

# **Sick Building Syndrome: Is Mould the Cause?**

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Disclosure statement:

Expert testimony in litigation involving  
claims of mold-induced injuries.

# Sick Building Syndrome (SBS)

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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)

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## 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

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Debate over nature of illness from indoor  
airborne fungal spores

# No debate

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- 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

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Moulds cause human disease  
*through 1 of 3 mechanisms:*

- 1) Infection
- 2) Allergy
- 3) Toxicity

*(Specific in each case)*

# No debate

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Moulds cause human disease

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# Fungal Infection

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

Diagnosis: *identifying the specific mould in diseased (inflamed) tissue*

# No debate

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**2) Allergy**

3) Toxicity

*(Specific in each case)*

# Fungal Allergy

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- 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*

# No debate

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*(Specific in each case)*

# Toxicity from Moulds (Mycotoxins)

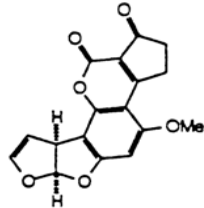
- Organic molecules synthesized by moulds
- Probably all moulds
- "Secondary metabolites" (*i.e. not necessary for growth or survival*)
- MW 200-500
- Non-volatile
- Synthesis variable and unpredictable
- Found in all mould structures (*hyphae, spores, etc*)

# Mycotoxins.

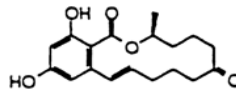
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- Acetoxyscirpenediol, Acetyldeoxynivalenol, Acetylneosolaniol, Acetyl T-2 toxin, Aflatoxin, Aflatrem, Altenuic acid, Alternariol, Austdiol, Austamide, Austocystin, Avenacein, Beauvericin, Bentenolide, Brevianamide, Butenolide, Calonectrin, Chaetoglobosin, Citrinin, Citreoviridin, Cochliodinol, Crotoxin, Cytochalasin E, Cyclopiazonic acid, Deacetylcalonectrin, Deoxynivalenol, Diacetoxyscirpenol, Destruxin B, Enniatins, Fructigenin, Fumagilin, Fumonisin B1, Fusaric acid, Fusarin, Gliotoxin, HT-2 toxin, Ipomeanine, Islanditoxin, Lateritin, Lycomarasmin, Malformin, Maltoryzine, Moniliformin, Monoacetoxyscirpenol, Neosolaniol, Nivalenol, NT-1 toxin, NT-2 toxin, Ochratoxin, Oxalic acid, Patulin, Penicillic acid, Penitrem, Roridin E, Rubratoxin, Rubroskyrin, Rubrosulphin, Rugulosin, Sambucynin, Satratoxins, Scirpentriol, Slaframine, Sterigmatocystin, T-1 toxin, T-2 toxin, Triacetoxyscirpendiol, Trichodermin, Trichothecin, Trichoverrins, Trichoverrols, Tryptoquivalene, Verrucaridin, Verruculogen, Viopurpurin, Viomellein, Viriditoxin, Yavanicin, Xanthocillin, Zearalenone

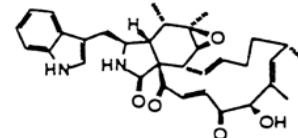
# Mycotoxins



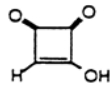
**Aflatoxin B<sup>1</sup>**



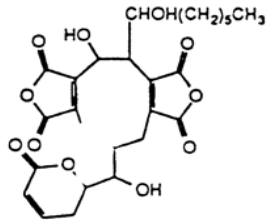
**Zearalenone**



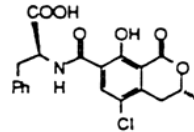
**Chaetoglobosin A**



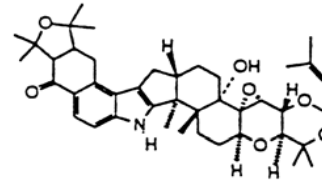
**Moniliformin**



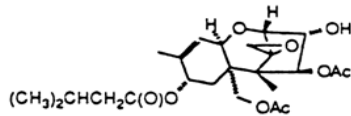
**Rubratoxin B**



**Ochratoxin A**

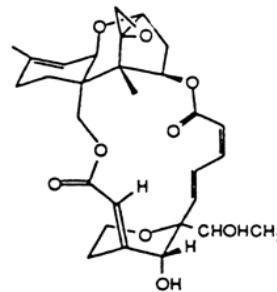


**Lolitre B**

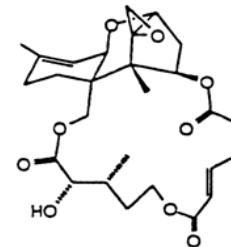


**T-2 Toxin**

**Trichothecenes**



**Satratoxin H**



**Verrucaric acid**

# Mycotoxins

Defined by effects on experimental animal models

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- 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

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Cytotoxicity  
Metabolic inhibition  
Hemolysis  
Plasmin effects  
Pulmonary effects  
Immunologic effects  
Cytokine effects  
Cholesterol effects  
Neurologic effects  
Others

# Human Mycotoxicity

*Case reports & epidemiologic evidence*

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## 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<sup>3</sup> air
  - complicated by bacterial endotoxin, etc.

# No debate

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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<sup>3</sup>*)

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- 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

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*(illness from indoor airborne fungal spores)*

## Mechanism(s) of disease?

- 1) Inhalational toxicity (*non-specific*)
- 2) Inhalational irritation (*non-specific*)

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# Proposed illnesses from mycotoxin

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

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# The Cleveland experience

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- 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

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- 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

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## 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

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CDC investigation - 1999

- Conclusion:
  - “ *a possible association between acute pulmonary hemorrhage ... and [mold] exposure ... was not proven*”

# Proposed illnesses from mycotoxin

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# Epistaxis from exposure to fungi &/or fungal products

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- Common symptom
- Publications reveals no clinical or experimental data

*Therefore: no evidence*

# Proposed illnesses from mycotoxin

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# Cognitive impairment by mycotoxins

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*“Toxic encephalopathy”*

- Short-term memory loss
- Poor attention span
- Difficult concentrating



# Cognitive impairment by mycotoxins

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- 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*

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- Baldo J et al. Neuropsychological performance of patients following mold exposure  
Appl Neuropsychol 2002. 9:193.
- Crago B et al. Psychological, neuropsychological, and electrocortical effects of  
mixed mold exposure. Arch Environ Health 2003.58:452.
- Campbell A et al. Neural autoantibodies and neurophysiologic abnormalities in  
patients exposed to molds in water-damaged buildings. Arch Environ Health  
2003.58:464.
- Kilburn, K. Indoor mold exposure associated with neurobehavioral and pulmonary  
impairment: a preliminary report. Arch Environ Health 2003.58:390.

–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???*

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Autoimmunity - *no studies, therefore no evidence*

Immune deficiency - *no studies, therefore no evidence*

# Proposed illnesses from mycotoxin

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- Other subjective complaints (fatigue, dyspnea, GI distress, neurologic complaints, etc.)

# *Subjective complaints*

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

***No studies - no evidence***

# Main areas of debate

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*(illness from indoor airborne fungal spores)*

## Mechanism(s) of disease?

- 1) Inhalational toxicity (*non-specific*)
- 2) Inhalational irritation (*non-specific*)

# Human fungal disease

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1 - Infection

2 - Allergy

3 - Toxicity

4 - Irritation??



# “Irritation or Aeroirritation”

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

- Usually a particulate; may be chemical
- Transient or temporary
- Probably dose-dependent

## (cf. Toxicity)

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Definition: *functional inhibition (or disturbance in the structure)*

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

**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.\**

*Allergy Asthma Proc. 2007 May-Jun;28(3):262-70.*

# “Irritation or Aeroirritation”

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## 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”

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14 Studies

*Buildings studied:*

10 - Houses or apartments

2 - Schools

1 - Office buildings

1 - Hospitals

# “Irritation or Aeroirritation”

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## 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”

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*\*“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)*

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## Presumptive Causes

$\beta$ -(1 $\rightarrow$ 3)-D-Glucans

mVOC

mycotoxins



# Fungal Irritation

*(from indoor airborne spores)*

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## $\beta$ -(1 $\rightarrow$ 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  $\beta$ -(1-3)-D-Glucans correlates with irritant upper airway and/or eye symptoms”*

*Hope, Simon*

# Fungal Irritation

*(from indoor airborne spores)*

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## 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)*

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Mycotoxins

No studies

# Summary

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- 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

Lees-Haley PR et al. Toxic mold and mycotoxins in neurotoxicity cases: Stachybotrys, Fusarium, Trichoderma, Aspergillus, Penicillium, Cladosporim, Alternaria, Trichothecenes. Psychol Reports 2003. 93:561.  
And others

- *In litigated cases:*

- Pre-exposure history often reported in unusually benign terms
  - Important stressors in life often discounted

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

# The Internet

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- 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