MOLD AS TOXIN

by

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The clinical effects associated with mold exposure can be divided into three categories — allergic effects, infectious effects and potential toxicologic effects. Allergic effects are manifest as primarily respiratory allergies. These are the disorders of hay fever or upper respiratory allergies, asthma and, in very rare cases, hypersensitivity pneumonitis that are most commonly discussed in scientific and medical literature.[1] Although allergic effects can occur from molds found both in the indoor and outdoor environment, they are more frequently associated with molds present in the outdoors, given the high concentrations found in ambient air.

Certain molds can produce active infection.[2] These infections are observed in immunocompromised individuals (e.g., patients on immunosuppressant medications or those with immunosuppressant diseases such as AIDS) or in highly sensitive individuals. In such cases, the mold exposure may lead to infection in the lungs, sinuses or even generalized throughout the body.

Mold infections are endemic in certain parts of the country. For example, there is a mold–related infection of the lung (San Joaquin Valley Fever) occurring regularly in the southwestern United States because of high concentrations of coccidioidomycetes in the outdoor environment. Infections associated with mold exposure are distinctive in their manifestations leaving individuals quite ill. The infections are treated with appropriate antifungal agents.

Recently, there has been some concern expressed about the third category of mold effects — the toxicity of compounds produced by certain mold species. This concern is the focus of this article.

Mycotoxins

Mycotoxins are large complex molecules produced by almost all fungi. There are thousands of mycotoxins produced by molds to which all of us are exposed everyday whether from indoor or outdoor sources. A single mold can produce several to a hundred mycotoxins. Several different molds may produce the same mycotoxin. The most common mycotoxin–producing genera are *Aspergillus, Penicillium, Alternaria, Fusarium* and *Stachybotrys.*[3–8]

The molds that produce mycotoxins are ubiquitous in our environment and are commonly detected in agricultural products, in soil, on plants, and in dusts present in commercial and residential buildings. While exposure to very high doses can adversely impact a variety of metabolic processes in animals and humans, there is no strong scientific support in the current literature to suggest that adverse health effects are caused by low–dose inhalation exposures potentially encountered in commercial and residential buildings.

Production of mycotoxins by any fungal species is highly dependent on growth conditions, e.g., nutrient availability, temperature, and humidity. Often these conditions are ideal when the presence of mycotoxins in environmental samples is investigated in a test laboratory. Such conditions are rarely present in the indoor environments of commercial or residential buildings. The presence of mold in homes or commercial buildings is not surprising given the ubiquitous nature of fungi. It must be emphasized that even though a mycotoxin–producing fungus may be present within a building, it does not mean that mycotoxins also are present in indoor ambient air.

Excluding poisonous mushrooms, 350 to 400 fungal products have been identified as being potentially toxic to animals or humans. From an agricultural perspective, the most classic example of a harmful mycotoxin is aflatoxin, which is produced by several species of *Aspergillus.*[9,10] The primary route of exposure is through ingestion of contaminated foods, e.g., peanuts, peas, bread, rice, various grains, eggs, and milk. Because this mycotoxin is a potent liver toxin and known carcinogen, it has been extensively studied.

Another highly studied mycotoxin is ochratoxin A, one among 20 different compounds produced by more than a dozen species of *Penicillium* and some species of *Aspergillus.* This mycotoxin has been shown to cause kidney damage following ingestion of large

quantities, and to be harmful to fetuses when tested in animals. The *Penicillium* genus also produces penicillin, a very beneficial mycotoxin. Despite the common view that *Alternaria* is a benign mold, different species of this mold are known to produce nearly 125 compounds of which one–quarter are toxic to animals and cell culture systems.

Trichothecenes are a group of over 100 mycotoxins that are produced within several fungal genera: *Fusarium, Thrichothecium, Cylindrocarpon, Myrothecium, Trichoderma, Verticinosporum, Cephalosporium, Memnoniella* and *Stachybotrys*.[11,12] These mycotoxins are most prevalent as contaminants of grain. Trichothecenes also have been isolated from various water damaged indoor environments. While *Fusarium* is believed to be the most important producer of trichothecenes, much public and media attention has focused on *Stachybotrys* for little good scientific reason.

Stachybotryotoxicoses was first identified as a fatal hemorrhagic disease in horses in 1931.[13,14] The disease was observed in Eastern Europe and Russia resulting from the presence of *Stachybotrys* and other fungi in moldy straw. Farm workers handling the moldy straw also reported symptoms of dermatitis, bloody rhinitis, cough and severe respiratory tract irritation. More recently, occupational stachybotryotoxicoses has been identified in farm workers, cottonseed oil plant workers, and various facilities where grain is processed or where plant material is used.[15] In these occupational settings, exposure is to high concentrations and symptoms include chest and upper respiratory irritation, fever, dermatitis and, in some rare cases, leukopenia.

It was reported recently that pulmonary hemosiderosis and hemorrhage in infants was associated with exposure to *Stachybotrys*.[16–18] However, subsequent review by the Center for Disease Control criticized the studies as lacking scientific rigor and rejected the authors' conclusion about an association of the disease with *Stachybotrys* exposure.[15]

Problems Assessing Mycotoxin Toxicity

Because the primary route of mycotoxin exposure for humans and animals is ingestion, the preponderance of research has focused on human and animal ingestion studies.[20–23] Thus, levels of mycotoxins present in human and animal foods are fairly well documented. For example, fumonisins B1 was measured in various corn products in ranges of 134 to 3,057 ppb.[24] Contamination of grain by aflatoxin can range from 1 ppb to 12,000 ppb.[25] Additionally, animal and human ingestion studies have identified no effect levels associated with major agricultural contaminants.[26–28] Using these no effect levels, tolerable daily intake levels have been developed for these mycotoxins in foods.[29] By contrast, there have been limited investigations of mycotoxins in indoor ambient air.

Several problems need to be resolved before we can begin gathering evidence of an association between inhalation exposure to mycotoxins and adverse health outcomes. One problem is the fact that there is insufficient evidence with which one can evaluate the relevance of mycotoxins produced in a laboratory culture setting as predictors of those that might be present in indoor ambient air. Data supporting comparability are extremely limited. A recent study has revealed that when comparing strains of mycotoxins present in pure cultures and spores, there is only a 60 percent match.[30]

Some fungal species have more consistent mycotoxin production than others. For example, of the molds analyzed, *Aspergillus fumagatus, Penicillium polonicum* and *Penicillium crustosum* exhibit consistent results between pure culture and spore extracts. *Aspergillus niger* and *Paecilomyces variotii* reveal inconsistent results between the two extracts, i.e., strains identified in pure culture were different from those identified in spores.

There is currently no research on differences that might exist with *Stachybotrys* species, today's popular mold concern. It is not possible to assume that mycotoxins detected in laboratory cultures would be present in spores or on particulates in ambient air simply because a particular fungal genus or species has been detected. We currently have no reliable analytical methods with which ambient air samples can be evaluated for the presence of mycotoxins.

A related problem is lack of knowledge about the potential quantity of mycotoxin that may be produced by spores present in ambient air. Fischer et al.[31] were able to estimate the quantity of two mycotoxins extracted from a sample of *Aspergillus fumigatus* in ng/m³ that was associated with an airborne density of 10 million colony forming units/m³. In samples where the spore density was an order of magnitude lower, mycotoxins could not be detected. Such high levels of mold are only approached in occupational settings.[32–35] Given that indoor mold concentrations

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detected in residential and commercial building are many orders of magnitude below occupational levels, it is highly unlikely that any mycotoxins potentially present would be in sufficient quantity to result in adverse health outcomes.

To put this finding into perspective, Burge developed a model whereby the potential accumulation of mold toxin in the lung could be estimated based on indoor ambient air concentrations.[36] Making assumptions about spore content and human inhalation dose frequency and duration, her results suggest that it would require 1,100 days with inhalation of 100 spores/m^3 to accumulate 1 ng of toxin in the lung. We currently have no information with which to determine whether an accumulation of 1 ng of toxic would be toxic to humans.

Although we can identify adverse health outcomes associated with ingestion of selected mycotoxins, the data about such outcomes associated with inhalation of mold are lacking.[37] The current literature does not provide compelling evidence that exposure at levels expected in most mold–contaminated indoor environments are likely to result in measurable health effects. Because of the attention given to exposure to *Stachybotrys*, there has been some research on mycotoxins produced by this genus. The results are inconclusive.

For example, investigators have found that the type of toxin observed can vary depending upon the building materials and conditions under which the mold grows.[38] Other studies indicate that the type of toxin present in environmental samples also differs even for a single species.[39,40] Also, potency varies among the various mycotoxins produced by this mold.[41] Currently, adverse effects have only been identified in animal studies and cell culture systems.[42–44] The doses used in the animal studies are substantially higher than could be expected in contaminated indoor ambient air. The results of the cell culture systems also are difficult to interpret because the relationship of the findings to human toxicity is unknown.

Although there have been several human studies attempting to identify associations between exposure to mold and adverse health outcomes, they are generally flawed in study design.[45] Often there are no identified control groups, or the case and control groups are not matched with sufficient care to allow ruling out confounding factors. Exposure levels are rarely, if ever, documented. Verification of self–reported health complaints is not made. Finally, the symptoms reported are nonspecific in nature. These flaws prevent drawing any conclusions about cause and effect relationships.

Symptoms are frequently over–reported when people believe their health has been threatened. A review of the scientific literature indicates that self–reported symptoms are unreliable when perceived hazards are the basis for complaints. Numerous authors have studied the unreliability of self–reported symptoms, particularly following perceived toxic exposures.[46–48] The most important reason given for this unreliability is the well–known phenomenon of reporting bias.

The term "reporting bias" is a standard epidemiological term, and not meant as a pejorative. Rather, it refers to the normal human tendency to connect physical phenomenon with unrelated causes, particularly when the perceived cause is viewed as a health threat. For example, individuals concerned about the quality of indoor or workplace air tend to report a wide range of health complaints. These increased complaints, unassociated with verified, actual disease, emphasize the intensity of the belief about a toxic risk held by the reporting individuals.

Additionally, it is important to determine whether symptoms are the result of an emotional response to a perceived mold toxicity or a real physiological response directly related to mold exposure. It is not possible to determine a cause from symptoms alone because physiological, psychological or social influences can produce identical symptoms.[49] The recognition of the origination of complaints, acknowledgment of reporting bias in patients' reporting of symptoms, as well as the public's fear of mold exposure are all important factors when evaluating human mold studies.

The symptoms most frequently reported in human studies of mold exposure are nonspecific and include fatigue, muscle pain, rashes, upper respiratory irritation and infections, dry and itchy eyes, etc. Yet, these same symptoms are experienced by the general population unrelated to mold exposure. As many as 20 percent of adults in the general population report significant fatigue and 30 percent report joint pain.[50] Barsky and Borus report that from 86 to 95 percent of the general population has at least one nonspecific symptom in a given two– to four–week period. Typically an adult has these types of symptoms every four to six days. Non–specific symptoms, unrelated to documented physiological, chemical or biological exposures are commonly regarded by the scientific/medical community as functional somatic syndromes.[51] They lack characteristic clinical presentations or distinct symptom complexes consistent with specific diseases.

Summary

Despite the considerable attention given by the public and media to exposure to molds and their mycotoxins, the literature indicates that such exposures are rather minor at potential indoor exposure concentrations. There is no doubt that mold exposure can lead to allergic reactions and infections for some specific populations, but there is no evidence that mycotoxins or mold present in indoor ambient air can lead to brain damage, cancer, chronic fatigue syndrome, fibromyalgia or a generalized group of nonspecific symptoms. The diversity among mold genera in the types and potency of mycotoxins produced, the inability to quantify mycotoxin levels in indoor ambient air, and the flaws in epidemiological studies all contribute to a lack of evidence for a cause–effect relationship between exposure to mycotoxins in indoor ambient air and clearly defined health outcomes.

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