AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

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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 paper.

The 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, eg, 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 non-immunocompromised individuals. In contrast, persons with severely impaired immune function, eg, 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, eg, penicillin, cyclosporine. Serious veterinary and human mycotoxicoses have been documented following 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 and other hypersensitivity 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 sinusitus (AFS), are briefly discussed for completeness, although indoor mold has not been suggested as a particular risk factor in the etiology of either.

1. *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, ie, 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, eg, *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] Since 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. While 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, etc.), 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] While 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.

2. *Hypersensitivity pneumonitis (HP*): 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 have 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]

3. *Uncommon allergic syndromes: Allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal sinusitis (AFS).*[11] These conditions 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 — allergic fungal sinusitis (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, eg, 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 while 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 ABPA 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, eg, 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.

1. *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, eg, patients with lymphoproliferative disorders including acute leukemia, cancer patients 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 southwest US) 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.

2. *Superficial fungal infections:* In contrast to 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, eg, *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 *Malassesia 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 (MVOCs) are low molecular weight alcohols, aldehydes, and ketones.[42] Having very low odor thresholds, MVOCs 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” (ODTS).[49] Exposures associated with ODTS 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 10^5-10^9 per cubic meter of air[52] or even 10^9-10^{10} spores per cubic meter,[53,54] extreme conditions not ordinarily encountered in the indoor home, school, or office environment.

“Sick building syndrome,” or “non-specific building-related illness,” represents a poorly defined set of symptoms (often sensory) that are attributed to occupancy in a building. Investigation generally finds no specific 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 1993-1994 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[78] – very small infants,[†] school-age children,[††] and adults.[†††] 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/min), 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 infeasible, but they are improbable and inconsistent with reported spore concentrations. For example, in data from 9,619 indoor air samples from 1,717 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, eg, 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, ie, 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 considerations 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.

Acknowledgments

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† 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]
†† 50th percentile body weight for 6-year-old boys, 22 kg; respiratory rate for children age 6-9, 10.0 m^3/day[78]
††† 50th percentile body weight for men aged 25-34 years, 77.5 kg; respiratory rate for men age 19-65, 15.2 m^3/day[78]

References

1. Solomon WR, Platts-Mills TAE. Aerobiology and Inhalant Allergens. In: Middleton E, Jr et al, eds. *Allergy: Principles and Practice.* St. Louis: Mosby Co.; 1998:367-403.

2. Horner WE, et al. Fungal allergens. *Clin Microbiol Rev*. 1995;8:161-79.

3. Billings CG, Howard P. Damp housing and asthma. *Monaldi Arch Chest Dis.* 1998;53:43-9.

4. Burr ML. Health effects of indoor molds. *Rev Environ Health.* 2001;16:97-103.

5. Macher J. Health effects of bioaerosols. In: Macher J, ed. *Bioaerosols: assessment and control.* Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1999:3-1 to -12.

6. Purokivi MK, et al. Changes in pro-inflammatory cytokines in association with exposure to moisture-damaged building microbes. *Eur Respir J.* 2001;18:951-8.

7. Roponen M, et al. Fungal spores as such do not cause nasal inflammation in mold exposure. *Inhal Toxicol*. 2002;14:541-9.

8. Fink J, Zacharisen MC. Hypersensitivity Pneumonitis. In: Middleton E, Jr. et al, eds. *Allergy: Principles and Practice.* St. Louis: Mosby Co.; 1998:994-1004.

9. Flaherty DK, et al. Multilaboratory comparison of three immunodiffusion methods used for the detection of precipitating antibodies in hypersensitivity pneumonitis. *J Lab Clin Med.* 1974;84:298-306.

10. California Department of Health Services, Environmental Health Investigations Branch: Misinterpretatin of *Stachybotrys* serology, 2000. www.dhs.ca.gov/ps/deodc/ehib/ehib2/topics/serologyf2.htm, accessed 2002.

11. Greenberger PA. Allergic bronchopulmonary aspergillosis, allergic fungal sinusitis, and hypersensitivity pneumonitis. *Clin Allergy Immunol.* 2002;16:449-68.

12. Greenberger PA, Patterson R. Diagnosis and management of allergic bronchopulmonary aspergillosis. *Ann Allergy*. 1986;56:444-8.

13. Cockrill BA, Hales CA. Allergic bronchopulmonary aspergillosis. *Ann Rev Med.* 1999;50:303-16.

14. Zhaoming W, Lockey RF. A review of allergic bronchopulmonary aspergillosis. *J Investig Allergol Clin Immunol.* 1996;6:144-51.

15. Slavin RG. Allergic bronchopulmonary aspergillosis. *Clin Rev Allergy.* 1985;3:167-82.

16. Katzenstein AL, Sale SR, Greenberger PA. Allergic Aspergillus sinusitis: a newly recognized form of sinusitis. *J Allergy Clin Immunol.* 1983;72:89-93.

17. deShazo RD, Swain RE. Diagnostic criteria for allergic fungal sinusitis. *J Allergy Clin Immunol.* 1995;96:24-35.

18. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal sinusitis. I. Demographics and diagnosis. *J Allergy Clin Immunol.* 1998;102:387-94.

19. Schubert MS. Fungal rhinosinusitis: diagnosis and therapy. *Curr Allergy Asthma*. Rep 2001;1:268-76.

20. Blonz ER. Is there an epidemic of chronic candidiasis in our midst? *JAMA.* 1986;256:3138-9.

21. Executive Committee of the American Academy of Allergy and Immunology. Clinical ecology. J *Allergy Clin Immunol.* 1986;78:269-71.

22. Hawkins C, Armstrong D. Fungal infections in the immunocompromised host. *Clin Haematol.* 1984;13:599-630.

23. Walsh TJ, Dixon DM. Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. *Eur J Epidemiol.* 1989;5:131-42.

24. Singh N. Trends in the epidemiology of opportunistic fungal infections: predisposing factors and the impact of antimicrobial use practices. *Clin Infect Dis.* 2001;33:1692-6.

25. Munoz P, Burillo A, Bouza E. Environmental surveillance and other control measures in the prevention of nosocomial fungal infections. *Clin Microbiol Infect.* 2001;7 Suppl 2: 38-45.

26. Ciegler A, et al. Mycotoxins: occurrence in the environment. In: Shank RC, ed. *Mycotoxins and N-nitroso Compounds: Environmental Risks.* Volume I. Boca Raton, FL: CRC Press, Inc.; 1981:1-50.

27. Committee on Protection Against Mycotoxins. National Research Council. Protection against trichothecene mycotoxins. 1983. Washington, DC, National Academy Press.

28. Hendry KM, Cole EC. A review of mycotoxins in indoor air. *J Toxicol Environ Health.* 1993;38:183-98.

29. Nikulin M, et al. *Stachybotrys atra* growth and toxin production in some building materials and fodder under different relative humidities. *Appl Environ Microbiol.* 1994;60:3421-24.

30. Rao CY. Toxigenic fungi in the indoor environment. In: Spengler JD, Samset JM, McCarthy JS, eds. *Indoor Air Quality Handbook*. McGraw Hill; 2001:46-2 and 46-4.

31. Nikulin M, et al. Experimental lung mycotoxicosis in mice induced by *Stachybotrys atra. Int J Exp Pathol.* 1996;77:213-8.

32. Jarvis BB, et al. Study of toxin production by isolates of *Stachybotrys chartarum* and *Memnoniella echinata* isolated during a study of pulmonary hemosiderosis in infants. *Appl Environ Microbiol.* 1998;64:3620-5.

33. Vesper SJ, et al. Hemolysis, toxicity, and randomly amplified polymorphic DNA analysis of *Stachybotrys chartarum* strains. *Appl Environ Microbiol*. 1999;65:3175-81.

34. Andersen B, Nielsen KF, Jarvis BB. Characterization of *Stachybotrys* from water-damaged buildings based on morphology, growth, and metabolic production. *Mycologia.* 2002;94(3):392-403.

35. Tobin RS, et al. Significance of fungi in indoor air: report of a working group. *Can J Public Health.* 1987;78:S1-S32.

36. Smith JE, et al. Cytotoxic fungal spores in the indoor atmosphere of the damp domestic environment. *FEMS Microbiol Lett.* 1992;79:337-43.

37. Rao CY, Burge HA, Chang JC. Review of quantitative standards and guidelines for fungi in indoor air. *J Air Waste Manag Assoc.* 1996;46:899-908.

38. Tuomi T, et al. Mycotoxins in crude building materials from water-damaged buildings. *Appl Environ Microbiol.* 2000;66:1899-904.

63. Robbins CA, et al. Health effects of mycotoxins in indoor air: a critical review. *Appl Occup Environ Hyg*. 2000;15:773-84.

64. Sudakin DL. *Stachybotrys chartarum:* current knowledge of its role in disease. *MedGenMed.* 2000;E11.

65. Page EH, Trout DB. The role of *Stachybotrys* mycotoxins in buildings related illness. *Am Ind Hyg Assoc J.* 2001;62:644-8.

66. Terr AI. *Stachybotrys:* relevance to human disease. *Ann Allergy Asthma Immunol.* 2001;87:57-63.

67. Burge HA. Fungi: toxic killers or unavoidable nuisances? *Ann Allergy Asthma Immunol.* 2001;87:52-6.

68. Centers for Disease Control and Prevention (CDC). Acute pulmonary hemorrhage/hemosiderosis among infants – Cleveland, January 1993-November 1994. *MMWR Morb Mortal Wkly Rep.* 1994;43:881-83.

69. Centers for Disease Control and Prevention (CDC). Update: pulmonary hemorrhage/hemosiderosis among infants – Cleveland, Ohio, 1993-1996. *MMWR Morb Mortal Wkly Rep.* 1997;46:33-5.

70. Montaña E, et al. Environmental risk factors associated with pediatric idiopathic pulmonary hemorrhage and hemosiderosis in a Cleveland community. *Pediatrics.* 1997;99:e5.

71. Etzel RA, et al. Acute pulmonary hemorrhage in infants associated with exposure to *Stachybotrys atra* and other fungi. *Arch Pediatr Adolesc Med.* 1998;152:757-62.

72. Centers for Disease Control and Prevention (CDC). Availability of case definition for acute idiopathic pulmonary hemorrhage in infants. *MMWR Morb Mortal Wkly Rep*. 2001;50:494-95.

73. Centers for Disease Control and Prevention (CDC). Update: pulmonary hemorrhage/hemosiderosis among infants – Cleveland, Ohio, 1993-1996. *MMWR Morb Mortal Wkly Rep.* 2000;49:180-84.

74. Creasia DA, et al. Acute inhalation toxicity of T-2 mycotoxin in mice. *Fundam Appl Toxicol.* 1987;8:230-5.

75. Creasia DA, et al. Acute inhalation toxicity of T-2 mycotoxin in the rat and guinea pig. *Fundam Appl Toxicol.* 1990;14:54-9.

76. Rao CY, Brain JD, Burge HA. Reduction of pulmonary toxicity of *Stachybotrys chartarum* spores by methanol extraction of mycotoxins. *Appl Environ Microbiol.* 2000;66:2817-21.

77. Rao CY, Burge HA, Brain JD. The time course of responses to intratracheally instilled toxic *Stachybotrys chartarum* spores in rats. *Mycopathologia*. 2000;149:27-34.

78. EPA Office of Research and Development. Volume I: General Factors. Exposure Factors Handbook. 1997 Aug. Washington, DC, US Environmental Protection Agency.

79. Nikulin M, et al. Effects of intranasal exposure to spores of *Stachybotrys atra* in mice. *Fundam Appl Toxicol*. 1997;35:182-8.

80. Shelton BG, et al. Profiles of airborne fungi in buildings and outdoor environments in the United States. *Appl Environ Microbiol*. 2002;68:1743-53.

81. Macher J. Bioaerosols: assessment and control. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1999.

82. American Industrial Hygiene Association. Report of Microbial Growth Task Force. Fairfax, VA: AIHA Press, 2001.

83. EPA Office of Air and Radiation, Indoor Air Division. Mold remediation in schools and commercial buildings. 2001 Mar. Washington DC, US Environmental Protection Agency.