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Indoor air quality and health
Does fungal contamination play a significant role?

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The quality of indoor air and its potential to adversely impact human health is a significant public health concern. In the 1980s, this concern was focused on the availability of a safe and comfortable environment in which to live and work [1]. After the oil embargo in 1973, homes and commercial buildings were constructed with a view of conserving energy. Homes were insulated tightly, and commercial buildings were constructed as hermetically sealed units that were dependent on the rate of fresh outside air that was drawn into the system. Building managers became aware of the minimal amount of outside fresh air that was required to ventilate the building in an effort to conserve the energy to heat and cool the building. Distinctions between building-related disease (eg, hypersensitivity pneumonitis, humidifier fever, Legionnaire's pneumonitis) and the symptoms of sick building syndrome were discussed frequently in the medical literature [2,3]. In the 1990s, there was a surge of juridic and media attention that sought to link sick building syndrome with a controversial and unscientific symptom complex of multiple chemical sensitivity (idiopathic chemical intolerance) [4].

In 1994, a series of events took place that shifted the paradigm from generic sick building syndrome to a toxic mold threat. In Cleveland, Ohio, 10 infants became seriously ill with pulmonary hemosiderosis and hemorrhage, 2 of whom died. The Centers for Disease Control and Prevention initially concluded that there was a causal link between inhalation of *Stachybotrys atra* mycotoxin and this cluster of cases [5]. Subsequent events have led to assertions related to the adverse health effects of toxic mold or fatal mold in various buildings [6]. New markets have been developed to conduct testing for the presence of indoor molds and to remediate mold damage. There also has been a proliferation of juristic activities in the United States related to mold-induced health effects [7]. In Western Europe,

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however, this issue is a nonentity. Many individuals who claim to be injured by exposure to mold have nonspecific health complaints that are alleged to be related to neurocognitive deficiencies, reminiscent of multiple chemical sensitivity. This article discusses mold-related disease and analyzes the scientific evidence that supports a causal link between indoor mold contamination and human illness.

Ecology of fungi

Fungi were among the first microorganisms to be recognized, because some fruiting structures were large enough to be seen without a microscope (eg, mushrooms, toadstools, yeasts, mildews, smuts, rusts). The word "mycology" is derived from "mykes," the Greek word for mushroom. Fungi are successful organisms, as evidenced by their ubiquity and abundance in nature. They comprise approximately 25% of the Earth's biomass and are essential components in the energy cycle as decomposers of organic material [8]. Of the estimated 250,000 species, less than 100 are known to be primary pathogens of humans or animals; the rest of the species are saprophytic [9].

Fungi are eukaryocytic organisms; their cell walls contain chitin or cellulose, and they are devoid of chlorophyll. They can be unicellular or multicellular, and there is a tendency to be multinucleate. Fungi can exist morphologically as yeasts or molds. A yeast is defined as a cell that reproduces by budding. Yeasts are generally unicellular and produce circular pasty or mucoid colonies. Molds are multicelled, filamentous forms of fungi that consist of thread-like filaments (hyphae) that interweave to form a mycelium. The resulting colonies are generally fuzzy. Most fungi reproduce by spores that are designed for airborne dispersal. The spores differ in number of cells, size, shape, and color [9].

Fungi require a continuous source of water, oxygen, organic material, and a suitable temperature for growth and development. Nutrient substrate is degraded by fungal enzymes and is absorbed. The amount of water that is required is dependent on the type of species, the nature of available nutrient, and the prevailing temperature. Species that require significant amounts of water (eg, *Acremonia*, *Chaetomium*, *Trichoderma*, *Fusarium*, *Rhodotorula*, *Stachybotrys*) produce slimy spores that are dispersed by water, insects, and animals with fur. Other species are xerophilic and prefer dryer conditions (eg, *Eurotium*, *Wallenia*). Many species are xerotolerant (eg, *Aspergillus sydowi*, *A. versicolor*, *Penicillium*). Aside from their essential role in aerobic decomposition, fungi are used in foods such as cheeses, soy sauce, and wine. A number of important pharmaceutical agents have been derived from fungi, including penicillin, cyclosporin, and ergotamine.

Indoor levels of fungi

In a well-constructed home without water contamination, the levels of airborne indoor fungi generally are a reflection of outdoor sources. Indoor levels are

Table 1
Examples of total mold counts in the United Sta

Location	March–June (spor
St. Louis	395–24,500
Las Vegas	8–673
Albany, NY	9–1534
Santa Barbara, CA	544–33,090

Data from the National Allergy Bureau, Americ
Pollen and mold counts. Available at: http://ww

expected to be below outdoor levels with
outdoor levels). Indoor sources such as
and clothing also can contribute to indo
also affects these levels. There is a false
without evidence of water incursion sh
piece of lumber, plywood, pressed bo
construction is contaminated from the o
problem unless a source of moisture f
Outdoor concentrations vary widely by
antly depending on the seasons, tempera
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collected by the National Allergy Bure
Asthma and Immunology (Table 1). Sp
include *Cladosporium*, *Alternaria*, *Pe*
outdoor species is wide and is dependen
most common indoor fungal species are
Alternaria, and *Aureobasidium*.

Assessment of indoor fungi

Because outdoor levels of fungi can
time (ie, minutes or hours), comparison
time periods has inherent pitfalls. Thi
relatively low concentrations of fungi d
many assessments of airborne concentr
outdoor samples are measured. It is rar
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fungi in the outdoor air are found durin

Sampling indoor environments for
variables that are related to the nature
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of outdoor sources. Indoor levels are

Table 1
Examples of total mold counts in the United States during different seasons

Location	March–June (spores/m^3)	September–December (spores/m^3)
St. Louis	395–24,500	5266–68,855
Las Vegas	8–673	15–186
Albany, NY	9–1534	1075–18,005
Santa Barbara, CA	544–33,090	767–555,833

Data from the National Allergy Bureau, American Academy of Allergy, Asthma and Immunology. Pollen and mold counts. Available at: http://www.aaaai.org. Accessed 2002.

expected to be below outdoor levels with similar species rankings (ie, 40%–80% of outdoor levels). Indoor sources such as plants, pets, and molds carried on footwear and clothing also can contribute to indoor levels. Thoroughness of housecleaning also affects these levels. There is a false assumption that a newly constructed home without evidence of water incursion should be devoid of fungi; however, every piece of lumber, plywood, pressed board, and other materials that are used in construction is contaminated from the outset. This contamination does not pose a problem unless a source of moisture facilitates proliferation of dormant spores. Outdoor concentrations vary widely by geographic location and can vary significantly depending on the seasons, temperature changes, humidity, wind, and time of day [10–12]. Examples of seasonal outdoor variability are tabulated from data collected by the National Allergy Bureau of the American Academy of Allergy, Asthma and Immunology (Table 1). Species that commonly are found outdoors include *Cladosporium*, *Alternaria*, *Penicillium*, and *Aspergillus*. The range of outdoor species is wide and is dependent on the effort made to identify them. The most common indoor fungal species are *Cladosporium*, *Penicillium*, *Aspergillus*, *Alternaria*, and *Aureobasidium*.

Assessment of indoor fungi

Because outdoor levels of fungi can vary substantially within a short period of time (ie, minutes or hours), comparison with indoor concentrations over similar time periods has inherent pitfalls. This issue is magnified when dealing with relatively low concentrations of fungi derived by a small number of samples. In many assessments of airborne concentrations of indoor fungi, only one or two outdoor samples are measured. It is rare that one or more noncomplaint control homes are checked simultaneously to provide a normal baseline for the geographic area and season of the year. For most species, the highest numbers of fungi in the outdoor air are found during summer and autumn [13].

Sampling indoor environments for fungi is complicated and is impacted by variables that are related to the nature of sample to collect (eg, airborne versus settled dust), selection of media for viable samples, and quantity and location of sampling [14]. Most indoor environments contain some amount of fungi. When assessing indoor air sampling data, a comparable number of samples should be

taken from proximal outdoor sites to determine whether indoor sampling levels fall within an expected range (ie, 40%–80% with similar rank order species of fungi). The exception to the latter is when snow is on the ground or there is a severe frost. Ideally, concurrent measurements should be taken from one or more control, noncomplaint homes. These expectations apply only to airborne sampling of viable or particulate fungi. Concentrations of fungi that are detected in bulk samples of various building materials and that are not exposed directly to indoor ambient air (eg, the space between siding and sheetrock, insulation material, or wallboard) are not indicative of what is being inhaled. In postulating exposure, a reasonable pathway to the breathing zone of the occupant must be apparent. It has been estimated that 70% of homes have mold growing behind the walls. Some fungal spores require movements of air for dispersal (eg, *Penicillium*, *Aspergillus*). Other species require mechanical disturbance, such as water, animals brushing against the growth, renovation, or building activities.

Although sampling methods are complex, the interpretation of sampling data is problematic. There are no uniform numeric standards for indoor airborne or surface fungi, and there is no uniformity among the more than 20 suggested guidelines [15]. There also is no uniform agreement or scientific support that deems any given level of colony forming units (CFU)/m^3 as acceptable. The guidelines that have been published are based on consensus efforts rather than scientific data. There is no known dose–response relationship between a specific ambient mold concentration and human health effects. The absence of uniform guidelines results from fungi's ubiquity, variable biologic properties, variability in geographic prevalence and seasonality; and from the vagaries of how sampling is carried out and the challenges presented by correct speciation. Because fungi are encountered indoors and outdoors, there is no way to ascribe development of sensitivity or adverse health effects to a specific indoor exposure.

Several reviews have found that average concentrations in indoor ambient air varies seasonally and geographically [16,17]. For 85 homes with airborne concentrations reported as total spore counts, the average levels ranged from 68 to 2307 spores/m^3 for indoor air and from 400 to 80,000 spores/m^3 for outdoor ambient air [16]. In another analysis of the literature Gots and colleagues found that in 820 residences without any health complaints, ambient air had an average of 1252 CFU/m^3; and the associated average outdoor level was 1524 CFU/m^3 [17].

Fungal spores in occupational settings

One of the major reasons that residential indoor standards have not been established is the absence of scientific evidence for adverse health effects in occupational settings with high concentrations of airborne fungi. In sawmills, the airborne concentrations have been reported to be as high as 1.5 million CFU/m^3 [18]. A study of differences in air concentrations on farms with and without adverse health effects revealed an average exposure concentration of 120 million

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Health effects of fungi

The health effects of exposure to ind
categories: irritational effects, nonspec
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reactions (eg, psychogenic agoraphobia

Irritant effects

In the absence of chemical contar
fungal contamination could cause trans
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with the most potent immunobiologic
are connected by 1-3-β-D interchain lir
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along with proteases and volatile orgar
been observed to possess inflammatory
cause mild, transient irritative symp
tissues. Administration of soluble
production of interleukins 1 and 2
compounds by fungi accounts for the
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odors can be intolerable (ie, cacosmia
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spores/m^3 in farms with no complaints [19]. The daily spore levels that were associated with adverse health effects were at least 10 times greater (ie, 1.2 billion spores/m^3). Indoor concentrations in spawning sheds on mushroom farms have been reported to be as high as 100,000 spores/m^3 [20]. Commercial composting activities have yielded airborne concentrations of mold greater than 8 million spores/m^3. As in commercial and residential dwellings, there are no standards for airborne concentrations of fungi in the occupational setting. Although hypersensitivity pneumonitis occasionally is reported in these worksites (ie, commercial composting sites, barns, mushroom farms), there have been no reports of brain damage or any other mold-related disorder, which have been alleged in indoor environments with comparatively modest airborne levels.

Health effects of fungi

The health effects of exposure to indoor fungal molds can be divided into six categories: irritational effects, nonspecific respiratory symptoms, allergic sensitization and hypersensitivity states, infection, mycotoxicosis, and psychogenic reactions (eg, psychogenic agoraphobia) (Table 2).

Irritant effects

In the absence of chemical contamination, there is evidence that indoor fungal contamination could cause transient, irritational symptoms [14]. One of the best-studied potential irritants are the glucans. Glucans are ubiquitous polymers of glucose that are found in the cell wall of plants and fungi. Glucans with the most potent immunobiologic effects consist of glucose subunits that are connected by 1-3-β-D interchain linkage. The major source of the latter are fungi. Although there are limited data about the presence of 1,3-β-D-glucans in organic dusts (quantities of up to 1 μg/m^3 have been measured in the ambient air of a cotton plant cardroom), there are little data about their presence in domestic housing. Most exposure to glucans occurs outdoors. These glucans, along with proteases and volatile organic compounds derived from fungi, have been observed to possess inflammatory and adjuvant properties [21]. They may cause mild, transient irritative symptoms in the ocular and upper airway tissues. Administration of soluble glucans has been shown to stimulate production of interleukins 1 and 2 [21]. The release of volatile organic compounds by fungi accounts for the mildew or musty odor that is attributed to mold. These odors can be a source of annoyance reactions, because such odors can be intolerable (ie, cacosmia). They also may induce anxiety about the indoor environment. Other volatile organic compounds account for the flavor and odor of certain cheeses (eg, brie, roquefort). It is doubtful this mechanism has a substantial role in the induction of respiratory symptoms, except in the most contaminated dwellings (eg, flooded buildings, buildings with long-standing water damage).

Table 2
Health effects from exposure to indoor fungi

Symptom complex/diagnosis	Suspected agent	Mechanism
Transient skin irritation, conjunctivitis, rhinitis	Glucans or volatile organic compounds (eg, ethanol, 8 and 9 carbon aldehydes)	Annoyance or irritational effects
Nonspecific, intermittent cough, wheezing	Relative humidity, dampness	Unknown; no dose–response relationships to airborne or settled mold spores
Allergic rhinitis	Fungal allergens (eg, Asp f 1,2,6,12; Alt a1; Cla h 1,2,3)	IgE sensitization symptoms usually arise in an outdoor setting
Allergic asthma	Fungal allergens	IgE sensitization symptoms usually arise in an outdoor setting
AFS, ABPM, SAM	Fungal antigens, including *Aspergillus*, *Chrysosporium*, *Curvularia*, *Bipolaris*	Robust IgE-mediated inflammation superimposed with mutations in the cystic fibrosis gene
Hypersensitivity pneumonitis	Fungal antigens (eg, *Aspergillus*, *Alternaria Penicillium*)	Antibody and cell-mediated mechanisms; symptoms arise in occupational setting
Infections (eg, histoplasmosis, coccidioidomycosis)	*Coccidiodes immitis*, *Histoplasma capsulatum*, *Cryptococcus neoformens*, dermatophytic infections, disseminated *Aspergillosis*, *Blastomycosis*	Inhalation of soil fungi in endemic areas or by immunocompromised hosts; most infections are acquired in outdoor setting
Organic dust toxic syndrome	Moldy grain or hay during harvesting activities	May be endotoxin mediated; self-limited and usually in an occupational setting
Mycotoxicosis (pharyngitis, chest pain, dermatitis, epistaxis, leukopenia)	Trichothecenes (ie, stachybotryotoxicosis)	Ingestion of contaminated grain; no conclusive evidence of inhalation-induced disease
Psychogenic disease (toxic agoraphobia)	Fear that health is threatened because of environmental danger (eg, chemical, microbial agent, mold toxin)	Nocebo effect and secondary gain related to litigation

Abbreviation: ABPM, allergic bronchopulmonary mycosis.

Nonspecific respiratory symptoms

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relative humidity and visual inspectio
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living in humid houses. Many of these h
included cough, wheezing, headache,
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Douwes et al employed an enzym
charides from *Aspergillus* and *Penicilli*
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respiratory symptoms [28].

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The studies that aim to find a re
dampness in the home and respirator
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Nonspecific respiratory symptoms

Several epidemiologic studies have concluded that humidity and dampness in buildings influence the prevalence of respiratory symptoms, especially in children. A study of 358 homes in Scotland that used a questionnaire and a determination of relative humidity and visual inspection concluded the major health effect of humidity and dampness was emotional distress [22]. Two larger studies from the United Kingdom found the highest prevalence of respiratory symptoms in children living in humid houses. Many of these homes had visible mold growth. Symptoms included cough, wheezing, headache, and episodic fever. There was a dose–response relationship for the severity of humidity, but no specific studies were carried out for mold [23,24]. In Canada, Dales and colleagues studied nearly 15,000 adults in six regions of the country using a questionnaire to explore respiratory health and home conditions. Home dampness and molds were associated with increased number of self-reported respiratory symptoms (odds ratios, between 1.5 and 1.6) [25]. In an extension of the same study, children's symptoms were evaluated, and the results confirmed those of previous studies [26]. In a study of 88 children with respiratory symptoms, Strachan and co-workers measured indoor levels of molds in three rooms on four occasions during the winter months. The investigators were unable to relate respiratory symptoms to the number of airborne viable fungal spores [27].

Douwes et al employed an enzyme immunoassay of extracellular polysaccharides from *Aspergillus* and *Penicillium* species in housedust as a marker for fungal exposure. Assay results correlated significantly with total culturable fungi and housedust allergens. There were mixed findings with self-reported dampness and respiratory symptoms. The authors could not exclude housedust mite allergen as a principal cause of symptoms and admitted that larger, prospective studies should be done to elucidate the relationship between fungal measurements and respiratory symptoms [28].

Taskinen and associates studied 93 children from three schools with moisture problems related to such problems as leaky roofs and burst water pipes, and 34 children from a control school. Levels of viable airborne fungi ranged from 140 to 530 colony-forming units (CFU)/m^3 in the three moisture-problem schools compared with 160 CFU/m^3 in the control school. Levels of IgG antibodies to fungal antigens were not significantly different between the two groups of children. High levels of IgG antibody to *Aspergillus* antigens were associated with allergic rhinoconjunctivitis, but not with asthma or other respiratory symptoms [29].

The studies that aim to find a relationship between fungal growth and dampness in the home and respiratory symptoms (mostly self-reported) have not produced strong associations. Reasons for this outcome include: (1) an inability to segregate other important indoor allergens from fungal allergens; (2) poor reproducibility of traditional counting of culturable propagules in housedust and airborne specimens; (3) inability to separate potential irritative effects of β-1-3 glucans, endotoxin, and volatile organic compounds; and (4)

absence of prospective, controlled studies to address these and other confounding issues [22–29].

Allergic sensitization and hypersensitivity states

Over the past several decades, major advances have been made in defining allergens in domestic dust, which are responsible for IgE-mediated respiratory illness [30]. The most significant indoor allergens in the United States are those from housedust mites, domestic pets (cats, dogs), and cockroaches. Other indoor allergens have been identified, such as rodent, fungal and avian allergens, but their roles are not as well defined. Fungal allergens occur primarily outdoors and are not considered to be a major cause of indoor allergic disease [30,31].

Allergens derived from fungi may represent an inherent part of the organism or may be generated by the organism and released into the environment. Most of the fungal allergens that have been identified are water-soluble glycoproteins [32], and some are enzymes. Although approximately 80 species of fungi are known to be allergenic, only a few specific allergenic moieties have been isolated and well characterized [33]. Historically it has been difficult to work with the fungi because of the presence of multiple strains within a species and because of the presence of significant cross-reactivity among strains within a species and between species.

The well-characterized fungal allergens include those from *Aspergillus*, *Alternaria*, and *Cladosporium* species. *Aspergillus* species can cause several pathogenic states. It is the most commonly encountered genus in the human environment. Its approximate 300 species are common to soil, water, and decaying vegetation throughout the world [34]. Four principal protein and glycoprotein antigens have been identified from *Aspergillus fumigatus* (Asp f 1, Asp f 2, Asp f 6, Asp f 12). To circumvent problems that plague standardization, researchers have attempted to obtain biologically active recombinant allergens (eg, the 18-kDa Asp f 1 has been cloned, expressed, and evaluated for its allergenicity) [35]. Most of the specific purified *Aspergillus* allergens are not commercially available. *Aspergillus* species have a prominent role in inducing allergic bronchopulmonary aspergillosis and in inducing rarer hypersensitivity disorders, including mucoid impaction syndrome, eosinophilic pneumonitis, extrinsic allergic alveolitis, and bronchocentric granulomatosis. Other saprophytic forms of respiratory disease include sinusoidal aspergillosis and aspergilloma [36].

Alternaria species are common atmospheric fungi that are found around the world. *Alternaria* and *Cladosporium* species are referred to as field fungi because of their ability to grow on plants in fields and on decaying plants as they become a part of the soil. Individuals often encounter these species in the outdoors. *Alternaria alternata* is prevalent in the warmer, humid climates of the southern United States [35]. *Alternaria* has been implicated in precipitating acute, at times fatal, bronchospasm in patients with asthma [35]. *Alternaria* antigens also have been involved in the development of hypersensitivity pneumonitis. At least six allergens have been identified from *Alternaria*, and most research has been directed toward allergens that are derived from *A alternata*. Most of these allergens are

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species, *Bipolaris* species, and other de
hawaiiensis, *D spicifer*, and *Alternaria*

Despite the growing interest in indoor
few guidelines and no standards to relial
problem exists with a given indoor level
compelling reason against the establis
residential buildings is the lack of evide
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Fungi can occasionally cause non-
common diagnostic entity is hypersensi
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d are water-soluble glycoproteins [32],
imately 80 species of fungi are known to
nic moieties have been isolated and well
difficult to work with the fungi because
a species and because of the presence of
within a species and between species.
s include those from *Aspergillus*, *Alter-*
gillus species can cause several patho-
ly encountered genus in the human
s are common to soil, water, and decay-
. Four principal protein and glycoprotein
ergillus fumigatus (Asp f 1, Asp f 2,
problems that plague standardization,
ologically active recombinant allergens
ned, expressed, and evaluated for its
purified *Aspergillus* allergens are not
cies have a prominent role in inducing
and in inducing rarer hypersensitivity
yndrome, eosinophilic pneumonitis, ex-
ntric granulomatosis. Other saprophytic
idal aspergillosis and aspergilloma [36].
spheric fungi that are found around the
ies are referred to as field fungi because
and on decaying plants as they become a
ounter these species in the outdoors.
warmer, humid climates of the southern
nplicated in precipitating acute, at times
ma [35]. *Alternaria* antigens also have
persensitivity pneumonitis. At least six
aria, and most research has been directed
alternata. Most of these allergens are

glycoproteins and have molecular weights between 25 and 50 kDa. Several groups have isolated the major allergenic component (ie, Alt a 1). Licorish et al provoked immediate and delayed asthmatic responses using *Alternaria* whole-spore challenges, but provoked only an immediate response with spore extracts [37].

Cladosporium herbarum is the most abundant fungus in the ecosphere and is a major source of fungal allergen. It is the dominant fungus in the cooler climates of northern United States, in Canada, and in Scandinavian countries. Three major *Cladosporium* allergens have been described (Cla h 1, Cla h 2, Cla h 3). *C herbarum* has been found to cross-react with *A alternata*.

A number of other fungal species have been investigated extensively. *Penicillium notatum* is present outdoors but is more important as an indoor allergen. The allergens that have been isolated are moieties that are larger than 64 to 68 kDa, and they account for only a portion of allergic reactivity in serum tested. *Penicillium* species shares a significant number of antigens with *A fumigatus*. *Basidiomycetes* species occur in high concentrations in the ambient air around the world. IgE-specific antibodies have been detected in patientss with allergic respiratory disease.

Fungi have been implicated as causes of allergic fungal sinusitis (AFS), which is a noninvasive form of fungal sinusitis that is seen in highly atopic individuals with fungal-specific IgE, intractable sinusitis, and nasal polyposis. AFS has been described as the upper airway equivalent of allergic bronchopulmonary mycosis. Venarske and deShazo reported five patients with simultaneous expression of both diseases. They termed the process sinobronchial allergic mycosis (SAM) [38]. Patients with SAM have chronic sinusitis, asthma, immediate cutaneous reactivity to fungal allergens, peripheral eosinophilia, and radiographic evidence of bronchiectasis. *A fumigatus* is believed to be the most common cause of fungal sinusitis in immunocompetent individuals. Other species also have been incriminated, including *Aspergillus flavus*, *Aspergillus niger*, *Sprothrix schenckii*, *Curvularia lunata*, *Candida* species, *Mucor* species, *Chrysosporium* species, *Bipolaris* species, and other dematiaceous fungi, including *Dreschslera hawaiiensis*, *D spicifer*, and *Alternaria* species [39].

Despite the growing interest in indoor air quality with respect to fungi, there are few guidelines and no standards to reliably determine whether a potential allergic problem exists with a given indoor level of fungal contamination. Perhaps the most compelling reason against the establishment of standards for commercial and residential buildings is the lack of evidence for a dose–response relationship between a given airborne level of fungal allergen and an adverse health effect (Box 1).

Fungi can occasionally cause non–IgE-mediated lung disease. The most common diagnostic entity is hypersensitivity pneumonitis (allergic alveolitis), a condition that is associated with cough, dyspnea, fever, and pulmonary infiltrates. Pathogenesis involves humoral and cellular immune responses to fungal and other organic antigens. Bronchial lavages in patients with acute hypersensitivity pneumonitis reveal a neutrophil alveolitis within the first 2 days of disease, followed by a lymphocytic alveolitis. The predominant lymphocyte is a CD8+ suppressor–cytotoxic cell. Elevated levels of IgG, IgM, and IgA have been found

Box 1. Impediments against establishment of indoor fungal levels

- Substantial variability of outdoor fungal levels over short periods of time
- Seasonal variation in ambient outdoor levels of fungi related to climate
- Limited data on the level of indoor fungal levels around the world
- The complexity of sampling indoor environments for fungi related to number of samples and the technology used
- Lack of standardized sampling equipment and culture media
- The diversity of biophysical properties of fungal species
- Presence of high airborne fungal levels in certain occupational settings without apparent adverse health effects
- Lack of evidence for a dose–response relationship between a given airborne level of fungal allergen and an adverse health effect

in lavage fluids, although their role in producing lung injury is unclear. The most common etiologic agents are *Thermophilic actinomycetes* and *Micropolyspora faeni* bacteria, which are the principle causes of classic farmer's lung disease [40,41]. Fungal antigens are causative agents in a variety of rarer forms of hypersensitivity pneumonitis (eg, malt worker's lung [*A clavatus*], humidifier lung [*Aureobasidium pullulans*], Woodman's disease [*Penicillium notatum*], maple bark disease [*Cryptostroma corticale*], cheese washer's lung [*Penicillium casei*]). Diagnosis depends on linkage to an appropriate offending antigen, the presence of antigen-specific IgG antibodies in the serum, a compatible symptom complex with pulmonary infiltrates, basilar crepitant rales, hypoxemia, and a reduction of diffusion capacity. Bronchial hyperreactivity may be present [42].

Fungal infection

Most fungal infections stem from the outdoor environment. Only a few fungal species are capable of causing infections in otherwise healthy individuals [42]. *Coccidioides immitis* is a soil saprophytic fungus that is found in arid climates of southwestern United States and Mexico. Outbreaks of human infection have occurred after dust storms and at construction sites. Theoretically, it can be disseminated any time the soil is disrupted, which often occurs in large farming districts. Clusters of disease arise approximately 2 weeks after exposure and range from a flu-like illness to frank pneumonitis. In about two thirds of cases, the illness is asymptomatic. Healthy individuals who manifest symptoms undergo a self-limited course that does not require treatment. Disseminated disease is seen in immunocompromised individuals, pregnant women, and Native Americans; in these cases, treatment with newer antifungal agents may be required [42].

Histoplasmosis is caused by *Histo* found in avian droppings. The major e the Mississippi River and its tributarie areas where soil is disrupted, after cle have shown that most individuals in er an immune response. Most healthy indi pneumonitic syndromes [42].

Cryptococcus neoformens is a so inhalation. Large numbers of this fun pigeon or bat droppings, and cluste exposures. Infections are more comr can occur in healthy subjects. In imr as meningoencephalitis, which presun lung [42].

Dermatophytic fungi cause common except in farmers and veterinarians wh capitis that is caused by *Microsporum a* most important of these infections. *Tru* in the general population and is respor feet and groin. It also causes a persister that can be intractable. *Candida albica*

Several authors have proposed that secondary to an overgrowth of yeast colleagues conducted a double-blind, in 1990 [43]. Other fungal infections defects in cell-mediated immunity an faulty heating, ventilation and air cond gillosis, blastomycosis).

Mycotoxicosis

Mycotoxins are low-molecular-we that have no physiologic function in vehicle for their inhalation. There are fungi are probably capable of producir strain, and environmental conditions, light, and nutrient substrate. Most my disrupting cellular structures or inter known to induce animal and human nated feed (ie, mycotoxicosis or alime be measured in environmental samples animal tissues.

A clinical misnomer may mislead u nitic syndromes that have been descr seems to represent a mild form of hype

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Histoplasmosis is caused by *Histoplasma capsulatum*, a soil fungus that is found in avian droppings. The major endemic area in the United States is along the Mississippi River and its tributaries. Clusters of cases have occurred around areas where soil is disrupted, after cleaning aviaries, or in spelunking. Studies have shown that most individuals in endemic areas have been exposed, illiciting an immune response. Most healthy individuals have subclinical infections or mild pneumonitic syndromes [42].

Cryptococcus neoformens is a soil fungus that may cause infection by inhalation. Large numbers of this fungus are found in soil contaminated with pigeon or bat droppings, and clusters of cases have been related to such exposures. Infections are more common in immunocompromised hosts, but can occur in healthy subjects. In immunocompetent hosts, infections manifest as meningoencephalitis, which presumably is spread hematologically from the lung [42].

Dermatophytic fungi cause common fungal infections that are not work related, except in farmers and veterinarians who are exposed to infected animals. Tinea capitis that is caused by *Microsporum audouini* and *Trichophyton tonsurans* is the most important of these infections. *T rubrum* causes most of the fungal infections in the general population and is responsible for an erythematous eruption of the feet and groin. It also causes a persistent onychomycosis, usually of the toenails, that can be intractable. *Candida albicans* can infect moist, damaged skin.

Several authors have proposed that a variety of physical ailments can arise secondary to an overgrowth of yeast (ie, the yeast connection). Dismukes and colleagues conducted a double-blind, controlled study that dispelled this theory in 1990 [43]. Other fungal infections usually occur in patients with significant defects in cell-mediated immunity and have been reported in association with faulty heating, ventilation and air conditioning systems (eg, disseminated aspergillosis, blastomycosis).

Mycotoxicosis

Mycotoxins are low-molecular-weight, nonvolatile secondary metabolites that have no physiologic function in the fungus. Spores (particulates) are the vehicle for their inhalation. There are more than 300 known mycotoxins. All fungi are probably capable of producing mycotoxins, depending on the species, strain, and environmental conditions, such as temperature, water availability, light, and nutrient substrate. Most mycotoxins are cytotoxic and are capable of disrupting cellular structures or interrupting cell processes. They have been known to induce animal and human disease by way of ingestion of contaminated feed (ie, mycotoxicosis or alimentary toxic aleukia) [44]. Mycotoxins can be measured in environmental samples with some difficulty, but not in human or animal tissues.

A clinical misnomer may mislead uninformed individuals about the pneumonitic syndromes that have been described in farmers. This symptom complex seems to represent a mild form of hypersensitivity pneumonitis. In the past, it has

been referred to as pulmonary mycotoxicosis or atypical farmer's lung [40,41]. It never has been proved that mycotoxins cause this hypersensitivity, and the condition more properly is referred to as organic dust toxic syndrome (ODTS). The syndrome usually is seen in late summer or early fall during the harvesting of moldy grain or hay. Its clinical presentation involves an influenza-like syndrome, with or without respiratory symptoms associated with leukocytosis and fever. A subclinical alveolitis may be present, and causative agents have not been defined precisely, although endotoxin is suspected to be the most likely offender [41]. ODTS has been called "silo unloaders disease" or "precipitin-negative farmer's lung" by Edwards et al [45]. The same symptom complex has been referred to as "grain fever syndrome." doPico and co-workers performed an inhalation challenge study to grain dust in 12 subjects [46]. The typical response was characterized by facial warmth, headache, malaise, myalgias, fever, chills, tracheal burning, chest tightness, dyspnea and cough. Bronchial lavage revealed a neutrophilic alveolitis, and pulmonary infiltrates generally are not seen. The mechanism of ODTS is unclear, but most patients have a self-limited course without any residual lung impairment [41,47].

Much of what is known about mycotoxin-induced disease in humans is derived from animal ingestion data and laboratory animal exposures [48]. There is limited information related to data of human ingestion. The tricothecenes are a commonly occurring category of mycotoxins that primarily inhibit protein synthesis. More than 150 tricothecenes are produced by various genera of fungi, including *Fusarium*, *Trichoderma*, *Cephalosporium*, *Tricothecium*, and *Stachybotrys* [49–51]. Diseases caused by tricothecene toxins initially were reported in eastern Europe and Russia, where clusters of stachybotryotoxicosis occurred in individuals who had contact with grain or hay and who lived in areas where stachybotryotoxicosis was enzootic in horses [52]. The condition was characterized by pharyngitis, chest pain, dermatitis, epistaxis and leukopenia [52,53]. *Fusarium* produces fumonisins that are capable of causing a similar illness. The condition occurred in individuals who were malnourished and who had consumed at least 2 kg of contaminated grain. High levels of fumonisins have been implicated in the development of equine leukoencephalomalacia and porcine pulmonary edema in the United States [54–56].

In 1987, a cluster of gastroenteritis secondary to ingestion of bread contaminated with *Aspergillus* and *Fusarium* occurred in India [57]. Several tricothecenes were isolated from samples of wheat. A similar outbreak occurred after ingestion of contaminated rice in China [58]. A tricothecene also was implicated in this cluster of disease. These outbreaks were related to ingestion of heavily contaminated grain, which resulted in exposure that is many orders above any inhalation exposure that might occur.

Psychogenic effects

In a society that is aware of the potential chemical or microbial threats from a variety of sources, the report of symptoms by one or more individuals within a

commercial building or family membe
sensitivity, objectivity, and scientific c
even with strong beliefs of temporality
a noxious agent in the building has
especially true when environmental th
ensued [59,60]. People often convert t
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Stachybotrys

Stachybotrys is a genus of fungi that
media. It has been the focus of many bu
The genus was described by Corda in
black saprophytic mold that grows w
humidity and low nitrogen content [5
within this genus, but the most comm
chartarum, *S atra*, and *S alternans*, w
species. *Stachybotrys* species produce
are unlikely to become airborne wit
movement. They are associated with *A.*
species and compete poorly with faste

Stachybotrys spores infrequently are
find indoors, even in spaces with exte
easily around compost or as a contamin
grains, mammalian fur) [64]. The spor
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trations of fungi were measured proxin
The samples were collected in response
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the outside air of 3.95% of the reside
Houston indicated a mean ambient a
57.7 spores/m^3 (with a standard deviat

A large number of *Stachybotrys* m
The genus is known to produce some 4
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al chemical or microbial threats from a
is by one or more individuals within a

commercial building or family members within a home has to be interpreted with sensitivity, objectivity, and scientific caution. Reports of nonspecific symptoms, even with strong beliefs of temporality to a place or building, do not establish that a noxious agent in the building has caused the symptoms [3,4]. This fact is especially true when environmental threats are perceived or when litigation has ensued [59,60]. People often convert their fears into somatic symptoms [61], as seen in pharmaceutical research in which patients who are given inactive placebo report significant side effects (known as the Nocebo effect) [62].

Stachybotrys

Stachybotrys is a genus of fungi that attracted a great deal of attention from the media. It has been the focus of many building investigations and forensic disputes. The genus was described by Corda in 1837 and is characterized as a greenish-black saprophytic mold that grows well on cellulose under conditions of high humidity and low nitrogen content [56,63]. There are approximately 50 species within this genus, but the most commonly encountered species are *Stachybotrys chartarum*, *S atra*, and *S alternans*, which are used as designates for the same species. *Stachybotrys* species produce spores in a slimy, mucilaginous mass that are unlikely to become airborne without dry conditions and significant air movement. They are associated with *Aspergillus*, *Penicillium*, and *Cladosporium* species and compete poorly with faster-growing fungal species.

Stachybotrys spores infrequently are isolated in outdoor air and are difficult to find indoors, even in spaces with extensive active growth. They can be isolated easily around compost or as a contaminant of agricultural produce (eg, hay, straw, grains, mammalian fur) [64]. The spores also have been detected in outdoor and indoor air of noncomplaint structures. This fungus has been reported in 2.9% of noncomplaint homes in southern California [65,66]. Ambient, airborne concentrations of fungi were measured proximal to 633 residences in the Houston area. The samples were collected in response to occupant reports of moderate-to-severe internal water damage within the structure. *Stachybotrys* species were detected in the outside air of 3.95% of the residences. Analysis of outdoor air samples in Houston indicated a mean ambient airborne concentration of *Stachybotrys* of 57.7 spores/m^3 (with a standard deviation of 49.8) [67].

A large number of *Stachybotrys* mycotoxins have been isolated and studied. The genus is known to produce some 40 tricothecenes, which have been found in the aerosolized spores of this fungus, indicating the potential for inhalation. Their potential biologic effects have been studied and fall into various categories of toxicity (eg, cytotoxicity, metabolic reactions, hemolysis, immunologic effects, coagulopathy); these effects have been reviewed by Terr [63].

There is an extensive amount of literature on disease caused by *Stachybotrys* in animals. Using intranasal instillation of tricothecenes in a murine model, significant alveolar, bronchiolar, and interstitial inflammation was noted [68]. In another study of the same murine model, however, the effects of inhalation under

simulated conditions of extensive surface growth and high air flow did not produce pulmonary disease [69].

Horses that were fed contaminated fodder in Siberia in the 1930s developed a hemorrhagic gastroenteritis with ulceration, pancytopenia, stomatitis, alveolitis, and a coagulopathy that usually was fatal after days or weeks [70]. The condition was reproduced by feeding horses *Stachybotrys* spores that were added to uncontaminated hay or by feeding them a pure culture of the fungus. After periods of heavy rainfall, other large animals similarly have been affected with stachybotryotoxicosis.

In a review of the *Stachybotrys* genus by Terr, human disease was discussed under the heading of three major pathogenetic pathways: infection, allergic disease, and toxicity [63]. Toxicity was discussed under the mechanisms of ingestion, skin contact, and inhalation. Inhalation-induced diseases included pulmonary hemorrhage and hemosiderosis in infants and claims of nonspecific, subjective complaints, including respiratory symptoms and toxic encephalopathy.

Infection

In the medical literature, there are no reliable reports of infection in humans (including immunocompromised individuals) caused by any species of *Stachybotrys*.

Allergic disease

Barnes and co-workers conducted a study to determine the frequency of antibodies directed against *S chartarum* in random samples taken from normal blood donors. Enzyme immunoassay indicated 65 of 192 sera samples (49%) contained IgG-specific antibodies and 13 of 139 sera samples (9%) contained IgE against *S chartarum*. This study suggests that there is immunologic reactivity to this species in asymptomatic individuals [71]. This finding is consistent with the observations of other species of fungi [72]. The investigators pointed out that it was not possible to determine whether the observed antibody responses were caused by exposure to *S chartarum* or by exposure to shared antigens from other fungal genera [71]. Kozak et al reported a young child whose asthma improved when he was removed from his home [65,66]. *Stachybotrys* spores were isolated in samples taken from water-damaged carpet but not in air samples. Allergy testing was not conducted, and any cause-and-effect claim to the child's worsening asthma was not proved. There are no case reports of allergic alveolitis or allergic sinusitis caused by *Stachybotrys* species in the medical literature.

Stachybotryotoxicosis

The data related to mycotoxicosis in animals has prompted investigation of farmers who may have consumed or been exposed to contaminated grain. Reports of a self-limited febrile illness with respiratory symptoms, dermatitis, and leukopenia have been attributed to stachybotryotoxicosis [56]. In these cases,

the workers were employed in grain ele
grain. After review of the limited cli
individuals' symptoms more likely wer
related to endotoxin and other mold-de

Skin contact

There is a single report of dermatit
who handled mold-contaminated, recyc
nated with *Stachybotrys*, *Chaetomium* ;
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up to 7500 *Stachybotrys conidia*/m^3 [7

Inhalation

The possible induction of human dis
toxin garnered much attention after a r
hemosiderosis and hemorrhage in infa
Cleveland between January 1993 and No
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Fung and Hughson addressed the h
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studies, 16 cross-sectional surveys, and
Evidence suggested that excessive m
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Page and Trout conducted a similar
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ybotryotoxicosis [56]. In these cases,

the workers were employed in grain elevators and facilities for processing moldy grain. After review of the limited clinical and laboratory information, these individuals' symptoms more likely were caused by organic dust toxic syndrome related to endotoxin and other mold-derived constituents [40,46].

Skin contact

There is a single report of dermatitis of the distal fingers in three workers who handled mold-contaminated, recycled paper pots. The pots were contaminated with *Stachybotrys*, *Chaetomium perithecia*, and other fungal species. This scaling dermatitis was attributed to the mycotoxin of *Stachybotrys*. No attempt was made to determine the pathogenesis (ie, immune versus irritant-induced versus toxic effect). There were no respiratory symptoms, despite the presence of up to 7500 *Stachybotrys conidia*/m^3 [73].

Inhalation

The possible induction of human disease by exposure to *Stachybotrys* mycotoxin garnered much attention after a report of a cluster of cases of pulmonary hemosiderosis and hemorrhage in infants living in water-damaged buildings in Cleveland between January 1993 and November 1994 [5]. Based on epidemiologic evidence in a case-control study, the illness was attributed to mycotoxicosis from inhaled *Stachybotrys*. Over the past 5 years, more than 100 cases of idiopathic pulmonary hemorrhage with or without hemosiderosis have been reported in infants throughout the United States. In some instances, the organism was recovered in the lung. The Centers for Disease Control and Prevention released the findings of an internal and external review of all data in the Cleveland cases, concluding that an association between pulmonary hemorrhage and hemosiderosis in infants and exposure to molds, *Stachybotrys* in particular, was not proved [74].

Fung and Hughson addressed the health effects of indoor fungal bioaerosol exposure in all English-language reports on indoor mold exposure and human health effects published from 1966 to January 2002 [75]. Five case-control studies, 16 cross-sectional surveys, and 7 case reports met the selection criteria. Evidence suggested that excessive moisture promotes mold growth and is associated with an increased prevalence of symptoms caused by irritation, allergy, and infection. The investigators concluded that specific toxicity caused by inhaled fungal toxins had not been established [75].

Page and Trout conducted a similar review of the literature and focused on the potential role of *Stachybotrys* mycotoxins in building-related illness. Thirteen articles were analyzed, and the investigators concluded that there was inadequate evidence to support a causal relationship between symptoms or illness among building occupants and exposure to *Stachybotrys* mycotoxins [76]. A number of investigators have associated subjective complaints of headache, memory loss, lack of concentration, and other nonspecific symptoms as evidence of brain damage caused by mycotoxins or other fungal products [77,78]. There is no

scientific evidence that *Stachybotrys* or other fungal species detected in indoor air or present on building materials cause brain damage [63,74–76].

Summary

Fungal contamination in buildings can vary greatly, and their presence in a dwelling does not necessarily constitute exposure. Measurement of mold spores and fragments varies depending on the methodology and instruments used. Meaningful comparison of data is rarely possible. The presence of a specific immune response to a fungal antigen only connotes that exposure to one or more related species has occurred, but not that there is a symptomatic clinical state. The response of individuals to indoor bioaerosols is complex and depends on age, gender, state of health, genetic makeup, and degree and time of bioaerosol exposure. In general, mold contamination in buildings is associated with incursion of water or moisture, which should be remedied as efficiently as possible. When disease occurs, it more likely is related to transient annoyance or irritational reactions. Allergic symptoms may be related to mold proliferation in the home environment. Because molds are encountered both indoors and outdoors, it is difficult to determine where the sensitivity initially arose and if the response is solely provoked by either an indoor or outdoor source. As an indoor allergen, mold is considered to be an infrequent participant in the induction of allergic disease when compared with housedust mites, animal dander, and cockroach allergens. Infection in healthy individuals is rare and usually is caused by an outdoor source. Building-related disease caused by mycotoxicosis has not been proved in the medical literature.

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