MYCOTOXINS OF ASPERGILLI; EXPOSURE AND HEALTH EFFECTS

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1. ABSTRACT

Mycotoxins derived from Aspergilli can be encountered both in domestic and occupational environments, and the exposure may lead to severe health hazards. Several Aspergillus species are associated with mycotoxin production: A. ochraceus with ochratoxin A, A. fumigatus with fumitremorgins, gliotoxin and verruculogen, A. versicolor with sterigmatocystin, and A. flavus and A. parasiticus with aflatoxins. Sterigmatocystin may also be produced by A. flavus, A. nidulans, A. rugulosus, and A. unguis. Exposure to mycotoxin may occur via enteric, inhalation or direct contact to skin and mucosa. Acute and chronic disorders, irritation, systemic reactions and even cancer may develop after the exposure to these toxins. Mycotoxins act as immunosupressants which may be in association with an increased prevalence of repeated infections found among the inhabitants of buildings with moisture problems.

2. INTRODUCTION

Mycotoxins are "natural products of fungi that evoke a toxic response when introduced in low concentrations to higher vertebrates by a natural route" (1). Mycotoxins are able to cause acute and chronic health effects in humans and animals that cannot be attributed to fungal infection or allergic reactions (2). The over 400 known mycotoxins are all complex organic compounds, most with molecular weights between 200 to 800 kD (3), and are not volatile at ambient temperatures.

All known mycotoxins are fungal secondary metabolites, which means that mycotoxin production need not be correlated with the growth and proliferation of the producing species. However, mycotoxin production is determined by the factors like induction, end-product inhibition, catabolite repression and phosphate regulation (4, 5). Therefore, even though some fungi can grow on almost any natural or synthetic materials, mycotoxin production occurs preferentially on materials that both allow these fungi to grow and provide the conditions for mycotoxin production.

3. PRODUCTION OF MYCOTOXINS

The production of mycotoxins has been long established in fungal isolates derived from agricultural environments. There is abundant data about the fungal species that are capable of producing each known mycotoxin, and about the growth media and conditions that induce production (6-9). It is known that the same subspecies might include both strains that produce mycotoxins and strains that lack this ability (4, 5). It has also been established that many of the known mycotoxin-producers are frequent colonizers in indoor environments (10-12). However, only very little is known about the presence of mycotoxins in indoor environments. In recent years the presence of a few selected mycotoxins have been verified in crude building materials contaminated with fungi (8, 13-17). In fact, most mycotoxins have yet to be extracted from either air samples or bulk materials derived from indoor environments.

Risk-assessment on the inhalation of mycotoxins cannot be made from the analysis of bulk samples of construction materials, in spite of that dose-response of airborne mycotoxin to humans is known. However, as most of the fungi isolated from damp indoor environments can elicit allergenic reactions in addition to being toxic (18), it seems that care should be exercised when moisture-damaged sites are torn down or renovated. Sterigmatocystin is an IARC class 2B carcinogen (9) and also has immunotoxic properties (7). In a recent study (19), Aspergillus versicolor and Stachybotrys chartarum were implicated as causes for building associated pulmonary disease in three adjacent office buildings. A. versicolor was found to be the predominant microbe in the indoor air while S. chartarum was isolated from bulk samples containing satratoxins (2-5 µg/g). Unfortunately, sterigmatocystin
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could not be isolated in that study, due to peak-interference in HPLC-UV. Previous to this study, satratoxins have been found in building materials by Johanning et al. (16 µg/g), Croft et al. (not quantified) and Anderson et al. (17 µg/g) (8,13,20). Recently, we extracted sterigmatocystin from water-damaged building materials contaminated by fungi (21).

4. MYCOTOXIN ANALYSES

Myological analyses of air and crude building materials are routinely performed in environmental laboratories to evaluate the extent and spread of damage in buildings with moisture-problems, and to assess the risk to residents. The isolation of toxigenic species does not substantiate the presence of mycotoxins. Even though strains of fungi probably responsible for producing the mycotoxin are not recovered in culture, the isolation of related microbes and the demonstration of mycotoxins in bulk materials should be considered significant (22). In this context, it is essential that the sources of mycotoxic fungal contamination should be removed and necessary precautions should be taken to prevent exposure to potentially harmful aerosolized particles during renovation of buildings with moisture-damage.

As the techniques to collect and analyze airborne propagules improve, mycotoxins can be analyzed more precisely from indoor air, which may enable us to assess the possible health consequences of mycotoxins to residents of water-damaged buildings. In future, the ubiquitous nature of mycotoxins in indoor environments can be established with added techniques to study more mycotoxins and their effects. There are specific techniques available to analyze most fungi present in environmental samples. Identifying the fungi responsible for producing mycotoxins in building materials will require using different techniques in combination with the enrichment and purification of fungi from building materials, and extracting toxins from the isolates for mycotoxin analyses.

5. ASPERGILLUS AND MYCOTOXINS

Several Aspergillus species are associated with mycotoxin production: A. ochraceus Wilhelm (ochratoxin A), A. fumigatus Fresenius (fumitremorgins, gliotoxin, verruculogen), A. versicolor (Vuillemin) Tiraboschi (sterigmatocystin), A. flavus Link ( aflatoxins), and A. parasiticus Speare (aflatoxins) (2, 23-25). Sterigmatocystin may also be produced by A. flavus, A. nidulans, A. rugulosus, and A. unguis (6, 7).

Aflatoxins (AFs) are a group of heterocyclic, oxygen-containing mycotoxins that possess the bisdifulano ring system common to aflatoxin-precursors including sterigmatocystin (26). AFs are produced by certain strains of A. flavus and A. parasiticus via a biosynthesis route including sterigmatocystin (AFB1, AFG1) or dihydrosterigmatocystin (AFB2, AFG2) as the immediate precursor (26). A. versicolor lacks the enzymatic pathway necessary to convert sterigmatocystin and dihydrosterigmatocystin to the corresponding AFs. Therefore, strains of A. versicolor are known to emit sterigmatocystin in large quantities (7, 23).

Other potent mycotoxins characteristic to Aspergillus spp. are the ochratoxins, particularly ochratoxin A. Citrinine has also been reported to occur in Aspergillus spp., some of which may be from misidentified strains of Penicillium citrinum, which is a potent producer of this mycotoxin (7, 23).

Production of AFs is known to coincide with the occurrence of A. flavus and A. parasiticus in damp, warm conditions (7, 27). Storage of corn and other food and feed in such conditions is known to be susceptible to AF production (27). A. versicolor, on the other hand, seems to be better adapted to conditions prevailing in damp building materials in water-damaged buildings, and has frequently been reported to coincide with the occurrence of sterigmatocystin in such residences (14, 19, 28). There are also indications that ochratoxin A and citrinine can occur in indoor environments (29), but as of yet, food and feed has been the source of most ochratoxin A and citrinine, as well as AFs (9, 30).

Airborne concentration of aflatoxin B1 found in dust collected during harvest and grain unloading has ranged from 0.04 to 92 ng/m3. Higher levels of aflatoxin B1 has been detected in the airborne dust samples collected from enclosed animal feeding buildings (5-421 ng/m3) and during bin cleaning (124-4849 ng/m3). Aflatoxin B1 up to 5100 ng/g were found in settled dust collected from an enclosed animal feeding building (31).

The presence of aflatoxin in respirable airborne peanut dust has been investigated (32). Dust concentrations varied from 10.5 to 65.1 mg/m3, and airborne aflatoxin B1 concentrations reached a maximum of 7.6 ng/m3.

Aflatoxins are potent carcinogens, produced by A. flavus and A. parasiticus in grains and seeds such as peanuts, maize, nuts and oilseeds. Ochratoxin A is nephrotoxic and probable carcinogen as well. It is produced by Penicillium verrucosum in cereal grains in cold climates, by A. carbonarius in grapes, wines and vine fruits, and by A. ochraceus occasionally in coffee beans.

In indoor climates, potentially toxinogenic strains belonging to different Aspergillus species commonly occur simultaneously, particularly in buildings with a history of water damage (28).

6. INHALATION EXPOSURE

Inhalation exposure to mycotoxins occurs by inhaling airborne particulates containing mycotoxins, including dust and fungal components. In agricultural settings, mycotoxics in both farm animals and humans can result from oral, dermal or inhalation exposure of mycotoxin-contaminated grain or dust (3, 33-38). In laboratory mammals, symptoms can be induced by systemic, oral, dermal, subcutaneous or inhalation exposure (9, 39), with inhalation exposure often being several orders of magnitude more toxic than oral or even systemic administration (40-42).
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Toxigenic fungi have been isolated from building materials and air samples in buildings with moisture problems, where the residents have suffered from non-specific symptoms possibly related to mycotoxin production, such as cough, irritation of eyes, skin and respiratory tract, joint ache, headache and fatigue (11, 14, 19, 43-48).

*Aspergillus* toxins may have an important role in causing direct effects in respiratory tract: damage of epithelia and mucous membranes can lead to pulmonary disorders. Amitani et al. (49) purified and characterized cilioinhibitory factors of *A. fumigatus*. A low-molecular weight cilioinhibitory factor was characterized by mass spectrometry as gliotoxin. Gliotoxin significantly slowed ciliary beat frequency in association with epithelial damage at concentration above 0.2 μg/ml. In the same investigation, fumagillin and helvolic acid from *A. fumigatus* were also cilioinhibitory but at much higher concentration. This may have an impact in developing respiratory distress during *Aspergillus* contamination in respiratory tract.

Mycotoxins can also provoke systemic reactions. Tremorgenic toxins from Aspergilli are able to cause symptoms via the central nervous system. Nausea, fever and fatigue are often associated with exposure to toxic fungi (14). In addition, some toxins are able to cause immunosuppression which in turn may lead to repeated infections (42).

Nasal exposure with aflatoxin B1 aerosol in rats suppressed alveolar macrophage phagocytosis at an estimated dose of 16.8 μg/kg with the effect persisting for approximately 2 weeks (50). Renal failure associated with respiratory distress was demonstrated in two farmers who had been exposed to ochratoxin A produced by *A. ochraceus* (51).

**7. FUTURE DIRECTIONS**

Exposure to microbes occurs both in occupational settings and in domestic environments. Bioaerosols are able to become a health risk to exposed persons who can develop allergic or toxic symptoms in respiratory tract, eyes or skin. Systemic reactions, disorders in central nervous systems and even cancer may develop due to the mycotoxin exposure. Exposure to toxin producing microbes increase the health risk and even small amounts of microbial contamination may lead to fatal outcomes. Development of new techniques to determine mycotoxin producing microbes and measure different toxins in work environments are utmost important in the near future. Risk assessment of mycotoxin exposure has to be more precise both in occupational and domestic settings. More information has to be achieved from research to practice about the pathogenesis of toxin-induced diseases in order to improve the diagnosis of these health outcomes and to prevent further new cases of disorders.

**8. REFERENCES**

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Key words: Mycotoxin, Aspergillus fumigatus, Inhalation Exposure, Moisture Problems, Review

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