



# Constructing PK Models

Interpretation of biomonitoring data using  
physiologically based pharmacokinetic modeling

Center for Human Health Assessment

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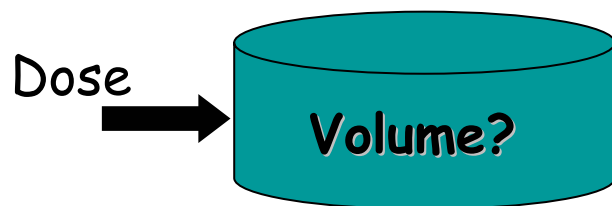
# Pharmacokinetics

- Studies of the change in chemical/metabolite distribution over time in the body
- Explores the quantitative relationship between Absorption, Distribution, Metabolism, and Excretion
- Classical Compartmental 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.

# Approaches to Pharmacokinetic Modeling

- Non-compartmental
  - Data summarization
- Compartmental
  - Statistical analysis
  - Interpolation
- Physiologically Based
  - Integration of Diverse Data
  - Extrapolation

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



**Purpose:** In a 1-compartment model, 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 ( $V$ )

# One-compartment model with bolus dose

- Basic assumption:
  - Well stirred, instant equal distribution within entire compartment
- **Volume of distribution =  $A/C$** 
  - In this 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 by movement out of compartments or by loss due to metabolism within the compartment

### • Zero-order process:

- rate is constant, does not depend on chemical concentration

$$\text{rate} = k \times C^0 = k$$

### • First-order process:

- rate is proportional to concentration of ONE chemical

$$\text{rate} = k \times C^1$$

# Describing the Rates of Chemical Processes - 2 Chemical Systems

## ● Second-order process:

- rate is proportional to concentration of both of the chemicals

$$\text{Rate} = k \times C_1 \times C_2$$

## ● Saturable processes\*:

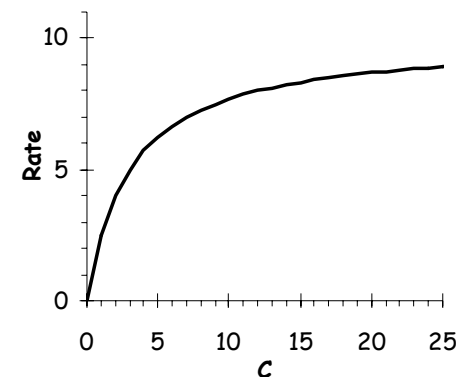
- Rate is dependent on interaction of two chemicals
- One reactant, the enzyme, is constant
- Described using Michaelis-Menten\* equation

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

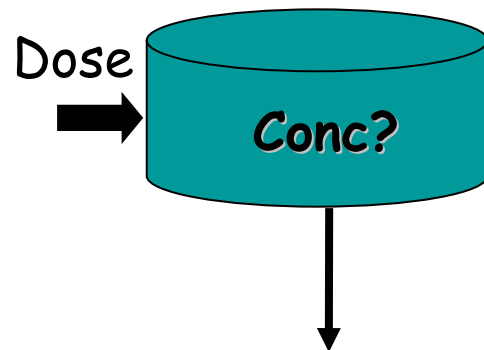
## \* Michaelis-Menten kinetics can describe:

- Metabolism
- Carrier-mediated transport across membranes
- Excretion

M-M kinetics



# 1-Comp model with bolus dose and 1<sup>st</sup> order elimination



**Purpose:** Examine how concentration changes with time

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

$$\begin{aligned} - dA/dt &= -k_e \times A, \text{ or dividing both sides by } Vd \\ - dC/dt &= -k_e \times C \end{aligned}$$

where  $k_e$  = elimination rate constant

**Concentration:**

- Rearrange and integrate above rate equation

$$\begin{aligned} C &= C_0 \times e^{-k_e \cdot t}, \text{ or} \\ \ln C &= \ln C_0 - k_e \cdot t \end{aligned}$$

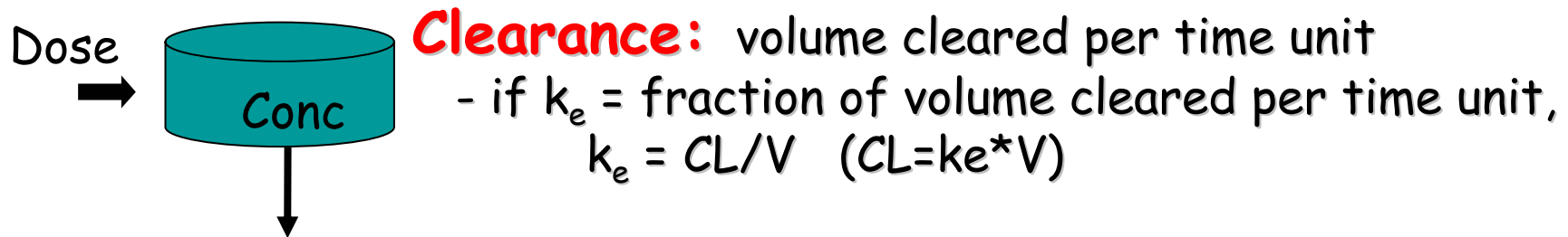
**Half-life ( $t_{1/2}$ ):**

- 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 1<sup>st</sup> order elimination



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)

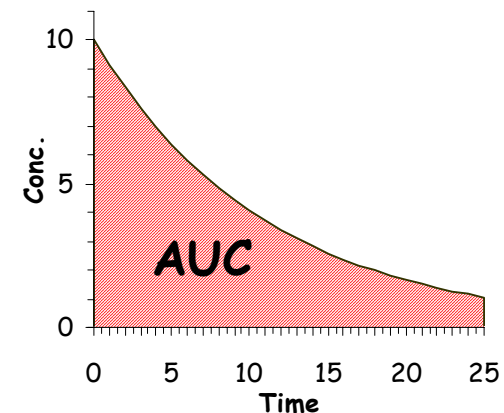
$$dA/dt = -k_e A = -k_e V C$$

$$dA/dt = -CL \cdot C$$

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

$$\text{Dose} = CL \cdot \text{AUC}$$

$$CL = \text{Dose} / \text{AUC}$$



# 1-Comp model with continuous infusion, 1st order elimination

## Calculating Clearance at Steady State

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

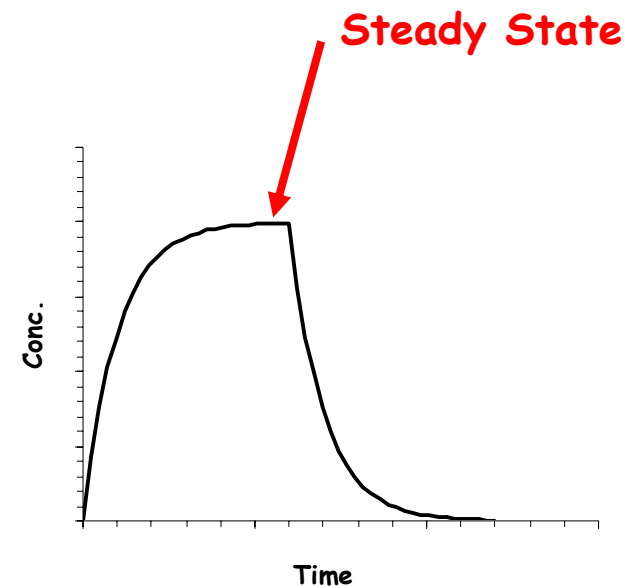
$$dC/dt = k_0/V - k_e \cdot C = 0$$

- Rearrange above equation:

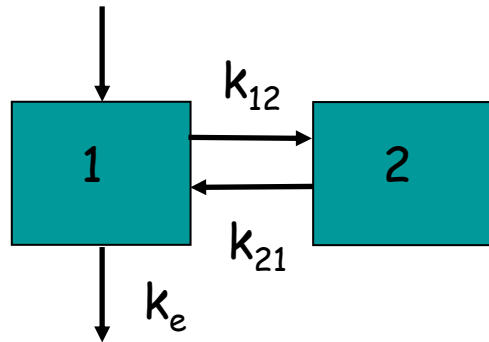
$$k_0/V = k_e \cdot C_{ss}$$

- Since  $CL = k_e \cdot V$ ,

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



## 2-Comp model with bolus dose and 1<sup>st</sup> order elimination



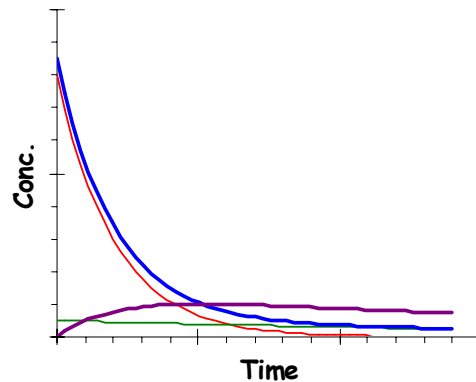
### Mass Balance Equations for Compartments

- Central Compartment (C1):

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

- Peripheral (Deep) Compartment (C2):

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

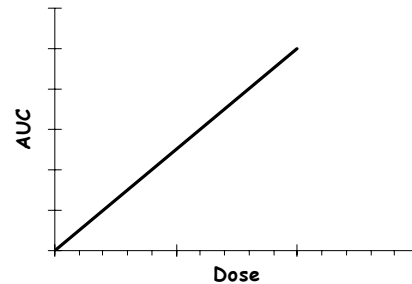
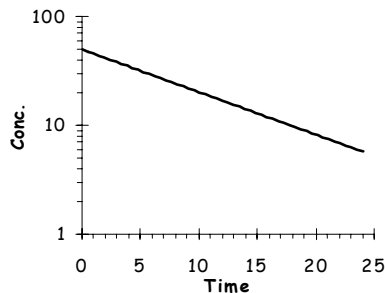


# Linear and Non-linear Kinetics

## Linear:

All elimination and distribution kinetics are 1<sup>st</sup> order

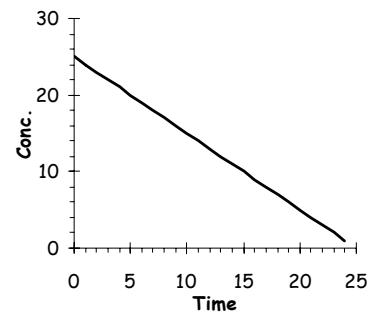
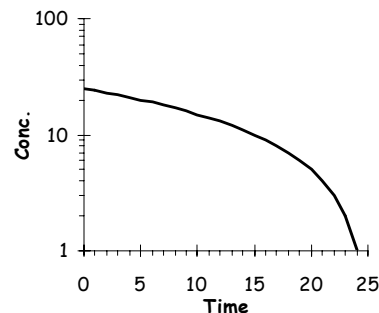
-Double dose → double concentration



## Non-l

At least one process is NOT 1<sup>st</sup> order

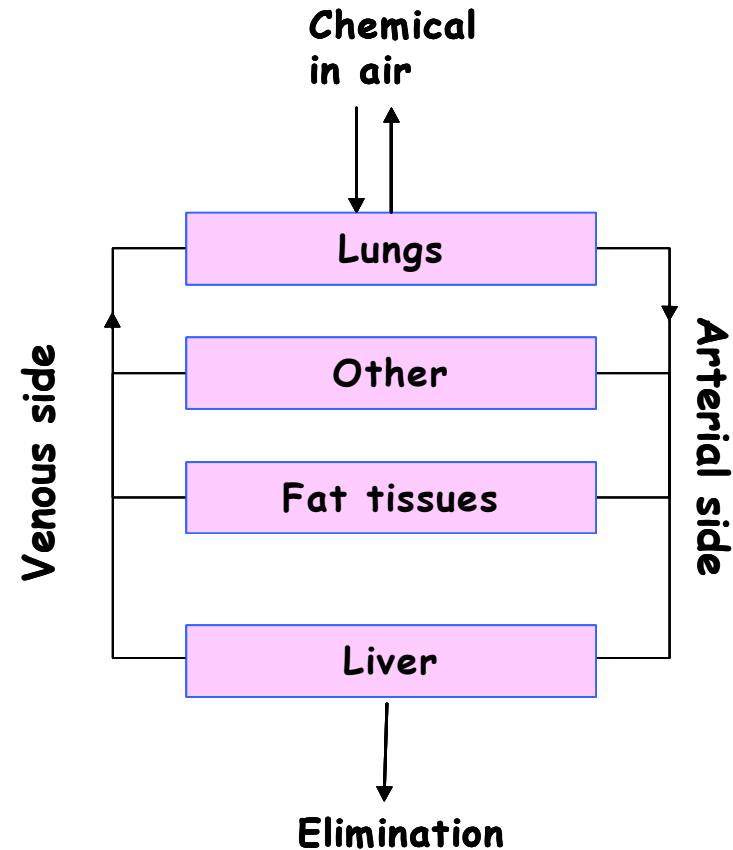
-No direct proportionality between dose and compartment concentration



# 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)

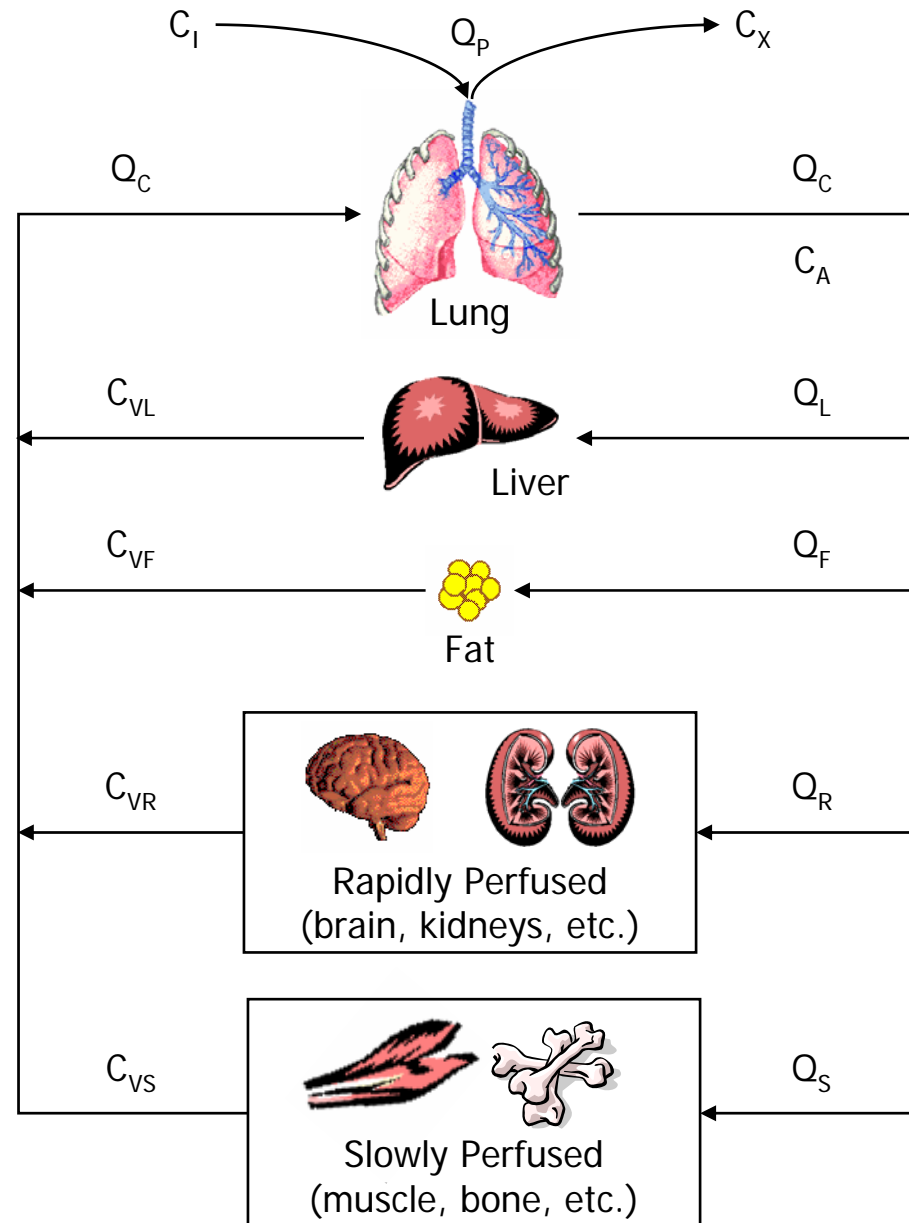


Simple model for inhalation

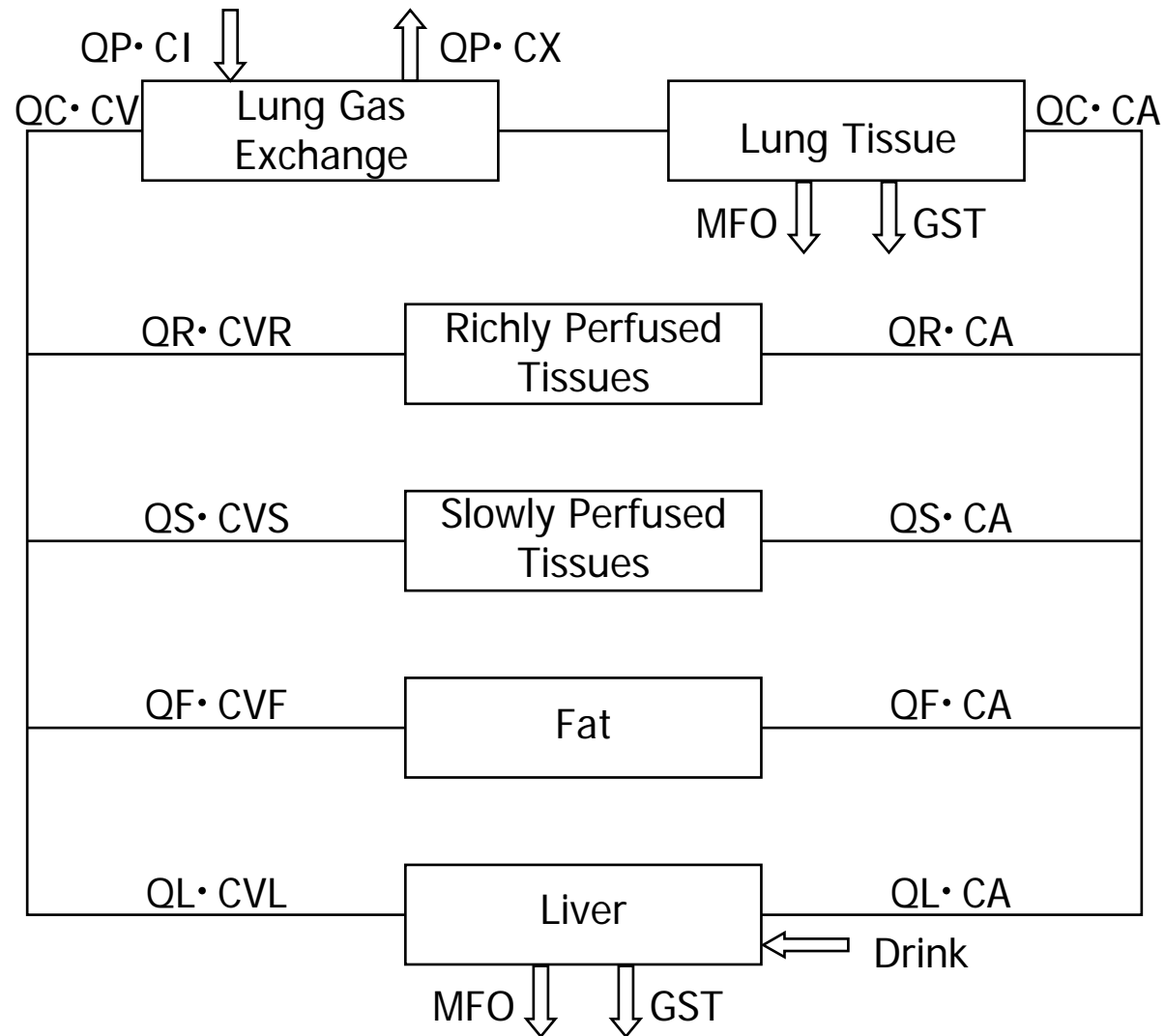
# Structuring PBPK Models

- What's needed and nothing more
  - Plausibility vs. Parsimony
- Considerations:
  - Uptake routes
  - Storage/sequestration/binding
  - Metabolism
  - Excretion
  - Target Tissue/Effect Compartment

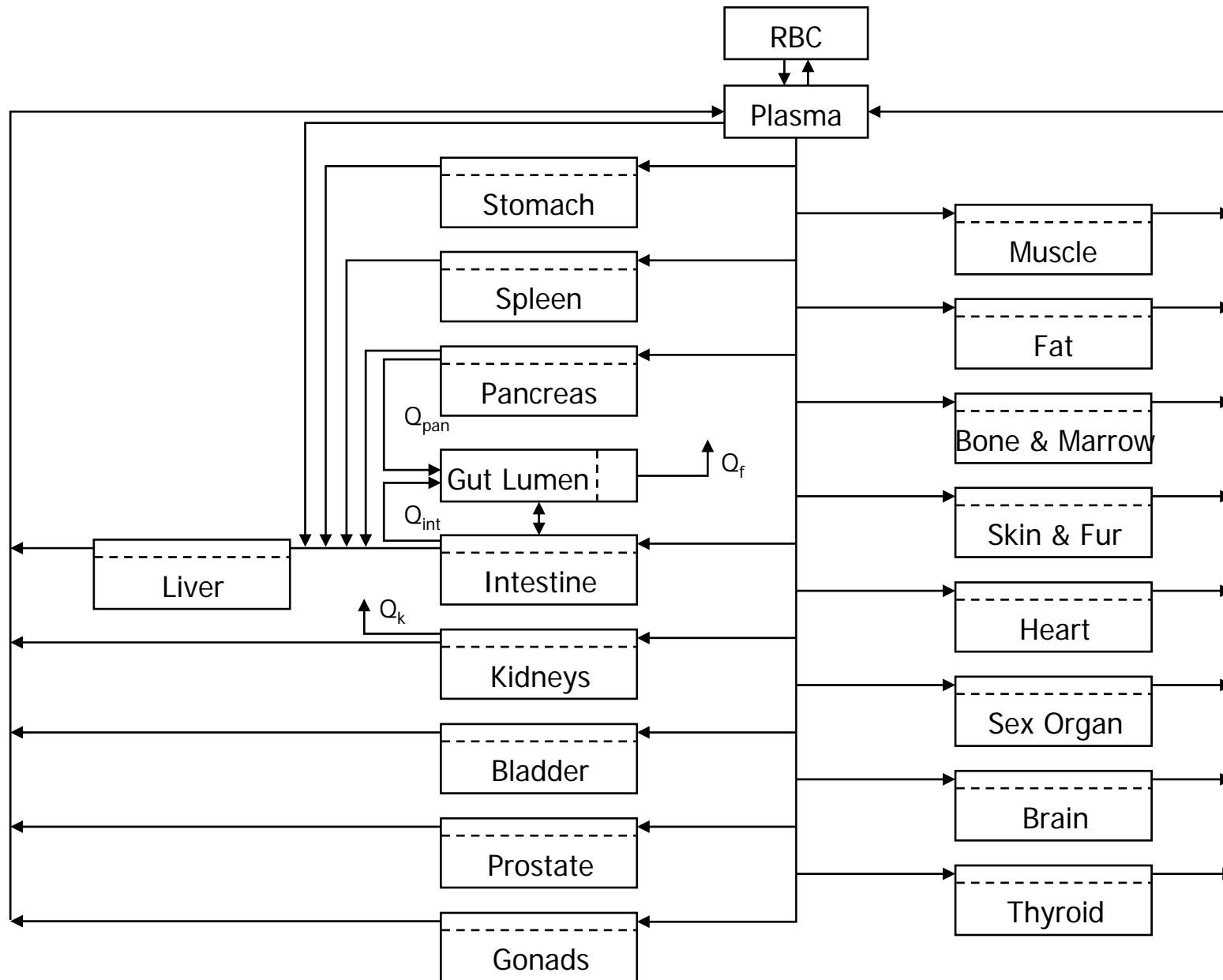
# Inhalation PBPK Model for Anesthetics



# Compartments in a Physiological Model for Methylene Chloride



# Generic IV PBPK Model (Lutz and Dedrick)



## Models in Perspective

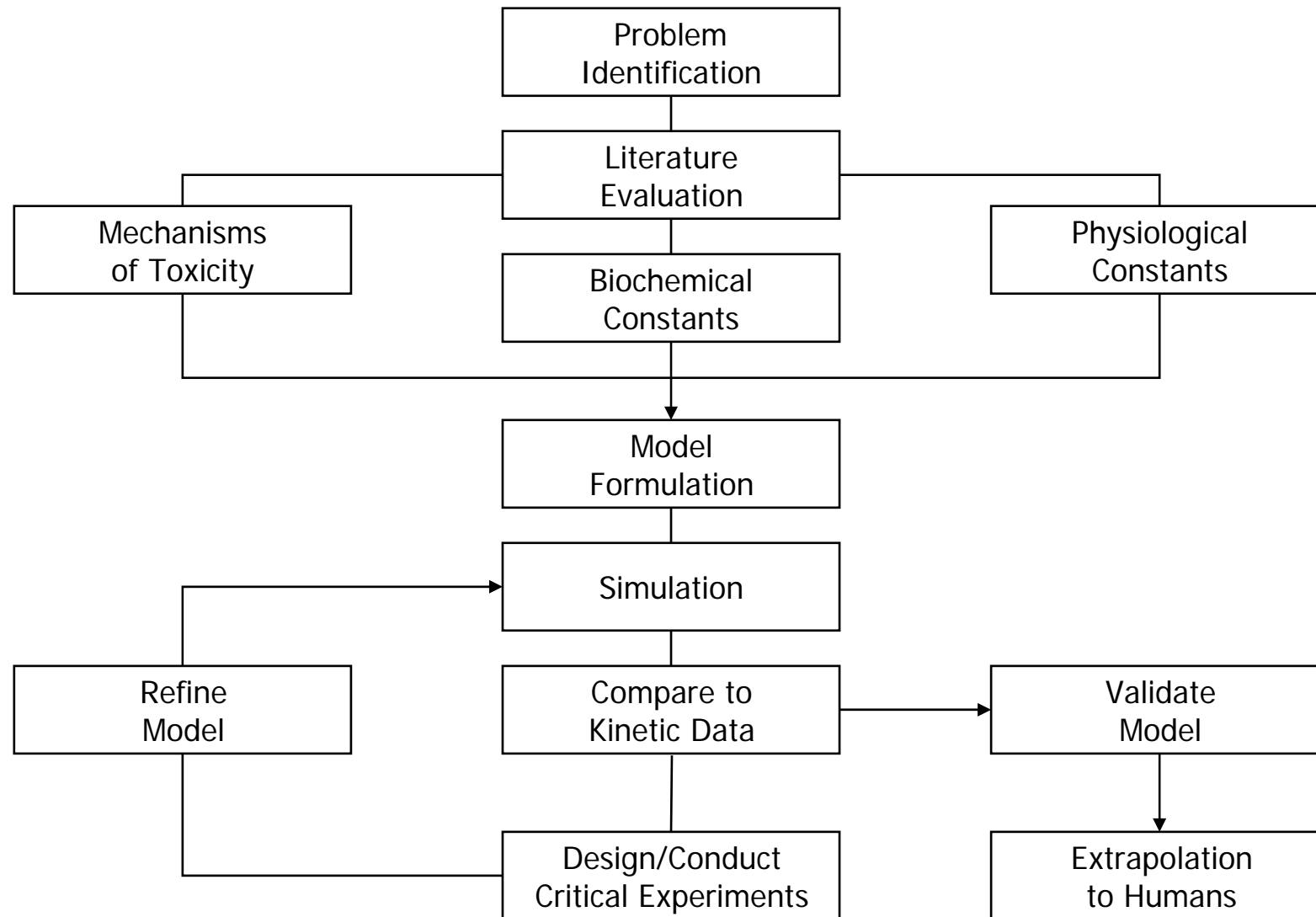
"...no model can be said to be 'correct'. The role of any model is to provide a framework for viewing known facts and to suggest experiments."

-- Suresh Moolgavkar

"All models are wrong and some are useful."

-- George Box

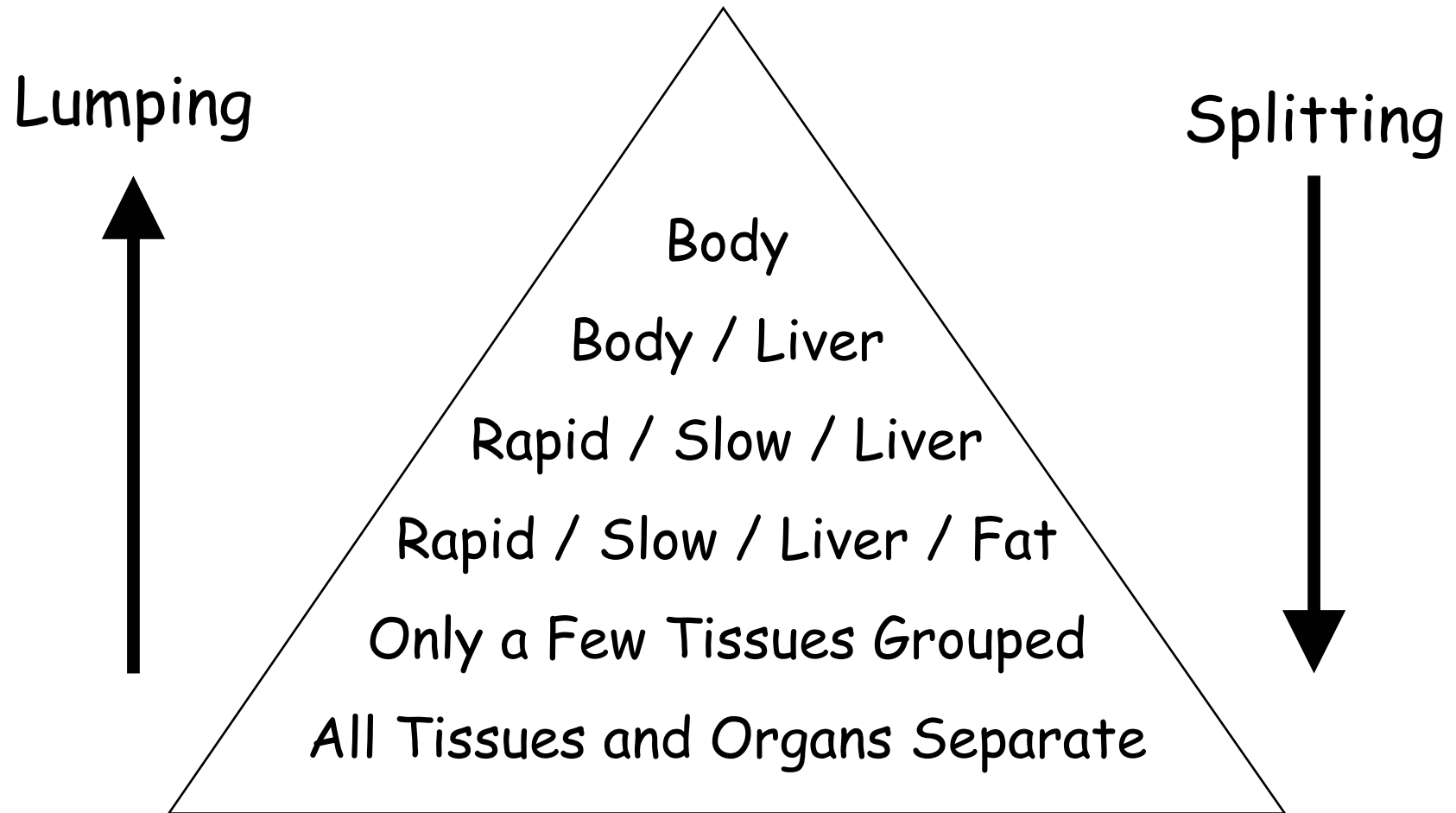
# Approach for Developing a PBPK Model



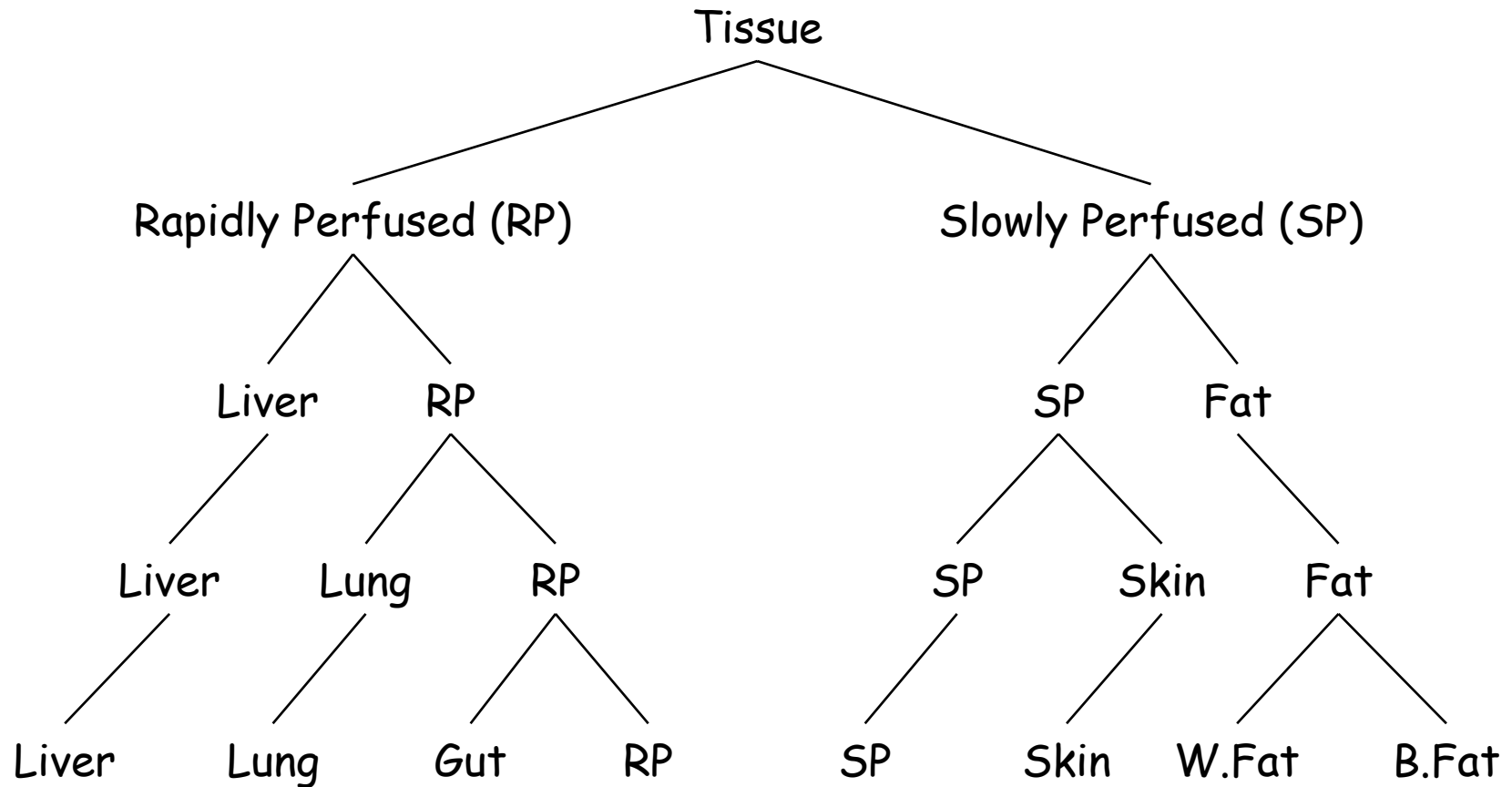
# Structuring the Model

- Tissue Grouping: 2 approaches
  - Lumping:  
“Tissues which are pharmacokinetically and toxicologically indistinguishable may be grouped together.”
  - Splitting:  
“Tissues which are pharmacokinetically or toxicologically distinct must be separated.”

# Alternative Approaches for Selecting a PBPK Model Structure



# Splitting Compartments in a PBPK Model



# Structuring the Model

## - Maintaining mass balance

The sum of the tissue blood flows must equal the total cardiac output:

$$\sum Q_i = Q_C$$

Seems obvious? -- Perhaps, but frequently violated inadvertently in models, particularly when adding new tissue compartments or varying parameters

-- e.g., when you split the skin compartment out of the slowly perfused tissue compartment, take its blood flow and volume out too!

# Structuring the Model

## Tissue Grouping Criteria:

- perfusion rate = blood flow / volume

$$R_T = Q_T / V_T$$

“rapidly” perfused: gut, liver, kidney, etc.

“slowly” perfused: muscle, skin, fat

- rate constant (/hr)

$$k_T = Q_T / (P_T * V_T)$$

where  $P = C_{Tissue} / C_{Blood}$  at equilibrium

(e.g., distinguishes fat from the other slowly perfused tissues for a lipophilic compound)

# Structuring the Model

- Tissue Grouping Considerations:
  - Storage (e.g., blood cells)
  - Excretion routes (e.g., hair)
  - Flow-limited metabolism (e.g., liver)
  - Uptake routes (e.g., skin)
  - Target Tissues
  - Distributional kinetics

Note: the same decisions need to be made for each metabolite, valence, or conjugate formed

# Building the Model

## Storage Compartments

- fat
- muscle
- liver
- kidney
- blood
- intestinal lumen

# Typical Storage Tissue Compartment

$$dA_T / dt = Q_T \times (C_A - C_{VT})$$

assuming venous equilibration:

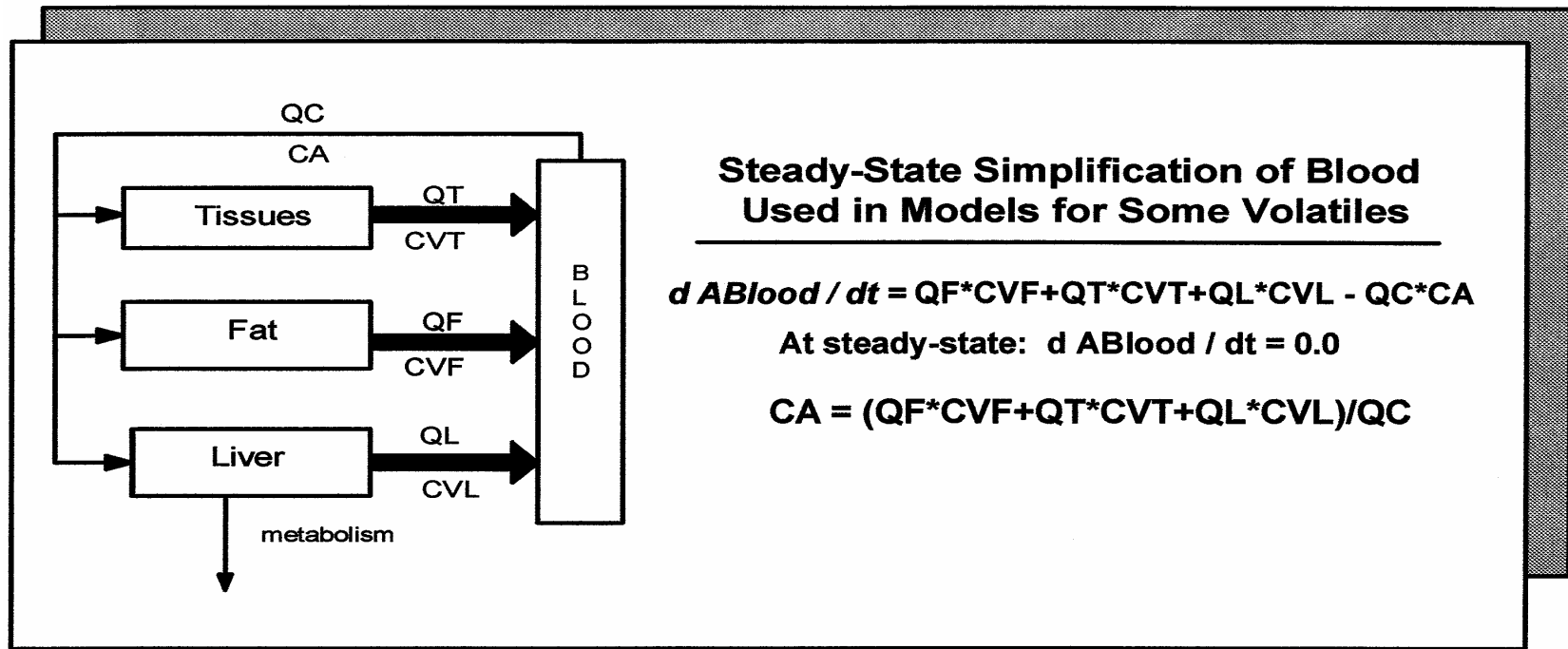
$$C_{VT} = C_T / P_T$$

Note: if  $V_T$  is constant:

$$dA_T / dt = d(C_T \times V_T) / dt = V_T \times dC_T / dt$$

so:

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



Blood compartment:

$$dA_B / dt = \Sigma(Q_T \times C_T / P_T) - Q_C \times C_B$$

assuming steady state:  $dA_B / dt = 0$

therefore:

$$C_B = \Sigma(Q_T \times C_T / P_T) / Q_C$$

# Building the Model

## Routes of Elimination

- liver (metabolism)
- kidney (urinary excretion)
- bile
- feces
- hair
- exhalation

Metabolizing Tissue (e.g., Liver):

$$dA_L / dt = Q_L \times (C_A - C_L / P_L) - dA_M / dt$$

where:

$$dA_M / dt = k_F \times C_L \times V_L / P_L \text{ (linear)}$$

and/or

$$V_{\max} \times C_L / P_L / (K_M + C_L / P_L)$$

(saturable)

# PBPK modeling Conventions

## "Ramseyan" Code for the Liver

$$RAL = QL * (CA - CVL) - RAM + RAO$$

$$RAM = (VMAX * CVL) / (KM + CVL) + KF * CVL * VL$$

$$RAO = KA * MR$$

$$AL' = RAL$$

$$init AL = 0.0$$

$$CL = AL / VL$$

$$CVL = CL / PL$$

$$AUCL' = CL$$

$$init AUCL = 0.0$$

In Berkeley Madonna, the differential equations have a different standard nomenclature:

AL', AM', AO' or

dAL/dt, dAM/dt, dAO/dt

See Berkely Madonna User Guide.

# Building the Model

## Distribution

- Perfusion (flow) limited
- Transport limited
- Diffusion limited
- Partitioning
- Binding

# Transport Limited Kinetics

$$VdC_T / dt = e_T \cdot Q_T \cdot (CA - (C_T / P_T)),$$

where  $(0 < e_T < 1)$

if  $e_T = 1$ , kinetics is blood-flow (perfusion) limited

# Diffusion Limited Kinetics

◆ Exchangeable compartment:

$$VdC_E / dt = (Q \bullet (C_A - C_E)) - (PA \bullet (C_E - (C_I / P_I)))$$

◆ Diffusion limited compartment

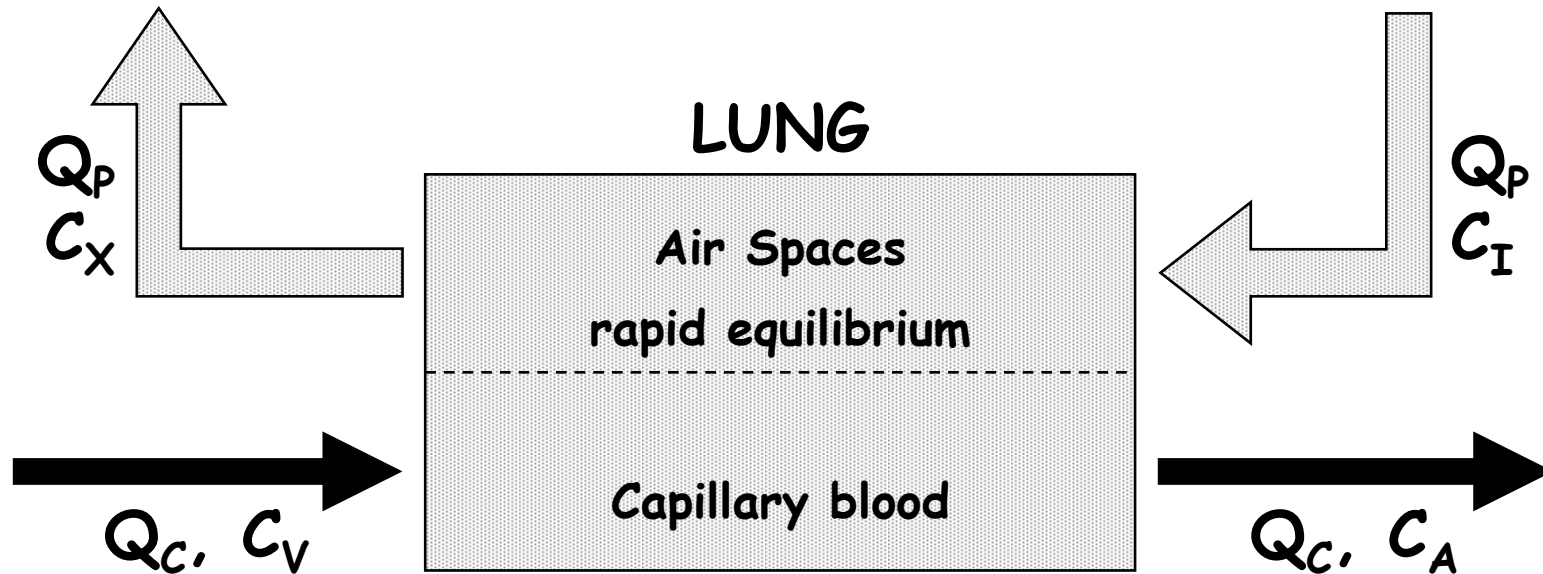
$$VdC_I / dt = PA \bullet (C_E - (C_I / P_I))$$

# Building the Model

## Uptake Routes

- inhalation
- drinking water
- oral gavage
- intravenous
- intraperitoneal
- Dermal
- Others (??)

# Lung Equations for Inhalation



$$dLung / dt = (Q_C \cdot (C_V - C_A)) + (Q_P \cdot (C_I - C_X))$$

At equilibrium:  $C_X = C_A / P_B$

$$dLung / dt = (Q_C \cdot (C_V - C_A)) + (Q_P \cdot (C_I - (C_A / P_B)))$$

At steady-state:  $dLung / dt = 0.0$

$$C_A = ((Q_C \cdot C_V) + (Q_P \cdot C_I)) / (Q_C + (Q_P / P_B))$$

# Uptake Routes

• Drinking water:

$$k_0 = (Dose \cdot BW) / 24.0$$

$$dA_L / dt = (Q_L \cdot (C_A - (C_L / P_L))) - (k_F \cdot C_L \cdot (V_L / P_L)) + k_0$$

• Oral gavage:

$$A_{St0} = Dose \cdot BW$$

$$dA_{St} / dt = -k_A \cdot A_{St}$$

$$dA_L / dt = (Q_L \cdot (C_A - (C_L / P_L))) - (k_F \cdot C_L \cdot (V_L / P_L)) + (k_A \cdot A_{St})$$

# Uptake Routes

Intravenous:

$$A_{B0} = Dose \bullet BW$$

or

$$C_V = ((Q_L \bullet C_{VL}) + \dots + (Q_F \bullet C_{VF}) + k_{IV}) / Q_C$$

where:

$$k_{IV} = \begin{cases} (Dose \bullet BW) / t_{IV}, & t < t_{IV} \\ 0.0, & t > t_{IV} \end{cases}$$

# One-compartment Dermal Structure

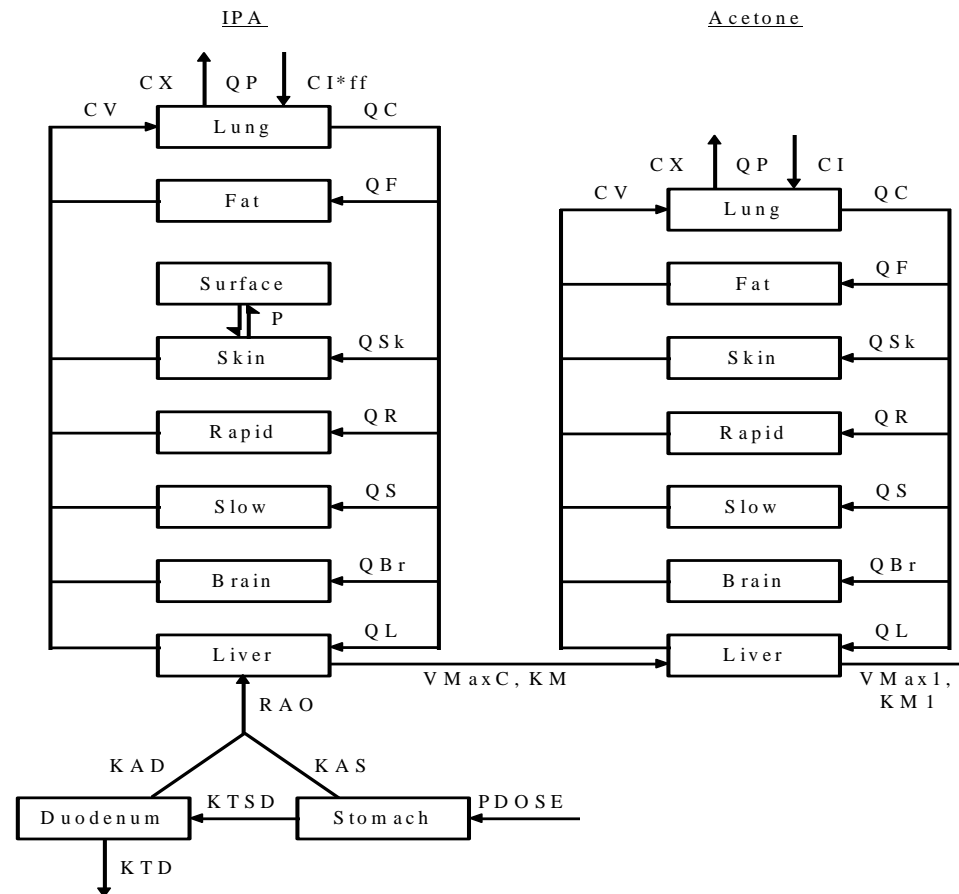
$$dA_{SFC} / dt = (K_P \cdot SA \cdot ((C_{Sk} / P_{SkL}) - C_{SFC}))$$

$$dA_{Sk} / dt = (K_P \cdot SA \cdot (C_{SFC} - (C_{Sk} / P_{SkL}))) + (Q_{Sk} \cdot (C_A - C_{Sk} / P_{SkB}))$$

Schematic of the PBPK model for isopropanol and its metabolite acetone

Designed for:

- oral
- inhalation
- Dermal exposure routes



# Building the Model

## Target Tissues

- metabolism
- binding
- pharmacodynamics

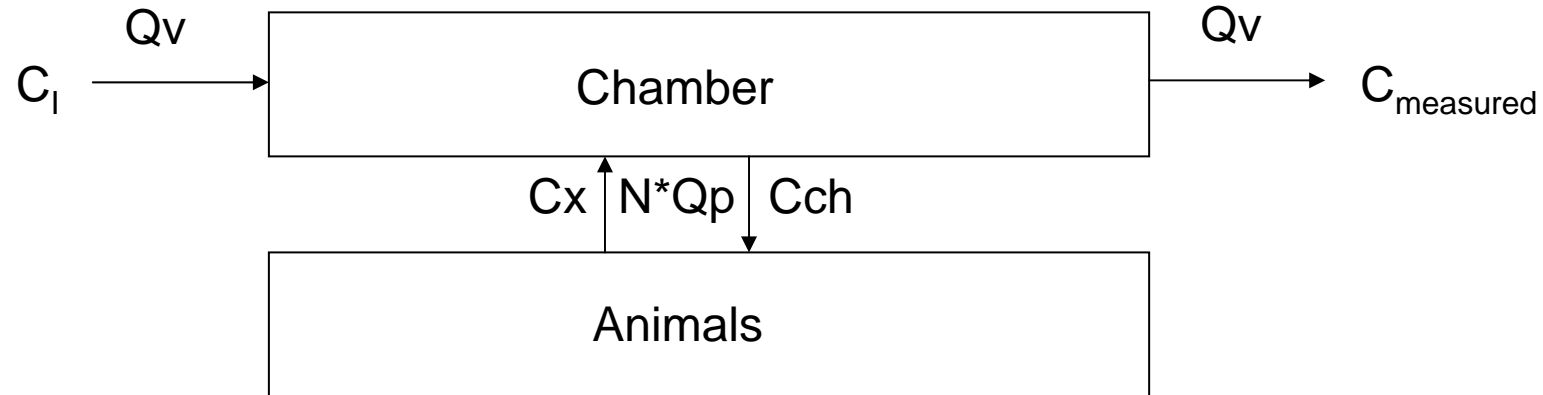
## Metabolite Compartments

- compartmental description
- physiologically based description

## Experimental Apparatus

- chamber
- sampling device

# Experimental Chamber Compartment



$$dA_{Ch} / dt = (N \cdot Q_P \cdot (C_X - C_{Ch})) + (Q_V \cdot (C_I - C_{Ch}))$$

where  $N$  = the number of animals in the chamber,

$Q_p$  = the single animal ventilation rate,

$Q_v$  = the chamber air ventilation rate,

$C_I$  = the chamber intake air concentration

$C_x$  = the exhaled air concentration

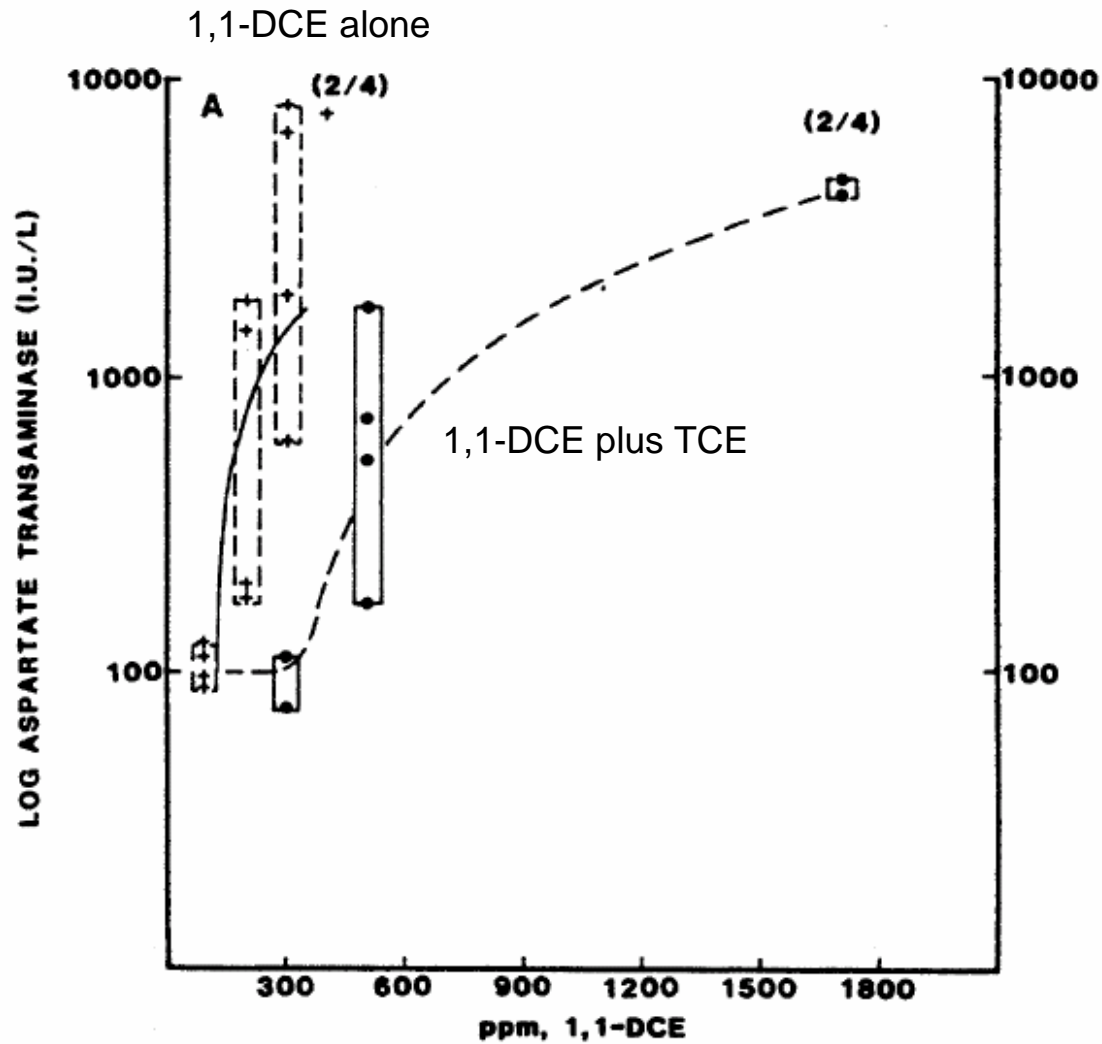
and  $C_{ch}$  = the chamber concentration

# Building the Model

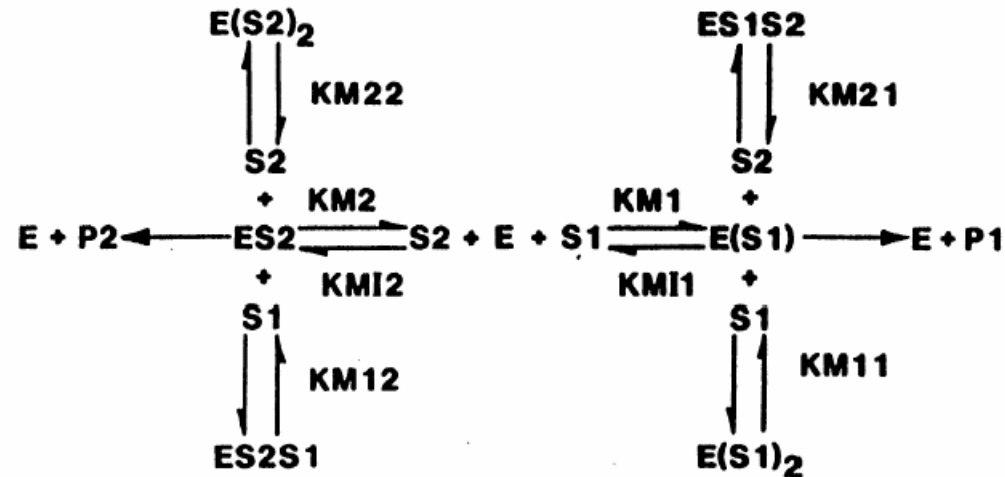
## Other complications

- Experimental problems
  - Loss of material
  - Preening
- Total radioactivity data
  - Represents sum of parent and metabolite concentrations
  - May require "other metabolites" compartment
- Tracer data
  - If kinetics are dose-dependent, need to model both unlabeled and labeled material
  - Similar problem for endogenous compounds
- Multiple chemical interactions
  - Competition
  - Inhibition/induction

# Observation: Co-exposure to TCE Decreases the Toxicity of 1,1-DCE



# Hypothesis: Metabolic Interaction



$$\frac{V_L d C_{L1}}{dt} = \frac{d A M T_{L1}}{dt} =$$

$$(Q_L C_{A1}) - (Q_L C_{V_{L1}}) - \frac{V_{\max 1} \cdot C_{V_{L1}}}{K_m(T_1) + C_{V_{L1}}(T_2)}$$

$$T_1 = 1 + C_{V_{L2}}/K_{mi2} + (C_{V_{L2}})^2/(K_{mi2} \times K_{m22})$$

$$T_2 = 1 + C_{V_{L2}}/K_{m21} + (C_{V_{L1}})/K_{m11}.$$

# INHIBITORY INTERACTIONS

For inhibition of metabolism of compound B by compound T:

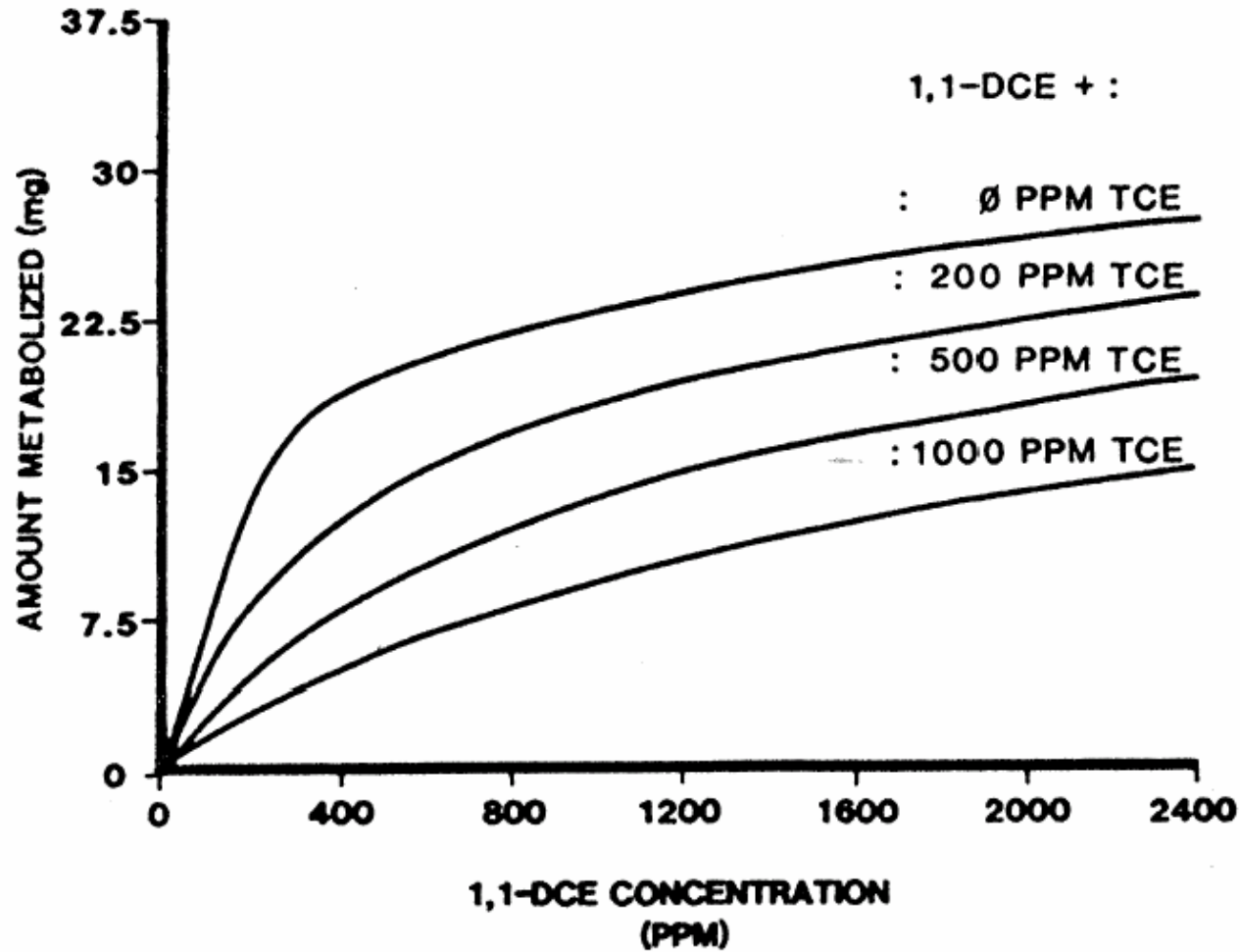
COMPETITIVE: 
$$\frac{dAMT_B}{dt} = (Q C_{aB}) - (Q C_{vB}) - \frac{V_{maxB} C_{vB}}{K_{mB}(1 + C_{vT}/K_{ITB}) + C_{vB}}$$

NON-COMPETITIVE: 
$$\frac{dAMT_B}{dt} = (Q C_{aB}) - (Q C_{vB}) - \frac{V_{maxB} C_{vB}}{(K_{mB} + C_{vB})(1 + C_{vT}/K_{ITB})}$$

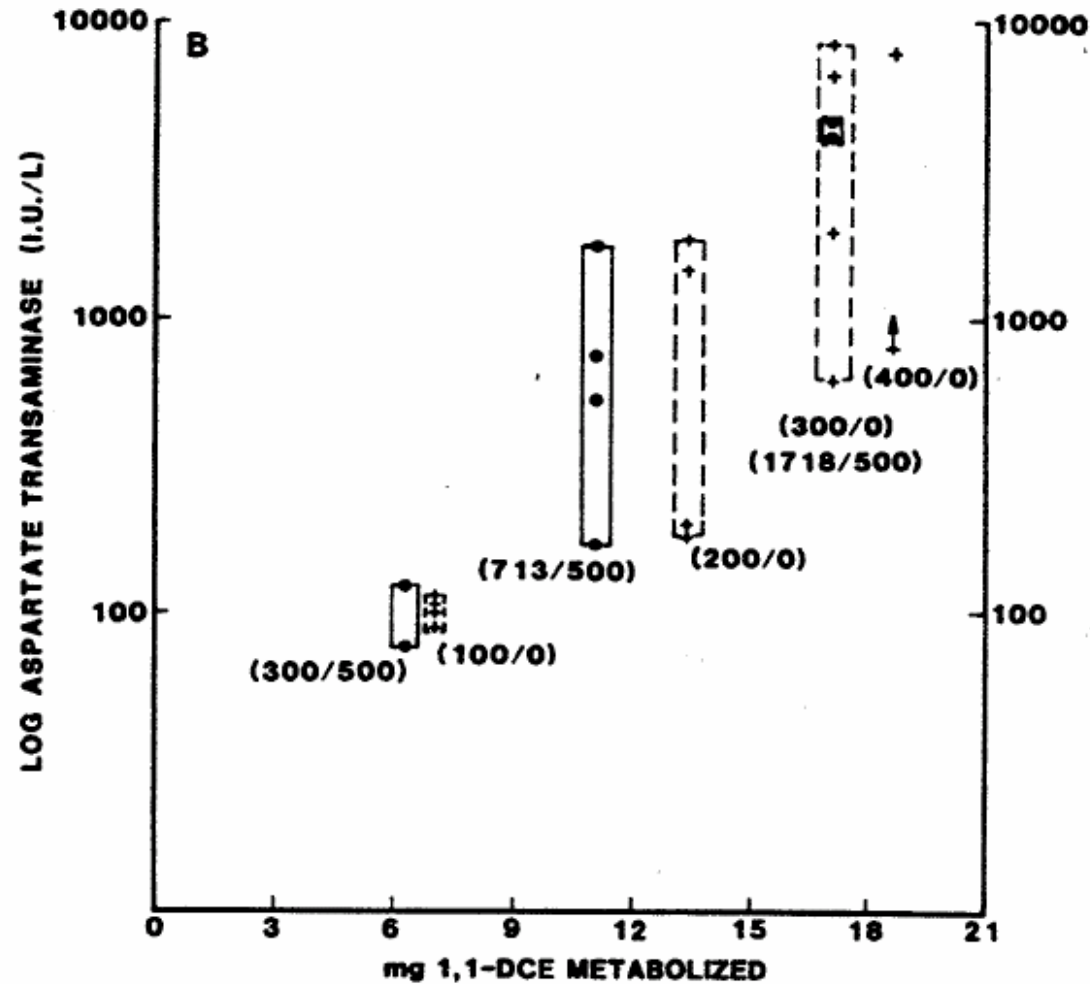
UNCOMPETITIVE: 
$$\frac{dAMT_B}{dt} = (Q C_{aB}) - (Q C_{vB}) - \frac{V_{maxB} C_{vB}}{K_{mB} + C_{vB}(1 + C_{vT}/K_{ITB})}$$

Result: Gas Uptake Kinetic Analysis of 1,1-DCE / TCE Mixtures was Most Consistent with Competitive Inhibition

# Predicted Inhibition of 1,1-DCE Metabolism by TCE (Assuming Competitive Inhibition)



# Verification: The Toxicity of 1,1-DCE Is Proportional to the Predicted Amount of 1,1-DCE Metabolized, with or without Co-exposure to TCE



# Linking Parent Compounds with Metabolites

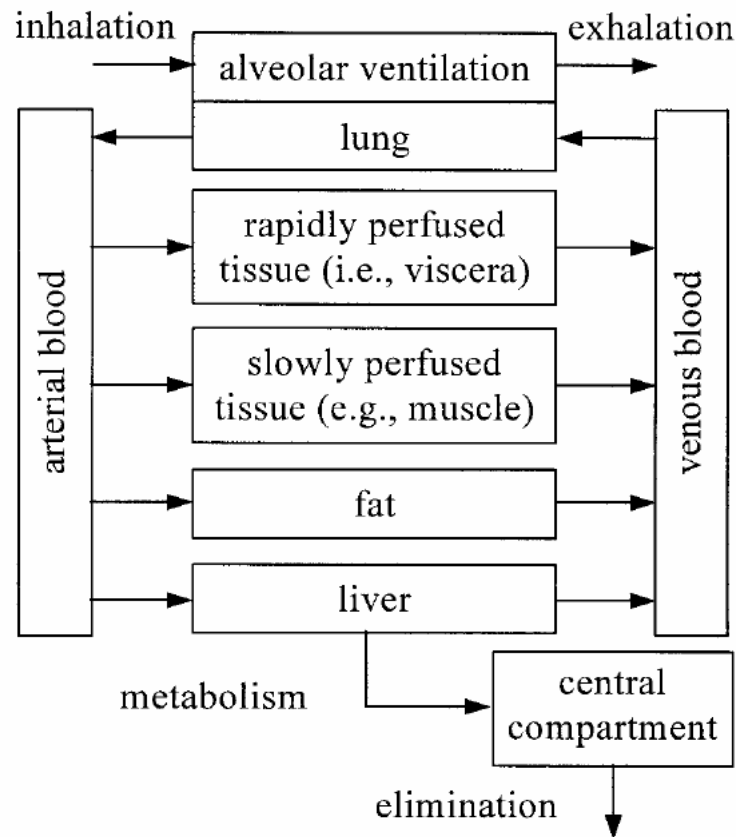


FIG. 1. Schematic diagram of the simple PBPK model for D<sub>4</sub> distribution in humans.

Human model for linear siloxane metabolites produced from metabolism of octamethylcyclotetrasiloxane. An initial metabolite distributes to a central compartment and is then metabolized to multiple downstream products.

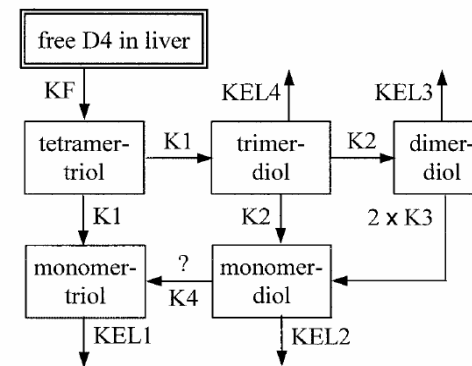
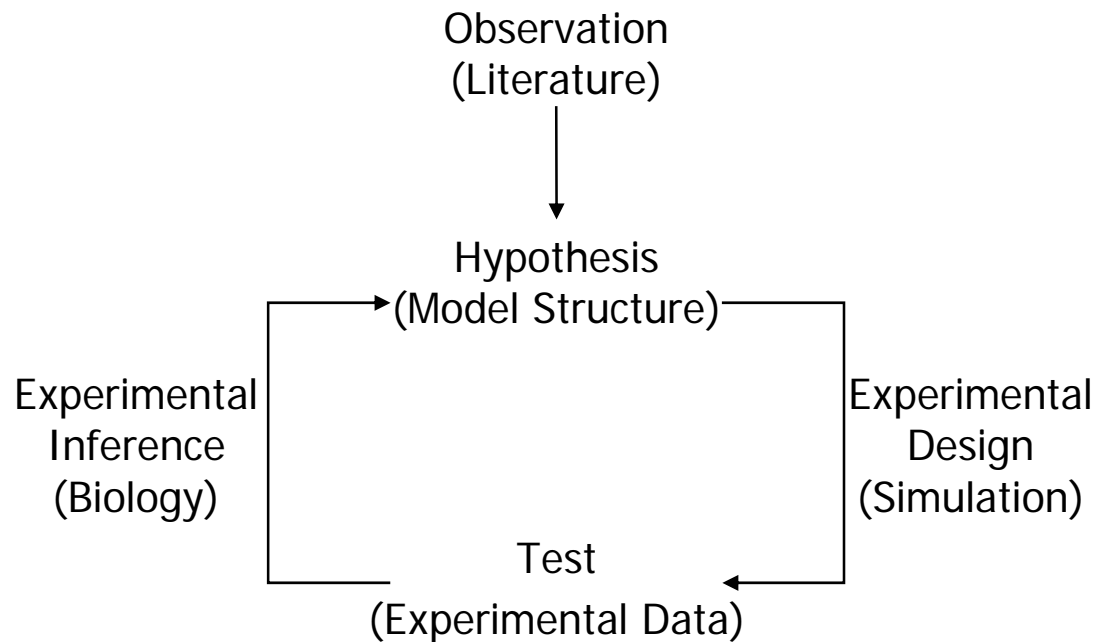


FIG. 4. Schematic diagram of the D<sub>4</sub> metabolism submodel.

# Summary

## PBPK Model Development

### Scientific Method



### Analysis

