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The Role of *Stachybotrys* Mycotoxins in Building-Related Illness

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Recently there has been increased attention among both the public and health professionals regarding the potential role of mycotoxins, primarily from fungi of the genus *Stachybotrys*, as etiologic agents related to illness among persons exposed in the indoor (nonindustrial) environment. Recommendations for the remediation of buildings are being made based in part on reported health effects believed to be due to mycotoxins. A search of NIOSHTIC (a literature database maintained by the National Institute for Occupational Safety and Health) and MEDLINE (from 1965 to present) for literature related to fungi, mycotoxins, and the indoor environment was conducted. References from relevant articles also were reviewed. This strategy yielded a total of 13 articles. Important issues concerning exposure assessment and case definitions are inadequately addressed in the literature reviewed, making it difficult to implicate mycotoxins as a cause of building-related illness. The literature review indicates that currently there is inadequate evidence supporting a causal relationship between symptoms or illness among building occupants and exposure to mycotoxins. Research involving the identification and isolation of specific fungal toxins in the environment and in humans is needed before a more definitive link between health outcomes and mycotoxins can be made.

Keywords: building-related illness, fungi, indoor, mycotoxins, *Stachybotrys*

Building-related illnesses include a variety of recognized disease entities that are characterized by objective clinical findings related to specific exposures in the indoor environment.[1] A number of microorganisms, including many species of bacteria and fungi, are well established as potential etiologic agents of building-related illnesses.[2] Recently there has been increased attention among both the public and health professionals regarding the potential role of mycotoxins as etiologic agents related to illness among persons exposed in the indoor environment. That type of concern has led to recommendations for the remediation of buildings based in part on the reported association of various health effects with exposure to mycotoxins.[3] The goal of this article is to clarify the available information concerning mycotoxins and their potential health effects in the indoor environment.

BACKGROUND

Fungus is a term used to encompass different plants of the Kingdom Fungi, which has five main phyla: Chytridiomycota, Zygomycota, Ascomycota, Basiodiomycota, and Deuteromycota. They are characterized by the absence of chlorophyll; examples include mushrooms, toadstools, yeasts, molds, mildews, smuts, and rusts.[4] Fungi comprise 25% of the biomass of earth;[5] therefore, human exposure to fungi is ubiquitous. Saprophytic fungi (i.e., those utilizing nonliving organic matter as a food source) inhabit soil, vegetation, water, or any reservoir that can provide an ample supply of nutrients. Fungi are thought to produce adverse health effects by several different mechanisms, some better understood than others, including (1) immunologic hypersensitivity to the fungus, (2) fungal infection (i.e., mycosis), and (3) toxic reactions.

Toxic reactions such as organic dust toxic syndrome have been reported among workers in a variety of agricultural and industrial settings and are thought to involve inhalation exposure to a poorly defined mixture of substances, possibly including fungi.[6–10] Mycotoxicosis specifically refers to a reaction to toxins produced by the fungus.[11] In addition, fungi can release volatile organic compounds (VOCs). More than 500 VOCs have been identified from a variety of fungi, the most common being ethanol.[5]

Many molds can produce mycotoxins,[5] which are nonvolatile fungal metabolites with the potential to cause toxic reactions.[5,12,13] There are more than 300 known mycotoxins.[14] Mycotoxin production is poorly understood, but thought to be affected by a variety of conditions such as fungal strain, genetic susceptibility of the host plant or commodity, moisture content, temperature, aeration, microbial population, and stress factors.[15] The tricothecenes are a commonly occurring category of mycotoxins. There are more than 150 tricothecenes produced by a variety of fungi,[16] including *Fusarium*, *Trichoderma*, *Stachybotrys*, *Cephalosprium*, and *Tricothecium*. All have a double bond at C-9 and C-10 and an epoxy ring at C-12,13, and are thus called 12,13-epoxy-tricothecenes. The tricothecenes are grouped into four classifications (A, B, C, and D) based on chemical properties and the fungi that produce them.[13] Their primary mechanism of action is inhibition of protein synthesis.[12,13]

Fungi of the genus *Stachybotrys* are found worldwide[17] and have been isolated from soil and a wide variety of substances rich in cellulose, such as hay, wood pulp, cotton, grains, various dead plant components, paper, and glue in book bindings.[18] Buildings where *Stachybotrys* growth problems are reported have typically experienced chronic water damage (e.g., due to leaking roofs or plumbing, floods, air conditioner condensation, etc.) and were kept at a temperature conducive to the growth of *Stachybotrys* (temperature range for optimal growth is 22.2–27.8°C). *Stachybotrys chartarum* (synonyms *atra*, *alternans*) is one of many fungi capable of producing trichothecene mycotoxins (examples of different tricothecenes include roridin, verrucarin, and the satratoxins) under certain environmental conditions. Tricothecenes have been found in the aerosolized spores of this fungus, indicating the potential for inhalation exposure to these compounds.[19]

METHODS FOR LITERATURE SEARCH

This review focuses on human illness reported to be related to exposure to fungal toxins (mycotoxins) in the indoor (nonindustrial) environment. With that goal in mind, the authors performed a literature search using the broadest terms available to generate the largest number of articles. The medical subject heading terms "mycotoxins" and/or "fungi" were crossed with "indoor air pollution" and/or "sick building syndrome" (the terms "indoor environment" and "indoor air" both fall under the medical subject heading "indoor air pollution"). A separate search was done on *Stachybotrys* because it is the fungus that has received the most attention in this area. These searches were performed in MEDLINE from 1965 to present and NIOSHTIC (a literature database maintained by the National Institute for Occupational Safety and Health). This strategy yielded more than 150 articles from which relevant articles were selected. Review articles and letters to the editor were not included. In addition to this strategy, the authors also reviewed relevant references cited in literature addressing this topic. Of note, the search strategy was not designed to provide for review of the extensive literature concerning laboratory studies of mycotoxins. A discussion provides a brief overview of related literature that adds perspective to the issue of potential health effects related to mycotoxin exposure.

RESULTS OF LITERATURE REVIEW

The search strategy yielded a total of 13 relevant articles. All but one article involve *Stachybotrys*; 6 of the articles describe the same investigation of pulmonary hemorrhage in infants.

One widely referenced investigation reports an outbreak of potential stachybotryotoxicosis secondary to mold contamination in a home.[20] In that case report, five occupants of a house reported a variety of symptoms, including cold and flu symptoms; sore throats; diarrhea; headaches; dermatitis; patches of hair loss; and fatigue. Medical investigations, not well described and apparently not conducted by the reporting authors, reportedly did not reveal any identifiable causes. In the home, a cold air return duct and an area of wood fiber board were contaminated with *Stachybotrys*. When the mold was cleaned up, the family members' symptoms were reported to resolve. Extracts from the molds were injected into experimental animals. The animals died within 24 hours, and autopsy revealed hemorrhagic necrosis of the internal organs, similar to that reported in veterinary cases of stachybotryotoxicosis. The authors inferred that mycotoxins were responsible for the symptoms of the occupants.

In 1996, Johanning et al. reported findings from a study of workers exposed to *Stachybotrys* in a water-damaged office environment.[21] The affected persons were 39 females and 14 males who worked in the building. The comparison group consisted of 11 females and 10 males who had no exposure to the problem building. Health complaints were assessed by means of a questionnaire. Affected persons had significantly more lower respiratory, dermatological, eye, constitutional (i.e., low-grade fever, tender/swollen lymph nodes, and myalgia), and chronic fatigue symptoms. Of 24 white blood cell, lymphocyte, and immunoglobulin tests, 3 showed statistically significant differences between exposed and comparison groups, or between exposure locations within the problem building. However, these differences are not likely to be clinically significant. Air and bulk samples from the problem building were positive for *Stachybotrys*, *Penicillium*, *Cladosporium*, and *Aspergillus*, but no environmental assessment was performed for the comparison group.

In 1998, Hodgson et al. reported a study of employees of two buildings with histories of water incursions.[22] The authors stated that more symptoms were reported among occupants of the problem building compared to occupants of comparison buildings. Information concerning response rate, demographic factors, smoking status, or job duties between the occupants of the exposed and comparison buildings were not reported; other studies have shown that these factors can influence the prevalence of reported symptoms among building occupants.[23,24] The authors reported that 17 of 47 self-selected individuals had some clinical evidence of pulmonary disease; similar testing to detect pulmonary disease was not conducted among "unexposed" workers. Exposure monitoring in the problem buildings revealed lower concentrations of fungi indoors compared with outdoors, with differences in the types of fungi detected (*Aspergillus versicolor* and *Stachybotrys chartarum* were detected indoors but not outdoors). Other than a casual observation, assessment for fungi in the comparison buildings was not described. Satratoxins were isolated from *Stachybotrys chartarum* contaminated ceiling tiles, but not from air samples.

Employees with two or more symptoms in the problem building did not have higher levels of antibodies to fungi identified in the building than did controls.

Sudakin reports on an investigation that was performed in 1996 in an office building in the Pacific Northwest where there had been health complaints.[25] The office building described had a history of maintenance problems and moisture incursion. The environmental evaluation found various bacteria and fungi present in air, bulk, and surface samples. The epidemiologic study, consisting of interviews and questionnaire administration, revealed that the most commonly reported symptoms were fatigue, headache, difficulty concentrating, and sinus congestion; no evidence of objective illness among building occupants was reported.

Auger et al. reported several cases of chronic fatigue and recurrent respiratory infections in persons living in homes where certain toxigenic fungi such as *Trichoderma*, *Penicillium*, and *Phoma* were found.[26] The authors propose that research concerning mycotoxins is important in the attempts to explain indoor environmental quality problems; no data (other than anecdotal reports) are provided in that brief communication.

In November 1994, the Centers for Disease Control and Prevention (CDC), private physicians, and public health officials in Cleveland, Ohio, reported a cluster of eight cases of acute pulmonary hemorrhage/hemosiderosis that had occurred during January 1993–November 1994 among infants in one area of the city.[27] Two additional cases were identified in December 1994.[28] A case-control study was performed in which past water damage to these homes was assessed by questionnaire.[29] This study revealed an association between acute pulmonary hemorrhage/hemosiderosis and parental reports of water-damage at home in the 6 months prior to the hemorrhage in the affected infant (odds ratio (OR) = 16.25; 95% confidence interval (CI) = 2.55 to infinity). In a follow-up investigation, air sampling was done to assess potential exposures in the homes of cases and controls by using an "aggressive sampling strategy (performed by purposely stirring up potential contaminants in the dwelling, for example, by vacuuming and banging on the air ducts).[30] *S. chartarum* was detected more frequently and in greater quantity in the homes of case-infants compared with those of controls.[28,31] The case-infants were also more likely to be black, male, live with a relative who coughed blood, and be exposed to tobacco smoke.[28] None of the cases had been breast fed, but 37% of the controls had; the cases also had lower birth weight.[28] The CDC has recently released the detailed findings of both internal[32] and external[33] reviews, which concluded that a possible association between pulmonary hemorrhage/hemosiderosis in infants and exposure to molds, specifically *Stachybotrys*, was not proven.[34]

Two recent case reports have been published concerning pulmonary hemorrhage in children. In the first,[35] an infant presented to an emergency department in respiratory distress and shock and was found to have pulmonary hemorrhage after the placement of an endotracheal tube. The infant recovered after appropriate supportive care. The infant's home was evaluated soon after he became ill. *Stachybotrys* spores, as well as spores of other fungal species, were found in air and surface samples from the infant's bedroom. In addition, a portion of the contaminated ceiling in the water-damaged closet of the bedroom was evaluated for the presence of mycotoxins; several tricothecenes, including specific types of roridin and satratoxin, were found.

In the second recent case report,[36] *Stachybotrys* was isolated from the bronchoalveolar lavage (BAL) fluid of a 7-year-old boy. This boy had had cough, fatigue, and recurrent pneumonia since age 5. At the time of the reported medical evaluation, findings included a left lower lobe consolidation, anemia, and a moderate amount of hemosiderin-laden macrophages in the BAL. Cultures of BAL fluid on Sabouraud-dextrose agar grew *Stachybotrys chartarum*. Much relevant clinical information that would be expected to be presented in this type of medical evaluation (such as evaluation of the etiology of the left lower lobe pneumonia) was omitted from the report. Surface cultures from the bronchoscopy suite and mycology lab were negative for *Stachybotrys*, but were positive for *Stachybotrys* in samples taken from the home, which had suffered extensive water damage. The patient was relocated to a relative's home (which was not evaluated for the presence of *Stachybotrys*) while his home was remediated. His symptoms reportedly resolved within 1 month after removal from the home.

DISCUSSION

Discussion of Reviewed Literature

In the literature summarized here, important issues need to be addressed involving either the clinical illnesses reported or the documentation of exposure to a potential causative agent(s), or both.

As a group, the articles reviewed present a wide spectrum of health effects attributed to mycotoxins. Case definitions are generally absent or poorly defined. For example, among frequently cited evaluations, Croft et al.[20] described five individuals with a variety of nonspecific symptoms, with an unclear description of medical evaluations performed. Hodgson et al.[22] used undefined clinical diagnoses and epidemiological case definitions, making interpretation of the reported symptoms and pulmonary function test results difficult. Johanning et al.[21] did not define cases, but rather compared employees of a problem building with those of a nonproblem building, finding an excess of nonspecific symptoms in the study population.

The issue of exposure characterization in the reviewed literature is also problematic. Due to a variety of reasons, including incomplete understanding of bioaerosols, our technical inability to document bioaerosol exposures that may be occurring, and also possibly lack of clinically relevant exposures among the study subjects, the reviewed literature presents inadequate evidence of actual exposure to fungi and/or mycotoxins in the environments studied. For example, the case-control study of pulmonary hemorrhage/hemosiderosis[28,29,31] did not include a systematic evaluation of water damage in the evaluated homes, and the air sampling performed several months after onset of illness (using aggressive sampling techniques) is unlikely to be representative of actual exposures to fungi in those homes. The articles by Johanning et al.[21] and Hodgson et al.[22] reported antibody testing, which potentially could be used as a measure of fungal (not necessarily mycotoxin) exposure; these tests revealed no evidence of increased exposure to any specific fungus among problem building occupants compared with the comparison group. Several of the studies have detected mycotoxins in samples from walls, ceiling tiles, and air ducts.[20,22,30] Identification of mycotoxin on a wall or in an air duct demonstrates only a potential for exposure and does not alone provide evidence of exposure, much less evidence linking reported symptoms to the fungi or fungal products.

Discussion of Related Literature

Human disease thought to be caused by the tricothecene mycotoxins was first reported in Russia. Between 1942 and 1947, there were epidemics of alimentary toxic aleukia (ATA), which was often

fatal and characterized by vomiting, skin inflammation, hemorrhaging of the gastrointestinal tract and mucous membranes, immunosuppression, and pancytopenia.[12,37–40] ATA was attributed to eating overwintered grain contaminated by *Fusarium* species, and T-2 toxin has been implicated as the causative agent.[37,38,40] The symptoms of ATA usually occurred after eating 2 kg of grain, and poor nutritional status appeared to be a risk factor.[37]

Stachybotryotoxicosis (mycotoxicosis produced by *Stachybotrys*) in humans has been described in case reports from eastern Europe and Russia from the 1940s through the 1970s. Russian investigators reported stachybotryotoxicosis in humans who had contact with straw or hay in areas where stachybotryotoxicosis was enzootic in horses.[41] The affected individuals reported in that study developed severe dermatitis, chest pain, sore throat, bloody rhinitis, cough, and (in some) leukopenia.[17,37,41] In experimental human studies, mold placed on the skin reproduced the clinical syndrome described above.[18,41] An outbreak of stachybotryotoxicosis in 1977 involved 25 workers who loaded and supplied moldy hay.[42] Symptoms were manifested within 24 hours of exposure, and consisted of dyspnea, sore throat, bloody nose or bloody nasal discharge, and burning and watering of the eyes. The affected workers had hyperemic, swollen, crusted skin on the face, and dermatitis in the groin and buttocks. Recovery occurred within 1 week after cessation of exposure. Skin scrapings and nasal and throat swabs grew *Stachybotrys chartarum*. Specimens from the straw also grew *Stachybotrys chartarum*. Other cases of stachybotryotoxicosis related to occupational exposure have been reported to have occurred among workers at farms; cottonseed oil mills; grain elevators and facilities used for reprocessing moldy grain; malt grain processing facilities; textile mills using plant fibers; and bindertwine factories.[35] The persons affected were reported to recover rapidly after cessation of workplace exposure, and reexposure resulted in more serious sequellae.[37] Compared to indoor, nonindustrial environments, the environments described above likely involved considerable differences in the extent of bioaerosol exposure of affected workers.

In 1987 an outbreak of gastrointestinal illness related to the consumption of bread made from wheat contaminated with *Aspergillus* and *Fusarium* occurred in India.[43] The symptoms resolved on cessation of consumption. Several trichothecenes, including deoxynivalenol, nivalenol, and acetyldeoxynivalenol were isolated from wheat samples. A similar illness was reported after consumption of moldy rice in China in the early 1990s.[44] T-2 toxin was reported to be the etiologic agent in that outbreak.

Veterinary stachybotryotoxicosis has been reported to affect both large and small animals. In the early 1900s in Russia and Europe, ingestion of mold-contaminated feeds (hay, grains, etc.) was thought to be responsible for disease manifested in animals by stomatitis, hemorrhage and necrosis of the gastrointestinal tract, leukopenia, and immunosuppression.[12,17,38,45] Veterinary dermal manifestations are characterized by ulcerations, hyperemia, edema, and tissue necrosis of varying severity. An atypical form has been reported to cause loss of reflexes, hyperirritability, loss of vision, and inability to move about.[37] One investigation has reported that the severity of stachybotryotoxicosis was dose-dependent and that trichothecene mycotoxins elaborated by the fungi were the responsible agents.[41]

In summary, review of this related literature reveals evidence of clinical illness (in humans and animals) caused by ingestion of significant quantities of mycotoxin-contaminated foodstuffs. Illness associated with less well-defined (likely inhalation and/or dermatologic) bioaerosol exposures in agricultural or industrial environments has also been reported. However, the relevance of these findings to the indoor (nonindustrial) environment is unclear.

CONCLUSIONS

This review of the literature indicates that there is inadequate evidence to support the conclusion that exposure to mycotoxins in the indoor (nonindustrial) environment is causally related to symptoms or illness among building occupants. Suspect building-related illnesses in the nonindustrial environment should continue to be evaluated using the appropriate environmental, medical, and epidemiologic tools. Research involving the identification and isolation of specific fungal toxins in the environment and in humans is needed before a more definitive link between health outcomes and mycotoxins can be made. To support hypotheses regarding potential adverse health consequences of mycotoxin exposure in the nonindustrial environment, objective measures of adverse health effects must be associated with some measure of mycotoxin exposure, and comparisons must be made with appropriate control populations; to date, such evidence has not been forthcoming. Remediation of fungus-contaminated environments is warranted to reduce the likelihood of known health effects related to fungal exposure, regardless of the potential for effects due to mycotoxins. Currently, there is inadequate evidence to support recommendations for greater urgency in cases where mycotoxin-producing fungi have been isolated.

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