

Principles of Toxicology

Poisonous Plants Class

Spring Semester 2008

Terminology

- **Toxicology** - the study of adverse effects of xenobiotics on living organisms.
- **Xenobiotic** - a chemical compound that is foreign to a living organism
- **Poison** – any agent capable of producing a deleterious response in a biological system.
- **LD₅₀** – median lethal dose, or the dose required to kill 50% of treated animals
- **Half Life (T_{1/2})** – time required for one half of a substance to be removed

Key Principles

- Dose-Response Relationship
- **Risk** - possibility of loss or injury
 - Risk = Hazard X Exposure
 - **Hazard** – intrinsic toxic properties
- Individual Sensitivity
 - Not all are created equal
 - Resistant and Susceptible

The Dose Makes the Poison

“All substances are poisons;
there is none which is not a poison.
The right dose differentiates a poison from
a remedy.”

Paracelsus (1493-1541)

Dose

- **Dose** - the measured quantity of a therapeutic agent to be taken at one time
- mg of agent / kg body weight
– (mg/kg)

Agent

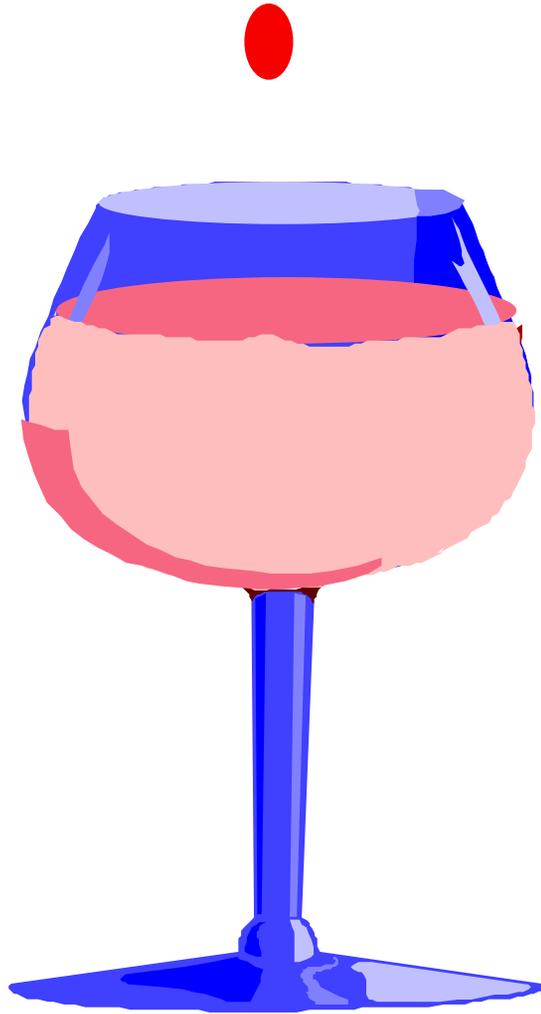
LD₅₀ (mg/kg)

Water	???
Ethyl alcohol	10,000
Salt (sodium chloride)	4,000
Iron (Ferrous sulfate)	1,500
Morphine	900
Mothballs (paradichlorobenzene)	500
Acetaminophen (Tylenol)	350
Aspirin	250
DDT	250
Cyanide	10
Strychnine sulfate	2
Nicotine	1
Tetrodotoxin (from fish)	0.1
Abrin (plant lectin)	< 0.0001
Botulinum Toxin	0.00001

Effects of Amount on Response



Effects of Size on Response



The Dose Makes the Poison

“Poisons and medicines are oftentimes the same substance given with different intents.”

Peter Mere Latham (1789-1875)

The Dose Makes the Poison

- Poisonous plants and nutritious feeds are oftentimes the same substance consumed at different amounts.
 - For example:
 - Alfalfa
 - Lupine
 - Etc

The Timing Makes the Poison

- **Teratogen** - of, relating to, or causing developmental malformations

FETAL ALCOHOL SYNDROME

Text and photographs by GEORGE STEINMETZ



Fetal Effects of MeHg



Thalidomide

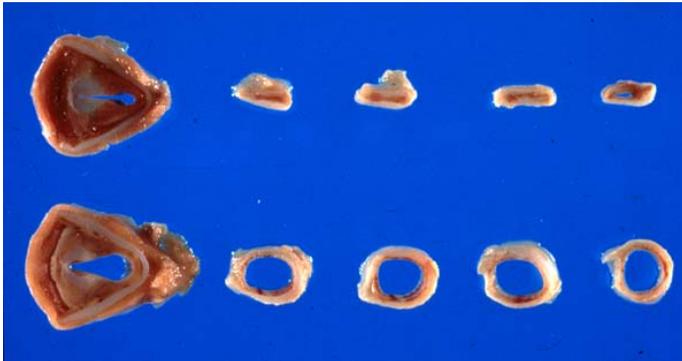


Crooked Calf



Example of Lupine-induced
“crooked calf disease”

Malformed Lamb



Fate of Plant Poisons in Livestock

- **Toxicokinetics** - the characteristic interactions of a xenobiotic and the body in terms of its absorption, distribution, metabolism, and excretion
- **ADME**
 - **A**bsorption
 - **D**istribution
 - **M**etabolism
 - **E**limination/Excretion

Exposure & Absorption

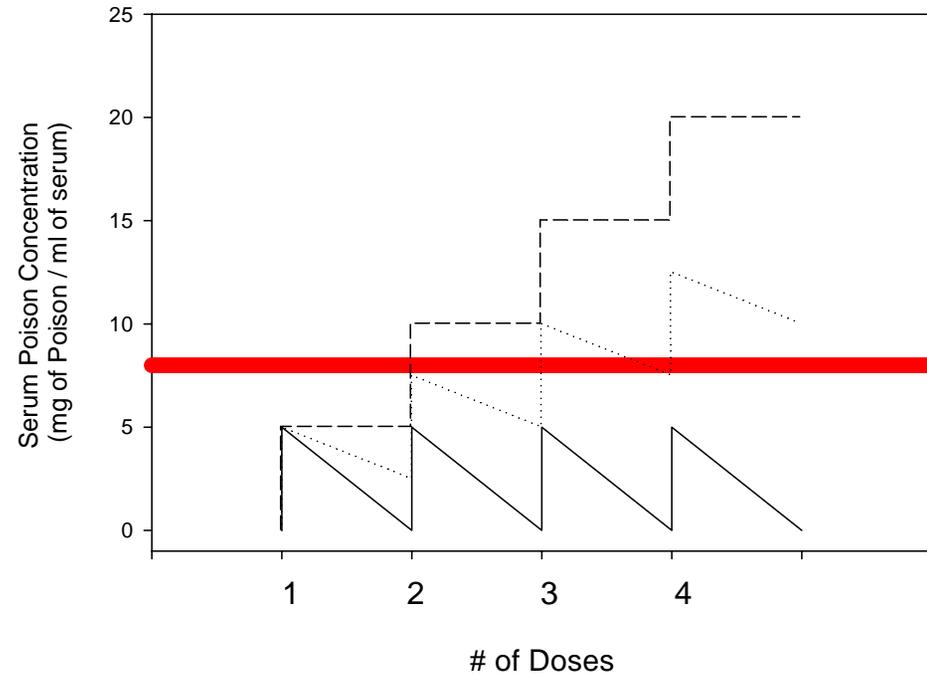
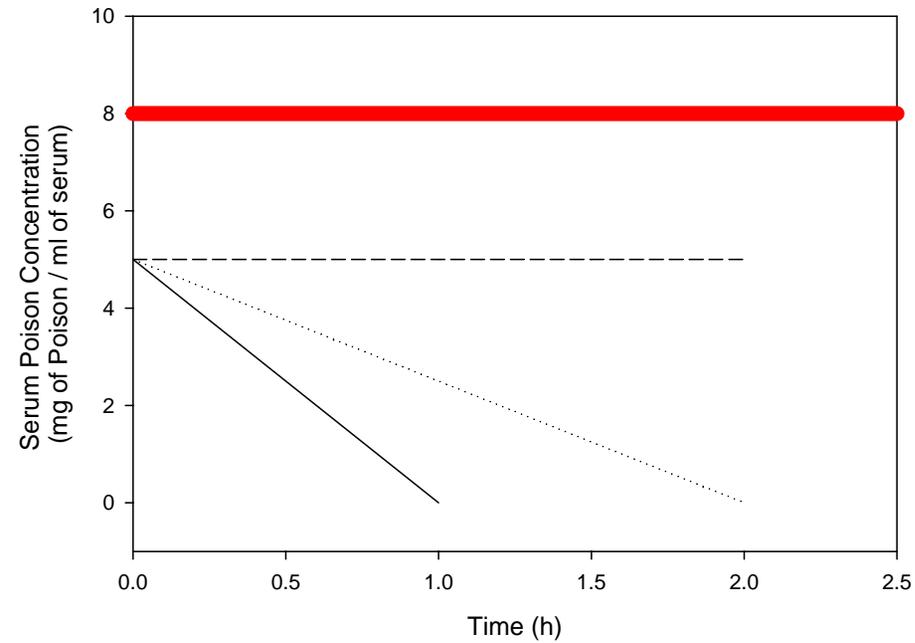
Route of exposure

- 1) Skin (dermal)
- 2) Lung (inhalation)
- 3) Oral (gut)

Frequency of Exposure

- Number of Exposures
 - 1 beer
 - 4 beers
- Time between Exposures
 - 4 Beers in an hour
 - 4 Beers in 4 Days

Single vs. Multiple Doses



Duration of Exposure

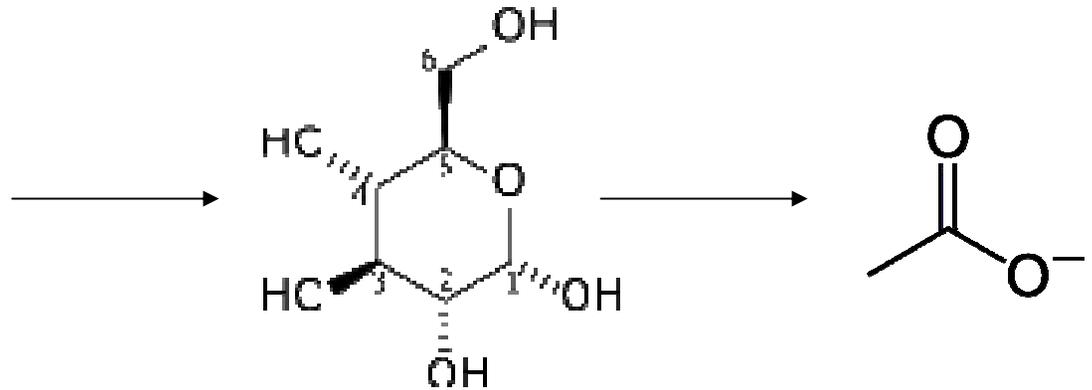
- Acute Exposure
- Sub-acute Exposure
- Sub-chronic Exposure
- Chronic Exposure

Distribution

- Where the compound goes and where it accumulates
 - (body water, fat, bone, muscle)
 - Water soluble (hydrophilic) vs. fat soluble (hydrophobic)

Metabolism

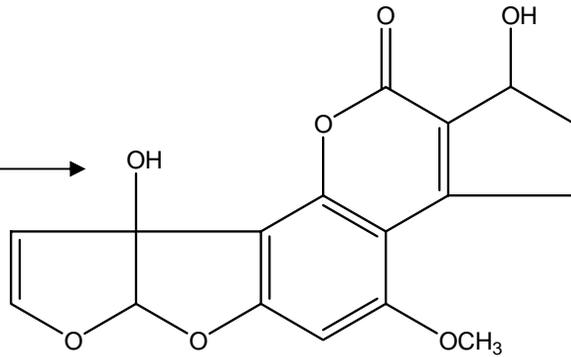
- How the body breaks down a xenobiotic
- What it turns into
- How fast it does it



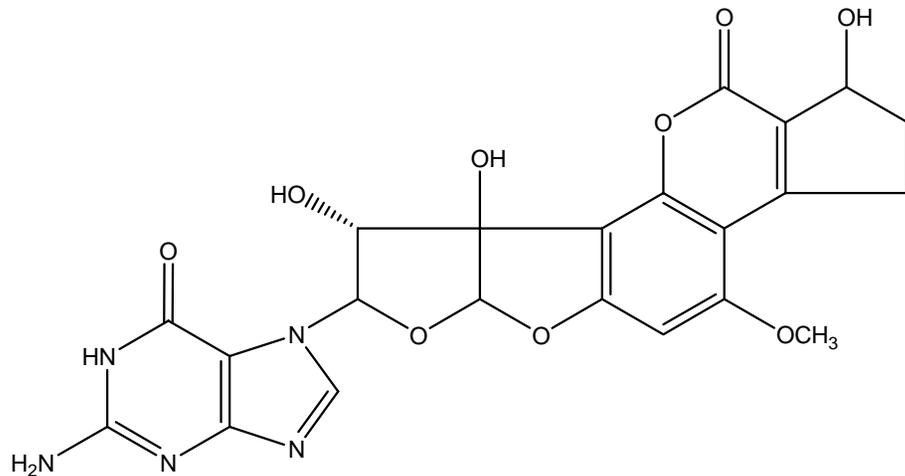
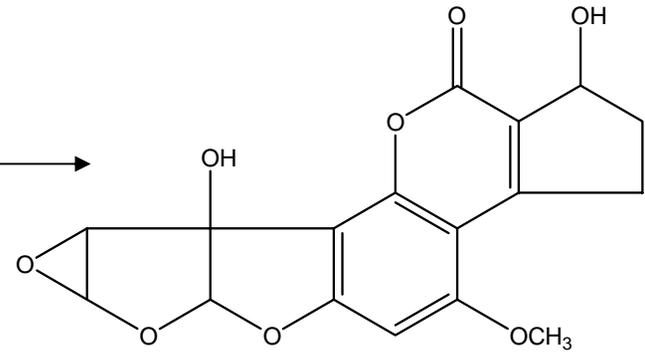
Metabolism



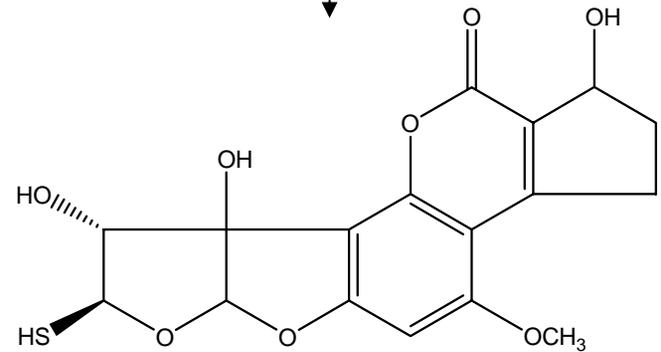
Aflatoxin B₁



Aflatoxin B₁-8,9-epoxide



Aflatoxin B₁-N⁷-guanine adduct

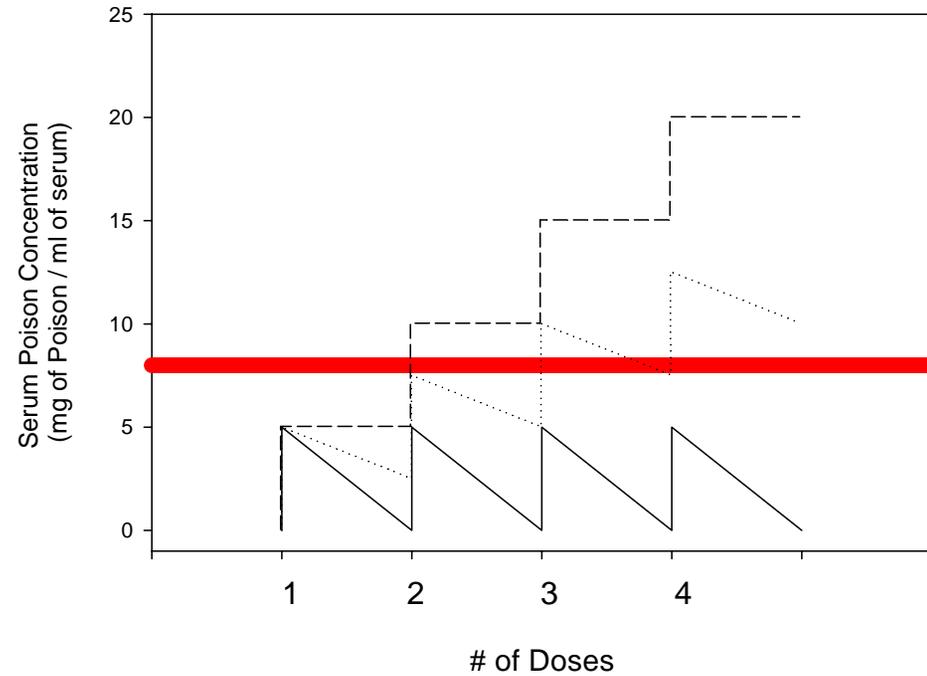
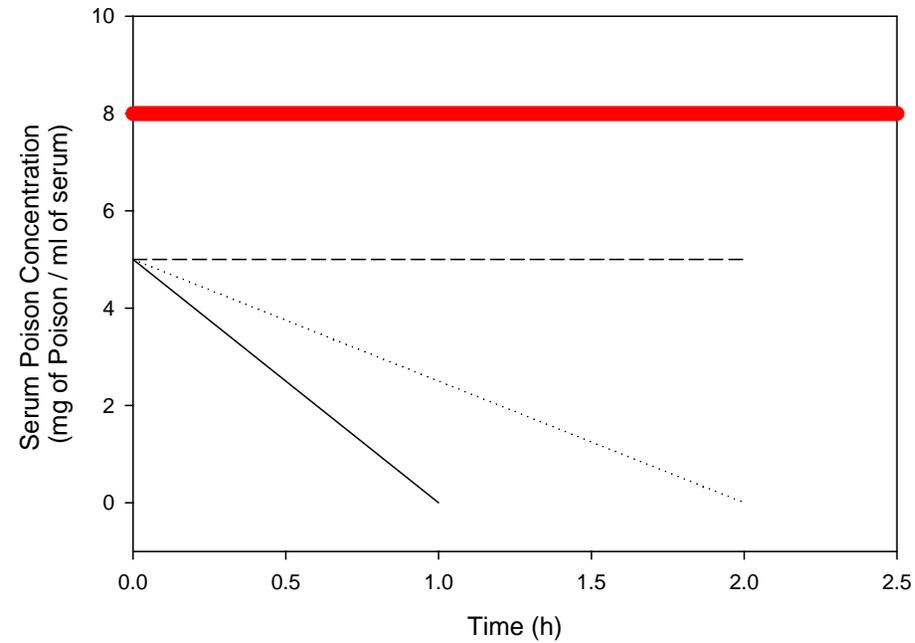


Aflatoxin B₁-glutathione adduct

Elimination/Excretion

- Removal of xenobiotic from body
 - Urinary
 - Fecal
 - Non-absorbed material
 - Biliary excretion
 - Exhalation
 - Milk
 - Sweat and Saliva

Single vs. Multiple Doses

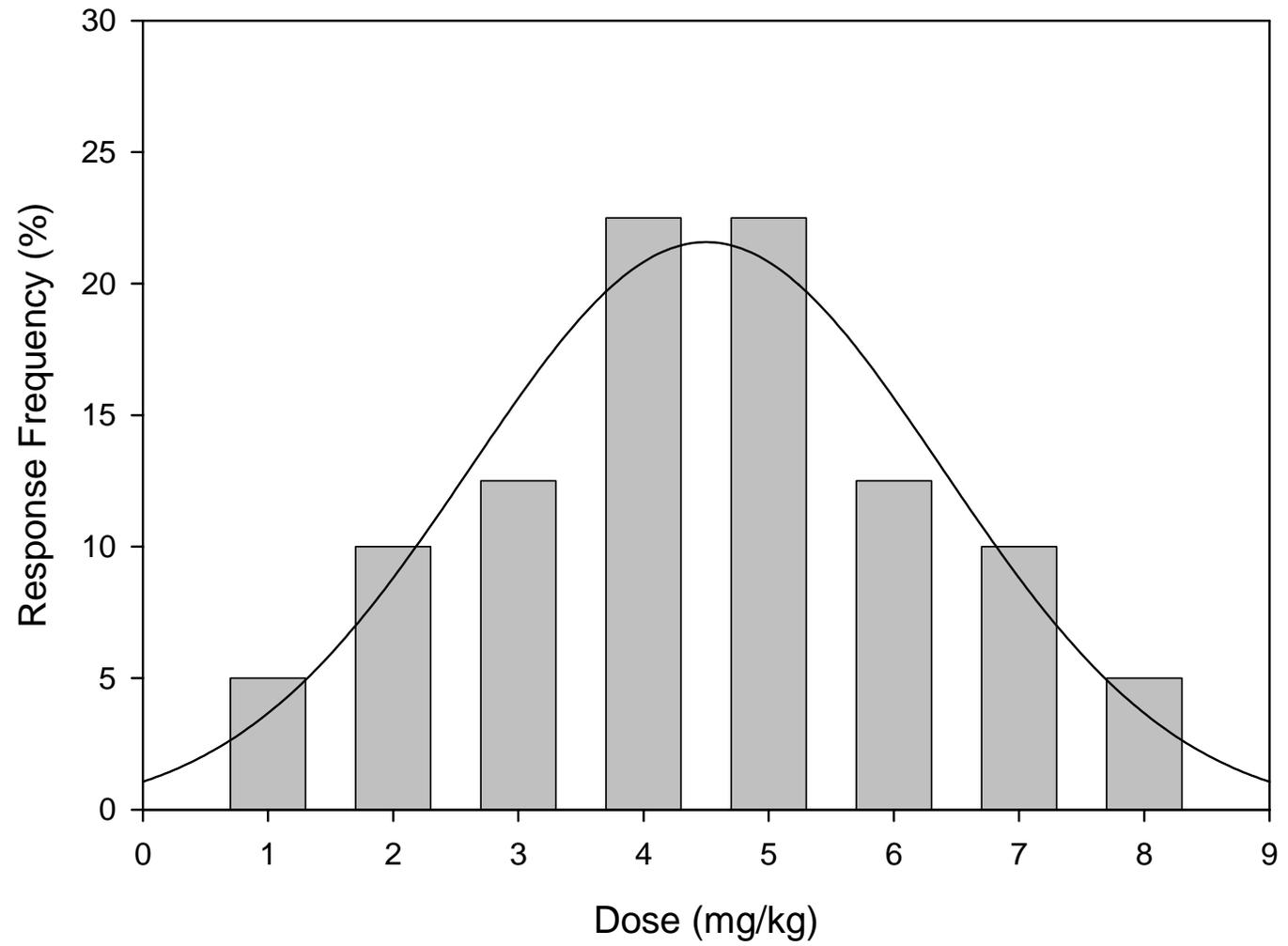


Individual Variation

“The sensitivity of the individual differentiates a poison from a remedy. The fundamental principle of toxicology is the individual’s response to a dose.”

Steven G. Gilbert (1997)

Dose-Response Relationship



Susceptibility & Variability

- Differences in ADME
- Young or Old
- Male or Female
- Environmental Differences
- Genetic Differences
- Species Differences

Risk Assessment

Process of estimating association between an exposure and the incidence of some adverse outcome

1-Determine risk of livestock grazing in a given area

2-Determine the cause of livestock deaths