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. This evidence-based statement from the American College of Occupational and Environmental Medicine (ACOEM) discusses the current state of scientific knowledge as to the nature of fungal- (mold-) related illnesses while emphasizing the possible relationships to indoor environments. Food-borne exposures, methods of exposure assessment, and mold remediation procedures are beyond the scope of this paper.

"Mold" is the common term for multicellular fungi that grow as a mat of intertwined microscopic filaments (hyphae). Many species of fungi live as commensal organisms in or on the surface of the human body. 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, e.g., in organ transplant isolation units.

Molds and other fungi may adversely affect human health through three processes: 1) allergy; 2) infection; or 3) toxicity. It is estimated 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 corporis), or nails (tinea onychomycosis). 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, e.g., 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, e.g., penicillin and 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. Present concern over human exposure to molds in the indoor environment appears to derive from a belief that inhalation exposures to mycotoxins cause numerous and varied, but generally nonspecific, symptoms.

There is scientific evidence that in certain cases, molds and other fungi may adversely affect human health, and mold has been associated with health issues ranging from coughs to asthma to allergic rhinitis. However, current scientific evidence does not support the existence of a causal relationship between inhaled mycotoxins in the home, school, or office environment and adverse human health effects. An evaluation of the relevant literature follows.

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 sinusitis (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, i.e., 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, e.g., *Cladosporium* and *Alternaria*, as well as pollens, can often be found at high levels indoors if there is access for outdoor air (e.g., 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.).
Serious fungal infections: 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. 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. 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 actinomycetes, which are not molds but rather 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. 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. 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 (e.g., 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.

Uncommon allergic syndromes: allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal sinusitis (AFS). These conditions are unusual variants of allergic (IgE-mediated) reactions in which fungi actually grow within a person'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, e.g., bronchiectasis. Bronchial disease and old cavitory 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. As fungi other than Aspergillus may cause this condition, the term "allergic broncho-pulmonary mycosis" has been suggested.

It has more recently become appreciated that a similar process may affect the sinuses — allergic fungal sinusitis (AFS). 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.

Recommendations

- Individuals with allergic airway disease should take steps to minimize their exposure to molds and other airborne allergens, e.g., animal dander, dust mites, and 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 and 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 other occupied space 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, e.g., in machining fluids and where stored organic materials are handled such as in agricultural and grain processing facilities. Engineering controls should be used to reduce potentially contaminated aerosol or particulate generation. If engineering controls are inadequate, personal protective equipment may be needed to minimize worker exposures to aerosols and particulate matter.

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, e.g., patients with hematologic neoplasms including acute leukemia, cancer patients receiving intense chemotherapy, or persons undergoing bone marrow or solid transplantation who receive potent immunosuppressive drugs. 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 immunocompromised states, at which time intensive measures are taken to avoid fungal, bacterial, and viral infection. 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. Candida albicans is a ubiquitous commensal organism on humans that becomes an important opportunistic pathogen for immunocompromised subjects. However, it and environmental fungi discussed above that are pathogens in healthy individuals as well (e.g., Cryptococcus associated with bird droppings, Histoplasma associated with bat droppings, Coccidioides endemic in the soil in the southwest U.S.) 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 on the Centers for Disease Control and Prevention (CDC) website 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, e.g., Trichophyton rubrum, can be found growing as an indoor mold. Others, such as Microsporum canis and T. mentagrophytes, can be found on indoor pets (e.g., 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 is 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 the development of superficial fungal infections.

**Pityriasis (Tinea) versicolor** is a chronic asymptomatic infection of the most superficial layers of the skin due to *Pityrosporum orbiculare* and Malassezia 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 who are immunocompromised need be concerned about the potential for serious 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 bird 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. 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. Thus, it does not necessarily follow from the mere presence of a toxigenic species that mycotoxins are also present.

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; 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.

In contrast, microbial volatile organic compounds (MVOCs) are low molecular weight alcohols, aldehydes, and ketones. 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.

Most descriptions of human and veterinary poisonings from molds involve eating moldy foods. 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. Related conditions including "pulmonary mycotoxicosis," "grain fever," and others are referred to more broadly as "organic dust toxic syndrome" (ODTS). Exposures associated with ODTS have been described as a "fog" of particulates or an initial "thick airborne dust" that "worsened until it was no longer possible to see across the room." Total microorganism counts have ranged from 10^5 to 10^9 per cubic meter of air or even 10^9 to 10^10 spores per cubic meter, 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. Critical reviews of the literature have 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 1993-94 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, 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. 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,” had not been causally linked to _S. chartarum_ exposure.

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 (e.g., 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 intoxication by the airborne route might be feasible.

Experimental data on the _in vivo_ toxicity of mycotoxins are scant. Frequently cited are the inhalation LC₅₀ values determined for mice, rats, and guinea pigs exposed for 10 minutes to T-2 toxin, a trichothecene mycotoxin produced by _Fusarium_ spp. Rats were most sensitive in these studies, but there was no mortality in rats exposed to 1.0 mg T-2 toxin/m³. 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 x 10³ ng/spore in a “highly toxic” _S. chartarum_ strain, s. 72. To provide perspective relative to T-2 toxin, 1.0 mg satratoxin H/m³ air would require 10¹⁰ (ten billion) of these spores/kg.

In single-dose _in vivo_ studies, _S. chartarum_ spores have been administered intranasally to mice or intratracheally to rats. High doses (30 x 10⁶ spores/kg and higher) produced pulmonary inflammation and hemorrhage in both species. A range of doses was administered in the rat studies and multiple, sensitive indices of effect were monitored, demonstrating a graded dose response with 3 x 10⁶ 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, school-age children, and adults. The no-effect dose in rats (3 x 10⁶ spores/kg) corresponds to continuous 24-hour exposure to 2.1 x 10⁶ spores/m³ for infants, 6.6 x 10⁶ spores/m³ for a school-age child, or 15.3 x 10⁶ spores/m³ 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 x 10⁶ spores/kg intratracheal bolus dose in rats is regarded as a 1-minute administration (3 x 10⁶ spores/kg/min), achieving the same dose rate in humans (using the same default assumptions as previously) would require airborne concentrations of 3.0 x 10⁹ spores/m³ for an infant, 9.5 x 10⁹ spores/m³ for a child, or 22.0 x 10⁹ spores/m³ for an adult.

In a repeat-dose study, mice were given intranasal treatments twice weekly for 3 weeks with “highly toxic” _S. chartarum_ spores at doses of 4.6 x 10⁵ or 4.6 x 10⁴ spores/kg (cumulative doses over 3 weeks of 2.8 x 10⁷ or 2.8 x 10⁶ spores/kg). The higher dose caused severe inflammation with hemorrhage, while less severe inflammation but no hemorrhage was seen at the lower dose of _S. chartarum_. Using the same assumptions as previously (and again ignoring dose-rate implications), airborne _S. chartarum_ spore concentrations that would deliver the non-hemorrhagic cumulative 3-week dose of 2.8 x 10⁵ spores/kg can be estimated as 9.4 x 10⁵ spores/m³ for infants, 29.3 x 10³ spores/m³ for a school-age child, and 68.0 x 10³ spores/m³ for adults (assuming exposure for 24 hours per day, 7 days a 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 buildings surveyed) the median airborne concentration was 12 CFU/m³ (95% CI 12 to 118 CFU/m³).

**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.
- 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.
- Indoor air samples with contemporaneous outdoor air samples can assist in evaluating whether or not there is mold growth.
When patients associate health complaints with mold exposure, treating physicians should evaluate all possible diagnoses, including those unrelated to mold exposure, i.e., 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.

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 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 asthma, molds should not be allowed to grow unchecked indoors.

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 non-impaired 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 certain conditions, produce mycotoxins that can adversely affect living cells and organisms by a variety of mechanisms, for example, the 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. One mold, Stachybotrys chartarum, is known to be able to produce mycotoxins under appropriate growth conditions. However, 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, even for the 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 existence of a causal relationship between inhaled mycotoxins in home, school, or office environments and adverse human health effects.

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References


