# Introduction to Pharmacokinetic Modeling

A Course on Physiologically Based Pharmacokinetic (PBPK) Modeling in Drug Development and Evaluation

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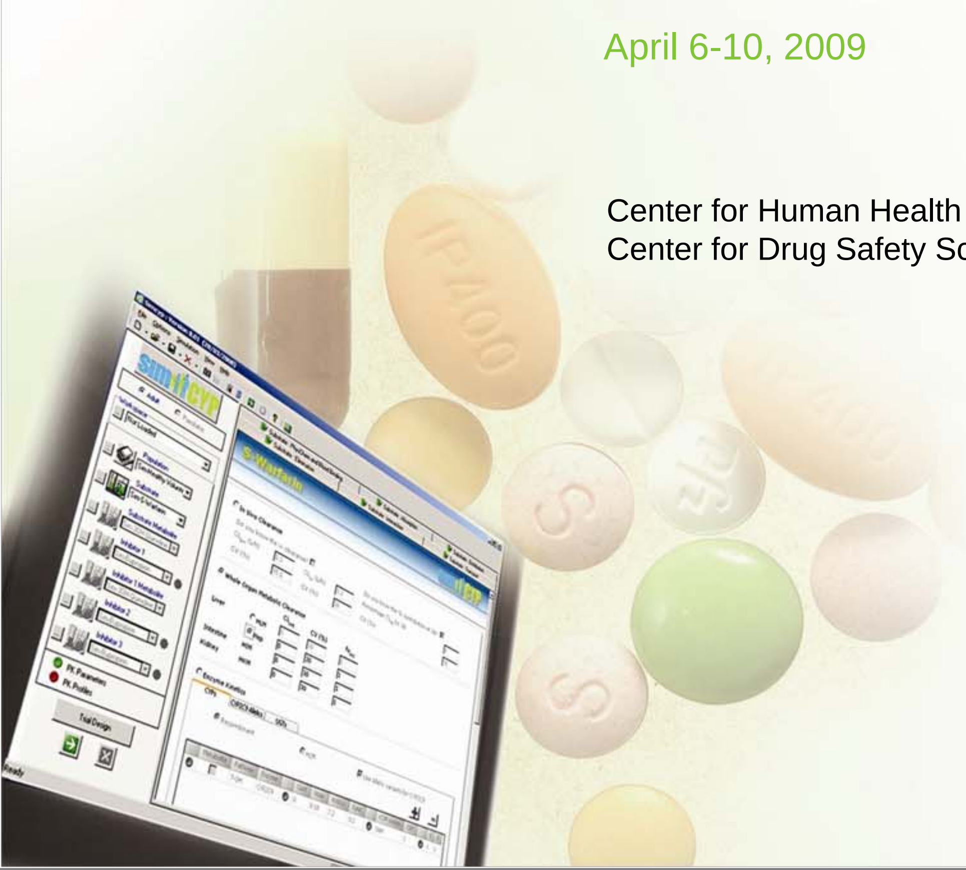
Center for Human Health Assessment
Center for Drug Safety Sciences



# 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.

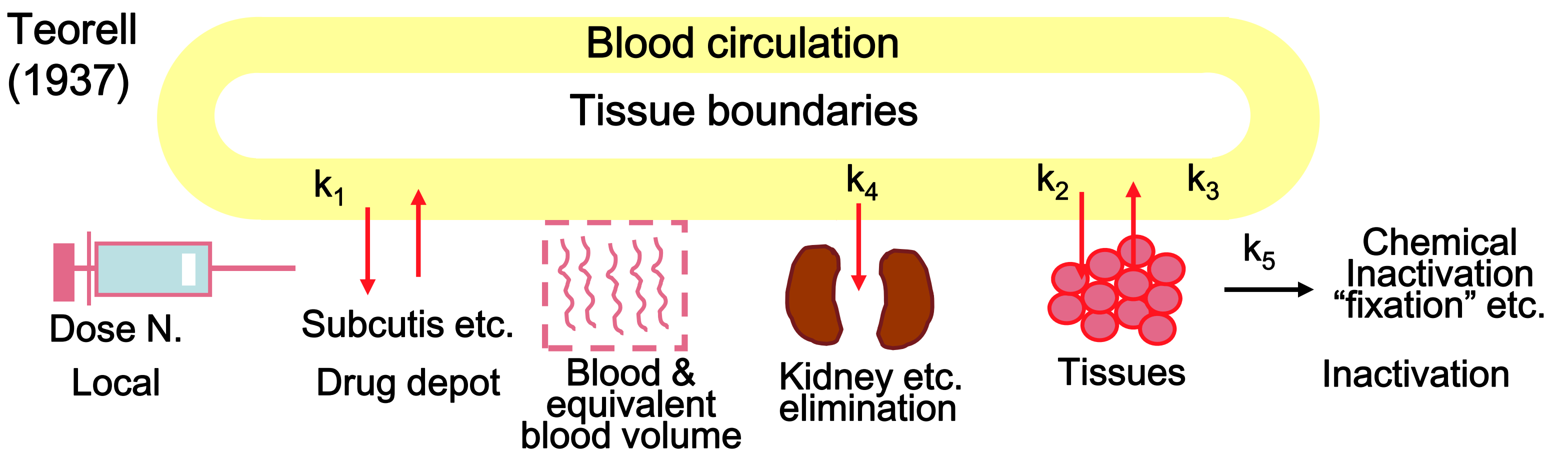
# Teorell (1937)

Provide a clear physiological description of determinants of drug disposition.

Lacked the ability to solve the series of equations and simplified the systems.  Over the years so-called compartmental PK analysis was developed to examine pharmacokinetic behavior.  These simplified models give equations that have exact solutions and have provided many useful insights despite their very much simplified depiction of animal physiology.

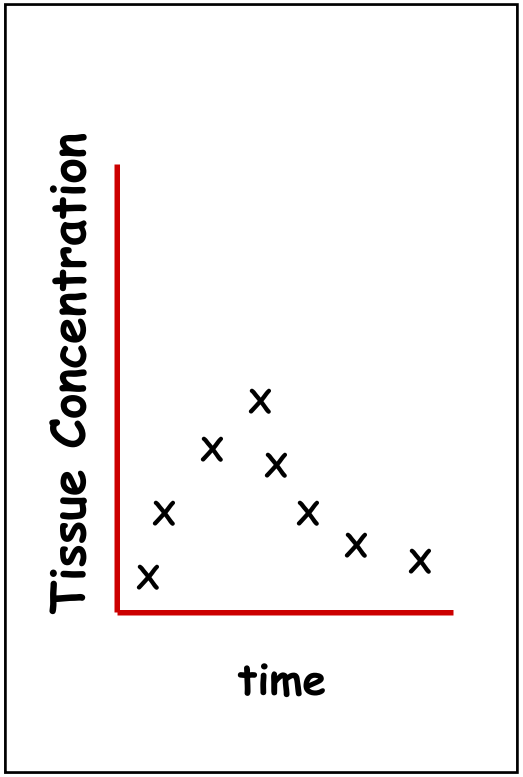
PK, more as study of systems of equations with exact solutions, rather than the study of PK processes.

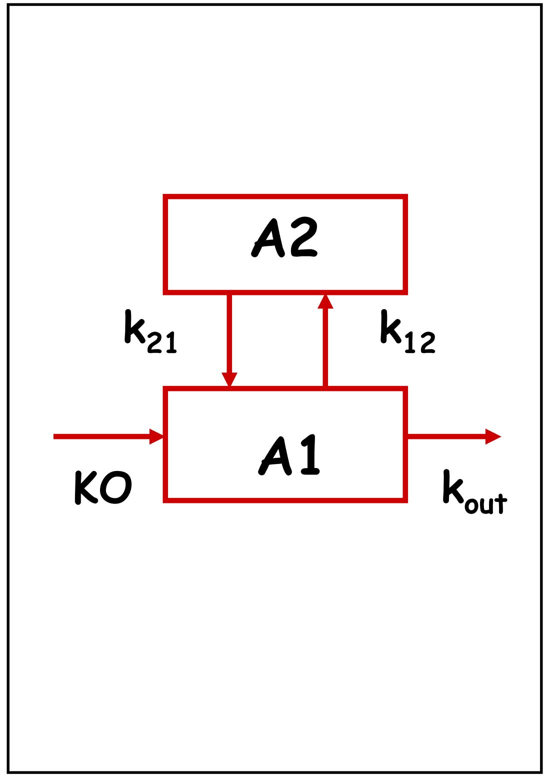
# Compartmental and physiological modeling of drugs

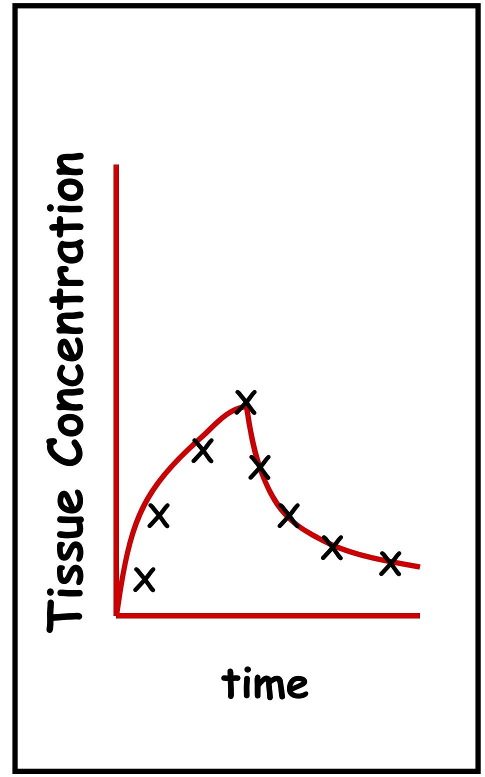



| | | | | | | |
|---|---|---|---|---|---|---|
| Symbol | | D | B | K | T | I |
| Amount | | x | y | u | z | w |
| Volume | | $V_1$ | $V_2$ | – | $V_3$ | – |
| Concentration | | $x/V_1$ | $y/V_2$ | – | $z/V_3$ | – |
| Perm. Coeff. | | $k_1'$ | – | $k_4'$ | $k_2'$ | – |
| Velocity | Out | K1=k1'/V1 | – | $K_4 = k_4'/V_2$ | $k_3=k_2'/V_3$ | $k_5$ |
| Constant | In | neglected | not existing | $k_2=k_2/V_2$ | – | – |
| Name of process | | Resorption | – | Elimination | Tissue take up as output | Inactivation |

# Conventional compartmental PK modeling



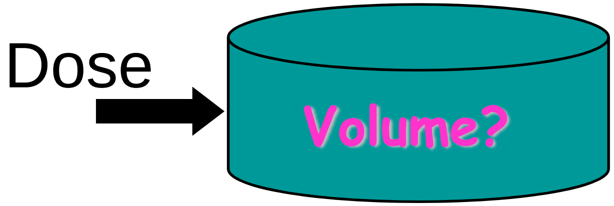




Collect Data → Select Model → Fit Model to Data

$$C_t = A\,e^{-ka\cdot t} + B\,e^{-kb\cdot t}$$

# 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 compound
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 compound (C)
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
  - 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 a compound is able to leave the container?

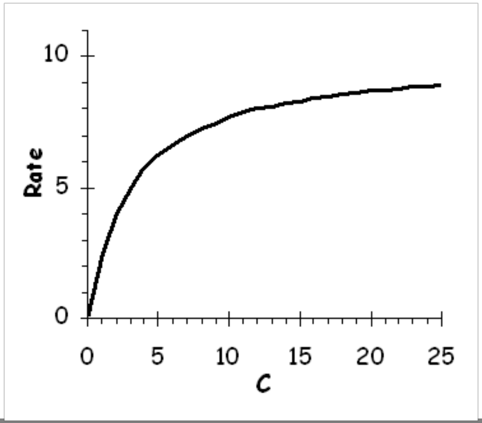
# Describing the rates of drug processes – one drug in the system

- Rate equations describe movement of drug between compartments
  - The previous example had instantaneous dosing.
  - Now, we need to describe the rate of loss from the compartment.
- <u>Zero-order process</u>
  - Rate is constant, does not depend on drug concentration ($Rate = k \times C^0 = k$).
- <u>First-order process</u>
  - Rate is proportional to concentration of ONE drug ($Rate = k \times C^1$).

# Describing the rates of drug processes – two drugs in the system

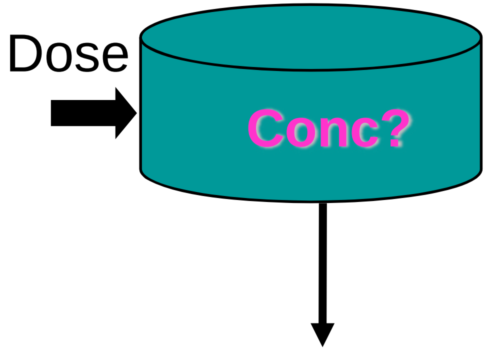
- <u>Second-order process</u>
  - Rate is proportional to concentration of both drugs (Rate = k × C1 × C2).
- <u>Saturable process</u>
  - Rate is dependent on interaction of two drugs.
  - One reactant, the enzyme, is constant.
  - Described using Michaelis-Menten equation Rate = (Vmax × C)/(C + Km).

M-M kinetics




- Michaelis-Menten kinetics can describe
  - Metabolism
  - Carrier-mediated transport across membranes
  - Excretion

# One-compartment model with bolus dose and first-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

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

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

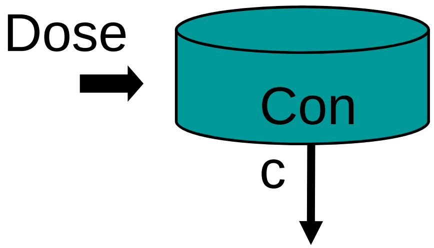
Half-life ($t_{1/2}$):

-Time to reduce concentration by 50%

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

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

# One-compartment model with bolus dose and first-order elimination




**Clearance:** volume cleared per time unit

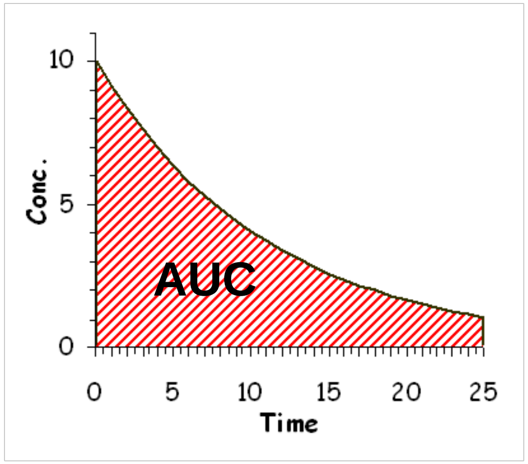
- if $k_e$ = fraction of volume cleared per time unit,

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

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)

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

$dA/dt = -CL \cdot C$

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

$Dose = CL \cdot AUC$

$CL = Dose / AUC$

# One-compartment model with continuous infusion and first-order elimination

## Calculating Clearance at Steady State:

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

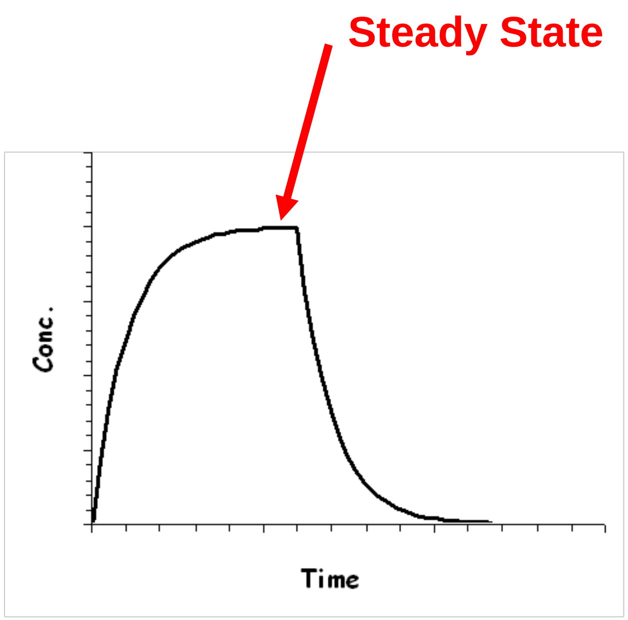
  $dC/dt = k_0/V \; - \; k_e \cdot C = 0$

- Rearrange above equation:

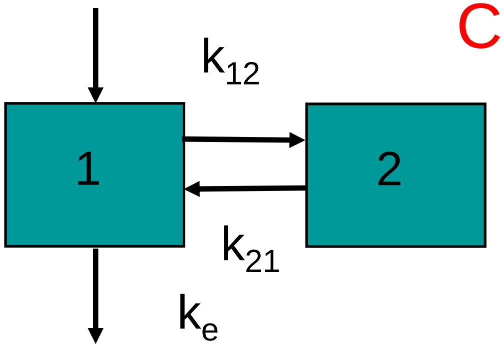
  $k_0/V \; = \; k_e \cdot C_{ss}$

- Since $CL = k_e \cdot V$ ,

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



# Two-compartment model with bolus dose and first-order elimination



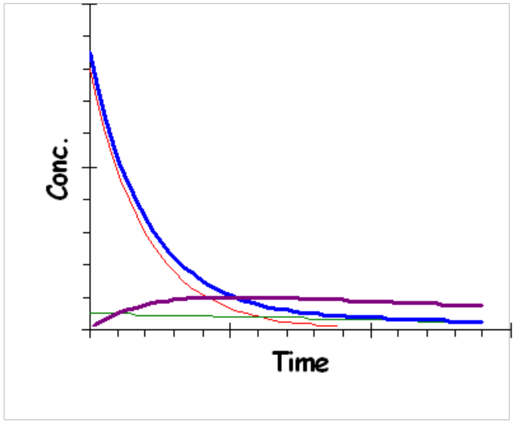

Calculating rate of change in each compartment:

- Central Compartment (C1):

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

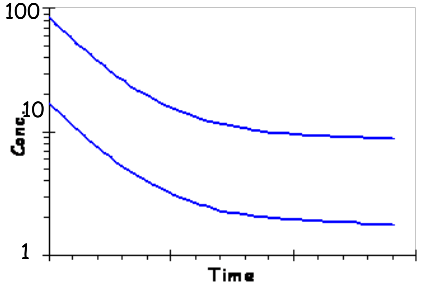
- Peripheral (Deep) Compartment (C2):

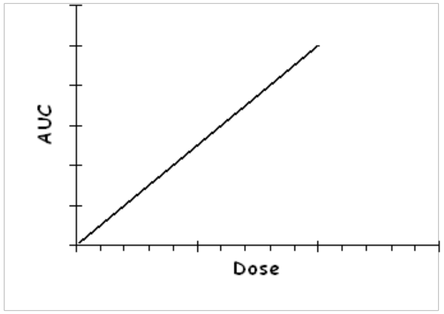
  $$dC2/dt = k_{12} \cdot C_1 - k_{21} \cdot C_2$$

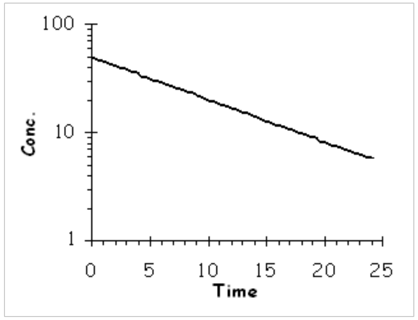


# Linear and non-linear kinetics

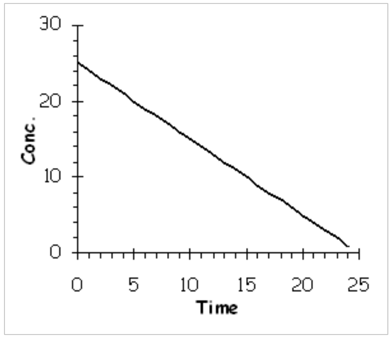
- Linear – all elimination and distribution kinetics are 1st order
  - Doubling dose → doubling concentration

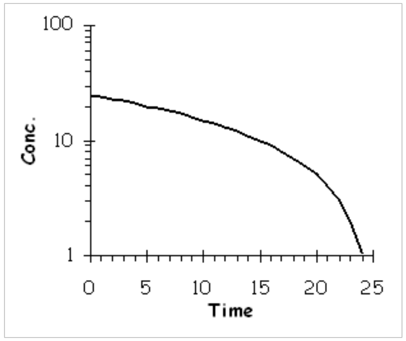



- Non-linear – at least one process is NOT 1st order
  - No direct proportionality between dose and compartment concentration.

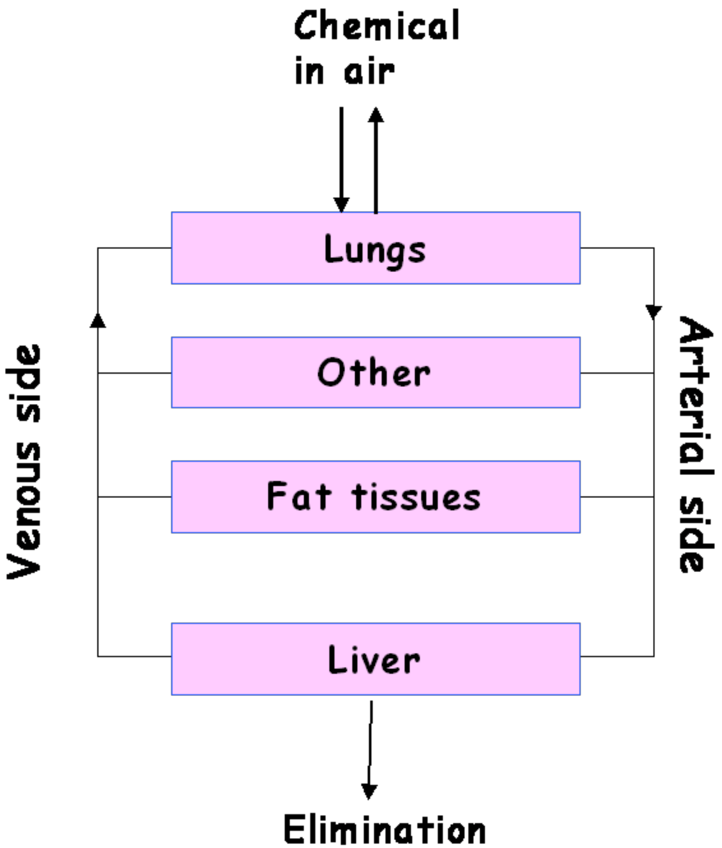


# PBPK models

Building a PBPK Model:

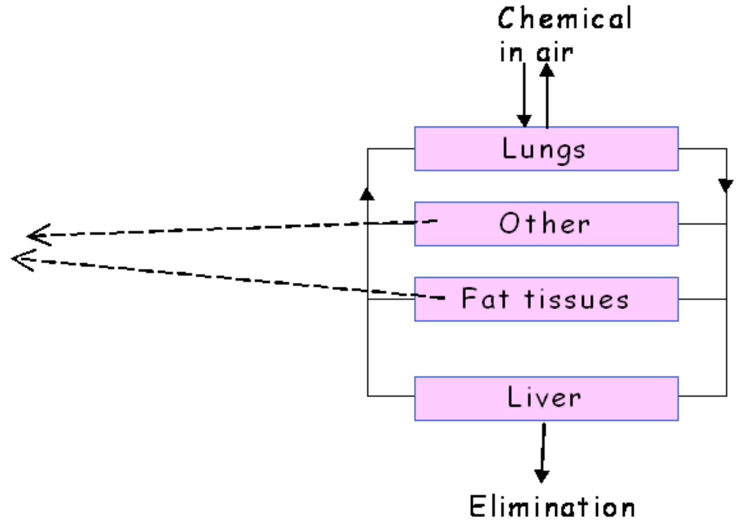
1. Define model compartments
   – Represent tissues
2. Write differential equation for each compartment
3. Assign parameter values to compartments
   – Compartments have defined volumes, blood flows
4. Solve equations for concentration
   – Numerical integration software (e.g. Berkeley Madonna, ACSL)




A simple model for inhalation

# Storage compartment in a PBPK model


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

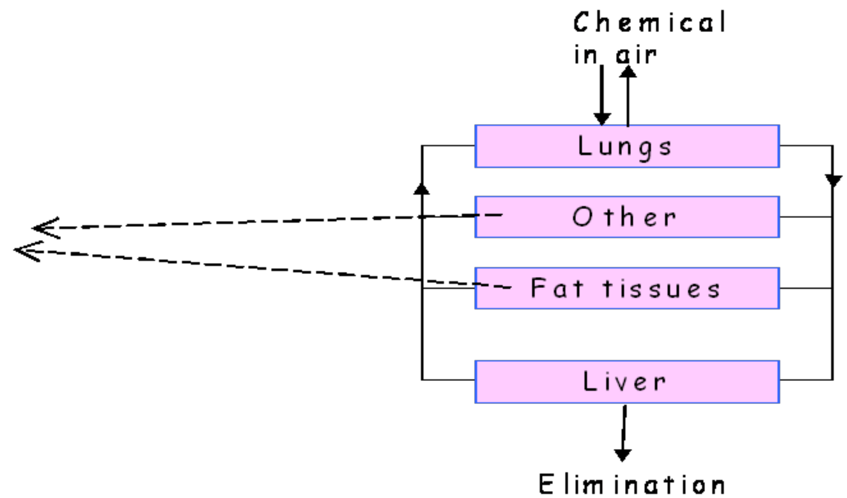
  where $C_{VT}$ = conc in tissue blood, $C_T$ = conc in tissue, $P_T$ = partition coefficient

  - Assume well-stirred compartment, so that,

    $C_{VT} = C_T/P_T$

# Storage compartment in a PBPK model


Same as 1-compartment model
with continuous infusion




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

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

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