Indoor fungal infestations and mycotoxicity: guidance for public health professionals and industrial hygienists

Robert Thiboldeaux, Ph.D., Toxicologist, Wisconsin Bureau of Environmental and Occupational Health, Department of Health and Family Services

Introduction and scope.
"Mold spores are omnipresent, and a constantly elevated humidity in given building containing organic components will inevitably lead to [fungal] growth and subsequent damage to the materials" (Gravensen, 1999). In recent years indoor fungal growth and airborne particles have gained the reputation of a serious health threat. The extent to which this perception is justified is controversial. We know that mold dust and spores can be allergenic, and that excessive exposure to fungal materials can cause infectious respiratory ailments. We also know that some mold species may produce toxic secondary metabolites. Less clear is the extent to which the presence of fungal material represents an imminent threat to human heath. Health experts agree that visible mold growth should be discouraged in the indoor environment, and that management of the indoor environment should take the form of controlling indoor humidity, disinfecting surfaces with visible mold growth, and discarding moldy articles. These are recommendations for general indoor sanitation and do not necessarily recognize indoor mold as an acute health threat. However, in recent years it has become common to confront visible indoor mold with professional assessments and drastic, costly remedies. Such measures may not be beneficial, and may cause unneeded economic stress and disruption. The purpose of this review is to provide guidance on indoor mold and mycotoxicity to the public health community. This review, while focusing on mycotoxicity, will argue that the health effects claimed to follow from inhalational exposure to fungal particles in residential, school, and office settings are poorly documented and probably multifactorial. A better understanding of the routes and effects of exposure to mold is needed in order to make proper public health decisions.

Indoor mold and building-related illnesses. The presence of indoor mold infestation is often implicated as the basis of disease in case studies of building-related illness (Hodgson, *et al.* 1998; Croft, *et al.* 1986; Apostolakos *et al.*, 2001). There is little evidence that humans are exposed to airborne mycotoxins or to microbial volatile organic compounds (MVOCs) at concentrations known to cause acute or irritating effects for single compounds, as established in animal studies (Burge, 1990; Pasanen, *et al.* 1999; The Nat'l Acadamies, 2004). Nonetheless, there are many case studies of individuals reporting non-specific or allergy-related symptoms attributed to sick-building syndrome, such as chronic headache, dizziness, confusion, sinus bleeding, and pulmonary effects (pneumonitis, pulmonary hemosiderosis, asthma).

Building-related illnesses are difficult to diagnose and interpret. Because the symptoms are non-specific and often allergy-related, people tend to ignore the problem, or their complaints are ignored by others, until the symptoms become chronic. Even then, it is difficult to make conclusive links to environmental factors.

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In cases of extreme infestation or heightened individual sensitivity, health effects do follow from exposure to mold. In any given indoor environment, a small percentage of people will present allergy symptoms. For example, the nationwide prevalence of asthma from all causes is around 7% of the population (Rhodes *et al.* 2003). The claim that many asthma cases are mold allergy-related is valid, based on case-control studies (Jaakkola *et al*. 2002; Zock *et al*. 2002). An important question is, given that fungi are ubiquitous, what level of infestation requires intervention to prevent a health risk? It is reasonable to expect that visible fungal growth represents unnecessary exposure, and should be absent from indoor spaces. Visible fungus indicates improper moisture management in the building. It is not reasonable, practical, or necessary that we live in a sterile, fungus-free environment, since most people are not adversely affected by the presence of molds and other fungi.

Fungi typically found in outdoor air compared to mold-infested buildings. Airborne mold, measured by colony forming units (CFUs) are normally more abundant outdoors than indoors during the growing season. However, the relative proportion of mold species is normally similar indoors and out. In the case of indoor infestation, the relative representation of mold species changes. Cooley, *et al.*, (1998) based on a study of 48 schools, report that in outdoor air in mild temperate regions of North America, five fungal genera predominate: *Cladosporium* (81.5%), *Penicillium* (5.2%), *Chrysoporium* (4.9%), *Alternaria* (2.8%), and *Aspergillus* (1.1%). In outdoor air samples *Cladosporium* is about 24-fold more predominant than the next-most common mold, *Penicillium.* Indoors, *Cladosporium* normally predominates over *Penicillium* in similar proportion, although total CFU counts are 3-4 fold lower. However, inside mold complaint buildings, Cooley *et al.* saw that *Penicillium sp.* are much more common, with *Cladosporium* being only about 3-fold more predominant. Furthermore, in 20 of 48 schools with indoor air complaints, *Penicillium sp.* were the dominant molds, being 4.7-fold more abundant in air than *Cladosporium*. Such changes in species representation are diagnostic of indoor mold infestation (Cooley, *et al.* 1998; Bartlett, *et al.* 1999), but do not necessarily indicate that an imminent health threat exists.

Indoor molds which produce mycotoxins of human health significance. All fungi produce secondary compounds that help them become established in their environment. Some of these chemicals are broadly antibiotic; others have antibiotic mechanisms specific to bacteria and other fungi and have been adopted as important medicines. A few of these chemicals, such as the aflatoxins, fumonisins, and sterigmatocystin (figure 1), are toxic in sufficient dose to humans and livestock. Hundreds of toxic secondary metabolites, or mycotoxins, produced by fungi have been described. These are structurally and functionally diverse, and vary greatly in toxicity. Those chemicals most frequently studied for their toxic effects are produced by the genera *Aspergillis, Penicillium, Stachybotrys,* and *Myrothecium.* A species may produce more than one toxin, and a particular toxin is not confined to a single genus, species, or strain. Furthermore, the production of mycotoxins by a fungal colony varies with environmental conditions (reviewed by Burge & Ammann, 1999).

Health effects of inhaled mycotoxins.
Almost all reports of known exposure in humans to these mycotoxins have been through the ingestion of stored food such as grain or peanuts that has been contaminated by fungi. Enzymic metabolism, following ingestion, of aflatoxins, fumonisins, sterigmatocystin, and other mycotoxic fungal compounds leads to the formation of reactive intermediates that are hepatotoxic (Campbell & Hayes, 1976). In residential situations, a class of mycotoxins known as the trichothecenes (figure 1), produced by molds of the genera *Stachybotrys, Fusarium*, and *Trichoderma*, have drawn attention for their possible effect on humans via the inhalation route.

The toxic effects of mold following ingestion are well-understood, but the toxic effects of inhaled mold particles are not well documented. Lung infections by molds have been best documented in agricultural workers and in healthcare settings involving immune-compromised patients. Exposure to molds (*e.g. Aureobasidium pullulans, Saccharopolyspora rectivirgula*) in domestic situations has been implicated in the development of hypersensitivity pneumonitis (Apostolakos *et al.*, 2001). However, Burge (2001) concluded that, "no case studies have unequivocally documented a cause/effect relationship for airborne mycotoxins or fungal volatiles in causing disease in humans, by inhalation, in residential, school, or office settings."

Studies concluding that trichothecenes inhibit RNA and protein synthesis are frequently cited as the mechanism of these mycotoxins. However, the epoxide moiety of these compounds (figure 1) suggests that the molecular targets are non-specific. The degradation of protein synthesis at the cellular level may reflect the choice of a higher cell function as a sensitive endpoint in these studies. The role of trichothecenes as an epoxide-mediated contact poison is supported both by the range of tissues affected by these compounds, and by *in vitro* evidence that tricothecenes are inactivated by epoxide hydrolase (Wannemacher & Wiener, 1997).

Exposure via the inhalation route: health effects of bioaerosols. The toxicity of some trichothecene mycotoxins have been well documented mammalian models. For example, the inhalational LD_{50} of T-2 toxin is 0.24 mg/kg in mouse, 0.05 mg/kg in rat, and 0.6-2.0 mg/kg in Guinea Pig (Wannemacher and Wiener, 1997). Less clear is whether a biologically relevant exposure to trichothecene can occur from the inhalation of trichothecene-containing spores or mold fragments in indoor situations. Reports of health effects from mold-infested buildings (Croft *et al*. 1986; Etzel and Dearborn, 1999; CDC, 1994; Robertson, 1999) document the presence of mold around building occupants with potentially related health effects, but do not verify actual exposure. In some cases (Robertson, 1999), authors acknowledge that "the absence of exposure data [...] does not support a valid medical claim relative to an aerosol-induced mycotoxicosis." This does not mean that the potential does not exist, or that people have not become sick. This shows that data gaps in the diagnosis of mycotoxicosis must be addressed before drawing firm conclusions.

Mycotoxins and the relationship to allergy. There is ample clinical and epidemiological evidence of the role of fungi in allergic disease (Burge 2001; Miller *et al.* 2004, The National Acadamies, 2004). There are also many studies using animal and *in vitro* models (*e.g.* Uzarski *et al. 2003*, Johnson and Sharma 2001, Bondy and Pestka 2000) describing the immunosuppressive effects of various mycotoxins. In the case of live animals, these studies invariably employ acute doses by the ingestion rather than inhalation route. Burge (2001) concluded that the primary result from fungal exposure is allergic disease, and that the evidence for inhalation disease resulting from mycotoxin exposure in residential and office settings is extremely weak. Although most evidence points to allergy as the major effect, our understanding of the effects of mold exposure is currently insufficient to dismiss other factors such as variation in individual metabolism, possible immunosuppression, and possible additive or synergistic effects from mycotoxin mixtures.

Allergies and mold exposure. Rapid allergic responses to otherwise innocuous antigens are viewed as an inappropriate immune response to ones environment (Roitt, *et al*. 1985). Immunoglobulin E (IgE) are antibodies involved in very rapid responses to antigens. The binding of antigen to IgE forms antigen-IgE complexes which then bind to the surface of mast cells, causing these cells to release histamines, leukotrienes, and other substances that cause vasodialation and smooth muscle contraction. Atopic individuals, who exhibit the clinical symptoms of allergy, produce more IgE than most, causing them to be more sensitive than most to antigens commonly present in the environment. Mold particles (spores and debris) are some of the most common biological triggers of allergy in our environment. A hypersensitivity to molds (and other allergens) manifests as the effects we associate with Type I allergy, such as eye and nose inflammation, fatigue, dizziness, rashes, asthma, eczema, and anaphalaxis (Golub, 1980).

Although studies have shown that molds and their associated mycotoxins have separate allergenic and toxic effects, the interaction of mycotoxicity and allergenicity following exposure to mold has been essentially unexplored. It is known that trichothecenes, and other fungal toxins, modulate or suppress the immune response in model animals (Bondy & Pestka, 2000; Venturini, *et al.* 1996; Smith *et al*. 1994; Jagadeesan *et al*. 1982). However, these animal studies administered mycotoxins orally or intravenously, rather than by inhalation. It is also known that, in general, hypersensitivity sometimes follows the immunosuppressive effects of toxic insult. This occurs when the immune response is selectively impaired, leading to dysregulation. Immune dysregulation can result in autoimmune disease by promoting recognition of self-antigens, and hyper-responsiveness associated with increased antibody and effector cell production (United Nations, *et al*. 1999, and references therein).

Based on *in vitro* and animal studies of the effects of mycotoxins and other toxins on immune function, it may be hypothesized that inhalational exposure to low levels of mycotoxin in indoor environments might modulate an individual's immune responses to mold exposure. Rare individuals may be affected by the presence of mold to a degree inconsistent with most of the population. At this time there is no established method to

assess such individuals, although such an assessment should test both general immune function and chemically verify exposure. Similarly, there is no common policy for how those affected, once assessed, should be accommodated in public settings. Although it is not usually reasonable to expect that workplaces and public buildings be free from mold particles, it is standard public health practice to maintain environmental toxicants below levels at which most people are affected. Worldwide, a number of environmental workgroups, agencies, and individual researchers have proposed indoor air standards for airborne fungi (reviewed by Rao *et al.*, 1996). Most of these recommendations range from 100-1000 CFU/m^3. There is concern that it may not be realistically possible to meet environmental standards that are sufficiently conservative to protect those most sensitive to the presence of airborne fungi. However, establishing action levels for airborne concentrations of fungi will ultimately be useful in determining the safety of workplaces and residences, and in making decisions about the need for building remedies.

Interactions between microbial volatile organic compounds and mycotoxins. Molds release volatiles (MVOCs) that damage textiles with unpleasant odors. Indoor microbial volatiles from molds may also have health implications. However, unequivocal evidence for health effects resulting from MVOCs is lacking. Several studies (Pasanen, *et al.* 1999; Wolkoff 1997, *ref. in* Gravesen, 1999) failed to detect indoor microbial volatiles above threshold levels (mg/m^3 range) for irritation. It is not known whether MVOCs, at concentrations below the mg/m^3 range, enhance mycotoxic and allergenic effects of other mold compounds.

What constitutes a significant exposure?

A significant exposure is one that elicits an immune reaction or chemical response in sensitive individuals.` Because people vary greatly in their immune response to environmental allergens, and because fungi are ever present in the environment, it may not be possible to manage airborne fungal particles at a level protective of those individuals most sensitive to their allergenic effects. This recognizes that in most cases, molds are to be categorized with pollen, dander, and mite frass as allergens to be managed but not eliminated. When people present with allergic hypersensitivity, the response is potentially linked to many different environmental allergens. Reed (1985) found that a positive skin test to *Alternaria* among patients with allergic asthma was more likely than a positive test to ragweed or cat, and that asthma symptoms persisted before and after the ragweed season. This illustrates that the presence of mold is to be expected, and that health effects are due more to individual sensitivity than to the presence or absence of exposure.

The medical and environmental assessment of mold exposure.

The U. S. Centers for Disease Control does not have a standardized method for the analysis of mycotoxins in biological samples (Jim Pirkle, CDC, *pers. comm*.). Several workers have published methods for the isolation and characterization of trichothecenes from both environmental and biological samples using conventional high-pressure liquid chromatography with a C_{18} column, or gas chromatography/mass spectroscopy (Jarvis & Hinkley, 1999). These methods are readily adaptable to serum or urine samples, and would provide a direct measure of exposure.

Enzyme-linked immunosorbent assays (ELISA) have been used to medically evaluate individuals occupying mold-infested buildings and suffering from pulmonary disease (Hodgson, *et al.* 1998). Immunoassays measure antibody titre to specific antigen, from serum samples. This is a measure of physiological response to exposure, rather than a direct measure of mycotoxin. Although the immunoassay is a useful and reasonably specific tool for determining individual exposure to fungi, the results often suffer from cross reactivity and false positives. Immunoassay results alone, being an indirect measure of exposure, cannot quantify mycotoxin dosage.

Difficulties in detecting toxigenic fungi. Although the size of fungal particles is adequate for collection from air samples, abundant species, such as *Penicillium spp.*, may overgrow and obscure less abundant species, such as *Stachybotrys chartarum,* when the particles are identified from plate cultures (Burge & Ammann, 1999). For example, *Stachybotrys chartarum*, which produces trichothecene-class secondary compounds, was found growing in 11 of 48 schools with fungal complaints by Cooley *et al.* (1998), but was never isolated from air samples. The exposure potential for airborne toxigenic molds can be most reliably assessed from air samples by comparing two or more methods, such as cultures of air and bulk samples against microscopic examination.

Stachybotrys chartarum infestations and exposure to mycotoxins. Of the many toxigenic mold species and the hundreds of mycotoxins that have been described, no single species has received more attention or controversy in recent years than *Stachybotrys chartarum.* This attention may or may not be justified. *S. chartarum* is widely distributed outdoors, although is less abundant than species of *Alternaria, Aspergillus, Cladosporium,* and *Penicillium*. *S. chartarum* thrives outdoors on damp plant debris, and will grow in damp indoor environments on cellulose-rich substrates such as paper, ceiling tile, and paper-covered gypsum wallboard. Mature conidia (spore-producing structures) are dark-brown in color, giving the characteristic "black" appearance of this mold. *S. chartarum* produces, under the proper conditions, several mycotoxins that include macrocyclic trichothecenes, roridin E, satratoxin H, sporidesmin G, triverrins, and verrucarol (Ajello, *et al*. 1998). Associations have been drawn between the presence of *S. chartarum* in mold-infested buildings, mycotoxins, and health problems suffered by people occupying those buildings (Croft *et al.* 1986; Hodgson, *et al.* 1998; Robertson, 1999). As discussed above, *S. chartarum* is not usually detected in indoor air samples, even when detected in bulk samples from solid substrates. This begs the question, "is the exposure pathway incomplete, or has there been a failure to detect *S. chartarum* in air. There is evidence that *S. chartarum* spores and mycelia do not readily form bioaerosols. There is also evidence (Burge & Ammann, 1999) that *S. chartarum* spores are short-lived and difficult to detect in culture. Preliminary efforts to quantify mycotoxin bioaerosols (T. Burk, Wisc. State Hygiene Laboratory, *pers. comm.)* indicate that large volumes of air, well above the normal range of daily inspiration by humans, must be sampled to obtain detectable amounts of mycotoxin. Health effects in workers in certain agricultural and industrial settings, and from homes heavily infested with *S. chartarum,* are suggestive of mold exposure, but the actual role of *S. chartarum* has not been confirmed (Burge & Ammann, 1999). The black color of *S. chartarum* makes this

species visually apparent in infested buildings; this may contribute to its reputation. Other molds, such as *Penicillium spp.,* are much more abundant (but less apparent), readily sporulate, and also produce mycotoxins.

Building assessment and remediation. The presence of visible mold growth in buildings, combined with information about building moisture and indoor humidity, is usually sufficient evidence of infestation for developing a remediation plan. In most cases no further biological testing is necessary. At a minimum, the moisture source or leak should be removed or repaired. Damp cellulose-containing substrates (wallboard, carpets, curtains, paneling, structural frames), rather than indoor relative humidity, is the primary determinant of mold growth. Surface disinfection may not be sufficient to prevent resurgence of mold growth or retention of unpleasant odors. This may be especially true of porous, fibrous, cellulose-rich materials such as wood paneling, paper-gypsum wall board, ceiling panels, and carpets. Removal and replacement of the surfaces may be necessary. The surface of affected surfaces should be disinfected. Household items contaminated with mold should be disinfected or discarded. Care should be taken to avoid items not discarded becoming sources of re-infestation. Affected items, including clothing, furniture, and plastic containers, may permanently retain unpleasant MVOC odors, even following disinfection and cleaning.

Public Health Education during remediation of schools. Recent years have seen increased attention placed on mold infested schools in Wisconsin. Mold infestation in schools presents a special case in risk management. Parents understandably demand some control over the environments where they place their children. Parents have a predictably low tolerance for either actual or perceived risk, and are often organized and active in school issues. The public response to mold-infested schools often presents extra challenges for school and public health officials. However, the school environment is also an opportunity for public health education on these issues. The public may be asked to participate in making decisions regarding the fate of a mold-infested school. Therefore, it is important that school and health officials be able to communicate the ubiquitous nature of fungi in the environment, the relative community of fungi found indoors compared to outdoors, the relative risk posed by the molds detected, and the range of options available to confront the problem.

HVAC systems in large buildings. In large buildings, the heating, ventilation, and air conditioning (HVAC) system is often implicated as a source of fungal infestation. Such problems may occur with moisture leakage or excessive condensation within HVAC ducts, especially when the ductwork is lined with insulation. Insulation can trap moisture and dust, providing a physical substrate for mold growth. Where HVAC systems are a source of fungal growth, the ductwork is an obvious pathway for the dispersion of fungal particles. HVAC systems should be designed and maintained to ensure they are not a source of fungal infestation.

Conclusions.

In most cases, molds are to be categorized with pollen, dander, and mite frass as allergens to be managed but not eliminated. It is generally recognized that controlling building moisture and humidity is the key to managing fungi and other microbial problems indoors. There is limited and inconclusive evidence that humans are exposed to mycotoxins or MVOCs at concentrations known to cause acute or irritating effects for single compounds. Nonetheless, a variety of health effects are documented to result from exposure to indoor bioaerosols. It is important to recognize that mold particles are complex mixtures of biological chemicals. These health effects usually have an allergenic basis. Toxigenic effects, if present, are poorly understood. Although it is necessary to understand the pharmacological effect of various fungal compounds in isolation, exposure normally occurs in concert. A complete understanding of the health effects of fungi demands that this fact be recognized and studied.

The presence of mold in a building does not in itself constitute a health threat. Although the control of indoor mold growth is preferred, a health-based assessment of the indoor environment *and* its occupants is needed to verify the extent of the health threat. Such a determination is critical in deciding upon an expensive course of action in a large commercial or public building. The health assessment should include:

1) Potential for exposure. An assessment of both the quantity and profile of fungi present in bulk and air samples.
2) Diagnosis of exposure. A symptom survey of building occupants (see below, investigative plan) to determine if there are health complaints consistent with mold exposure.
3) Verification of exposure. An exposure assessment (*e.g.* a urine work-up of mold metabolites and/or an immuno-assay for IgE specific to molds present) is needed to establish a link between the presence of molds with potential health effects and building occupant's health complaints.

Recommendations

Moisture management. Indoor mold problems are ultimately moisture management problems. Removing the moisture source is the minimum public health recommendation in any case of indoor fungal infestation.

Affected surfaces should be disinfected or replaced. Household surfaces and items contaminated with mold should be disinfected or discarded. Care should be taken to ensure that items not discarded are not sources of re-infestation. Affected items, including clothing, furniture, and plastic containers, may permanently retain unpleasant MVOC odors, even following disinfection.

Medical diagnosis. Strict criteria should be established for the diagnosis of mold exposure, by qualified health professionals, in order to make accurate health

recommendations and to avoid unnecessary building remedies. These criteria should include evidence of exposure ("abundant" allergen in indoor air; serum IgE to same allergen), and symptoms of allergy following clinical exposure to the allergen (Reed, 1985).

Formulation of an investigative plan for large buildings. A questionnaire of building occupants (Ammann, 1999; Cooley, *et al*. 1998) is useful in differentiating complaint from non-complaint areas. The questionnaire can help identify a mold problem and determine what areas or rooms are responsible for the problem. The question categories recommended by Cooley, *et al.* are:

- Record of the type of symptoms reported.
- The pattern of symptom expression: when do they start, end, and when are they worst?
- Does the complainant have pre-existing symptoms, such as allergies or asthma?
- Are there nuisance complaints, or reports of discomfort to noise, temperature, or odors?
- Are most of the complaints confined to occupants of specific rooms?
- A repeat questionnaire following building remediation can help assess the success of the cleanup.

Public health education. It is important that school and health officials be able to communicate the effects of indoor mold exposure to the public. The key messages that should be conveyed are: the ubiquitous nature of fungi in the environment, the relative community of fungi found indoors compared to outdoors, the relative risk posed by the molds detected, and the range of options available to confront the problem. Health education resources, for example *Tools for Schools* (USEPA, 2002) are becoming widely available as aids in preparing materials for distribution to the public.

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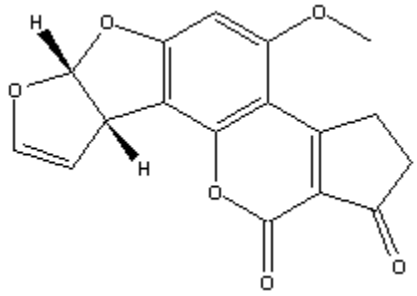
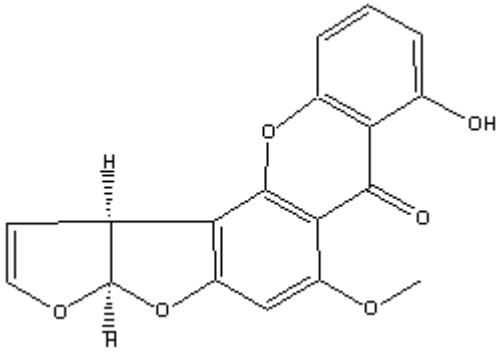
Figure 1. Chemical structures of selected mycotoxins.

Aflatoxin B1



Sterigmatocystin



Trichothecene T-2 toxin