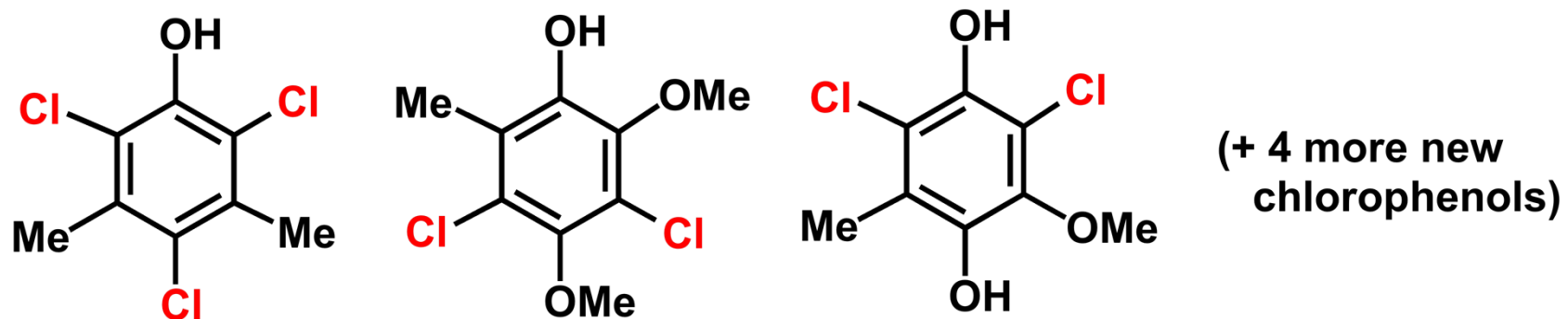


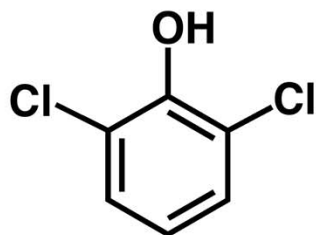
Chlorinated Fungicides Produced by the Edible Japanese Lily



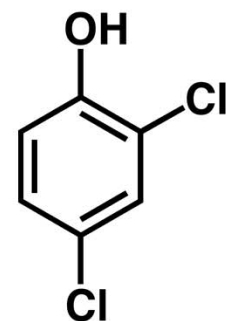
- produced by the edible Japanese lily (*Lilium maximowiczii*) in direct response to attack by the pathogenic plant fungus *Fusarium oxysporum* at the site of infection
- chloroperoxidase, hydrogen peroxide, and chloride are all used by the lily in this biosynthesis
- these 7 chlorophenols were previously unknown compounds and have no anthropogenic counterparts

K. Monde *et al.* *Journal of Natural Products*, 1998, 61, 913.

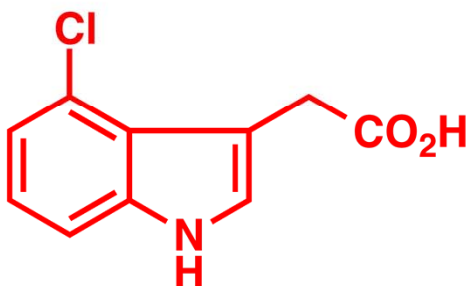
Naturally Occurring Chlorinated Phenols



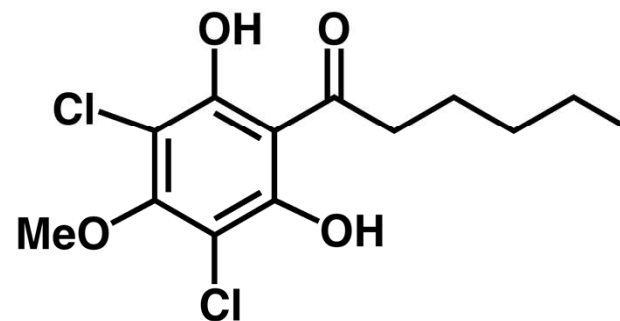
- Sex pheromone of 14 species of tick
- Radiolabeled chloride experiments indicate that the compound is biosynthesized by the tick



- Growth hormone produced by the soil fungus *Penicillium* sp.

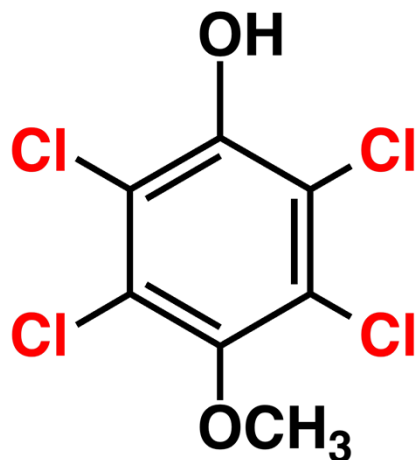


- Plant growth hormone found in peas, several beans, lentils, vetch



- Slime mold (*Dictyostelium discoideum*)
- Hormone that triggers the transformation of undifferentiated cells into fruiting bodies

Natural Chlorinated Phenol in Wild Boar



Drosophilin A - a natural fungal metabolite first isolated in 1952

Produced by these fungi: *Drosophila subatrata*, *Fomes fastuosus*, *Fomes robiniae*, *Phellinus yucatensis*, *Agaricus bisporus*

Found in wild boar meat

Suspected source is the boars' diet of mushrooms

Drosophilin A is one of more than 100 naturally occurring terrestrial chlorinated phenols

W. Vetter et al., *J. Agric. Food Chem.* 2011.

G. W. Gribble, *Prog. Chem. Org. Nat. Prod.* 91, 1 (2010)

***Myriad natural chemicals are
in **ALL** of our
food and drink***

Chemicals in Some Foods

- Mango - **76 chemicals** identified (toluene 41 ppb; dimethylstyrene 2.5 ppb)
- Papaya - **106 chemicals** identified (toluene 4.6 ppb; styrene 0.1 ppb; pyridine 0.1 ppb; PhCHO 0.3 ppb; PhCH₂CHO 0.8 ppb; Ph-N=C=S)
- Cooked Egg - **141 chemicals** identified (indole, furans, thiazoles, thiophenes, pyrroles, pyrazines, aldehydes, ketones, alcohols, phenols, 2-cresol)
- Roasted Coffee - **826 volatile chemicals** identified, 16 of which are carcinogenic in rodents (1 cup = 10 mg (40 ppm) of rodent carcinogens)
- Heated Licorice Oil - **63 volatile chemicals** identified (most abundant are pyrroles, furans, carboxylic acids) (indole present in unheated juice)
- Bread - more than **540 volatile chemicals** identified
- Pear – more than **300 volatile chemicals** identified
- Cabbage - **49 chemicals** identified
- Coffee – **202 chemicals** identified (34 pyridines and pyrazines; also hydrocarbons, aldehydes, phenols, acids, alcohols, furans, thiophenes)

Chemicals in Coffee Aroma

Sample: 5g ground coffee in 40mL vial
 SPME Fiber: 50/30µm DVB/Carboxen/PDMS (StableFlex fiber)
 Extraction: headspace, 30 min, 65°C
 Desorption: 270°C, 5 min

Column: SUPELCOWAX 10, 30m x 0.25mm ID,
 0.25µm film

Oven: 40°C (5 min) to 230°C at 4°C/min

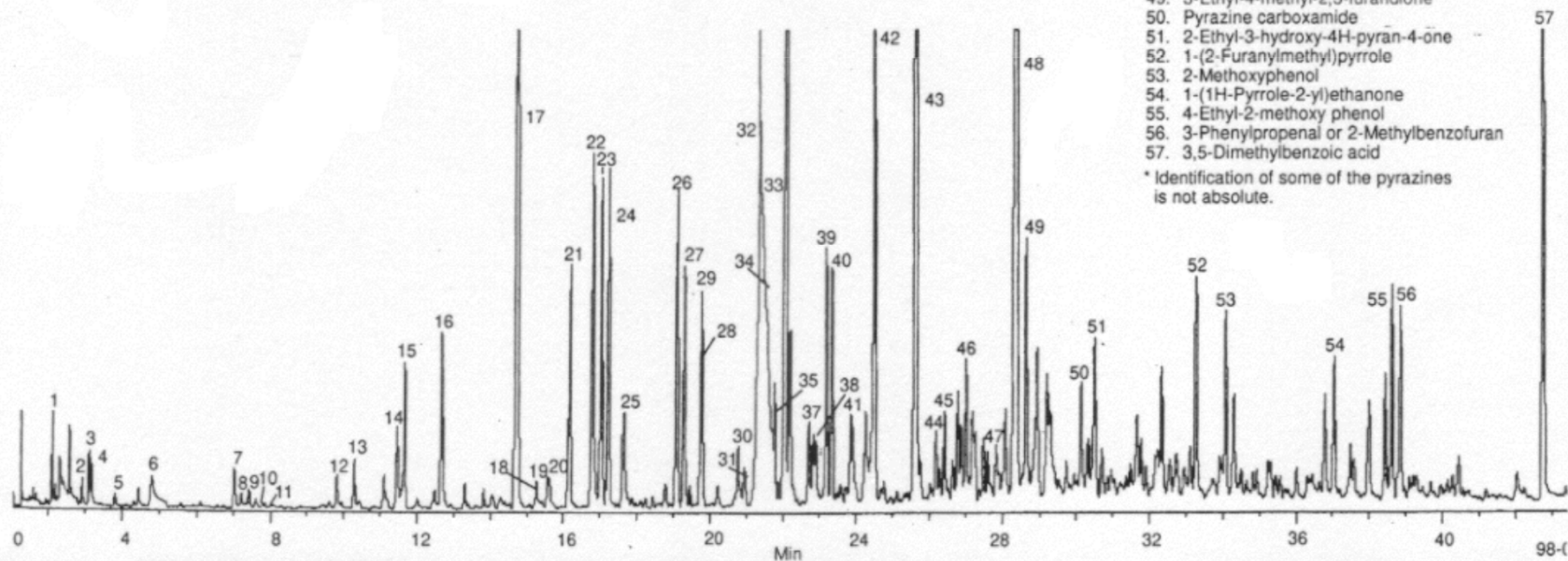
Det.: ion trap MS, m/z = 30-350,
 0.6 sec/scan

Inj.: splitless/split (closed 0.5 min),
 270°C (0.75mm ID inlet liner)

Coffee Components*

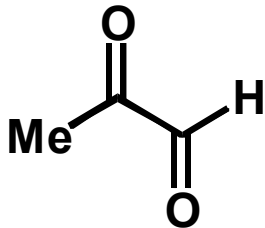
- | | | |
|----------------------------|----------------------------------|--|
| 1. 2-Methyl furan | 17. Methyl pyrazine | 33. Glycerol |
| 2. 2-Butanone | 18. 4-Methyl thiazole | 34. 2,3-Diethylpyrazine |
| 3. 2-Pentanone | 19. 3-Hydroxy butanone | 35. 2-Ethyl-3,6-dimethylpyrazine |
| 4. 3-Methyl butanal | 20. Dimethyl phenol (isomer) | 36. 2-Furancarboxaldehyde |
| 5. 2,5-Dimethylfuran | 21. 1,2-Ethanediol monoacetate | 37. 2-Isopropenylpyrazine |
| 6. 2-Acetyloxy-2-propanone | 22. 2,5-Dimethylpyrazine | 38. 3,5-Diethyl-2-methylpyrazine |
| 7. 2-Ethyl hexanol | 23. 2,3-Dimethylpyrazine | 39. Furfural formate |
| 8. Dimethylsulfoxide | 24. 2-Ethylpyrazine | 40. 2-Furonyl ethanone |
| 9. Phenol | 25. 2,6-Dimethylpyrazine | 41. Methyl benzoylformate |
| 10. Hexanal | 26. 2-Ethyl-6-methylpyrazine | 42. Furanmethanol acetate |
| 11. 2-Methyl thiophene | 27. 2-Ethyl-5-methylpyrazine | 43. 5-Methyl-2-furancarboxaldehyde |
| 12. n-Methyl pyrrole | 28. Trimethylpyrazine | 44. Furanmethanol propionate |
| 13. 4-Methylphenol | 29. 2-Ethyl-3-methylpyrazine | 45. Furfanyl furan |
| 14. 2-Ethyl pyrrole | 30. 2,6-Diethylpyrazine | 46. Pyridine methanol |
| 15. Pyridine | 31. 2-Ethenylpyrazine | 47. 2-Methyl-5-propenylpyrazine |
| 16. Pyrazine | 32. 2-Ethyl-3,5-dimethylpyrazine | 48. Furanmethanol |
| | | 49. 3-Ethyl-4-methyl-2,5-furandione |
| | | 50. Pyrazine carboxamide |
| | | 51. 2-Ethyl-3-hydroxy-4H-pyran-4-one |
| | | 52. 1-(2-Furanyl)methylpyrrole |
| | | 53. 2-Methoxyphenol |
| | | 54. 1-(1H-Pyrrole-2-yl)ethanone |
| | | 55. 4-Ethyl-2-methoxy phenol |
| | | 56. 3-Phenylpropenal or 2-Methylbenzofuran |
| | | 57. 3,5-Dimethylbenzoic acid |

* Identification of some of the pyrazines
 is not absolute.

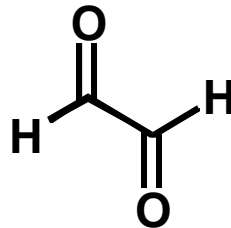


Coffee and Cancer?

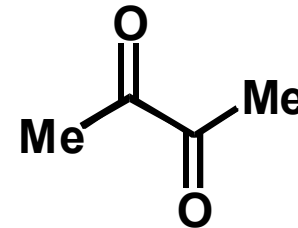
- no strong evidence that coffee drinking is related to any particular cancer
- **some, but not all, early studies showed a link to pancreatic cancer, but now shown to be incorrect**
- pure **caffeine is not carcinogenic**
- **green coffee beans are not mutagenic**
- **roasted coffee beans are mutagenic**
- some of the mutagens in coffee are:



methylglyoxal
(strong mutagen)



glyoxal
(modest mutagen)

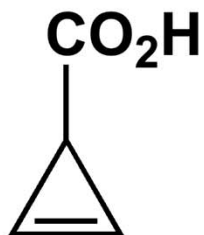


diacetyl
(weak mutagen)

Coffee May Prevent Cancer?!

- **A Study of 90,000 Japanese shows that daily coffee drinking reduced liver cancer by 50%**
- **3-4 cups are better than 1-2 cups**
- **Liver cancer risk factors are hepatitis, cirrhosis, chronic inflammation, excess alcohol**

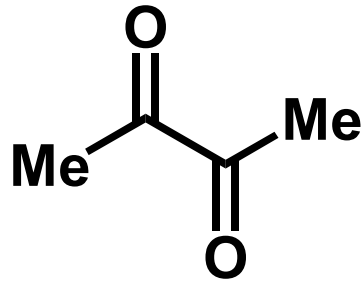
Toxic ("Edible") Mushroom



cycloprop-2-ene carboxylic acid

- Found in the Asian toxic mushroom *Russula subnigricans*
- Causes fatal rhabdomyolysis
- Several cases in Japan
- LD₁₀₀ = 2.5 mg/kg (oral or i.p.) in mice
- 500 grams of mushroom contains 360 mg of the toxin
- In humans two or three pieces are probably a fatal dose

Nature Chem Bio. 5, 465 (2009)

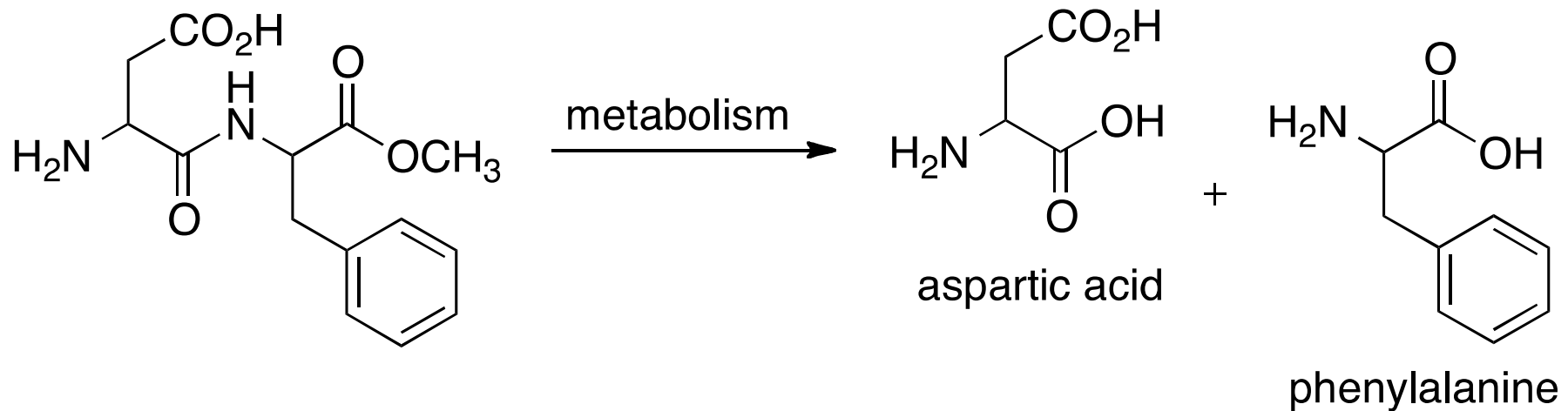


Popcorn and Diacetyl

diacetyl

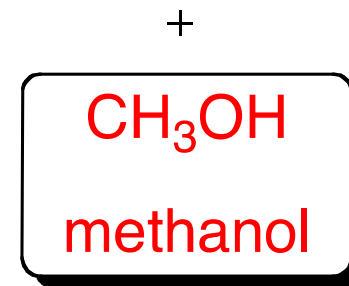
- Diacetyl is the familiar aroma compound in butter, microwaved popcorn, and “buttery” barrel-fermented white wines (typically Chardonnay, Sauvignon Blanc, and white Burgundy) (< ppb?)
- Microwave popcorn plant workers have high rates of chronic cough, shortness of breath, and other lung-function abnormalities (“bronchiolitis”)
- Levels of 1.3 - 98 ppm diacetyl in the “mixing room”

Aspartame ("NutraSweet")



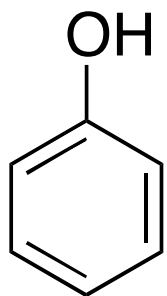
Methanol is found naturally in many beverages:

Diet soda:	24 mg
Orange juice:	18 mg
Apple juice:	21 mg
Grape juice:	46 mg
Tomato juice:	85 mg
(12 oz of each)	



Highly toxic but only in
large (multigram) doses

Phenol – A Jekyll-and-Hyde Chemical



Natural: decaying organic matter such as vegetables, coal, insect sex pheromone

Commercial: antiseptic, mouth wash, air freshener, chemical intermediate, polymer precursor

Highly corrosive to skin

Affects central nervous system

Can cause convulsions

Fatal in large doses

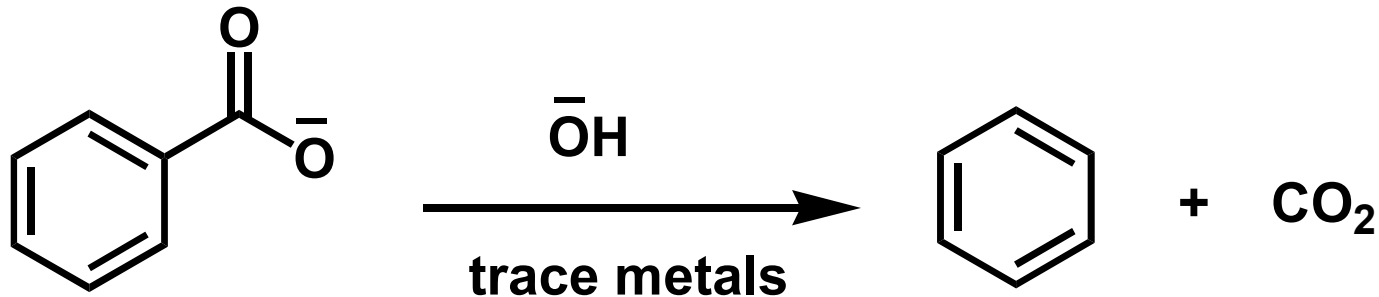
Some Benzene Sources

- **Benzene is found in:**

tobacco smoke	tomatoes
auto exhaust	Canadian beer
cooked chicken	bourbon
cod fish	volcanoes
pineapples	moon rocks

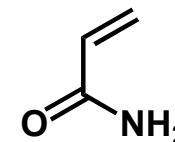
- **Toronto air contains 13 ppb benzene and 30 ppb toluene (mainly from automobiles; gasoline evaporation?)**
- **Titan atmosphere (2007)**

Benzene in Beverages



- **USDA limit in beverages is 5 ng/g (5 ppb)**
- **Benzoate is an antioxidant/antimicrobial agent, like ascorbic acid (Vitamin C), which also occurs naturally in some juices (e.g. cranberry juice)**
- **Benzene formation is accelerated by heat and light, and inhibited by chelating agents**
- **Calcium removes chelating agents, thus increasing benzene**

Acrylamide and Cancer

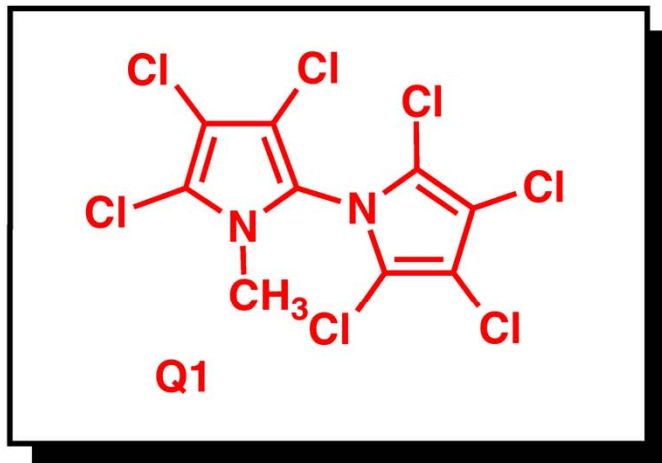


- Mice, rats – multiple organ site tumors when given acrylamide in drinking water or by other means
- Rodents and humans + acrylamide give glycidamide, which is also carcinogenic and reactive with DNA, as is acrylamide
- The “Michael” acceptor acrylamide also reacts with proteins and hemoglobin, and is detoxified with glutathione
- **Highly exposed workers may be at a 50% increased risk for pancreatic cancer**
- 1/3 rd of our calories contain acrylamide (0.5 µg/kg/day is the average dietary intake; higher in children)
- Swedish study (2003) showed **no correlation between dietary exposure to acrylamide and bladder, breast, rectum, or kidney cancer**. Colon cancer showed an **inverse relationship**.

J. Agr. Food Chem., 56, 5984 (2008); *Brit. J. Cancer*, 88, 84 (2003); *J. Agr. Food Chem.* 56, 6013 (2008)

"Q1" — A Naturally Occurring Bioaccumulative Environmental Contaminant

- $C_9H_3N_2Cl_7$
- African and Antarctic samples
- seals, porpoises, bird eggs (penguin, skua, gentoo, chinstrap), whales, **human milk**
- 27-350 $\mu\text{g/kg}$
- Lower concentrations in Northern hemisphere mammals



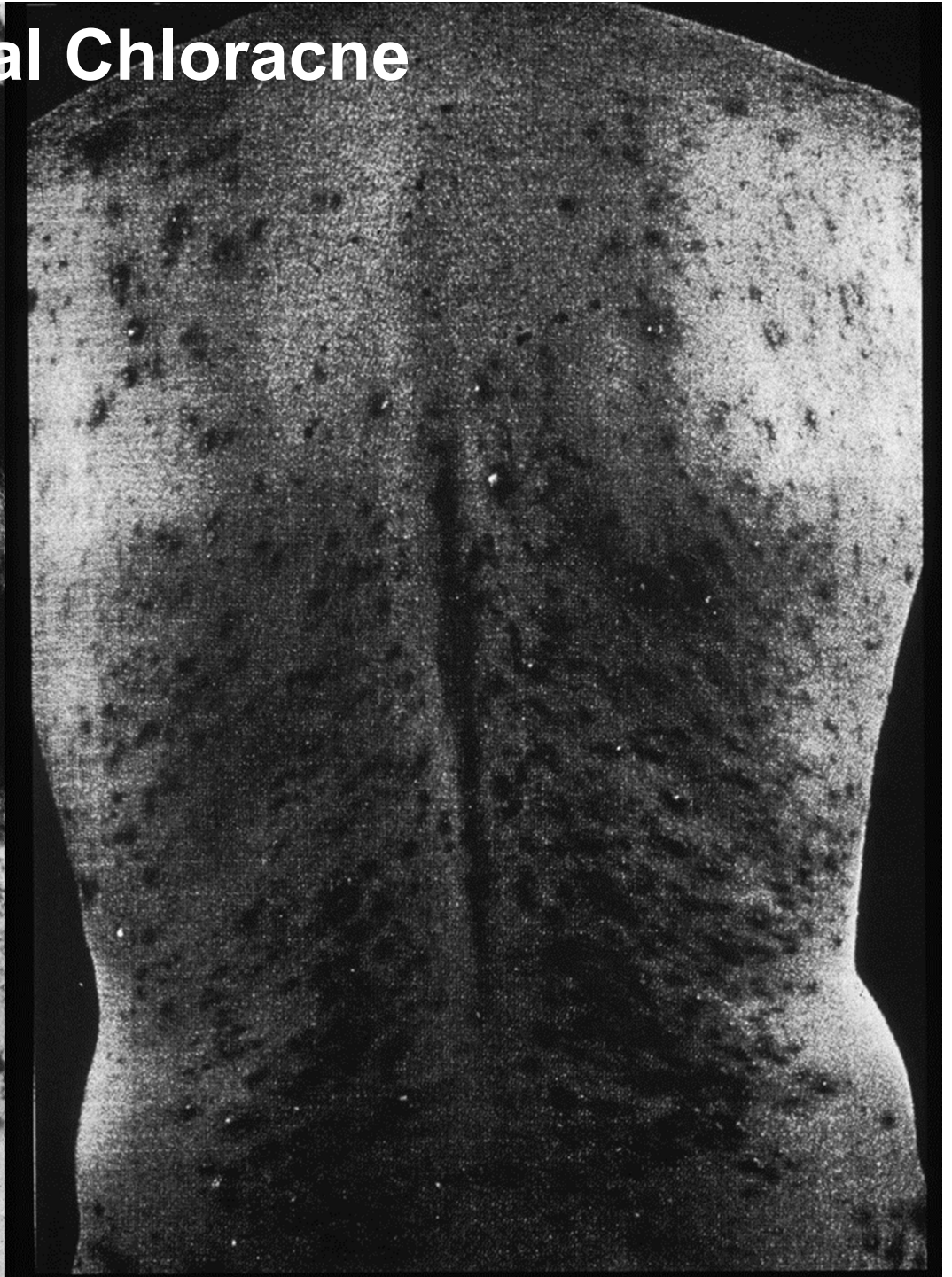
W. Vetter et al., *Environ. Pollut.* 2000, 110, 401.

W. Vetter et al., *Mar. Pollut. Bull.* 1999, 38, 830.

W. Vetter, G.W. Gribble et al., *Angew. Chem. Inter. Ed.* 2002, 41, 1740.

*In addition to 5,000 other
organohalogen compounds,
Nature also makes
polychlorinated
dibenzo-p-dioxins and
dibenzofurans!*

Industrial Chloracne



Dioxin Poisoning of Xnudlgldq#Suhvlgdqw#Y lnwru#

\xvkfkhqr



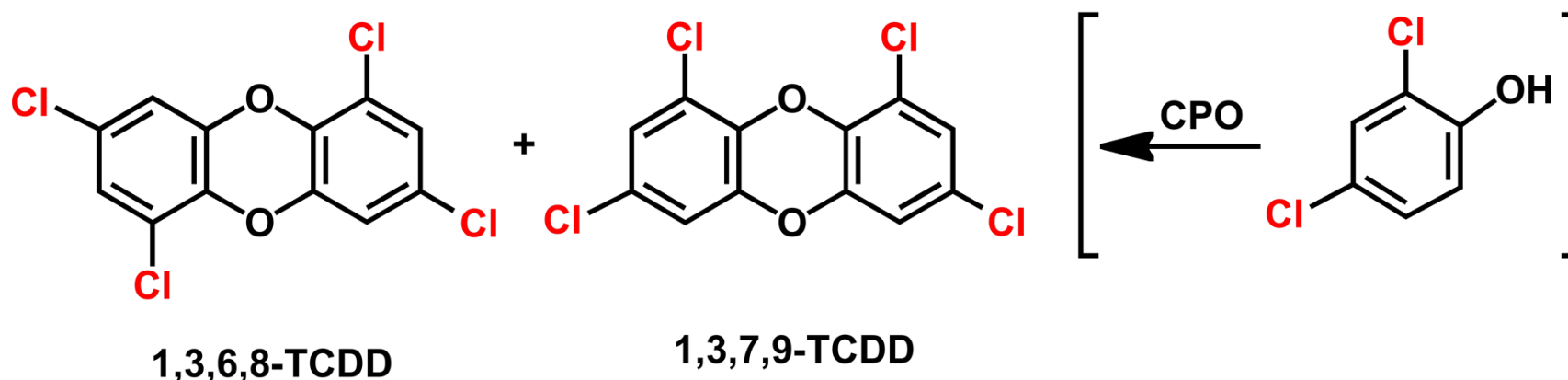
Before

After exposure

Some Recent Developments

- W F G G +%g l r { l q % , # d q g # r w k h u # g l r { l q v # d u h # s u r g x f h g # l q # i r u h v w # i l u h v # + d q # h v w l p d w h g # 4 6 3 # s r x q g v # d q q x d o | # l q # F d q d g d , / # d q g # e | # h q } | p d w l f # d f w l r q # r q # f k a r u r s k h q r o v / # z k l f k # q d w x u h # d o v r # v | q w k h v l } h v l # # K h q f h / # g l r { l q v f d q # e h # f r q v l g h u h g # w r # e h # q d w x u d q # s u r g x f w \$
- D q # 4 ; : : # v r l # v d p s c h # z d v # i r x q g # w r # f r q w d l q # g l r { l q v / # d v # v h y h u d q # r w k h u # v w x g l h v # k d y h # d o v r # i r x q g l
- W k h # X I V l # f k h p l v w # + d # j u d g x d w h # v w x g h q w # d w # R k l r # V w d w h , # z k r # i l u v w # v | q w k h v l } h g # q x p h u r x v # k d a r j h q d w h g # g l r { l q v # l q # j u d p # t x d q l w l h v + \$ \$, l q # 4 < 8 : # z d v # d d y h # d q g # z h o # l q # 4 < 4 / # d o k r x j k # k h # v x i i h u h g # i u r p # v h y h u h # f k a r u d f q h l
- W k h # X n u d l q l d q # S u h v l g h q w # Y l n w r u # \ x v k f k h q n r z d v # d s s d u h q w d | # s r l v r q h g # o d v w # | h d u # z l w k # g l r { l q v # d q g # v x i i h u h g # i u r p # v h y h u h # f k a r u d f q h / # l q # r q h # r i # w k h # k l j k h v w # g l r { l q # h { s r v x u h v # u h f r u g h g # l q # k x p d q v l
- 4 / 6 / 9 / ; W F G G # v k r z v # d f w l y l w | # d j d l q v w # k x p d q # e u h d v w # f d q f h u l
- K d } d u g r x v # z d v w h # l q f l q h u d w l r q # z r u n h u v # d u h # q r w # r f f x s d w l r q d o | # h { s r v h g # w r # g l r { l q v # r u # g l e h q } r i x u d q v # # + F k h p r v s k h u h 9 : / # 8 : 7 # + 5 3 3 : , ,

Natural Dioxins from Canadian Peat Bogs

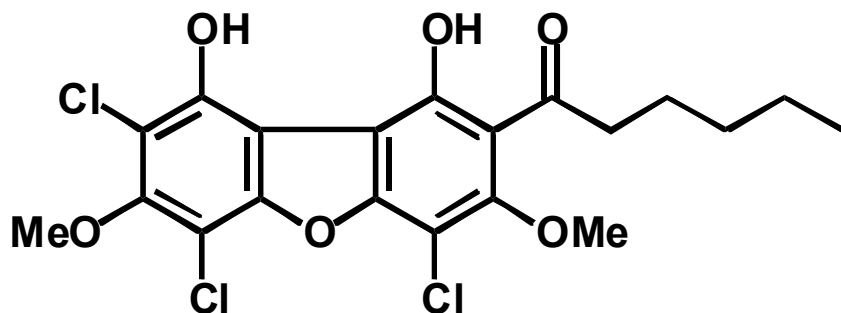


- found in six New Brunswick peat bogs along with chloroform and chlorophenols
- these two dioxins are not normally present in known sources (anthropogenic) of dioxins
- believed to be formed naturally from 2,4-dichlorophenol and soil chloroperoxidase (CPO)
- reaction can be duplicated in the laboratory
- $^{36}\text{Cl}^-$ is incorporated into the dioxins
- also present is **2,4,6,8-tetrachlorodibenzofuran**

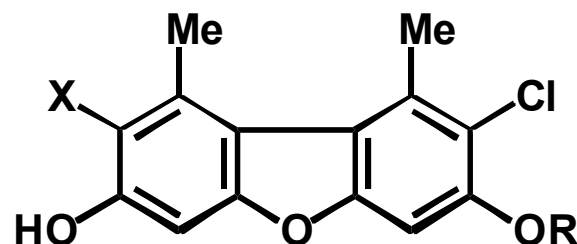
P.J. Silk *et al.* *Chemosphere*, 1997, 35, 2865.



Natural Chlorinated Dibenzofurans



AB0022A



X = Cl, R = H

X = R = H

X = H, R = Me

- isolated from the slime mold *Dictyostelium purpureum*
- antibacterial activity
- structure confirmed by synthesis

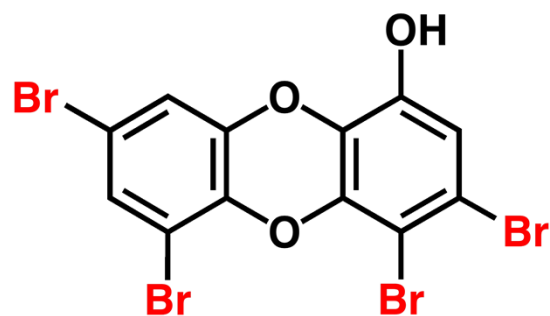
T. Sawada *et al.*, *J. Antibiotics* 2000, 53, 959.

T. Tanahashi *et al.*, *Phytochemistry* 2001, 58, 1129.

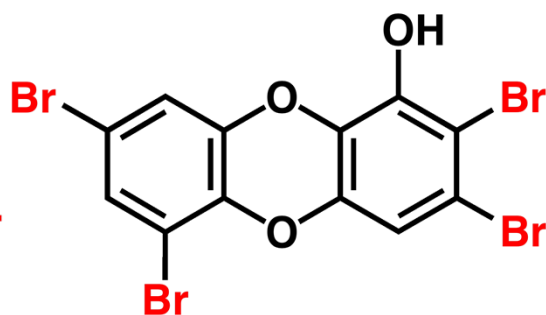
- isolated from the lichen *Lecanora cinereocarpa*



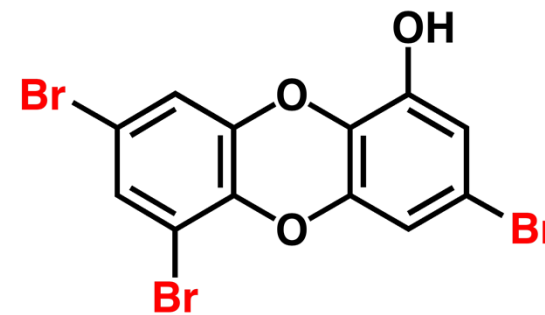
Natural Brominated Dioxins from Marine Sponges



spongiadioxin A



spongiadioxin B

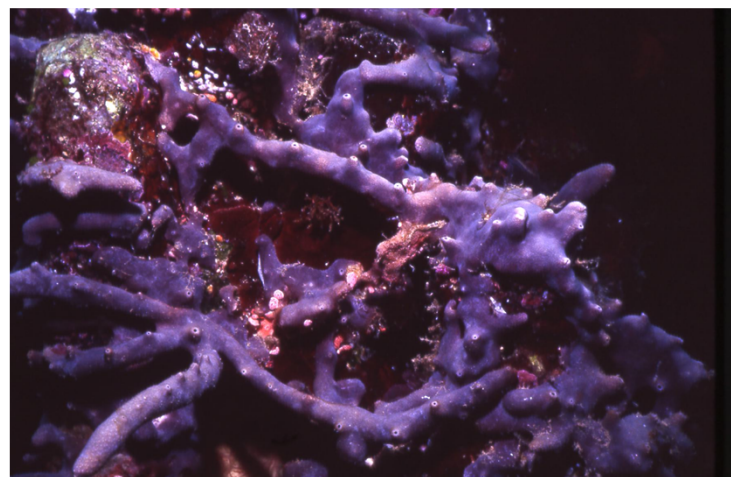


spongiadioxin C

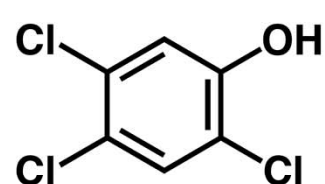
- Isolated from the Australian sponge *Dysidea dendyi*
- Third report of sponge derived brominated dioxins
- LD₅₀ (mice) = 150 mg/kg (TCDD = 0.001 mg/kg)
- Cytotoxic against mouse Ehrlich carcinoma cells
- Structures established by X-ray and synthesis

[+ methyl ethers of all 3
and several brominated
diphenyl ethers.]

N.K. Utkina *et al.*, *J. Nat. Prod.* 2001, 64, 151;
J. Nat. Prod. 2002, 65, 1213

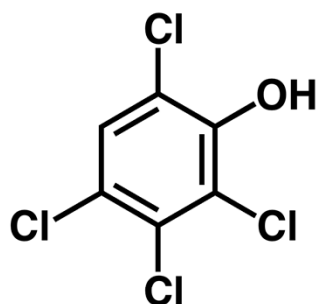
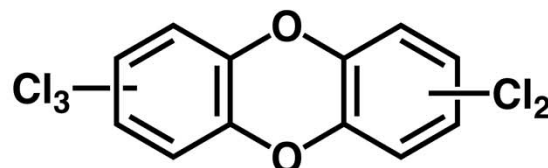


Myeloperoxidase Induced Dioxin Formation from Chlorophenols

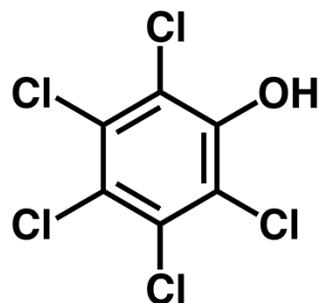
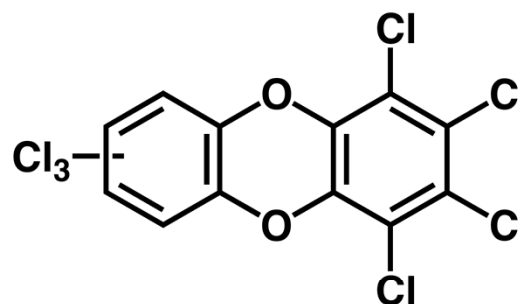


Human white blood
cell myeloperoxidase

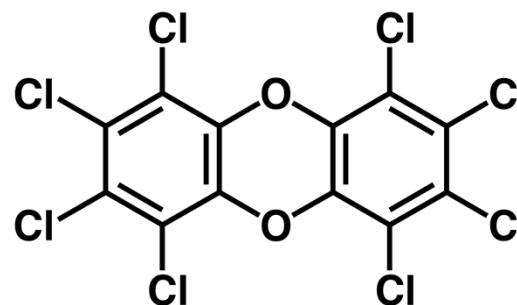
major dioxin in each case:



Human white blood
cell myeloperoxidase



Human white blood
cell myeloperoxidase



Thus, a human biosynthesis of dioxins from chlorophenols is possible

***Natural and synthetic
food toxins***

Aflatoxins – Natural Carcinogens

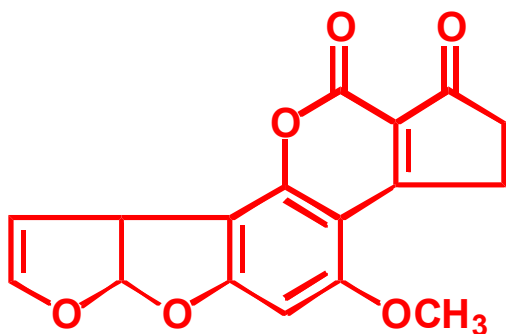
Turkey X disease in England in 1960

100,000 dead in few months

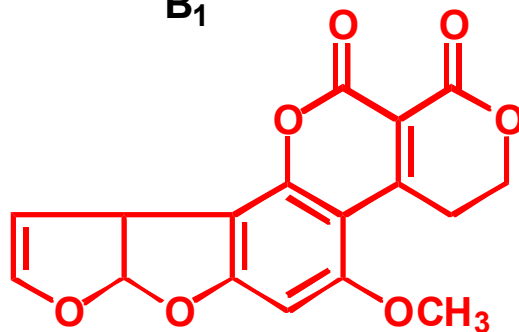
Traced to Brazilian peanut food and a mold *Aspergillus flavus*

1961: toxic fungus isolated

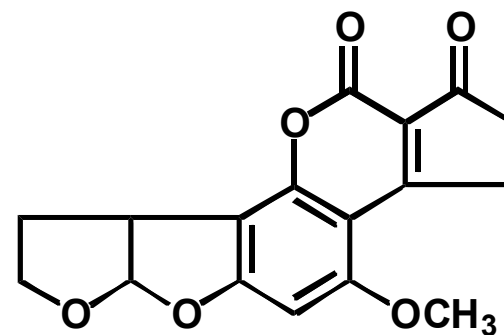
1963: four toxins identified (Büchi, MIT)



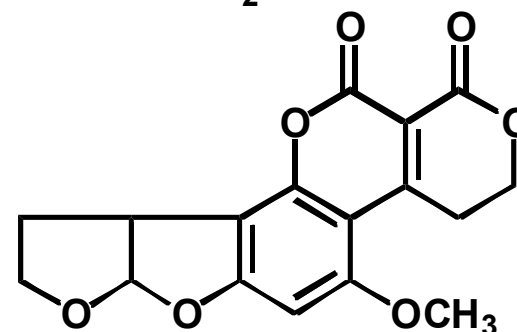
B₁



G₁



B₂



G₂

15 ppb → 100% liver/lung tumors in rats after 1 year

1 yr at 2 ppb → 40% liver tumors in trout

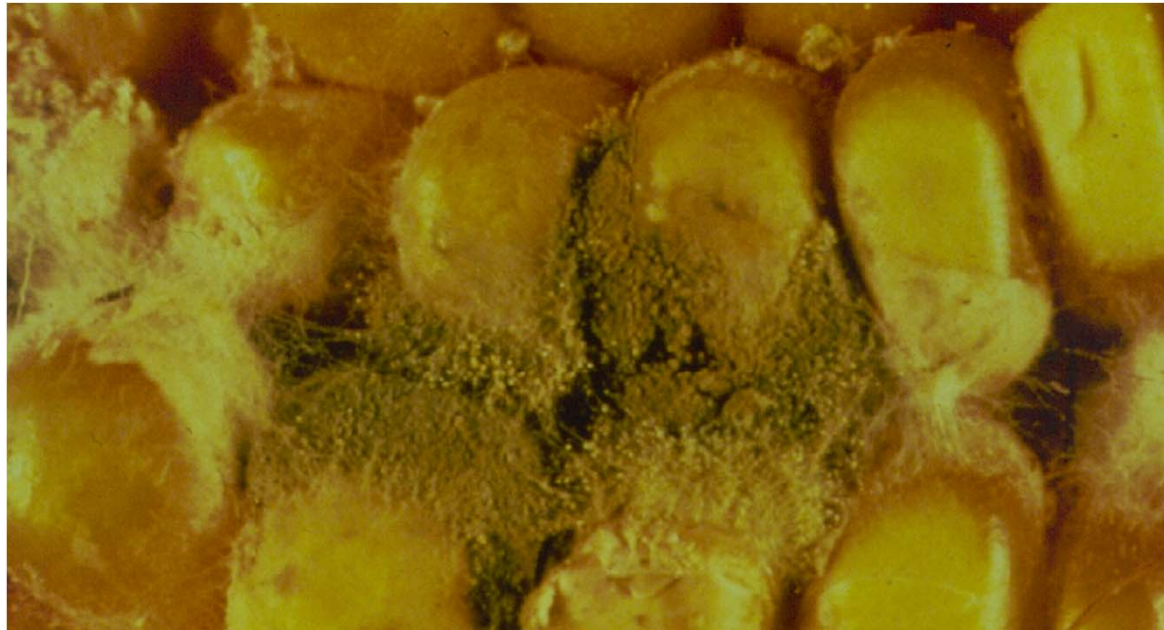
toxicity: B₁ > G₁ > B₂ > G₂

Aflatoxin and Liver Cancer

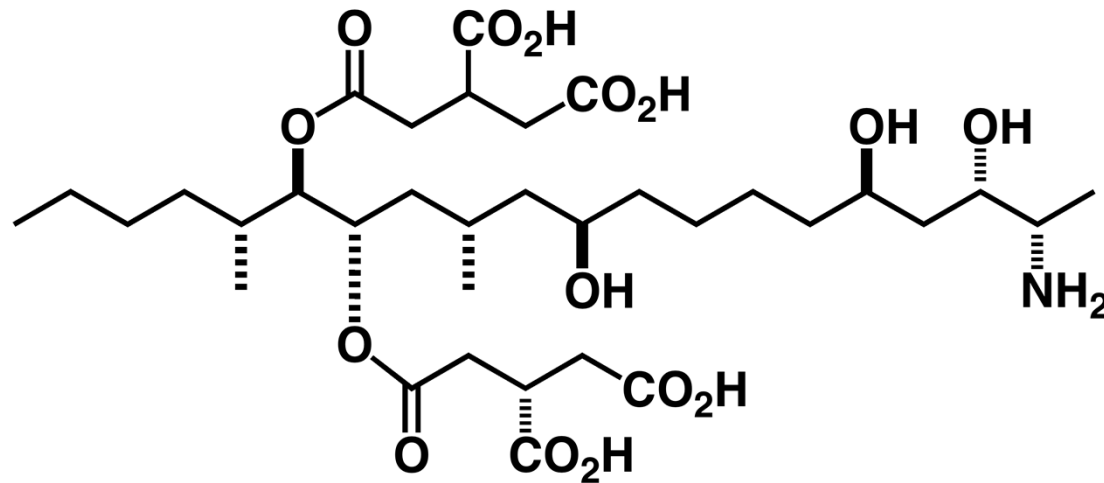
- Implicated in causing **liver cancer**
- 65% of the people in Qidong City, China showed signs of aflatoxin exposure
- This city has the **highest incidence of liver cancer in China**, and many times higher than the rates in Western countries
- Peanuts grown by African peanut farmers are very susceptible to aflatoxin contamination, which is favored by hot, moist conditions that promote **fungal growth on the peanuts**

Aflatoxin Poisoning

- Aflatoxin contaminated pet food discovered in 2005 in the U.S.
- 23 dogs and cats died and more were sickened
- Deaths from liver disease and failure
- The fungus was present on corn used in pet food
- In 1998 more than 80% of the corn crop in Texas was contaminated



Fumonisin Poisoning



Fumonisin B1 - the most prevalent member of a family of toxins, the fumonisins, and produced by *Fusarium* molds, such as *Fusarium verticillioides* and *Fusarium moniliforme*, which occur in corn, wheat, and other cereals

These toxins are hepatotoxic and nephrotoxic in all species tested (horses, cattle, swine)

Linked to esophageal cancer in humans

May be the cause of fatal birth defects in babies whose mothers consumed corn tortillas contaminated with fumonisin during pregnancy in 1991 in Texas



Bacteria

***The **real** killer in our
food***

Food-borne bacterial illness

- **Food-Borne Infections in US annually: 325,000 hospitalizations and 5,000 deaths**
- **Spinach (10-2006): *E. coli* (0157:H7), 204 sickened, 102 hospitalized, 31 kidney failures, 5 deaths**
- **Lettuce (2007): *E. coli* (0157:H7), 150 sickened, many kidney failures**
- **Celery (2010): *Listeria*?, 10 sickened, 10 deaths (Texas)**
- **Cantaloupe (9-2011): *Listeria*, 72 sickened, 16 deaths across 18 states**

Nature is not benign!

***Natural is not necessarily
better than Synthetic***

***Remember,
The Dose Makes the
Poison!***



Thanks for coming!

*(Let me know if you would like a copy of
this presentation)*

Lynn Smallwood