Principles of Toxicology: The Study of Poisons

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The study of the adverse effects of a toxicant on living organisms

- Adverse effects
  - any change from an organism's normal state
  - dependent upon the concentration of active compound at the target site for a sufficient time.
- Toxicant (Poison)
  - any agent capable of producing a deleterious response in a biological system
- Living organism
  - a sac of water with target sites, storage depots and enzymes

What is a Poison?

All substances are poisons;
there is none that is not a poison.
The right dose
differentiates a poison and a remedy.

Paracelsus (1493-1541)

Dose

The amount of chemical entering the body

This is usually given as

mg of chemical/kg of body weight = mg/kg

The dose is dependent upon

* The environmental concentration
* The properties of the toxicant
* The frequency of exposure
* The length of exposure
* The exposure pathway

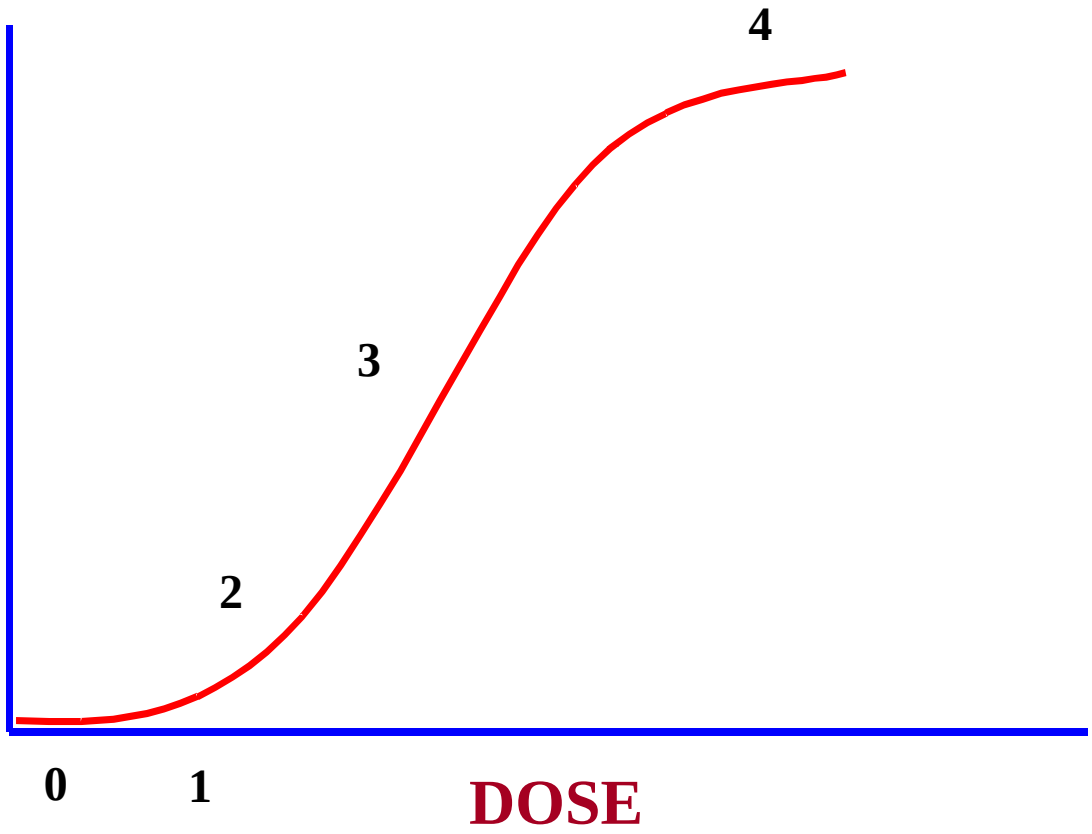
What is a Response?

The degree and spectra of responses depend upon the dose and the organism--describe exposure conditions with description of dose

- Change from normal state
  - could be on the molecular, cellular, organ, or organism level--the symptoms
- Local vs. Systemic
- Reversible vs. Irreversible
- Immediate vs. Delayed
- Graded vs. Quantal
  - degrees of the same damage vs. all or none

Dose-Response Relationship:

As the dose of a toxicant increases, so does the response.



0-1 NOAEL
2-3 Linear Range
4 Maximum Response

DOSE DETERMINES THE BIOLOGICAL RESPONSE

LD_{50}

- Quantal responses can be treated as gradient when data from a population is used.
- The cumulative proportion of the population responding to a certain dose is plotted per dose--10-30 fold variation w/in a population
- If Mortality is the response, the dose that is lethal to 50% of the population LD_{50} can be generated from the curve
- Different toxicants can be compared--lowest dose is most potent

LD_{50} Comparison

Chemical	LD_{50} (mg/kg)
Ethyl Alcohol	10,000
Sodium Chloride	4,000
Ferrous Sulfate	1,500
Morphine Sulfate	900
Strychnine Sulfate	150
Nicotine	1
Black Widow	0.55
Curare	0.50
Rattle Snake	0.24
Dioxin (TCDD)	0.001
Botulinum toxin	0.0001

Exposure: Pathways

- Routes and Sites of Exposure
  - Ingestion (Gastrointestinal Tract)
  - Inhalation (Lungs)
  - Dermal/Topical (Skin)
  - Injection
    - intravenous, intramuscular, intraperitoneal

- Typical Effectiveness of Route of Exposure

  iv > inhale > ip > im > ingest > topical

Exposure: Duration

Acute	< 24hr	usually 1 exposure
Subacute	1 month	repeated doses
Subchronic	1-3mo	repeated doses
Chronic	> 3mo	repeated doses

Over time, the amount of chemical in the body can build up, it can redistribute, or it can overwhelm repair and removal mechanisms

ADME: Absorption, Distribution, Metabolism, and Excretion

- Once a living organism has been exposed to a toxicant, the compound must get into the body and to its target site in an active form in order to cause an adverse effect.
- The body has defenses:
  - Membrane barriers
    - passive and facilitated diffusion, active transport
  - Biotransformation enzymes, antioxidants
  - Elimination mechanisms

Absorption:

ability of a chemical to enter the blood (blood is in equilibrium with tissues)

- Inhalation--readily absorb gases into the blood stream via the alveoli. (Large alveolar surface, high blood flow, and proximity of blood to alveolar air)
- Ingestion--absorption through GI tract stomach (acids), small intestine (long contact time, large surface area--villi; bases and transporters for others)
  - 1st Pass Effect (liver can modify)
- Dermal--absorption through epidermis (stratum corneum), then dermis; site and condition of skin

Distribution:

the process in which a chemical agent translocates throughout the body

- Blood carries the agent to and from its site of action, storage depots, organs of transformation, and organs of elimination
- Rate of distribution (rapid) dependent upon
  - blood flow
  - characteristics of toxicant (affinity for the tissue, and the partition coefficient)
- Distribution may change over time

Distribution: Storage and Binding

- Storage in Adipose tissue--Very lipophylic compounds (DDT) will store in fat. Rapid mobilization of the fat (starvation) can rapidly increase blood concentration
- Storage in Bone--Chemicals analogous to Calcium--Fluoride, Lead, Strontium
- Binding to Plasma proteins--can displace endogenous compounds. Only free is available for adverse effects or excretion

Target Organs: adverse effect is dependent upon the concentration of active compound at the target site for enough time

- Not all organs are affected equally
  - greater susceptibility of the target organ
  - higher concentration of active compound
- Liver--high blood flow, oxidative reactions
- Kidney--high blood flow, concentrates chemicals
- Lung--high blood flow, site of exposure
- Neurons--oxygen dependent, irreversible damage
- Myocardium--oxygen dependent
- Bone marrow, intestinal mucosa--rapid divide

Target Sites: Mechanisms of Action

- Adverse effects can occur at the level of the molecule, cell, organ, or organism
- Molecularly, chemical can interact with

  Proteins Lipids DNA
- Cellularly, chemical can
  - interfere with receptor-ligand binding
  - interfere with membrane function
  - interfere with cellular energy production
  - bind to biomolecules
  - perturb homeostasis (Ca)

Excretion:

Toxicants are eliminated from the body by several routes

- Urinary excretion
  - water soluble products are filtered out of the blood by the kidney and excreted into the urine
- Exhalation
  - Volatile compounds are exhaled by breathing
- Biliary Excretion via Fecal Excretion
  - Compounds can be extracted by the liver and excreted into the bile. The bile drains into the small intestine and is eliminated in the feces.
- Milk Sweat Saliva

Metabolism:

adverse effect depends on the concentration of active compound at the target site over time

- The process by which the administered chemical (parent compounds) are modified by the organism by enzymatic reactions.
- 1^{o} objective--make chemical agents more water soluble and easier to excrete
  - decrease lipid solubility
    --> decrease amount at target
  - increase ionization
    --> increase excretion rate --> decrease toxicity
- Bioactivation--Biotransformation can result in the formation of reactive metabolites

Biotransformation (Metabolism)

- Can drastically effect the rate of clearance of compounds
- Can occur at any point during the compound's journey from absorption to excretion

Compound	Without Metabolism	With Metabolism
Ethanol	4 weeks	10mL/hr
Phenobarbital	5 months	8hrs
DDT	infinity	Days to weeks

Biotransformation

- Key organs in biotransformation
  - LIVER (high)
  - Lung, Kidney, Intestine (medium)
  - Others (low)
- Biotransformation Pathways
  * Phase I--make the toxicant more water soluble
  * Phase II--Links with a soluble endogenous agent (conjugation)

Individual Susceptibility

--there can be 10-30 fold difference in response to a toxicant in a population

- Genetics-species, strain variation, interindividual variations (yet still can extrapolate between mammals--similar biological mechanisms)
- Gender (gasoline nephrotox in male mice only)
- Age--young (old too)
  - underdeveloped excretory mechanisms
  - underdeveloped biotransformation enzymes
  - underdeveloped blood-brain barrier

Individual Susceptibility

- Age--old
  - changes in excretion and metabolism rates, body fat
- Nutritional status
- Health conditions
- Previous or Concurrent Exposures
  - additive --antagonistic
  - synergistic

Toxicology

- Exposure + Hazard = Risk
- All substances can be a poison
- Dose determines the response
- Pathway, Duration of Frequency of Exposure and Chemical determine Dose
- Absorption, Distribution, Metabolism & Excretion
- The extent of the effect is dependent upon the concentration of the active compound at its site of action over time
- Bioactivation: compounds to reactive metabolites
- Individual variation of the organism will affect ADME