Developments in Industrial Microbiology Volume 31
(Journal of Industrial Microbiology, Suppl. No. 5)
Editor: C.L. Pierce
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23. Mycotoxins as potential occupational hazards

W.G. Sorenson

Immunology Section, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV 26505, U.S.A.

SUMMARY

Exposure to fungi is common in many occupational settings, especially in agriculture. Presently numerous mycotoxins are recognized, and appreciable amounts can occur in airborne spores. Thus it can be expected that mycotoxins are inhaled when workers and others are exposed to airborne spores of toxigenic fungi, whether in the office, or in a silo, grain elevator, or barn. Furthermore, recent data demonstrate that certain mycotoxins are acutely toxic to pulmonary alveolar macrophages and that some mycotoxins, especially the macrocyclic trichothecenes, are immunotoxic. Although further studies are needed, data currently available suggest that pulmonary exposure to mycotoxins could have deleterious effects on health either directly or in combination with other components of that exposure.

INTRODUCTION

Fungi are among the principal microorganisms involved in biodeterioration and are found in many substrates and occupational settings. Occupations and/or workplaces that may involve exposure to fungi include grain harvesting, storage and processing, sawmills and wood pulp mills, mushroom cultivation, waste treatment, and even office workers, librarians, and museum workers. In fact, virtually any occupation which brings workers into close association with biodeterioration processes offers the possibility of exposure to fungi and their spores.

As might be expected, a very large number of workers are potentially at risk. For example, over 5 million U.S. grain handlers, lumber and woodworkers and farm workers are believed to be at risk of developing occupational asthma and rhinitis [31]. Similarly, workers at risk of various hypersensitivity pneumonitides involving fungi include approximately 3 million farm workers, mushroom workers, and malt workers combined [11].

The present paper is an updated summary of a previously published paper [33].

There are many ways in which fungi affect human health. For example, fungi are the principal cause of plant disease and have had a major impact on mankind throughout history [1]. Fungi also affect human health by direct infections, allergy and hypersensitivity, and by the production of toxic metabolites, i.e. mycotoxins [28]. Mycotoxin contamination in foodstuffs and human and animals diets has been extensively reviewed elsewhere [39, 40, 44]. Therefore, this overview will be restricted to pulmonary exposure.

Because mycotoxins occur in complex organic matrices which include intact spores and/or other hyphal elements, bits of substrate, viable and nonviable microorganisms, and other environmental contaminants, the overall result of exposure may be the combined effect of one or more mycotoxins plus

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other inhaled substances of fungal or nonfungal origin. Therefore, pulmonary exposure to mycotoxins should be considered in the context of possible exposure to potential pathogens or allergenic microorganisms, as well as to the mycotoxins or other chemical agents present. The net result could include diminished resistance to infection and/or adverse reactions of the immune system.

HYPERSENSITIVITY

Although there are many gaps in our knowledge of the cause-effect relationships between fungi and clinical allergy, there appears to be no doubt that some fungi are related to respiratory allergy in a significant proportion of atopic individuals. It is interesting that many of the fungi reported to be allergenic in humans are also toxigenic. Some of the better known toxigenic fungi which have been reported as causative agents of human allergies include *Alternaria alternata*, several species of *Aspergillus* (*A. clavatus*, *A. flavus*, *A. fumigatus*, *A. niger*, *A. terreus*, and *A. versicolor*), *Cladosporium cladosporioides*, *Stachybotrys atra*, and *Trichothecium roseum* [41]. It is not known whether mycotoxins play any role in the development of human allergy, but it is conceivable that toxins within the spore, in the presence of specific allergens, could play a role in sensitization to the allergen.

Farmers' lung disease (FLD) is a hypersensitivity reaction which occurs in the lung in response to inhaled thermophilic actinomycetes and certain fungi [10, 28]. Organic dust toxic syndrome (ODTS) is a new syndrome, possibly associated with the presence of fungi and/or mycotoxins. ODTS is thought to be distinct from FLD even though its exact etiology is unknown [26]. ODTS has been reported to be common on dairy farms in New York State when the dry uppermost silage in concrete-stave silos is removed after several weeks to months of storage [26]. Total dust levels of > 100 mg/m^3 and respirable dust levels of > 20 mg/m^3 were reported in some silos with numbers of microorganisms in excess of 10^9/g of dust [22].

The role of 'polyclonal cell activators' as possible agents in the pathogenesis of inflammatory diseases in the lung has received increasing attention recently [48]. Polyclonal cell activators are substances which stimulate cells of the immune system by immunologically non-specific mechanisms. In addition to endotoxin or lipopolysaccharide (LPS), examples of such substances include plant lectins such as concanavalin A, chemicals such as phorbal esters, and grain dust extracts. Polyclonal cell activators may be especially important in occupational lung disease because they can directly activate large populations of lymphocytes and/or macrophages. This may result in the activation of much larger cell populations and the generation of greater amounts of inflammatory mediators than would occur through antigenic stimulation.

Olenchock et al. [24] have demonstrated that conidia of *A. fumigatus* and *A. terreus* aerosolized in high concentrations can cause acute hypoxemia and activation of the alternative pathway of complement in rabbits. It is not known what component of these fungus spores incited the reaction. If the response of rabbits exposed to *Aspergillus* conidia can be considered comparable to ODTS, it is possible that some component of the fungal spore has properties similar to bacterial endotoxin and which, if present in sufficiently high concentrations, could incite ODTS.

TOXIC VOLATILE COMPOUNDS OF FUNGI

Various fungi produce numerous volatile compounds [5, 15, 18, 19, 29, 32]. The emphasis of most of these studies was to identify major characteristic odors, methodology was not consistent, and, in most cases, no toxicity studies were undertaken. The relevance of these studies for human health is uncertain because: (1) the composition of the volatile mixture may vary with the methodology used, (2) relevant concentrations of fungal volatile compounds in the home or workplace are not known, and (3) little information is available in the literature on the toxicity of these compounds. Those fungal volatile compounds for which toxicity data are available have rather high (> 300 mg/kg) LD_{50} val-

ues [33], but some are reported to be carcinogenic [23]. *Scopulariopsis brevicaulis* and other fungi have been shown to release volatile arsenic compounds from suitable substrates [4]. Most of the known mycotoxins are nonvolatile, but if volatile agents produced by fungi can be shown to be toxic, their impact on human health should be considered.

OCCURRENCE OF AFLATOXIN IN WORKPLACE AEROSOLS

Although extensive literature has been developed since the discovery of the aflatoxins, relatively little is known of the occurrence of these substances in airborne grain or other organic dust. In addition, virtually nothing is known of the inhalation hazard to workers and others exposed to contaminated airborne dust. At least two studies have provided circumstantial evidence for the association of cancer in humans with inhalation of aflatoxin-contaminated dust: (1) chemical engineers working with contaminated peanut dust [9]; and (2) biochemists working to purify aflatoxins by preparative thin-layer chromatography [8]. Van Nieuwenhuize et al. [46] have reported an epidemiological study of workers in a peanut-processing plant in The Netherlands. In the latter study, rates of multiple kinds of cancer were more than 3 times those reported in the matched control group. In a follow-up study in the same plant, Hayes et al. [16] demonstrated that mortality for total cancer and respiratory cancer in the aflatoxin-exposed group of peanut-oil-press workers was higher than expected based on standardized mortality ratio (SMR) analysis. Sorenson et al. [34] and Burg et al. [2] have reported the presence of aflatoxins in respirable airborne corn dust, sometimes in concentrations of several hundred parts per billion. Also, Sorenson et al. [35] reported on the occurrence of aflatoxins in airborne respirable peanut dust. These results showed that airborne peanut dust from contaminated lots of peanuts contained up to 612 ppb of aflatoxin B_1 (AFB_1). If one assumes a breathing rate of 3 m^3/h and an airborne aflatoxin concentration of 1.0 ng/m^3 (100 ppb at a dust concentration of 50 mg/m^3), a worker would inhale 15 ng/h and 120 ng in an 8-h workshift. At present, there is a paucity of information concerning the risk of inhaling such amounts of aflatoxin, but the extreme genotoxic potential of aflatoxin suggests that the risk may be real. Olsen et al. [25] did a retrospective study of cancer risk and occupational exposure to aflatoxin among livestock feed processing workers in Denmark. Their study was based on a data linkage system which allows linkage of personal identity numbers for individual workers, companies, employment histories back until 1964, and cases of cancer reported to the Danish Cancer Registry. The average concentration of organic dust in these companies was ca. 100 mg/m^3, crops imported for feed production have been highly contaminated (average level of 140 ppb in prepared cattle feed), and the estimated daily pulmonary exposure was ca. 170 ng. The Danish investigators noted elevated risks for liver cancer and cancers of biliary tract in their worker population, which increased by 2- 3-fold significance after a 10-year latency and they reported that exposure to aflatoxins in the imported feed is the most likely explanation for their findings. Our estimate of a possible daily exposure to 120 ng B_1 by the pulmonary route is consistent with the Danish estimate and is conservative (a light to moderate breathing rate was chosen and much higher dust and aflatoxin contamination levels have been reported in the literature).

OCCURRENCE OF MYCOTOXINS IN FUNGAL SPORES

Wicklow and Shotwell [47] studied toxigenic strains of *A. flavus* and *Aspergillus parasiticus* and reported aflatoxin levels in the hundreds of thousands of ppb in the conidia of certain of these strains. These studies suggest the possibility of a substantial risk to agricultural workers exposed to dust containing large numbers of conidia of these fungi. Darke et al. [7] reported that the airborne dust around combine harvesters of cereal in England consisted predominantly of fungus spores and hyphal fragments with spore concentrations as high

as 200 million spores/m^3 of air. Recently, Croft et al. [6] reported an outbreak of unexplained illness, occurring over a five-year period, which appeared to be related to the extensive occurrence of *S. atra* contamination of home duct work and ceiling fiberboard. The fiberboard and air samples collected from the home contained substances which elicited characteristic trichothecene toxicity when injected into mice. The toxic extracts were subsequently shown by these investigators to contain macrocyclic trichothecenes. Their study raised the possibility that *S. atra* was the etiologic agent for this outbreak of illness via its toxic metabolites. Sorenson et al. [38] incubated *S. atra* on sterile rice, and then aerosolized the rice by acoustic vibration after it had been sterilized and dried. The distribution of particles (mass and number) was monitored on an aerodynamic particle sizer interfaced with a computer. Dust was collected on preweighed glass-fiber filters and extracted with 90% aqueous methanol. Extracts were tested in vitro for biological activity against rat alveolar macrophages and mouse thymocytes and for the presence of specific trichothecenes. Most of the particles were respirable (the mass median diameter was 5 μm). Microscopic analysis of the generated dust revealed that 85% of the dust particles were conidia of *S. atra*, and another 6% were hyphal fragments. Thus, > 90% of the particles were of fungal origin. The extracts strongly inhibited protein synthesis and thymocyte proliferation. Purified satratoxin H was also highly toxic in the same systems. Each of the individual filters contained satratoxin H (average, 9.5 ng/mg of dust) and satratoxin G, and trichoverrols A and B were found in lesser amounts in some, but not all, of the filters. These results establish that the conidia of *S. atra* contain trichothecene mycotoxins. The trichothecene mycotoxins are acutely toxic to a variety of mammalian species [45], strongly inhibit protein, DNA, and RNA synthesis in eucaryotic cells [14, 45], and are immunotoxic in rats and mice [20, 30, 42, 43]. In addition, the symptoms of stachybotryotoxicosis in humans suggest immunotoxic effects [12]. The identification of trichothecene mycotoxins in airborne respirable conidia of *S. atra* demonstrates the possibility for pulmonary exposure of workers and others to these highly toxic substances. They also may help to explain the findings of previous researchers who identified human stachybotryotoxicosis and other illness caused by exposure to moldy hay, contaminated duct work, and carpets heavily contaminated by *S. atra*.

EFFECTS OF MYCOTOXINS IN THE LUNG

Relatively little information is available in the literature pertaining to the effects of specific mycotoxins on the cells and tissues of the lung, even though these cells would be the first to contact inhaled mycotoxins. Some of the work from our laboratory dealing with the effects of mycotoxins on rat alveolar macrophages in vitro will be briefly described [13, 14, 36, 37]. Pulmonary macrophages perform several important functions in the lung including phagocytosis of living and nonliving foreign particles, regulation of T-lymphocyte proliferation, provision of T-helper activity for antibody production, and production of mediators of cellular immunity [21]. Thus, cytotoxic damage to alveolar macrophages could lead to serious pulmonary and/or systemic damage.

Short-term cytotoxicity was studied by the chromium release assay, inhibition of protein and RNA synthesis was studied by monitoring the incorporation of [^{3}H]-leucine and [^{3}H]-uridine, respectively, and phagocytosis was studied with the use of ^{51}Cr-labeled sheep erythrocytes opsonized with specific antibody. T-2 toxin, patulin, and penicillic acid were shown to cause dose- and time-dependent chromium release, inhibition of protein and RNA synthesis, and inhibition of phagocytosis [13, 14, 36, 37]. T-2 toxin also inhibited the ability of macrophages to respond to activation stimuli, e.g. lymphokines produced in response to endotoxin [14]. In this experiment, lymphocytes were cultured in the presence of LPS obtained from *Escherichia coli*; supernatant fluids from these cultures were used to activate alveolar macrophages. Incorporation of radiolabeled glucosamine was used as the indicator of macrophage activation. Richard et al. [27] exposed Wistar male weanling rats to aerosols

of killed *A. fumigatus* spores alone or to killed *A. fumigatus* spores containing 1000 or 5000 ppm AFB_1. The animals were exposed for 2 h/day and 5 days/week for 4 consecutive weeks and necropsy was performed on a portion of the animals in each group at 3 weeks and 1 year post-exposure. Hepatic lesions were only observed in rats exposed to 1000 or 5000 ppm AFB_1 and only one neoplasm was observed. No lung lesions were observed 1 year after exposure to aflatoxin-free spores or in unexposed animals. Lung lesions of varying severity were observed in 5 of the 8 rats exposed to 1000 ppm AFB_1, and were more marked in rats exposed to the higher level of aflatoxin. The authors estimate that the animals exposed to 5000 ppm AFB_1 received a total exposure of 0.006 mg/kg. This is well below the reported LD_{50} of 6.0 mg/kg (i.p.) for AFB_1 in the male rat [3]. The authors believe that the general response of the exposed animals appeared to be that of a compromised host.

FUTURE RESEARCH NEEDS

At the present time, little information is available on the concentration of airborne mycotoxins in the home or workplace. Although fungi are known to produce a variety of volatile substances, virtually all of the known mycotoxins are nonvolatile. Therefore, pulmonary exposure to the mycotoxins would need to occur by inhalation of spores and/or small substrate particles containing the toxins. There is a need for additional information on the airborne concentrations of selected mycotoxins in specific workplace settings, such as grain elevators, silos, and grain processing operations whenever there is reason to believe contamination by toxigenic fungi may be a problem.

A limited number of studies exist to show that fungal spores can contain significant or even very high levels of certain mycotoxins such as aflatoxin or satratoxin H. Additional studies are needed to determine whether exposure to fungus spores may constitute a significant health risk by virtue of their mycotoxins as well as by their ability to stimulate adverse immunologic response. Only a very limited amount of information is available in the literature relating to inhalation toxicity of the mycotoxins. Further inhalation studies are needed to provide information as to the risk associated with exposure to these compounds. Very little is known of the ability of tissues of the lung to metabolize mycotoxins and to elaborate metabolites which may have modified toxicity to lung tissues, or may be more or less easily transported out of the lung to other tissues. Further information is needed regarding the toxicity of mycotoxins for the various cells and tissues of the lung.

ACKNOWLEDGEMENT

The author thanks Ms. Janet Simpson for her excellent technical assistance during the course of the studies from our laboratory cited herein. Mention of company names or products does not constitue endorsement by the National Institute for Occupational Safety and Health.

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