Toxicant Distribution

- **Distribution**: the process in which a chemical agent, after first gaining entry into the blood, translocates throughout the fluid compartments of the body.
  - Bloodstream carries the toxicant to its sites of biotransformation, action, storage, and elimination.
  - Important concerns:
    - the rate of distribution
    - the role of exposure route on distribution outcome

Body Water and Volume of Distribution

- Apparent volume of distribution ($V_D$)
  - Relates the toxicant concentration in different fluid compartments
  - Theoretical volume of water required to distribute toxicant equally (L/kg)
  - Indicates the extent of the distribution of a toxicant within the body fluids
- Where is the water?
  - Blood plasma: 4-5% of total body weight
  - Interstitial fluid (the fluid surrounding the cells of body tissues): approx. 15% of total body weight
  - Intracellular fluid (the fluid contained within the cells): approx. 40% of total body weight; 28 L of water
Distribution of body water and movement of toxicant between compartments

\[ V_S = \frac{D}{[C_P]} \]

where \( D \) is the dose of the toxicant in milligrams and \([C_P]\) is the plasma concentration of the toxicant in milligrams per liter of plasma (mg/L).

Blood Flow and Barriers to Distribution

- A toxicant in the blood will move in the plasma and either be stored, metabolized, or eliminated
  - The distribution of toxicants from the blood to the tissues and organs of the body may not be uniform.
  - Certain body parts (placenta, knees, brain) are barriers to distribution
    - Entry is restricted (i.e., slowed) and toxicity is reduced
    - This is related to specialized vasculature

Toxicant Storage

- Occurs primarily in fat and bone (connective tissues), kidneys, and liver
  - Fat is especially accumulated in subcutaneous tissue.
  - It is here where lipophilic toxicants are stored and are mobilized back into the blood for further distribution, metabolism, elimination, or redeposition.
- Liver and kidneys store toxicants more efficiently than other organs
  - Relatively high blood flows
- Liver tissue has greatest capacity for biotrans.
  - Especially vulnerable to injury
  - Examples: alcohol poisoning, household cleaners, herbicides/pesticides
Toxicant Storage (2)

• Bone is important, too
  – Relatively poor blood flow
  – Significant mobilization of Pb, Sr, F under specific circumstances
    • While a broken bone is being repaired
    • During pregnancy (from maternal to fetal compartments)
    • For example, Pb may be substituted for Ca, and F may be substituted for OH-
  – Heavy metals stored in the bone may reside there for decades.

Toxicant Elimination

• Critical for the reduction of toxicity or potential toxicity in the body
• Encompasses all of the processes used by the body that lead to a decrease in the amount of toxicant
• These processes are as follows:
  – Renal elimination
  – Fecal elimination
  – Pulmonary elimination
  – Biotransformation
  – Elimination via minor routes (e.g., sweat, milk, hair, and nails)

Elimination Processes

• Renal
  – One of the most important routes
  – Influenced by toxicant properties:
    • Molecular size
    • Solubility
    • Degree of ionization
  – Toxicants eliminated via
    • Filtration
    • Re-absorption
    • Secretion
Fecal and Pulmonary Elimination

- Fecal elimination via:
  - Direct discharge
  - Excretion in bile
  - Diffusion across intestinal capillaries

- Pulmonary elimination
  - Large surface area → important route for volatile liquids/gases
    - Elimination via diffusion from blood to alveoli
  - Important factors:
    - Δconcentration between blood and alveoli
    - Vapor pressure
    - Solubility: low solubility in blood → more rapid elimination

Minor Routes of Elimination

- Milk
  - Mother → nursing infant
  - Cow → people
    - Any concern with lipophilic toxins?
    - Chemicals that behave in the body similar to calcium (e.g., Pb) can also be excreted into the milk.
    - Toxicant transport into milk occurs primarily by diffusion
    - The ΔpH between blood plasma and milk (about 7.4 and 6.5, respectively) favors higher concentrations of organic bases in milk compared with organic acids.

- Saliva
  - Toxicants that are eliminated to some extent in saliva are usually swallowed, thus prolonging residence time in the body.

Minor Routes of Elimination (2)

- Sweat, tears
  - Elimination → skin irritation

- Semen
  - Nontrivial concentrations of Pb and DDT have been found
  - Correlations between toxin and fetal malformation has been shown
  - Effects on sexual partners unknown

- Hair, nails
  - Very negligible elimination route
  - Although Mg, As have been found
Biotransformation

• Synonymous with metabolism
  – The sum of all chemical processes of the body that modify endogenous or exogenous chemicals.

• Impacted by “host” factors:
  – age
  – gender
  – existing disease
  – genetic variability (toxicogenetics)
  – nutritional status

Age

• Biotransformation varies greatly with age:
  – Developing fetus and young kids have limited biotransformation capability
    • Due to a lack of important enzymes
    • Enzymes are optimal by young adulthood
  – Elderly also have limited capability (functional loss due to aging)
  – Enzyme fluctuations are at their lowest in early adulthood, which corresponds to the most efficient time in our lives for biotransformation (metabolism).
    • One reason that diet and exercise “works” when we’re young

Gender and Nutrition

• Gender
  – Differences in hormones account for gender-specific variability

• Nutrition
  – Specific vitamin, mineral, and protein deficiencies can decrease the body’s ability to synthesize essential enzymes.
  – Biotransforming enzymes cannot be synthesized without amino acids, carbohydrates, and essential vitamins and minerals
Disease and Genetic Variability

• Disease
  – The liver is the principal organ for biotransformation
    • Hepatitis can significantly reduce the biotransformation capacity of the liver, thus further contributing to a decline in the health of the affected individual.
  
• Genetic variability
  – Consider the "extrapolations" artifact present in laboratory toxicity testing

The Key: Enzymes

• Recall that they are catalysts → RATES
• Enzyme defects are very problematic
• Enzymes detoxify many chemicals
  – Render them less harmful
  – Render them more water soluble → elimination
• Sometimes the metabolite is MORE harmful, though
  – "Bioactivation"
• Tissues where biotransformation proceeds:
  – Liver, lungs, kidneys, intestines, placenta, skin
• Different enzymes of the body may compete for the same toxicant
  – Result is different metabolites that may greatly vary in their toxicity

Example: Bioactivation

CHCl₃ → P450 (Enzyme) → Phosgene (Metabolite)

Chloroform (Parent) → More Toxic/Reactive

Less-toxic
The Key: Enzymes

- The biology of metabolism is beyond the scope of EVE 491/591
- Your text includes more of the detail, but I'm not holding you responsible for it.

Case Study #2 “Kermit to Kermette?”

Refer to the handout provided (Part 1).

Questions

1. Does atrazine appear to alter male frog development at any concentration?
2. If atrazine does affect male frog development, what is the lowest concentration and dose that appears to have the effect?
3. The chemical DDT was banned for use in the U.S. in the 1960s. For years afterwards, however, American manufacturers of DDT continued to export it to third world countries that had not yet banned its use. How does this observation relate to the use of atrazine in the U.S. today?