# The Role of Mycotoxins in Building-related Illness

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Workplace Safety and Health

# National Institute for Occupational Safety and Health

- Four missions
  - Research
  - Develop and recommend criteria for OSHA/MSHA standards
  - Respond to requests for investigation of workplace hazards – health hazard evaluations (HHE)
  - Training

# Introduction

- Increased attention regarding role of mycotoxins, primarily from *Stachybotrys*, as causes of illness in the indoor environment
- Recommendations for building remediation based on reported health effects believed due to mycotoxins

# Sick Building Syndrome

- Common, nonspecific symptoms
  - headache, fatigue, irritability, difficulty concentrating, mucous membrane irritation, chest tightness, and skin irritation
- Occur while in the building, but resolve shortly after leaving it
- Typically no objective findings
- Distinct from SBS are building-related illnesses

# Building-related Illness

- Variety of recognized disease entities
  - Allergic rhinitis, asthma, hypersensitivity pneumonitis, Legionnaires' Disease, and humidifier fever
- Characterized by objective clinical findings related to specific exposures in the indoor environment
- Can be caused by microorganisms, including many species of bacteria and fungi

# Fungi

- Fungus is a term used to encompass different plants of the Kingdom Fungi
- Characterized by the absence of chlorophyll
  - Mushrooms, toadstools, yeasts, molds, mildews, smuts, and rusts
- Fungi comprise 25% of the biomass of earth
  - Human exposure to fungi is ubiquitous
- Thousands of fungal species; < 100 species cause human and animal disease

# Fungi

- Saprophytic varieties (those utilizing non-living organic matter as a food source) inhabit soil, vegetation, water, or any reservoir that can provide an ample supply of a nutrient substrate
- Generally, the indoor levels expected to be below outdoor levels with consistently similar ranking among the microbial species

# Health Effects of Fungi

- Allergy
- Infection (i.e., mycosis)
- Toxic reactions
  - Organic dust toxic syndrome
  - Mycotoxicosis specifically refers to a reaction to toxins produced by the fungus
- In addition, more than 500 VOCs identified from a variety of fungi
  - Most common is ethanol

# Fungal Allergy

- Based on a genetic predisposition
- Examples
  - Allergic rhinitis, asthma, allergic bronchopulmonary aspergillosis (ABPA), and extrinsic allergic alveolitis (hypersensitivity pneumonitis)

# Mycoses

- Systemic
  - Histoplasmosis and coccidioidomycosis
- Local
  - Ringworm, thrush, and monilial vaginitis.
- Indoor fungi do not usually cause infection
  - Bird droppings near air intakes can be a source of *Histoplasma capsulatum* and *Cryptococcus neoformans* if disturbed
  - *Aspergillus fumigatus* is a well known hazard to the immunocompromised

# Mycotoxins

- Non-volatile fungal metabolites
- Produced by many molds
- More than 300 known mycotoxins
- Mycotoxin production is poorly understood, thought to be affected by conditions such as fungal strain, genetic susceptibility of the host plant or commodity, moisture content, temperature, aeration, microbial population, and stress factors

# Important Mycotoxins

| Fungal Species | Toxin |
|---|---|
| **Aspergillus** | |
| *Aspergillus parasiticus* | Aflatoxin |
| *Aspergillus flavus* | |
| *Aspergillus versicolor* | Sterigmatocystin |
| *Aspergillus terreus* | Patulin |
| | Citrinin |
| **Fusarium** | |
| *Fusarium moniliforme* | Zearalenone |
| *Fusarium spp.* | Tricothecenes |
| **Penicillium** | |
| *Penicillium viridicatum* | Ochratoxin |
| *Penicillium spp.* | Citrinin |
| | Patulin |
| **Stachybotrys** | |
| *Stachybotrys chartarum (atra)* | Tricothecenes |

# Tricothecenes

- Commonly occurring, more than 150
- Produced by variety of fungi
  - *Fusarium*, *Trichoderma*, *Stachybotrys*, *Cephalosporium*, and *Tricothecium*
- Examples - roridin, verrucarin, satratoxins
- Primary mechanism of action is inhibition of protein synthesis
- Induce redness and irritation of the skin

# *Stachybotrys*

- Found worldwide
- Buildings with *Stachybotrys* growth problems usually have chronic water damage
- *Stachybotrys chartarum* (synonyms *atra*, *alternans*) is one of many fungi capable of producing trichothecene mycotoxins

# Alimentary Toxic Aleukia (ATA)

- Human disease from tricothecenes that was first reported in Russia from 1942-1947
- Often fatal, characterized by vomiting, skin inflammation, hemorrhaging of the GI tract & mucous membranes, immunosuppression, & pancytopenia
- Attributed to eating overwintered grain contaminated by *Fusarium* species
- T-2 toxin implicated as the causative agent

# Other Mycotoxicoses

- 1987 - GI illness from consumption of bread made from wheat contaminated with *Aspergillus* and *Fusarium* occurred in India
  - Deoxynivalenol, nivalenol, acetyldeoxynivalenol were isolated from wheat samples
- Similar illness reported after consumption of moldy rice in China
  - T-2 toxin implicated

# Veterinary Stachybotryotoxicosis

- Reported in large and small animals
- Stomatitis, hemorrhage and necrosis of the gastrointestinal tract, leukopenia, immunosuppression, and skin ulcerations, hyperemia, edema, and tissue necrosis of varying severity
- Atypical form - loss of reflexes, hyperirritability, loss of vision, and inability to move about

# Human Stachybotryotoxicosis

- Russians reported stachybotryotoxicosis in humans with contact with straw or hay in areas where stachybotryotoxicosis was enzootic in horses
- Severe dermatitis, chest pain, sore throat, bloody rhinitis, cough, and leukopenia
- Mold placed on the skin reproduced the clinical syndrome described above

# Human Stachybotryotoxicosis

- 1977 - 23 workers loading moldy hay developed dyspnea, sore throat, bloody nasal discharge, burning & watering eyes, and hyperemic, swollen, crusted skin on the face, & dermatitis in the groin & buttocks
- Symptoms manifested within 24 hours of exposure
- Recovery within 1 week of cessation of exposure

# Human Stachybotryotoxicosis

- Skin scrapings, nasal and throat swabs, and straw grew *Stachybotrys chartarum*
- Compared to indoor, non-industrial environments, the environments described above involved considerable differences in the extent of bioaerosol exposure or ingestion of significant quantities of mycotoxin-contaminated foodstuffs

# Mycotoxins in Indoor Environments

- Thirteen relevant articles
- All of the articles except one involve *Stachybotrys*; six of the articles describe the same investigation of pulmonary hemorrhage in infants

# Croft, et al., 1986

- 5 home occupants with cold & flu symptoms, sore throats, diarrhea, headaches, dermatitis, hair loss, and fatigue
- Medical investigations found no causes
- Cold air return duct & area of wood fiber board were contaminated with *Stachybotrys*
- When mold was cleaned up, symptoms resolved
- Extracts from the molds were injected into experimental animals, which died

# Johanning, et al., 1996

- 39 females and 14 males exposed to *Stachybotrys* in a water-damaged office environment
- Comparison group of 11 females & 10 males
- Health effects assessed by questionnaire
- Affected persons had significantly more lower respiratory, dermatological, eye, constitutional and chronic fatigue symptoms

# Johanning, et al., 1996 (cont)

- 3/24 WBC & immunoglobulin tests different between exposed and comparison
  - CD3% = 75.7 in comparison & 73.7 in exposed
  - WBC = 6.1 in comparison and 6.3 in exposed
  - #NK cells = 42 in comparison & 55 in exposed
- No difference in specific IgG/IgE
- Air & bulk samples from problem building positive for *Stachybotrys*, *Penicillium*, *Cladosporium* and *Aspergillus* - no assessment performed for comparison group

# Hodgson, et al., 1998

- Study of two buildings with history of water incursions
- More symptoms were reported among occupants of problem building compared to occupants of comparison buildings
  - Subjects with sx more likely to participate
- Response rate, demographic factors, smoking status, or job duties between the occupants of the exposed and comparison buildings were not reported

# Hodgson, et al., 1998 (cont)

- 17/47 self-selected individuals had evidence of pulmonary disease (testing not done on unexposed)
- Neuropsych testing better in exposed
- Lower concentrations of fungi indoors than outdoors; differences in types of fungi
- Fungal assessment in comparison buildings was casual observation only

# Hodgson, et al., 1998 (cont)

- Satratoxins isolated from *Stachybotrys chartarum* contaminated ceiling tiles, but not air samples
- Employees with ≥ 2 symptoms in problem building did not have higher levels of antibodies to fungi identified in the building than did unexposed

# Sudakin, 1998

- Office building with health complaints and history of moisture incursion
- Various bacteria and fungi present in air, bulk, and surface samples
- Epi study, consisting of interviews and questionnaire administration, revealed most common symptoms were fatigue, headache, difficulty concentrating, & sinus congestion
- No evidence of objective illness among building occupants was reported

# Auger et al., 1994

- 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
- Propose that research concerning mycotoxins is important in the attempts to explain indoor environmental quality problems

# Acute Pulmonary Hemorrhage/Hemosiderosis

- 8 cases of acute pulmonary hemorrhage during 1/93-11/94 among infants in Cleveland (2 additional cases in 12/94)
- Case-control study - past water damage to homes assessed by questionnaire
  - Cases more likely to reside in homes where parents report water damage in the 6 months prior to the hemorrhage (OR =16.25; 95% CI =2.55 to infinity)

# Pulmonary Hemorrhage/Hemosiderosis

- Aggressive air sampling in follow-up investigation
- *S. chartarum* detected more often & in greater quantity in case homes than controls
- Cases more likely to be black, male, live with a relative who coughed blood, exposed to tobacco smoke, and not to be breast fed
- Cases had significantly lower birth weight

# Pulmonary Hemorrhage/Hemosiderosis

- The CDC has recently released the detailed findings of both internal and external reviews which concluded that a possible association between pulmonary hemorrhage/hemosiderosis in infants and exposure to molds, specifically *Stachybotrys*, was not proven

# Flappan, 1999

- Infant with respiratory distress & shock
- Pulmonary hemorrhage noted on intubation
- Elevated WBC, PT; cultures negative
- Home was evaluated soon after illness
- *Stachybotrys* & other fungal spores found in air & surface samples in infant's bedroom
- Tricothecenes, including roridin & satratoxin found on closet ceiling of infant's bedroom

# Elidemir, et al., 1999

- *Stachybotrys* isolated from BAL fluid of 7 y.o. boy with LLL pneumonia and hemosiderin-laden macrophages
- Cough, fatigue, & recurrent pneumonia since age 5
- Surface cultures of bronchoscopy suite & mycology lab negative for *Stachybotrys*
- *Stachybotrys* found in samples from home
- Pt. relocated & symptoms resolved within 1 month

# Pulmonary Hemorrhage – Chicago (unpublished)

- 7 infants with acute pulmonary hemorrhage from 4/92-11/94
- Case-control study - questionnaire, environmental survey, laboratory evaluation
- No significant difference in race, gender, birth weight, breast feeding, exposure to tobacco smoke, recent water leakage or flooding in home
- *Stachybotrys* more common in control homes, *Trichoderma* in case homes
- Overall, more fungi in control homes

# Methodologic Issues

- Case definitions are generally absent or poorly defined
- Documentation of exposure to a potential causative agent(s) lacking
- Both

# Clinical Illness

- Wide spectrum of health effects
- Case definitions generally absent or poorly defined
  - Croft et al. - nonspecific symptoms &unclear description of medical evaluations
  - Hodgson et al. - undefined clinical diagnoses and epidemiological case definitions
  - Johanning et al. - did not define cases; compared employees of problem building with non-problem building, finding an excess of nonspecific symptoms in the study population

# Exposure Characterization

- Pulmonary hemorrhage – no systematic evaluation of water damage, aggressive sampling months after onset of illness unlikely to be representative of actual exposures to fungi in those homes
- Johanning et al. & Hodgson et al. - antibody testing, ? measure of fungal (not mycotoxin) exposure; found no increased exposure to any specific fungus among problem building occupants compared to comparison

# Exposure Characterization

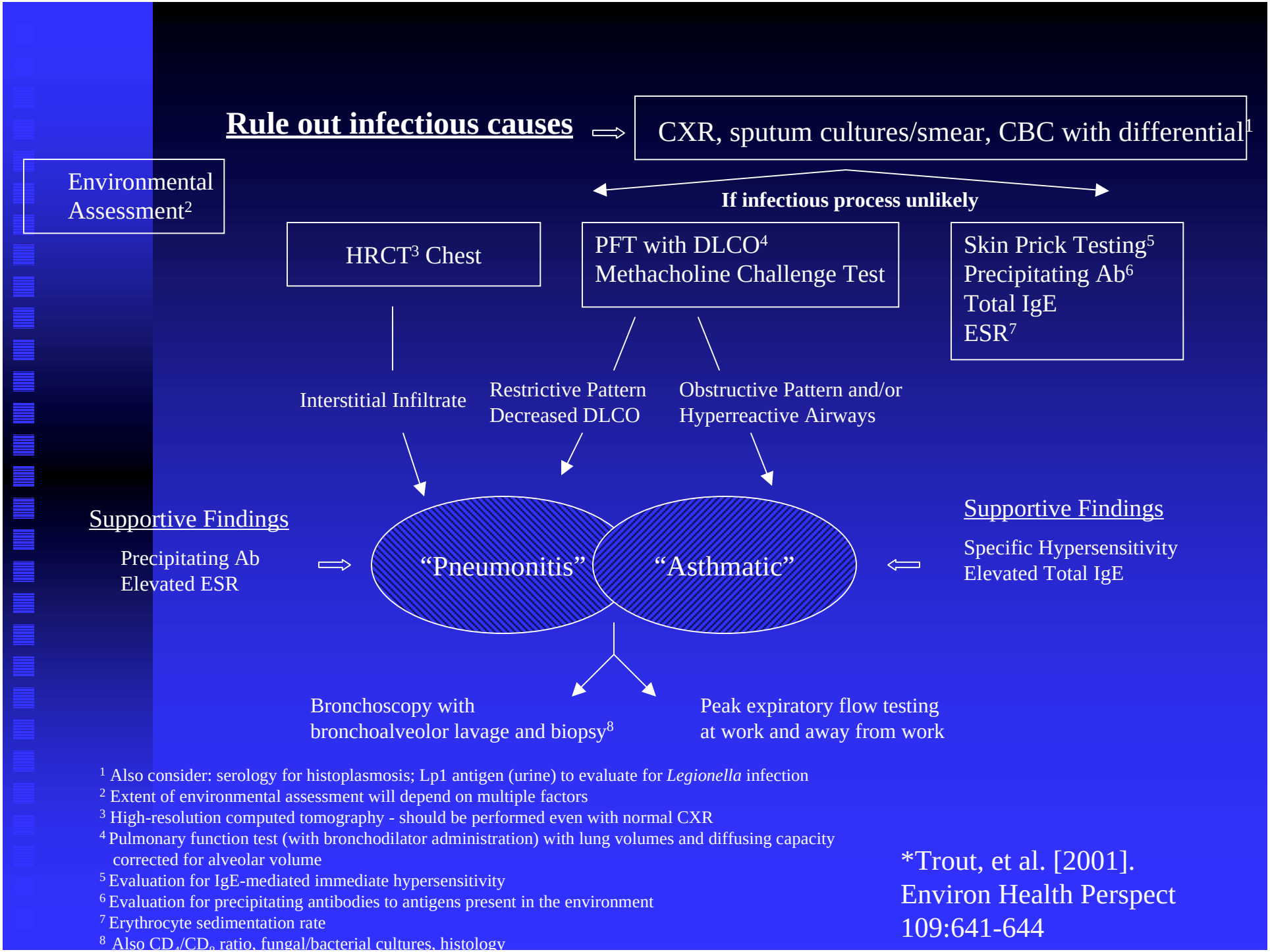
- Several studies have detected mycotoxins in samples from walls, ceiling tiles, and air ducts
- Identification of mycotoxin on a wall or in air duct demonstrates only a potential for exposure, and does not alone provide evidence of exposure, much less evidence linking reported symptoms to the fungi or fungal products

# Conclusions

- Molds are a potential health hazard
  - Allergy
  - Infection
  - Toxicosis
    - Evidence of clinical illness (in humans and animals) from ingestion of significant quantities of mycotoxin-contaminated foodstuffs
    - Illness associated with bioaerosol exposures in agricultural or industrial environments has also been reported
    - Relevance of these findings to the indoor (non-industrial) environment is unclear

# Conclusions

- Inadequate evidence that mycotoxins in indoor (non-industrial) environments causes symptoms or illness among building occupants
- Identification & isolation of fungal toxins in the environment & humans is needed
- Objective measures of adverse health effects must be associated with some measure of mycotoxin exposure
- Comparisons made with appropriate controls




[1] Also consider: serology for histoplasmosis; Lp1 antigen (urine) to evaluate for *Legionella* infection
[2] Extent of environmental assessment will depend on multiple factors
[3] High-resolution computed tomography - should be performed even with normal CXR
[4] Pulmonary function test (with bronchodilator administration) with lung volumes and diffusing capacity corrected for alveolar volume
[5] Evaluation for IgE-mediated immediate hypersensitivity
[6] Evaluation for precipitating antibodies to antigens present in the environment
[7] Erythrocyte sedimentation rate
[8] Also $CD_4/CD_8$ ratio, fungal/bacterial cultures, histology

*Trout, et al. [2001]. Environ Health Perspect 109:641-644

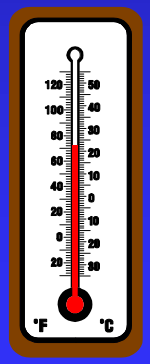
# Indoor Mold Remediation

- Follow the guidelines described in the Environmental Protection Agency's document, "Mold Remediation in Schools and Commercial Buildings" available at http://www.epa.gov/iaq/molds/toc.html
- Identification of mold not necessary

# Fungal Requirements

Moisture

Substrate



Temperature

# Indoor Mold Prevention

# Indoor Mold Prevention

- The key is to control interior moisture
  - Repair leaks
  - Prevent condensation through insulation, increasing surface temperature, or increasing air circulation
  - Vent any moisture-producing equipment or appliances to the outdoors
  - Maintain interior relative humidity below 60% (ideally between 30% and 50% to minimize mold growth)

# Indoor Mold Prevention (cont)

- Ensure that air conditioning systems are adequately drained to prevent standing water
- Clean up and dry any wet or damp spots within 48 hours
- Ensure that water drains away from the building foundation
- Routinely inspect and maintain the building and building systems