, and nasal resistance after a naturally or experimentally induced common cold.[80] Six randomized trials with 319 participants were identified. The results supported the use of warm-vapor inhalations in the common cold in terms of relief of symptoms (OR: 0.31 [95% CI: 0.16 to 0.60]; relative risk: 0.56 [95% CI: 0.4 to 0.79]). Results on symptom score indices were equivocal, but none demonstrated a worsening of scores. There was no evidence of decreased viral shedding measured by virus isolation in nasal secretions or measurement of viral titers in nasal washings from the treatment group. Minor adverse effects caused by thermal stress were reported in all the studies.

The potential benefit in cold symptoms must be balanced with the risk of increased growth and exposure to house dust mites and mold with increased humidity. Therefore, the general use of humidifiers should be avoided. If used for treatment of the common cold, their use should be limited, and they must be cleaned frequently to prevent mold growth and according to the manufacturers' instructions.

Remediation

Indoor water damage and/or mold overgrowth should be remediated to avoid irritant upper respiratory effects, possible sensitization to mold, possible injury from mycotoxins, and/or exacerbation of underlying mold allergy and to avoid structural damage to the building. A Finnish case-control investigation examined whether exposure to molds in the school was associated with an increased occurrence of respiratory symptoms and whether renovation of water-damaged areas affected the respiratory health of the exposed children. Results showed a significant decrease in respiratory symptoms after renovation.[81]

Who Should Perform the Cleanup?

According to current EPA guidelines, an individual can usually clean up areas less than 10 ft.[2] If there has been a lot of water damage and/or mold growth covers more than 10 ft^2; the heating, ventilation, and air conditioning (HVAC) system is involved; or the water and/or mold damage was caused by sewage or flood water, it may be wise to consider hiring a professional and consulting the EPA guide "Mold Remediation in Schools and Commercial Buildings."[82]

Cleanup Guidelines

The CDC[83] and EPA[84] (or call 800-438-4318) offer practical guidelines for cleaning up mold problems. The main way to control mold is to remove the water source and high-humidity conditions that promote spore growth. In the event of flooding, use fans or heaters to dry out the area if it has been less than 48 hours since the flood. After 48 hours, mold may already be forming on surfaces, and the use of fans would only act to disseminate them. Certain moldy materials, such as carpets and ceiling tiles, may be difficult to clean and should be discarded. When cleaning moldy areas, individuals should take precautions to limit exposure to airborne mold. In general, nonporous surfaces with mold growth can be cleaned with soap and water. Biocides are substances that can destroy living organisms, and a biocide, such as chlorine bleach, may also be used. EPA guidelines include avoiding breathing in mold or mold spores (N-95 respirator) and wearing gloves and goggles. If possible, the person with symptoms from mold exposure should not perform the cleanup.

The CDC has published extensive guidelines for mold cleanup.[85] Advice includes removal of mold growth from hard surfaces with commercial products, soap and water, or a bleach solution of 1 cup of bleach in 1 gallon of water. For extensive mold growth after the floods of Hurricane Katrina, the CDC recommendations included use of bleach.[86] Bleach is not recommended for use on porous surfaces, because its ionic structure prevents it from penetrating the materials; it also accelerates the deterioration of materials and wears down the fibers of porous materials. The use of bleach remains controversial. The debate centers, in part, on the belief that dead mold still retains its ability to trigger reactions in susceptible hosts. The first study to test the effect of allergic

individuals of mold spores treated with common household bleach found that the bleach not only kills mold but also neutralizes the mold allergens that cause mold-related health complaints. Specifically, a spray application of sodium hypochlorite–containing disinfectants onto mold-contaminated building materials killed *A fumigatus*, modified the surface characteristics of *A fumigatus conidia*, reduced recognition of *A fumigatus* mold by enzyme-linked immunosorbent assay, and resulted in loss of skin-test reactivity to the treated mold in individuals allergic to *A fumigatus*.[87]

If bleach is used, it should not be combined with ammonia or other household cleaning products, and the area should be well ventilated during use.

ADDITIONAL CONSIDERATIONS IN MEDICAL MANAGEMENT

Patient care for mold- or dampness-related illness often focuses on medical therapy, and remediation and/or environmental control of excessive mold growth is not emphasized. If remediation is not possible, removal of the patient from the environment should be seriously considered when the condition is severe or progressive over time, especially for serious illness such as hypersensitivity pneumonitis or poorly controlled asthma.

For families who rent, many housing conditions may be beyond their immediate control. Tenants have basic housing rights, and health departments and legal aid services may be able to help.[88] Pediatricians can play an important role in advocating for patients and their families by working with the local public health department and housing officials to address these issues.

CONCLUSIONS

Cause-and-effect relationships between fungal exposure and allergic disease, asthma, and hypersensitivity pneumonitis are consistently supported by epidemiologic studies. Evidence of adverse health effects of ingested mycotoxins is also abundant. However, the best evidence of a possible causal relationship between inhaled mycotoxins and respiratory illness is a single case-control study of AIPH in infants from Cleveland. Indoor dampness, by itself, seems to be associated with increased respiratory illness and symptoms, although the exact mechanism and etiologic agents are not known. Because the indoor environment is a source of many different exposures (bacteria, tobacco smoke, dampness, dust and dust mites, pet dander, and mold), it is impossible to unequivocally attribute a cause-and-effect relationship to any one specific agent. There is substantial evidence that damp, moldy environments are unhealthy, and the CDC and the EPA have developed guidelines for cleaning up the mold and fixing the moisture problem.

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RESOURCES FOR PARENTS

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US Environmental Protection Agency. Indoor air: mold. Available at: www.epa.gov/mold

Centers for Disease Control and Prevention, Department of Health and Human Services. Mold. Available at: www.cdc.gov/mold

RESOURCE FOR PEDIATRICIANS

Storey E, Dangman KH, DeBernardo RL, et al. *Guidance for Clinicians on the Recognition and Management of Health Effects Related to Mold Exposure and Moisture Indoors*. Farmington, CT: University of Connecticut, Division of Occupational and Environmental Medicine; 2004. Available at: http://oehc.uchc.edu/clinser/MOLD%20GUIDE.pdf