BASIC PRINCIPLES OF TOXICOLOGY

DEFINITIONS:

Toxicology: **The study of the adverse effects of a toxicant on living organisms.**
Toxicology is an applied science that incorporates biology, chemistry, physiology, pathology, physics, statistics, and sometimes immunology or ecology to help solve problems in forensic medicine, clinical treatments, pharmacy and pharmacology, public health, industrial hygiene, veterinary science, agriculture, and more, as well as giving basic insight into how an organism functions.

Toxicologist: A living organism who studies the nature of these adverse effects at the molecular, celllular, organ, organ system, organism, or even community level by understanding what the agent does to the system and what the system does to the agent.

Toxicant (Poison): Any agent capable of producing a deleterious response in a biological system.
"All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy." Paracelsus (1493-1541)

The shape, size, and solubility of the toxicant will determine how easily it enters the body, how it will distribute within the body, and the rate of its excretion from the body.

Dose: The amount of chemical entering the body.
This is usually given as milligrams of chemical per kilogram of body weight (mg/kg) so that dose can be compared across specimens. How much, how often (duration and frequency), and how the dose is administered are all important parameters.

Adverse Effect (Response): Any change from an organism's normal state that is irreversible at least for a period of time. Producing an adverse effect depends on the concentration of the active compound at the target site.
A description of the dose and the conditions of exposure must accompany a description of the adverse effect due to a chemical. An effect or response can be graded (variations of the degree of damage) or quantal (all or none; i.e., mortality or tumor development).

Living Organism: The species, strain, individual genetic variation, gender, age, health conditions, nutrition, and previous and concurrent exposures can affect how an organism responds to a chemical exposure.

Risk Assessment: Quantitative estimate on the potential effects of various types of chemical exposure on human health. RISK= HAZARD + EXPOSURE

AXIOMS OF TOXICOLOGY:

- There is essential uniformity in the biochemistry in similar species--among biological mechanisms in mammals. This allows for extrapolation from animal data for predictions in humans.
- Any substance can provoke a dysfunction or injury at some degree of exposure—the dose makes the poison. Attenuation of injury can be achieved by dilution; i.e., lowering the dose of the agent. Complications can occur when there is exposure to more than one agent, even at non-toxic doses.
- There is a dosage or exposure level that has no effect on the health of animals—as measured by methods which have a finite sensitivity to measure dysfunction or injury.
- Toxicological data from animal experiments can be used to assess the degree of exposure or dosage that will not adversely affect human health. However, potential or real differences in animals or humans (as well as variations in species) each mandate that judgmental factors be applied when extrapolating form animal threshold doses in order to insure an adequate margin of safety for humans.

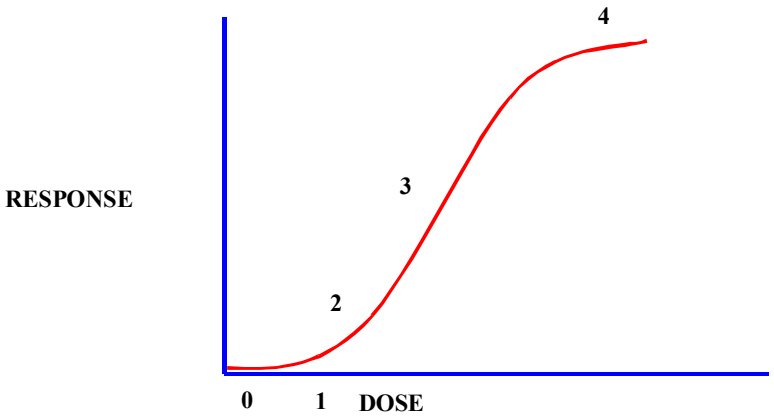
- The single most important factor that determines the potential harmfulness of a chemical is the relationship between the concentration of the chemical at its site of action and the effect that is produced.

The Dose-Response Relationship is of paramount importance in toxicology.

Dose determines the biological response.

Dose-Response curve: The relationship between the dose of a chemical (dependent variable) and the response produced (independent variable) follows a predictable pattern. As the dose of a toxicant increases, so does the response, either in terms of the proportion of the population responding or in terms of the severity of the graded responses. For most toxicants, at very low amounts, there will be no detectable effect of the chemical (NOAEL: no observed adverse effect level). In the midrange of doses, the amount of damage will increase as the dose increases (the linear 16-84% of the curve). Larger amounts of chemical will cause increasingly more severe biological responses until a maximum level of damage is reached. Additional toxic effects may also appear along with increased doses, depicting both dose response and dose effect relationships.

0-1= no adverse effect level
2-3 = linear portion of the curve
4 = maximal response or effect



Quantal responses can be treated as a gradient when data from a population is used. The cumulative proportion of the population responding to a certain dose is plotted for each dose. A similar S-shaped curve is produced since there can be a 10-30 fold variation within a population. If one uses mortality as the response, the dose that is lethal to 50% of the population (LD_{50}) can be calculated from the generated curve. Different toxicants can be compared, and the one with the lowest LD_{50} is the most potent. There are differences in between exposure routes and animals.

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

Chemical	LD50 (with route and animal)
Caffeine	620mg/kg—oral mouse 192mg/kg—oral rat 105mg/kg—iv rat 68mg/kg—iv mouse
Chlorine (LC 50)	293ppm/1hr—rat 137ppm/1hr—mouse
THC (from marijuana)	175mg/kg—iv mouse 155mg/kg—iv rabbit 100mg/kg—iv dog
Mercury (I) Chloride	210 mg/kg—oral rat 8 mg/kg—iv mouse
Mercury (II) Chloride	37 mg/kg—oral rat 10 mg/kg—oral mouse
Arsenic acid (V oxidation state)	48 mg/kg—oral rat
Arsenic trioxide (III oxidation state)	20 mg/kg—oral rat
Dimethylarsenic acid (methylated arsenic form used as a cotton defoliant)	700 mg/kg—oral rat

EXPOSURE:

An organism must be exposed to an agent before there is a risk. The physical properties of the chemical and the concentration of the chemical in the environment are important in determining the extent of the exposure.

Toxic effects in a biological system are not produced unless the agent or its metabolic breakdown (biotransformation) products reach appropriate target sites in the body at a concentration and for a length of time sufficient to cause toxicity. We need to define, HOW MUCH, HOW LONG, and HOW OFTEN.

Doses of Chemicals:

Dose = Amount / Animal Mass i.e. mg/kg of animal body weight

A given dose can be compared across animal species

Example: Need to administer 100mg/kg dose of the drug to a mouse, a rat, and a human.
20g mouse would get **2mg** of drug
200g rat would get **20mg** of drug
70kg human would get **7g** of the drug

Duration of Exposure:

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

Toxic Effects: Acute vs Chronic
Overtime, the amount of chemical in the body can build up, it can redistribute, or it can overwhelm repair mechanisms.
Toxicologists are most interested in what is the most common scenario, chronic exposure to low doses.

	Single Dose	Repeated Dose
Benzene	CNS Depression	Leukemia

Frequency of Exposure:

The frequency of the exposure affects the concentration at the target site—can build up to a steady level--why some medications are taken three times a day vs. once a day to give the wanted effect.

Route and Site of Exposure:

Ingestion (gastrointestinal tract)
Inhalation (lungs)
Dermal / topical (skin)
Parenteral (intravenous--iv, intramuscular—im, intraperitoneal—ip)

Typical Effectiveness of Route of Exposure

iv > inhalation > ip > im > ingestion > topical

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION OF TOXICANTS (ADME):

The toxicant may have to pass many barriers to get to its site of action

Absorption:

Absorption--the ability of a chemical agent to enter the blood.
Similar blood levels are more likely to give similar effects than similar administered doses. Blood is in equilibrium with the other tissues and target sites.

Intravenous	No limiting factors in absorption (100% bioavailable)
Inhalation	Must penetrate alveolar sacs of lungs but then into capillary bed
Ingestion	Requires absorption through GI tract and is subject to 1st pass effect
Intraperitoneal	Like ingestion (still 1st pass effect) but does not require absorption through the GI tract
Dermal/Topical	Requires absorption through the skin

Distribution:

Distribution—the process in which a chemical agent translocates throughout the body. The blood carries the agent to and from its site of action, storage depots, organs of biotransformation, and organs of elimination. The rate of distribution is usually rapid, and is determined primarily by blood flow and the chemical characteristics of the toxicant (its affinity for the tissue and the partition coefficient). The distribution of a chemical may change over time.

Storage—DDT in Fatty tissues
Lead and Fluoride in Bone

Metabolism:

Metabolism (biotransformation)—the process by which administered chemicals (parent compounds) are modified by the organism, usually via enzymes. The primary objective of metabolism is to make chemical agents more water soluble and easier to excrete by

Decreasing lipid solubility → Decreased amount that reaches target
Increasing ionization → Increased rate of excretion → Decrease toxicity

In some situations, biotransformation results in the formation of reactive metabolites—Bioactivation.
Whether it is the parent compound or the metabolite, it is the active compound that does the damage.

Excretion:

Toxicants are eliminated from the body by several routes.

Urinary excretion
Water soluble products are filtered out of the blood and excreted into the urine.

Exhalation
Volatile compounds are exhaled through breathing

Biliary Excretion via Fecal Excretion
Compounds can be extracted by the liver, biotransformed, and excreted into the bile. The bile drains into the small intestine where the eliminated compound can be excreted into the feces. Fecal excretion also rids the body of non-absorbed compounds which pass through the GI tract.

MORE ON METABOLISM:

Biotransformation can occur at any point during the compound's trek from absorption to excretion.

Biotransformation can drastically effect the rate of clearance of compounds

	Without Biotransformation	With Biotransformation
Ethanol	4 weeks	10mL/hr
Phenobarbital	5 months	8hr
DDT	infinity	days to weeks

Key organs of Biotransformation:

LIVER (High)
Lung, Kidney, Intestine (Medium)
Others (Low)

Biotransformation Pathways

Phase I enzymes: Makes the toxicant more soluble
Phase II Enzymes: Links with a soluble agent (conjugation)

Individual Susceptibility:

Individual variation of the organism will affect the absorption, distribution, metabolism, and excretion of the toxicant, and there fore the effect of the toxicant.

There can be a 10-30 fold difference in response to a toxicant in a population due to:

Genetics—species, strain variations, inter-individual variations
Gender
Age (young and old)
Nutritional status
Health conditions
Previous or concurrent exposure to other substances