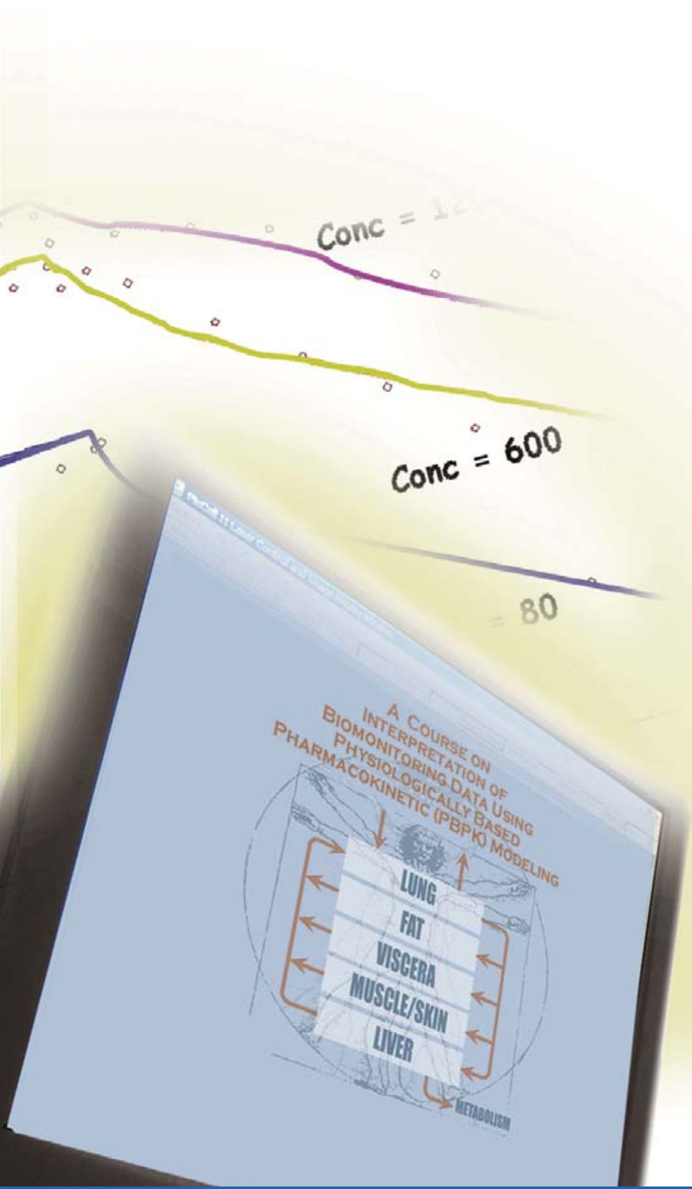
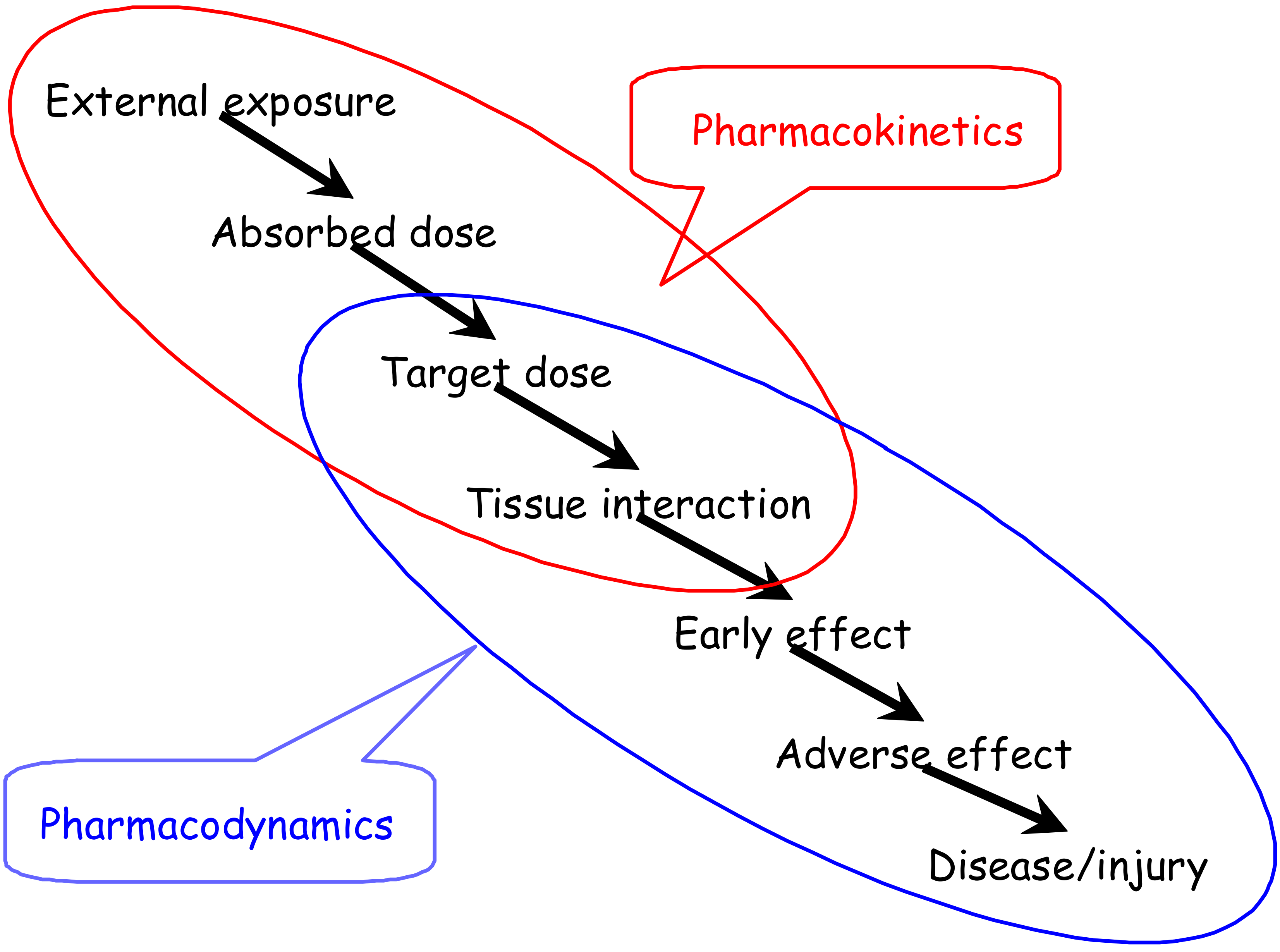


Pharmacokinetics in Toxicology Research

Center for Human Health Assessment
A Course on Physiologically Based Pharmacokinetic (PBPK) Modeling and Risk Assessment

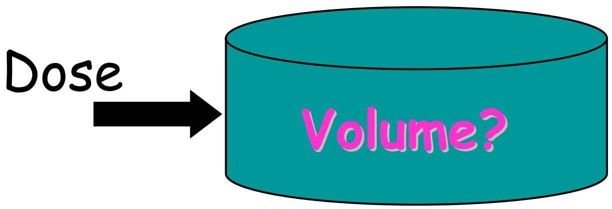
February 11 – February 15, 2008


External exposure
Absorbed dose
Target dose
Tissue interaction
Early effect
Adverse effect
Disease/injury
Pharmacokinetics
Pharmacodynamics

Pharmacokinetics

- Studies of the change in chemical distribution over time in the body
- Explores the quantitative relationship between Absorption, Distribution, Metabolism, and Excretion of a given chemical
- Classical models
  - 'Data-based', empirical compartments
  - Describes movement of chemicals with fitted rate constants
- Physiologically-based models:
  - Compartments are based on real tissue volumes
  - Mechanistically based description of chemical movement using tissue blood flow and simulated *in vivo* transport processes.

Example of Simple Kinetic Model: One-compartment model with bolus dose



Purpose: In a simple (1-compartment) system, determine volume of distribution

Terminology:

Compartment = a theoretical volume for chemical
Steady-state = no net change of concentration
Bolus dose = instantaneous input into compartment

Method:

1. Dose: Add known amount (A) of chemical
2. Experiment: Measure concentration of chemical (C) in compartment
3. Calculate: A 'compartmental' Volume (V)

Example of Simple Kinetic Model: One-compartment model with bolus dose

- Basic assumption:
  - Well stirred, instant equal distribution within entire compartment

- **Volume of distribution** = *A/C*
  - In this classical model, V is an operational volume
    - V depends on site of measurement

- This simple calculation only works IF:
  - Compound is rapidly and uniformly distributed
  - The amount of chemical is known
  - The concentration of the solution is known.

What happens if the chemical is able to leave the container?

Describing the Rates of Chemical Processes - 1 Chemical in the System

- Rate equations:
  - Describe movement of chemical between compartments
    - The previous example had instantaneous dosing
    - Now, we need to describe the rate of loss from the compartment

- Zero-order process:
  - rate is constant, does not depend on chemical concentration

    $rate = k \times C^0 = k$

- First-order process:
  - rate is proportional to concentration of ONE chemical

    $rate = k \times C^1$

Describing the Rates of Chemical Processes - 2 Chemical Systems

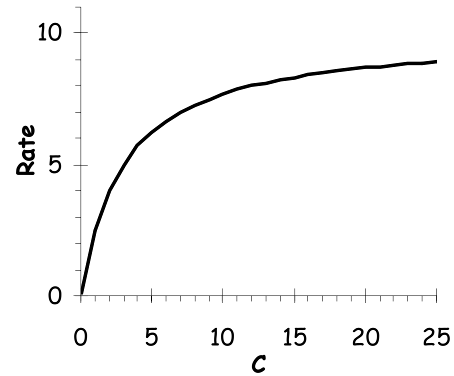
- <u>Second-order process</u>:
  - rate is proportional to concentration of both chemicals

    $Rate = k \times C_1 \times C_2$

- <u>Saturable processes</u>*:
  - Rate is dependent on interaction of two chemicals
  - One reactant, the enzyme, is constant
  - Described using Michaelis-Menten* equation

    $Rate = (V_{max} \times C) / (C + K_m)$

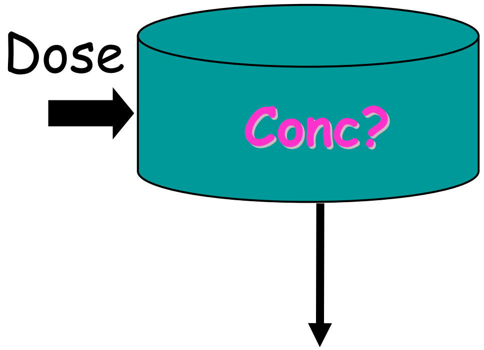
M-M kinetics



*Michaelis-Menten kinetics can describe:

- Metabolism
- Carrier-mediated transport across membranes
- Excretion

1-Comp model with bolus dose and 1st order elimination



Purpose: Examine how concentration changes with time

Mass-balance equation (change in C over time):

- $dA/dt = -k_e \times A$, or
- $dC/dt = -k_e \times C$

where k_e = elimination rate constant

Concentration;

- Rearrange and integrate above rate equation

$$C = C_0 \times e^{-ke \cdot t}, \text{ or}$$

$$\ln C = \ln C_0 - k_e \cdot t$$

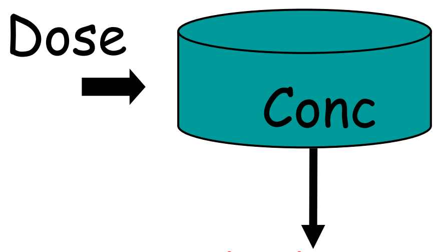
Half-life ($t_{1/2}$):

-Time to reduce concentration by 50%

-replace C with $C_0/2$ and solve for t

$$t_{1/2} = (\ln 2)/k_e = 0.693/k_e$$

1-Comp model with bolus dose and 1st order elimination



Clearance: volume cleared per time unit

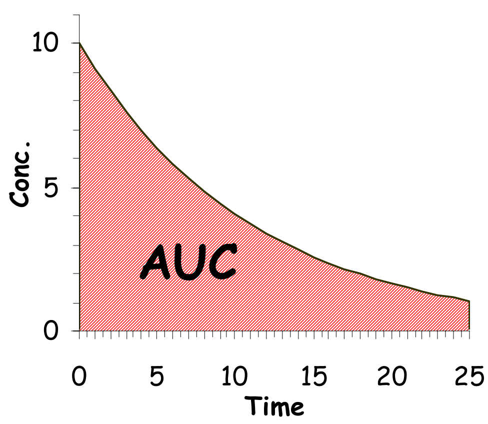
- if k_e = fraction of volume cleared per time unit,

  $k_e = CL/V$ $(CL = ke*V)$

Calculating Clearance using Area Under the Curve (AUC):

AUC = average concentration

- integral of the concentration
- $\int C\,dt$



CL = volume cleared over time (L/min)

$dA/dt = -k_e A = -k_e V C$

$dA/dt = -CL \cdot C$

$\int dA = -CL \int C\,dt$

$Dose = CL \cdot AUC$

$CL = Dose / AUC$

1-Comp model with continuous infusion and 1st order elimination

Calculating Clearance at Steady State:

- At steady state, there is no net change in concentration:

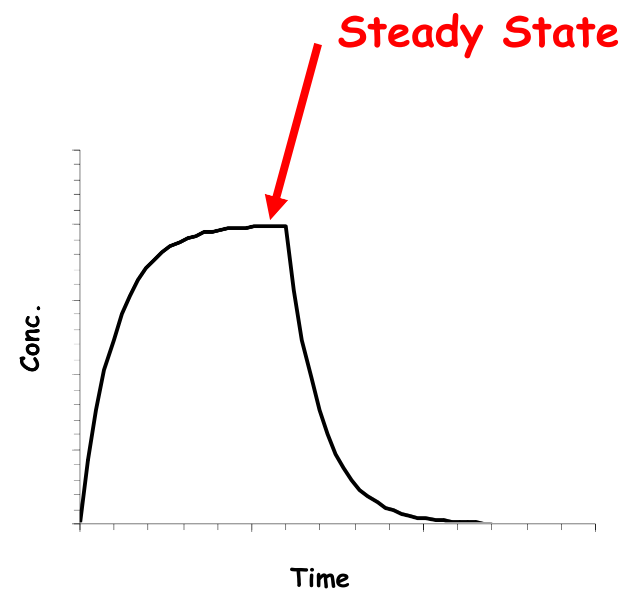
  $$dC/dt = k_0/V - k_e \cdot C = 0$$

- Rearrange above equation:

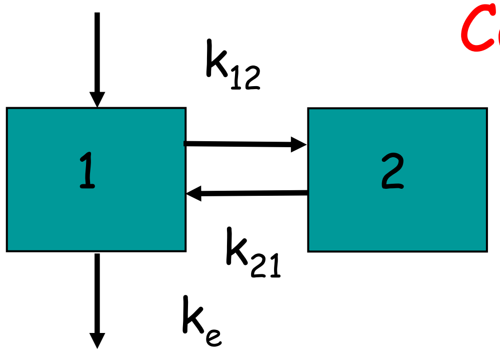
  $$k_0/V = k_e \cdot C_{ss}$$

- Since $CL = k_e \cdot V$,

  $$CL = k_0/C_{ss}$$



2-Comp model with bolus dose and 1st order elimination



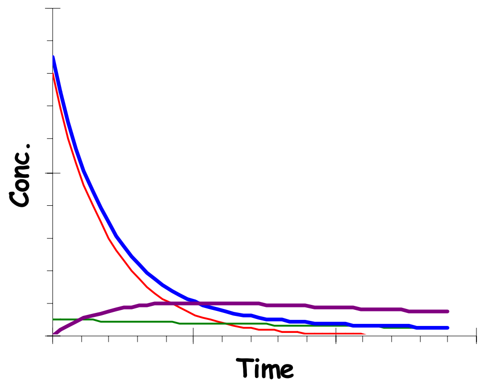
Calculating Rate of Change in Chemical:

- Central Compartment (C1):

  $$dC1/dt = k_{21} \cdot C_2 - k_{12} \cdot C_1 - k_e \cdot C_1$$

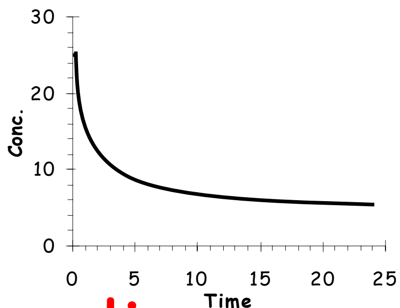
- Peripheral (Deep) Compartment (C2):

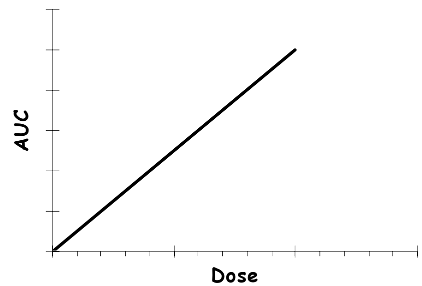
  $$dC2/dt = k_{12} \cdot C_1 - k_{21} \cdot C_2$$

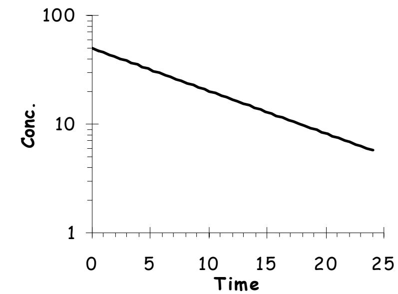


Linear and Non-linear Kinetics

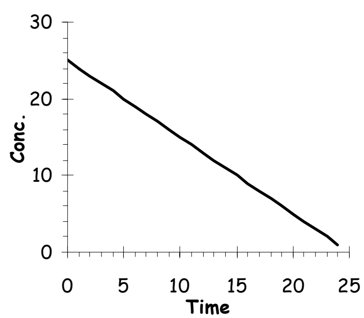
- **Linear:**
  - All elimination and distribution kinetics are 1st order
    - Double dose → double concentration

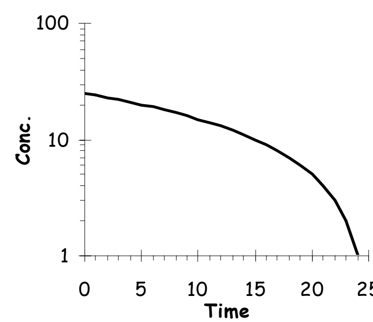






- **Non-linear:**
  - At least one process is NOT 1st order
    - No direct proportionality between dose and compartment concentration

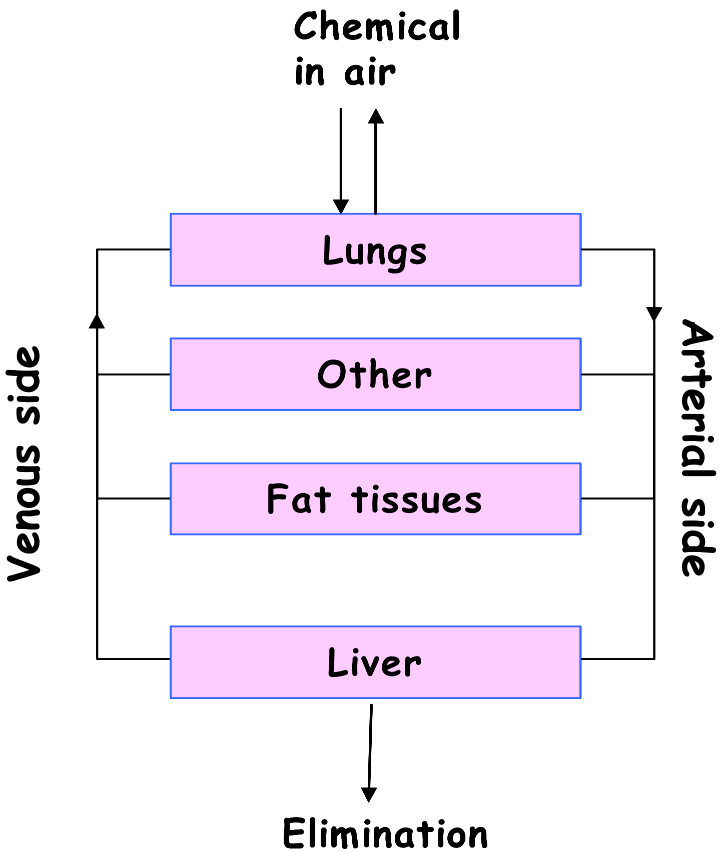




PBPK Models

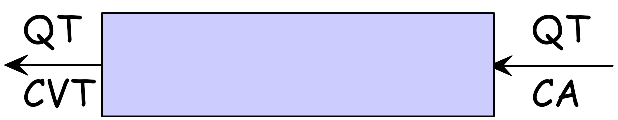
Building a PBPK Model:

1. Define model compartments
   - Represent tissues
2. Write differential equation for each compartment
3. Assign parameter values to compartments
   - Compartments have defined volumes, blood flows
4. Solve equations for concentration
   - Numerical integration software (e.g. Berkeley Madonna, ACSL)

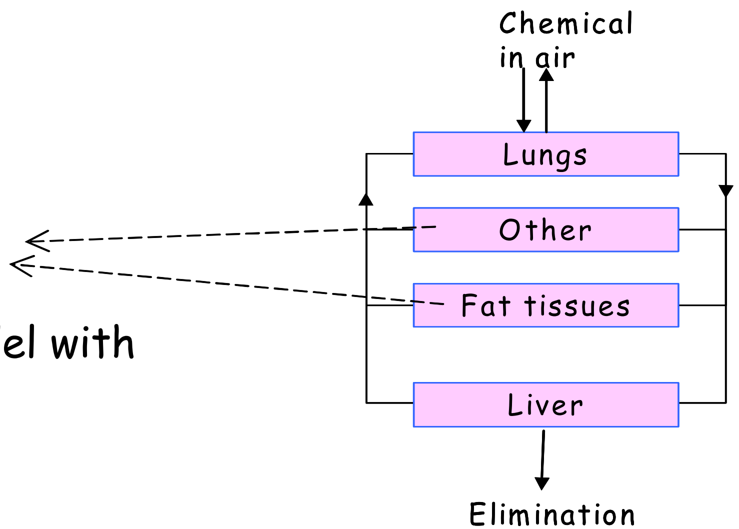


Simple model for inhalation

PBPK Model Compartment Types - Storage compartment



Same as 1-compartment model with continuous infusion



- Rate in = $Q_T \cdot C_A$

  where Q_T = tissue blood flow, C_A = arterial blood conc

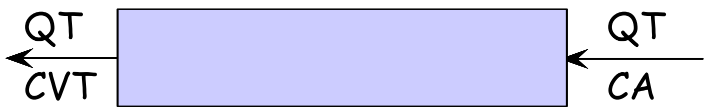
- Rate out = $Q_T \cdot C_{VT} = Q_T \cdot C_T / P_T$

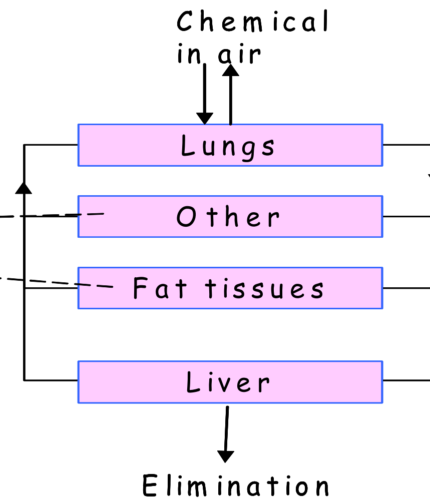
  where C_{VT} = conc in tissue blood, C_T = conc in tissue, P_T = partition coefficient

  - Assume Well-stirred compartment, so that,

    $C_{VT} = C_T / P_T$

PBPK Model Compartment Types - Storage compartment





Same as 1-compartment model with continuous infusion

- Calculating Change in Amount:
  - Change in amount = rate in – rate out

$$dA/dt = Q_T \times (C_A - C_T/P_T)$$

$$dC/dt = Q_T \times (C_A - C_T/P_T)\ /V$$