Distribution and Storage of Toxicants

Food Toxicology
Instructor: Gregory Möller, Ph.D.
University of Idaho

Learning Objectives

- Identify the ways toxicants are distributed in the body.
- Recognize the relationship between route of absorption and pathway for distribution.
- Describe factors affecting distribution.
- Define volume of distribution.
- List storage sites.
- Discuss how storage influences toxicant half-life.
- Review case studies and model of storage and distribution.

Absorption → Distribution

- Absorption through skin, lung or intestinal tissue is followed by passage into the interstitial fluid.
    - Interstitial fluid (~15%); intracellular fluid (~40%); Blood plasma (~8%).
- Toxicant is absorbed and enters the lymph or blood supply and is mobilized to other parts of the body.
- Toxicant can enter local tissue cells.

Distribution

- Lymphatic system.
    - Lymph capillaries, nodes, tonsils, spleen, thymus, lymphocytes.
    - Drains fluid from systems.
    - Slow circulation.
- Cardiovascular system.
    - Heart, arterial and venous vessels, capillaries, blood.
    - Fast circulation.

- Major distribution by blood.

Blood System

- Erythrocytes.
  - Red blood cells.
- Leukocytes.
  - White blood cells.
- Platelets.
  - Thrombocytes.
- Plasma.
  - Non-cellular fluid.

Entering the Bloodstream

- Where a toxicant enters the bloodstream affects the toxicity.
  - Digestive system.
    - Portal vein carries toxicants to the liver, a major site for detoxication.
  - Respiratory system.
    - Directly into pulmonary circulation.
    - Particulates can slowly migrate through lymph system.
  - Percutaneous.
    - Enters the peripheral blood supply and can impact tissues far away.

Factors Affecting Distribution

- Physical or chemical properties of the toxicant.
- Concentration gradient.
  - Volume of distribution (dose/plasma concentration).
- Cardiac output to the specific tissues.
- Detoxication reactions.
  - Protein binding.
- Tissue sensitivity to the toxicant.
  - Adipose tissue; receptors.
- Barriers that inhibit migration.
  - Blood-brain and placental.

Plasma Protein Binding

- Some toxicants can bind to plasma proteins such as albumin.
- Affects distribution and $T_{1/2}$.
  - Free toxicant in equilibrium with bound and available for distribution and endpoint effect.
  - Plasma concentration is a good indicator of toxicant concentration at site of action.

– The apparent volume of
distribution, V_D (liters), is
the total volume of body fluids
in which a toxicant is distributed.

Distribution and Composition of
Body Fluid Components
Distribution To and From Liver

- Portal vein allows first pass of digestive route to the liver.
- High cardiac output to the liver ensures a major potential for toxicant interaction and systemic exposure.
- Enterohepatic recirculation allows
  for recycled exposure.
  - Blood $\rightarrow$ Liver $\rightarrow$ Bile Ducts
    $\rightarrow$ Intestine $\rightarrow$ Portal Vein
    $\rightarrow$ Blood (repeat).

Liver and Gall Bladder
Hepatic Fine Structure
Distribution Endpoint Model
Storage

- Accumulation of toxicants in specific tissues.
- Binding to plasma proteins.
  - Albumin most abundant and common binder.
- Storage in bones.
  - Heavy metals, especially Pb.
- Storage in liver.
  - Blood flow; biotransformation.
- Storage in the kidneys.
- Storage in fat.
  - Lipophilic compounds.

Case Study: Bone Storage in Chicken
Case Study: Bone Storage in Chicken
Case Study:
Lead Poisoning From Mobilization of Bone Stores During Thyrotoxicosis

37-yo female smoker with a history of childhood lead exposure (pica; lead paint chips) and adult lead exposure 7-yrs earlier (lead paint house renovation) presents with fatigue, cramps, insomnia, weight loss, muscle ache and tremor.

She had elevated PbB (51 µg/dl) and erythrocyte protoporphyrin (EP), enlarged thyroid. Bone Pb levels of 154 and 253 µg/g (normal 5-10 µg/g). Hyperthyroidism indicated by thyroid hormone levels.

Case Study:
Lead Poisoning From Mobilization of Bone Stores During Thyrotoxicosis

Radioactive iodine test revealed diffusely enlarged and hyperactive thyroid consistent with Graves disease. Serum osteocalcin (bone protein) levels were elevated indicating increased bone turnover. Treated for thyroid disease including I^{131} thyroid ablation therapy.

25 wks later PbB levels were 19 µg/dl and osteocalcin levels were normal. Bone stores unchanged. At 52 wks PbB levels were 17 µg/dl.

Route of Exposure

- GI tract exposure sends toxicant directly to the liver via the portal system for "first pass" detoxication.
    - GI to lymph system slower.
- Respiratory or skin exposure can have greater systemic effects.
- Rate of metabolism can impact systemic effects.
    - Slow metabolism will allow wider distribution.

Disposition Models

- Tissues as compartments.
    - Blood, fat, bone, liver, kidneys, brain.
    - Concentration vs. time.
- One compartment open model
    - 1st order kinetics.

Disposition Models, 2

- Two compartment open model.
- Enters blood and to another compartment (liver?), before being excreted or returned.
- Typically more complex.

Case Study: Cu Disposition in Ovine
Case Study: Disposition, 2
Case Study: Disposition, 3
Structural Barriers

- Blood-brain barrier.

- Brain has specialized cells, astrocytes, which limit passage of water soluble molecules from the capillary endothelium and the neurons of the brain.
- Placental barrier.
  - Consists of several cell layers between the maternal and fetal circulatory vessels in the placenta.
- Slows toxicant passage chemically/structurally.

PBBs (Polybrominated Biphenyls) in Michigan 1973

- Polybrominated biphenyls (PBBs) are man-made chemicals that were used as fire retardants in plastics that were used in a variety of consumer products.
- PBB is a relatively stable substance that is insoluble in water but highly soluble in fat. Manufacture of PBBs was discontinued in the US in 1976.

PBB Michigan 1973

- In early 1973, both PBB (sold under the trade name FireMaster) and magnesium oxide (a cattle feed supplement sold under the trade name NutriMaster) were produced at the same St. Louis, Michigan plant.
- A shortage of preprinted paper bag containers led to 10 to 20 fifty-pound bags of PBB accidentally being sent to Michigan Farm Bureau Services in place of NutriMaster.

PBB Michigan 1973

- This accident was not recognized until long after the bags had been shipped to feed mills and used in the production of feed for dairy cattle.
- By the time the mix-up was discovered in April 1974, PBB had entered the food chain through milk and other dairy products, beef products, and contaminated swine, sheep, chickens and eggs.

PBB Michigan 1973

- As a result of this incident, over 500 contaminated Michigan farms were quarantined.

- Approximately 30,000 cattle, 4,500 swine, 1,500 sheep, and 1.5 million chickens were destroyed, along with over 800 tons of animal feed, 18,000 pounds of cheese, 2,500 pounds of butter, 5 million eggs, and 34,000 pounds of dried milk products.

PBB Michigan 1973

- Some PBB-exposed Michigan residents complained of nausea, abdominal pain, loss of appetite, joint pain, fatigue and weakness.
  - However, it could not clearly be established that PBBs were the cause of these health problems.
- There is stronger evidence that PBBs may have caused skin problems, such as acne, in some people who ate contaminated food.
  - Some workers exposed to PBBs by breathing and skin contact for days to months also developed acne.

PBB Michigan 1973
PBB Michigan 1973

- Increased rates of neurologic, immunologic, dermatologic, and musculoskeletal effects have been noted in the Michigan PBB cohort; however, these effects do not show a consistent relationship with serum PBB levels.
- Numerous negative correlation study results.
- Spontaneous abortion rates were elevated among second-generation women born after the Michigan PBB incident.

Modeling for Risk Assessment

- An approach to understanding the exposure linkage to human disease in the risk assessment process.
- A "proxy" for situational, specific clinical data.
- Can be done for toxicant systems with a high degree of background knowledge.
- PB PK - Physiologically based pharmacokinetic model

Predicting Blood Pb Levels

- **I**ntegrated **E**xposure **U**ptake **B**io**K**inetic Model for Lead in Children.
  - The IEUBK model.
- The model software (IEUBKwin Model, v1.0) and the description are available at:
  http://www.epa.gov/superfund/
  programs/lead/products.htm
- Also: LeadSpread

http://www.dtsc.ca.gov/
AssessingRisk/leadspread.cfm

The IEUBK Model

- Attempts to predict blood-lead levels (PbB) for children exposed to Pb in their environment.
- The model allows the user to input relevant absorption parameters, (*e.g.*, the fraction of Pb
  absorbed from water)
  as well as rates for intake
  and exposure.

The IEUBK Model

- Using these inputs, the IEUBK model then rapidly calculates and recalculates a complex set of equations to estimate the potential concentration of Pb in the blood for a hypothetical child or population of children (6 months to 7 years).
  - Measured PbB concentration is
    not only an indication of exposure,
    but is a widely used index to discern
    future health problems.
  - Childhood PbB concentrations at
    or above 10 μg/dL of blood present
    risks to children's health.

Model Overview, Exposure

- *Exposure Component*: compares Pb concentrations in food and environmental media with the amount of Pb entering a child's body.
- The exposure component uses environmental media-specific consumption rates and Pb
  concentrations to estimate
  media-specific Pb intake
  rates.

Model Overview, Uptake

- *Uptake Component*: compares Pb intake into the lungs or digestive tract with the amount of Pb absorbed into the child's blood.

Model Overview, Biokinetics

- *Biokinetic Component*: shows the transfer of Pb between blood and other body tissues, or the elimination of Pb from the body altogether.

Model Overview, Probability

- *Probability Distribution Component*: shows a probability of a certain outcome.
  - *e.g.*, a PbB concentration greater than 10 μgPb/dL in an exposed child based on the parameters used in the model.

Simulation

- The IEUBK model standardizes exposure by assuming age-weighted parameters for intake of food, water, soil, and dust. The model simulates continual growth under constant exposure levels (on a year-to-year basis).
- In addition, the model also simulates Pb uptake, distribution within the body, and elimination from the body.

IEUBK - Risk Assessment

- The IEUBK model is intended to:
  - Estimate a typical child's long-term exposure to Pb in and around his/her residence.
  - Provide an accurate estimate of the geometric average PbB concentration for a typical child aged six months to seven years.
  - Provide a basis for estimating the risk of elevated PbB concentration for a hypothetical child;

IEUBK - Risk Assessment, 2

  - Predict likely changes in the risk of elevated PbB concentration from exposure to soil, dust, water, food, or air following concerted action to reduce such exposure.
  - Provide assistance in determining target cleanup levels at specific residential sites for soil or dust containing high amounts of Pb.
  - Provide assistance in estimating PbB levels associated with the Pb

concentration of soil or
dust at undeveloped sites.

IEUBK Model, Benefits

- The IEUBK model is designed to facilitate calculating the risk of elevated PbB levels,
  – Helpful in demonstrating how results may change when the user enters different parameters.
  – A tool to assess PbB concentrations in children exposed to Pb.
  – Greatest advantage to the user is that it takes into consideration the several different media through which children can be exposed.

IEUBK Input, Demonstration

- Outdoor air Pb concentration: default (ug/m^3).
- Pb concentration in drinking water: default (μg/L).
- Soil Pb levels: 800 mg/kg.
- Indoor dust Pb levels: default (mg/kg).
- Maternal blood lead level: 10 μg/dl
- All other parameters are default values.
- Graph distribution probability % for 12-24 month old children.
- Result: 51% of children12-24 mos have blood Pb > 10 μg/dl.