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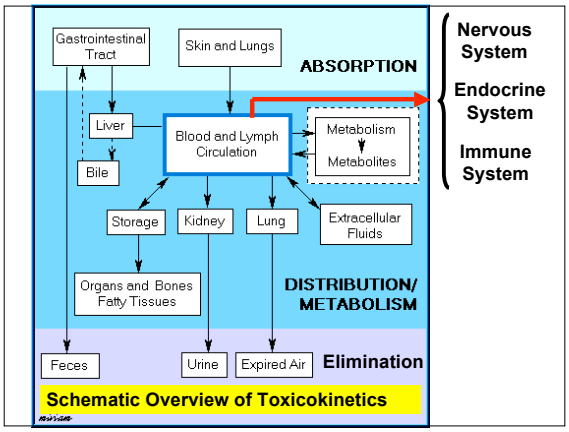
ES/RP 531
Fundamentals of Environmental Toxicology

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

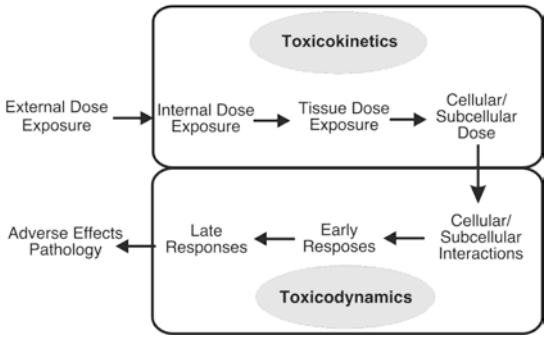
Exposure ≠ Hazard

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



Schematic Overview of Toxicokinetics

Conceptual Model of Role of Toxicokinetics & Toxicodynamics in Generation of Toxicity
(from Heinrich-Hirsch et al. 2001 Toxicol. Letters 120:131)

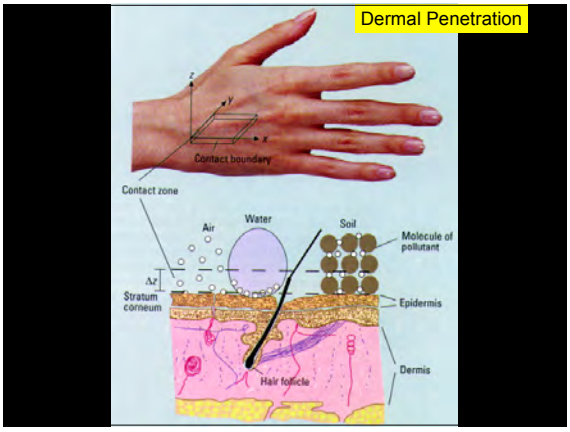


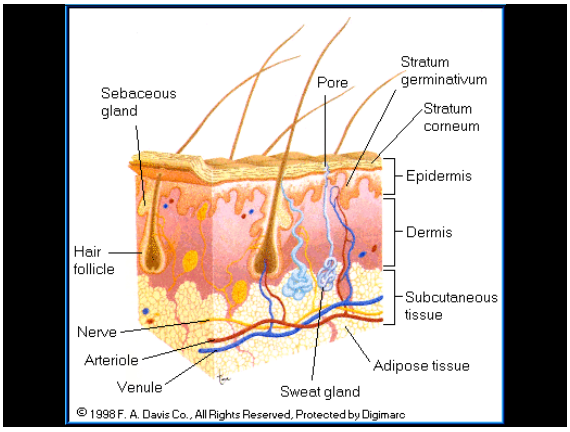
Absorption (Penetration)

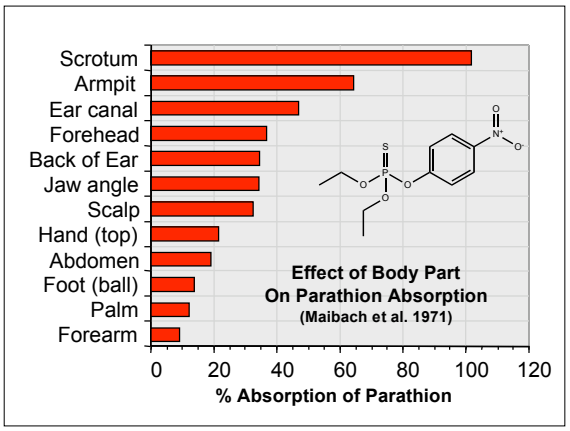
- Contaminant or toxicant crosses the outermost barrier of an organism
  - Chemical transfers from site of contact into the cells and eventually into the general circulation
    - Skin, cuticle, cell wall
- Also applicable to crossing integument of gastrointestinal tract (oral or ingestion exposures)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

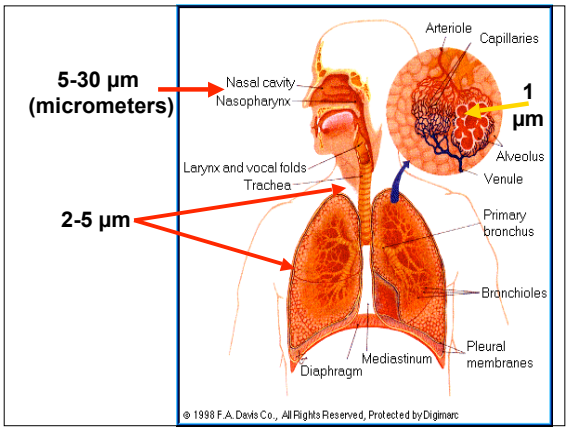






Route of Exposure--Inhalation

- 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

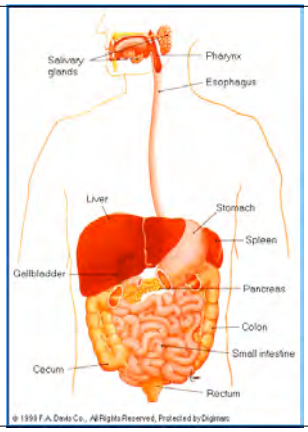


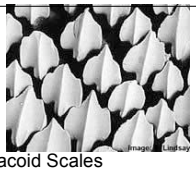
Route of Exposure--Oral

- 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





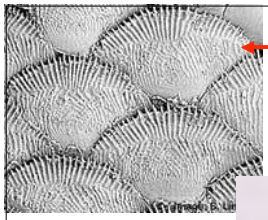
Placoid Scales
(Broadnose sevengill Shark)

Cosmoid scales
(Queensland Lungfish)

http://www.amonline.net.au/fishes/students/scales/

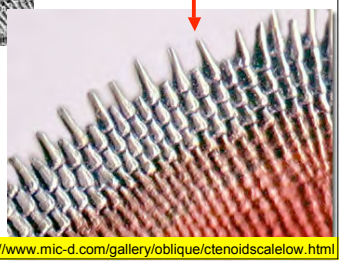
Ganoid scales
(Florida gar)

Cycloid scales
(Jungle Perch)



Ctenoid scale
(Paradise fish)

Close-up showing radial growth rings of ctenoid scale

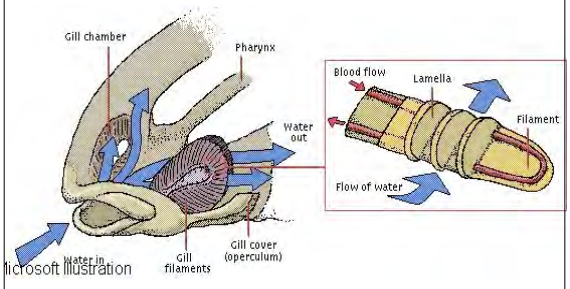


Scales overlap, making penetration through skin very slow

http://www.mic-d.com/gallery/oblique/ctenoidscalelow.html

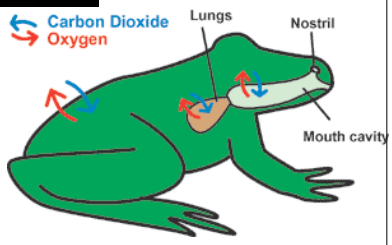
http://www.oup.co.uk/oxed/children/yoes/pictures/nature/fishgills/

http://www.kwic.com/~pagodavista/schoolhouse/species/fish/fishgill.htm



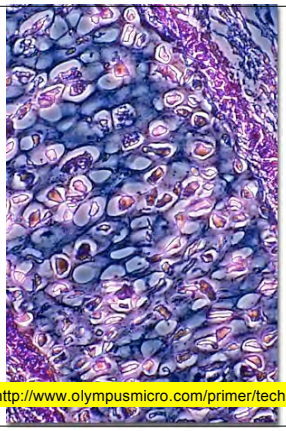
http://www.thefrog.org/biology/skin/skin.htm

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



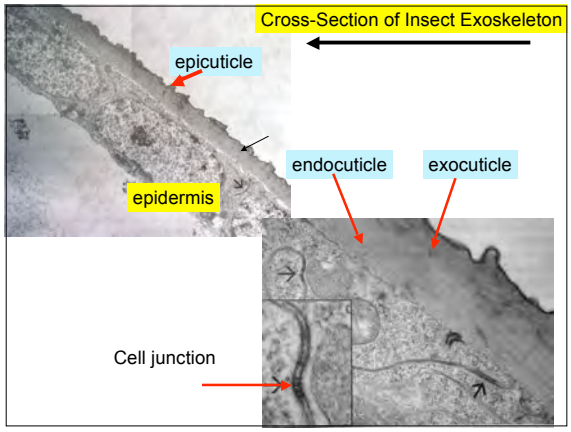
Adult: Breathing through nostrils, with mouth closed; also breathe through skin

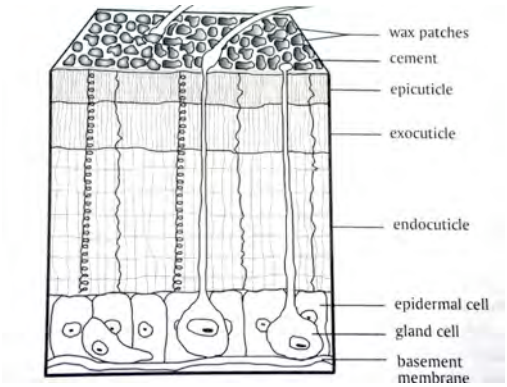
http://www.thefrog.org/biology/breathing/breathing.htm

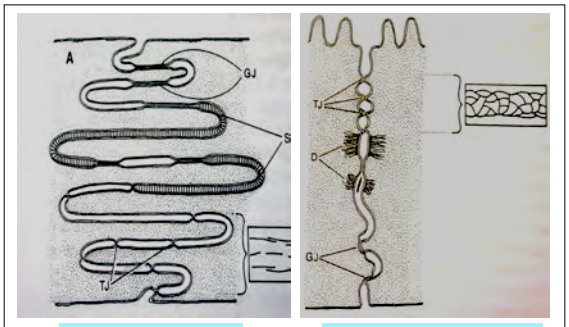


A stained thin section of bird skin (epidermis); thinner & more delicate than other verteberates. Covered with feathers. Absortion through feet, even though keratinized. Preening can lead to exposure through gastrointestinal tract.

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



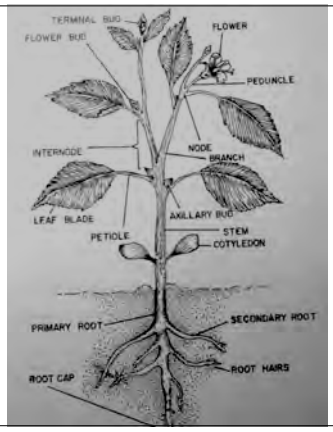


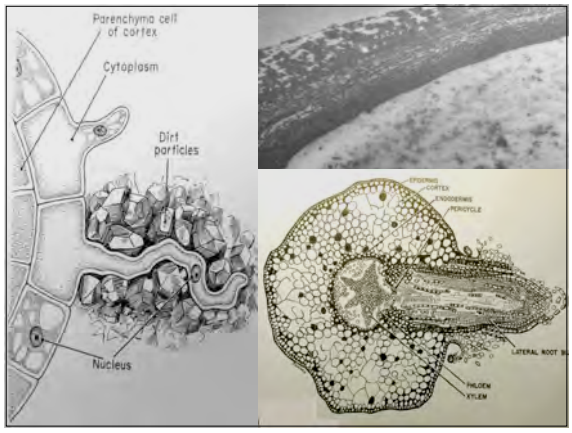


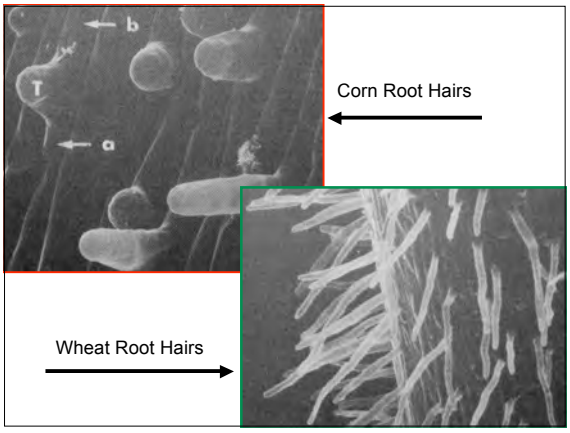
Insect Cell Junctions

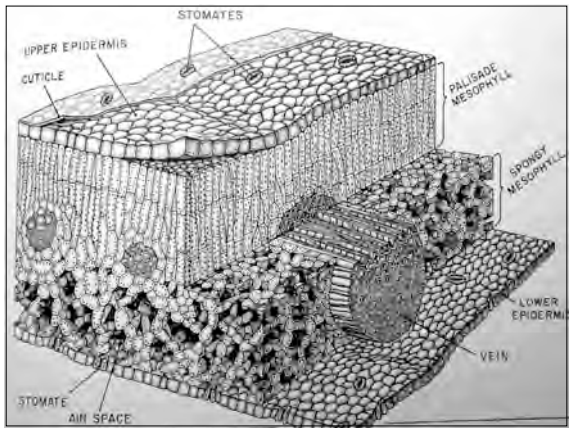
Vertebrate Cell Junctions

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





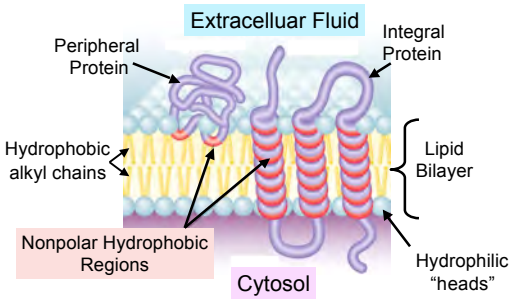




Mechanistic Considerations

- 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**

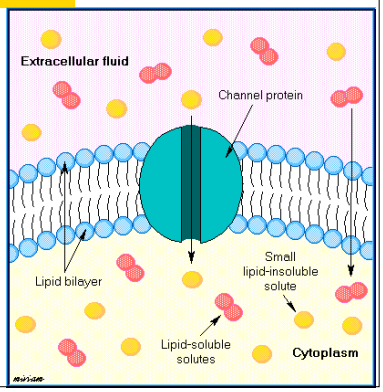
The Cell Membrane: A lipid bilayer punctuated by proteins et al.



Drawing modified from Randall et al. (2002) *Animal Physiology*, W.H. Freeman & Co.

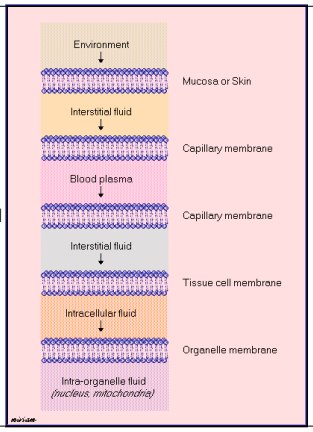
Absorption

- Controlled by thermodynamic processes
  - Consider nature of cell membrane



Absorption

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



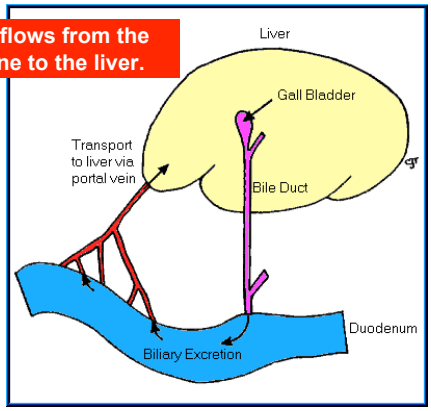
Hydrophobicity

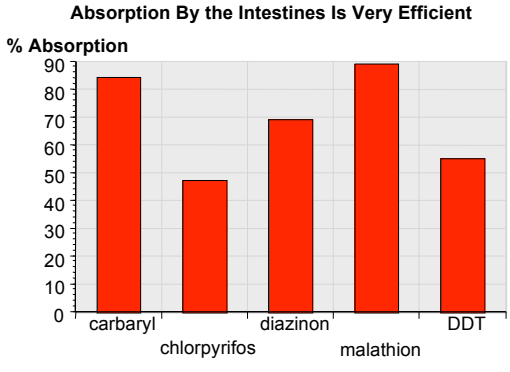
- Surrogate measure is Kow, the octanol:water partition coefficient
- Higher the value, the more the tendency to partition into an "oily" (lipid-dominated) phase (matrix)
  - Free energy at a minumum
  - Entropy at a maximum
- Thus, hydrophobic compounds cross cell membranes more easily than hydrophilic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



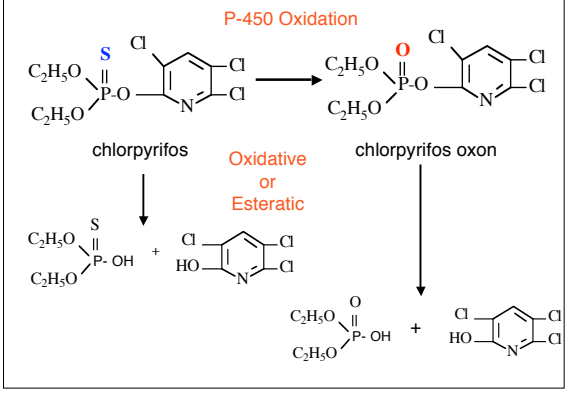


Distribution

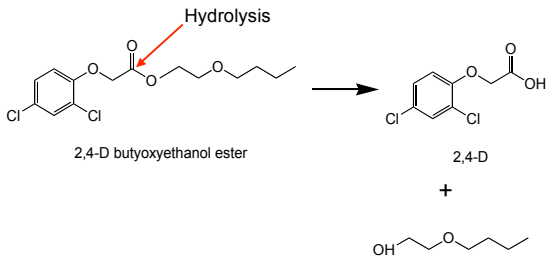
- Extent influenced by:
  - Water solubility (WS)
    - Kow and WS are inversely correlated
    - Patitioning into plasma or interstitial and intercellular fluids limits uptake by fat tissue and central nervous system (CNS)
  - Lipid solubility (measured by Kow)
    - Partitioning into adipose (fat), CNS, or other organs having high lipid content
  - Plasma protein binding
    - 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 & O_2
    - Located on endoplasmic reticulum
  - Hydrolysis
    - Mediated by esterases (hydrolases)
    - Cytoplasmic; plasma
    - Attack ester linkages
  - Reductions
    - Transfer of electrons to carbon, nitrogen

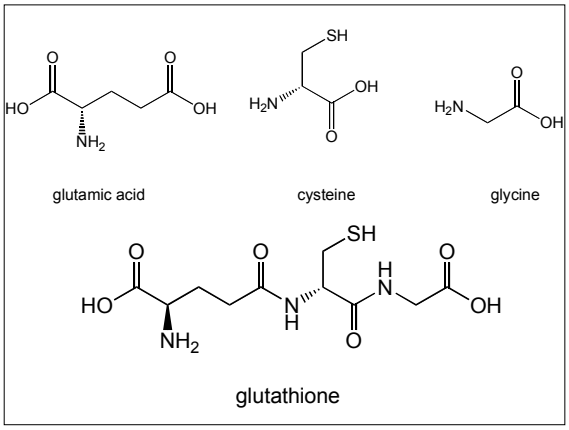


Herbicide Activation

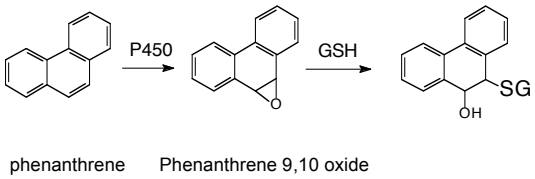


Elimination

- 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



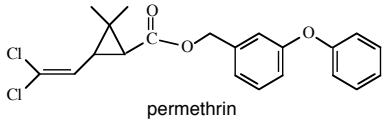
Oxidation and Conjugation of a Polyaromatic Hydrocarbon



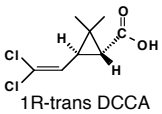
Selectivity

- 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

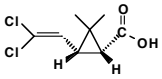
Pyrethroid Metabolism



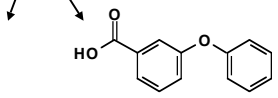
permethrin



1R-trans DCCA

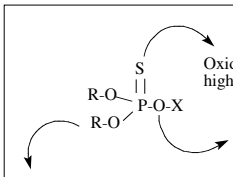


1R-cis DCCA



PBA

Metabolism Influences Selectivity



R is an alkyl group usually of 1 or 2 C; both R groups usually the same

Table based on Krueger 1960 J. Econ. Entom. 53:25

Ratio of Indicated Parameter

Parameter	Parathion	Diazinon	Dimethoate
P=O roach/mouse	3.0	12	2.3
$CHCl_3$ roach/mouse	1.5	1.2	11
LD50 mouse/roach	6.0	20	70