Principles of Toxicology

Poisonous Plants Class

Spring Semester 2010

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.
- **LD_{50}** – 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

- **Risk** - possibility of loss or injury
  - Risk = Hazard X Exposure
  - **Hazard** – intrinsic toxic properties

- Individual Sensitivity
  - Not all are created equal
    - Resistant and Susceptible

Dose

- **Dose** - the measured quantity of a therapeutic agent to be taken at one time

- mg of agent / kg body weight
  - (mg/kg)

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)

Agent	LD_{50} (mg/kg)
Water	42,860
Sucrose	14,000
Ethyl alcohol	10,000
Salt (sodium chloride)	4,000
Iron (Ferrous sulfate)	1,500
Morphine	900
Mothballs	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

The Dose Makes the Poison

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

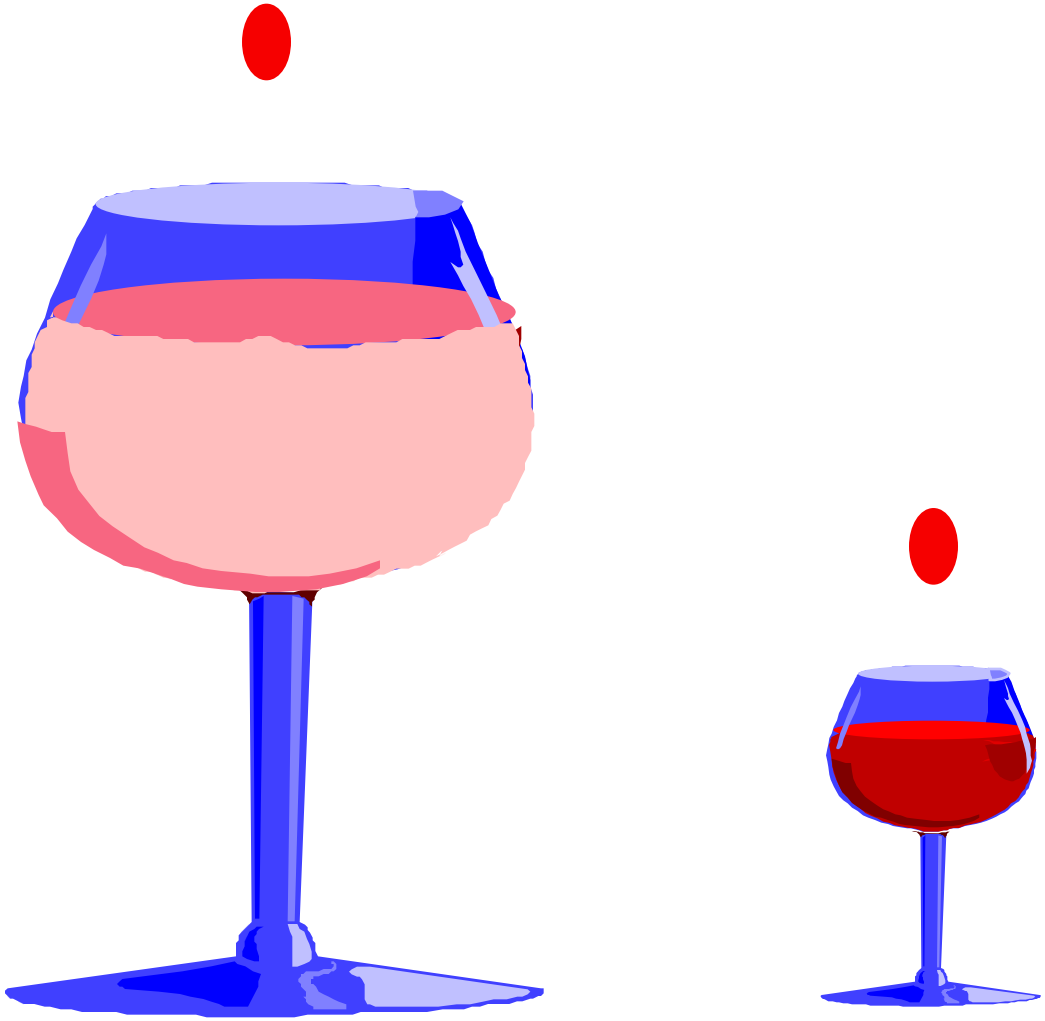
Peter Mere Latham (1789-1875)

The Dose Makes the Poison

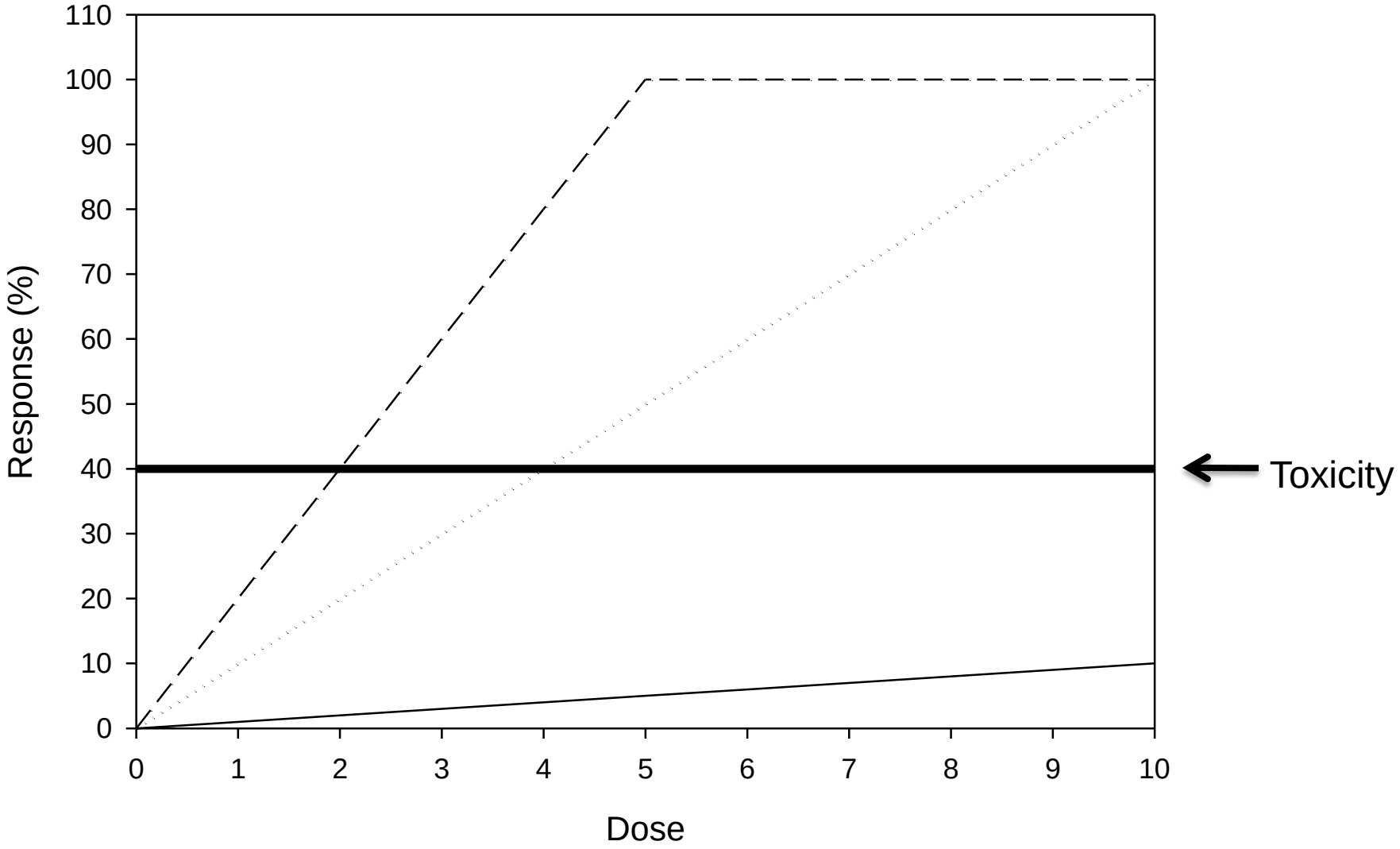
- Poisonous plants and nutritious feeds are oftentimes the same substance consumed at different amounts.
  - For example:
    - Alfalfa
    - Lupine
    - Larkspur
    - Etc

Effects of Amount on Response

Effects of Size on Response



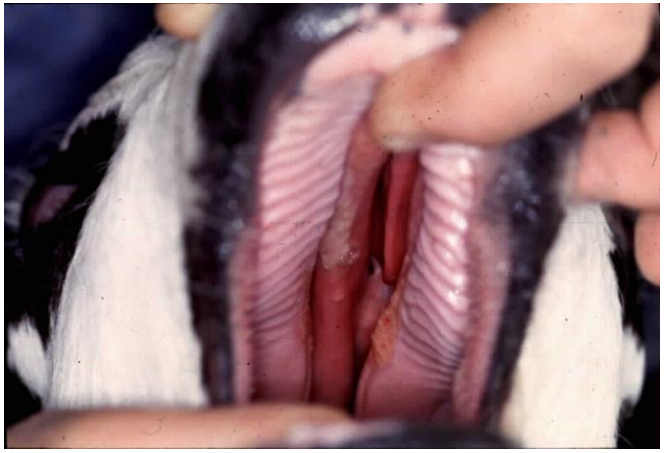
Dose-Response Relationship



The Timing Makes the Poison

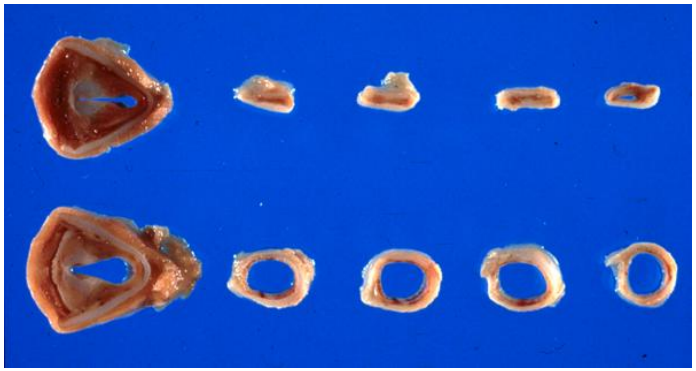
- **Teratogen** - of, relating to, or causing developmental malformations
  - i.e., something that will produce birth defects

Crooked Calf



Example of Lupine-induced
“crooked calf disease”

Malformed Lamb



Fate of Plant Poisons in Livestock

- Risk = Hazard X Exposure
- **Toxicokinetics –** what happens to a xenobiotic once it enters a body; in terms of its absorption, distribution, metabolism, and excretion
- ADME
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**limination/Excretion

Exposure & Absorption

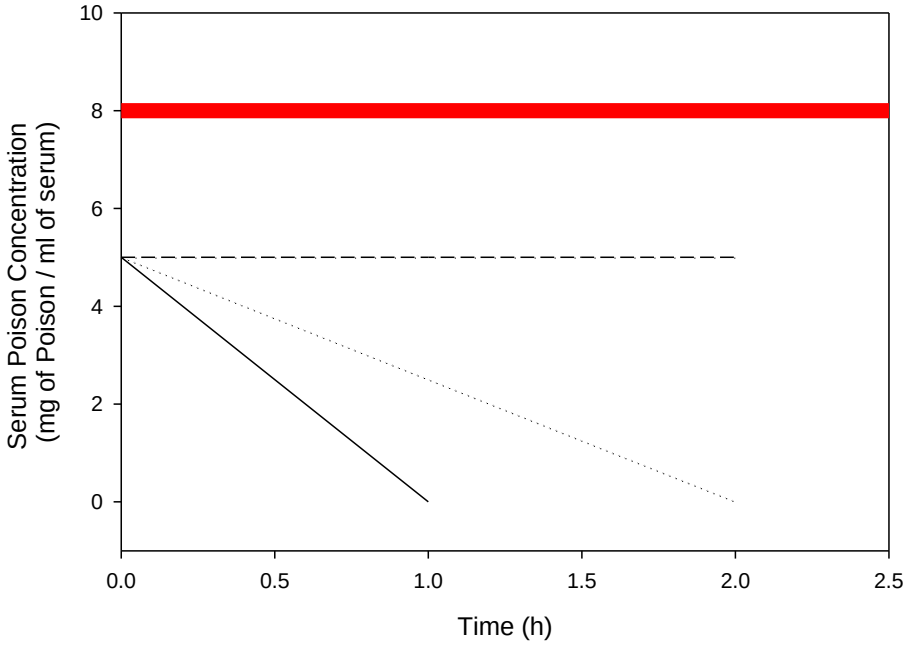
Route of exposure

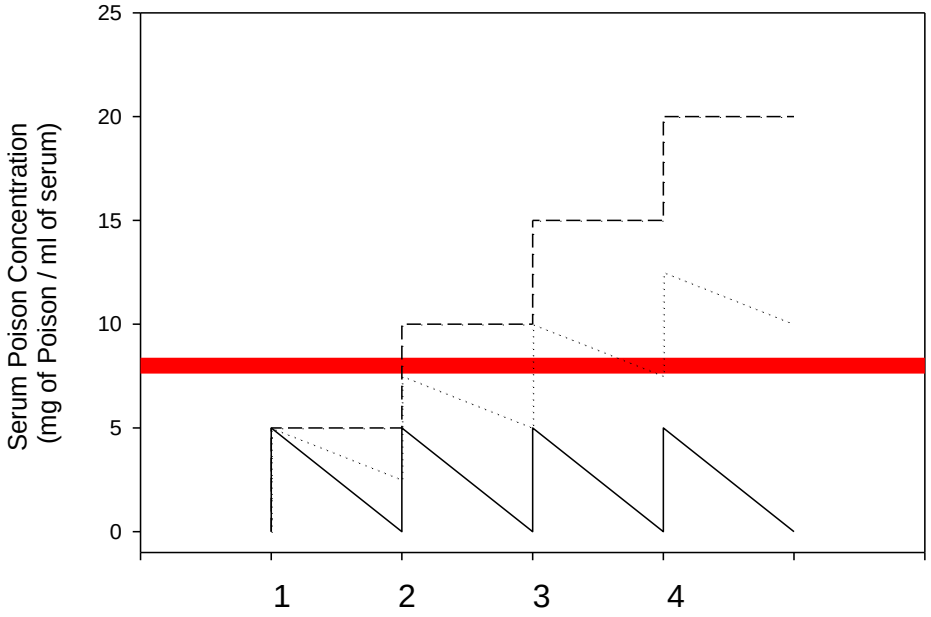
1) Skin (dermal)
2) Lung (inhalation)
3) Oral (gut)

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

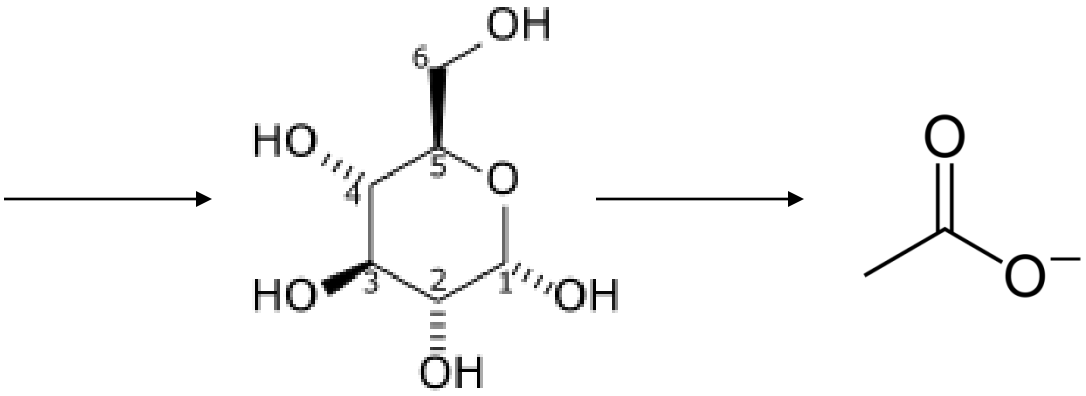
- Acute Exposure
- Sub-acute Exposure
- Sub-chronic Exposure
- Chronic Exposure

Distribution

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

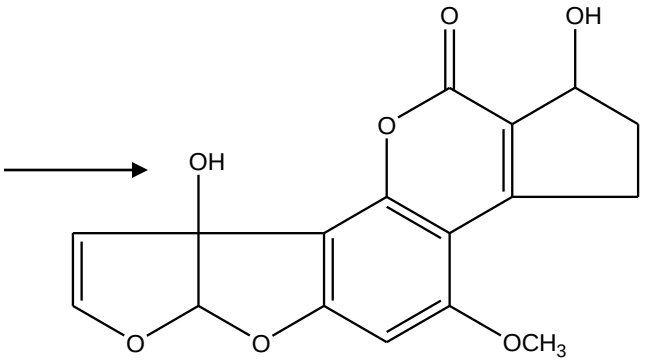
Metabolism

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

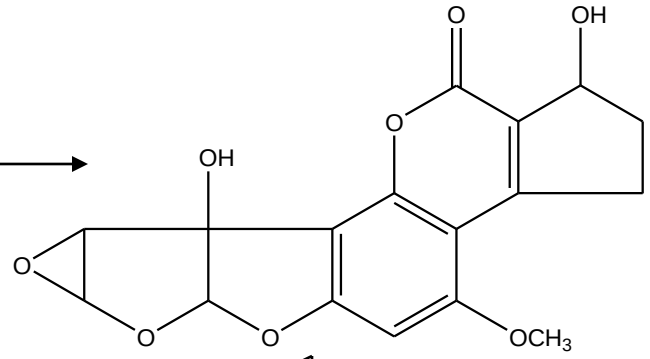


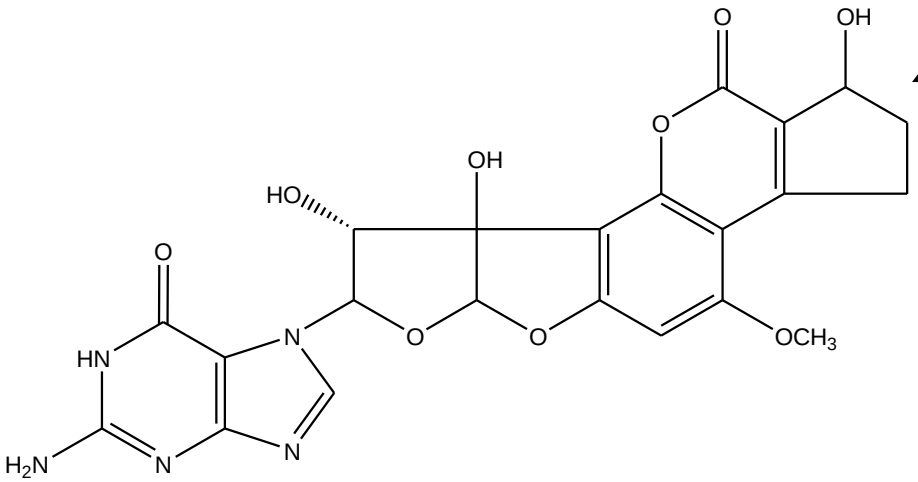
Metabolism

Aflatoxin B_1

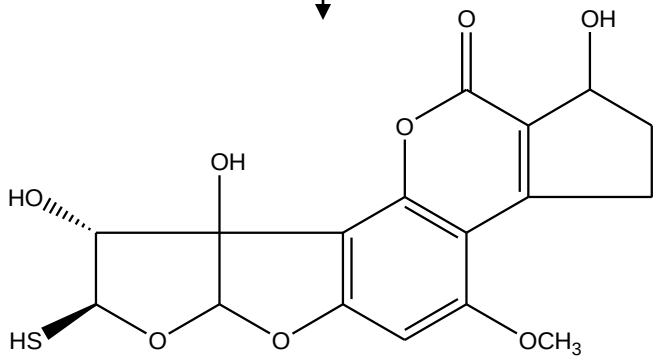


Aflatoxin B_1-8,9-epoxide





Aflatoxin B_1-N^7-guanine adduct

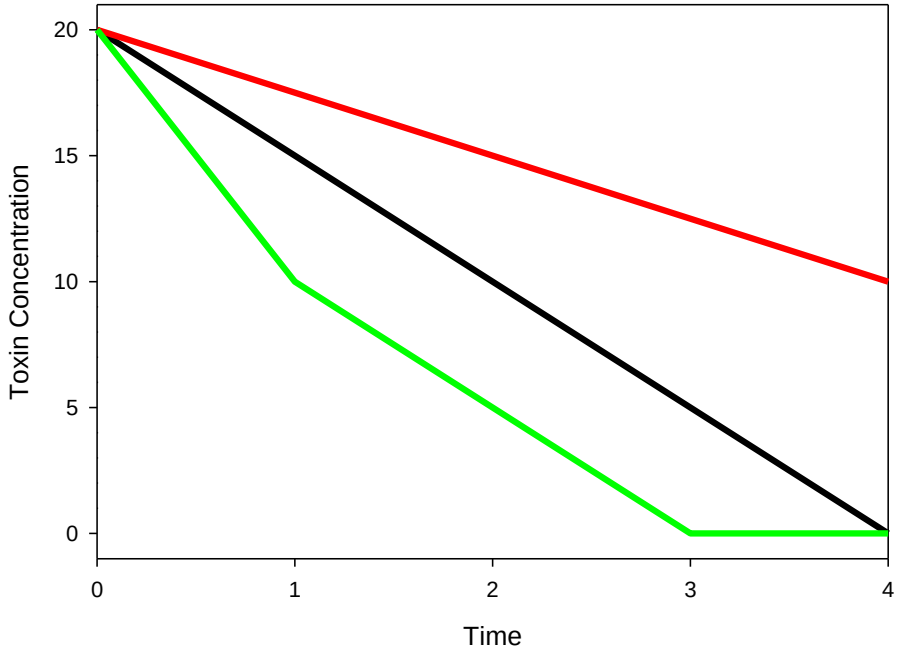


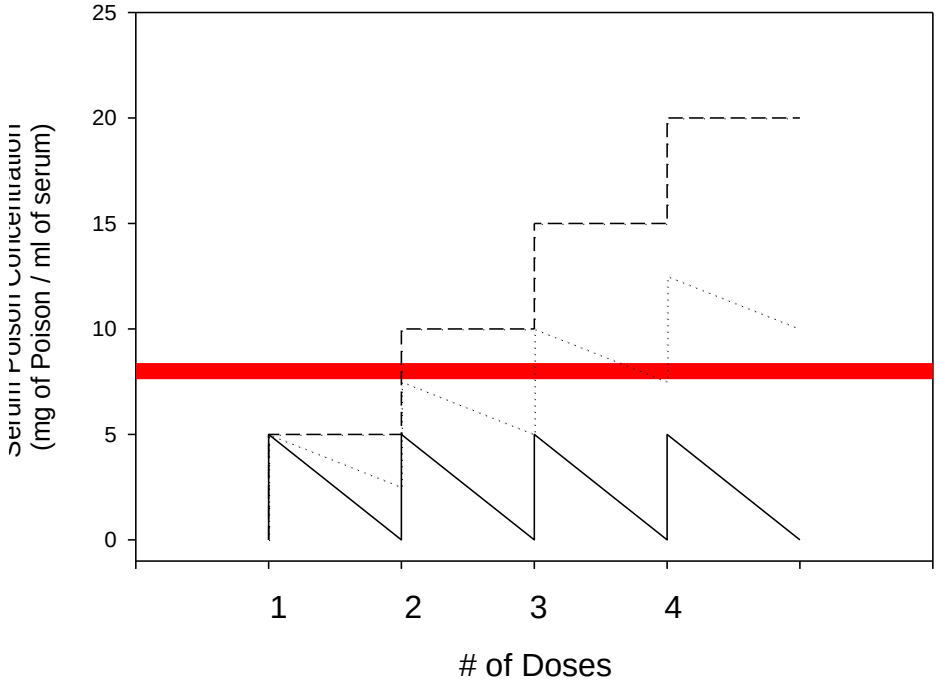
Aflatoxin B_1-glutathione adduct

Elimination/Excretion

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

Slow vs. Rapid Elimination



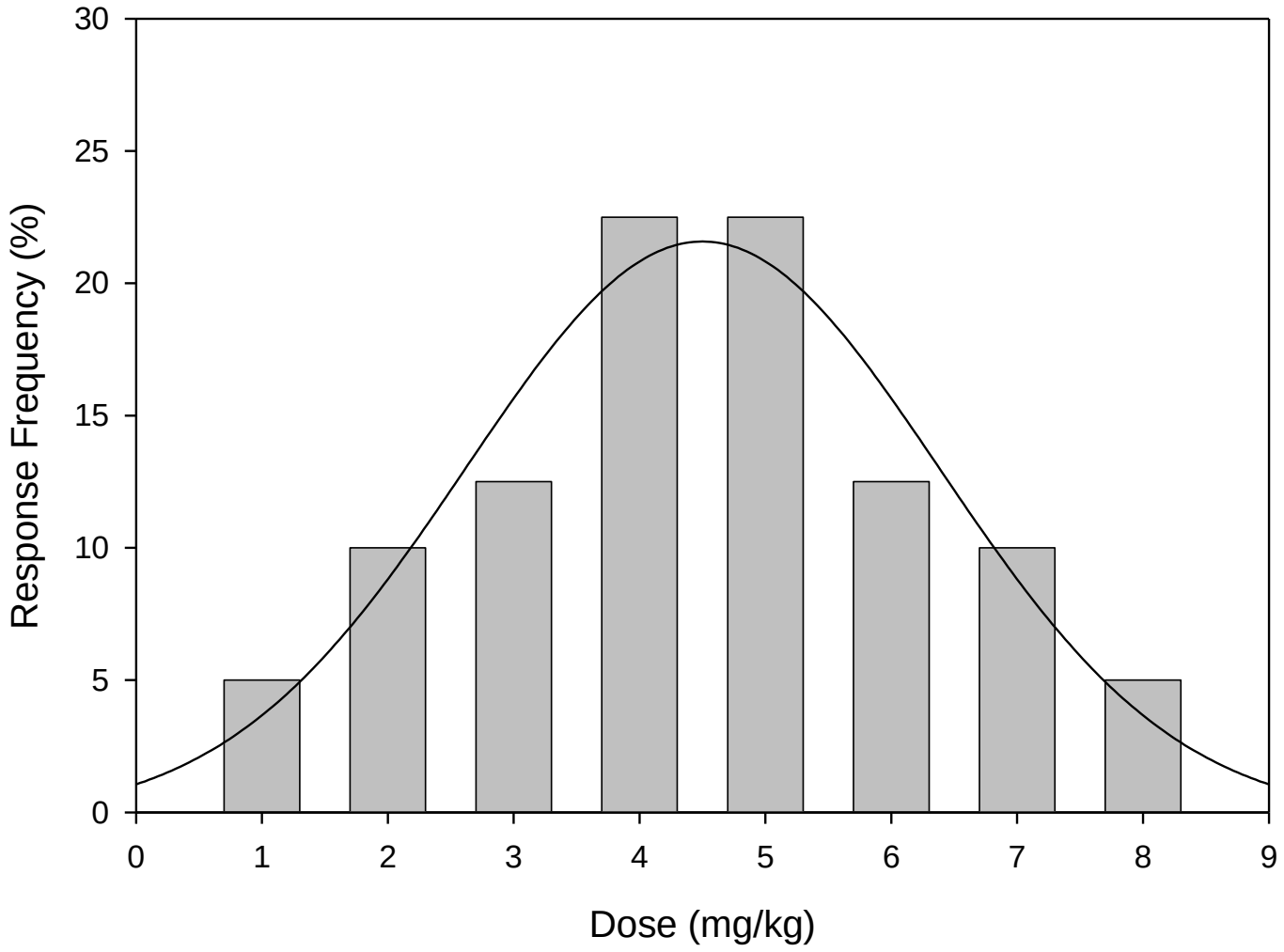


Individual Variation

"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

-Determine risk of livestock grazing in a given area