BIO/FOR 430/530:
Biotechnologies: Agriculture, Food & Resources Issues

Spring 2009
Natural Toxins and Synthetic Chemicals

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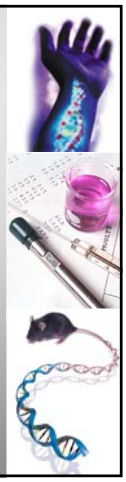
Lecture Key Concepts



- Be familiar with examples of plant, fungi, bacterial, animal (vertebrate and invertebrate) poisons.
- Be able to discuss aflatoxin and caffeine in detail.
- Consider the beneficial applications of these natural poisons to society.

Dietary pesticides (99.99% all natural)*

Abstract: The toxicological significance of exposures to synthetic chemicals is examined in the context of exposures to naturally occurring chemicals. We calculate that 99.99% (by weight) of the pesticides in the American diet are chemicals that plants produce to defend themselves. Only 52 natural pesticides have been tested in high-dose animal cancer tests, and about half (27) are rodent carcinogens; these 27 are shown to be present in many common foods. We conclude that natural and synthetic chemicals are equally likely to be positive in animal cancer tests. We also conclude that at the low doses of most human exposures the comparative hazards of synthetic pesticide residues are insignificant.

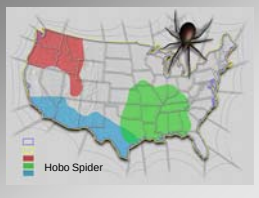
Ames et al. 2000

Scorpions

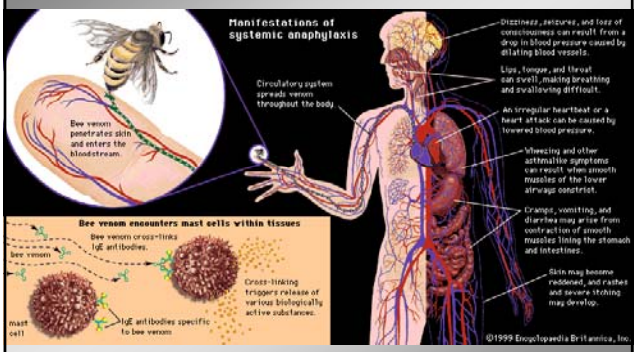
Most North American scorpion bites result in pain, swelling, and tenderness, but are not fatal. There are several species in the Middle East and Africa that are extremely toxic and result in numerous deaths. These species are aggressive and often enter homes and livestock areas.

A protein in scorpion venom called chlorotoxin can bind to cancer cells and make them glow, assisting doctors to distinguish healthy cells from cancerous cells.

Spiders



Bees, wasps, hornets and yellow jackets



Gila Monster

The only poisonous lizard in North America, occurs in SW deserts. Their teeth contain two groves that release a nerve toxin from the lower jaw. The toxin is not injected, rather it flows into the wound when the lizard chews on its victim.

There are no confirmed cases of fatal Gila monster bites. After biting, the lizard holds on tenaciously, resulting in extreme pain, edema and rapid drop in blood pressure. The toxin contains many chemicals including helodermin, which has been shown to slow the growth of lung cancer cells.

Rattlesnakes

Rattlesnake bites are rarely fatal, but extremely painful and may result in local amputation due to tissue destruction. The Western Diamonback is responsible for more reports to Poison Control than any other snake.

According to an article in the New England Journal of Medicine,* rattlesnakes can still envenomate people 20-60 minutes after decapitation. Many of these reports occurred in young men while intoxicated.

Suchard and LoVecchio, 1999

Snake Venom

The World Health Organization estimates that there are over 1 million snake bites each year in Africa, resulting in 20000 deaths. About 10 million anti-venom sera vials are needed to treat snake and scorpion bites worldwide.

Poison Dart Frogs

Small frogs (< 1") indigenous to Central & Latin America. Some species secrete a lipophilic toxin through their skin. These frogs do not produce the toxin, rather they sequester toxins from prey, such as ants & mites.

A chemical extracted from skin called epibatidine is used as a painkiller. It is 200X more potent than morphine. They are being tested as muscle relaxants and heart stimulants.

Tetrodotoxin

Tetrodotoxin is used by animals to discourage consumption by predators.

Low doses of tetrodotoxin produce tingling sensations and numbness around the mouth, fingers, and toes.

As little as 1 - 4 mg of the toxin can kill an adult.

A Small Dose of Toxicology, modified

Jellyfish Toxins

There are over 10,000 species of jellyfish. About 1% are toxic to man including:

- -true jellyfish
- -man-of-wars
- -box jellyfish
- -sea anemones & corals

The tentacles of jellyfish are covered with stinging cells (nematocytes). These are sacs containing venom attached to a hollow tube & barb.

Box jellyfish

Portugese Man-of-War

Death Cap Mushrooms

The most dangerous mushrooms are the “death cap” (*Amanita phalloides*) or the “death angel” (*Amanita ocreata*).

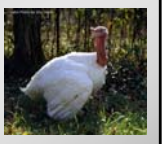
Most susceptible are children < 10 years of age.

Initial symptoms are nausea, vomiting, diarrhea and irregular heart rate.

Amatoxin is very potent: only 0.1 - 0.3 mg/kg is fatal.

A Small Dose of Toxicology, modified

Aflatoxin:



Extensively studied fungal toxin (mycotoxin).

Turkey X disease
- 1960, England
- Thousands of farm animal deaths
- Disease traced to fungal contamination of peanut meal
  - *Aspergillus flavus*

- Human health significance
  - Acute high-level dietary exposures leading to liver (hepatic) injury and failure (aflatoxicosis)
  - Chronic high-level dietary exposure as a risk factor for liver carcinogenesis

Aflatoxin Occurrence

Aspergillus flavus and *Aspergillus parasiticus* as mycotoxigenic species
- Worldwide distribution

Production dependent on strain, environmental factors
- Pre-harvest: heat and drought conditions stimulate production
- Post-harvest (storage): production stimulated by warm temperatures, high humidity
- *A. flavus* (Strain AF 36) as example of importance of genetics

Aspergillus Ear Rot

Aflatoxin & Agriculture

Foods, feeds, and commodities at risk of contamination
- -Corn, nuts, cereal, cottonseed, rice, crude sugar, beans
- -Animal products
- -Dried fruits & tobacco

•Clusters and outbreaks
- –Tropical environments
- –Poor nutritional status
- –Maize as primary nutrition
- –Contaminated maize
- –Africa & China

Tobacco curing in flue

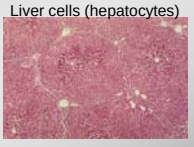
Photo: Rick Ward

Aflatoxin Toxicology

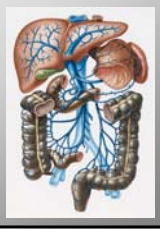
Acute aflatoxicosis can result from high level, dietary exposure.

Acute liver (hepatic) injury can result in death from hepatic failure.

Liver cells (hepatocytes)



Aflatoxin is a potent carcinogen, particularly for hepatocellular carcinomas. It is thought that exposure to Hepatitis B virus plays a synergistic role in the cancer causing potential for aflatoxin.



Plants & Skin Irritants

Allergic Dermatitis – Plant Rashes, itchy skin
- Philodendron, poison ivy, cashew, bulbs of daffodils, hyacinths, tulips (antibody mediated)

Allergic Dermatitis – Pollen Sniffles & sneezing, runny eyes
- Ragweed (North America), Mugwort (Europe), grasses (antibody mediated)

Contact Dermatitis Oral – Swelling and inflammation of mouth Skin – pain & stinging sensation
- Dumb cane (Dieffenbachia)Nettles (Urtica)

Contact Dermatitis Skin – pain & stinging sensation
- Calcium oxalate crystals coated with inflammatory proteins – contain histamine, acetylcholine

Ricin

Ricin is found in castor beans. These beans are processed around the world for castor oil.

There have been numerous attempts to make ricin into a biowarfare agent. Different forms include powders, mists, pellets and water solutions.

Ricin has been used experimentally to kill cancer cells.

Nightshade (Atropa belladonna)

Used in the Roman Empire and during the Middle Ages both as a cure and a poison.

Women used preparations to dilate their pupils a sign of allure and beauty.

Atropine is drug responsible for effects. This chemical also counteracts the effects of pesticides and chemical warfare agents that act by inhibiting acetylcholinesterase.

A Small Dose of Toxicology, modified

Cannabis

The active ingredient, THC, occurs in various concentrations in plants belonging to the genus *Cannabis*. THC is the psychoactive compound that produces the "high" associated with marijuana.

Several medicinal uses of THC have been recognized including a lessening of ocular pressure in glaucoma patients, increased appetite, decreased nausea, pain relief and a general feeling of well-being. Since 1996, 12 states have legalized medical marijuana.

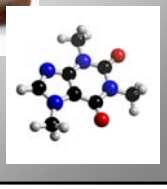
Foxglove

Belongs to the Digitalis genus. Known as "Dead Man's Bells" and "Witches' Gloves."

Just a few bites of the leaves are fatal, usually from cardiac distrurbances. Fatal accidents of children drinking water from a vase have been reported.

The pharmaceutically active compounds extracted from leaves are digitoxin & digoxin. These drugs are useful in regulating pulse for cardiac arrhythmias and to slow pulse during atrial fibrillation.

The top stimulate consumed across the globe.



Caffeine

Date	Event
~850	- Coffee beans discovered in Ethiopia
~1100	- First coffee trees and roasting of coffee beans.
1475	- Constantinople – the world's first coffee house.
1600s	- Coffee enters Europe and moves quickly to the Americas
1700s	- Coffee house open throughout Europe.
1723	- First coffee plants are introduced into the Americas.
1822	- First espresso machine is created in France.
1938	- First instant coffee invented by the Nestlé company.
1971	- Starbucks opens its first location in Seattle, Washington's Pike Place Market.

A Small Dose of Toxicology, modified

Effects of Caffeine

Desirable effects: stimulant, increased alertness & concentration, energy, bronchial dilator

Toxicity: restlessness, jitters, anxiety, insomnia, elevated or irregular heart rate

No tolerance: most develop little or no tolerance to the nervous system effects

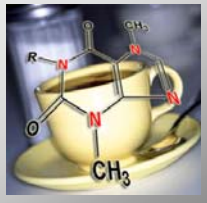
Withdrawal effects: transient but persistent, headache, low energy, inability to concentrate

A Small Dose of Toxicology, modified

Physiology of Caffeine

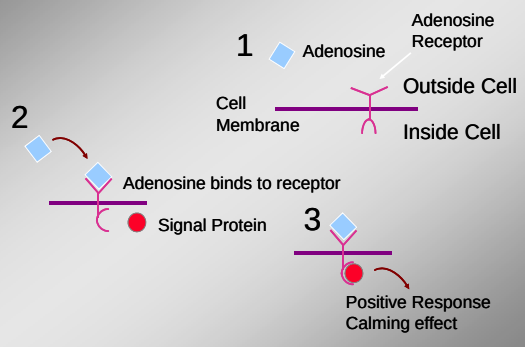
Caffeine is rapidly absorbed into all compartments and peak blood levels occur in ~ 30 minutes. Caffeine crosses the blood-brain-barrier and placenta. It is metabolized by the liver and excreted in urine.

Time till excretion:
Average adult – 3-5 hrs
Child less that 6 months – 24 hrs
Pregnant – 7-8 hrs
Smoker – 2-3 hrs
(varies between individuals)



A Small Dose of Toxicology, modified

Normal Action of Adenosine



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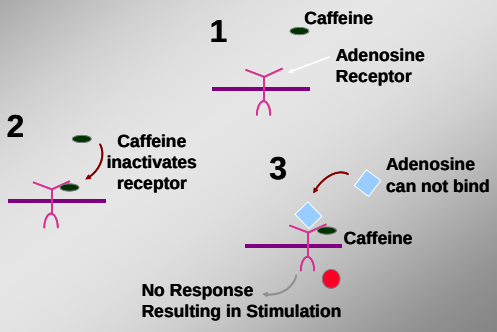
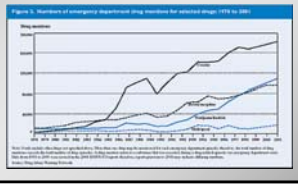
Mode of Action for Caffeine



A Small Dose of Toxicology, modified

Cocaine

The coca plant from South America is refined into cocaine. This powerfully addictive CNS stimulant increases dopamine levels. Cocaine is snorted, smoked and injected. This deadly addiction has resulted in thousands of ER visits and $billions$ spent on enforcement.



Past uses include:
- -Coca Cola® (until 1903)
- -pain relievers
- -lozenges
- -wines

Microcystins:

Globally, microcystins are the most commonly detected cyanobacterial toxin in freshwaters (including Oregon).

The toxins are water soluble and tend to be released when the blooms die and the cells lyse. The liver is the ultimate target organ for toxic effects and storage/distribution.

Microcystins are quite toxic with low doses required for lethal effects (i.e. the dose-response curve is steep).

Microcystin Disease Outbreaks:

Severe gastro-enteritis epidemic in Brazil developed with over 2000 cases reported (88 deaths). Results pointed to a massive bloom of *Anabaena and Microcystis* in reservoir.

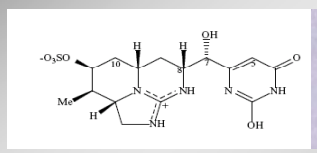
Epidemiological association between liver cancer in rural Chinese populations infected with Hepatitis-B and drinking water contaminated with microcystins.

In Brazil, 117 patients developed liver disease (50+ deaths) attributed to dialysis with microcystin-contaminated water

Atlantic salmon reared in B.C. and Washington dieing of progressive liver disease from an unidentified organism producing microcystins; severe economic losses.

Cylindrospermopsin:

Cylindrospermopsin is typically associated with tropical regions of the globe. Recently, this toxin has been detected in higher latitudes of North America, Europe and Japan.



Main target of toxicity is the liver. Other organs such as the thymus, kidneys, lungs, intestinal tract and heart may be affected.

Palm Island Mystery:

In 1979, a major bloom occurred in a reservoir of Palm Island, Australia (water was chlorinated but unfiltered). Residents complained of a bad taste and smell of drinking water, so the water was treated with copper sulfate to kill the bloom.

Shortly after, > 100 children and 10 adults developed malaise, anorexia, vomiting, enlarged liver, headache and stomach pain. Kidney malfunction, bloody diarrhea and urine were also reported. In a few cases, the loss of electrolytes was so severe that patients suffered from hypovolemic shock.

A culture of the reservoir water revealed the presence of *Cylindrospermopsis raciborskii.*

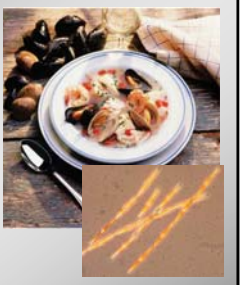
Red Tide

Marine algae, *Karenia brevis*, create blooms that can make oceans appear reddish brown. While red tides have enormous environmental impact due to depletion of dissolved oxygen, some blooms produce brevetoxin, a potent nerve toxin.

No deaths have been attributed to red tides. When the toxin is aerosolized, coughing, sneezing and respiratory discomfort have been observed in beach goers and surfers in Florida.

Domoic Acid

Bans on harvesting razor clams occur periodically as a result of domoic acid contamination. This toxin is produced by an algae called *Pseudo-nitzschia*. The toxin is referred to as “amnesic shellfish poisoning” given its effect on short-term memory (can result in irreversible lesions of the brain).



In 1987, over 100 people in Canda (PEI) became ill after consuming blue mussels in various restaurants. Many became violently sick, including cases of seizure, permanent memory loss and coma. Three elderly patients died.

Botulism

This is a rare but serious paralytic illness caused by nerve toxins produced by the bacterium *Clostridium botulinum*. Foodborne botulism is caused by eating contaminated foods and wound botulism occurs when spores enter and grow in the intestines.

Classic symptoms include double vision, slurred speech, dry mouth and muscle weakness. If left untreated, paralysis of the arms, legs and respiratory muscles occur. Symptoms generally occur 18 to 36 hours after eating contaminated food.

Anthrax

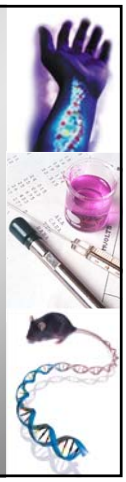
Bacillus anthracis produces spores that cause severe disease. All major routes of exposure can result in disease.

Humans can be infected with anthrax from handling infected animal products (ex. hides) or breathing dormant spores in animal products (ex. wool).

Humans have also been infected when anthrax is weaponized. In 2001, shortly after 9/11, anthrax was deliberately spread through the U.S. postal system. The exposure to inhalational anthrax resulted in 22 infections, and several deaths.

Lecture Key Concepts

- Be familiar with examples of plant, fungi, bacterial, animal (vertebrate and invertebrate) poisons.
- Be able to discuss aflatoxin and caffeine in detail.
- Consider the beneficial applications of these natural poisons to society.



- What does this lecture suggest about the differentiation between SYNTHETIC & NATURAL?
- Should we regulate natural versus synthetic differently?
- What about labeling of products that state “All-Natural?”