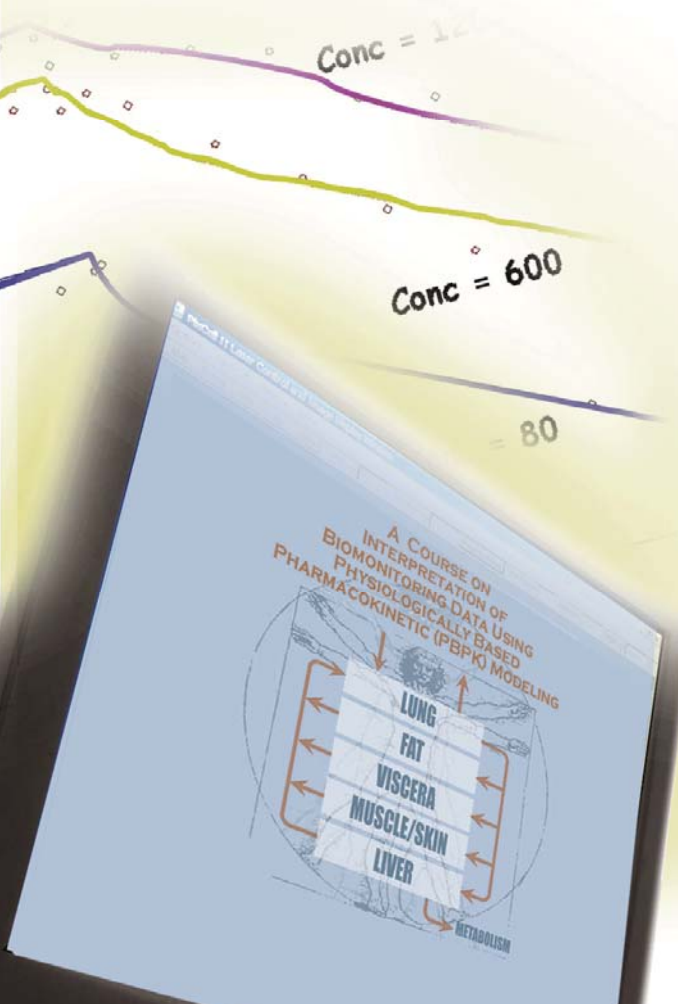


Construction of a Physiologically Based Pharmacokinetic Model

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

February 11 – February 15, 2008



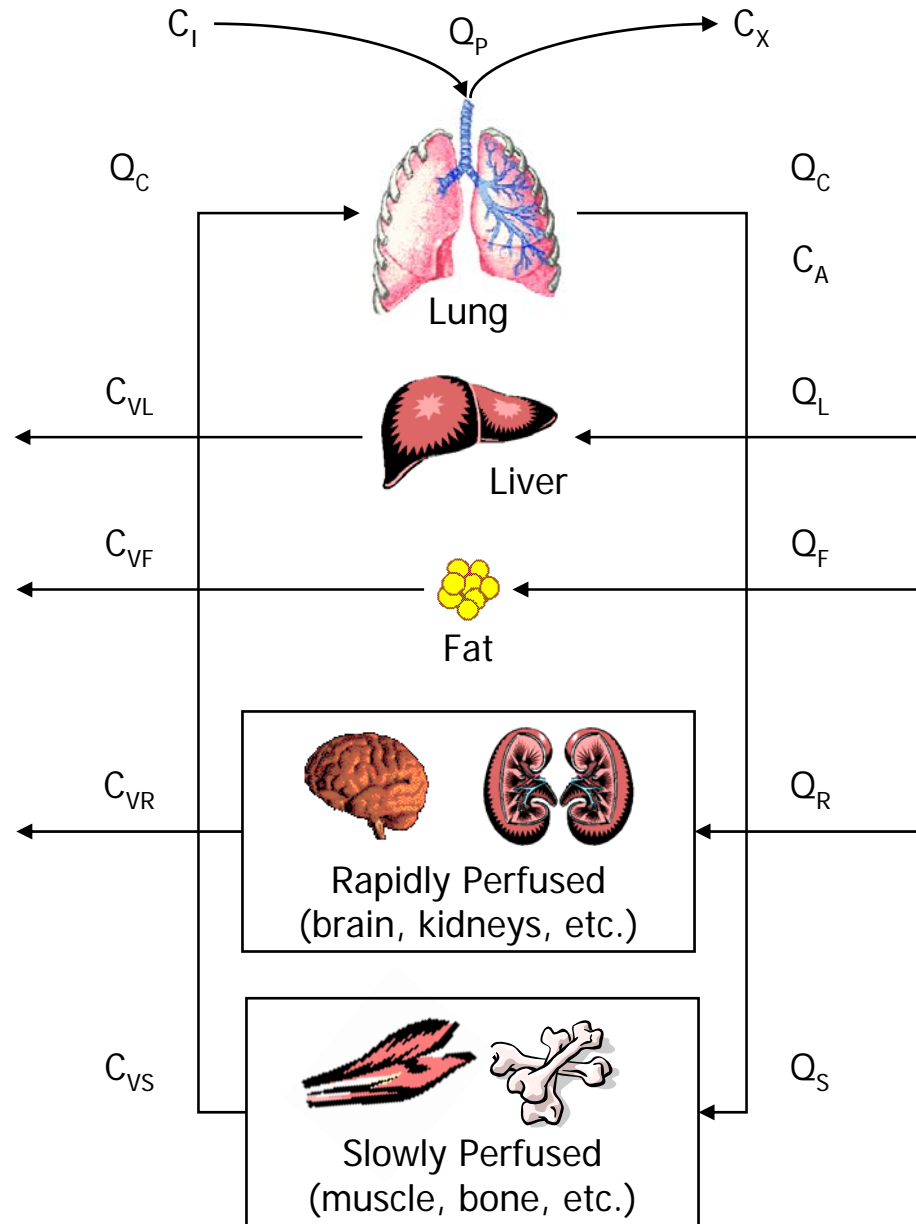
Alternative Approaches to Pharmacokinetic Modeling

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

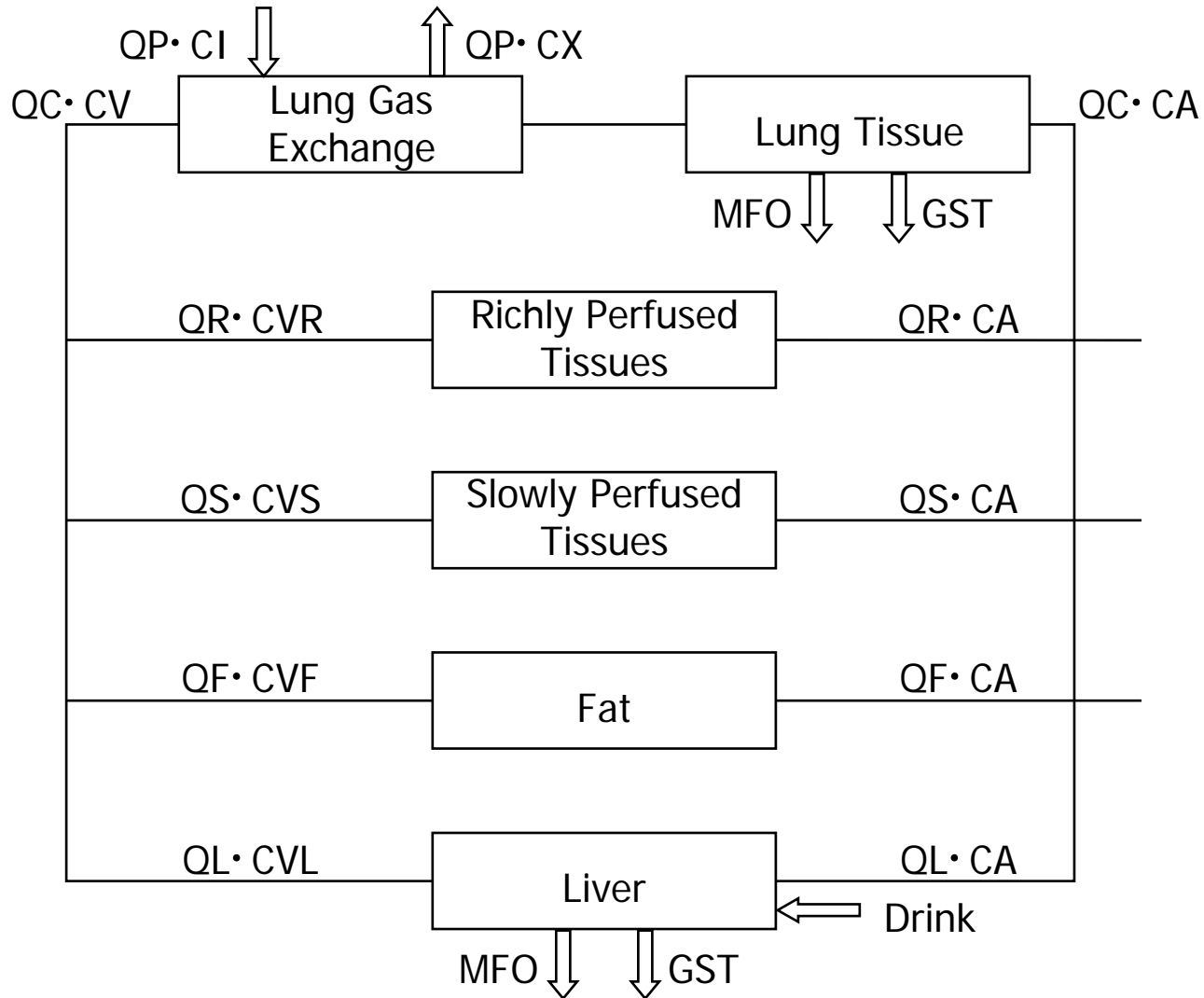
Structuring the Model

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

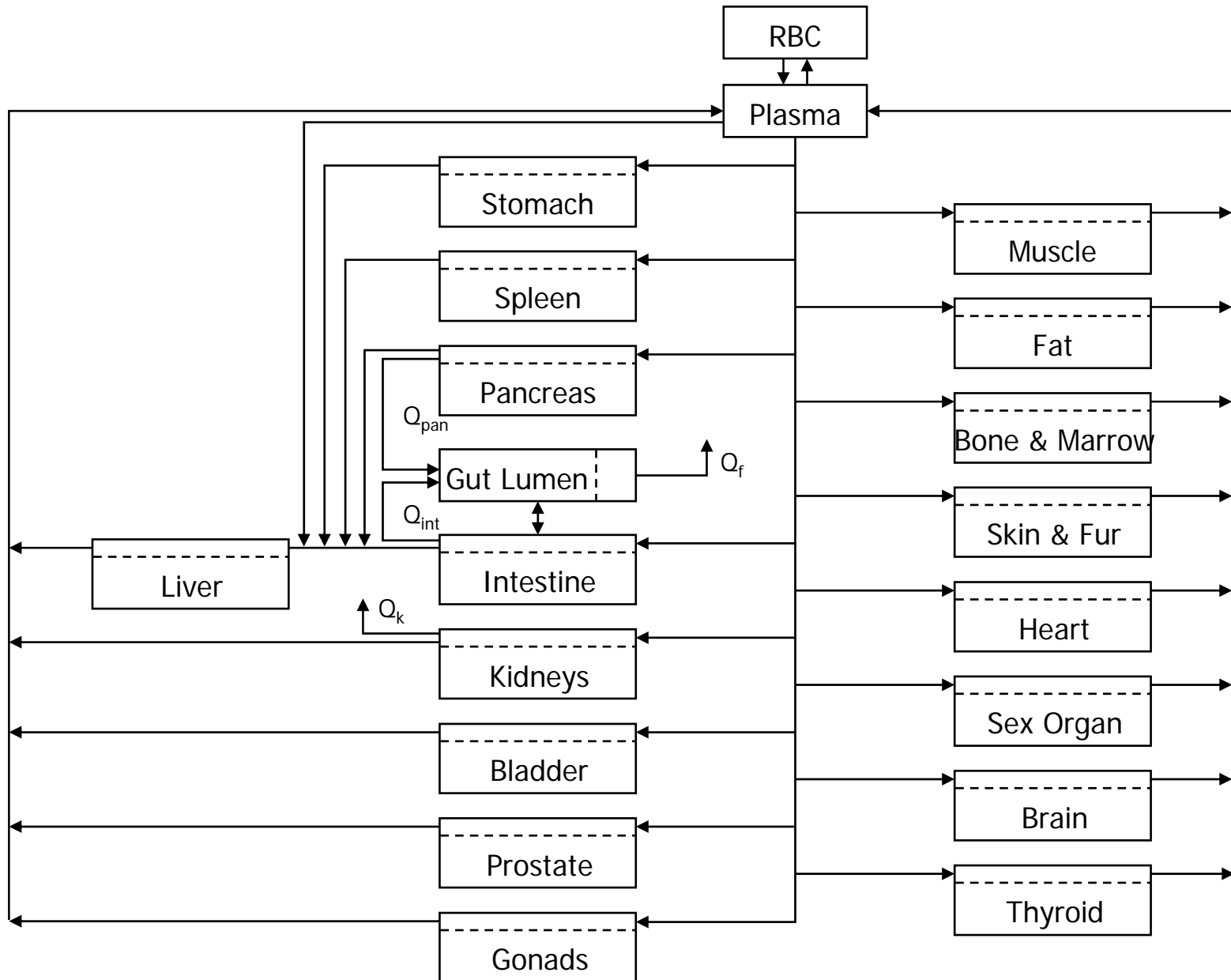
Generic Inhalation PBPK Model for Anesthetics



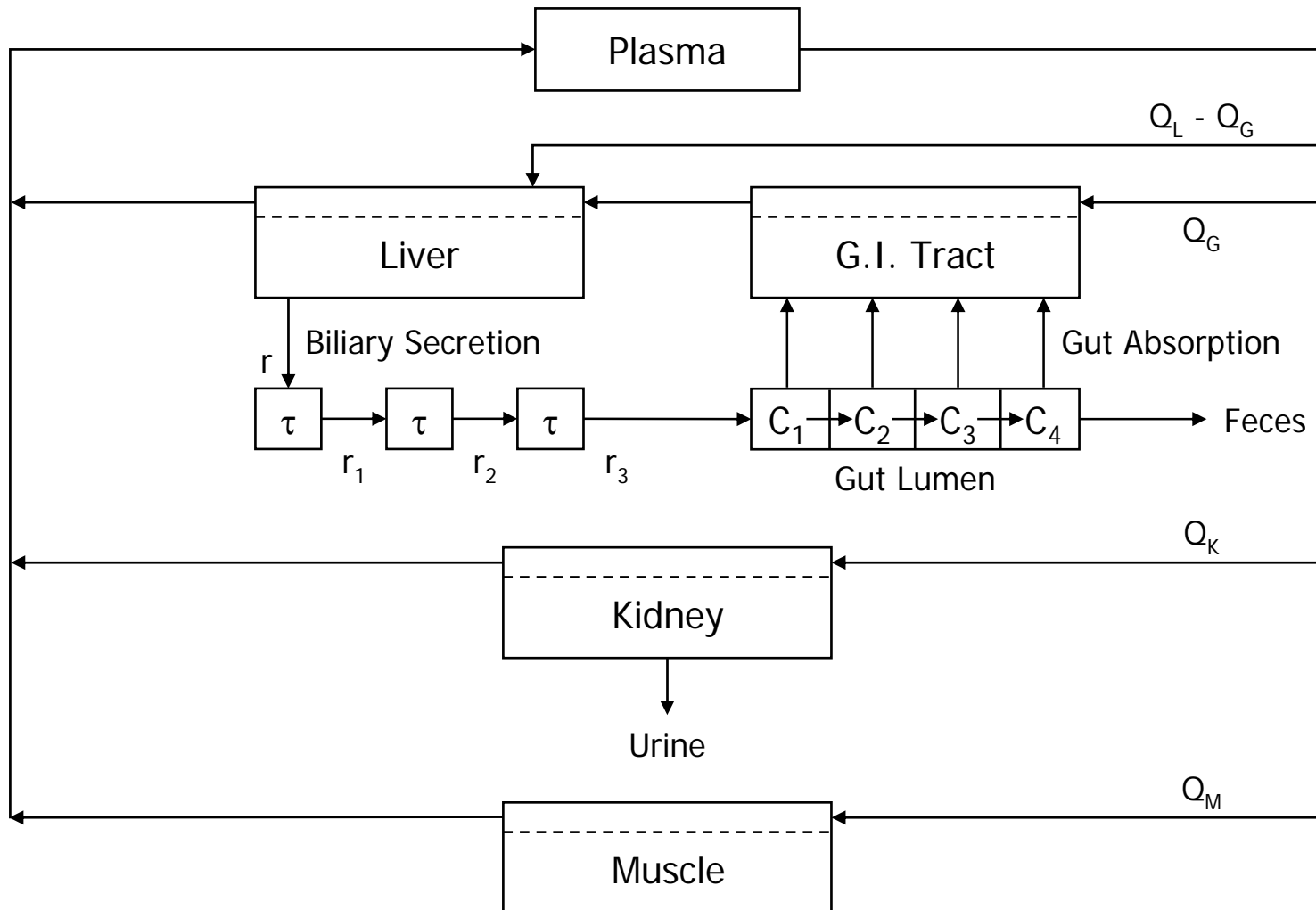
Compartments in a Physiological Model for Methylene Chloride



Generic IV PBPK Model (Lutz and Dedrick)



Compartments in a Physiological model for Methotrexate



Models in Perspective

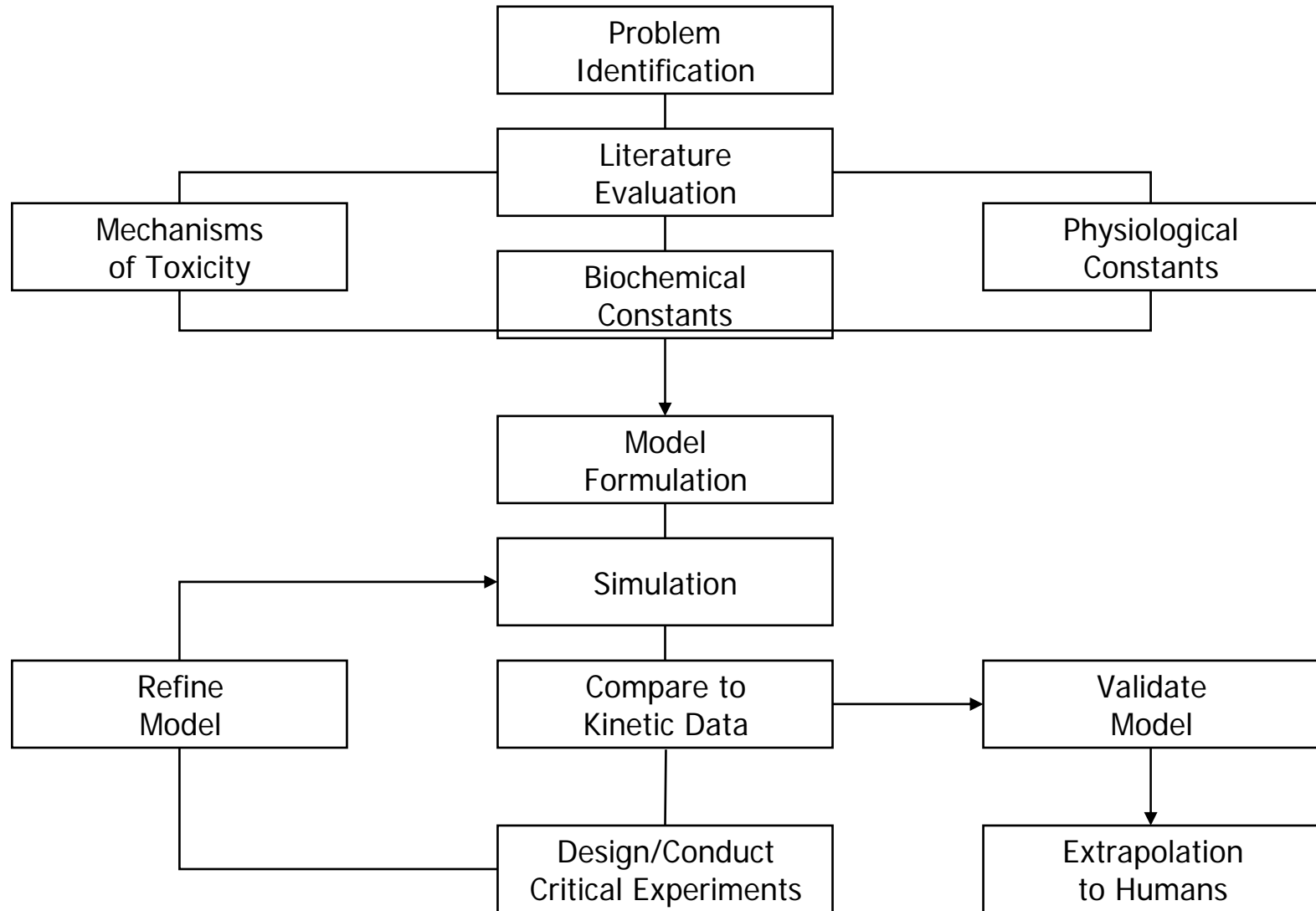
“...no model can be said to be ‘correct’. The role of any model is to provide a framework for viewing known facts and to suggest experiments.”

-- Suresh Moolgavkar

“All models are wrong and some are useful.”

-- George Box

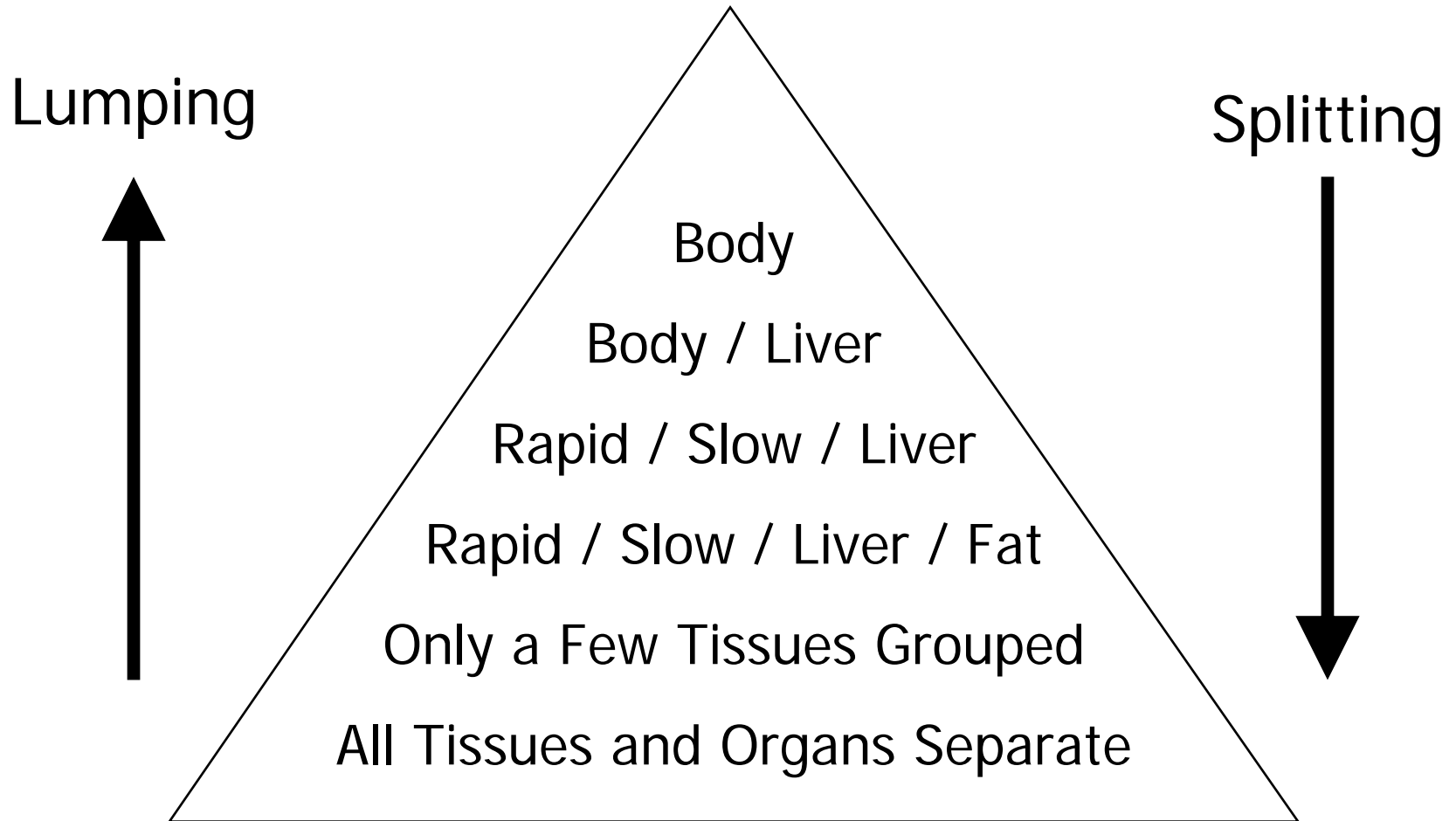
Approach for Developing a PBPK Model



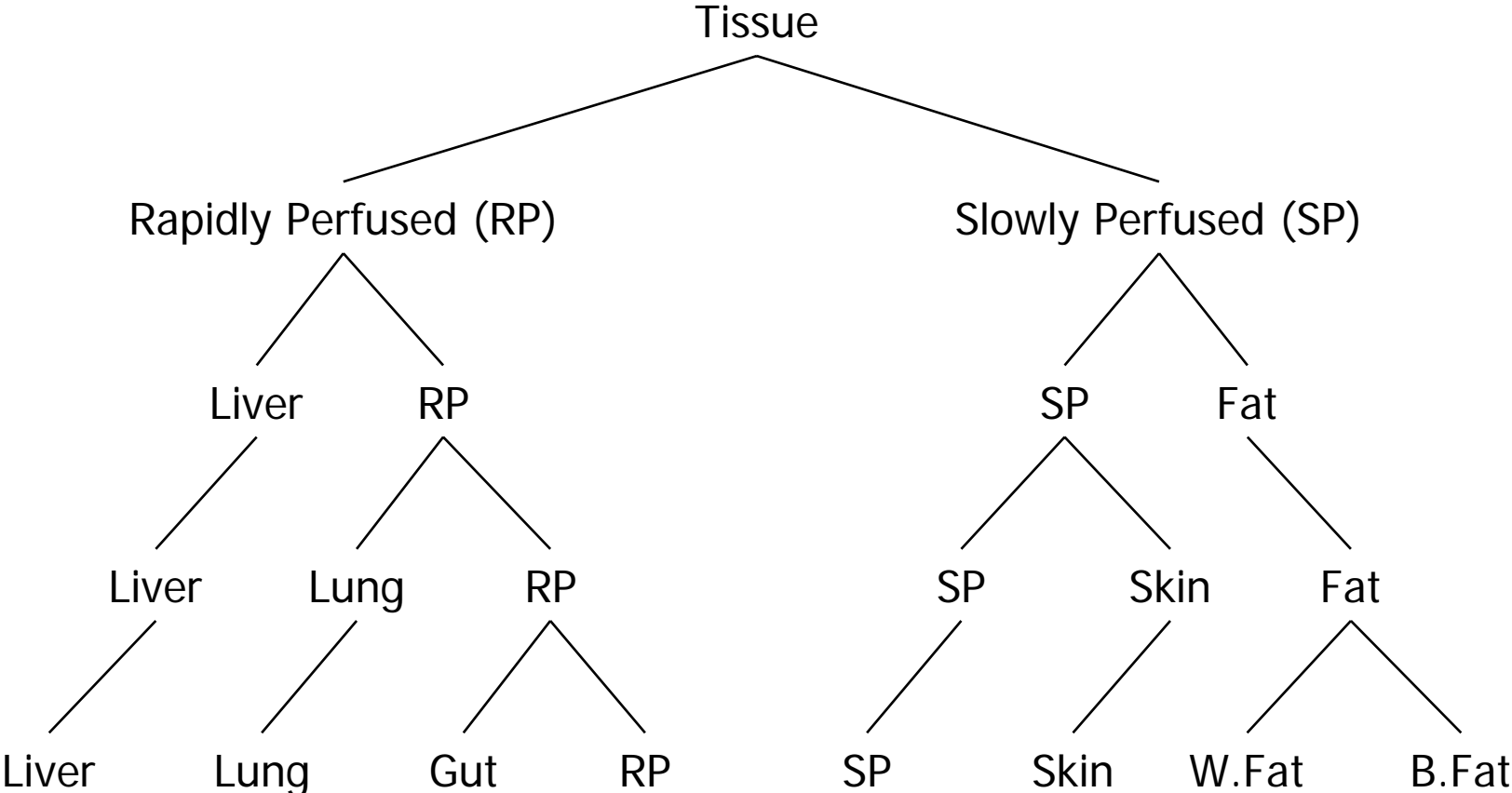
Structuring the Model:

- 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

— time 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 (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:

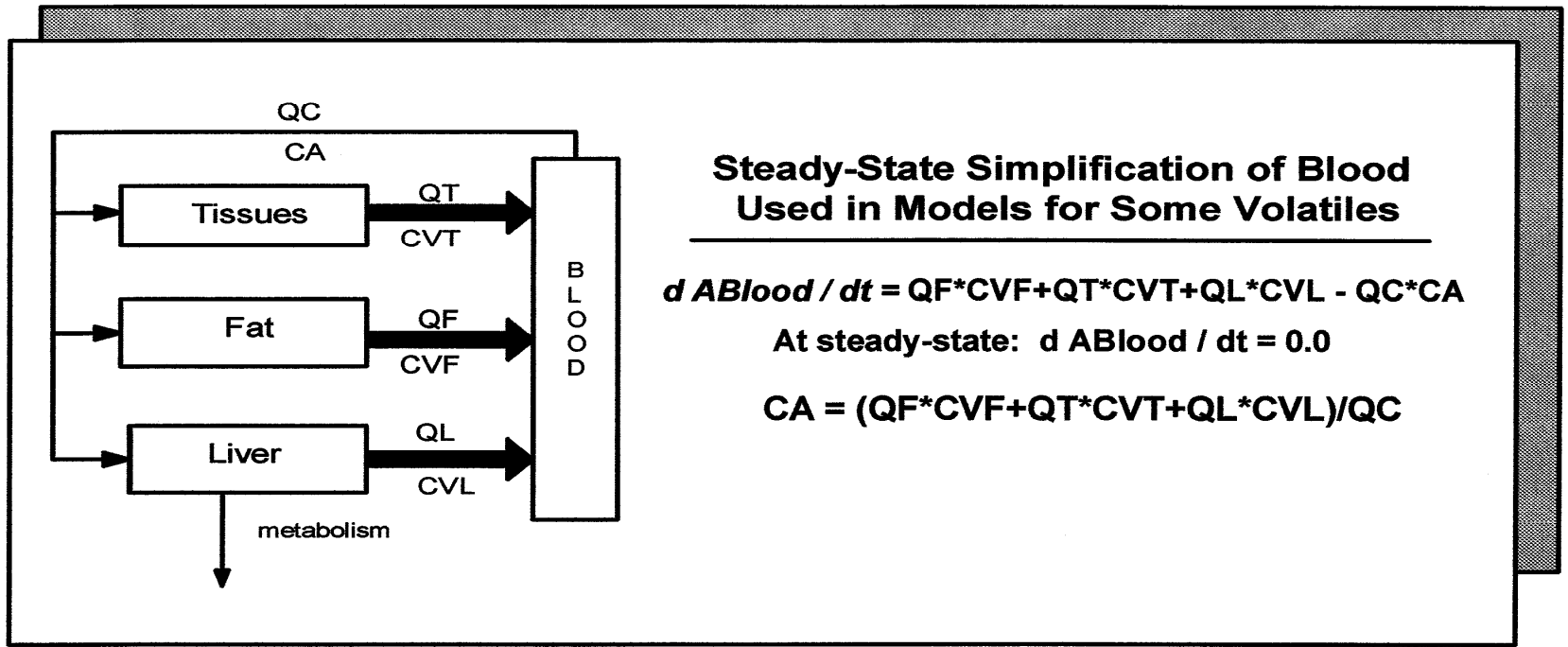
$$C_{VT} = C_T / P_T$$

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:

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

assuming steady state: $dA_B / dt = 0$

therefore:

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

Building the Model:

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:

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

and/or

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

(saturable)

PBPK modeling conventions:

“Ramseyan” Code for the Liver

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

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

$$RAO = KA * MR$$

$$AL' = RAL$$

$$init AL = 0.0$$

$$CL = AL / VL$$

$$CVL = CL / PL$$

$$AUCL' = CL$$

$$init AUCL = 0.0$$

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:

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

- Diffusion limited compartment

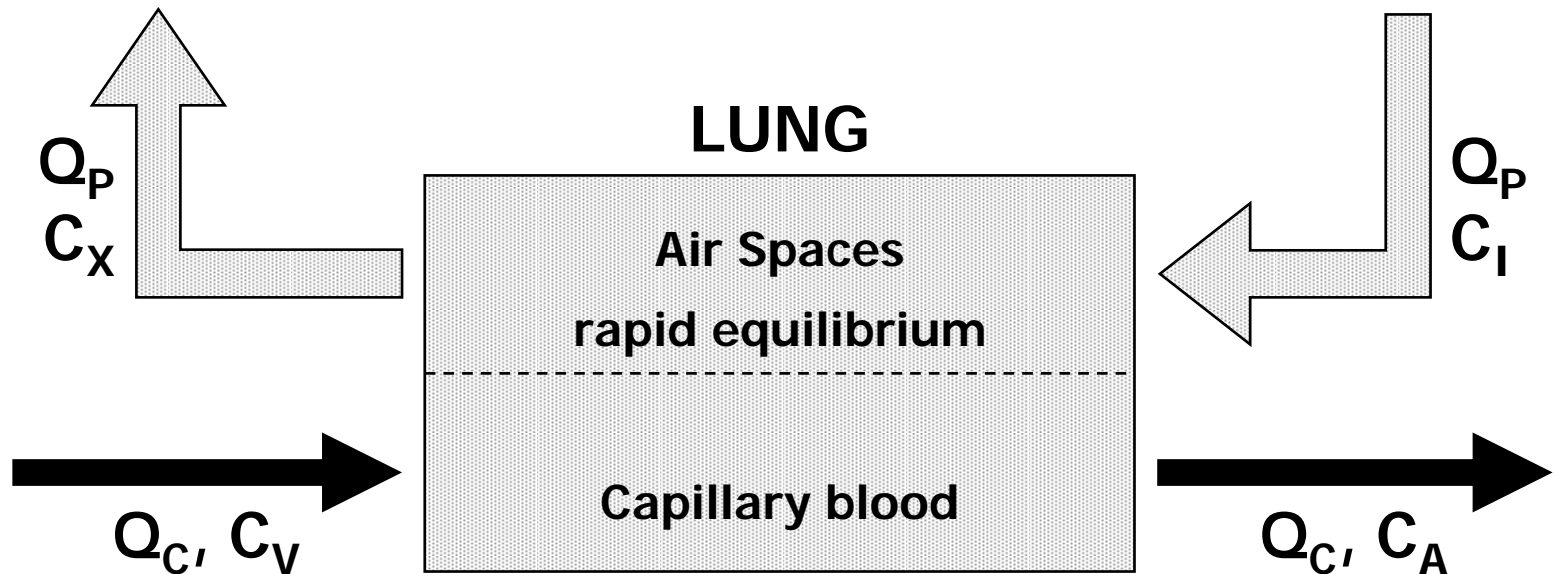
$$VdC_I / dt = PA \bullet (C_E - (C_I / P_I))$$

Building the Model:

Uptake Routes

- inhalation
- drinking water
- oral gavage
- intravenous
- intraperitoneal
- dermal

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:

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

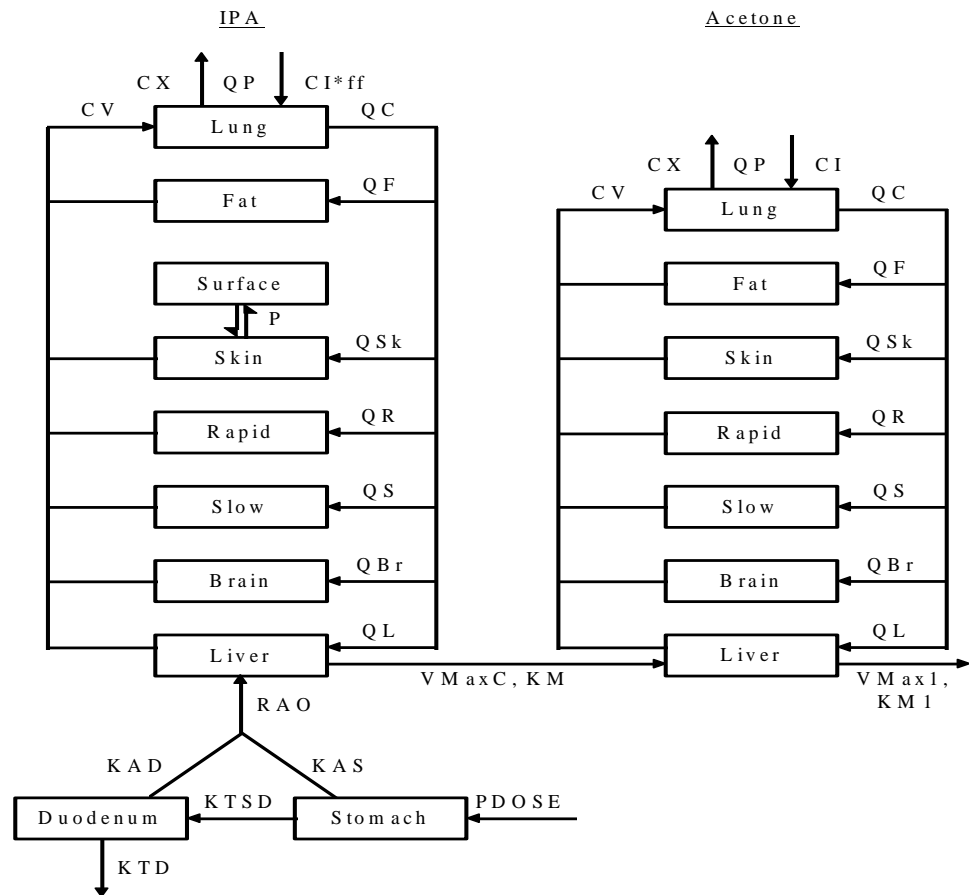
One-compartment Dermal Structure

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

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

- 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

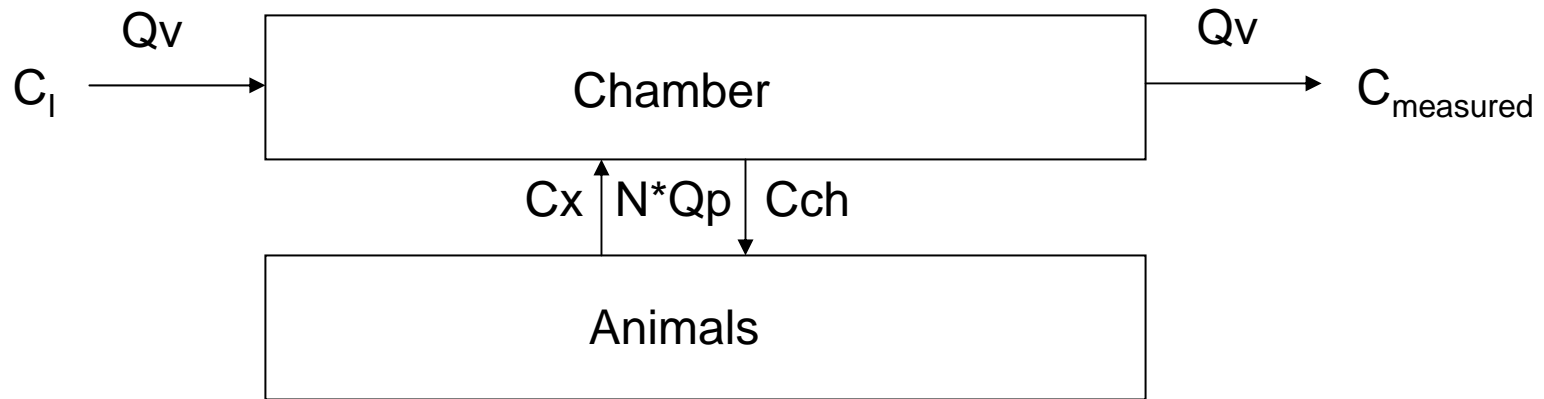
Metabolite Compartments

- 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

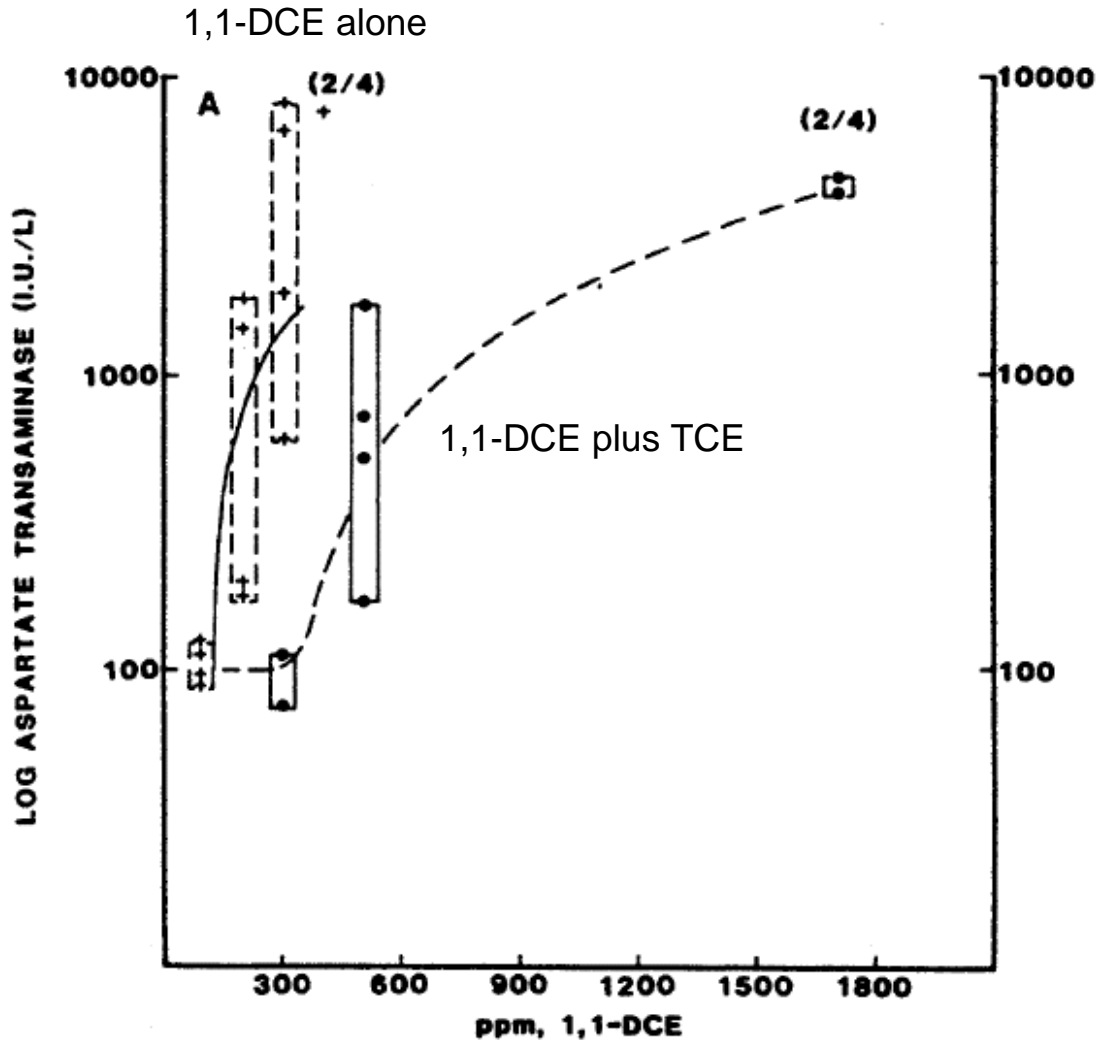
and C_{ch} = the chamber concentration

Building the Model:

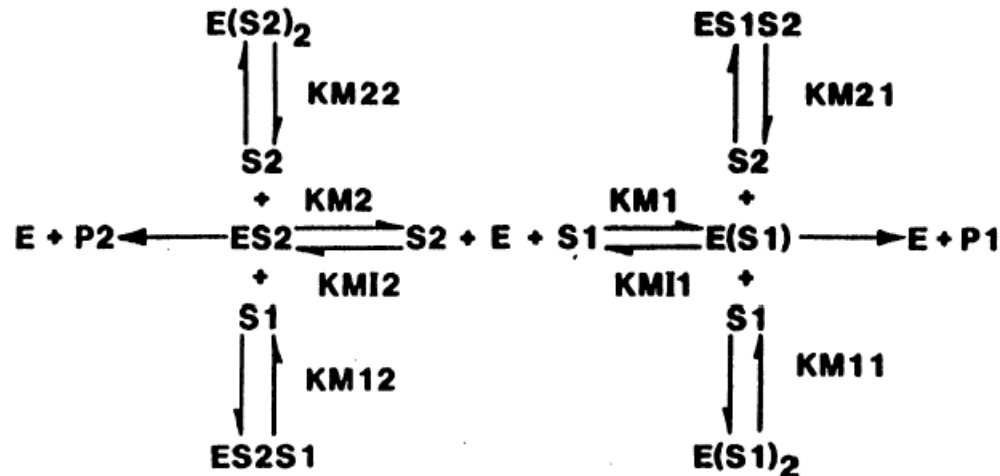
Other complications

- 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



$$\frac{V_L d C_{L1}}{dt} = \frac{dAMT_{L1}}{dt} =$$

$$(Q_L C_{A1}) - (Q_L C_{V_{L1}}) - \frac{V_{max1} \cdot C_{V_{L1}}}{K_m(T_1) + C_{V_{L1}}(T_2)}$$

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

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

INHIBITORY INTERACTIONS

For inhibition of metabolism of compound B by compound T:

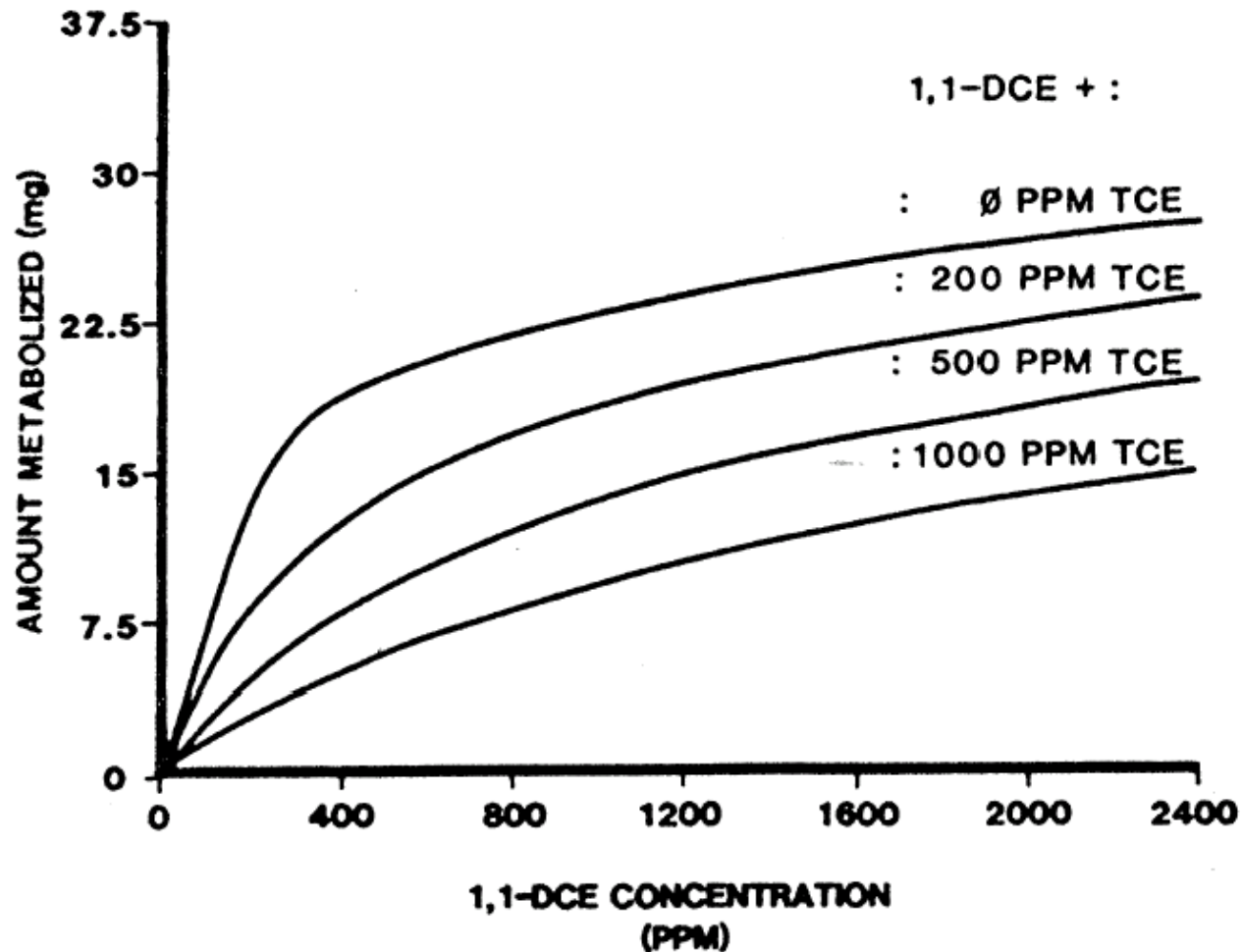
COMPETITIVE:
$$\frac{dAMT_B}{dt} = (Q C_{aB}) - (Q C_{vB}) - \frac{V_{maxB} C_{vB}}{K_{mB}(1 + C_{vT}/K_{ITB}) + C_{vB}}$$

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

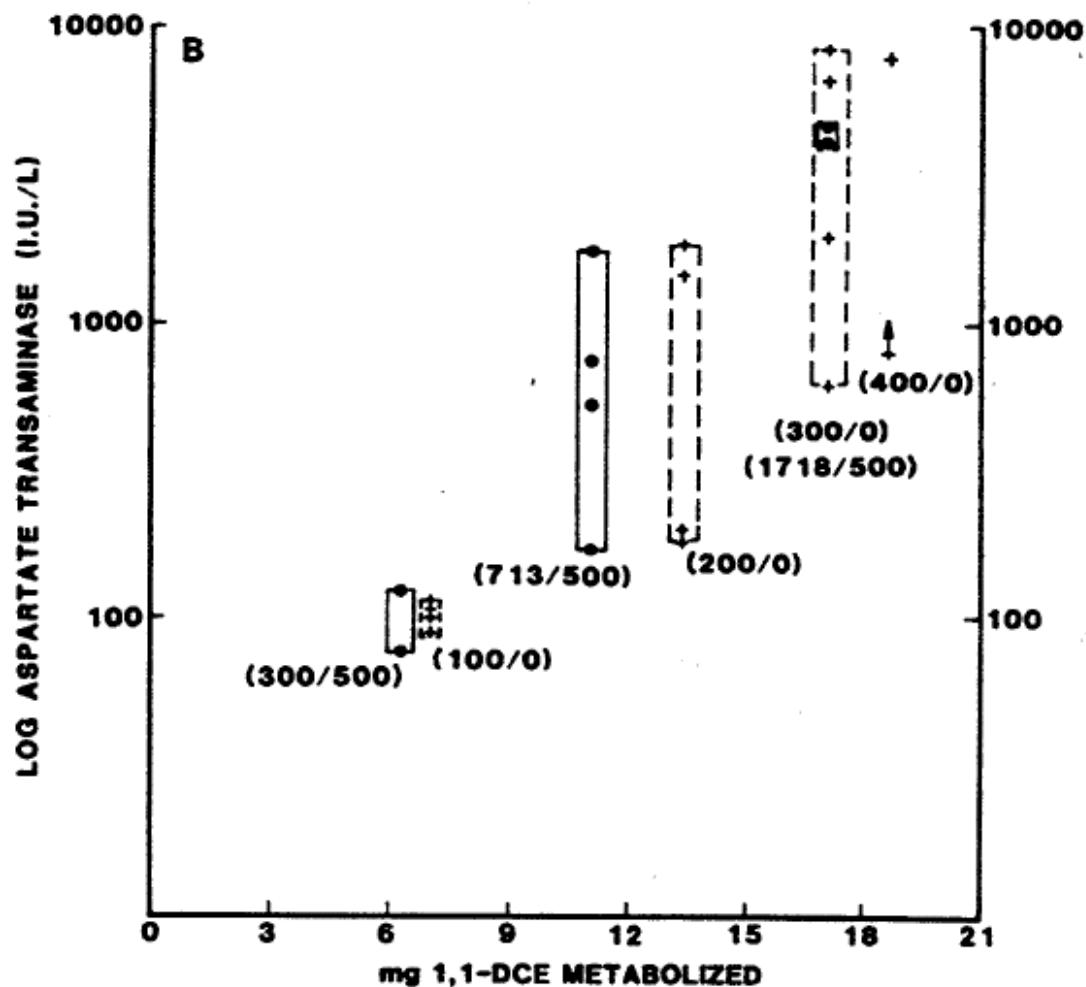
UNCOMPETITIVE:
$$\frac{dAMT_B}{dt} = (Q C_{aB}) - (Q C_{vB}) - \frac{V_{maxB} C_{vB}}{K_{mB} + C_{vB}(1 + C_{vT}/K_{ITB})}$$

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)

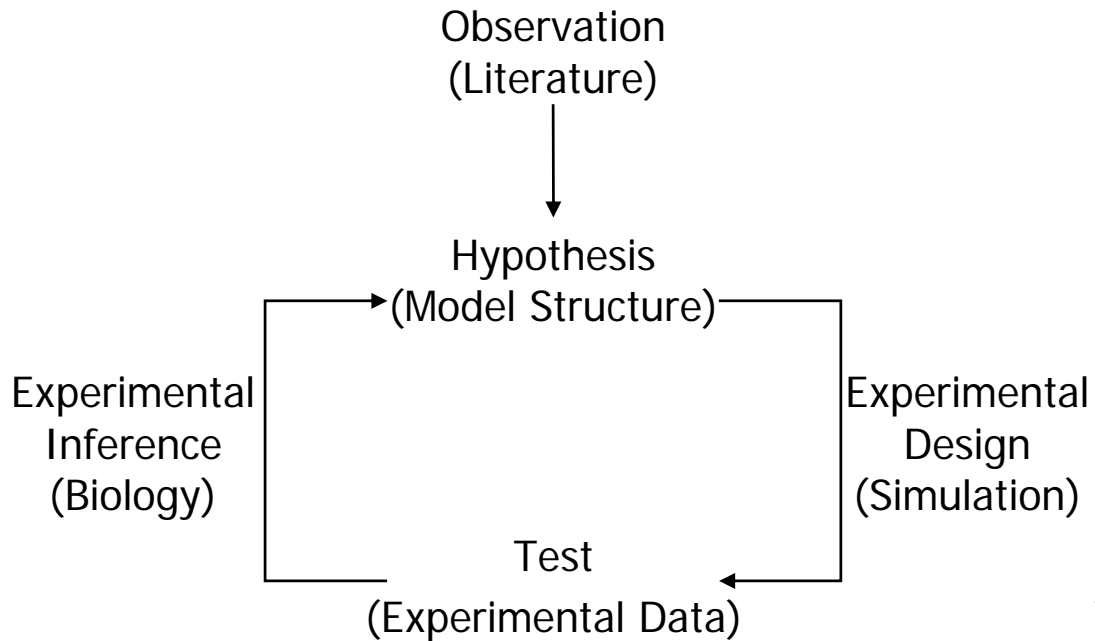


Verification: The Toxicity of 1,1-DCE Is Proportional to the Predicted Amount of 1,1-DCE Metabolized, with or without Co-exposure to TCE



Summary: PBPK Model Development

Scientific Method



Analysis

