Sick Building Syndrome: Is Mould the Cause?

Abba I Terr, MD
Disclosure statement:
Expert testimony in litigation involving claims of mold-induced injuries.
**Sick Building Syndrome (SBS)**

*Definition*: Illness in occupants of building, because of a defect in building structure or because of its use.

- **Disease**: 
  - acute or chronic
  - any cause (micro-organism, chemical fume, or particulate)
  - any mechanism (usually infectious, allergic, toxic, irritant)
- Any number or percentage of occupants
- Any type of building
- Sometimes termed “Building-Related Illness” (BRI)

*e.g.*: *Legionnaire’s disease*: 1976 epidemic of Gram-negative bacterial pneumonia in guests attending American Legion convention @ Philadelphia’s Bellevue-Stratford Hotel. *Legionella pneumophila* contaminating condensate of A/C system and potable water.
Sick Building Syndrome (SBS)

*Other definitions:*

e.g. Illness in which building occupants experience acute health and comfort effects that appear to be linked to time spent in a building, but no specific illness or cause can be identified.
Controversy

Debate over nature of illness from indoor airborne fungal spores
Moulds (Fungi) - microorganisms
Numerous species (>100,000)
> 500,000,000 years
Ubiquitous
25% of earth’s biomass
Airborne spores found indoors as well as outdoors

No debate
Moulds cause human disease through 1 of 3 mechanisms:

1) Infection
2) Allergy
3) Toxicity

(Specific in each case)
No debate

Moulds cause human disease via 1 of 3 mechanisms:
1) Infection
2) Allergy
3) Toxicity

(Specific in each case)
Fungal Infection

• Usually cutaneous or pulmonary in immunocompetent host
• May be systemic in immunocompromised host

Diagnosis: identifying the specific mould in diseased (inflamed) tissue
Moulds cause human disease via 1 of 3 mechanisms:
1) Infection
2) Allergy
3) Toxicity

(Specific in each case)
Fungal Allergy

1) Bronchial asthma (atopic)
2) Hypersensitivity pneumonitis (HP, HSP)
3) Allergic bronchopulmonary aspergillosis (ABPA)
4) Allergic fungal sinusitis (AFRS, AFS)

Diagnosis:

(1) compatible clinical expression
   (history, PE, functional studies, lab, imaging)
(2) appropriate immune response to the specific mould
Moulds cause human disease via 1 of 3 mechanisms:
1) Infection
2) Allergy
3) Toxicity

(Specific in each case)
Toxicity from Moulds (Mycotoxins)

• Organic molecules synthesized by moulds
• Probably all moulds
• "Secondary metabolites" (i.e. not necessary for growth or survival)
• MW 200-500
• Non-volatile
• Synthesis variable and unpredictable
• Found in all mould structures (hyphae, spores, etc)
Mycotoxins.

Mycotoxins

Aflatoxin B¹
Zearalenone
Chaetoglobosin A
Moniliformin
Rubratoxin B
Ochratoxin A
Lolitrem B
T-2 Toxin

Trichothecenes

Satratoxin H
Verrucarin A
Mycotoxins
Defined by effects on experimental animal models

• Numerous studies
• Deliberate attempt to induce toxicity
• Variety of animals
• Variety of animal models
  – in vitro biochemical reactions
  – Isolated tissues
  – Isolated organs
  – Intact animal

• Variety of exposure methods
  – oral, inhaled, etc

Therefore, mycotoxicity is defined by dosage in a prescribed experimental method using a particular animal species.
Trichothecenes

Cytoxicity
Metabolic inhibition
Hemolysis
Plasmin effects
Pulmonary effects
Immunologic effects
Cytokine effects
Cholesterol effects
Neurologic effects
Others
Human Mycotoxicity
Case reports & epidemiologic evidence

By ingestion *(almost always)*
- mushroom poisoning
- ergotism
- “alimentary toxic aleukia,” “yellow rice disease,” aflatoxicosis, “endemic nephropathy”

By inhalation *(rare)*
- Pulmonary mycotoxicosis (ODTS)
  - occupational disease of farmers
  - “Silo Unloader’s Disease”
  - mycotoxin concentration unknown, but massive
  - inhalation of $10^{5-10}$ mould spores/$M^3$ air
  - complicated by bacterial endotoxin, etc.
Moulds cause human disease via 1 of 3 mechanisms:
1) Infection
2) Allergy
3) Toxicity by ingestion

( Specific in each case )
Threshold level of human pathogenicity
(airborne spores/M^3)

- **Allergy** – *unknown*
  - Induction
    *Genetic factors*
  - Provocation
    *Varies with the individual, duration & intensity of exposure, presence of other aeroallergens*

- **Infection** – *unknown*
  *Varies with underlying susceptibility (eg. immunodeficiency)*

- **Toxicity** – *unknown*
Main areas of debate
(illness from indoor airborne fungal spores)

Mechanism(s) of disease?

1) Inhalational toxicity (non-specific)
2) Inhalational irritation (non-specific)
Main areas of debate
(illness from indoor airborne fungal spores)

Mechanism(s) of disease?

1) Inhalational toxicity *(non-specific)*
2) Inhalational irritation *(non-specific)*
Proposed illnesses from mycotoxin

- Infantile pulmonary hemorrhage (hemosiderosis)
- Epistaxis
- Encephalopathy
- Immune toxicity
  - Autoimmunity
  - Immune deficiency
- Other subjective complaints (fatigue, dyspnea, GI distress, neurologic complaints, etc.)
Proposed illnesses from mycotoxin

• Infantile pulmonary hemorrhage (hemosiderosis)
• Epistaxis
• Encephalopathy
• Immune toxicity
  Autoimmunity
  Immune deficiency
• Other subjective complaints (fatigue, dyspnea, GI distress, neurologic complaints, etc.)
The Cleveland experience

- Initially, a cluster of cases of pulmonary hemorrhage/hemosiderosis in very young infants  
  (10 cases in 2 years (1993-4) in localized urban area)
- **Method:** Environmental survey
- **Result:** Risk factors in the homes  
  - Water-damage  
  - Adult smokers
The Cleveland experience

- A number of publications, concluding that the disease in very young infants was probably caused by a toxin from inhaled Stachybotrys spores.
- Guidelines by AAP
- Media coverage
- Congressional hearings
- Litigation
The Cleveland experience

CDC investigation - 1999

• 2 expert panels reviewed the data
• “serious shortcomings,” e.g.
  – Sampling of cases and control homes differed and not standardized
  – Results skewed by extremely high outlying values
  – Concerns about quantitation of water damage
  – Concerns about whether exposure measurements to Stachybotrys or its toxins were clinically significant (vs. contamination)
The Cleveland experience

CDC investigation - 1999

• Conclusion:

“a possible association between acute pulmonary hemorrhage … and [mold] exposure … was not proven”
Proposed illnesses from mycotoxin

- Infantile pulmonary hemorrhage (hemosiderosis)
- Epistaxis
- Encephalopathy
- Immune toxicity
  - Autoimmunity
  - Immune deficiency
- Other subjective complaints (fatigue, dyspnea, GI distress, neurologic complaints, etc.)
Epistaxis from exposure to fungi &/or fungal products

• Common symptom
• Publications reveals no clinical or experimental data

Therefore: no evidence
Proposed illnesses from mycotoxin

- Infantile pulmonary hemorrhage (hemosiderosis)
- Epistaxis
- Encephalopathy
- Immune toxicity
  - Autoimmunity
  - Immune deficiency
- Other subjective complaints (fatigue, dyspnea, GI distress, neurologic complaints, etc.)
Cognitive impairment by mycotoxins

“Toxic encephalopathy”

- Short-term memory loss
- Poor attention span
- Difficult concentrating
Cognitive impairment by mycotoxins

- Extensive literature on mushroom ingestion poisoning
  - Multiorgan failure; esp hepatic, renal
  - Uremic encephalopathy

- Reports of “encephalopathy” from inhalation of mold spores?
"Toxic encephalopathy" from exposure to mold spores


–patient selection bias
–“neuropsychologic” data subjective
–lack of a valid comparison group(s)
  (comparison with premorbid estimates of intelligence, normative data, etc.)
–no mycotoxin exposure measurements

Does abnormal psychologic testing indicate "toxic encephalopathy" from mycotoxins?

No credible evidence
Proposed illnesses from mycotoxin

• Infantile pulmonary hemorrhage (hemosiderosis)
• Epistaxis
• Encephalopathy
• Immunologic effects
  Autoimmunity
  Immune deficiency
• Other subjective complaints (fatigue, dyspnea, GI distress, neurologic complaints, etc.)
Mycotoxicity as a cause of immune dysregulation???

Autoimmunity - *no studies, therefore no evidence*

Immune deficiency - *no studies, therefore no evidence*
Proposed illnesses from mycotoxin

- Infantile pulmonary hemorrhage (hemosiderosis)
- Epistaxis
- Encephalopathy
- Immune toxicity
  - Autoimmunity
  - Immune deficiency
- Other subjective complaints (fatigue, dyspnea, GI distress, neurologic complaints, etc.)
Subjective complaints

fatigue, headache, dyspnea, GI distress, etc
induced by mold or mycotoxin?

No studies - no evidence
Main areas of debate
(illness from indoor airborne fungal spores)

Mechanism(s) of disease?

1) Inhalational toxicity (non-specific)
2) Inhalational irritation (non-specific)
Human fungal disease

1 - Infection
2 - Allergy
3 - Toxicity
4 - Irritation??
“Irritation or Aeroirritation”

Definition: functional stimulation of nasal mucous membranes, conjunctivae, or skin

• Usually a particulate; may be chemical
• Transient or temporary
• Probably dose-dependent
Definition: functional inhibition (or disturbance in the structure)

- Usually a chemical
- Permanent (usually) or temporary
- Dose-dependent

(cf. Toxicity)
Excess dampness and mold growth in homes: An evidence-based review of the aeroirritant effect and its potential causes

Andrew P. Hope, M.D.,*# and Ronald A. Simon, M.D.*

“Irritation or Aeroirritation”

16 Studies

1 - Asthma only - no irritation
1 - Allergic rhinitis (single case report)
14 - Symptoms consistent with respiratory mucous membrane irritation

4 - Adults
8 - Children
2 - All ages
“Irritation or Aeroirritation”

14 Studies

Buildings studied:

10 - Houses or apartments
2 - Schools
1 - Office buildings
1 - Hospitals
“Irritation or Aeroirritation”

14 Studies

All epidemiologic questionnaires: ? Significant symptom-exposure correlation

Number of subjects studied: 25 - 33,606

Objective clinical tests (physical exams, etc.) included?

13 - NO

1 - limited EENT

Objective environmental measurements included?

10 - NO (both symptoms & environmental conditions by questionnaire)

4 - Some measurements

1 - Airborne chemicals only
1 - Endotoxin, house dust mite
1 - Dust cultured for mould, others
1 - Airborne mould & humidity*

“Irritation or Aeroirritation”

*“After full remediation in one [moisture-damaged] school, elevated concentrations and increased frequency of indoor air fungi normalized and a significant decrease in prevalence of 10 of the 12 symptoms studied was observed among schoolchildren.”*
Fungal Irritation
(from indoor airborne spores)

Presumptive Causes

\[ \beta-(1\rightarrow3)-\text{D-Glucans} \]

\[ \text{mVOC} \]

\[ \text{mycotoxins} \]
Fungal Irritation
(from indoor airborne spores)

β-(1→3)-D-Glucans

• Structural cell wall polyglucose compounds of all fungi.
• Surrogate markers of mould presence.

“the preponderance of [human experimental and] epidemiologic studies have been unable to show consistently that exposure to β-(1-3)-D-Glucans correlates with irritant upper airway and/or eye symptoms”

Hope, Simon
Fungal Irritation
(from indoor airborne spores)

mVOC

- microbial volatile organic compounds (fungal)
- Small organic molecules: alcohols, aldehydes, ketones
- Byproducts of metabolism of microbes
- Volatile, odorous
- Studies of commercial VOCs: nasal & eye sensory irritation well above odor threshold

“…calculat[ed] levels of VOCs in the problem buildings would be unlikely by this prediction model [i.e. murine irritation threshold] to cause irritant symptoms [in humans].”

Hope, Simon
Fungal Irritation
(from indoor airborne spores)

Mycotoxins

No studies
Summary

• Moulds are responsible for disease of humans through:
  – Allergy
  – Infection
  – Toxicity from ingestion

• Moulds are unlikely to cause human disease through:
  – Toxicity from inhalation
  – Irritation from inhalation

• These controversial concepts arise, not from scientific curiosity or clinical suspicion, but rather through:
  – Litigation
  – The media
  – The internet
**Litigation effects on Neuropsychological Tests**


And others

- **In litigated cases:**
  Pre-exposure history often reported in unusually benign terms
  Important stressors in life often discounted

- **In litigated brain injury cases,** results of neuropsychological testing are often more impaired than are the results in *nonlitigated* cases
The Internet

- Fungi: 16,900,000
- Molds: 10,300,000
- Indoor molds: 1,190,000
- Mold illness: 835,000

- PubMed by text word: 44588
- PubMed by title word: 7667