General Principles of Toxicology

DEFINITIONS & TERMINOLOGY

- Toxicology is the study o the adverse effects of chemicals on living organisms.
- **Poisons**: are drugs that have almost exclusively harmful effects
- However, Paracelsus (1493–1541) famously stated that *"THE DOSE MAKES THE POISON"*
- **Toxins??** biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons (lead and iron)
- Toxicology: is the branch of pharmacology that deals with the **undesirable effects of chemicals on living systems**
- Molecular toxicology: the study of the effects of toxicants at the molecular levels…..cell growth, differentiation, genes, DNA, RNA, proteins

TOXICOLOGY DISCIPLINES

- **Environmental toxicology**:

  focuses on the impacts of chemical pollutants in the environment on biological organisms, study the effects of chemicals that are contaminants of food, water, soil, or the atmosphere

- **Industrial (occupational) toxicology**:
  - Toxic exposure in the workplace or during product testing.

- **Clinical (medical) toxicology**: is concerned with disease caused by or uniquely associated with toxic substances focus on the diagnosis, management and prevention of poisoning or ADEs.

TOXICOLOGY DISCIPLINES

- **Forensic toxicology**: the use of toxicology to aid medical and legal investigation of death.

is a hybrid of analytic chemistry and fundamental toxicologic principles that focuses primarily on the medicolegal aspects of the harmful effects of chemicals on humans and animals.

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)

What is a Poison??

- *Poisoning or exposure??*

- Many people consider that poisoning start the moment exposure occurs
- In reality, we are exposed to a wide variety of toxic substances each day from food and water that we ingest, and air that we breath

What is Response?

- Change from normal state – could be molecular, cellular, organ, or organism level……the symptoms
- The degree and spectra of responses depend upon the dose and the organism
  - ✓ Immediate vs. Delayed (carcinogenic)
  - ✓ Reversible vs. Irreversible (liver vs. brain, teratogenic effect)
  - ✓ Local vs. Systemic
  - ✓ Graded vs. Quantal……degrees of the same damage vs. all or none
- Allergic Reactions & Idiosyncratic Reactions….ADRs

Characteristics of Exposure

1. 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

Characteristics of Exposure

2. Exposure: Pathways

- ❑ Routes and Sites of Exposure:
  - ✓ **Ingestion** (GIT), (first pass effect)
    - Ex. Lidocaine and Verapamil (antiarrhythmic drugs)
  - ✓ **Inhalation** (Lungs): rapid absorption, because of large alveolar surface area
  - ✓ **Dermal/Topical** (Skin), absorption varies with area of application and drug formulation, but usually absorption is slower than other routes
  - ✓ **Injection**
    - Intravenous, intramuscular, intraperitoneal
- ❑ Typical response of Routes and Sites of Exposure:

i.v > inhalation > i.p > i.m > oral > topical

Characteristics of Exposure

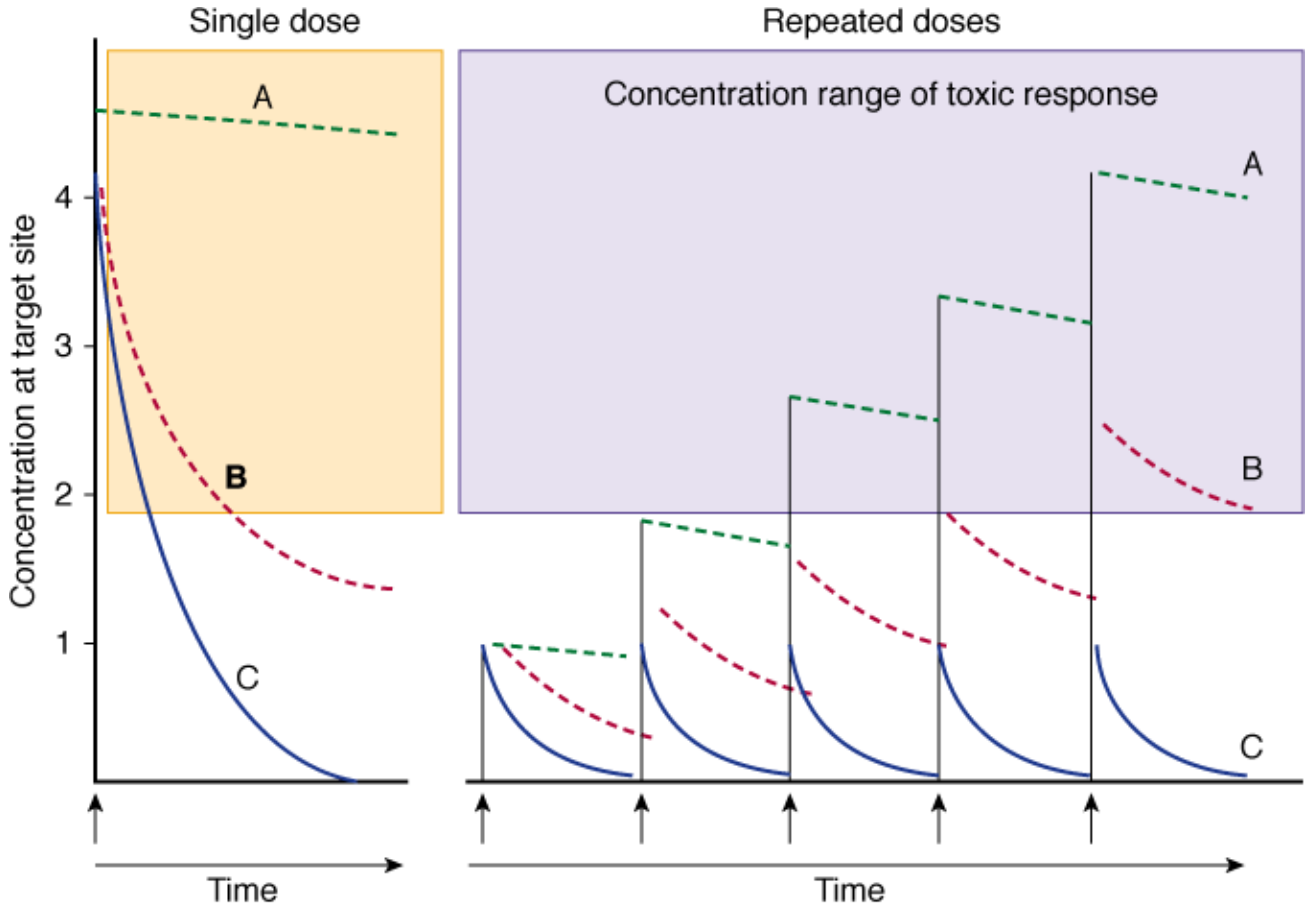
3. Duration and frequency of exposure

- Toxicologists usually divide the exposure of experimental animals to chemicals into 4 categories……:

Acute	< 24hr	Usually 1 exposure
Sub-acute	1 month	Repeated exposure
Sub-chronic	1-3 months	Repeated exposure
Chronic	> 3 months	Repeated exposure

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

The other time-related factor that is important in the temporal characterization of repeated exposures is the **frequency** of exposure



The relationship between elimination rate and frequency of exposure

Dose Response Relationship

- The magnitude of drug effect depends on the drug concentration at the receptor site, which is in turn determined by the dose of drug administered and by factors of the drug pharmacokinetic profile
- There is a *graded dose-response relationship* in each individual and a *quantal dose-response relationship* in a population

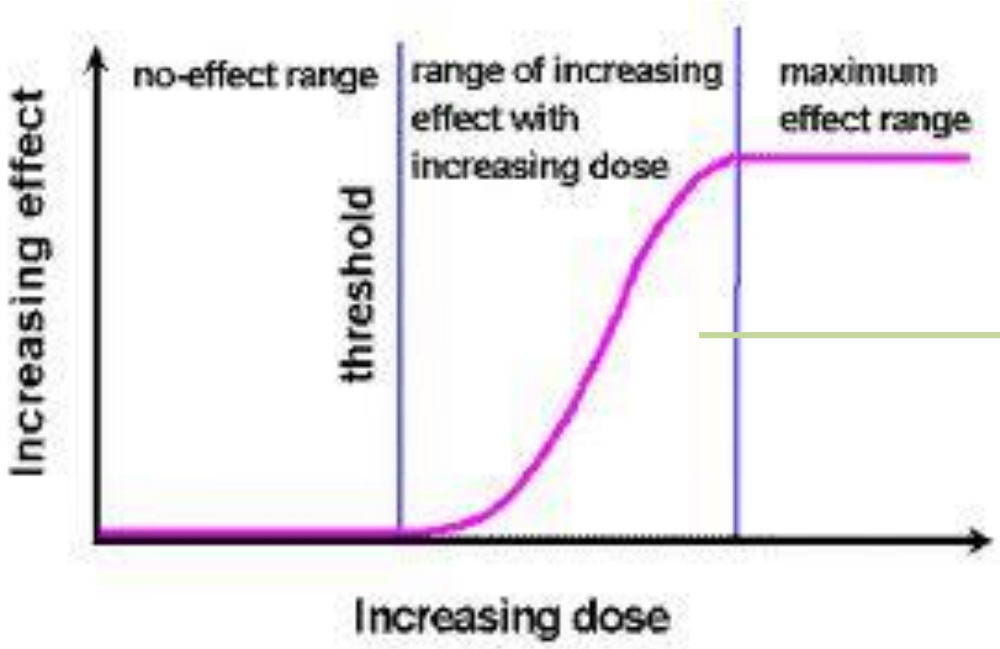
Graded-dose response relationship

- The response to a drug is a graded effect, meaning that the the measured effect is continuous over a range of doses

- Graded dose response curves are constructed by plotting the magnitude of the response against increasing doses of a drug (or log dose)

Dose-Response Relationship

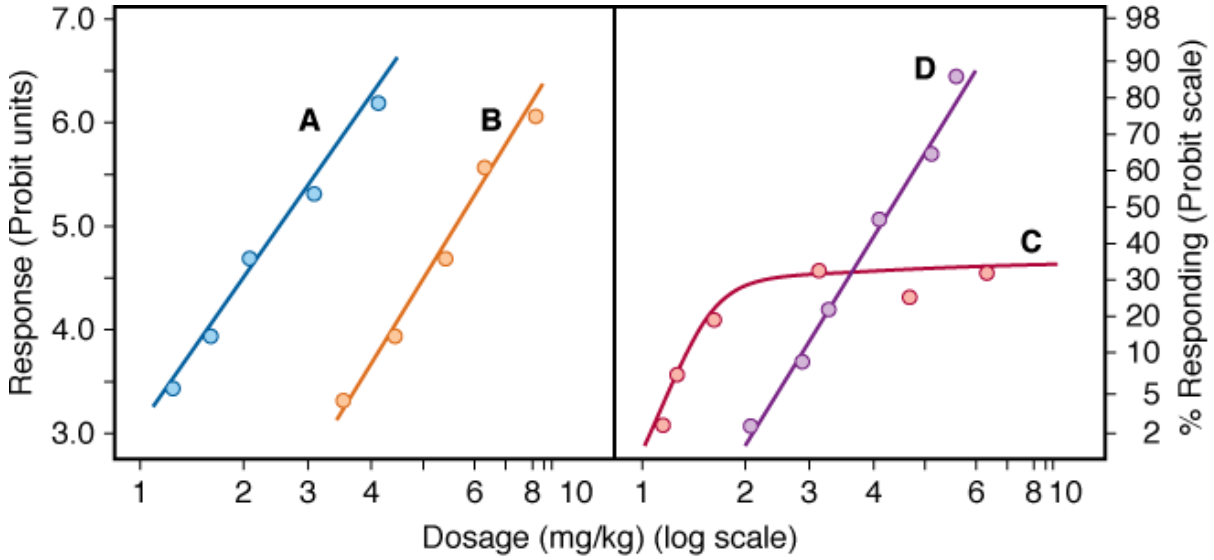
- As the dose of a toxicant increases, so does the response



Steep curve….relative small dose changes cause large response changes

Graded-dose response relationship

- Two important properties of drugs can be determined by the graded dose response curves:
  - **Potency**
  - **Maximal toxicity**

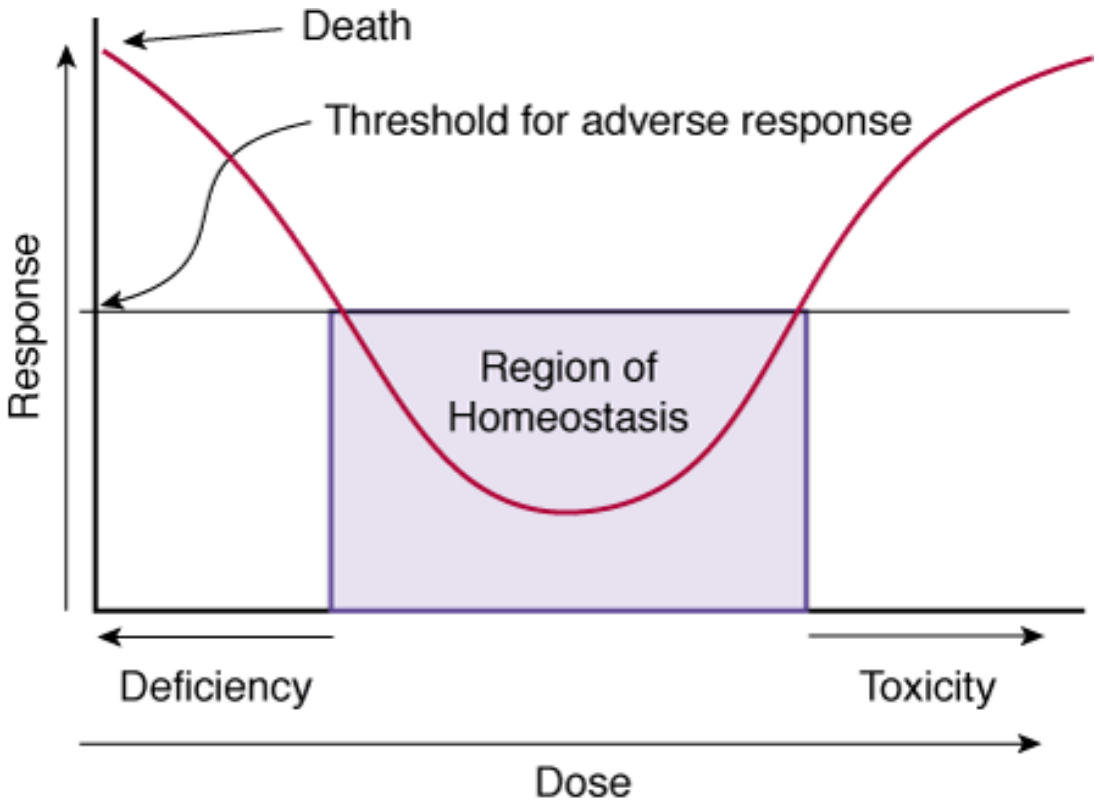


Source: Klaassen CD, Watkins JB: *Casarett & Doull's Essentials of Toxicology, 2nd Edition:* http://www.accesspharmacy.com

‘U’ Shape of the Dose-Response Curve

- For substances that are required for normal physiologic function and survival (e.g., vitamins and essential trace elements such as chromium, cobalt, and selenium), the shape of the “graded” dose–response relationship in an individual over the entire dose range is actually U-shaped.

‘U’ Shape of the Dose-Response Curve



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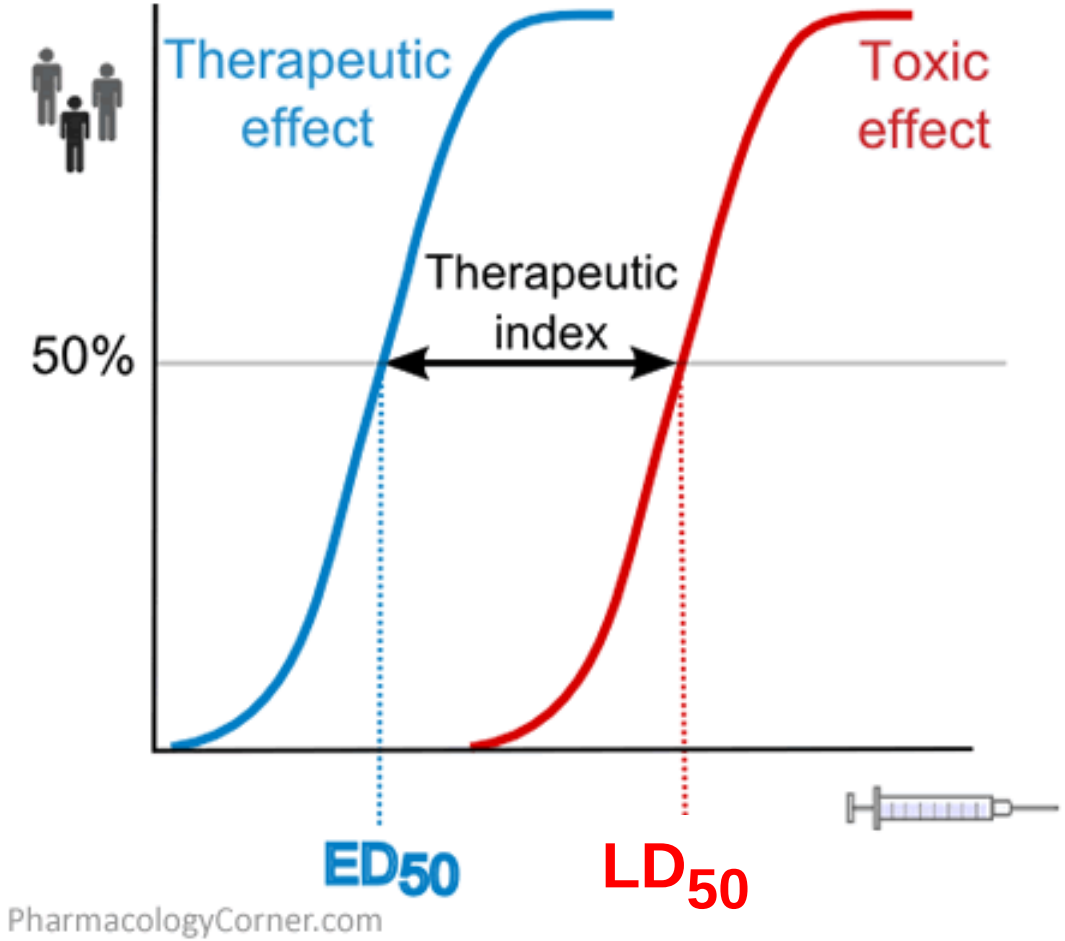
Evaluating the Dose Response Relationship

- The quantal (all or none) dose-effect curve is often characterizes the distribution of responses to different doses in **a *population*** of individual organisms
  - Median toxic dose(TD_{50}): the dose at which 50% of individuals/population exhibit a particular toxic effect
  - If the toxic effect is death of the animal, a median lethal dose (LD_{50}) may be experimentally defined
  - Median effective dose (ED_{50}):……..??



- ✓ **TI = TD_{50} / ED_{50}**
- ✓ For non-drug chemicals: **Margin of Safety**

Shift to the left….shift to the right!!!

!!!……Molecular Target Concept

Agonist

Antagonist

Pharmacodynamics

- In the field of pharmacology, an **inverse agonist** is an agent that binds to the same receptor as an **agonist** but induces a pharmacological response opposite to that antagonist. A**ntagonist** has no activity in the absence of an **agonist** or **inverse agonist** but can block the activity of either.

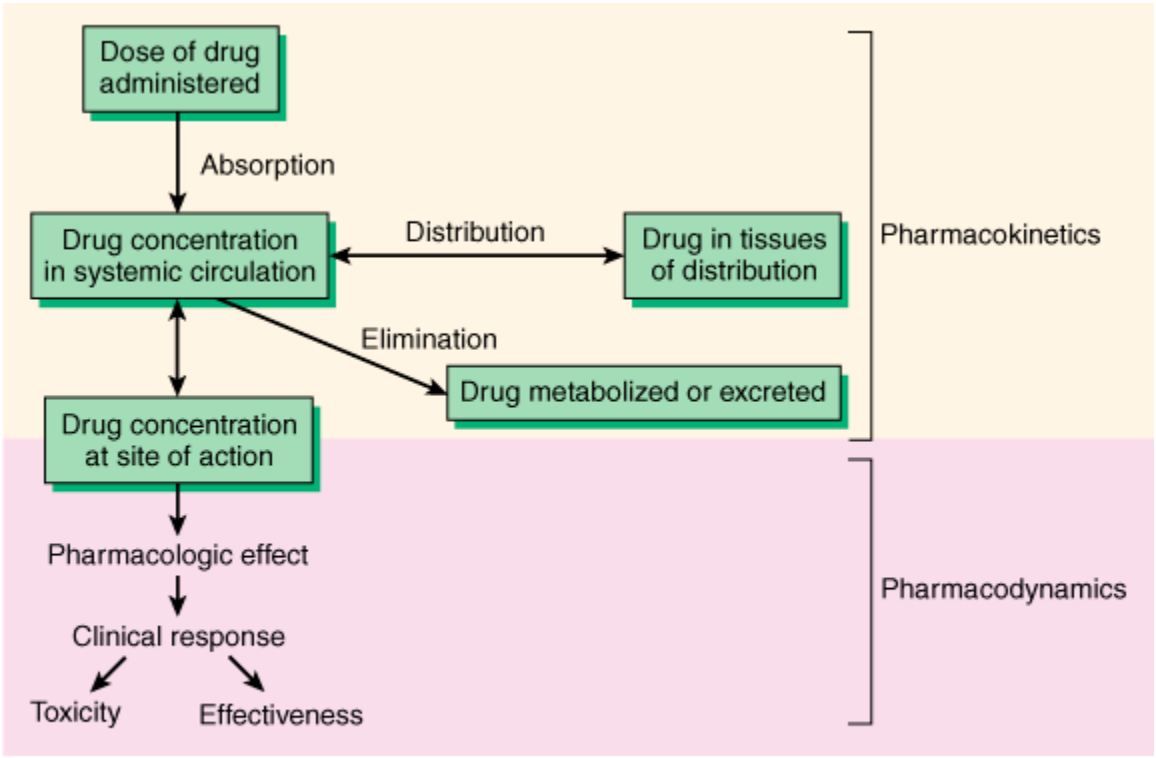
Toxicodynamics & Kinetics

- The toxicity of a substance depends on the dose
- The concentration of a chemical at the site of action is usually proportional to the dose
- But……same dose of two different chemical may lead to vastly different concentrations???
- …….Disposition…..

Toxicokinetics: Disposition (ADME)

- Toxicokinetics is the quantitation of the time course of toxicants in the body during the processes of **absorption**, **distribution**, **biotransformation**, and **excretion** or clearance of toxicants
- In other words, toxicokinetics reflects how the body handles toxicants as indicated by the plasma concentration of that xenobiotic at various time points
- The end result of these toxicokinetic processes is a **biologically toxic dose** of the toxicant/s

Toxicodynamics & Kinetics

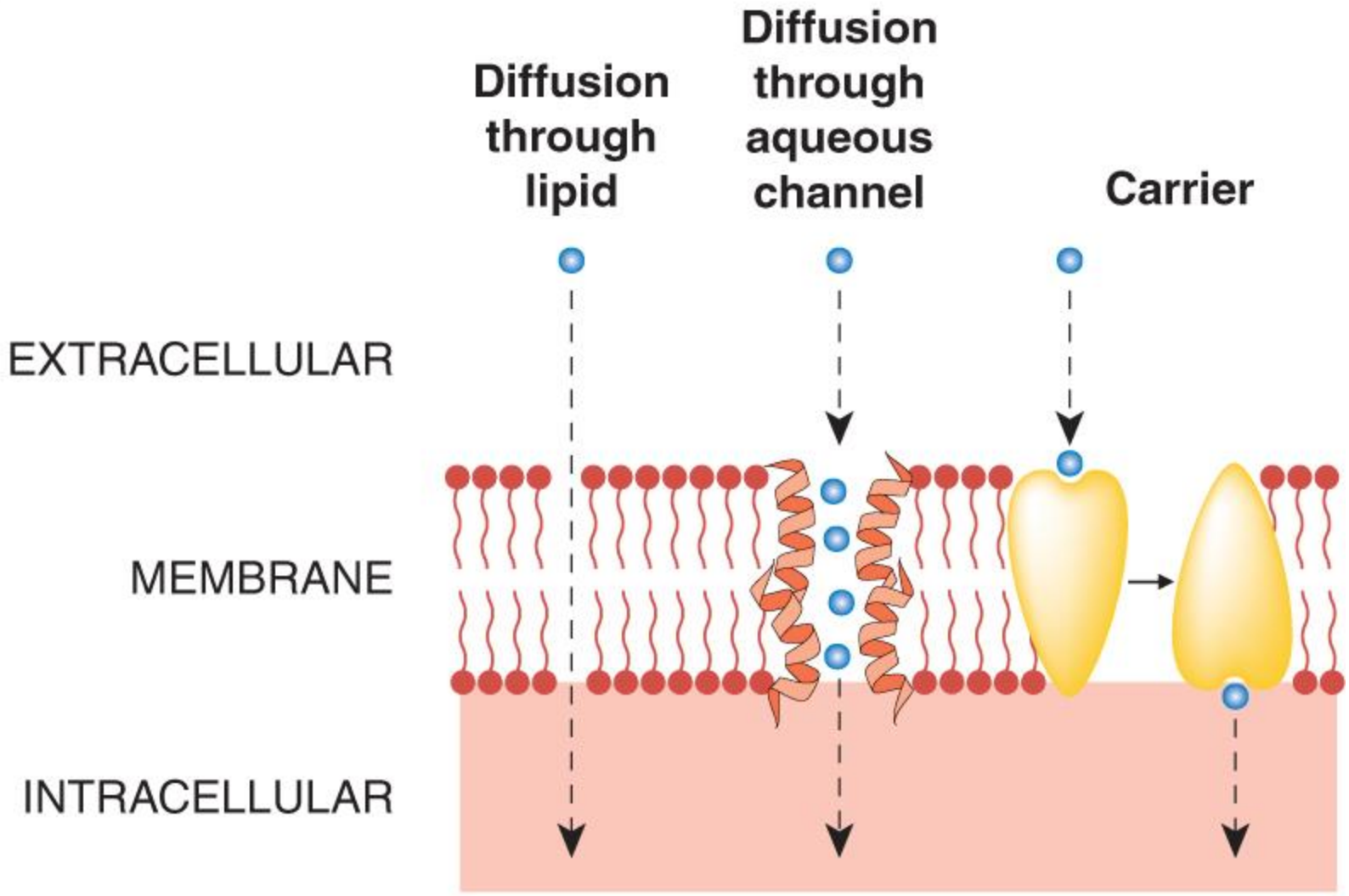


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Toxicokinetics: ADME

- 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, simple diffusion (pH, protein-bound??), facilitated (saturable, selective), active (ABC transporters), or special carriers
  - Biotransformation enzyme, antioxidants
  - Elimination mechanisms



Absorption

- Ability of a chemical to enter the blood stream (GI tract, skin, lungs)
- **Absorption: RATE & EXTENT**
- The rate is of toxicological importance coz is the main determinant of the peak plasma concentration
- The extent determines the total body exposure or internal dose

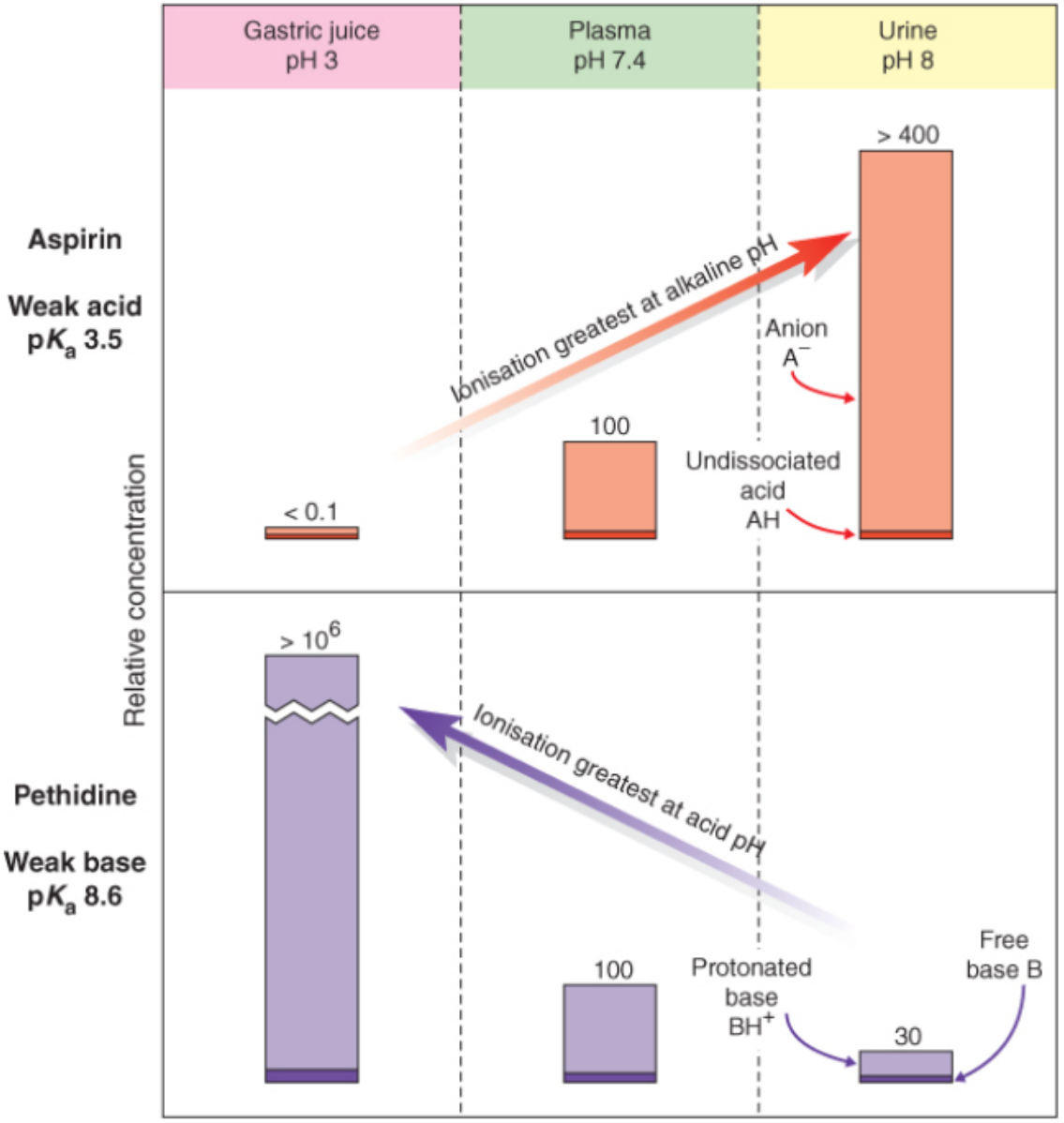
Absorption

- **Route of exposure**
- **Inhalation**: readily absorb gases into the blood via the alveoli (large alveolar surface, high blood flow)
- Particle size is the main determinant, ≤ 1µm penetrate the alveolar sacs of the lungs (nanoparticles!!)
- **Enteral administration**: particle size, surface area, blood flow rate, pKa, Pgp, intestinal motility??
- ✓ First-pass effect (intestine and/or liver can modify)

$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

For acids: $pH = pK_a + \log \frac{[A^-]}{[HA]}$

For bases: $pH = pK_a + \log \frac{[B]}{[BH^+]}$



Absorption

- ❑ **Dermal**: fortunately not very permeable
- ✓ Absorption through epidermis by passive diffusion (stratum corneum thickness, condition of skin, blood flow, small size)
- ✓ …..then dermis by diffusion….systemic circulation
- ❑ **Parenteral**: I.V, I.P, I.M, S.C

- ❑ **Physicochemical properties of the toxicant..**

Distribution

- The process in which a chemical agent translocates throughout the body…reversible process
- Blood carries the agent to and from its site of toxicity, storage depots, organ of transformation, and organs of elimination
- Storage in adipose tissue: very lipophilic compounds (DDT) will store in fat
- Liver and kidney: high binding capacity for several chemicals
- Storage in bone: chemicals analogues to calcium, fluoride, lead, strontium

Distribution: storage & binding

- The rate of distribution dependent upon
  - ✓ Blood flow
  - ✓ Characteristics of toxicant (affinity for the tissue, and the partition coefficient)
- Binding plasma proteins: in equilibrium with the free portion, displacement by another agent
- BBB……tight capillary endothelial cells.

ELIMINATION =

EXCRETION + METABOLISM

Elimination

- **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 compound 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 (biotransformation)

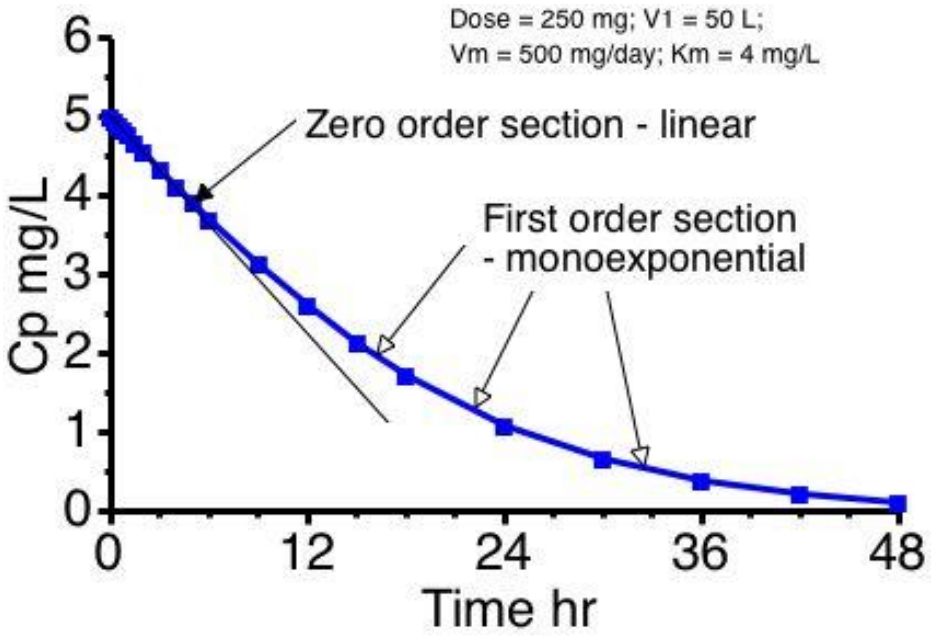
- Toxic response depends on the concentration of active compound at the target site over time
- The process by which the administered chemical (parent compound) are modified by the organsim by enzymatic reactions
- 1st objective – make chemical agents more water soluble and easier to excrete
  - Increase solubility ---- decrease amount at target
  - Increase ionization ---- increase excretion rate ---- decrease toxicity
- **Bioactivation/toxication** ---- biotransformation can result in the formation of reactive metabolites

Metabolism (biotransformation)

- Can drastically affect the rate of clearance of compounds
- Can occur at any point during the compound's journey from absorption to excretion
- Key organs in biotrasnformation
  - Liver (principal)
  - Lung, kidney, intestine
  - Others
- Biotransformation pathways
  - Phase I: make the toxicant more water soluble
  - Phase II: links with a soluble endogenous agent

Classical Toxicokinetics

- Drugs highly charged or polar are excreted by the kidney…1st order elimination
- Lipid soluble drugs, first metabolized by liver….if enzymes saturated…zero order elimination



Factors influencing Toxicity

1. COMPOSITION OF THE TOXIC AGENT
2. DOSE & CONCENTRATION
3. ROUTE OF EXPOSURE
4. METABOLISM OF THE TOXICANT
5. STATE OF HEALTH
6. AGE & MATURITY
7. NUTRITIONAL STATE
8. GENETICS
9. GENDER
10. ENVIRONMENTAL FACTORS

Factors influencing Toxicity

1. Composition of the toxic agent:

- A basic fallacy: responsible toxicant is the pure substance
- Physiochemical composition of toxicant: solubility, charge, hydrophobicity, powder/dust

- Solid vs Liquid
- Poisoning is more with liquid and small particles (particle size)

Factors influencing Toxicity

1. **Composition of the toxic agent:**

- E.g: Cr^{3+} relatively non-toxic, Cr^{6+} causes skin and nasal corrosion and lung cancer
- PH: strong acids or bases vs mild acids and basics
- Stability: paraldehyde…..acetaldehyde (nausea, pulmonary edema)

Factors influencing Toxicity

2. **Dose and concentration:**

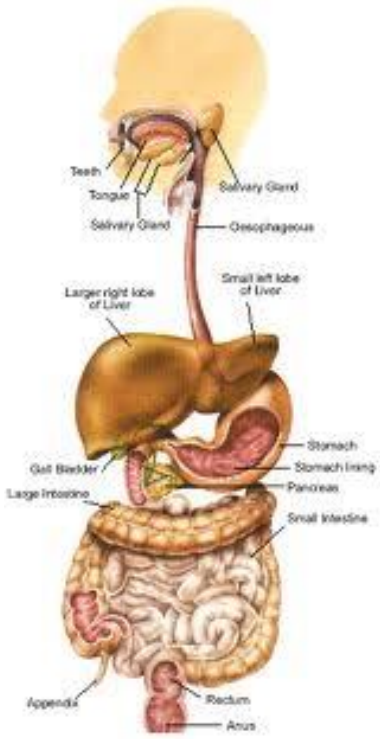
- Most important factor: e.g. acute ethanol exposure causes CNS depression, chronic exposure liver cirrhosis
- Diluted solutions Vs concentrated solution (easily absorbed)

3. **Route of exposure:** oral, inhalation, dermal
    - Affect time of onset, intensity and duration
    - Predict the degree of toxicity and the organ mainly affected

Factors influencing Toxicity

Oral is related to:

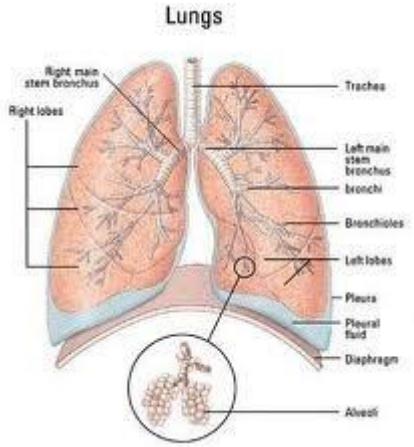
- Rate of disintegration & dissolution
- Degree of ionization
- Solid forms? Tendency to clump together
- Presence of food: protein and fat delay absorption, carbohydrate beverages increase absorption
- Chance to readily metabolize…and “hoped” detoxify!! 1st pass effect



Factors influencing Toxicity

Inhalation:

- Particle size is a limited factor ≤ 1μm



Dermal:

- Penetration is time dependent
- Skin condition
- Nature of the toxicant (irritant)

Factors influencing Toxicity

4. Metabolism of the toxicant

✓ 1st pass effect

- NOT ALWAYS
- MeOH $\xrightarrow{Ox.}$ Formaldehyde + Formic acid …serious side effects

5. State of health:

- Hepatic, renal insufficiency
- Diarrhea or constipation may decrease or increase the time of contact between chemical and absorptive site
- Hypertension may exacerbate response to chemical with sympathomimetic activity

Factors influencing Toxicity

6. Age and maturity

- Chloramphenicol….grey baby syndrome
- Geriatric….generalized decrease in blood supply to tissue…..decrease in toxicity….(not always)
  - P.O drugs….absorption decrease
  - Diseases (hepatic, renal, CV)….decrease detoxification, excretion, distribution

Factors influencing Toxicity

7. Nutritional state

- Empty stomach or food contents (pH, high fat,….)
  - ➢ Ca^{2+} in milk and tetracycline
  - ➢ Fatty food increase absorption of griseofulvin
  - ➢ Tyramine rich food and MAO inhibitors
  - ➢ Hypoalbuminemia: greater amount of free drug

Factors influencing Toxicity

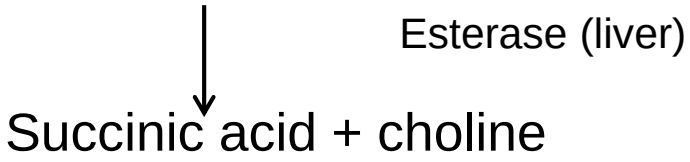
9. Gender

- Difference in absorption…..
- Difference in metabolism rate….
- Differences in quantities of muscle mass and fat tissue….in i.m injection

Factors influencing Toxicity

8. Genetics: ***(Genetic toxicology….normal Gaussian curve)***

- Species, strain variation, inter-individual variations
- Succinylcholine metabolized by **pseudocholisterenase** into succinylmonocholine + choline then….



- G6PD deficiency….. may cause hemolytic anemia

Toxicology….summary!

- All substances can be poison
- Dose determines the response
- Pathway, duration, frequency of exposure and chemical determine dose
- The extend 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 absorption, distribution, metabolism, & excretion