



The Socrates Award Lecture 2002
Toxic Mold

Professor Roger Coulombe
Utah State University
Logan, Utah USA

Toxic Molds



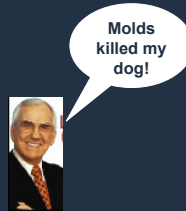
2

Toxic Molds: The Hype



3

Toxic Molds: The Hype



4

Molds
killed my
dog!



5

Toxic Molds: The Hype



6



Time July 2, 2001



CBS 48 hrs September 2000



Fargo Forum, May 1, 1997

Toxic Molds

- Allergy: sensitization to mold or products

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Toxic Molds

- Allergy: sensitization to mold or products
- Mycosis: direct infection of fungi
- Irritation: mechanical effects of spores, mycelial debris, VOCs
- Mycotoxicosis: response to toxin ("mycotoxin")

Toxic Molds

Fungus	Allergy	Mycosis	Irritation	Mycotoxicosis
<i>Stachybotrys</i>	+	±	+	+
<i>Coccidioides</i>	±	+	±	-
<i>Claviceps</i>	+	+	+	+
<i>Fusarium</i>	+	±	+	+
<i>Aspergillus</i>	+	+	+	+

+ reported, ± possible, - not reported
 Fung et al., *Clinical Tox.* 36: 79-86 (1998)

Mycotoxins

- Resting stage secondary metabolites
 - Low MW, not required for growth...

13

Mycotoxins

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- Polyketide, amino acid, or terpene precursor...

14

Mycotoxins

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- Polyketide, amino acid, or terpene precursor...
- Why?
 - Storage products? Competitive advantage?

15

Mycotoxins

- Resting stage secondary metabolites
 - Low MW, not required for growth..
- Polyketide, amino acid, or terpene precursor...
- Why?
 - Storage products? Competitive advantage?
- Beneficial: antibiotic; adverse: toxic, carcinogenic

16

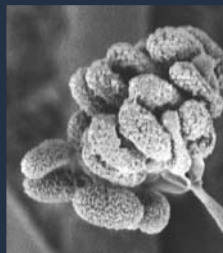
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<i>Aspergillus</i>	+	+	+	+

17

Stachybotrys

- *S. chartarum* (aka. *atra*)
- Hay and cellulose products favorite substrates
- Water-damaged buildings



18

Stachybotrys



Straw contaminated with *S. chartarum* (top); clean straw (bottom).

- Persons handling this contaminated straw could develop stachybotryotoxicosis

Stachybotrys



Mold growth on water-damaged interior wall



There's gold in mold

Stachybotryotoxicosis

- Animals:
 - irritation of mouth, throat, and nose...
 - Shock...
 - dermal necrosis...
 - leukopenia...
 - pulmonary (alveolar, bronchiolar, interstitial) inflammation and hemorrhage...
 - nervous disorder; death

Stachybotryotoxicosis

- 19th Century Russia: numerous veterinary and human epidemics
 - ATA “Alimentary Toxic Aleukia”

25

Stachybotryotoxicosis

- 19th Century Russia: numerous veterinary and human epidemics
 - ATA “Alimentary Toxic Aleukia”
- 1931 Ukraine
 - inhalation of mold from hay and contaminated bedding

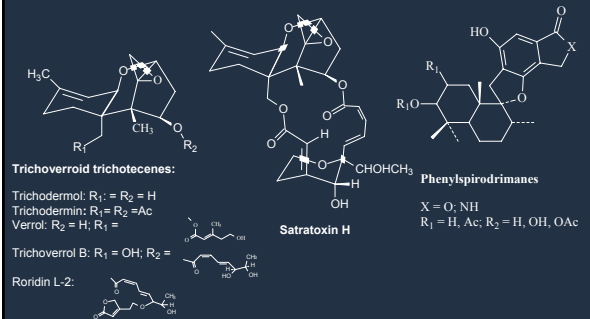
26

Stachybotryotoxicosis

- 19th Century Russia: numerous veterinary and human epidemics
 - ATA “Alimentary Toxic Aleukia”
- 1931 Ukraine
 - inhalation of mold from hay and contaminated bedding
- Occupational cases at:
 - Cottonseed oil plants
 - Grain elevators
 - Malting
 - Textile mills
 - Binder twine factories

27

Toxins from *S. chartarum*



28

Stachybotryotoxicosis

- People: inhalation, dermal exposure
 - dermatitis...
 - inflammation of mucous membranes...
 - upper respiratory symptoms..
 - fever..
 - Leukopenia...
 - headache, fatigue...
 - then recovery...
- Cause of Infantile Pulmonary Hemorrhage (IPH)?

29

Stachybotrys-IPH link?

- Cleveland (1994): IPH “cluster” in one neighborhood
- 10 cases; one expired

All associated with:

CDC. MMWR 1994;43:881-3.
 CDC. MMWR 1997;46:33-5.

30

Stachybotrys-IPH link?

- Major household water damage 6 mo before illness
- Increased levels of measurable household fungi, including the toxin-producing mold *S. chartarum*.
- Toxins isolated from fungal cultures

CDC. MMWR 1994;43:881-3.

CDC. MMWR 1997;46:33-5.

Montaña E, *et al.*. Pediatrics 1997;99:117-24.

Etzel RA, *et al.*. Arch Pediatr Adolesc Med 1998;152:757-62.

Jarvis BB, *et al.*. Appl Environ Microbiol 1998;64:3620-5.

31

S. chartarum and IPH: No association

- Samples from “sick homes” analysed more rigorously
 - Twice the number of air samples
 - More aggressive, non-standard sampling methods

(MMWR 49(09);180-4 March 10, 2000)

32

S. chartarum and IPH: No association

- Samples from “sick homes” analysed more rigorously
 - Twice the number of air samples
 - More aggressive, non-standard sampling methods
- No standard methods for:
 - Defining “water damage”
 - Inspecting and recording data
 - Defining IPH
 - Any pulmonary bleeding qualified

33

CDC

Data insufficient to support association between *S. chartarum* and IPH

MMWR 49(09);180-4 March 10, 2000)

34

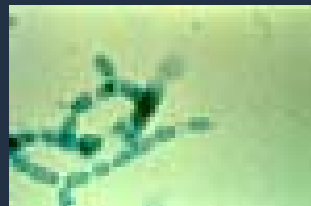
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35

Coccidioides

- *Coccidioides immitis*



36

Coccidioidomycosis

- First described - 1894 (California)
- Inhalation of fungal hyphae..
- Most cases asymptomatic, self resolving...

37

Coccidioidomycosis

- California 1894
- San Joaquin Valley Fever *aka* "Valley Fever"
- Endemic in Southwestern U.S.
- CDC: "emerging disease" –
 - Changing demographics
 - AIDS definer



38

Coccidioidomycosis - symptoms

- Primary coccidioidomycosis:
 - Acute bronchitis: fever, cough, chills, sore throat
 - pneumonia
 - leukocytosis

Diffuse thin-walled cavities



Coccidioidomycosis - symptoms

- Primary coccidioidomycosis:
 - Acute bronchitis: fever, cough, chills, sore throat
 - pneumonia
 - leukocytosis
- Progressive:
 - low grade fever
 - anorexia, weight loss
 - skin ulcerations - face, abdomen
 - abscesses
 - progressive cyanosis
 - renal, hepatic involvement



40

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41

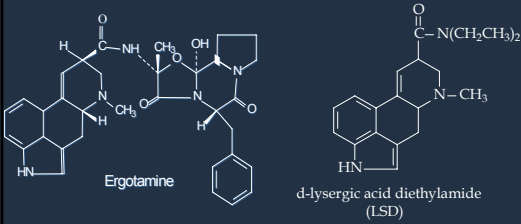
Claviceps

- *Claviceps purpurea, paspalli*
- grows in wet and overwintered grains: rye, barley, wheat
- sclerotia or "ergots"
- "Ergotism"
 - gangrene and/or convulsions and gastrointestinal symptoms
 - ↓ weight gains, milk production, reproductive efficiency



42

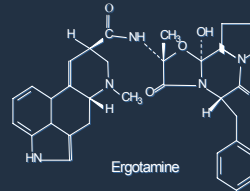
Ergotamine



43

Ergotamine

- Ergotamine:
 - Analogue of lysergic acid dimethylamide (LSD)
 - Vasoconstrictor
- hallucinations, gangrene
- *St. Anthony's fire*



44

A new spin on Salem witches

By Peter H. Gott, M.D.
Newspaper Enterprise Association

DEAR DR. GOTT:
Could the witches of Salem have suffered from physical ailments?

DEAR READER:
Historical documents indicate that 24 of the 30 victims suffered from "fits." Rather than convulsions, which in modern parlance involves loss of consciousness, the young women in Salem may well have exhibited spasmodic movements without fainting. They also complained of sensations of being bitten and pricked. In addition, they were reported to have experienced temporary blindness, deafness and speechlessness. They had hallucinations and out-of-body experiences, such as flying through the air. They were nauseated and weak. Some died, as did several cows in the communities. All these symptoms were blamed



on witchcraft when, in fact, they were probably the results of epidemic ergot poisoning from tainted rye bread and contaminated rye grass.

Ergot is a natural alkaloid with effects similar to that of the hallucinogen LSD. Produced by a fungus in rye, ergot colors the flour cherry red. Baking, unlike boiling, does not diminish the toxicity.

In Salem (and similar communities), rye harvested in August usually lay without being threshed in barns until winter, an open invitation for fungal growth. Moreover, because of bad weather, there was a food scarcity in Salem during the summer of 1692. Thus, residents may have been forced unknowingly to rely on contaminated grain harvested more than a year before.

There are many other historical examples of societies that punished the socially unacceptable because of presumed religious reasons, most often heresy and consorting with the devil, when in fact the victims suffered from undiagnosed illnesses or poisonings of one kind or another.

This lesson should continue to give us pause.

11-30-02
Herald Journal,
Logan UT

47

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46

Fusarium

- *F. sporotrichioides* and *graminearum*
- Corn, wheat, barley
- Veterinary and Public Health
- Major toxins:
 - Trichothecenes, zearalenone, fumonisin



47

Fusarium mycotoxins

- Trichothecenes, Zearalenone, Fumonisin

48

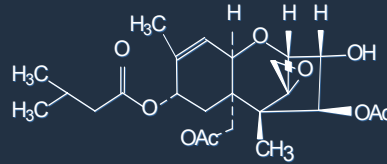
Fusarium mycotoxins

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49

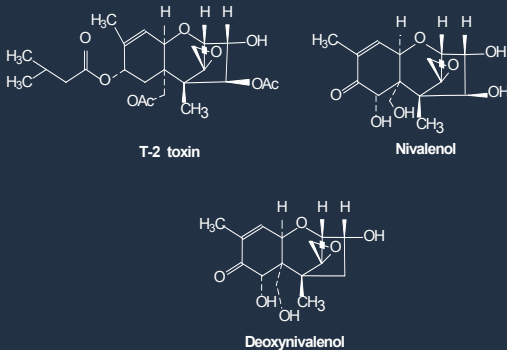
Tricothecenes

- Sesquiterpenoid tetracyclic compounds



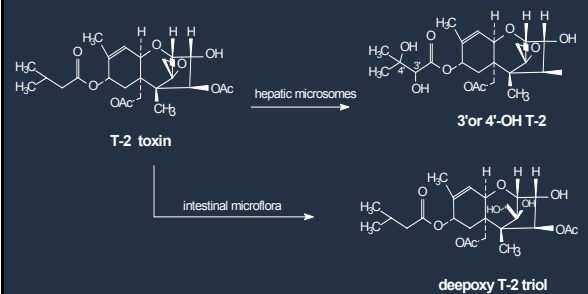
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Tricothecenes



51

Metabolism of T-2 toxin...



52

Metabolism of T-2 toxin...

- Metabolites are **less toxic** than T-2

53

T-2 toxin: Toxicity

- Digestive disorders:
 - Feed refusal, vomiting, bloody diarrhea, intestinal inflammation
- Hemorrhage
 - Stomach, heart, intestines, lung, bladder, kidney
- Edema
- Oral lesions
- Blood disorders
- Immunotoxic

54

T-2 toxin: Mechanism of action

- Binds to ribosomes; 1: 1
- Inhibits all steps of protein synthesis
 - Initiation, elongation, termination

55

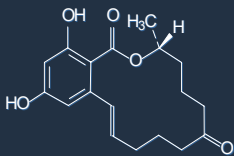
Fusarium mycotoxins

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56

Zearalenone

- *F. graminearum* and *F. sporotrichioides*
- Corn, wheat, barley, oats, sorghum, hay
- High humidity, low temps (Autumn harvest in upper Midwest)
- Often coincident with T-2



57

Zearalenone: toxicity

- Swine (>0.1 ppm): estrogenic effects
 - vulvovaginitis, swollen mammae
- Swine (50-100 ppm): ↓ reproduction
 - Cycling, conception, ovulation, implantation
- Boars (>0.1 ppm): feminization
 - Testicular atrophy, enlarged nipples
- Cows: ↓ conception rates

58

Zearalenone: mechanism of action

- Binds to estrogen receptor
- ZEN binding affinity: = 17 β estradiol; < estradiol
- Estrogen receptor affinity: swine > rat > chicken

59

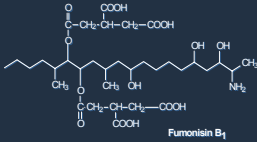
Fusarium mycotoxins

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60

Fumonisin

- *F. moniliforme* (universal in corn)
- Corn, wheat, barley, oats, sorghum, hay
- High humidity, low temps (Autumn harvest in upper Midwest)
- Often coincident with T-2
- Horses, pigs most susceptible
- FB₁ most toxic



61

Fumonisin B1: toxicity

- Neurotoxicity: Equine leukoencephalomalacia (ELEM)
 - “Moldy corn toxicosis”
 - Rapid onset (few hours)
 - Feed and water refusal, lameness, ataxia, paralysis
 - Severe cerebral edema, focal malacia (softening), liquefaction of white matter

62

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- Pulmonary Edema: Porcine pulmonary edema syndrome (PPE)
 - Hydrothorax and lung edema
 - Usually fatal

63

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 - Severe cerebral edema, focal malacia (softening), liquefaction of white matter
- Pulmonary Edema: Porcine pulmonary edema syndrome (PPE)
 - Hydrothorax and lung edema
 - Usually fatal
- Liver cancer and liver toxicity

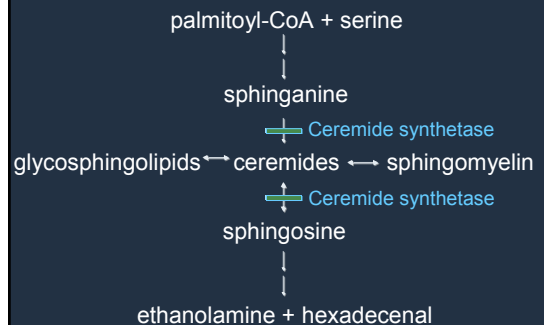
64

Fumonisin B1: animal toxicity

- Horses (1-126 ppm):
 - fatal ELEM
 - Liver toxicity at higher doses
- Swine (<1 – 5 ppm) :
 - Low dose: hepatic toxicity
 - High dose: acute pulmonary edema, hepatic toxicity
- Sheep:
 - nephritis

65

Fumonisin B1 inhibits ceramide synthetase



66

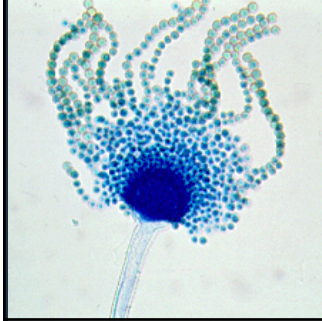
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67

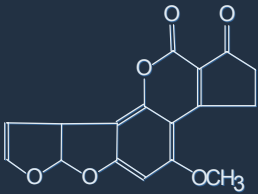
Aspergillus

- Dietary carcinogen



Aflatoxin B1

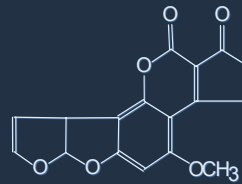
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– corn, peanuts, wheat, rice...



69

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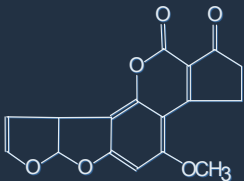
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- Animal carcinogen - 5 ppb



70

Aflatoxin B1

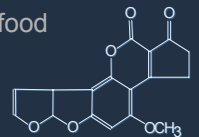
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- Animal carcinogen - 5 ppb
- FDA “action level” - 20 ppb



71

Aflatoxin B1

- (*Aspergillus flavus*)-universal food contaminant
– corn, peanuts, wheat, rice...
- Animal carcinogen - 5 ppb
- FDA “action level” - 20 ppb
- Human liver carcinogen
– binds to N⁷ Gua
– G→T in p53 codon 249



72

Aflatoxin B₁

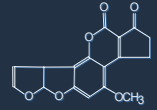
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- Human liver carcinogen
 - binds to N⁷ Gua
 - G→T in p53 codon 249
- Lung cancer risk (respirable grain dusts > 4000 ppb AFB₁)
 - food industry, grain harvesting, transport, storage, processing



73

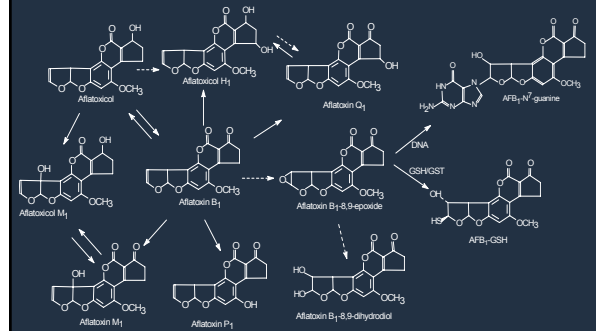
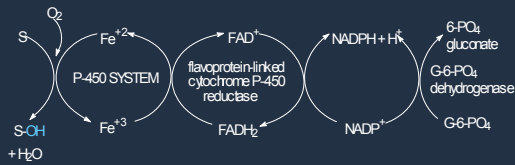
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 - binds to N⁷ Gua
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- lung cancer risk (respirable grain dusts > 4000 ppb AFB₁)
 - food industry, grain harvesting, transport, storage, processing
- Requires bioactivation

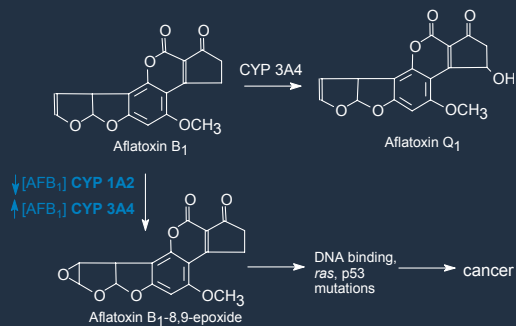


74

Cytochrome P450 (CYP) reaction sequence



76

AFB₁ activation: enzymology

77

Inhaled AFB₁ human cancer risk?

78

Questions?

