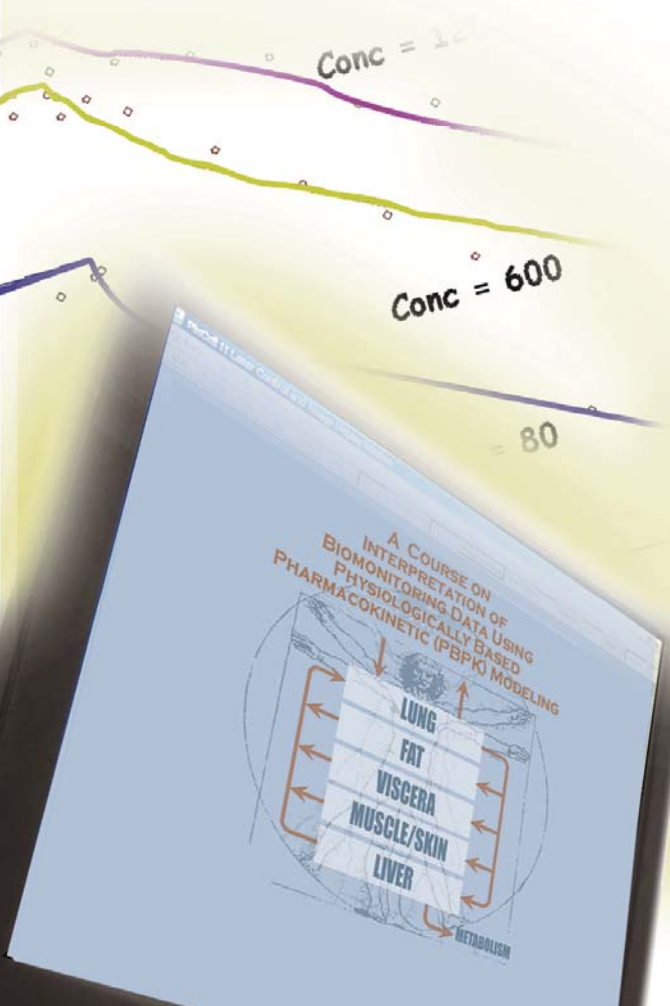


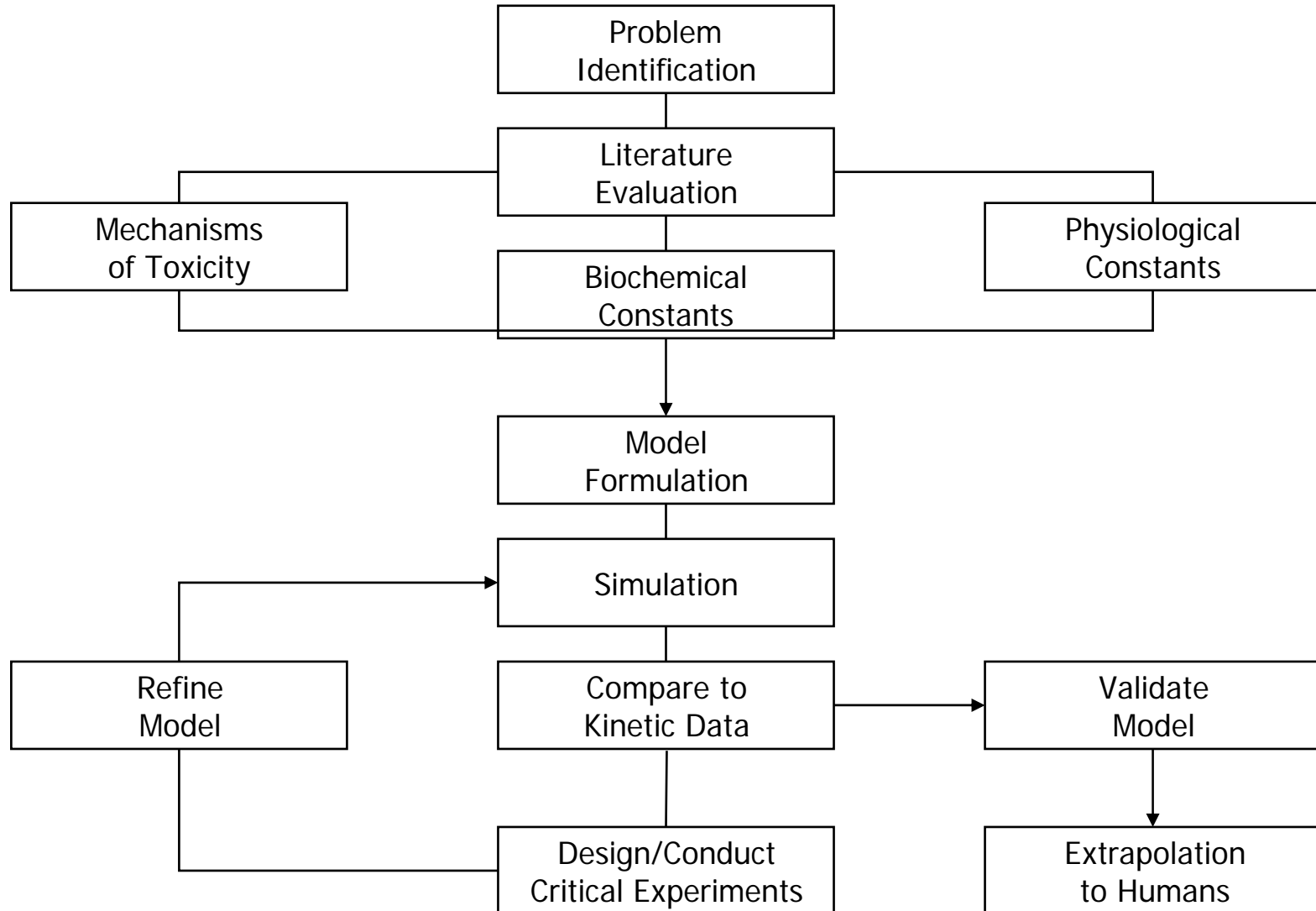
# PBPK Modeling: Parameter Estimation

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

February 11 – February 15, 2008



# Approach for Developing a PBPK Model



# Parameterizing the Model:

Allometry:  $Y = a \times X^b$

In this case,  $Y$  is a PB-PK parameter and  $X$  is the body weight

The constants  $a$  and  $b$  are usually derived empirically from cross-species comparisons but are routinely applied for within-species (growth) scaling as well

Allometric scaling is only an approximation, and is not a substitute for the use of species-specific parameters

# Parameterizing the Model:

- Allometry:  $Y = a \times X^b$ 
  - Volumes:  $b \cong 1$   $VF = VFC \times BW$   
(units: L or kg)
  - Flows:  $b \cong 0.75$   $QC = QCC \times BW^{0.75}$   
(units: L/hr)  $QP = QPC \times BW^{0.75}$
  - Clearances:  $b \cong 0.75$   $Vmax = Vmaxc \times BW^{0.75}$   
(units: L/hr) (assuming Km is not scaled)
  - Rate constants:  $b \cong -0.25$   $KF = KFC / BW^{0.25}$   
(units: hr<sup>-1</sup>) (Clearance = KF x VL)

# Parameterizing the Model:

## Physiological Parameters

- Physiological literature  
“resting” values
- Modeling literature  
“ad hoc” estimates
- Direct measurement  
body weight  
fat content  
ventilation rate (activity)

# Typical Physiological Parameters for Pharmacokinetic Models

	Units	Mouse	Rat	Monkey	Human
<b>Tissue Volumes</b>					
Body Weight	(kg)	0.02	0.3	4.0	80.0
Body Water	(fraction of BW)	0.65	0.65	0.65	0.65
Plasma	"	0.04	0.04	0.04	0.04
RBCs	"	0.03	0.03	0.03	0.03
Muscle	"	0.34	0.36	0.48	0.33
Skin	"	0.17	0.195	0.11	0.11
Fat	"	0.10 <sup>d</sup>	0.07 <sup>d</sup>	0.05 <sup>d</sup>	0.21 <sup>d</sup>
Liver	"	0.046	0.037	0.027	0.023
Gut Tissue	"	0.031	0.033	0.045	0.045
Other Organs	"	0.049	0.031	0.039	0.039
Intestinal Lumen	"	0.054	0.058	0.053	0.053

<sup>d</sup> Varies substantially (lower in young animals, higher in older animals)

# Typical Physiological Parameters for Pharmacokinetic Models

	Units	Mouse	Rat	Monkey	Human
<b>Ventilation</b>					
Alveolar	(L/hr/kg <sup>0.75</sup> ) <sup>a</sup>	29.0 <sup>b</sup>	15.0 <sup>b</sup>	15.0 <sup>b</sup>	15.0 <sup>b</sup>
<b>Blood Flows</b>					
Total	(L/hr/kg <sup>0.75</sup> ) <sup>a</sup>	16.5 <sup>c</sup>	15.0 <sup>c</sup>	15.0 <sup>c</sup>	15.0 <sup>c</sup>
Muscle	(fraction of total)	0.18	0.18	0.18	0.18
Skin	"	0.07	0.08	0.06	0.06
Fat	"	0.03	0.06	0.05	0.05
Liver (arterial)	"	0.035	0.03	0.065	0.07
Gut (portal)	"	0.165	0.18	0.185	0.19
Other Organs	"	0.52	0.47	0.46	0.45

<sup>a</sup> Scaled allometrically:  $QC = QCC * BW^{0.75}$

<sup>b</sup> Varies significantly with activity level (range: 15-40)

<sup>c</sup> Varies with activity level (range: 15-20)

# Parameterizing the Model:

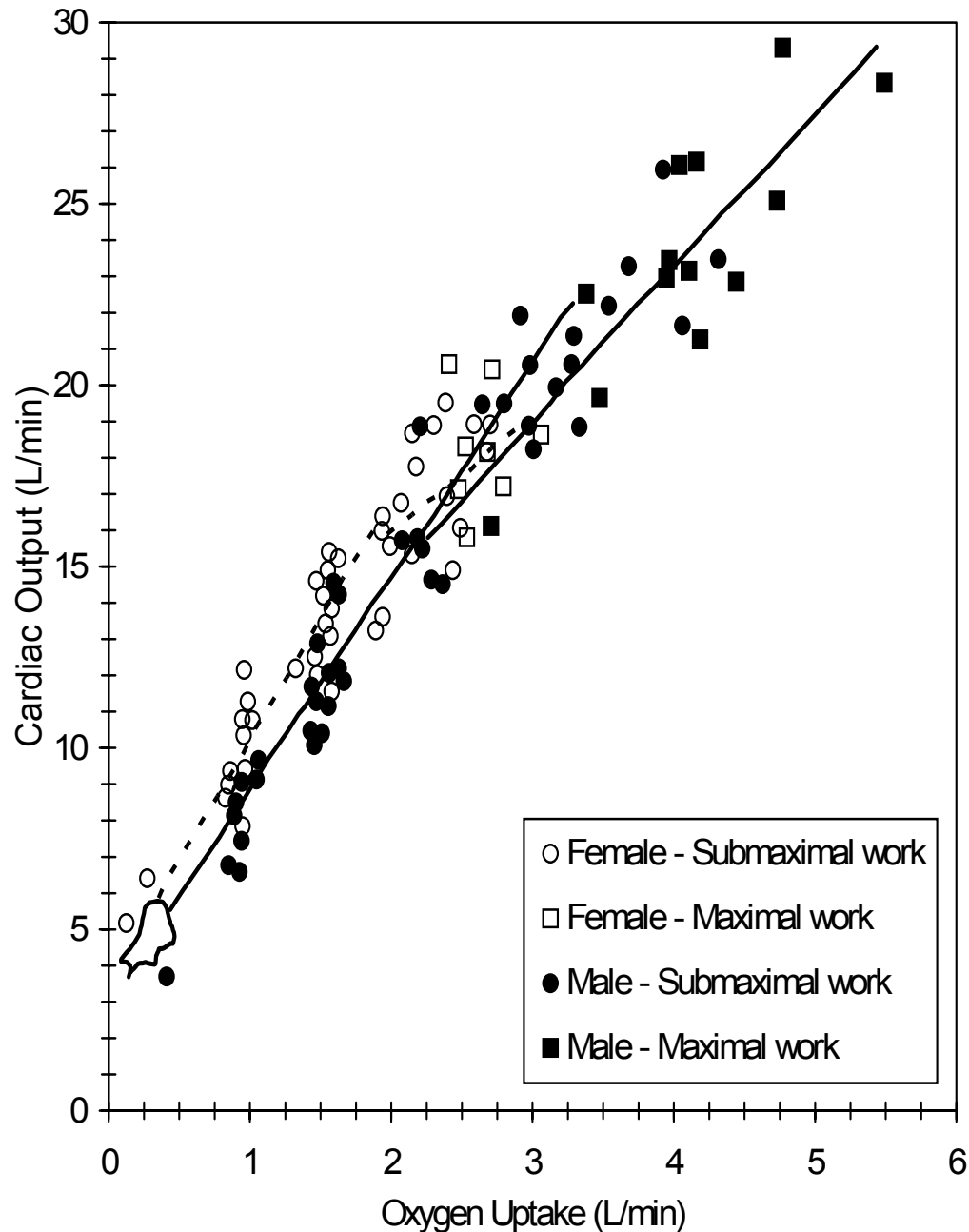
## Maintaining mass balance

**The blood flows to the tissues **MUST** add up to the total blood flow, i.e.:**

$$\Sigma Q_i = Q_C$$

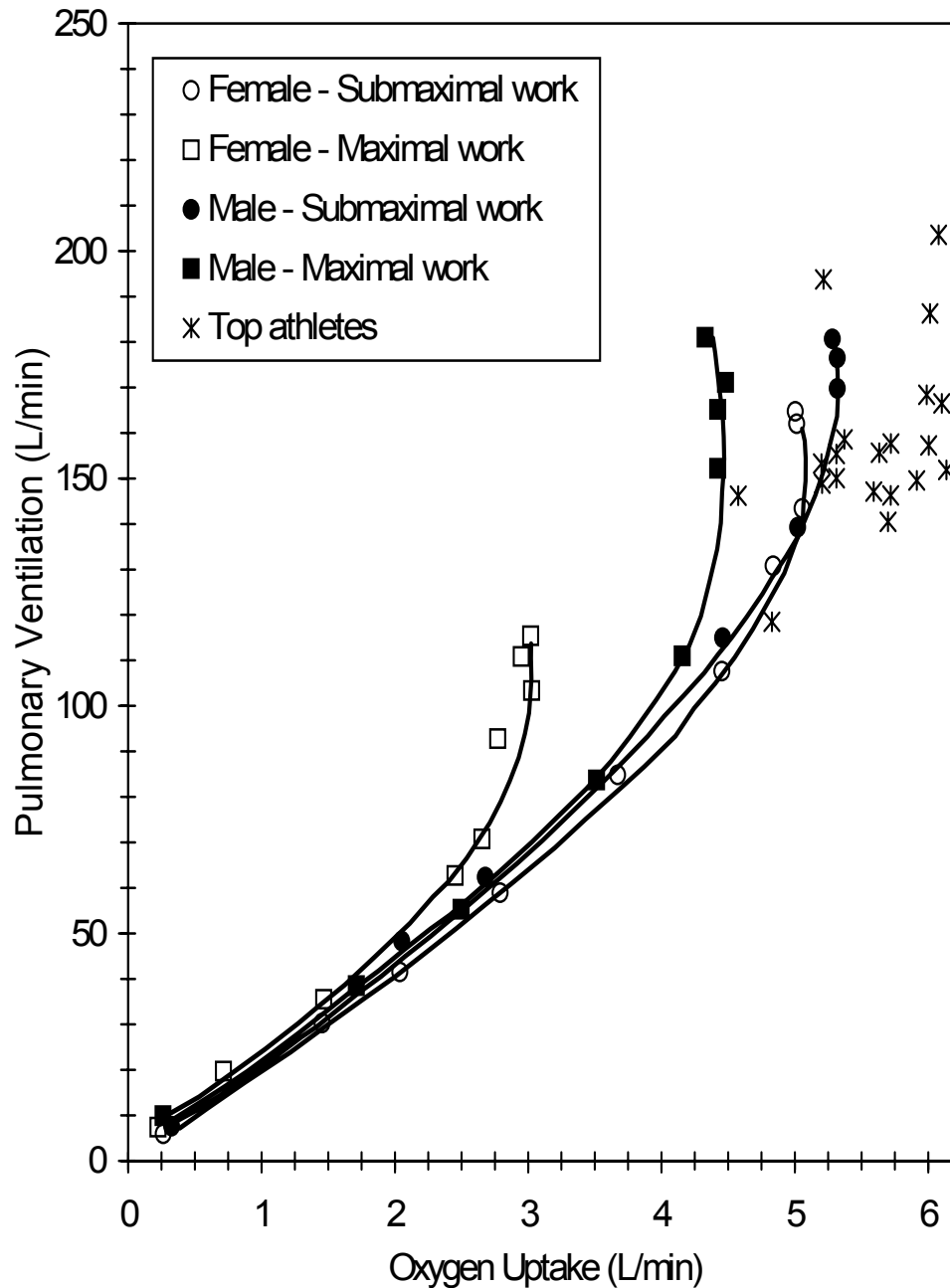
Getting that déjà vu feeling?

You'll probably get it again the first time one of your models crashes. (Hint, hint.)



**Cardiac output at rest and during exercise** in relation to oxygen uptake from 23 subjects sitting on a bicycle ergometer. Regression lines (broken lines for women) were calculated for experiments where the oxygen uptake was (1) below 70 percent and (2) above 70 percent of the individual's maximum. (From P.-O. Åstrand *et al.*, 1964)

(Figure is reproduced from I. Åstrand, 1983)



## Pulmonary ventilation at rest and during exercise

(running or cycling). Four individual curves are presented. Several work loads gave the same maximal oxygen uptake. Work time from 2 to 6 minutes. Stars denote individual values for top athletes measured when maximal oxygen uptake was attained. (Data from Saltin and P.-O. Åstrand, 1967.) Individuals with maximal oxygen uptake of 3 L/min or higher usually fall within the shadowed area. Note the wide scattering at high oxygen uptakes.

(Figure is reproduced from I. Åstrand, 1983)

# Effect of Activity on Pharmacokinetic Parameters and Relative Cancer Risk for Methylene Chloride <sup>a</sup>

Parameter	Flow Rate (L/min)	
	Rest	Light Work
Alveolar Ventilation	7.0	17.4
Cardiac Output	5.2	8.4
Liver Blood Flow	1.6	1.7
Relative Lung Cancer Risk <sup>b</sup>	1	1.8

<sup>a</sup> Dankovic and Bailor, 1994

<sup>b</sup> Based on the PBPK model of Andersen *et al.*, 1987

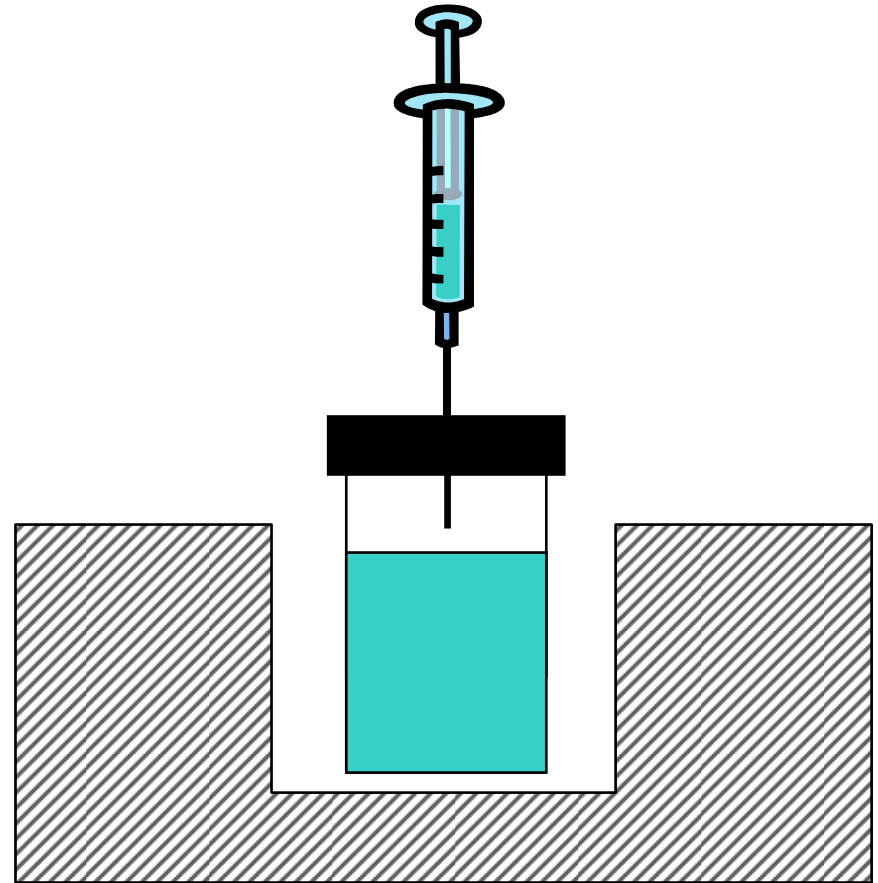
# Partition Coefficients (Volatiles: Vial Equilibrium)

## Measure

- Blood/Air
- Tissue/Air

## Calculate

- Tissue/Blood



# Parameterizing the Model:

## Experimental Determination

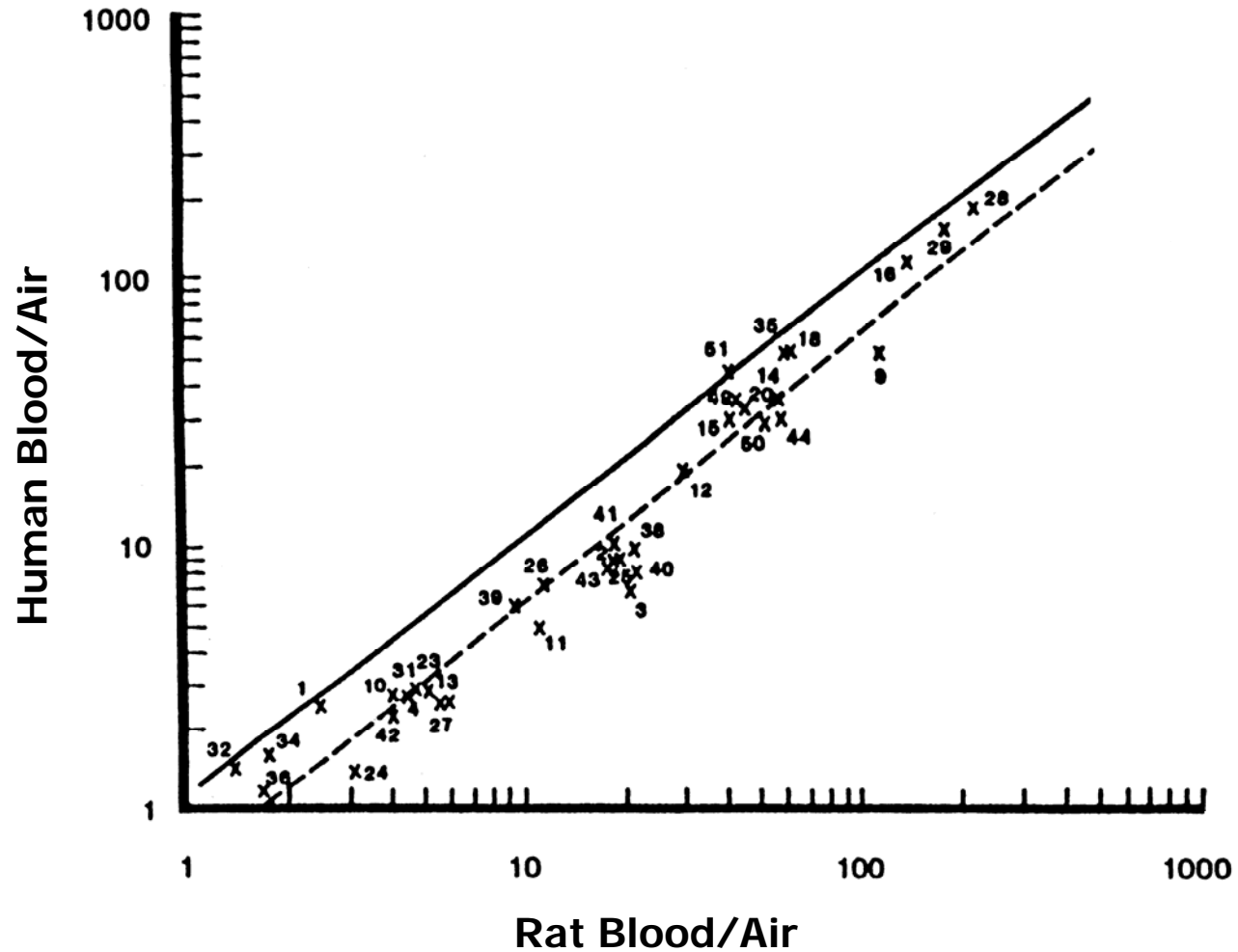
### – Partition Coefficients:

- in vitro: vial equilibration ( $C_{\text{Tissue}}/C_{\text{air}}$ )  
dialysis ( $C_{\text{Tissue}}/C_{\text{buffer}}$ )  
ultrafiltration ( $C_{\text{Tissue}}/C_{\text{buffer}}$ )
- in vivo: steady state ( $C_{\text{Tissue}}/C_{\text{Blood}}$ )

### – Metabolism:

- in vitro: tissue homogenate  
cell suspension  
tissue slice  
cell gas uptake
- in vivo: direct measurement of metabolites

# Partition Coefficients of Volatile Chemicals

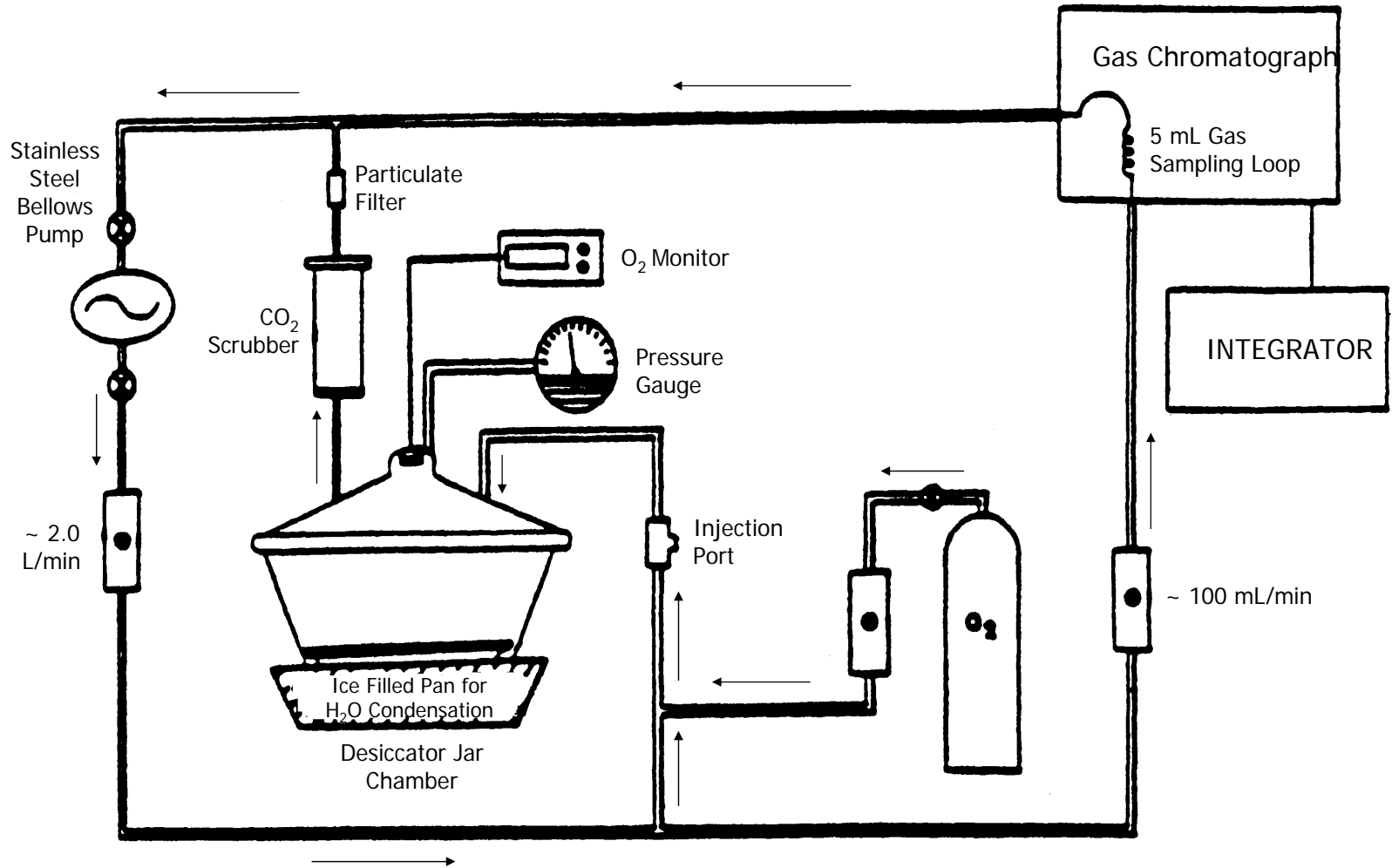


# Parameterizing the Model:

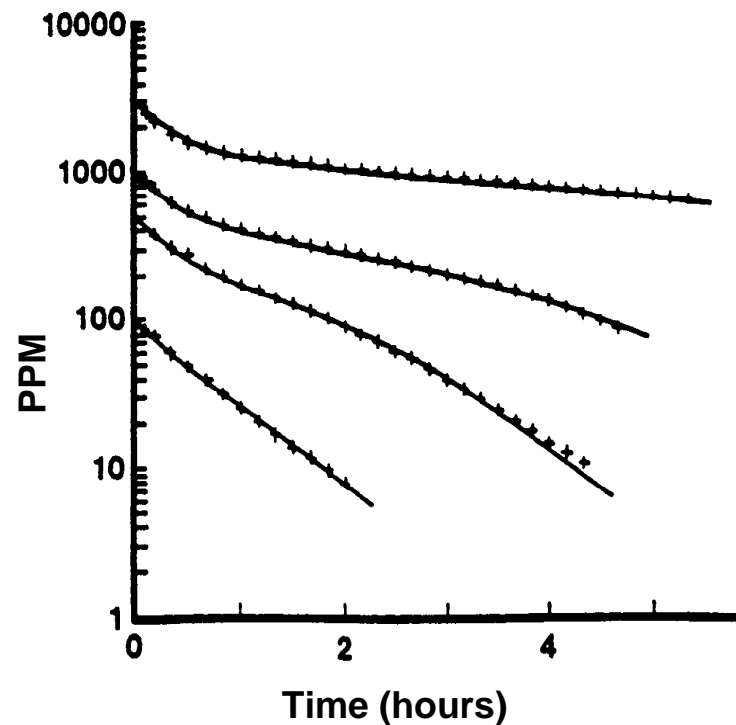
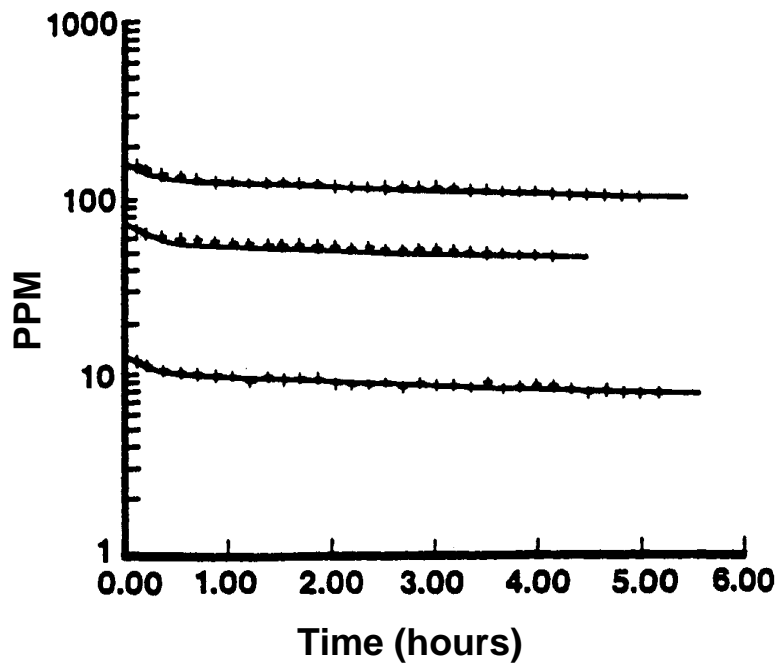
## Parameter Estimation by Data Fitting

- Uptake
  - oral absorption
  - dermal permeability
- Distribution
  - partition coefficients
  - binding
- Metabolism
  - gas uptake chamber analysis
  - exhaled breath chamber analysis
  - iv dosing kinetic analysis
- Elimination
  - urinary excretion
  - enterohepatic recirculation

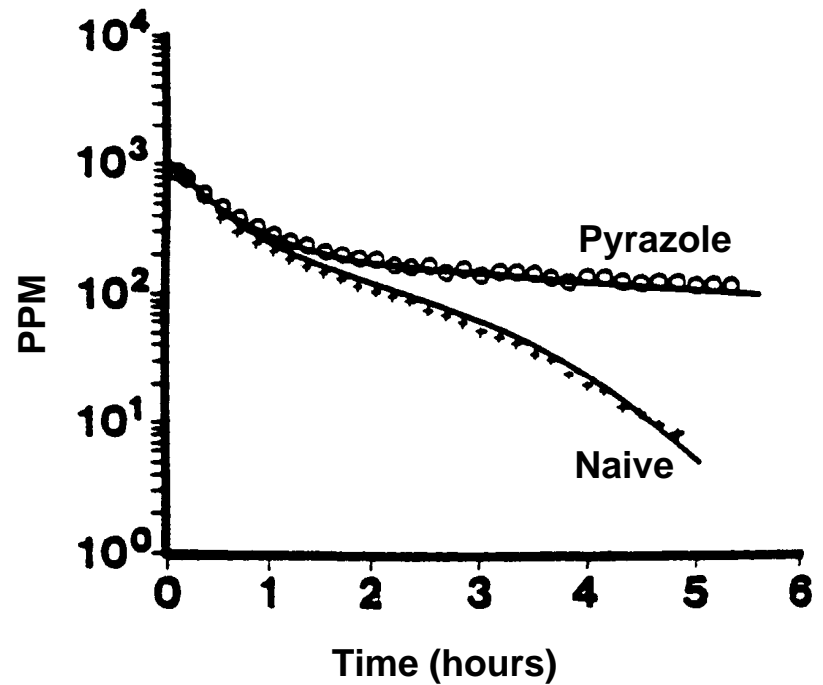
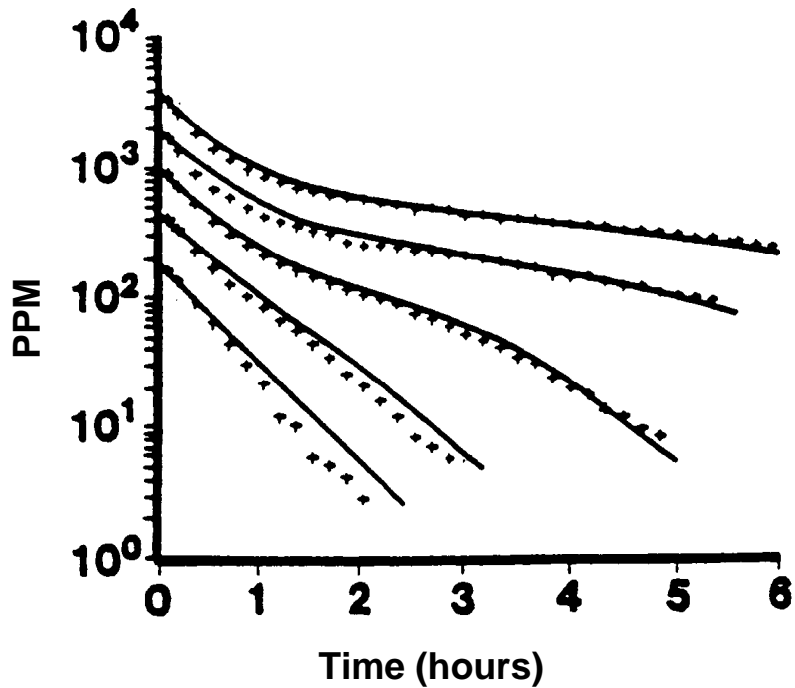
# Closed Chamber Gas Uptake Apparatus



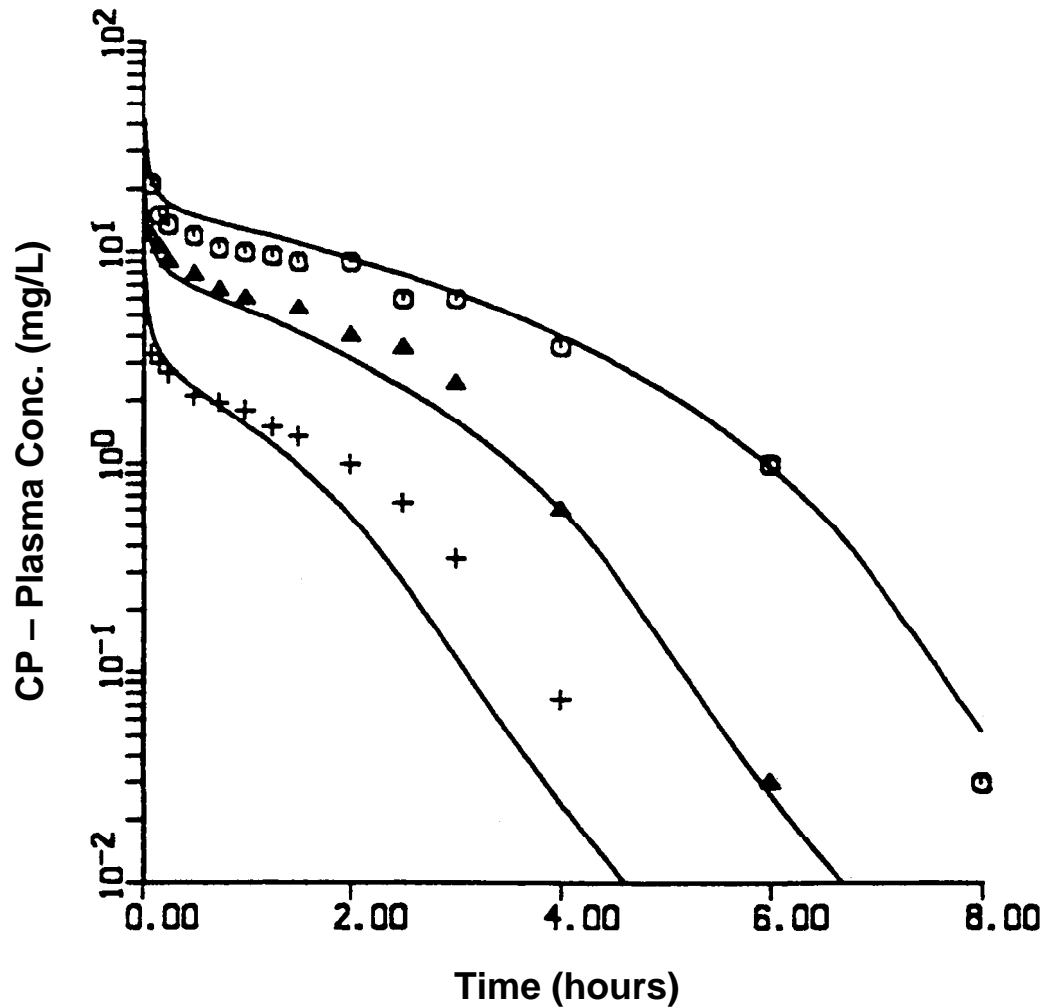
# Dihalomethane: Closed Chamber Gas Uptake Studies



# Bromochloromethane Closed Chamber Gas Uptake Studies



# All-Trans Retinoic Acid Monkey IV – 5, 2.5, 1 mg/kg



# Parameterizing the Model:

## Back to the Drawing Board: Model Error

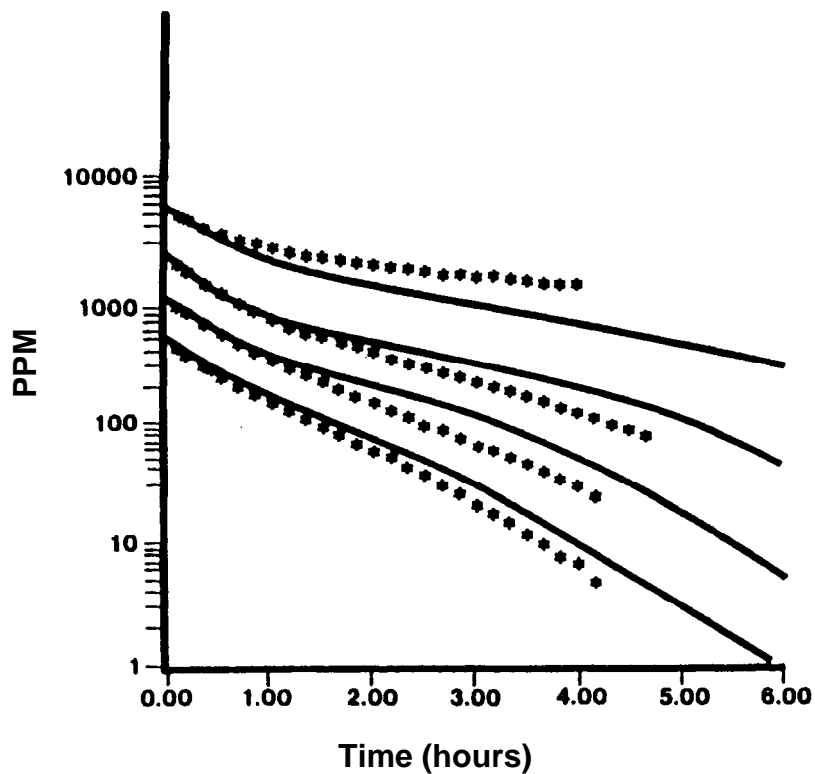
- “Models are often most informative when they fail”
  - Systematic discrepancies between model predictions and data may indicate that a biological determinant has been overlooked
  - The nature of the discrepancies may suggest an improved kinetic hypothesis / model structure
- Examples:
  - Cofactor (e.g., GSH) depletion
  - Inhibition / induction of metabolism
  - Saturable / inducible binding
  - Active transport
  - Enterohepatic recirculation



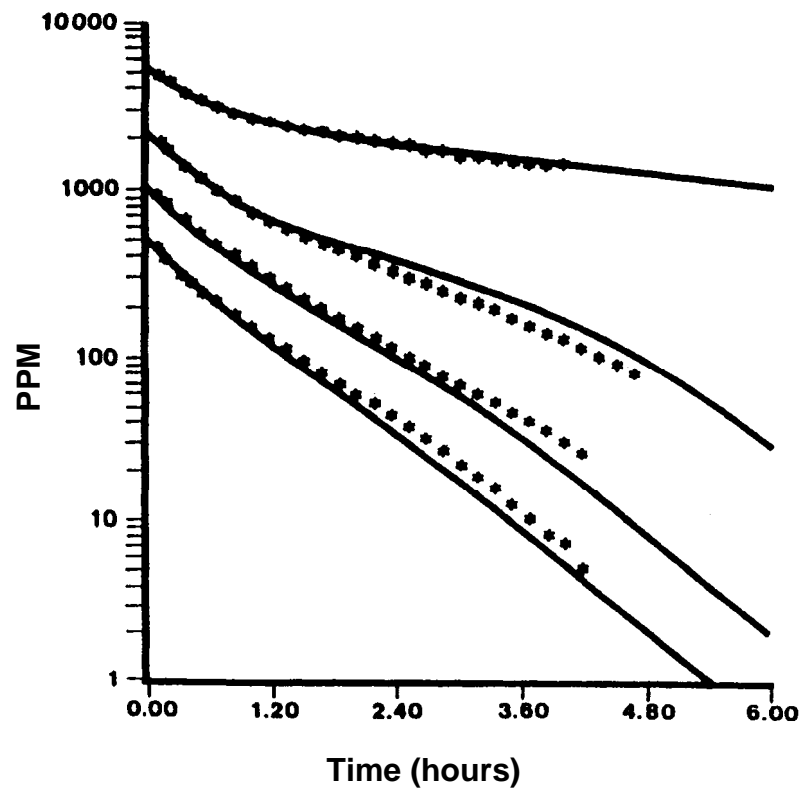
# Revising the Model: Allyl Chloride

## Step 2: Evaluating the Alternative Structure

Saturable Oxidation – First Order Conjugation



Saturable Oxidation – GSH Depletion



# Revising the Model: Allyl Chloride

## Step 3: Verifying the Underlying Hypothesis

TABLE 1 Predicted Glutathione Depletion Caused by Inhalation Exposures to Allyl Chloride

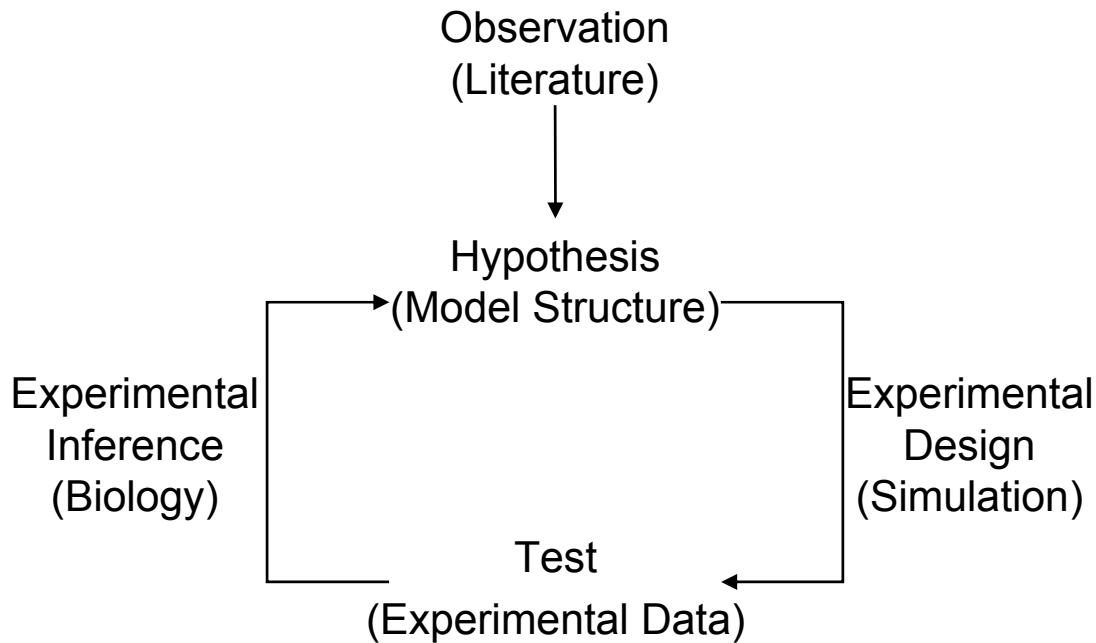
Concentration (ppm)	Depletion ( $\mu M$ )	
	Observed	Predicted
0	7,080 $\pm$ 120	7,088 <sup>a</sup>
10	7,290 $\pm$ 130	6,998
0	7,230 $\pm$ 80	7,238 <sup>a</sup>
100	5,660 $\pm$ 90	5,939
0	7,340 $\pm$ 180	7,341 <sup>a</sup>
1,000	970 $\pm$ 10	839
0	6,890 $\pm$ 170	6,890 <sup>a</sup>
2,000	464 $\pm$ 60	399

Note: Glutathione depletion data were graciously supplied by John Waechter, Dow Chemical Co., Midland, Mich.

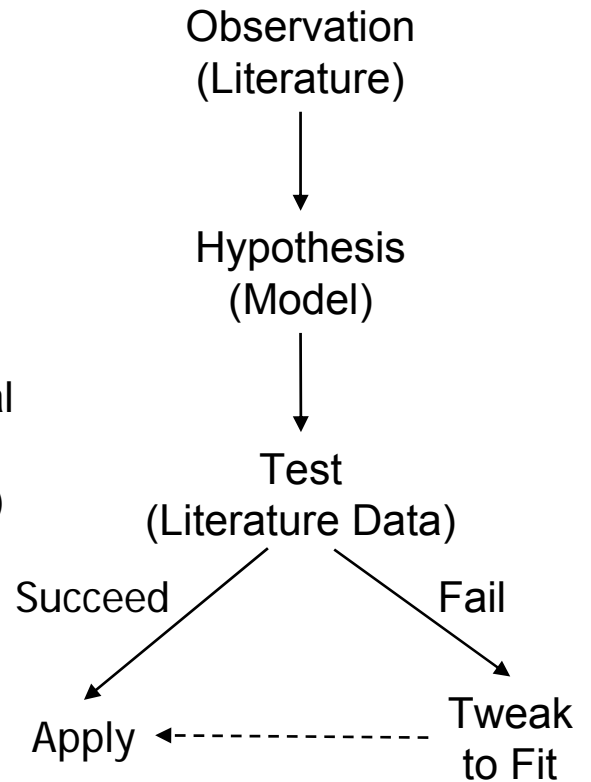
<sup>a</sup>For the purpose of this comparison, the basal glutathione consumption rate in the model was adjusted to obtain rough agreement with the controls in each experiment. This basal consumption rate was then used to simulate the associated exposure.

# Summary: PBPK Model Development

## Scientific Method



## Analysis



# Parameterizing the Model:

## Parameter Estimation Issues

- Identifiability
- Colinearity (correlation)
- Sensitivity

# Parameter Optimization: “Fitting the model to the data”

## Issues:

- Multiple parameter fitting
  - Colinearity
  - Local Minima
- Weighting

$$\text{ObjectiveFunction} = \frac{(\text{Predicted} - \text{Observed})^2}{\text{Observed}^{\gamma}}$$

- $\gamma =$  heteroscedasticity parameter
  - $\gamma = 0$  : absolute weighting
    - constant variance
    - linear plot
    - follows mass
  - $\gamma = 2$  : relative weighting
    - constant coefficient of variance
    - logarithmic plot
    - follows rates

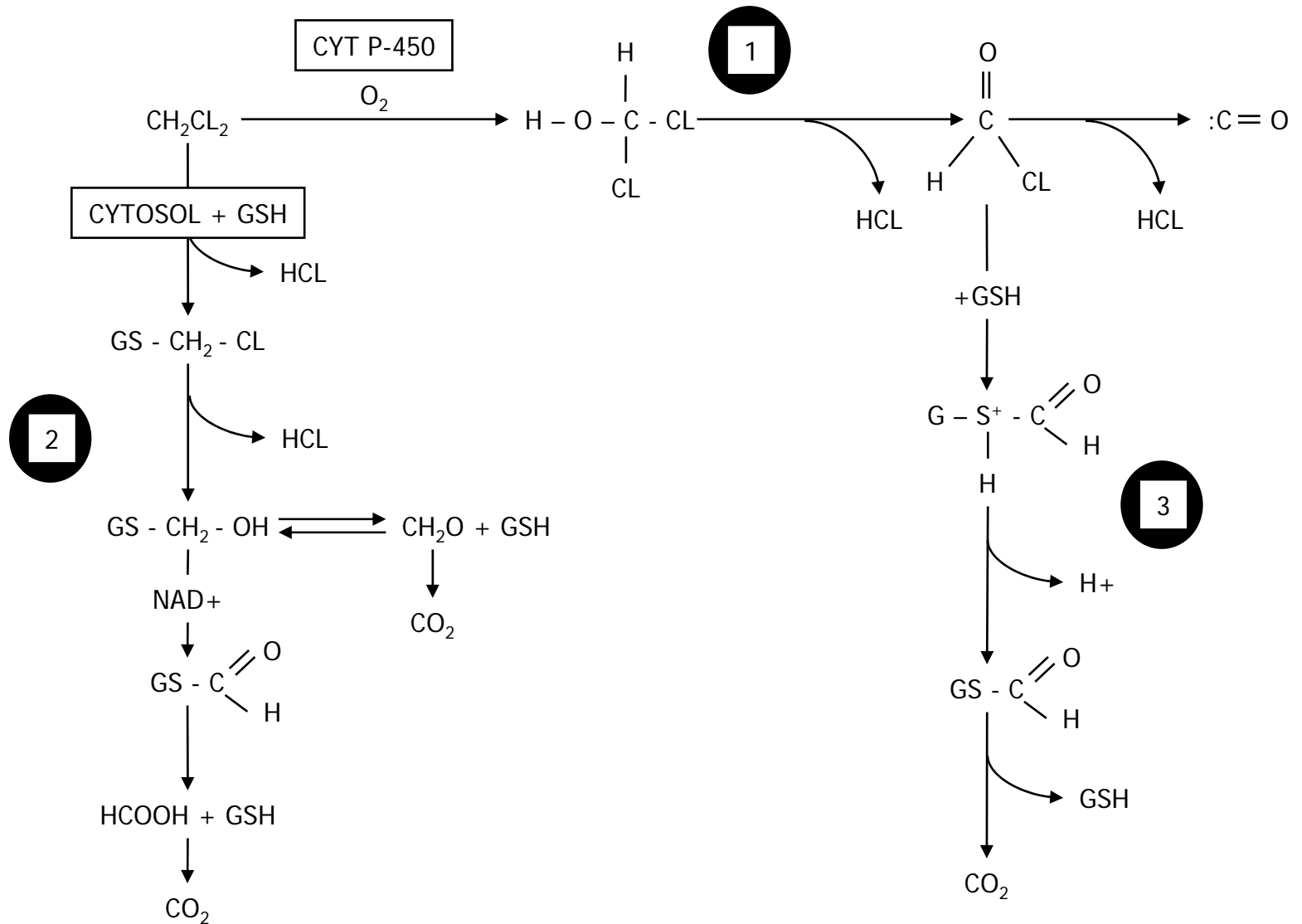
# Parameter Colinearity (Correlation)

Parameters in PBPK models are not always independent:

- VMaxC and KM
- VMaxC and KfC
- QCC and QPC

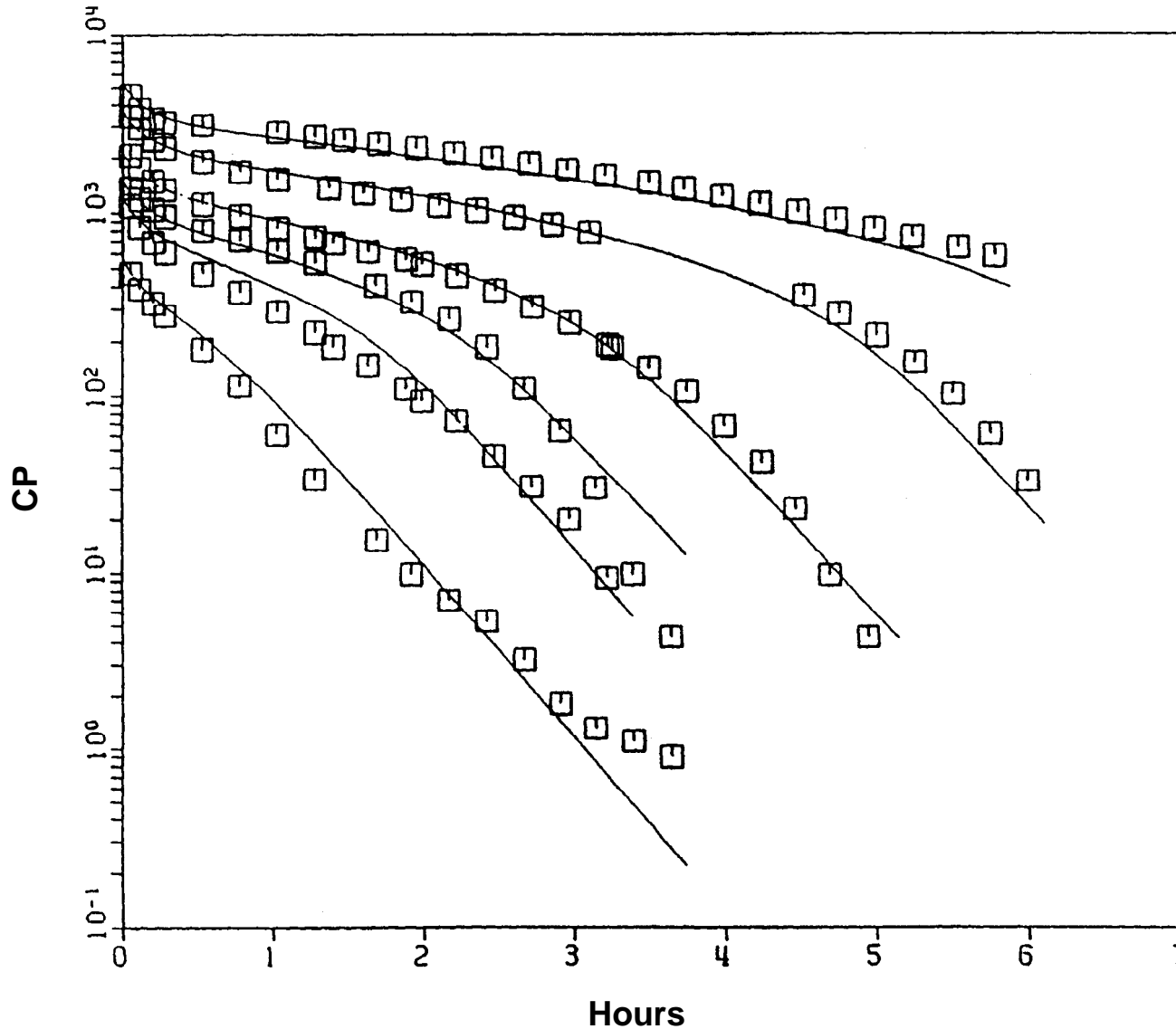
Ignoring parameter interdependence can distort sensitivity analysis, uncertainty analysis and parameter optimization

# Metabolism of Methylene Chloride

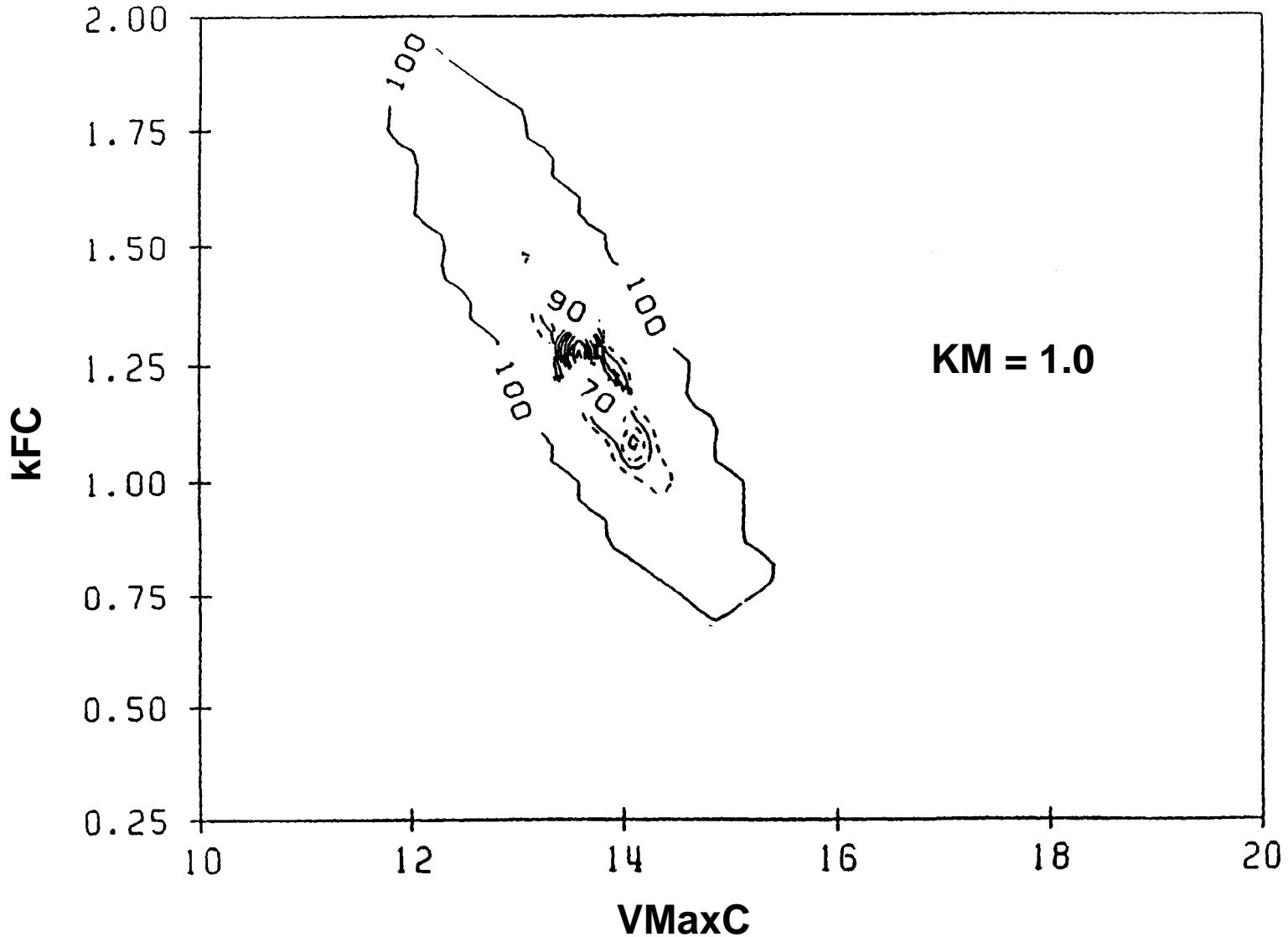


# Female Mice, Methylene Chloride

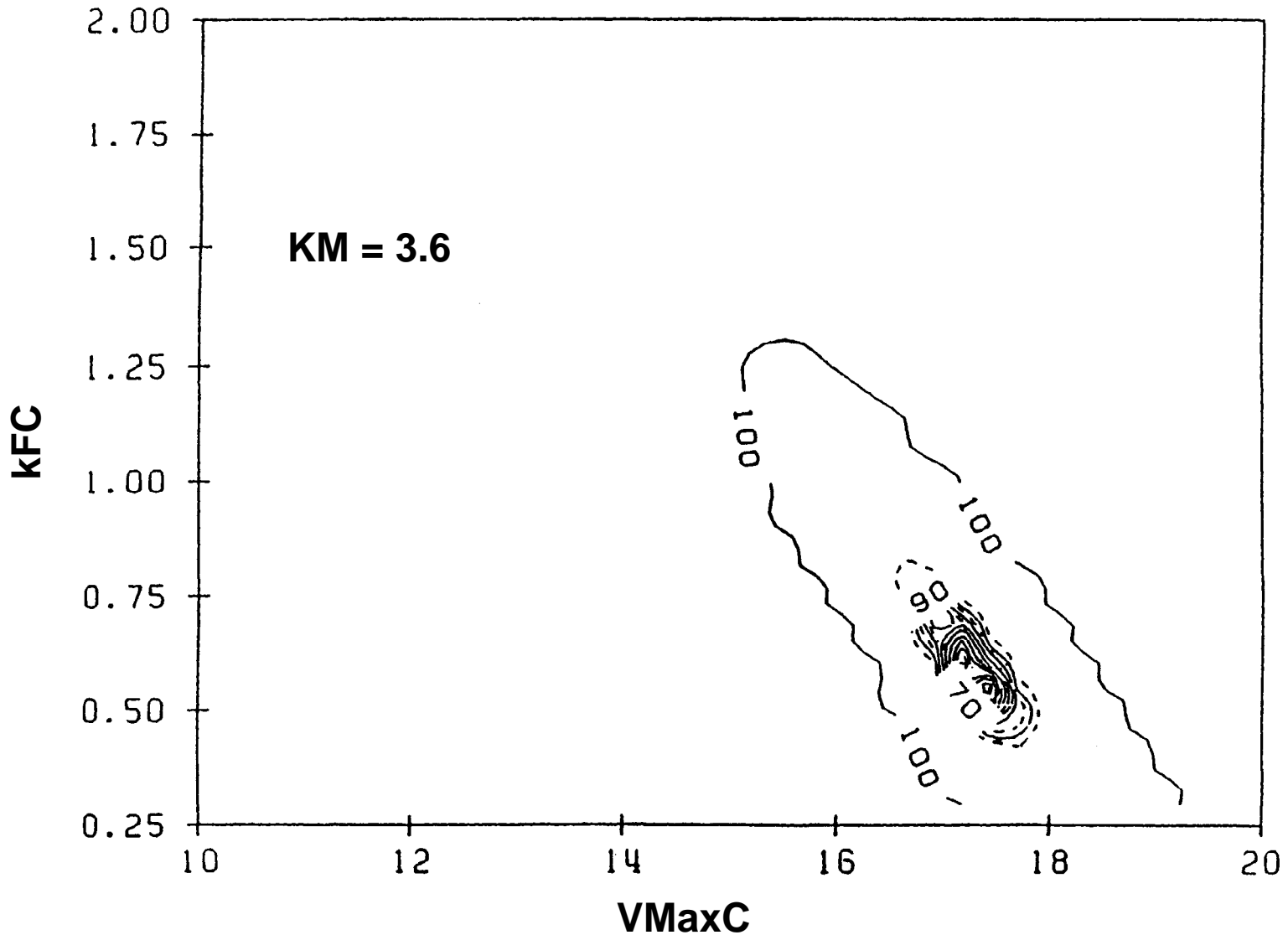
$V_{MaxC}=13.4$ ,  $KM=1.4$ ,  $k_{FC}=1.5$



# Contour Plot of Confidence Regions for Conditional Joint Probability

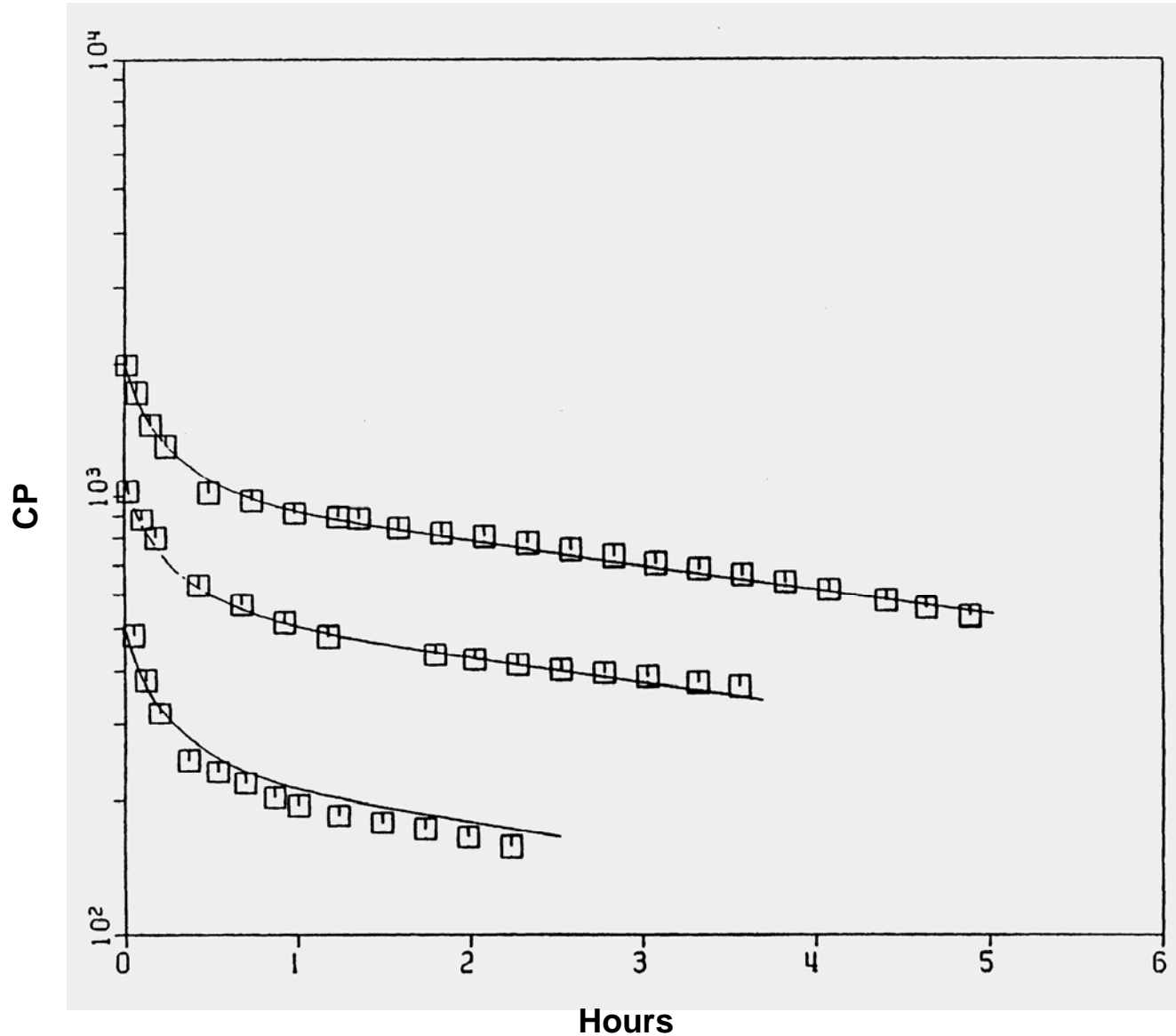


# Contour Plot of Confidence Regions for Conditional Joint Probability

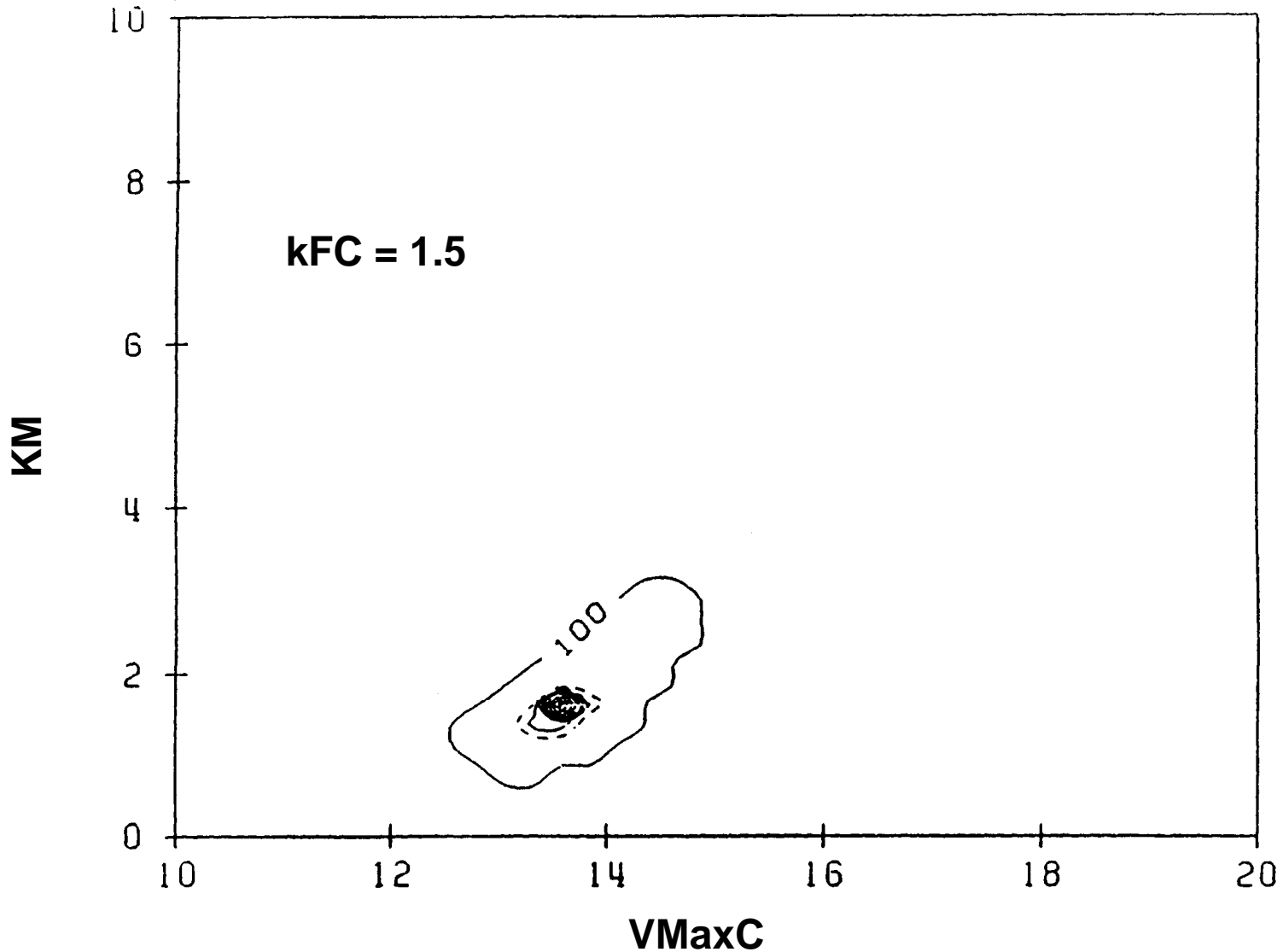


# Female Mice, Trans Pretreated

$V_{MaxC}=0.25$ ,  $KM=1.0$ ,  $k_{FC}=1.57$



# Contour Plot of Confidence Regions for Conditional Joint Probability

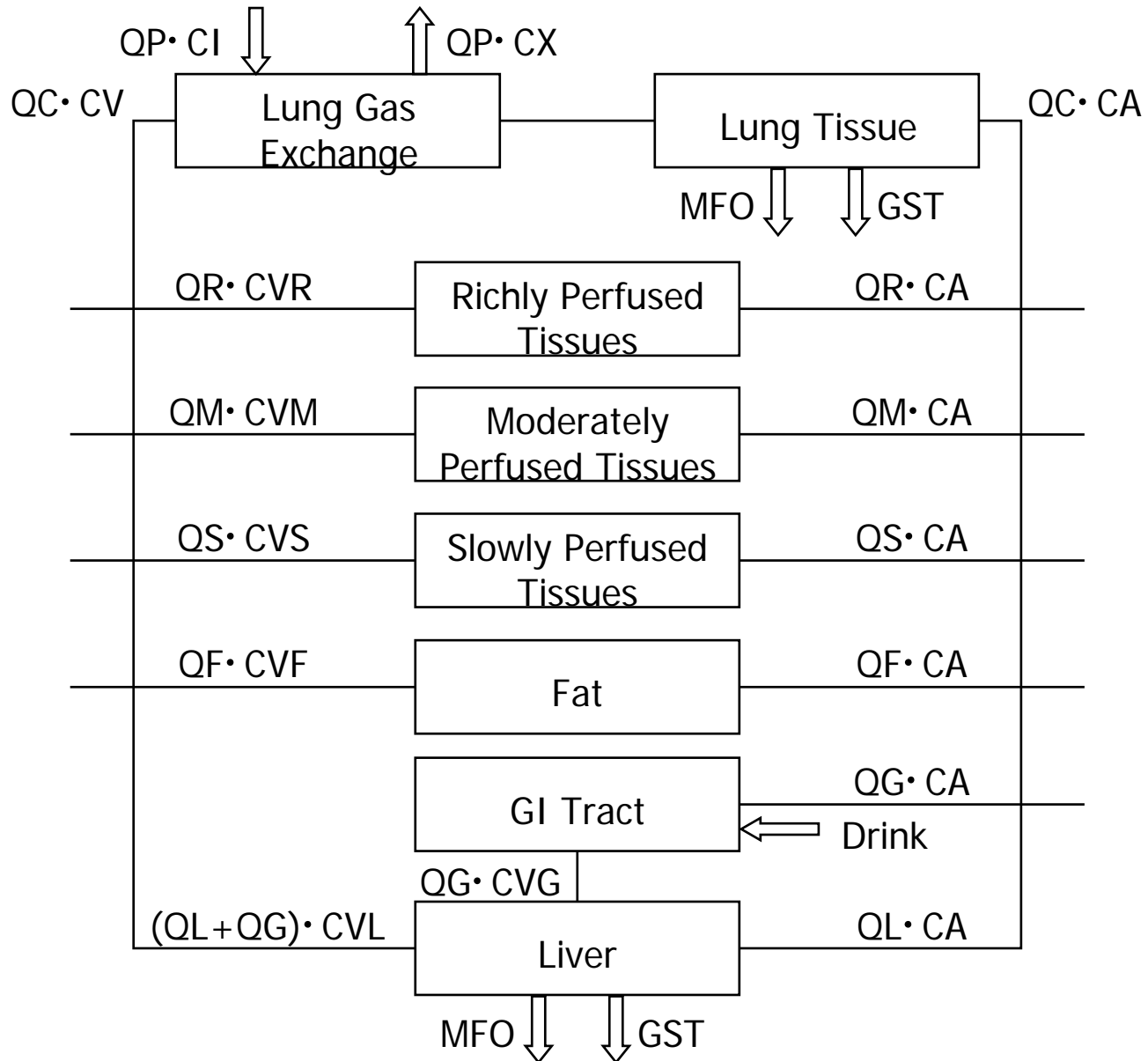


# Parameter Sensitivity Coefficient: (Log Normalized)

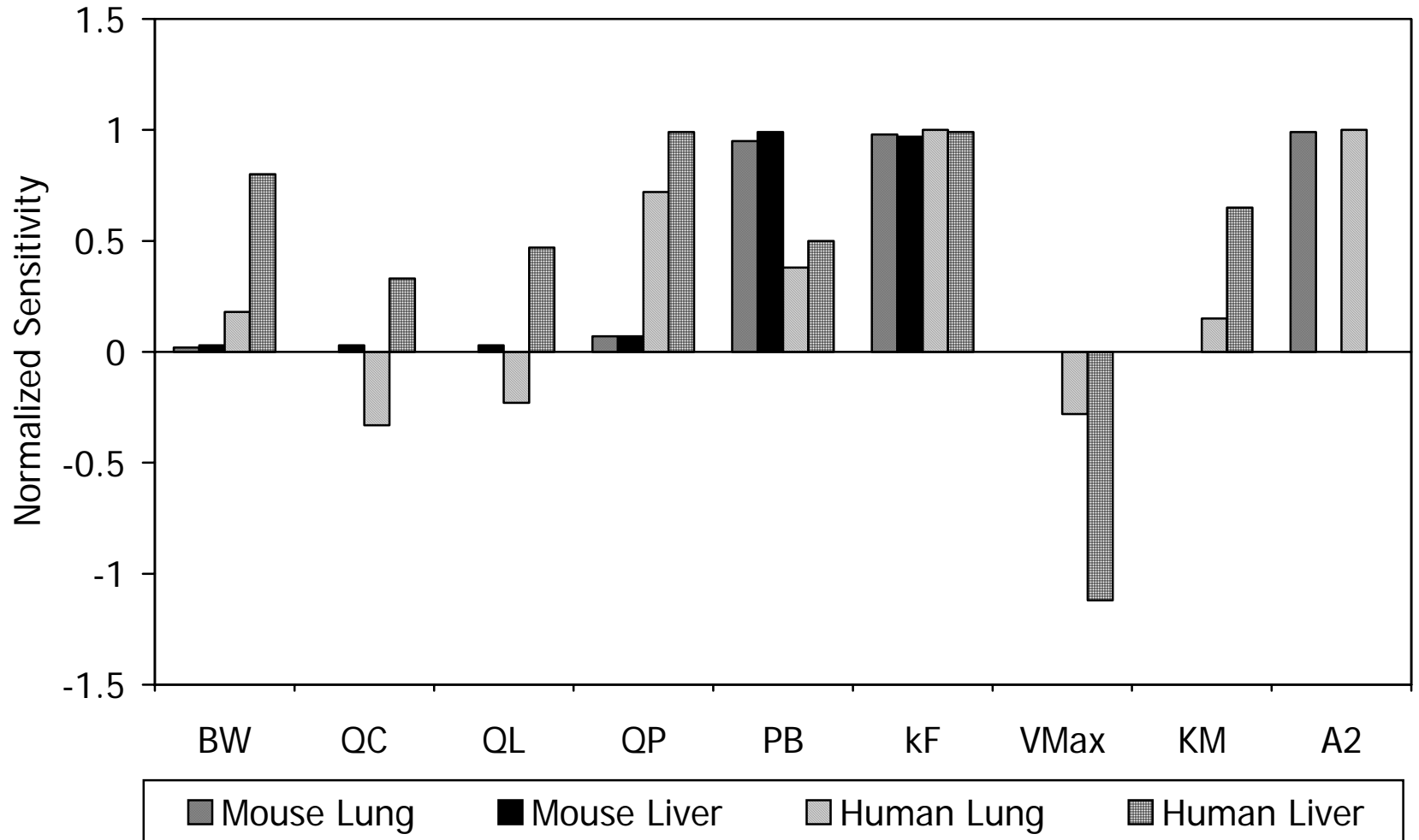
$$\frac{\text{Fractional Change in Model Output}}{\text{Fractional Change in Parameter}}$$

- **If Normalized Coefficient  $\gg 1$ , parameter error is amplified and model output may be highly uncertain**

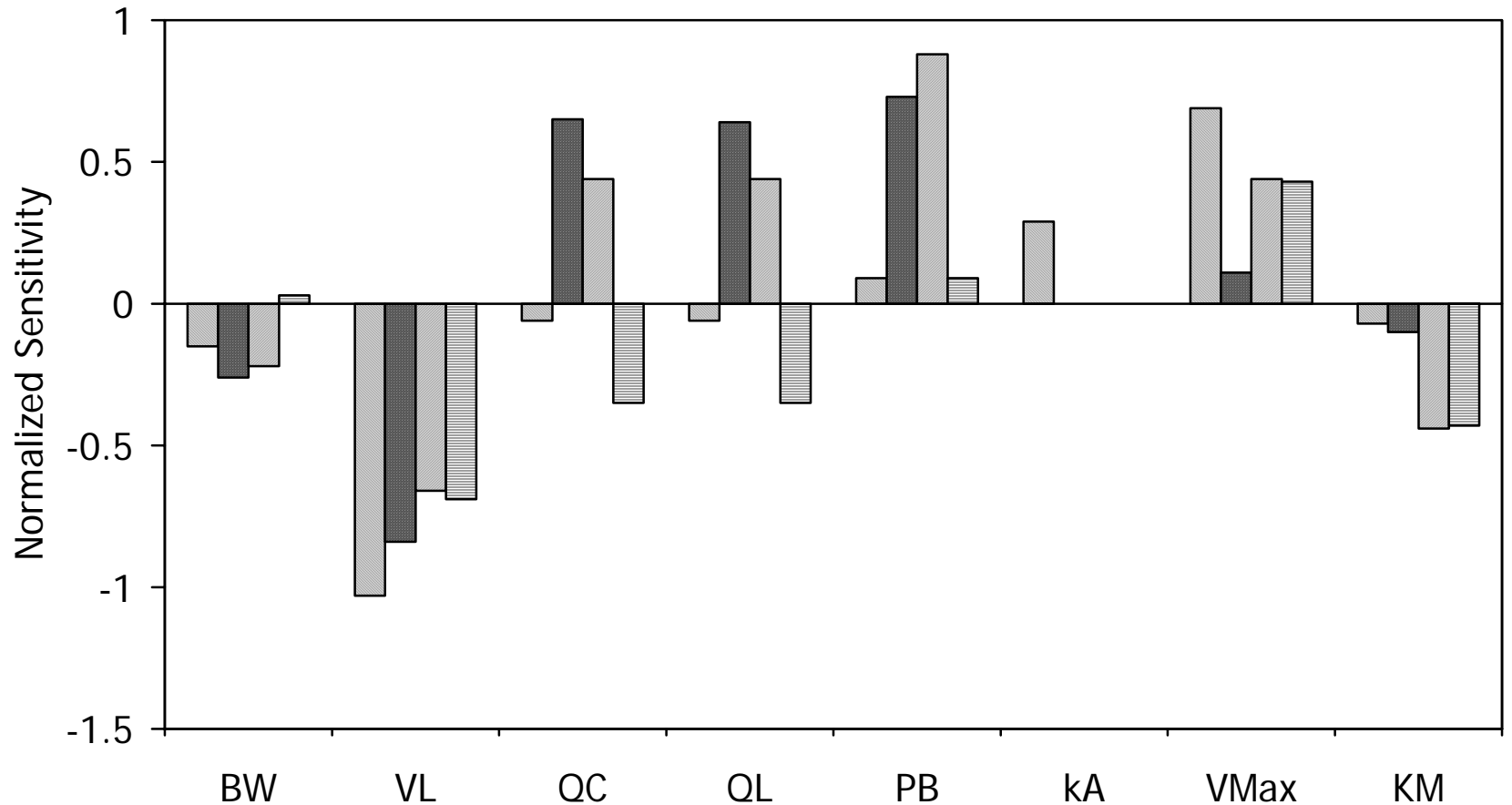
# Methylene Chloride (MeCl<sub>2</sub>) Model



# Parameter Sensitivities for MeCl<sub>2</sub> GST Pathway Metabolism Metric

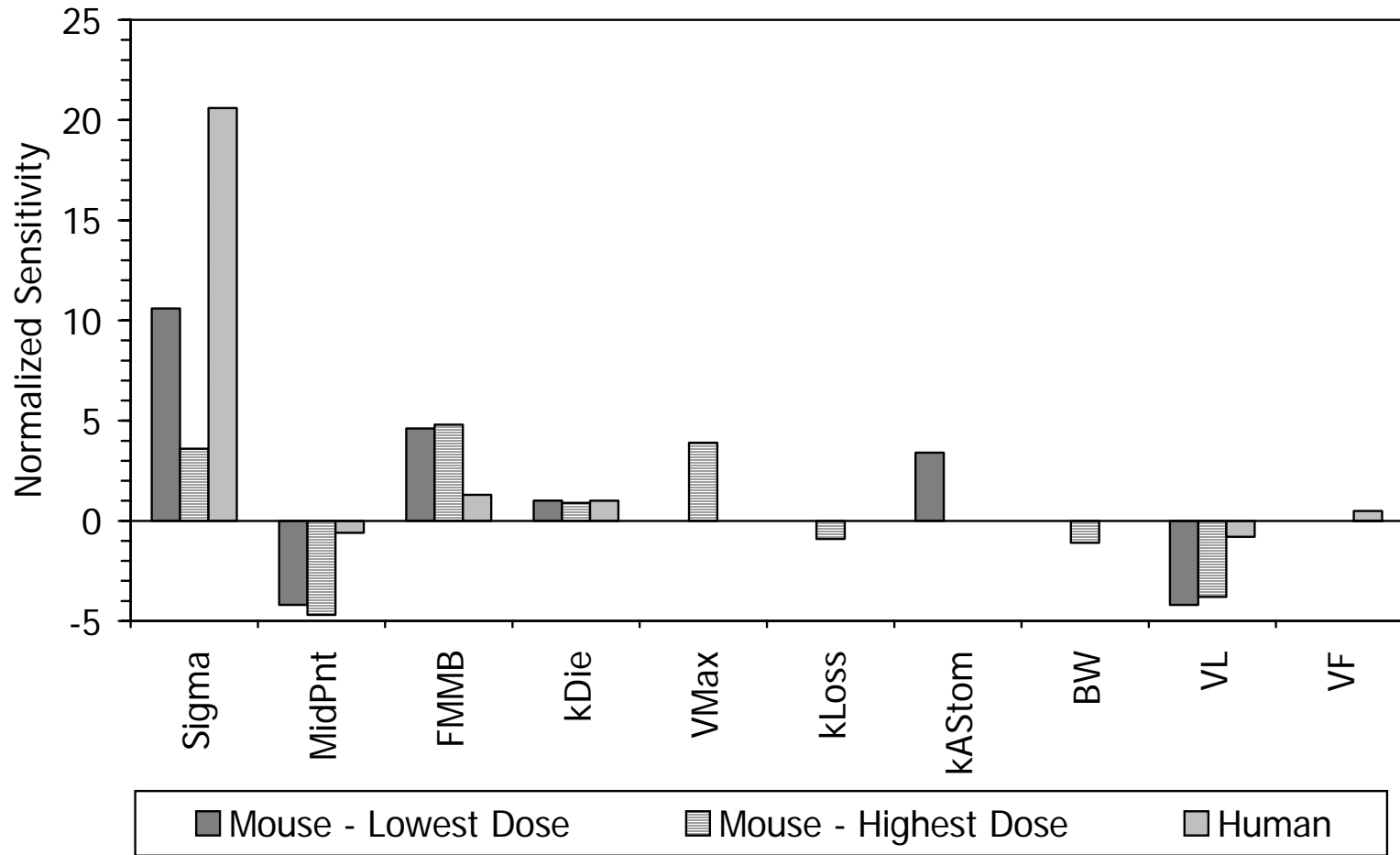


# Parameter Sensitivities for Vinyl Chloride Metabolism Metric

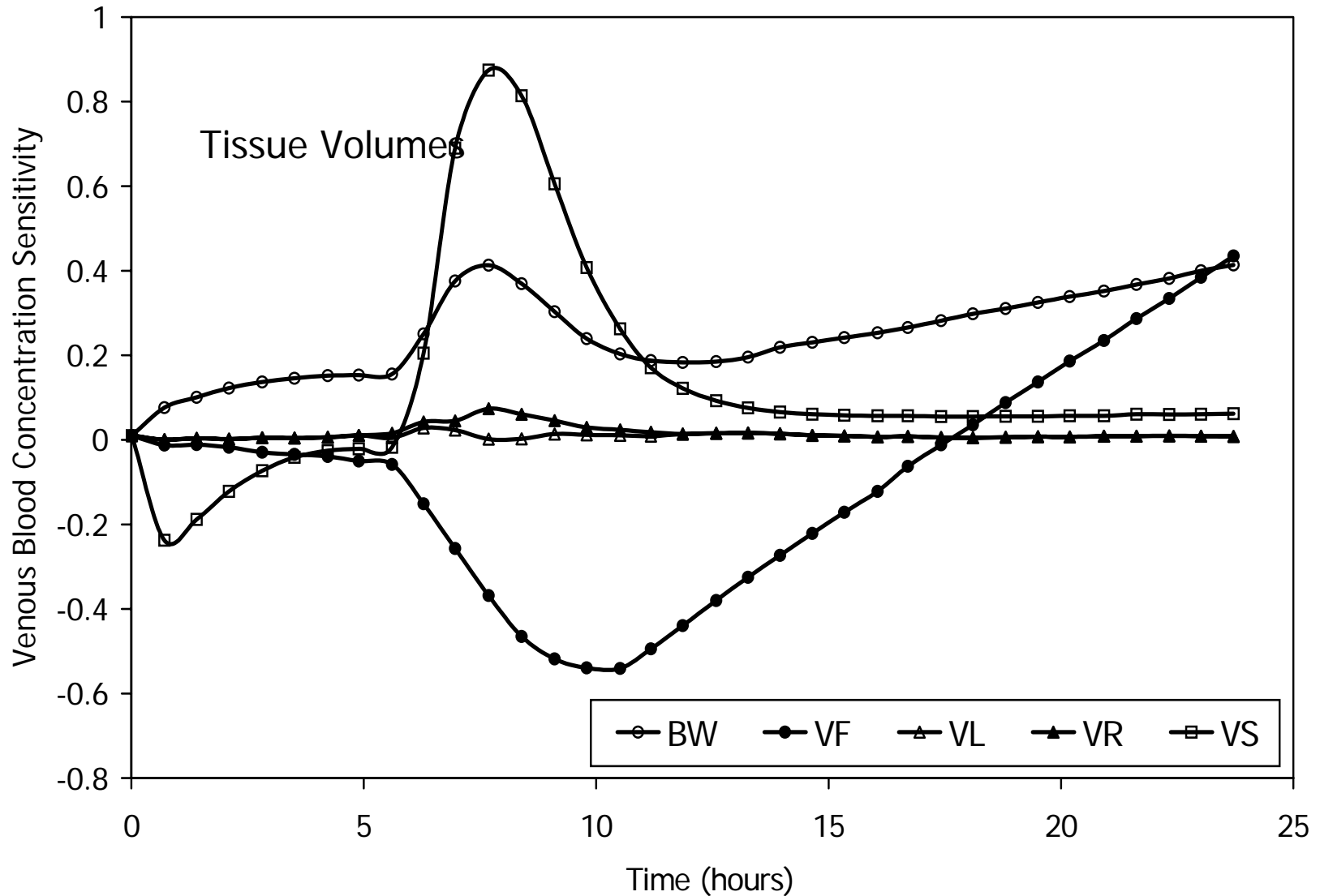


Legend: Rat Gavage (light gray), Rat Inhalation (dark gray), Human Inhalation (medium gray), Human Drinking Water (hatched)

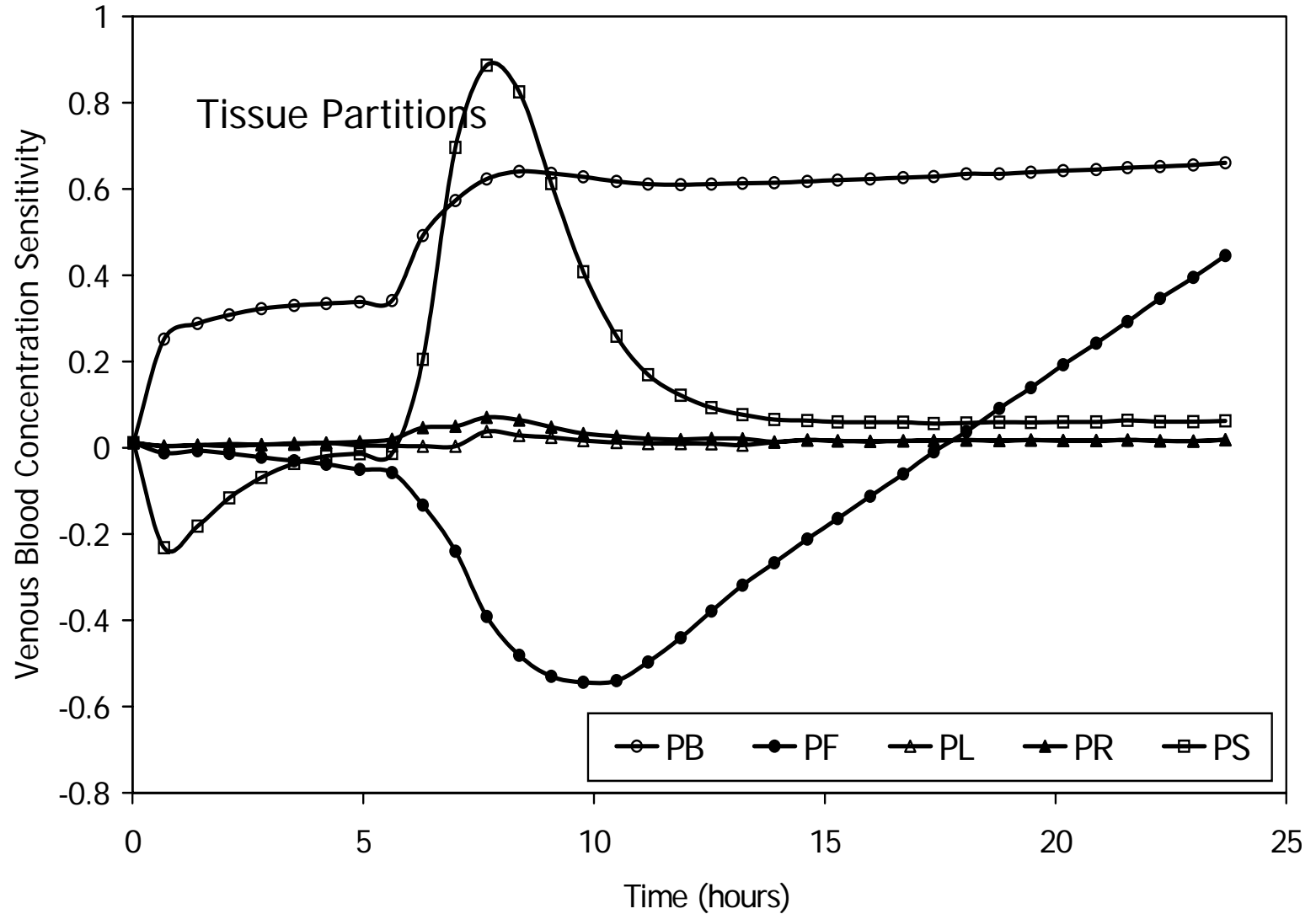
# Parameter Sensitivity for Chloroform Risk Metric (Percent Cell Death)



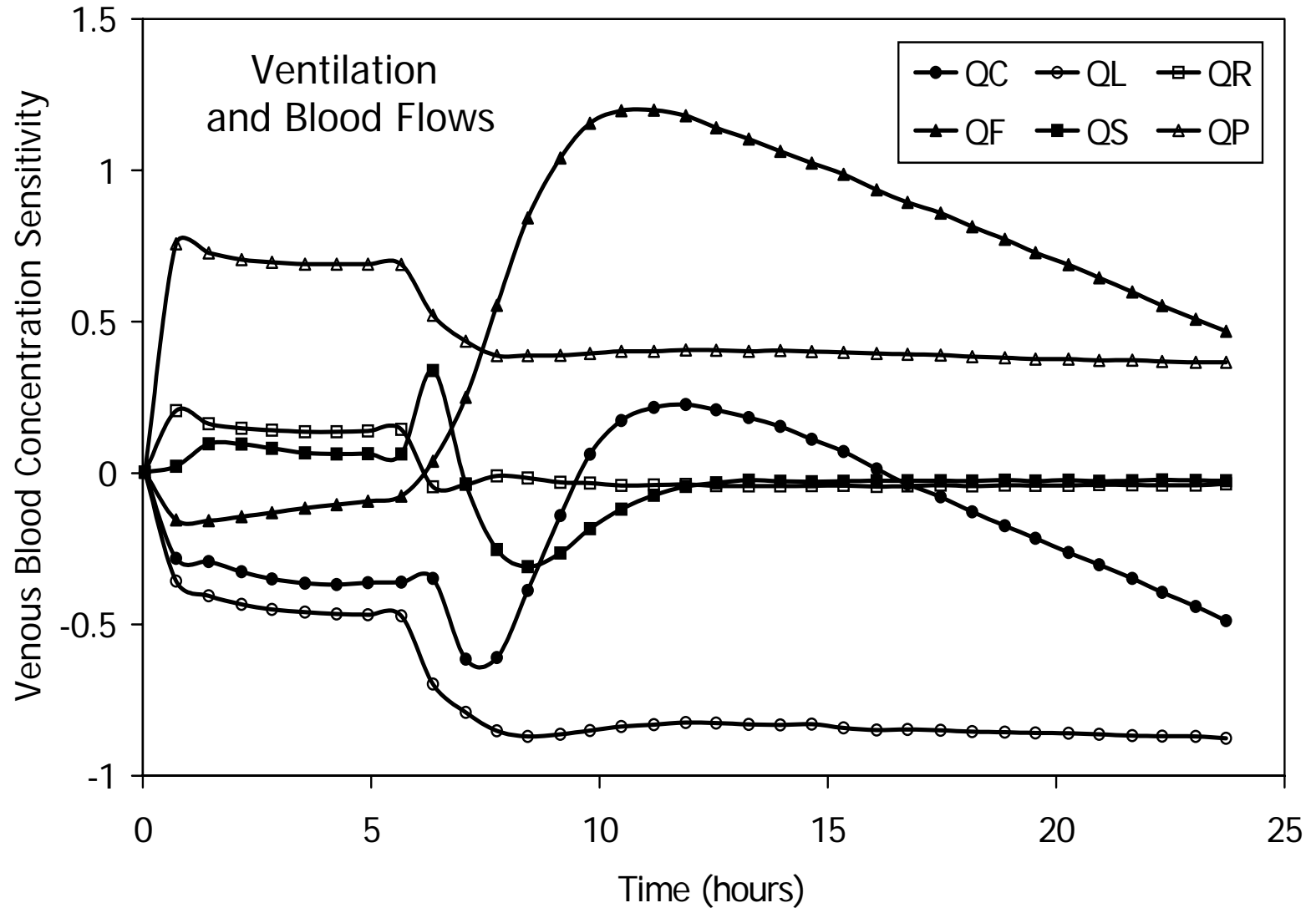
# Time-dependent Sensitivities – MeCl<sub>2</sub>



# Time-dependent Sensitivities – MeCl<sub>2</sub>



# Time-dependent Sensitivities – MeCl<sub>2</sub>



# Time-dependent Sensitivities – MeCl<sub>2</sub>

