ES/RP 531
Fundamentals of Environmental Toxicology

Lecture 4/5
Pharmacokinetics (Toxicokinetics)
&
Pharmacodynamics (Toxicodynamics)
Part 1

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Exposure ≠ Hazard
- Must consider toxicokinetics & toxicodynamics
- Basic processes
  - Absorption
  - Distribution
  - Elimination
- Measure
  - Extent of process
  - Rate of process

Absorption (Penetration)
- Contaminant or toxicant crosses the outermost barrier of an organism
  - Chemical transfers from site of contact into the cells and eventually into the general circulation
    - Skin, cuticle, cell wall
  - Also applicable to crossing integument of gastrointestinal tract (oral or ingestion exposures)
  - Also applicable to crossing integument of lungs or other ventilatory organs (inhalational exposures)

Route of Exposure--Dermal
- Absorption
  - Movement into the outer most dead layer, the stratum corneum
  - Facilitated by skin lesions
- Penetration
  - Movement through corneum
  - Diffusion into capillaries
  - Influenced by temperature & humidity
Dermal Penetration

**Effect of Body Part On Parathion Absorption (Maibach et al. 1971)**

<table>
<thead>
<tr>
<th>Body Part</th>
<th>% Absorption of Parathion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrotum</td>
<td>0</td>
</tr>
<tr>
<td>Armpit</td>
<td>20</td>
</tr>
<tr>
<td>Ear canal</td>
<td>40</td>
</tr>
<tr>
<td>Forehead</td>
<td>60</td>
</tr>
<tr>
<td>Back of Ear</td>
<td>80</td>
</tr>
<tr>
<td>Jaw angle</td>
<td>100</td>
</tr>
<tr>
<td>Scalp</td>
<td>120</td>
</tr>
<tr>
<td>Hand (top)</td>
<td>0</td>
</tr>
<tr>
<td>Abdomen</td>
<td>20</td>
</tr>
<tr>
<td>Foot (ball)</td>
<td>40</td>
</tr>
<tr>
<td>Palm</td>
<td>60</td>
</tr>
<tr>
<td>Forearm</td>
<td>80</td>
</tr>
</tbody>
</table>

**Route of Exposure--Inhalation**
- Inhaled material must be a gas, vapor, or fine particle
- Lining of nose, upper throat, and lung with continuous layer of mucous
- Swallowing can make an inhalational exposure an oral exposure
- Inhalation potential depends on particle size

**Route of Exposure--Oral**
- The veins draining the esophagus, intestines, and rectum flow directly into the portal vein, which empties into the liver.
  - All ingested material delivered to the liver before entering general circulation
    - Allows liver to activate or detoxify compounds
  - The drainage of the mouth cavity is into the jugular vein; allows direct entry into systemic circulation
Drainage via jugular vein into general circulation

Drainage via portal vein into liver

Placoid scales (Broadnose sevengill Shark)
Cosmoid scales (Queensland Lungfish)

Ganoid scales (Florida gar)
Cycloid scales (Jungle Perch)

Ctenoid scale (Paradise fish)
Close-up showing radial growth rings of ctenoid scale

Scales overlap, making penetration through skin very slow

http://www.oup.co.uk/oxed/children/yoes/pictures/nature/fishgills

http://www.thefrog.org/biology/skin/skin.htm

Larval (tadpole) stage:
Breathing occurs through skin as well as gills

http://www.thefrog.org/biology/breathing/breathing.htm

Adult:
Breathing through nostrils, with mouth closed; also breathe through skin

A stained thin section of bird skin (epidermis); thinner & more delicate than other vertebrates. Covered with feathers. Absorption through feet, even though keratinized. Preening can lead to exposure through gastrointestinal tract.

http://www.olympusmicro.com/primer/techniques/phasegallery/birdskin.html

Cross-Section of Insect Exoskeleton

epicuticle
epidermis
endocuticle
exocuticle
Cell junction

Cell junction

Note difference in cell junctions; a lot of interdigitation in insect cells and very narrow tight junctions make diffusion of toxicants less likely between cells
Mechanistic Considerations

- Waxy layers on invertebrate cuticle & plant leaves
- Mucilaginous layers on plant roots
- Possible movement along junctions between cells into interstitial spaces
- Lipid bilayer of cell membranes

Absorption

- Controlled by thermodynamic processes
  
- Consider nature of cell membrane
Absorption

- Diffusion is the main mechanism driving partitioning across membranes.
- Extent controlled by Kow (hydrophobicity parameter) of chemical.
- Rate controlled by concentration (first-order process).

Hydrophobicity

- Surrogate measure is Kow, the octanol-water partition coefficient.
- Higher the value, the more the tendency to partition into an "oily" (lipid-dominated) phase (matrix).
- Free energy at a minimum.
- Entropy at a maximum.
- Thus, hydrophobic compounds cross cell membranes more easily than hydrophilic compounds.
- However, extremely hydrophobic compounds might be trapped in lipid layers.

Distribution

- The process of reversible transfer of a chemical from general circulation into the tissues.
  - Animals: blood ---> organs.
  - Plants: xylem/phloem ---> foliage/fruit.
- Usually very rapid.
  - Rate limited by rate of blood ("sap") flow.
  - Polarity of the chemical (or hydrophobicity).

Blood flows from the intestine to the liver.

Absorption By the Intestines Is Very Efficient

- Extent influenced by:
  - Water solubility (WS).
  - Lipid solubility (measured by Kow).
  - Plasma protein binding.
- Extent influenced by:
  - Partitioning into plasma or interstitial and intercellular fluids limits uptake by fat tissue and central nervous system (CNS).
  - Causes reduction in tissue distribution and retains compounds longer in circulation.
  - Tissue protein binding.
  - Causes more extensive distribution among tissues.
Elimination

Metabolism—Interaction with enzymes
- Detoxification
- Activation
  - Phase I
  - Oxidations
    - Cytochrome P450 mediated; require NADPH & O₂
    - Located on endoplasmic reticulum
  - Hydrolysis
    - Mediated by esterases (hydrolases)
    - Cytoplasmic; plasma
    - Attack ester linkages
  - Reductions
  - Transfer of electrons to carbon, nitrogen

Herbicide Activation

Hydrolysis

2,4-D butoxyethanol ester → 2,4-D + OH

Elimination

Metabolism
- Interested in reactivity and rate of reaction
- Phase II reactions—Conjugations
  - Chemicals usually conjugated to glutathione (a tripeptide) or sugar moiety (glucose; galactose) after initial oxidation (or other metabolism)
  - Water solubility increased, facilitating filtration by kidneys and eventual excretion
  - Acylanilide herbicides safened by inducers of glutathione-S-transferases

Oxidation and Conjugation of a Polyaromatic Hydrocarbon

phenanthrene → Phenanthrene 9,10 oxide
Selectivity

- The differential toxicity of a compound between a pest organism and a nontarget organism
  - Conferred by unique mode of action or insensitive biochemical target (pharmacodynamics)
    - Common among herbicides
      - Sulfonylureas, imidazolinones, glyphosate, phenoxys
      - Insecticides
        - Microbial insecticides; insect growth regulators
  - Conferred by extent (reactivity) and/or rate of metabolism (toxicokinetics)
    - Pyrethroids

Pyrethroid Metabolism

Metabolism Influences Selectivity

- Oxidation to O leads to higher toxicity
- R is an alkyl group usually of 1 or 2 C; both R groups usually the same

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parathion</th>
<th>Diatrin</th>
<th>Dimethoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-O roach/mouse</td>
<td>3.0</td>
<td>12</td>
<td>2.3</td>
</tr>
<tr>
<td>CHCl₃ roach/mouse</td>
<td>1.5</td>
<td>1.2</td>
<td>11</td>
</tr>
<tr>
<td>LD50 mouse/roach</td>
<td>6.0</td>
<td>20</td>
<td>70</td>
</tr>
</tbody>
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Table based on Krueger 1960 J. Econ. Entom. 53:25