

Stachybotrys chartarum **(*chartarum* = *atra* = *alternans*)** **and Other Problems Caused** **by Allergenic Fungi**

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ABSTRACT

Stachybotrys chartarum is a cellulose-decaying fungus with worldwide distribution. It grows well at room temperature and with humidity above 93%. *S. chartarum* requires special media high in cellulose and low in sugar and nitrogen to compete with *Penicillium* and *Aspergillus*. Ninety percent of field-collected spores are not culturable. *S. chartarum* can produce macrocyclic trichothecenes but is highly dependent on strain and environmental conditions. In strains implicated in mycotoxicosis, not all produce detectable trichothecenes. Therefore, the presence of *S. chartarum* is not proof of toxin presence. Trichothecenes are potent inhibitors of protein and DNA synthesis. By the inhalation route, occupational stachybotrytoxico $\acute{s}$ is causes chest and upper airway symptoms, fever, leucopenia, dermatitis; starts in 2–3 days of exposure; and lasts 3 weeks. Investigation of the environment of the cluster of pulmonary hemorrhage in 10 infants in Cleveland, Ohio, and similar cases elsewhere are presented. The Centers for Disease Control and Prevention considers *S. chartarum* a serious health threat. However, even though there are now techniques of measuring *S. chartarum* conidia and estimating trichothecene mycotoxin in indoor air samples, no standards exist that relate to health effects. Those standards available are numerical or com-

parison of indoor/outdoor counts or both. Upper limit of noncontaminated indoor environment is 100–1000 colony-forming units (CFU) m³. There is no compelling evidence that exposures expected in most mold-contaminated indoor environments are likely to result in measurable health effects. However, when the health care worker suspects a problem in the home environment, a questionnaire and home visit may be helpful. High indoor exposures are associated with infrequent ventilation or vacuuming, pets, visible mold, and old carpets. To screen the indoor air, an experienced pollen and mold counter could use a Burkard personal air sampler. Health-based exposure standards for molds and mycotoxins do not exist. When available data indicate extremely high mold levels, cleanup consisting of removal of all contaminated material, cleaning accessible heating, ventilation, and air-conditioning parts and filters, and preventive maintenance are indicated. There is a brief summary of the diseases of plants, animals, and humans caused by several common allergenic fungi and the mycotoxins they produce. (Allergy and Asthma Proc 24:1–7, 2003)

During the 1930s, tens of thousands of horses in the Ukraine began to die. They suffered severe inflammation of the skin and respiratory tract (stomatitis, rhinitis, and conjunctivitis), hemorrhaging and tissue necrosis, pancytopenia, and neurological disorders. Death could occur in less than a day. Scientists eventually connected the disease to eating fodder contaminated with a mycotoxin trichothecene produced by *Stachybotrys atra*, a common cellulose-decomposing fungus. Nikita Krushchev owed some of his early rise to prominence to his recognition that horses, vital to the Russian economy and the Red Army transportation system of the day, needed clean, dry fodder.¹

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USA Weekend, October 12–14, 2001 printed an update “Mold’s Untold Damage.” A Travis County, Texas district court jury awarded Melinda Ballard, Ron Allison, and their five-year-old son, Reese, \$32 million in their fight against Farmers Insurance Group, which the family says mishandled their claim for mold damage. They argued that the insurance company had failed to cover repairs to leaky pipes soon enough to prevent the “toxic” mold *S. atra* from overrunning their 22-room mansion near Austin.

Experts believe the verdict could lead to a surge in mold-related litigation. No firm numbers exist but there are hundreds, perhaps thousands, of cases in which alleged victims are suing insurance businesses, construction companies, school systems, and employers.²

This sets the stage for why you need to know something about *Stachybotrys*. My review will be from the perspective of an allergist.

Stachybotrys has been identified in several other outbreaks of diseases in animals. It has also attracted attention as a possible agent in idiopathic pulmonary hemorrhage in infants in the Cleveland, Ohio area as an inhalant.^{3,4} The Centers for Disease Control and Prevention (CDC), Atlanta, GA, reported a community-based case-control study of the homes of the geographic cluster of 10 cases of pulmonary hemorrhage and hemosiderosis in infants recently dismissed from the hospital in the Cleveland, Ohio area. The authors concluded that these infants were more likely than controls to live in homes with toxigenic *S. atra* and other fungi growing in the house.⁵ However, the presence of *Stachybotrys* spores or toxin in the air was not confirmed. Frequently, environmental tobacco smoke was present in the infants’ homes and could have triggered acute bleeding.⁶ The CDC subsequently published a review of their studies associated with this outbreak and concluded that the studies were inconclusive and did not prove *Stachybotrys chartarum* was responsible.⁷ A strain of *S. chartarum* has been isolated from the lung of a pulmonary hemorrhage and hemosiderosis patient in Texas (designated the Houston strain).⁸ More recently, a case of infant pulmonary hemorrhage was reported in Kansas City associated with positive air samples for *Stachybotrys* spores from the patient’s bedroom as well as surface samples from the patient’s closet and attic ceiling. Material from the attic ceiling was highly toxigenic.⁹

Stachybotrys has been isolated from a variety of sources including contaminated grains, tobacco, indoor air, insulator foams, and water-damaged buildings with high humidity.¹⁰ *S. chartarum* is a cellulose-decaying fungus with a worldwide distribution. It grows optimally at room temperatures when the relative humidity is above 93%.¹¹

Recovery of *Stachybotrys* from the indoor environment presents many challenges. *Stachybotrys* species grow slowly when cultured with other fungi. Although able to inhibit the growth of other fungi, *Actinomyces*, and other bacteria, *S. chartarum* can compete with fungi such as *Penicillium* and *Aspergillus* only on specialized culture

media (e.g., high cellulose and low sugar and nitrogen). In bulk samples, the number of *S. chartarum* colonies detected and the frequency of recovery (*S. chartarum* colonies/total fungal colonies recovered) on cellulose agar can be 100 times higher than on glucose agar.¹²

S. chartarum spores can survive for long periods at temperatures as low as -40°C . However, it has been estimated that up to 90% of field-collected spores may not be culturable; therefore, culture estimates of spore concentrations may be underestimated.¹³

The genus *Stachybotrys* was first described by Corda in 1837.² The genus is defined by the successive production of black phialospores that collect in a mucilaginous mass at the apex of clustered, inflated phialides. There are ~50 species in the genus.

S. chartarum is characterized by relatively large ovate spores with smooth to irregularly warty walls. The reported spore size range is $3-4 \times 7-10 \mu\text{m}$ with extensive variation among different isolates.¹⁴ Because the spores are hydrophilic, they tend to agglomerate and are aerosolized most readily under dry conditions with physical agitation.¹⁴

Stachybotrys mycotoxins are macrocyclic trichothecenes, a group of chemically related fungal metabolites produced by various species of *Fusarium*, *Trichothecium*, *Tricoderma*, *Cephalosporium*, *Cylindrocarpum*, and *Myrothecium* as well as *Stachybotrys*.¹⁵ Recent studies indicate that only about one-half of the strains of *S. chartarum* produce these trichothecenes. Mycotoxins are not volatile. Mycotoxins are natural products usually produced in response to environmental stimuli only by specific groups of organisms and only during part of their life cycle.²

Particular mycotoxins can be produced by more than one fungal species or fungal genus. Fungal species typically can produce more than one mycotoxin. Often, a mycotoxin can elicit more than one type of toxic effect (that is, antiviral, antibacterial, antifungal, immunosuppressive, carcinogenic, mutagenic, cytotoxic, teratogenic, and neurotoxic) and the degree of toxicity varies greatly.¹² Although the majority of individual strains of toxigenic species are genetically capable of toxin production, mycotoxin production is highly dependent on fungal species and strain and environmental conditions such as temperature cycling, water activity, light, and growth substrate.¹² Thus, growth of toxigenic fungal species in an indoor environment will not necessarily indicate whether or not mycotoxins are present.¹²

At least eight major macrocyclic trichothecenes have been identified from *S. chartarum* isolates: satratoxins F, G, and H; roridin E; verrucarins B and J; and trichoverrols A and B.¹² The macrocyclic trichothecenes are soluble in all common solvents and sparingly in water at room temperature. Not all strains of *S. chartarum* can produce mycotoxins in detectable amounts in the laboratory setting.¹⁶ In surveys of *S. chartarum* strains implicated in mycotoxicoses, not all strains were toxic in tissue culture assays or produced detectable trichothecenes. Therefore, the presence of *S. chartarum* growth is not proof of toxin presence.¹²

Tricothecenes are potent inhibitors of protein and DNA synthesis. They interact with ribosomes (binding the ribosomal peptidyl transferase) and interfere with the initiation and elongation events. The biologically active structure is the epoxide group.¹² All of the tricothecene mycotoxins are capable of inducing immunosuppression, skin necrotization, vomiting, leucocytosis, and leucopenia in experimental animals.¹⁷

Occupational stachybotryotoxicosis has been reported in farm workers, workers in cottonseed oil plants and grain elevators, workers at facilities for reprocessing moldy grain and processing malt grain, textile mills using plant fibers, and binder twine factories.¹⁸ Symptoms included chest and upper respiratory symptoms, fever, dermatitis, and leukopenia in some cases. The clinical symptoms develop within 2–3 days of contact with an average duration of 3 weeks.¹²

The CDC considers *S. chartarum* a serious health threat.¹⁹ One relatively well-defined case of symptoms related to exposure to *Stachybotrys* involved a home with heavy infestation of *S. chartarum*.²⁰ Water damage had occurred in the house over a period of years. Extensive fungal growth was evident on the ceiling of an upstairs bedroom and in the air ducts, and *S. chartarum* spores were collected from room air samples and identified microscopically but not cultured. Tricothecenes were extracted from bulk samples of contaminated ceiling tile and air-duct dust.¹² The variety of symptoms reported by the occupants of this house were headache, sore throats, hair loss, flu symptoms, diarrhea, fatigue, dermatitis, and general malaise, which are consistent with the nonspecific nature of indoor air quality complaints.²¹ There were no objective measured disease outcomes, and other possible causes for the reported symptoms were not ruled out. The cleanup workers experienced skin and respiratory irritation. Reported symptoms of the occupants of the house ceased after the mold was removed. Although the symptoms were attributed to *S. chartarum*, other fungal aerosols were not ruled out as possible causes or contributors to symptoms. The presence of other molds is likely because the water infiltration and mold growth had been occurring for 4 or 5 years.²²

Existing quantitative standards/guidelines for fungi in indoor air issued by governmental agencies are based on baseline data (rather than health effects data) and are either numerical or indoor/outdoor comparisons or a combination of both. Quantitative standards/guidelines range from <100 colony-forming units (CFU)/m³ to >1000 CFU/m³ (total fungi) as the upper limits for noncontaminated indoor environments. Major issues with existing quantitative standards and guidelines are the lack of connections to human dose-response data; reliance on short-term grab samplers analyzed only by culture; and the absence of standardized protocols for data collection, analysis, and interpretation.²³ Quantitative measurement of *S. chartarum* conidia using a real-time detection polymerase chain reaction product analysis has been developed.²⁴ Only recently has a sensitive

method been proposed to estimate tricothecene mycotoxins in the air samples and this technique remains to be validated. This method does not measure tricothecenes directly, but quantifies the level of protein inhibition from material collected on an air sample.²⁵ Exposure standards for airborne indoor mycotoxins do not exist.²²

Although there is evidence of a relationship between high levels of inhalation exposure and direct contact to mycotoxin-containing fungi or mycotoxins and demonstrable effects in animals and health effects in humans, the current literature does not provide compelling evidence that exposures expected in most mold-contaminated indoor environments are likely to result in measurable health effects.²²

A 2001 literature review of the role of *Stachybotrys* mycotoxins in building-related illness by E.H. Page and D.B. Trout of the Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, CDC, indicates that currently there is inadequate evidence supporting a causal relationship between symptoms or illness among building occupants and exposure to mycotoxins.²⁶

Having said all this, what tools does the allergist/clinical immunologist have to assess the patient's home? Much can be learned by a home visit by medical personnel. Questionnaires are commonly used to obtain information about house characteristics in order to predict the household aeroallergen exposure levels. An interview-administered home visit report has been validated by examining the home against observations made by a researcher; measurement of relative humidity, cat allergen, and ergosterol; a biomarker of fungal exposure; and a biochemical test.²⁷ Others examining 1000 homes in the northeastern United States have found only a weak relationship between house characteristics, as described by questionnaire, and the presence of fungal propagules in indoor air. Only temperature, relative humidity, season, and cats inside homes had a statistically significant impact on the presence of fungal propagules in indoor air.²⁸ High indoor fungal exposures were associated with infrequent ventilation or vacuuming, presence of pets, visible mold, and old carpets in 485 houses examined in 1 year in Melbourne, Australia.²⁹ Actual measurement are required for fungal exposure assessment.

Those few allergists/clinical immunologists familiar with air sampling with a Burkard volumetric spore trap on a regular schedule should be able to screen rooms by using the personal Burkard portable air sampler to identify fungal spores. However, if the physician is aware of visible mold growth in the home and he believes it is a health risk to the patient, cleanup should be recommended.

Even though health-based exposure standards for molds and mycotoxins do not yet exist, there is general agreement that active fungal growth in indoor environments is unsanitary and must be corrected, the point at which mold contamination becomes a threat to health is unknown.²²

Whether fungi such as *Stachybotrys* should be treated differently than other fungi, when considering cleanup or

sampling exposures, is controversial. The information about health effects and exposure in the current scientific literature does not warrant the use of more conservative measures for mold remediation based on the presence of a particular fungal species as an example in asbestos cleanup. The available data indicate that immediate cleanup is needed, regardless of the genus or species identified, if contamination in indoor environments result in extremely high airborne mold levels.²²

A usual remediation program includes removal of all contaminated wallboard, paneling, and carpet in the water-damaged areas of the home. Sodium hypochlorite solution is used to clean all surfaces during remediation.⁴ Appropriate, cleaning of accessible components of heating ventilation and air-conditioning units should be performed, air filters should be regularly replaced, and preventive maintenance programs should be implemented.³⁰

Now I want to make some general remarks. The fungi we identify as important to our patients as inhalant allergens have other important effects as plant pathogens, as producers of mycotoxin in our food, and as infectious agents in human disease. To illustrate a few:

1. *Alternaria*. Early blight of potatoes; blight on carrots,² lemon black rot, and brown spot³¹; leaf spot on broccoli³²; tomato black rot³³; produces mycotoxin tenuazonic acid, which is nephrotoxic, hepatotoxic, and hemorrhagic¹²; fungal rhinosinusitis³⁴; and cutaneous ulcerative alternariosis.³⁵
2. *Aspergillus*. Black mold rot of lettuce and ripe tomatoes²; *Aspergillus flavus*, and *Aspergillus parasiticus* produce classic mycotoxins, aflatoxins. These fungi are storage contaminants of peanuts, pecans, peas, bread, cheese, rice, corn, barley, grain, sorghum, wheat, and cotton seed.¹⁸ However, in temperate zones, invasion of these crops by *A. flavus* before harvest is of prime importance. Invasion of peanuts occurs as a result of drought stress and related factors. Preharvest invasion in maize is partly dependent on insect damage to cobs, but the fungus can also invade down the silks of the developing ears. Cereals are a common substrate for growth of *A. flavus* but unlike the case of nuts and oil seeds, small grain cereal spoilage by *A. flavus* is almost always the result of poor handling. Aflatoxins are found in milk, eggs, and livers of animals that have consumed contaminated feed.¹⁸

Since the discovery of aflatoxin, it has become the most widely reported food-borne mycotoxin reflecting its economic and medical importance, ease of recognition, and its wide occurrence.³⁶

Acute toxicity of aflatoxins to humans has been observed only rarely. In 1974, an outbreak of hepatitis that affected 400 people in India, of whom 100 died, almost certainly resulted from aflatoxins. The outbreak was traced to maize heavily contaminated with *A. flavus*. Aflatoxin B₁ has been shown in animal species to be the

most potent liver carcinogen known. Human liver cancer has a high incidence in Central Africa and parts of Southeast Asia; therefore, a link with aflatoxins appears likely.³⁶

Under recent agreements, 15 µg/kg of total aflatoxins is likely to become the maximum level permitted in all food commodities in world trade.³⁶ In industrialized countries, stringent sorting and cleanup procedures are used to reduce aflatoxins to low levels in foods with perceived risk (such as peanuts).³⁶ Nonindustrialized countries are less fortunate.

Aspergillus ochraceus produces ochratoxin A, which is a nephrotoxic fungal metabolite occurring in foodstuffs. The fungus grows on damp field grain, usually barley or oats. Epidemiological studies link ochratoxin with *Endemic Balkan Nephropathy*, a fatal kidney condition reported among people living near the Danube River and its tributaries in Yugoslavia, Bulgaria, and Romania.^{2,37}

Case reports of inhalation exposure to laboratory workers have associated lung disease and cancer with aflatoxin exposure, and epidemiology studies suggest higher cancer rates in workers in peanut processing.²²

As an infectious agent, *Aspergillus* can cause fungal sinusitis and invasive aspergillosis, the most serious form of pulmonary aspergillosis, which involves the invasion of viable tissue. It occurs predominantly with patients with preexisting lung damage and can spread to other organs and distant sites in the body.³⁸ Saprophytic aspergillosis involves colonization of the airways without invasion or damage of viable tissue and may present as a fungus ball.³⁸ *Aspergillus* species have emerged as the most common infectious cause of pneumonic mortality in bone marrow/stem cell transplant recipients.³⁹

Extrinsic allergic alveolitis and allergic bronchopulmonary aspergillosis often are confused but should not be difficult to distinguish. Extrinsic allergic alveolitis is nonatopic and is marked by chills, fever, chest pains, cough, dyspnea, and restrictive lung disease. The immunologic hallmark is the presence of precipitating antibody to the suspected antigen. Allergic bronchopulmonary aspergillosis is atopic and is marked by low-grade fever; obstructive pulmonary function, marked by elevated serum immunoglobulin E levels; and positive immediate and late response on skin tests.^{40,41} Allergic bronchopulmonary aspergillosis may occur in ~25% of patients with asthma and 10% of patients with cystic fibrosis.³⁸ Allergic fungal rhinosinusitis presents with a constellation of nasal polyposis, crust formation, and sinus cultures yielding *Aspergillus*. This disease has a clinical similarity to allergic bronchopulmonary aspergillosis.⁴²

3. *Fusarium*. Tomato foot and root rot, lettuce and cucumber root rot, and rice sheath rot are caused by the *Fusarium* species. *Fusarium moniliforme* occurs worldwide on corn intended for human and animal consumption. A

closely related species *Fusarium proliferatum* also occurs frequently on corn (yellow dent corn, white dent corn, white and yellow popcorn, and sweet corn). Both organisms are able to produce fumonisins. Fumonisins have been found in corn and corn-based foods worldwide. Corn-based food products that have the most frequent and highest fumonisin levels, besides whole kernel corn, are corn meal, corn flour, and corn grits. Corn flakes, corn pops, corn chips, and tortilla chips typically have been found negative when tested for fumonisins. Popcorn, sweet corn, and hominy corn have been found with sporadic low levels of fumonisins.⁴³

High levels of fumonisins in the 1989 U.S. corn crop resulted in large-scale field outbreak of equine leukoencephalomalacia and porcine pulmonary edema syndrome in the United States. *F. moniliforme* was prevalent in moldy home-grown corn consumed by people in high-incidence areas of esophageal cancer in the Transkei region (Bantu) of South Africa and in China.⁴⁴

Trichothecene toxins deoxynivalenol (also known as vomitoxin) and nivalenol are among the many trichothecene mycotoxins produced by *Fusarium* species. The major source of the toxins is *Fusarium graminearum*, a species endemic in wheat and other cereals throughout the world.³⁶ This species has been responsible for large-scale human toxicosis in India, China, Japan, and Korea. Symptoms in humans include anorexia, nausea, vomiting, headache, abdominal pain, diarrhea, chills, giddiness, and convulsions.³⁶ The principal causal agent of alimentary toxic aleukia is attributed to *Fusarium poae* and *Fusarium sporotrichioides*.³⁶ Alimentary toxic aleukia consists of septic angina, endemic panmyelotoxicosis, and alimentary hemorrhagic aleukia and was responsible for the death of at least 100,000 Russian people between 1942 and 1948 who ingested grain left under winter snow²² and is attributed to the T-2 toxin.⁴⁵

Zearalenone is an estrogenic toxin also produced by *F. graminearum* and closely related species.³⁶ Maize, barley, and wheat grains infected with *F. graminearum* and containing zearalenone cause genital problems in domestic animals, especially pigs. Zearalenone has been implicated in several incidences of precocious pubertal changes in children.³⁶ *Fusarium* and its toxin zearalenone were extracted from the buckwheat grown in China in an epidemic area with "endemic breast-enlargement disease."⁴⁶

In humans, allergic bronchopulmonary mycosis due to *Fusarium vasinfectum* has been described.^{47,48} Infection due to *Fusarium* species are an increasing cause of serious potentially fatal disease in patients with cancer.⁵⁰

4. *Cladosporium*. The most abundant spore universally on all continents: peach scab and leaf mold of tomato.^{2,49} *Cladosporium* produces several mycotoxins including epicladosporic acid, which is immunosuppressive and may be responsible for outbreaks of alimentary toxic

aleukia (ATA) because it was isolated from samples of grain consumed by the patients.²

As an infectious agent, *Cladosporium* can cause subcutaneous nodules, phaeophyphomycosis, in response to a skin puncture such as a thorn, like the more familiar *sporotrichosis*.^{2,51} Pulmonary disease caused by *Cladosporium* include allergic bronchopulmonary mycosis⁵² and hypersensitivity pneumonitis.⁵³ Chronic sinusitis due to *Cladosporium* is reported.⁵⁴

5. *Penicillium*. Stored organic material such as compost, silage, hay, or grain supports the growth of fungi that favor low oxygen levels, dryness, and heat such as *Penicillium spp.*⁵⁵ Indoors, fungi grow in wet environments such as basements, window sills, and shower stall surfaces. *Aspergillus* and *Penicillium* are dominant indoors.⁵⁵ *Penicillium viridicatum* has been reported almost exclusively from temperate zones such as barley and wheat in northern Europe. This species also produces ochratoxin A, a mycotoxin discussed under *Aspergillus*.³⁶ *Penicillium* species produce a number of other mycotoxin, the best known of which are penicillin and griseofulvin. *Penicillium crustosum* produces roquefortine C. The low levels and relatively low toxicity of roquefortine make the consumption of blue cheese safe for the consumer.⁵⁶

Penicillium can cause chronic suppurative otitis media,⁵⁷ pneumonia, pericarditis,⁵⁸ and disseminated infection in immunosuppressed patients with malignant disease or patients infected with human immunodeficiency virus.⁵⁹ *Penicillium* species cause allergic fungal sinusitis⁶⁰ and hypersensitivity pneumonitis (Woodman's disease).⁶¹

In summary, I have reviewed the literature concerning *Stachybotrys chartarum* and have not found scientific data to support the current public concern about health effects. I have described the developing technology to investigate the association of airborne fungal spores and mycotoxins and human disease. I have outlined the fascinating roles in plant diseases, mycotoxin production, contamination of our food, and infectious diseases caused by some common allergenic fungi.

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