EXHIBIT E

ACOEM EVIDENCE-BASED STATEMENT

Adverse Human Health Effects Associated with Molds in the Indoor Environment

In recent years, the growth of molds in home, school, and office environments has been cited as the cause of a wide variety of human ailments and disabilities. So-called "toxic mold" has become a prominent topic in the lay press and is increasingly the basis for litigation when individuals, families, or building occupants believe they have been harmed by exposure to indoor molds. This evidence-based statement from the American College of Occupational and Environmental Medicine (ACOEM) discusses the state of scientific knowledge as to the nature of fungal-related illnesses while emphasizing the possible relationships to indoor environments. Particular attention is given to the possible health effects of mycotoxins, which give rise to much of the concern and controversy surrounding indoor molds. Food-borne exposures, methods of exposure assessment, and mold remediation procedures are beyond the scope of this statement.

Fungi are eukaryotic unicellular or multicellular organisms that, because they lack chlorophyll, are dependent upon external food sources. Fungi are ubiquitous in all environments and play a vital role in the Earth's ecology by decomposing organic matter. Familiar fungi include yeasts, rusts, smuts, mushrooms, puffballs, and bracket fungi. Many species of fungi live as commensal organisms in or on the surface of the human body. "Mold" is the common term for multicellular fungi that grow as a mat of intertwined microscopic filaments (hyphae). Exposure to molds and other fungi and their spores is unavoidable except when the most stringent of air filtration, isolation, and environmental sanitation measures are observed, for example, in organ transplant isolation units.

Molds and other fungi may adversely affect human health through three processes: 1) allergy; 2) infection; and 3) toxicity. One can estimate that about 10% of the population has allergic antibodies to fungal antigens. Only half of these, or 5%, would be expected to show clinical illness. Furthermore, outdoor molds are generally more abundant and important in airway allergic disease than indoor molds, leaving the latter with an important but minor overall role in allergic airway disease. Allergic responses are most commonly experienced as allergic asthma or allergic rhinitis ("hay fever"). A rare, but much more serious immune-related condition, hypersensitivity pneumonitis (HP), may follow exposure (usually occupational) to very high concentrations of fungal (and other microbial) proteins.

Most fungi generally are not pathogenic to healthy humans. A number of fungi commonly cause superficial infections involving the feet (*tinea pedis*), groin (*tinea cruris*), dry body skin (*tinea corporus*), or nails (*tinea onchomycosis*). A very limited number of pathogenic fungi, such as *Blastomyces*, *Coccidioides*, *Cryptococcus*, and *Histoplasma*, infect nonimmunocompromised individuals. In contrast, persons with severely impaired immune function, for example, cancer patients receiving chemotherapy, organ transplant patients receiving immunosuppressive drugs, AIDS patients, and patients with uncontrolled diabetes, are at significant risk for more severe opportunistic fungal infection.

Some species of fungi, including some molds, are known to be capable of producing secondary metabolites, or mycotoxins, some of which find a valuable clinical use, for example, penicillin and cyclosporine. Serious veterinary and human mycotoxicoses have been documented after ingestion of foods heavily overgrown with molds. In agricultural settings, inhalation exposure to high concentrations of mixed organic dusts, which include bacteria, fungi, endotoxins, glucans, and mycotoxins, is associated with organic dust toxic syndrome, an acute febrile illness. The present alarm over human exposure to molds in the indoor environment derives from a belief that inhalation exposures to mycotoxins cause numerous and varied, but generally nonspecific, symptoms. 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.

Allergy and Other Hypersensitivity Reactions

Allergic responses to indoor molds may be immunoglobulin E (IgE) or immunoglobulin G (IgG) mediated, and both types of response are associated with exposure to indoor molds. Uncommon allergic syndromes, allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal sinusitis (AFS), are briefly discussed for completeness, although indoor mold has not been suggested as a particular risk factor in the etiology of either.

Immediate Hypersensitivity

The most common form of hypersensitivity to molds is immediate type hypersensitivity or IgE-mediated "allergy" to fungal proteins. This reactivity can lead to allergic asthma or allergic rhinitis that is triggered by breathing in mold spores or hyphal fragments. Residential or office fungal exposures may be a substantial factor in an individual's allergic airway disease depending on the subject's profile of allergic sensitivity and the levels of indoor exposures. Individuals with this type of mold allergy are "atopic" individuals, that is, have allergic asthma, allergic rhinitis, or atopic dermatitis and manifest allergic (IgE) antibodies to a wide range of environmental proteins among which molds are only one participant. These individuals generally will have allergic reactivity against other important indoor and outdoor allergens such as animal dander, dust mites, and weed, tree, and grass pollens. Among the fungi, the most important indoor allergenic molds are *Penicillium* and *Aspergillus* species.[1] Outdoor molds, for example, *Cladosporium* and *Alternaria*, as well as pollens, can often be found at high levels indoors if there is access for outdoor air (eg, open windows).

About 40% of the population are atopic and express high levels of allergic antibodies to inhalant allergens. Of these 25%, or 10% of the population, have allergic antibodies to common inhalant molds.[2] Because about half of persons with allergic antibodies will express clinical disease from those antibodies, about 5% of the population is predicted to have, at some time, allergic symptoms from molds. Although indoor molds are well-recognized allergens, outdoor molds are more generally important.

A growing body of literature associates a variety of diagnosable respiratory illnesses (asthma, wheezing, cough, phlegm), particularly in children, with residence in damp or water-damaged homes (see reviews[3–5]). Recent studies have documented increased inflammatory mediators in the nasal fluids of persons in damp buildings, but found that mold spores themselves were not responsible for these changes.[6,7] Although dampness may indicate potential mold growth, it is also a likely indicator of dust mite infestation and bacterial growth. The relative contribution of each is unknown, but mold, bacteria, bacterial endotoxins, and dust mites can all play a role in the reported spectrum of illnesses, and can all be minimized by control of relative humidity and water intrusion.

Hypersensitivity Pneunomitis

HP results from exaggeration of the normal IgG immune response against inhaled foreign (fungal or other) proteins and is characterized by: 1) very high serum levels of specific IgG proteins (classically detected in precipitin tests performed as double diffusion tests) and 2) inhalation exposure to very large quantities of fungal (or other) proteins.[8] The resulting interaction between the inhaled fungal proteins and fungal-directed cell-mediated and humoral (antibody) immune reactivity leads to an intense local immune reaction recognized as HP. As opposed to immediate hypersensitivity (IgE-mediated) reactions to mold proteins, HP is not induced by normal or even modestly elevated levels of mold spores. Most cases of HP result from occupational exposures, although cases have also been attributed to pet birds, humidifiers, and heating, ventilating, and air conditioning (HVAC) systems. The predominant organisms in the latter two exposures are thermophilic Actinomyces, which are not molds but rather are filamentous bacteria that grow at high temperatures (116°F).

The presence of high levels of a specific antibody, generally demonstrated as the presence of precipitating antibodies, is required to initiate HP but is not diagnostic of HP.[9] More than half of the people who have occupational exposure to high levels of a specific protein have such precipitin antibodies but do not have clinical disease.[8] Many laboratories now measure IgG to selected antigens by using solid phase immunoassays, which are easier to perform and more quantitative than precipitin (gel diffusion) assays. However, solid phase IgG levels that are above the reference range do not carry the same discriminatory power as do results of a precipitin test, which requires much greater levels of antibody to be positive. Five percent of the normal population has levels above the reference value for any one tested material. Consequently, a panel of tests (eg, 10) has a high probability of producing a false-positive result. Screening IgG antibody titers to a host of mold and other antigens is not justified unless there is a reasonable clinical suspicion for HP and should not be used to screen for mold exposure.[10]

Uncommon Allergic Syndromes: ABPA and AFS

These conditions[11] are unusual variants of allergic (IgE-mediated) reactions in which fungi actually grow within the patient's airway. ABPA is the classic form of this syndrome, which occurs in allergic individuals who generally have airway damage from previous illnesses leading to bronchial irregularities that impair normal drainage, eg, bronchiectasis.[12,13] Bronchial disease and old cavitary lung disease are predisposing factors contributing to fungal colonization and the formation of mycetomas. *Aspergillus* may colonize these areas without invading adjacent tissues. Such fungal colonization is without adverse health consequence unless the subject is allergic to the specific fungus that has taken up residence, in which case there may be ongoing allergic reactivity to fungal proteins released directly into the body. Specific criteria have been recognized for some time for the diagnosis of ABPA.[14,15] As

fungi other than *Aspergillus* may cause this condition, the term "allergic bronchopulmonary mycosis" has been suggested.

It has more recently become appreciated that a similar process may affect the sinuses—AFS.[16] This condition also presents in subjects who have underlying allergic disease and in whom, because of poor drainage, a fungus colonizes the sinus cavity. *Aspergillus* and *Curvularia* are the most common forms although the number of fungal organisms involved continues to increase. As with ABPA, the diagnosis of AFS has specific criteria that should be used to make this diagnosis.[17–19]

Recommendations

- Individuals with allergic airway disease should take steps to minimize their exposure to molds and other airborne allergens, for example, animal dander, dust mites, pollens. For these individuals, it is prudent to take feasible steps that reduce exposure to aeroallergens and to remediate sources of indoor mold amplification. Sensitized individuals may need to keep windows closed, remove pets, use dust mite covers, use high-quality vacuum cleaners, or filter outdoor air intakes to minimize exposures to inhalant allergens. Humidification over 40% encourages fungal and dust mite growth, so should be avoided. Where there is indoor amplification of fungi, removal of the fungal source is a key measure to be undertaken so as to decrease potential for indoor mold allergen exposure.
- ABPA and AFS are uncommon disorders whereas exposure is ubiquitous to the fungal organisms involved. There is no evidence to link specific exposures to fungi in home, school, or office settings to the establishment of fungal colonization that leads to APBA or AFS.
- Once a diagnosis of HP is entertained in an appropriate clinical setting and with appropriate laboratory support, it is important to consider potential sources of inhaled antigen. If evaluation of the occupational environment fails to disclose the source of antigens, exposures in the home, school, or office should be investigated. Once identified, the source of the mold or other inhaled foreign antigens should be remediated.
- Appropriate measures should be taken in industrial workplaces to prevent mold growth, for example, in machining fluids and where stored organic materials are handled such as in agricultural and grain processing facilities. Engineering controls and personal protective equipment should be used to reduce aerosol generation and minimize worker exposures to aerosols.

Although it is not relevant to indoor mold exposure, it should be mentioned that there is a belief among some health practitioners and members of the public regarding a vague relationship between mold colonization, molds in foods, and a "generalized mold hypersensitivity state." The condition was originally proposed as the chronic Candida syndrome or Candida hypersensitivity syndrome but now has been generalized to other fungi. Adherents may claim that individuals are colonized with the mold(s) to which they are sensitized and that they react to these endogenous molds as well as to exposures in foods and other materials that contain mold products. The proposed hypersensitivity is determined by the presence of any of a host of non-specific symptoms plus an elevated (or even normal) level of IgG to any of a host of molds. The claim of mold colonization is generally not supported with any evidence, eg, cultures or biopsies, to demonstrate the actual presence of fungi in or on the subject. Instead, proponents often claim colonization or infection based on the presence of a wide variety of nonspecific symptoms and antibodies detected in serologic tests that represent no more than past exposure to normal environmental fungi. The existence of this disorder is not supported by reliable scientific data.[20,21]

Infection

An overview of fungi as human pathogens follows. Exposure to molds indoors is generally not a specific risk factor in the etiology of mycoses except under specific circumstances as discussed below for individual types of infection.

Serious Fungal Infections

A very limited number of pathogenic fungi, such as *Blastomyces*, *Coccidioides*, *Cryptococcus*, and *Histoplasma* infect normal subjects and may cause a fatal illness. However, fungal infections in which there is deep tissue invasion are primarily restricted to severely immunocompromised subjects, for example, patients with lymphoproliferative disorders, including acute leukemia, cancer patients who are receiving intense chemotherapy, or persons undergoing bone marrow or solid transplantation who get potent immunosuppressive drugs.[22] Uncontrolled diabetics and persons with advanced AIDS are also at increased risk. Concern is greatest when patients are necessarily in the hospital during their most severe immunocompromise, at which time intense measures are taken to avoid fungal, bacterial, and viral infection.[23] Outside the hospital, fungi, including *Aspergillus*, are so ubiquitous that few recommendations can be made beyond avoidance of known sources of indoor and outdoor amplification, including indoor plants and flowers because vegetation is a natural fungal growth medium.[24,25] *Candida albicans* is a ubiquitous commensal organism on humans that becomes an important pathogen for immunocompromised subjects. However, it and other environmental fungi discussed above that are pathogens in normals as well (eg, *Cryptococcus* associated with bird droppings, *Histoplasma* associated with bat droppings, *Coccidioides* endemic in the

soil in the southwestern United States) are not normally found growing in the office or residential environment, although they can gain entry from outdoors. Extensive guidelines for specific immunocompromised states can be found at the Centers for Disease Control and Prevention (CDC) web site at www.cdc.gov.

Superficial Fungal Infections

In contrast with serious internal infections with fungi, superficial fungal infections on the skin or mucosal surfaces are extremely common in normal subjects. These superficial infections include infection of the feet (*tinea pedis*), nails (*tinea onychomycosis*), groin (*tinea cruris*), dry body skin (*tinea corporis*) and infection of the oral or vaginal mucosa. Some of the common organisms involved, for example, *Trychophyton rubrum*, can be found growing as an indoor mold. Others, such as *Microsprum canis* and *T. mentagrophytes* can be found on indoor pets (eg, dogs, cats, rabbits, and guinea pigs). As a common commensal on human mucosal surfaces, *C. albicans* can be cultured from more than half of the population that has no evidence of active infection. *C. albicans* infections are particularly common when the normally resident microbial flora at a mucosal site are removed by antibiotic use. Local factors such as moisture in shoes or boots and in body creases and loss of epithelial integrity are important in development of superficial fungal infections.

Pityriasis (*Tinea*) *versicolor* is a chronic asymptomatic infection of the most superficial layers of the skin due to *Pityriasis ovale* (also known as *P. orbiculare* and *Masassezia furfur*) manifest by patches of skin with variable pigmentation. This is not a contagious condition and thus is unrelated to exposures but represents the overgrowth of normal cutaneous fungal flora under favorable conditions.

Recommendations

- Only individuals with the most severe forms of immunocompromise need be concerned about the potential for opportunistic fungal infections. These individuals should be advised to avoid recognizable fungal reservoirs, including but not limited to indoor environments where there is uncontrolled mold growth. Outdoor areas contaminated by specific materials, such as pigeon droppings, should be avoided as well as nearby indoor locations where those sources may contaminate the intake air. Individuals with *M. canis* and *T. mentagrophytes* infections should have their pets checked by a veterinarian. No other recommendations are warranted relative to home, school, or office exposures in patients with superficial fungal infections.

Toxicity

Mycotoxins are "secondary metabolites" of fungi, which is to say mycotoxins are not required for the growth and survival of the fungal species ("toxigenic species") that are capable of producing them. The amount (if any) and type of mycotoxin produced is dependent on a complex and poorly understood interaction of factors that probably include nutrition, growth substrate, moisture, temperature, maturity of the fungal colony, and competition from other microorganisms.[26–30] Additionally, even under the same conditions of growth, the profile and quantity of mycotoxins produced by toxigenic species can vary widely from one isolate to another.[31–34] Thus, it does not necessarily follow from the mere presence of a toxigenic species that mycotoxins are also present.[35–38]

When produced, mycotoxins are found in all parts of the fungal colony, including the hyphae, mycelia, spores, and the substrate on which the colony grows. Mycotoxins are relatively large molecules that are not significantly volatile;[39,40] they do not evaporate or "off-gas" into the environment, nor do they migrate through walls or floors independent of a particle. Thus, an inhalation exposure to mycotoxins requires generation of an aerosol of substrate, fungal fragments, or spores. Spores and fungal fragments do not pass through the skin, but may cause irritation if there is contact with large amounts of fungi or contaminated substrate material.[41] In contrast, microbial volatile organic compounds are low molecular weight alcohols, aldehydes, and ketones.[42] Having very low odor thresholds, microbial volatile organic compounds are responsible for the musty, disagreeable odor associated with mold and mildew and they may be responsible for the objectionable taste of spoiled foods.[42,43]

Most descriptions of human and veterinary poisonings from molds involve eating moldy foods.[41,43–46] Acute human intoxications have also been attributed to inhalation exposures of agricultural workers to silage or spoiled grain products that contained high concentrations of fungi, bacteria, and organic debris with associated endotoxins, glucans, and mycotoxins.[47,48] Related conditions, including pulmonary mycotoxicosis, grain fever, and others, are referred to more broadly as organic dust toxic syndrome.[49] Exposures associated with organic dust toxic syndrome have been described as a "fog" of particulates[50] or an initial "thick airborne dust" that "worsened until it was no longer possible to see across the room."[51] Total microorganism counts have ranged from 10^5 to 10^9 per cubic meter of air[52] or even 10^9 to 10^{10} spores per cubic meter,[53,54] extreme conditions not ordinarily encountered in the indoor home, school, or office environment.

Sick building syndrome, or nonspecific building-related illness, represents a poorly defined set of symptoms (often sensory) that are attributed to occupancy in a building. Investigation generally finds no spe-

cific cause for the complaints, but they may be attributed to fungal growth if it is found. The potential role of building-associated exposure to molds and associated mycotoxins has been investigated, particularly in instances when *Stachybotrys chartarum* (aka *Stachybotrys atra*) was identified.[55–58] Often referred to in the lay press by the evocative, but meaningless terms, "toxic mold" or "fatal fungus," *S. chartarum* elicits great concern when found in homes, schools, or offices, although it is by no means the only mold found indoors that is capable of producing mycotoxins.[35,36,59,60] Recent critical reviews of the literature[35,61–67] concluded that indoor airborne levels of microorganisms are only weakly correlated with human disease or building-related symptoms and that a causal relationship has not been established between these complaints and indoor exposures to *S. chartarum*.

A 1993 to 1994 series of cases of pulmonary hemorrhage among infants in Cleveland, Ohio, led to an investigation by the CDC and others. No causal factors were suggested initially,[68] but eventually these same investigators proposed that the cause had been exposures in the home to *S. chartarum* and suggested that very young infants might be unusually vulnerable.[69–71] However, subsequent detailed re-evaluations of the original data by CDC and a panel of experts led to the conclusion that these cases, now called 'acute idiopathic pulmonary hemorrhage in infants,"[72] had not been causally linked to *S. chartarum* exposure.[73]

If mycotoxins are to have human health effects, there must be an actual presence of mycotoxins, a pathway of exposure from source to susceptible person, and absorption of a toxic dose over a sufficiently short period of time. As previously noted, the presence of mycotoxins cannot be presumed from the mere presence of a toxigenic species. The pathway of exposure in home, school, and office settings may be either dermal (eg, direct contact with colonized building materials) or inhalation of aerosolized spores, mycelial fragments, or contaminated substrates. Because mycotoxins are not volatile, the airborne pathway requires active generation of that aerosol. For toxicity to result, the concentration and duration of exposure must be sufficient to deliver a toxic dose. What constitutes a toxic dose for humans is not known at the present time, but some estimates can be made that suggest under what circumstances an intoxication by the airborne route might be feasible.

Experimental data on the in vivo toxicity of mycotoxins are scant. Frequently cited are the inhalation LC_{50} values determined for mice, rats, and guinea pigs exposed for 10 minutes to T-2 toxin, a trichothecene mycotoxin produced by *Fusarium* spp.[74,75] Rats were most sensitive in these studies, but there was no mortality in rats exposed to 1.0 mg T-2 toxin/m^3. No data were found on T-2 concentrations in *Fusarium* spores, but another trichothecene, satratoxin H, has been reported at a concentration of 1.0×10^{-4} ng/spore in a "highly toxic" *S. chartarum* strain *s.* 72.[31] To provide perspective relative to T-2 toxin, 1.0 mg satratoxin H/m^3 air would require 10^{10} (ten billion) of these s. 72 *S. chartarum* spores/m^3.

In single-dose in vivo studies, *S. chartarum* spores have been administered intranasally to mice[31] or intratracheally to rats.[76,77] High doses (30×10^6 spores/kg and higher) produced pulmonary inflammation and hemorrhage in both species. A range of doses were administered in the rat studies and multiple, sensitive indices of effect were monitored, demonstrating a graded dose response with 3×10^6 spores/kg being a clear no-effect dose. Airborne *S. chartarum* spore concentrations that would deliver a comparable dose of spores can be estimated by assuming that all inhaled spores are retained and using standard default values for human subpopulations of particular interest—very small infants (5th percentile body weight for 1-month-old male infants, 3.16 kg; respiratory rate for infants under 1 year of age, 4.5 m^3/day[78]), school-age children (50th percentile body weight for 6-year-old boys, 22 kg; respiratory rate for children ages 6 to 9, 10.0 m^3/day[78]), and adults (50th percentile body weight for men aged 25 to 34 years, 77.5 kg; respiratory rate for men age 19–65, 15.2 m^3/day[78]). The no-effect dose in rats (3×10^6 spores/kg) corresponds to continuous 24-hour exposure to 2.1×10^6 spores/m^3 for infants, 6.6×10^6 spores/m^3 for a school-age child, or 15.3×10^6 spores/m^3 for an adult.

That calculation clearly overestimates risk because it ignores the impact of dose rate by implicitly assuming that the acute toxic effects are the same whether a dose is delivered as a bolus intratracheal instillation or gradually over 24 hours of inhalation exposure. In fact, a cumulative dose delivered over a period of hours, days, or weeks is expected to be less acutely toxic than a bolus dose, which would overwhelm detoxification systems and lung clearance mechanisms. If the no-effect 3×10^6 spores/kg intratracheal bolus dose in rats is regarded as a 1-minute administration (3×10^6 spores/kg/minute), achieving the same dose rate in humans (using the same default assumptions as previously) would require airborne concentrations of 3.0×10^9 spores/m^3 for an infant, 9.5×10^9 spores/m^3 for a child, or 22.0×10^9 spores/m^3 for an adult.

In a repeat-dose study, mice were given intranasal treatments twice weekly for three weeks with "highly toxic" *s.* 72 *S. chartarum* spores at doses of 4.6×10^6 or 4.6×10^4 spores/kg (cumulative doses over three weeks of 2.8×10^7 or 2.8×10^5 spores/kg).[79] The higher dose caused severe inflammation with hemorrhage, while less severe inflammation but no hemorrhage was seen at the lower dose of *s.* 72 spores. Using the same assumptions as previously (and again ignoring

dose-rate implications), airborne *S. chartarum* spore concentrations that would deliver the non-hemorrhagic cumulative three-week dose of 2.8×10^5 spores/kg can be estimated as 9.4×10^3 spores/m^3 for infants, 29.3×10^3 spores/m^3 for a school-age child, and 68.0×10^3 spores/m^3 for adults (assuming exposure for 24 hours per day, 7 days per week, and 100% retention of spores).

The preceding calculations suggest lower bound estimates of airborne *S. chartarum* spore concentrations corresponding to essentially no-effect acute and subchronic exposures. Those concentrations are not unfeasible but they are improbable and inconsistent with reported spore concentrations. For example, in data from 9619 indoor air samples from 1717 buildings, when *S. chartarum* was detected in indoor air (6% of the buildings surveyed) the median airborne concentration was 12 CFU/m^3 (95% CI 12 to 118 CFU/m^3).[80]

Recommendations

- The presence of toxigenic molds within a home, school, or office environment should not by itself be regarded as demonstrating that mycotoxins were present or that occupants of that environment absorbed a toxic dose of mycotoxins.
- Indoor air samples with contemporaneous outdoor air samples can assist in evaluating whether or not there is mold growth indoors; air samples may also assist in evaluating the extent of potential indoor exposure. Bulk, wipe, and wall cavity samples may indicate the presence of mold, but do not contribute to characterization of exposures for building occupants.
- After the source of moisture that supports mold growth has been eliminated, active mold growth can be eliminated. Colonized porous materials, for example, clothing or upholstery, can be cleaned using appropriate routine methods, eg, washing or dry cleaning clothing, and need not be discarded unless cleaning fails to restore an acceptable appearance.
- When patients associate health complaints with mold exposure, treating physicians should evaluate all possible diagnoses, including those unrelated to mold exposure, that is, consider a complete appropriate differential diagnosis for the patient's complaints. To the extent that signs and symptoms are consistent with immune-mediated disease, immune mechanisms should be investigated.
- The possibility of a mycotoxicosis as an explanation for specific signs and symptoms in a residential or general office setting should be entertained only after accepted processes that are recognized to occur have been appropriately excluded and when mold exposure is known to be uncommonly high. If a diagnosis of mycotoxicosis is entertained, specific signs and symptoms ascribed to mycotoxins should be consistent with the potential mycotoxins present and their known biological effects at the potential exposure levels involved.

Summary

Molds are common and important allergens. About 5% of individuals are predicted to have some allergic airway symptoms from molds over their lifetime. However, it should be remembered that molds are not dominant allergens and that the outdoor molds, rather than indoor ones, are the most important. For almost all allergic individuals, the reactions will be limited to rhinitis or asthma; sinusitis may occur secondarily due to obstruction. Rarely do sensitized individuals develop uncommon conditions such as ABPA or AFS. To reduce the risk of developing or exacerbating allergies, mold should not be allowed to grow unchecked indoors. When mold colonization is discovered in the home, school, or office, it should be remediated after the source of the moisture that supports its growth is identified and eliminated. Authoritative guidelines for mold remediation are available.[81–83]

Fungi are rarely significant pathogens for humans. Superficial fungal infections of the skin and nails are relatively common in normal individuals, but those infections are readily treated and generally resolve without complication. Fungal infections of deeper tissues are rare and in general are limited to persons with severely impaired immune systems. The leading pathogenic fungi for persons with nonimpaired immune function, *Blastomyces*, *Coccidioides*, *Cryptococcus*, and *Histoplasma*, may find their way indoors with outdoor air but normally do not grow or propagate indoors. Due to the ubiquity of fungi in the environment, it is not possible to prevent immune-compromised individuals from being exposed to molds and fungi outside the confines of hospital isolation units.

Some molds that propagate indoors may under some conditions produce mycotoxins that can adversely affect living cells and organisms by a variety of mechanisms. Adverse effects of molds and mycotoxins have been recognized for centuries following ingestion of contaminated foods. Occupational diseases are also recognized in association with inhalation exposure to fungi, bacteria, and other organic matter, usually in industrial or agricultural settings. Molds growing indoors are believed by some to cause building-related symptoms. Despite a voluminous literature on the subject, the causal association remains weak and unproven, particularly with respect to causation by mycotoxins. One mold in particular, *Stachybotrys chartarum*, is blamed for a diverse array of maladies when it is found indoors. Despite its well-known ability to produce mycotoxins under appropriate growth conditions, years of intensive study have failed to establish exposure to *S. chartarum* in home, school, or office environments as a cause of adverse human health effects. Levels of exposure in the indoor environment, dose-response data in animals, and dose-rate con-

siderations suggest that delivery by the inhalation route of a toxic dose of mycotoxins in the indoor environment is highly unlikely at best, even for the hypothetically most vulnerable subpopulations.

Mold spores are present in all indoor environments and cannot be eliminated from them. Normal building materials and furnishings provide ample nutrition for many species of molds, but they can grow and amplify indoors only when there is an adequate supply of moisture. Where mold grows indoors there is an inappropriate source of water that must be corrected before remediation of the mold colonization can succeed. Mold growth in the home, school, or office environment should not be tolerated because mold physically destroys the building materials on which it grows, mold growth is unsightly and may produce offensive odors, and mold is likely to sensitize and produce allergic responses in allergic individuals. Except for persons with severely impaired immune systems, indoor mold is not a source of fungal infections. Current scientific evidence does not support the proposition that human health has been adversely affected by inhaled mycotoxins in home, school, or office environments.

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Position paper

The medical effects of mold exposure

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Exposure to molds can cause human disease through several well-defined mechanisms. In addition, many new mold-related illnesses have been hypothesized in recent years that remain largely or completely unproved. Concerns about mold exposure and its effects are so common that all health care providers, particularly allergists and immunologists, are frequently faced with issues regarding these real and asserted mold-related illnesses. The purpose of this position paper is to provide a state-of-the-art review of the role that molds are known to play in human disease, including asthma, allergic rhinitis, allergic bronchopulmonary aspergillosis, sinusitis, and hypersensitivity pneumonitis. In addition, other purported mold-related illnesses and the data that currently exist to support them are carefully reviewed, as are the currently available approaches for the evaluation of both patients and the environment.
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Key words: *Mold, fungi, hypersensitivity, allergy, asthma*

Exposure to certain fungi (molds) can cause human illness. Molds cause adverse human health effects through 3 specific mechanisms: generation of a harmful immune response (eg, allergy or hypersensitivity pneumonitis [HP]), direct infection by the organism, and toxic-irritant effects from mold byproducts. For each of these defined pathophysiologic mechanisms, there are scientifically documented mold-related human diseases that present with objective clinical evidence of disease. Recently, in contrast to these well-accepted mold-related diseases, a number of new mold-related illnesses have been hypothesized. This has become a particular issue in litigation that has arisen out of unproved assertions that exposure to indoor molds causes a variety of ill-defined illnesses. Many of these illnesses are characterized by the absence of objective evidence of disease and the lack of a defined pathology and are typically without specificity for the involved fungus–fungal product purported to cause the illness.

Abbreviations used
ABPA: Allergic bronchopulmonary aspergillosis
CRS: Chronic rhinosinusitis
HP: Hypersensitivity pneumonitis
MVOC: Volatile organic compound made by mold
VOC: Volatile organic compound

In this position paper we will review the state of the science of mold-related diseases and provide interpretation as to what is and what is not supported by scientific evidence. This is important for members of the allergy–clinical immunology community, who are frequently asked by patients, parents, and other interested parties to render opinions about the relationship of mold exposure to a variety of patient complaints. Given the nature of this document, key rather than exhaustive citations are provided. The latter can be found in documents such as the Institute of Medicine reports ''Damp indoor spaces and health''[1] and ''Clearing the air: asthma and indoor air exposure.''[2]

THE RELATIONSHIP OF MOLDS TO ALLERGY AND ASTHMA

It is estimated that approximately 10% of the population have IgE antibodies to common inhalant molds.[3] About half of these individuals (5% of the population) are predicted to have, at some time, allergic symptoms as a consequence of exposure to fungal allergens.[4] Although indoor fungal allergen exposure occurs, outdoor exposure is generally more relevant in terms of sensitization and disease expression. The role of indoor fungi in the pathogenesis of allergic disease has been extensively reviewed in recent reports from the Institute of Medicine of the National Academy of Science.[1]

Sensitization to fungi, particularly *Alternaria alternata*, has been linked to the presence, persistence, and severity of asthma.[5] Exposure to atmospheric fungal spores

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(principally in the outdoor environment) has been related to asthma symptoms and medication use in children with asthma.[6]

The association of asthma symptoms and exposure to indoor fungi is less clearly established. Literature reviews suggest that children living in damp houses, homes with visible mold growth, or both were more likely to experience lower respiratory tract symptoms of cough and wheeze than children who do not.[7,8] Recent prospective epidemiologic studies have shown that infants at risk for asthma, defined by a maternal history of asthma, who are exposed to high concentrations of indoor fungi (in addition to cockroach allergen and nitrogen dioxide sources) in the first year of life are at risk for persistent wheezing and cough.[9,10] These and similar epidemiologic reports fall short of prospective studies that control for confounding factors, such as humidity and other airborne allergens and irritants.

Molds are often presumed to be an important cause of the other atopic manifestations, including allergic rhinitis and, to a far lesser degree, atopic dermatitis. Abundant published data have established that sensitization (by skin testing, circulating IgE antibodies, or both) to one or more airborne molds occurs in these diseases, although sensitization is less frequent to molds than to pollens, animal danders, and house dust mite.

Current studies do not conclusively demonstrate a causal relationship of airborne mold exposure and clinical manifestations of allergic rhinitis. The data on outdoor molds (eg, *Alternaria* species and basidiomycetes) purportedly causing allergic rhinitis are indirect and conflicting.[11-13] Studies attempting to correlate indoor molds with symptomatic allergic rhinitis are even more problematic because of such methodological uncertainties as lack of quantitative mold sampling[14-16] and inclusion of upper respiratory tract infections.[17]

Published reports document mold sensitivity in some children and adults with atopic dermatitis.[18-20] However, there are no publications that establish a causal role for airborne molds in this disease rather than the IgE antibodies simply reflecting an expected concomitant of their atopic state. There are no credible reports in the medical literature documenting indoor exposure to molds as a cause of the nonatopic IgE-mediated diseases (eg, urticaria-angioedema and anaphylaxis).

Conclusions:

- Atopic patients (those with allergic asthma, allergic rhinitis, and atopic dermatitis) commonly have IgE antibodies to molds as part of polysensitization.
- Allergic responses to inhaled mold antigens are a recognized factor in lower airway disease (ie, asthma).
- Currently available studies do not conclusively prove that exposure to outdoor airborne molds plays a role in allergic rhinitis, and studies on the contribution of indoor molds to upper airway allergy are even less compelling.
- Exposure to airborne molds is not recognized as a contributing factor in atopic dermatitis.
- Exposure to airborne molds is not recognized as a cause of urticaria, angioedema, or anaphylaxis.
- Patients with suspected mold allergy should be evaluated by means of an accepted method of skin or blood testing for IgE antibodies to appropriate mold antigens as part of the clinical evaluation of potential allergies.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS AND SINUSITIS

Allergic bronchopulmonary aspergillosis (ABPA) is a well-recognized clinical entity affecting individuals with asthma or cystic fibrosis.[21] A variety of fungi in addition to *Aspergillus fumigatus* can produce a similar clinical picture. The critical element in ABPA is an underlying anatomic change in the lung and not a specific mold exposure because at-risk individuals will have ongoing exposures caused by the ubiquitous nature of the fungi involved. Exposure to *A fumigatus* can occur both from indoor and outdoor sources.

Allergic fungal sinusitis is similar to ABPA in that it is a localized hypersensitivity condition resulting from fungal growth in an area of abnormal tissue drainage.[22] Although originally attributed primarily to *A fumigatus*, other fungi, particularly mitosporic (formerly known as Deuteromycetes or imperfect fungi) fungi are more commonly implicated (eg, *Curvularia* and *Bipolaris* species). Almost uniformly there is allergic sensitization to multiple allergens, including the fungus implicated in the affected sinus. Criteria for this condition have been well delineated, and it is generally readily distinguishable from typical chronic sinusitis. Specific criteria for diagnosis include eosinophilic mucus demonstrating noninvasive fungi, type 1 hypersensitivity (history, positive skin test result, or positive *in vitro* test result to allergens), nasal polyposis, and characteristic radiographic findings.

It has recently been proposed that most cases of chronic rhinosinusitis (CRS) are attributable to sensitivity to fungi. In particular, *Alternaria* species were suspected because most patients had these organisms recovered by means of culture from sinus surgery specimens. However, these organisms are frequently recovered from the nasal cavities of healthy individuals. Although some evidence for an immune response to these fungi in patients with CRS has been presented, clear-cut evidence for this as the cause of CRS is still lacking, and treatment with intranasal antifungal agents (eg, amphotericin) has not been conclusively demonstrated to be an effective treatment.[23]

Conclusions:

- ABPA and allergic fungal sinusitis are manifestations of significant hypersensitivity to fungi, particularly A*spergillus* species.
- Data supporting the role of fungi in CRS are lacking at this time.

HYPERSENSITIVITY PNEUMONITIS

HP, also referred to as extrinsic allergic alveolitis, is a disease that exists in acute, subacute, and chronic forms but with considerable overlap. It is an allergic disease in which the allergen is inhaled in the form of an organic dust of bacterial, fungal, vegetable, or avian origin. Both sensitization and the elicitation of the disease state generally require high-dose exposure, prolonged exposure, or both to the causative allergen. Many cases are, in fact, occupational because of this. There are reports of a similar, if not identical, disease from workers exposed to inhaled chemicals, especially isocyanates. A few instances of the disease have been attributed to systemically administered drugs.

HP is rare, and most cases have been reported in certain occupations, such as farming, and in hobbyists, such as persons who raise pigeons. It is not a reportable disease, and therefore prevalence and incidence are difficult to estimate. The immunopathogenesis of the disease is believed to be cell-mediated (delayed) hypersensitivity. Allergen-specific precipitins are often present in serum and are important is establishing exposure. Precipitins might also play a role in the mechanism of the acute phase of the disease. HP results in acute episodes of noninfectious, immunologically mediated interstitial pneumonitis (ie, alveolitis), which might eventually produce restrictive irreversible lung disease.

The diagnosis requires a clinical and environmental history, relevant physical examination findings, chest radiography or computed tomographic scanning, high-resolution computed tomographic scanning, pulmonary function testing, bronchoalveolar lavage, and transbronchial or open lung biopsy. Specific diagnosis of the responsible allergen is performed by testing for IgG antibody to the allergen extract, typically by testing for the presence of precipitins in the Ouchterlony double-diffusion assay. In some instances provocation inhalation challenge to the suspected allergen extract might be necessary to replicate pertinent clinical and laboratory responses. Finally, a favorable response to the elimination of the inhaled antigen, administration of prednisone, or both is confirmatory. Because a differential diagnosis covers a number of respiratory diseases, an accurate diagnosis of HP demands that the clinical diagnosis be ensured.

Exposure to domestic specific indoor fungal spores is an extremely unlikely cause of HP, except in highly unusual circumstances, such as workplace exposure.

Conclusions:

- HP is an uncommon but important disease that can occur as a result of mold exposure, particularly in occupational settings with high levels of exposure.

INFECTION

Superficial mold infections (eg, tinea cruris, onychomycosis, and thrush) are common in healthy individuals and result primarily from local changes in the cutaneous or mucosal barrier, resident microflora, or both.[24,25] These infections are not the result of environmental exposure, except occasionally as related to certain animal vectors. Indeed, molds of the *Malassezia* genus are resident on the vast majority of human subjects and only become evident as ''tinea versicolor'' during periods of more exuberant growth. A limited number of molds (eg, coccidiomycosis, histoplasmosis, and blastomycosis) are aggressive pathogens in otherwise healthy persons. Acquisition of these infections is generally related to specific outdoor activities-exposures. Individuals with recognized primary and secondary immunodeficiency disorders are at increased risk for infection with a wide range of opportunistic fungi, with the risk varying with the degree and nature of the specific immunodeficiency. Opportunistic fungal infections are typically associated with cellular rather than (isolated) humoral immunodeficiencies. Generally, host factors, rather than environmental exposure, are the critical factor in the development of opportunistic mold infection in immunocompromised individuals because exposure to potential fungal opportunistic pathogens (eg, *Aspergillus* species) is ubiquitous in normal outdoor and indoor environments. Accepted histologic and microbiologic methods should be used to make the diagnosis of fungal infection.

Conclusions:

- Common superficial fungal infections are determined by local changes in the skin barrier, resident microflora, or both.
- A very limited number of aggressive fungal pathogens can be acquired through specific outdoor exposures.
- Host factors, rather then environmental exposure, are the main determinant of opportunistic fungal infection.

TOXIC EFFECTS OF MOLD EXPOSURE

Ingestion

Ingestion of mycotoxins in large doses (generally on the order of a milligram or more per kilogram of body weight) from spoiled or contaminated foods can cause severe human illness.[26] Toxicity from ingested mycotoxins is primarily a concern in animal husbandry, although human outbreaks do occur occasionally when starvation forces subjects to eat severely contaminated food. Specific adverse effects from a given toxin generally occur in a narrower and better-defined dose range than for immunologic or allergic effects that might vary across much broader dose ranges. Some mycotoxins, such as ocratoxins and aflatoxins, are commonly found in food stuffs, including grain products and wines, and peanut products, respectively, such that there are governmental regulations as to the amounts of allowable aflatoxin in foods.[27,28] Acute high-intensity occupational exposures to mixed bioaerosols have given rise to a clinical picture called ''toxic dust syndrome.'' The nature of the responsible agent or

agents in that condition remains undefined, and the observed adverse effects reported have been transient. Such exposures are highly unlikely in nonoccupational settings.

Toxicity caused by inhalation

The term *mold toxicity* as used here refers to the direct injurious effects of mold-produced molecules, so-called mycotoxins, on cellular function. Toxicity should not be used to refer to changes related to innate immune responses (eg, nonspecific inflammation caused by mold particulates) or to adaptive immune responses (eg, induction of IgE or IgG antibodies). Mycotoxins are low-molecular-weight chemicals produced by molds that are secondary metabolites unnecessary for the primary growth and reproduction of the organisms. In-depth review of the toxicology of mycotoxins and their potential for adverse health effects can be found elsewhere.[1,2] It is important to emphasize key principles of toxicology relevant to patient concerns about possible toxic effects from mold exposure.

Only certain mold species produce specific mycotoxins under specific circumstances. Importantly, the mere presence of such a mold should not be taken as evidence that the mold was producing any mycotoxin. For a toxic effect to occur in a subject, (1) the toxin must be present, (2) there must be a route of exposure, and (3) the subject must receive a sufficient dose to have a toxic effect. In the nonoccupational setting the potential route of exposure is through inhalation. Mycotoxins are not volatile and, if found in the respirable air, are associated with mold spores or particulates. They are not cumulative toxins, having half-lives ranging from hours to days depending on the specific mycotoxin. Calculations for both acute and subacute exposures on the basis of the maximum amount of mycotoxins found per mold spore for various mycotoxins and the levels at which adverse health effects are observed make it highly improbable that home or office mycotoxin exposures would lead to a toxic adverse health effects.[1,29]

Thus we agree with the American College of Occupational and Environmental Medicine evidence-based statement and the Institute of Medicine draft, which conclude that the evidence does not support the contention that mycotoxin-mediated disease (mycotoxicosis) occurs through inhalation in nonoccupational settings. Furthermore, the contention that the presence of mycotoxins would give rise to a whole panoply of nonspecific complaints is not consistent with what is known to occur; when a toxic dose is achieved (eg, through ingestion of spoiled foods), there is a specific pattern of illness seen for specific mycotoxins.

Conclusions:

- The occurrence of mold-related toxicity (mycotoxicosis) from exposure to inhaled mycotoxins in nonoccupational settings is not supported by the current data, and its occurrence is improbable.

IRRITANT EFFECTS OF MOLD EXPOSURE

The Occupational Health and Safety Administration defines an irritant as a material causing ''a reversible inflammatory effect on living tissue by chemical action at the site of contact.'' Irritant effects are dose related, and the effects are transient, disappearing when the exposure has decreased or ceased.

Molds produce a number of potentially irritating substances that can be divided into volatile organic compounds (VOCs) and particulates (eg, spores, hyphae fragments, and their components). The threshold level of irritant response depends on the intrinsic properties of the specific material involved, the level plus length of exposure, and the innate sensitivity of the exposed tissues (eg, the skin versus nasal mucosa).

VOCs made by molds (MVOCs) are responsible for their musty odor. MVOCs include a wide range of alcohols, ketones, aldehydes, esters, carboxylic acids, lactones, terpenes, sulfur and nitrogen compounds, and aliphatic and aromatic hydrocarbons.[30] Although levels causing irritant effects have been established for many VOCs, MVOC levels measured in damp buildings are usually at a level so low (on the order of nanograms to micrograms per cubic meter) that exposure would not be expected to cause complaints of irritation in human subjects.[31] Because there are other sources of VOCs indoors, measurement of indoor airborne concentrations of MVOCs is rarely done.

Mold particles (spores, hyphal fragments, and their structural components) are not volatile. These structural mold compounds (particulates) have been suggested to cause inflammation through deposition on mucus membranes of their attached glucans and mannans. However, whether such effects occur clinically remains unproved. In fact, subjects exposed to airborne concentrations of between 215,000 and 1,460,000 mold spores/m^3 at work showed no differences in respiratory symptoms at work versus while on vacation nor was there evidence of increased inflammatory markers in their nasal lavage fluids related to their mold exposure at work.[32] Thus mold particulates generally found indoors, even in damp buildings, are not likely to be irritating.

It should be emphasized that irritant effects involve the mucus membranes of the eyes and upper and lower respiratory tracts and are transient, so that symptoms or signs persisting weeks after exposure and those accompanied by neurologic, cognitive, or systemic complaints (eg, chronic fatigue) should not be ascribed to irritant exposure.

Conclusions:

- The occurrence of mold-related irritant reactions from exposure to fungal irritants in nonoccupational settings are theoretically possible, although unlikely to occur in the general population given exposure and dose considerations.
- Such irritant effects would produce transient symptoms-signs related to the mucus membranes of the eyes and upper and lower respiratory tracts but would

not be expected to manifest in other organs or in a systemic fashion.
- Further information about thresholds for irritant reactions in at-risk populations is needed to better define the role of molds, mold products, and other potential irritants in such individuals.

IMMUNE DYSFUNCTION

The question has been raised as to whether mold or mycotoxin exposure can induce disorders of immune regulation. At this time, there is no credible evidence to suggest that environmental exposure to molds or their products leads to a state of clinically significant altered immunity expressed as either immunodeficiency or autoimmunity. The published literature in this regard is of particularly poor quality and should not be relied on as scientifically valid.[33,34] Individuals who have had intense occupational mold exposures do not manifest opportunistic infections or other findings of immunodeficiency, and thus even the most intense form of airborne mold exposure is not a recognized cause of secondary immunodeficiency in human subjects. Some mycotoxins are immunosuppressive and used for this purpose clinically (eg, cyclosporine). However, the doses involved are not relevant to what might have been found in the environment. Doses that might be seen in environmental exposures are discussed in other sections of this article (toxicity and environmental sections). Testing of a wide range of nonspecific immunologic parameters, such as immunophenotyping of lymphocytes beyond those parameters having known clinical utility (eg, total B and CD3, CD4, and CD8 cells) or measurement of serum cytokines is not appropriate for assessing subjects for immunodeficiency in general and for mold-induced immune dysregulation specifically.[35]

There is also no reliable evidence for mold exposure in any setting being a linked to the induction of autoimmune diseases in human subjects. Although certain viral and bacterial infections appear to have a relationship to the induction-precipitation of autoimmune diseases, such an association has not been established for any known mold exposure. The measurement of clinically useful tests of autoimmunity (eg, antinuclear antibody), much less testing of a broad array of nonvalidated autoantibodies (eg, putative antibodies to central or peripheral myelin), is not indicated, and such testing should not be used to indicate mold exposure or mold-related disease.

This practice of testing many nonvalidated immune-based tests, as has been done previously to suggest an immunologic basis for idiopathic environmental intolerance (multiple chemical sensitivity), is expensive and does not provide useful information that will be of benefit in diagnosis, management, or both of disease and is to be discouraged.

Conclusions:

- Exposure to molds and their products does not induce a state of immune dysregulation (eg, immunodeficiency or autoimmunity).
- The practice of performing large numbers of nonspecific immune-based tests as an indication of mold exposure or mold-related illness is not evidence based and is to be discouraged.

LABORATORY ASSESSMENT

Patient assessment

Measurement of IgE antibodies to mold proteins. Assessment for IgE antibodies to mold antigens has clearly been validated as a measure of potential allergic reactivity to mold. This assessment can be done through either *in vivo* or *in vitro* testing. The relative strengths of these different forms of testing have been reviewed recently.[36,37] In general, there is a weaker correlation between *in vivo* and *in vitro* testing for IgE antibodies to mold antigens than for other antigens, partly as a result of the heterogeneity of extractable mold proteins. A positive IgE antibody level to mold proteins without appropriate clinical evaluation should not necessarily be taken as an indicator of clinical disease. In addition, the presence of IgE antibodies to a mold cannot be used to determine the dose or timing of prior exposures. Although IgE antibodies to *Stachybotrys* species can be detected through *in vitro* or *in vivo* testing, such testing should be discouraged. *Stachybotrys* species is unlikely to be a relevant clinical allergen in human subjects because it is poorly aerosolized and far less common than other well-established mold allergens.

Measurement of IgG antibodies to mold proteins. Assessment of IgG antibodies to mold proteins can be performed through immunoprecipitation–double diffusion or solid-phase immunoassays.[37] Such testing has demonstrated value in assessment of individuals with suspected HP or allergic bronchopulmonary mycosis. Immunoprecipitation assays have been classically used for the assessment of HP, and although they measure all classes of antibodies present, they are primarily detecting IgG antibodies. Such testing (immunoprecipitation or solid-phase IgG testing) is appropriate to perform only in the setting of a clinical picture, including history, physical examination, imaging studies, and other laboratory assessments, suggesting HP or allergic bronchopulmonary mycosis as part of the differential diagnosis. Use of these tests as screening procedures for these diseases in the absence of an appropriate clinical picture is discouraged.

Immunoprecipitation testing remains the standard approach because the presence of precipitating antibodies is strong supportive evidence in the appropriate clinical setting. However, as many as half of highly exposed individuals might have precipitating antibodies in the absence of any clinical disease. Solid-phase immunoassays have not been widely used for the specific diagnosis of these diseases. Although newer assays are quantitative, the actual level of IgG antibody that would be associated with either HP or ABPA has not been defined. Therefore a level of mold antigen–specific IgG antibody above a statistically defined reference range cannot be taken as evidence for HP or ABMA with the same strength as immunoprecipitation testing. Limited studies suggest that

the level of a specific IgG antibody that would be associated with HP could be 5-fold or greater than the upper limit of the nondiseased group reference range. Use of older-generation, semiquantitative, solid-phase immunoassays is not recommended.

Testing for IgG antibodies to mold proteins cannot be used as a surrogate to assess either the level or timing of specific mold exposures.[38] This is not surprising given the widespread occurrence of molds in the environment.

Measurement of antibodies of isotypes other than IgG (eg, IgA and IgM) to mold is not useful to assess mold exposure. However, the differential response of IgM and IgG antibodies is useful in diagnosis with specific organisms (eg, coccidioidomycosis). IgM levels have not been shown to relate to specific airborne exposures to molds in the absence of infection because mold exposure is common and generally ongoing. Measurement of IgA antibodies to airborne molds has not been shown to be related to a specific timing of exposure, and the claim that increased IgA antibodies to mold represents a more recent exposure than IgG antibodies is not supported by scientific evidence. Measurement of salivary IgA to mold as a marker of mold exposure has not been shown to have scientific validity.

Measurement of antibodies to mycotoxins. Mycotoxins are not proteins but low-molecular-weight chemicals. There is no scientific basis to support measurement of alleged naturally occurring antibodies to various mycotoxins as a marker of exposure to mycotoxins. Evidence of natural exposures from ingestion in human subjects and animals and use of these compounds in clinical medicine does not support the concept of naturally occurring antibodies. Such testing has not been validated and cannot be relied on as an indication of exposure to any mycotoxin.[39]

Conclusions:

- Measurement of antibodies to specific molds has scientific merit in the assessment of IgE-mediated allergic disease, HP, and allergic bronchopulmonary mycosis.
- Measurement of antibodies to molds cannot be used as an immunologic marker to define dose, timing, and/or location of exposure to mold antigen inhalation in a noninfectious setting.
- Testing for antibodies to mycotoxins is not scientifically validated and should not be relied on.

Measurement of molds and mold product exposure in the patient's environment

An in-depth analysis of methods to measure fungal organisms, mold products, and mycotoxins in the environment is outside the bounds of this article. Such information is reviewed in depth elsewhere.[40,41]

Measurement of fungi in the subject's environment. Measurement of airborne fungal spores in the subject's environment by using culture methods, nonculture methods, or both is commonly used. Air testing provides the most relevant measure of exposure and is usually reported as colony-forming units or spores per cubic meter of air. However, this testing suffers from the drawback that it is a snapshot that does not integrate exposure over time and provides data only about the location of sampling. Indoor testing must be compared with outdoor testing and preferably with more than one outdoor sample. Currently there are no standards as to what constitutes acceptable levels of outdoor or indoor airborne fungal spores.

Given these caveats, the levels of airborne fungal spores found in an indoor setting can be considered in relative and absolute terms. Indoor fungal spores arise from outdoor sources present within soil and vegetation. Therefore an increase in indoor-outdoor concentrations of specific fungi indicates the presence of an indoor source. Depending on clinical or other indications, it might be necessary to locate the source and, if necessary, take appropriate action. Total fungi spores that are greater in concentration in indoor than outdoor air might be potential evidence of increased fungal presence indoors. However, in normal indoor environments xerophillic fungi, such as *Aspergillus* and *Penicillium* species, might be found indoors at levels above those measured outdoors on a given day. Even when the fungal levels are greater indoors than those outdoors, health risks would be limited in most cases, except to the subject specifically allergic to the mold in question. Absolute fungal spore levels indoors can be put into context when one realizes that outdoor levels can reach tens of thousands of fungal spores per cubic meter and hundreds of thousands per cubic meter or higher around rotting vegetation compost or in agricultural settings, such as in grain elevators.

Bulk, surface, and within-wall cavity measurements of fungi, although sometimes indicating the presence of fungi, do not provide a measure of exposure. Fungi found in these places require a route of exposure through air (aerosolization and entry into the patient's respirable air) that involves many factors not included in these measurements. Such testing should not be used to assess exposure.

Measurement of fungal products in the patient's environment

Another approach to measure of potential fungal exposure is to test for fungal products in the environment.

Structural fungal materials. Testing for the levels of general mold structural material (eg, β-glucans in settled dust) has been used to try to integrate levels of potential exposure to molds in general over time. Although an interesting research avenue, such testing does not provide any information as to the nature of the specific fungi involved or their source (indoor or outdoor), is not useful for predicting health effects, and has not found general acceptance, as discussed elsewhere.

Mycotoxins. Specific molds can produce, under some conditions, a variety of mycotoxins or none at all. Thus measurements of spores cannot be used as surrogates of mycotoxin exposure. Mycotoxins can be measured directly. A variety of methodologies based on mass

spectroscopy have been applied to bulk samples with heavy fungal growth to identify the presence of mycotoxins; however, potential levels of mycotoxins in nonagricultural air samples are too low to be measured practically with this technology. The occurrence of mycotoxins in bulk sampling does not provide evidence of exposure because mycotoxins themselves are nonvolatile. Thus exposure requires inhalation of mycotoxin-containing spores or fungal fragments in the respirable air. For example, satratoxin H can be found in a sample of material with heavy *Stachybotrys chartarum* growth, but *Stachybotrys* species are not easily aerosolized. Testing with crude cytotoxicity of extracted bulk materials suffers from a lack of sensitivity and specificity. Such testing cannot be relied on to predict or evaluate health effects.

VOCs. See section on irritant effects above.

Conclusions:

- Sampling of both indoor and outdoor air for mold spores provides a measure of potential exposures and can be useful in certain clinical conditions, but it has many shortcomings.
- Bulk, surface, and within-wall cavity measurement or molds or mycotoxins, although having potential relevance for other purposes, cannot be used to assess exposure.
- Testing for airborne mycotoxins in nonagricultural environments cannot be used to diagnose mold exposure.

REMEDIATION

Issues regarding remediation of mold are beyond the scope of this article. Indoor mold growth should be addressed. These matters are reviewed at length in the Institute of Medicine 2004 report ''Damp indoor spaces and health.'' For an overview, the reader can refer to the Occupational Health and Safety Administration document ''A brief guide to mold in the workplace.''[42] The true challenges of mold remediation are currently being addressed in the flood-ravaged areas struck by hurricane Katrina, which will unfortunately provide a rich environment for the study of both mold-induced disease and mold remediation.[43,44]

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