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Fall 2005

ES/RP 531
Fundamentals of Environmental Toxicology

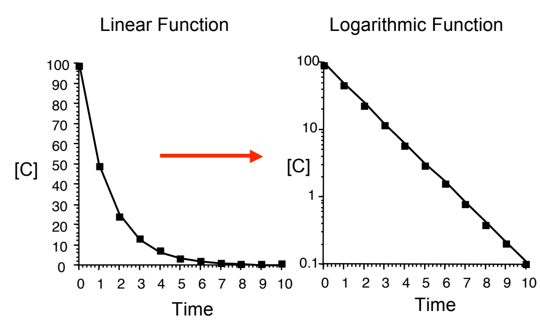
Lecture 4/5
Pharmacokinetics (Toxicokinetics)
&
Pharmacodynamics (Toxicodynamics)
Part 2

Reaction Rate (Kinetics)

- Importance of metabolism in detoxification or activation of a toxicant depends on
  - Capability of detox. enzymes for catalyzing the reaction
    - Dependent on ability of toxicant to form a complex with the detox. enzyme
  - Rate of reaction
    - Faster reactions will increase the rate of elimination of the toxicant
    - Less re-circulating to blood and tissues

Reaction Rate

- Described by mathematical functions known as rate laws
  - Describe the relationship between tim and the concentration of the toxicant
- Two commonly used functions
  - Power rate law
    - First-order rate equation
  - Hyperbolic kinetics
    - Michaelis-Menton Kinetics



Reaction Kinetics

Rate Law = a mathematical function or differential equation describing the turnover rate of a compound as a function of the concentration

Power Rate Law

$$Rate = \frac{-dC}{dT} = kC^n$$

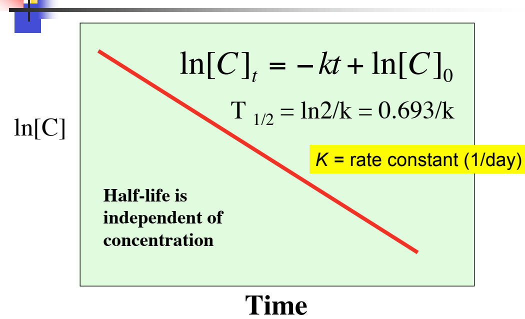
First Order when n = 1

$$\frac{d[C]_t}{dt} = -k[C]_0 \quad \textbf{Differential eq.}$$

or

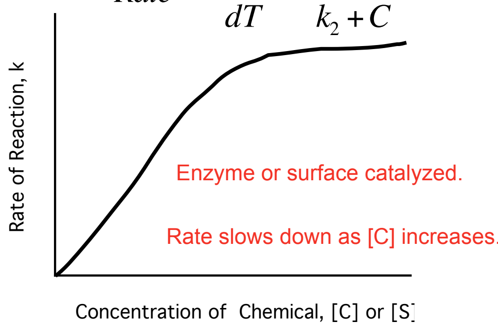
$$[C]_t = [C]_0 \bullet e^{-kt} \quad \textbf{Integrated eq.}$$

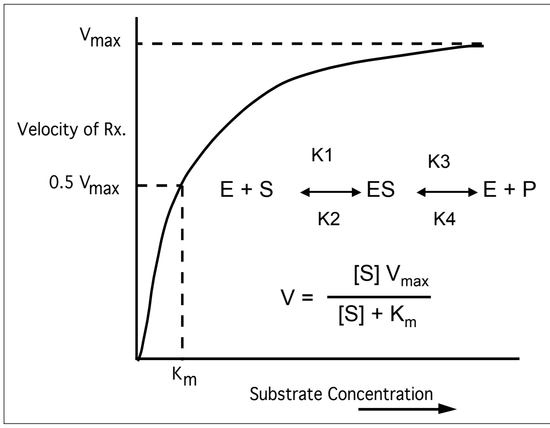
Linearization of First-Order Function



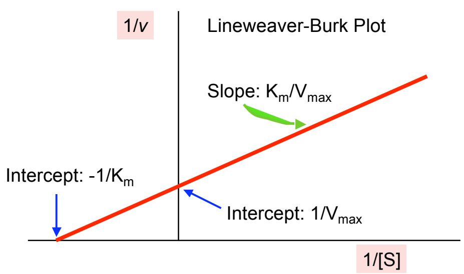
Hyperbolic Kinetics

$$Rate = \frac{-dC}{dT} = \frac{k_1 C}{k_2 + C}$$



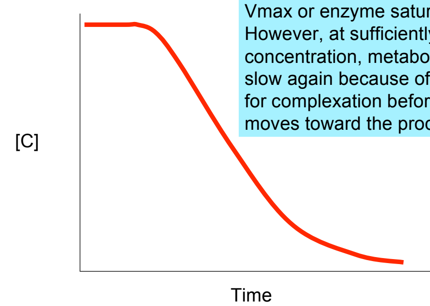


Double Reciprocal Plot for Calculation of Vmax & Km



Practical Application of Michaelis-Menton Kinetics

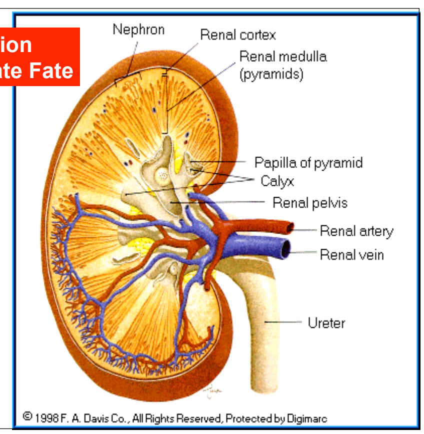
Disappearance of toxicant speeds up as concentration decreases below the level associated with Vmax or enzyme saturation. However, at sufficiently low concentration, metabolism might slow again because of necessity for complexation before reaction moves toward the product side.



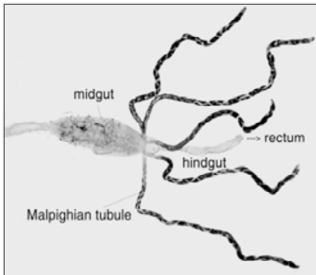
Elimination

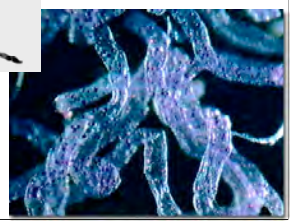
- Excretion
  - Metabolic reactions result in more water soluble compounds, facilitating excretion
  - Reduction in amount of parent compound available to target sites
  - Clearance
    - Volume of blood (or plasma) cleared of chemical per unit time
  - Routes
    - Expired air, saliva, bile, feces, urine, milk, hair
  - Extent less important than rate
    - All compounds eventually 100% excreted

Excretion
The Ultimate Fate

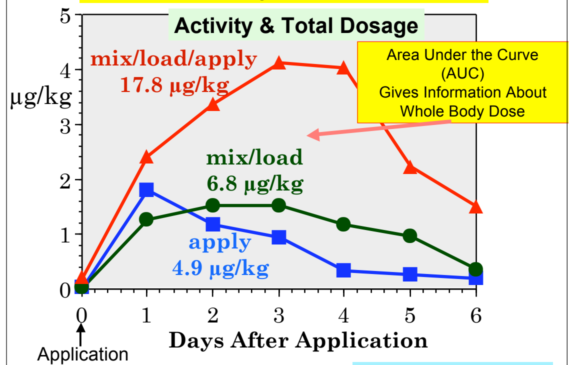


Insects have Malpighian tubules that function analogously to kidneys





2,4-D Excreted By Ground Applicators



Adapted from Nash et al. '82

Toxicokinetics & Exposure Route

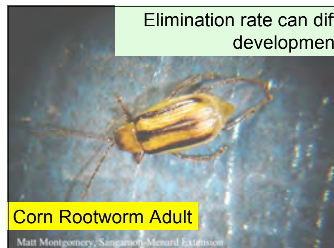
Based on Nolan et al. (1984) Tox. Appl. Pharm. 73:8

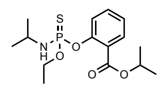
Chlorpyrifos	0.5 mg/kg Oral	5 mg/kg Dermal
Absorption Half-Life (hr)	0.5	23
Elimination Half-Life (hr)	27	ND
Plasma Distribution/Time (ug/mL/h)	46	6.2
% Dose Recovered in Urine	70	1.3
Plasma Cholinesterase (% of Predose)	15	70
Erythrocyte Cholinesterase (% of Predose)	70	80
Signs/Symptoms of Toxicity	No	No

Elimination rate can differ among different development stages

Experiment by

Hsin & Coats (1986) Pestic. Biochem. Physiol. 25:336





isofenphos

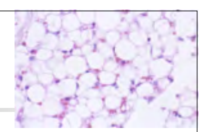
Metabolism and Excretion Influences Selectivity

Corn Rootworm Hours After Dosing with Isofenphos

Hsin & Coats (1986) Pestic. Biochem. Physiol. 25:336

Life Stage	1	2	4	8	24
Adult					
External Rinse	17	11	8	5	1
Internal Extract	71	65	54	44	16
Container Rinse	4	4	10	18	35
Container Parent	3	2	3	2	1
Larvae					
External Rinse	7	2	1	0.4	0.2
Internal Extract	59	46	38	21	10
Container Rinse	9	13	19	33	43
Container Parent	9	11	14	21	23

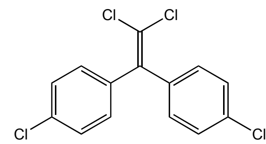
Storage



- Type of elimination mechanism
  - Influenced by rate of metabolism and hydrophobicity
    - Example: DDT
      - Slow metabolic rate
      - High Kow
  - Temporary mechanism in that chemical is released from storage sites
    - Equilibrium between adipose tissue and blood
    - Of concern for very recalcitrant compounds
- Concept of bioconcentration factor (ecotox.)
  - Ratio of matrix (or food) concentration to concentration in an organism

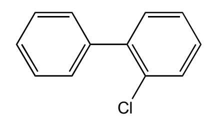
Case Study

- Uptake, metabolism, and elimination of two hydrophobic contaminants by midge larvae
  - Experiment from Lydy et al. (2000) Arch. Environ. Contam. Toxicol. 38:163
- Exposed midge larvae in water to either DDE or 2-chlorobiphenyl (2-CB)



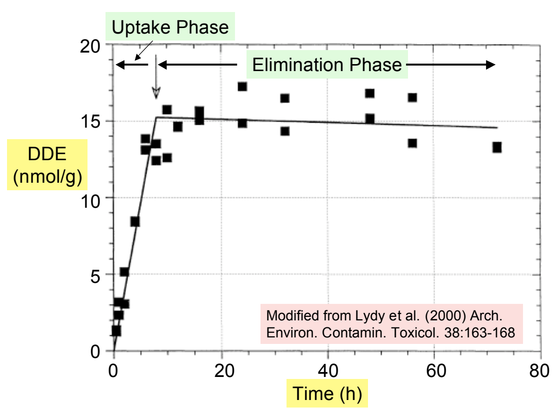
DDE
WS: ~40 µg/L
Log Kow: ~5.7

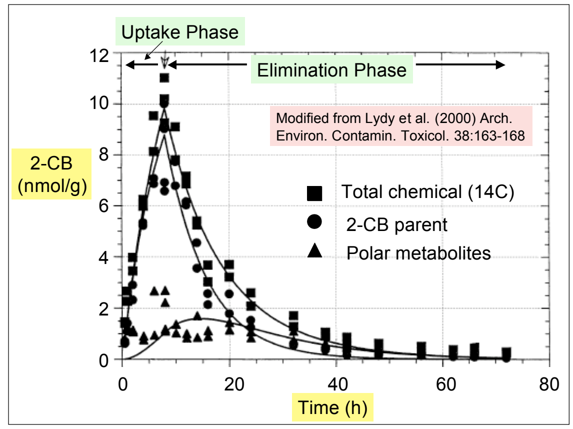
Nominal Water Concentration: 7.3 µg/L

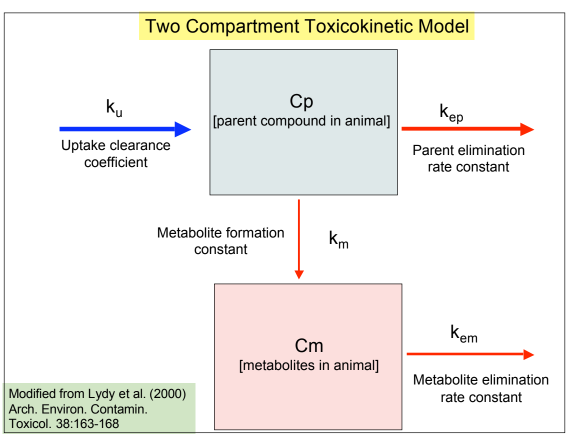


2-chlorobiphenyl
WS: ~5900 µg/L
Log Kow: ~4.49

Nominal Water Concentration: 5.1 µg/L







Toxicokinetic Functions

DDE

- $C_a = k_u * C_w * t$
  - C_a = total DDE in midge
  - C_w = DDE concentration in water
  - K_u = uptake clearance coefficient

2-chlorobiphenyl

- $dCtot/dt = (k_u Cw) - (k_{ep} Cp) - (k_{em} Cm)$
  - Ctot = total 2-CB residues in midge larvae

Modeling Results (Lydy et al. 2000)

Parameter	DDE	2-CB
K_u (mL/g/h)	84.1	66.0
K_{ep} (h^{-1})	[redacted]	0.100
K_{em} (h^{-1})	[redacted]	0.073
K_m (h^{-1})	[redacted]	0.031
BCF	[redacted]	504
T1/2 (days)	[redacted]	5.7

Toxicokinetics & Plants

- All mechanisms & processes same as in animals
- However, must consider dose transfer from the environment (ditto if considering aquatic and soil dwelling animals)
  - Other parameters important
    - Soil sorption coefficient (Koc)
    - Air:water transfer coefficient (K_H)

Conceptual Model of Relationships