

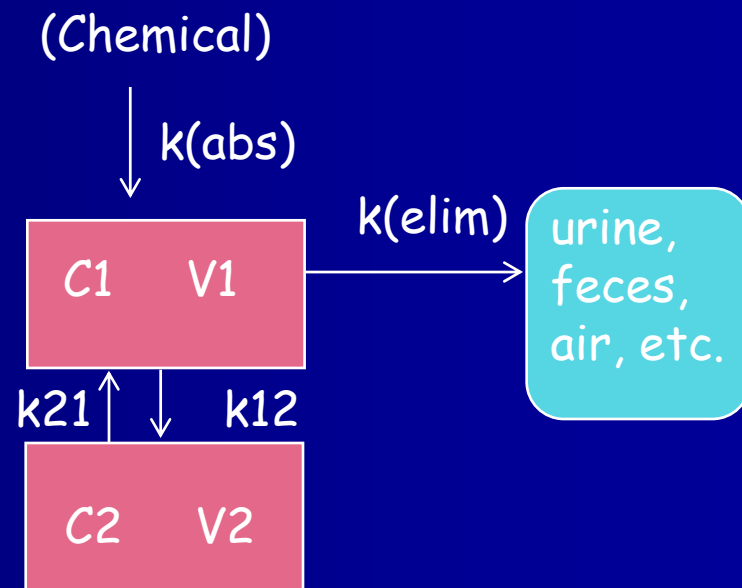
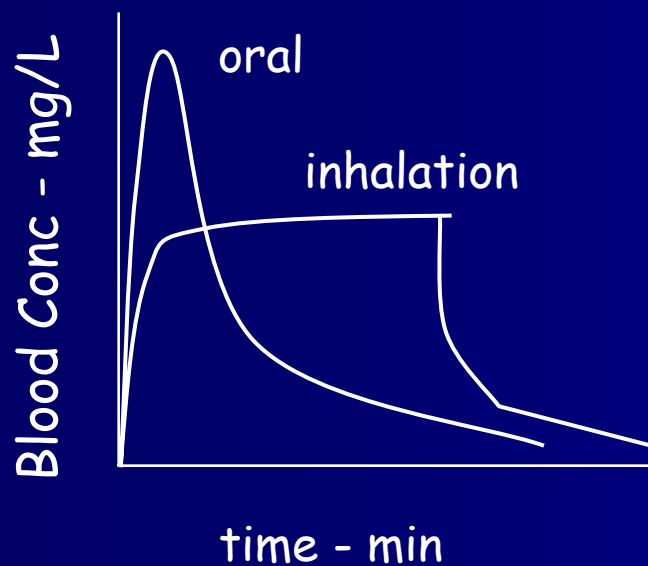
Overview of PBPK Modeling and Its Value in Risk Assessment

Harvey Clewell

**Director, Center for Human Health Assessment
CIIT Centers for Health Research**

Pharmacokinetics

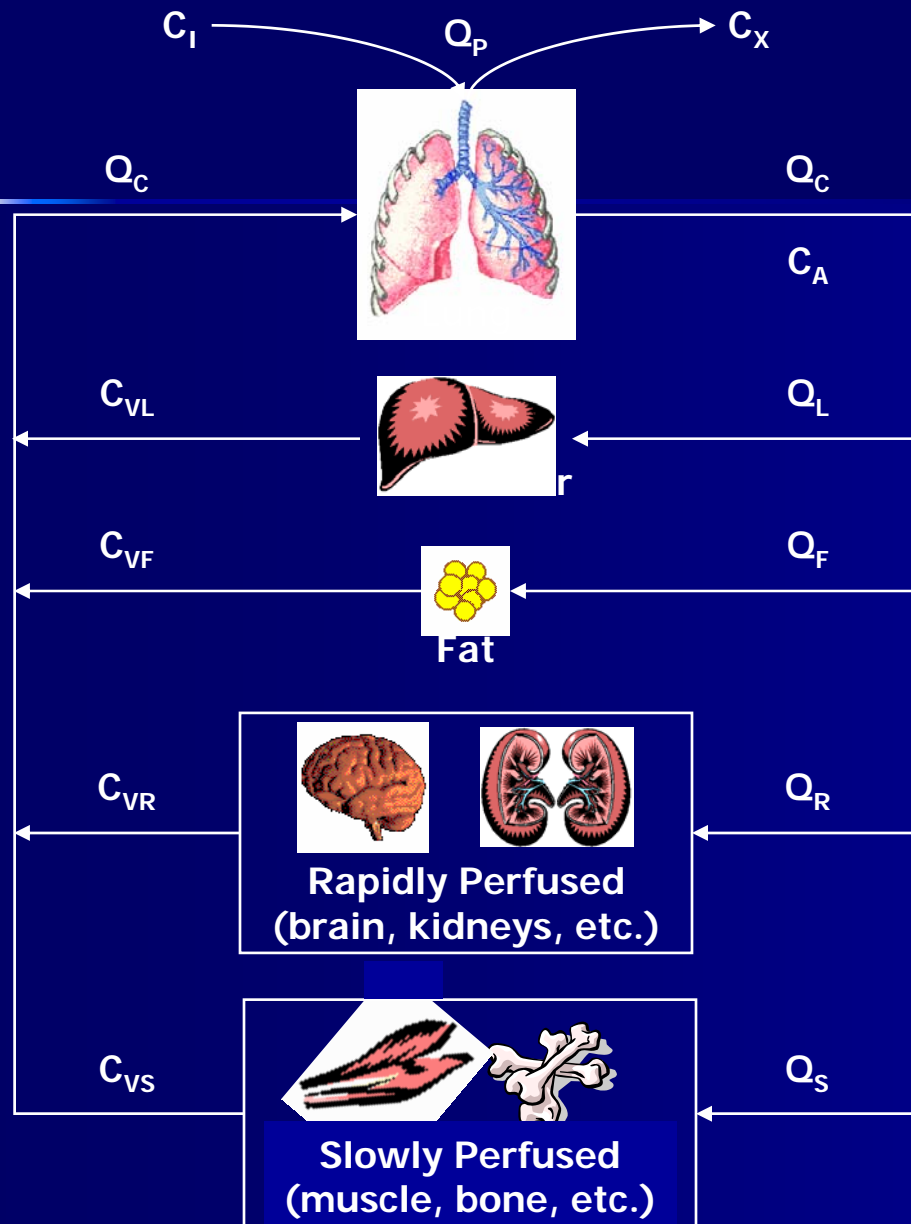
The study of the quantitative relationships between the absorption, distribution, metabolism, and eliminations (A-D-M-E) of chemicals from the body.



Value of Alternative Approaches to Pharmacokinetic Modeling

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

Physiologically Based Pharmacokinetic Model



- Physiological Structure & Dose Route Relationships
- Species-specific Tissue Volumes, Blood Flows
- Directly Incorporate In Vitro Metabolism, Binding, etc.

Physiologically Based Pharmacokinetic Model

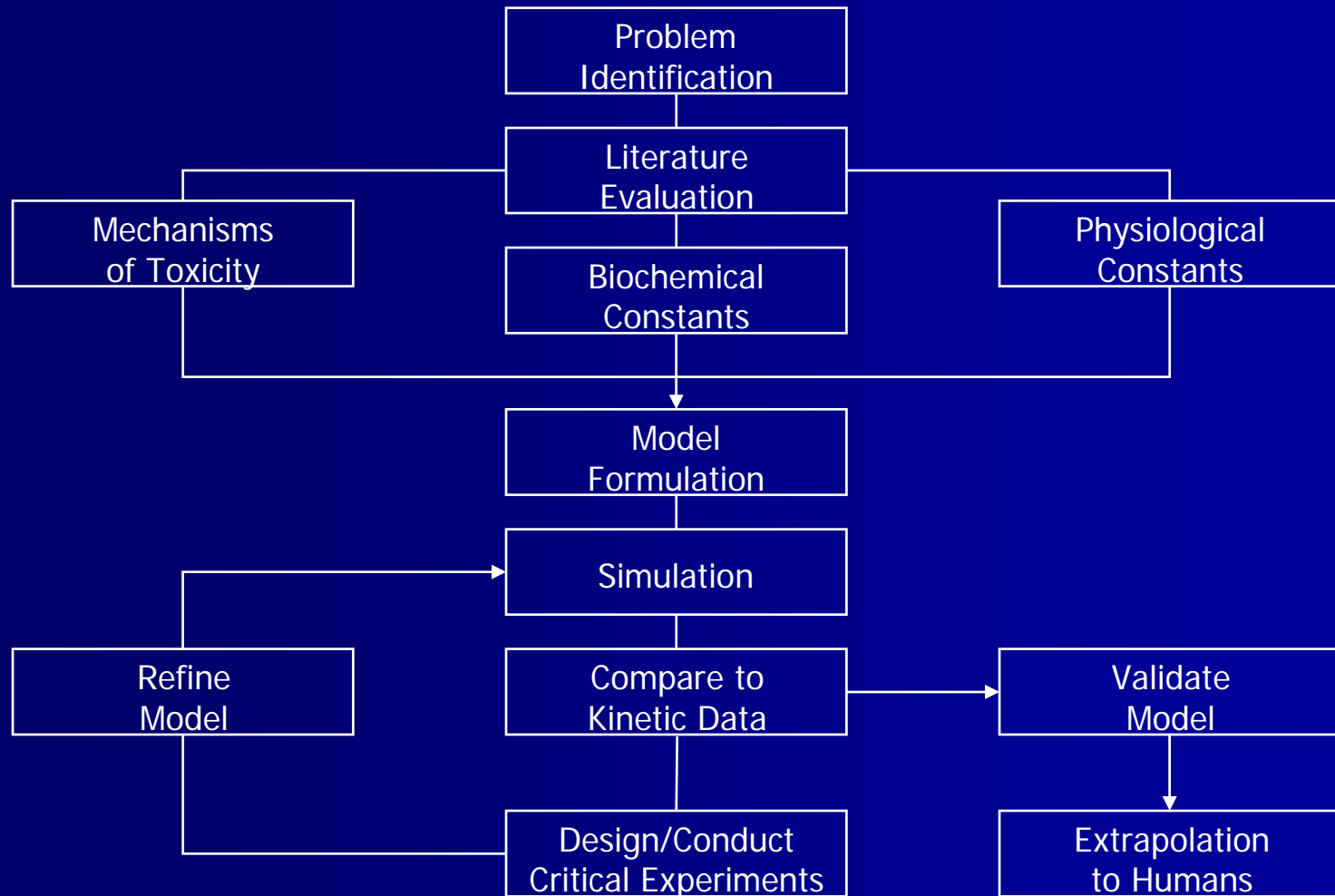
Basis of Description

- Model structure
 - anatomy
 - metabolism / transport processes
- Model parameters
 - physiological data (organ weights, blood flows)
 - biochemical data (partition coefficients, metabolism)
- Model equations
 - system of mass-balance differential equations
 - one equation for each tissue
 - connected by equation for blood

Metabolizing Tissue (e.g., Liver):

$$dA_L / dt = Q_L \times (C_A - C_L / P_L) - V_{\max} \times C_L / P_L / (K_M + C_L / P_L)$$

PBPK Models Represent Quantitative Structural Hypotheses

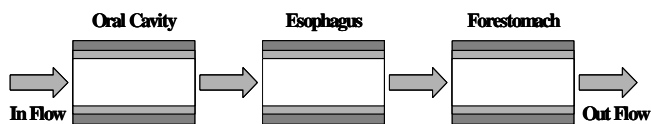


Structuring the Model

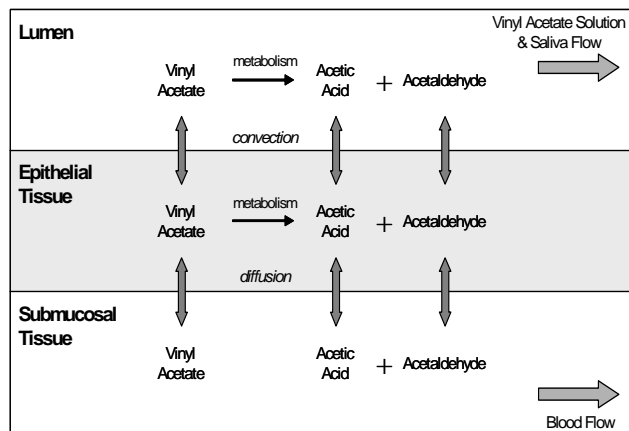
- What's needed and nothing more
 - Plausibility vs. Parsimony
- Considerations:
 - Uptake routes
 - Storage / sequestration / binding
 - Metabolism
 - Excretion
 - Target Tissue / Effect Compartment

PBPK Models Can Have Very Different Structures

Oral Vinyl Acetate Model



General Model Structure

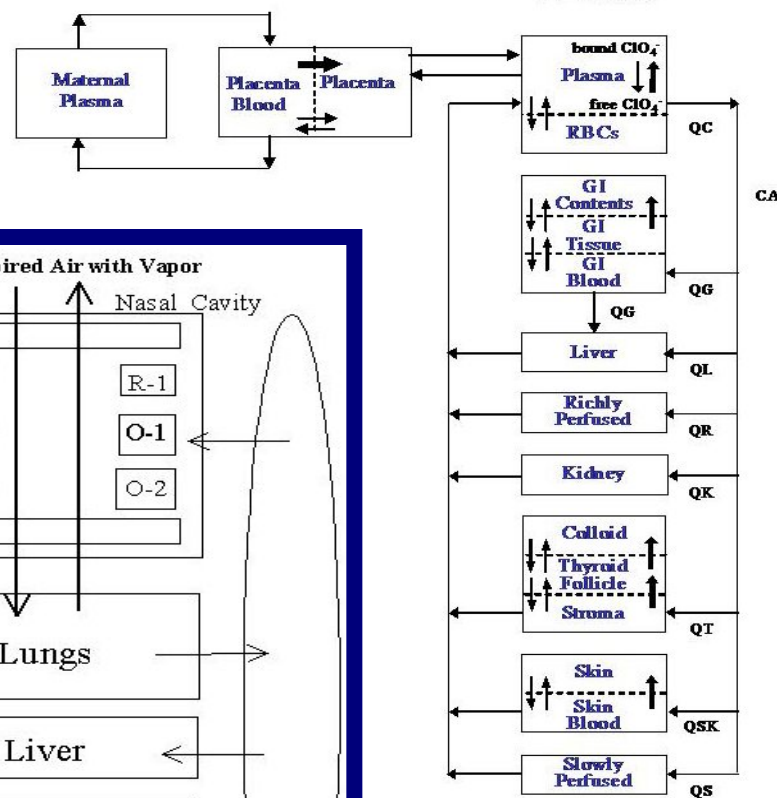


Unit Compartment Structure

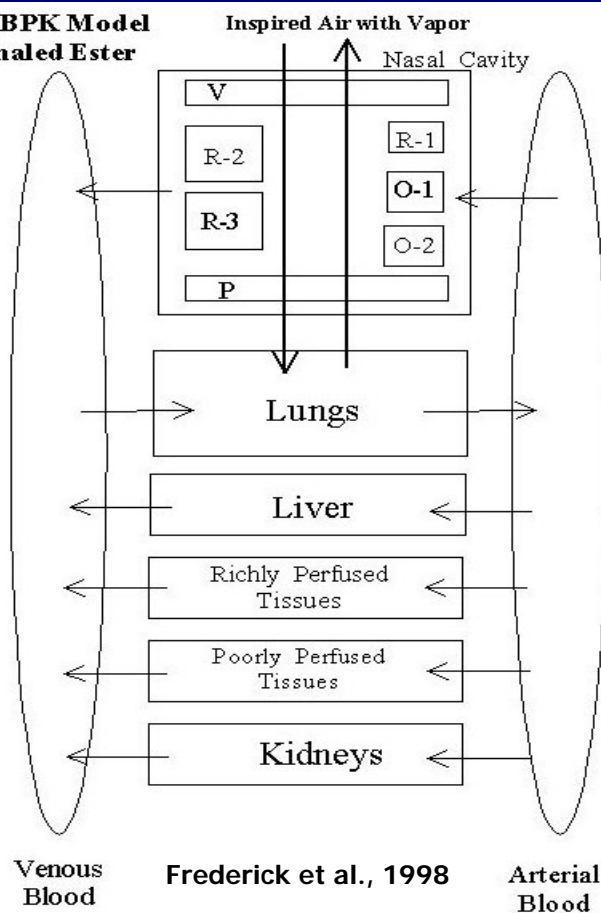
Fetal Perchlorate Model

R.A. Clewell et al., 2003a

FETUS:



CFD-PBPK Model of Inhaled Ester



Venous Blood

Frederick et al., 1998

Arterial Blood

ADVANTAGES OF PBPK MODELING

- Codification of facts and beliefs (organize available information)
- Expose contradictions in existing data/beliefs
- Explore implications of beliefs about the chemical
- Expose serious data gaps limiting use of the model
- Predict response under new/inaccessible conditions
- Identify essentials of system structure
- Provide representation of present state of knowledge
- Suggest and prioritize new experiments

Yates, F.E. (1978). *Good manners in good modeling: mathematical models and computer simulation of physiological systems.* *Amer. J. Physiol.*, 234, R159-R160. 1978.

Andersen et al. (1995). *Applying simulation modeling to problems in toxicology and risk assessment: a short perspective.* *Toxicol. Appl. Pharmacol.*, 133, 181-187.

Why are PBPK Models Used in Human Health Risk Assessment?

- Assess the *biological determinants* that govern the kinetic behavior
- Calculate *tissue dose metrics* for risk assessment calculations
- Support *extrapolation* across dose-routes, between species, from high to low dose levels, and over various dosing scenarios
- Assess *mechanisms of response (PD)* based on their relationship with dose metrics for target tissues

Role of PBPK Modeling in Risk Assessment

The primary role of a PBPK model in risk assessment is to define the relationship between an external measure of (administered) exposure/dose and an internal measure of (biologically effective) exposure/dose in both the experimental animal and the human

Uses of PBPK Modeling in Human Health Risk Assessment by EPA

- Methylene Chloride (inhalation CSF)
- 2-Butoxy Ethanol (RfC)
- Vinyl Chloride (RfC, RfD, oral and inhalation CSF)
- Dioxin
- Trichloroethylene
- Perchloroethylene
- Styrene
- Isopropanol

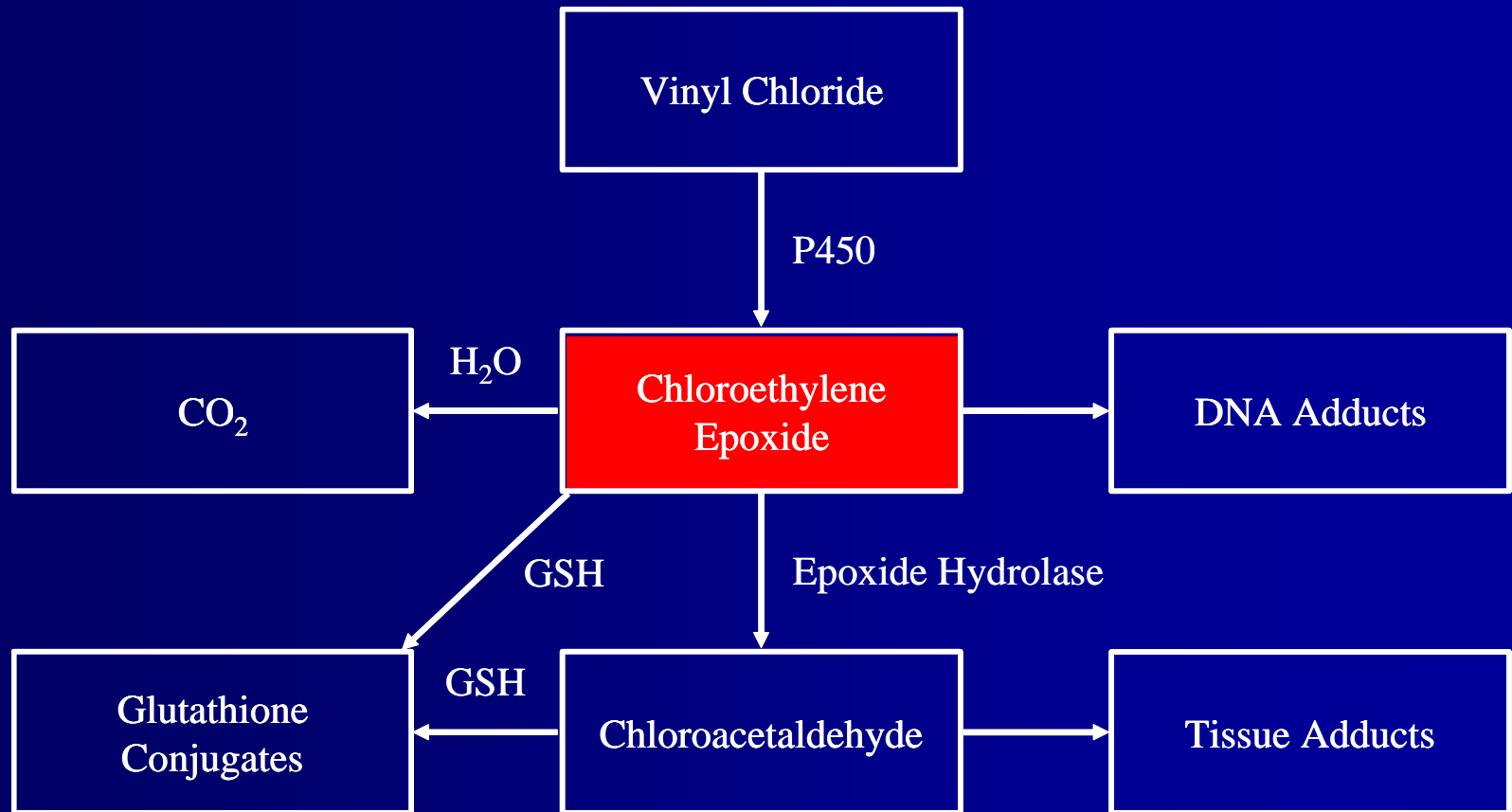
Example of the Use of a PBPK Model to Improve Dosimetry in a Risk Assessment:

Vinyl Chloride

Mode of Action Information

- Cross-species correspondence of a rare tumor type: liver angiosarcoma in mouse, rat, and human
- Carcinogenic at doses with no evidence of enhanced cell proliferation, receptor interaction, or cytotoxicity
- Mutagenic; metabolized to reactive intermediates associated with DNA adduct formation and mistranscription
- Expect linear dose-response below the experimental range

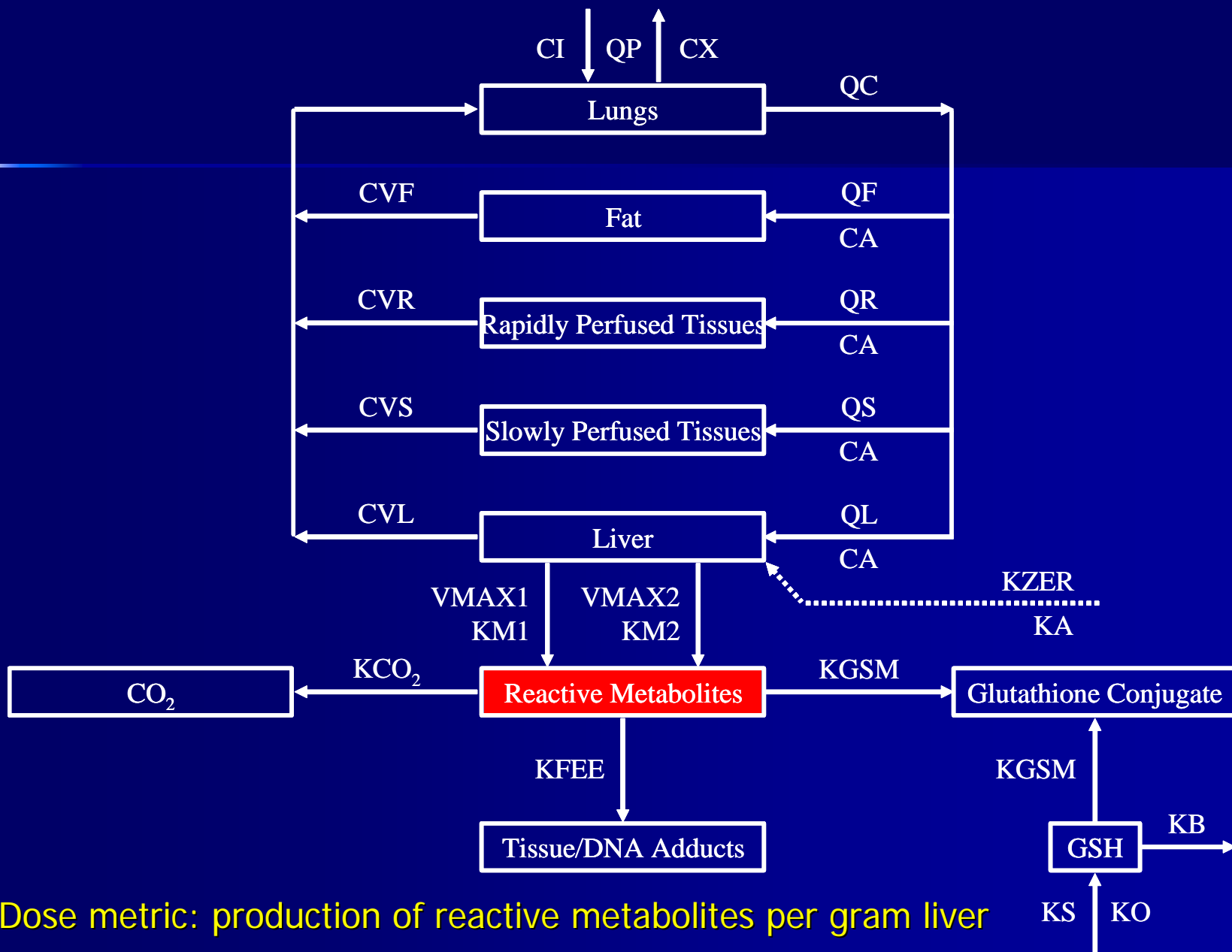
Metabolism of Vinyl Chloride



Dose metric: concentration (AUC) of chloroethylene epoxide

PBPK Model for Vinyl Chloride

(Clewell et al. 2001)

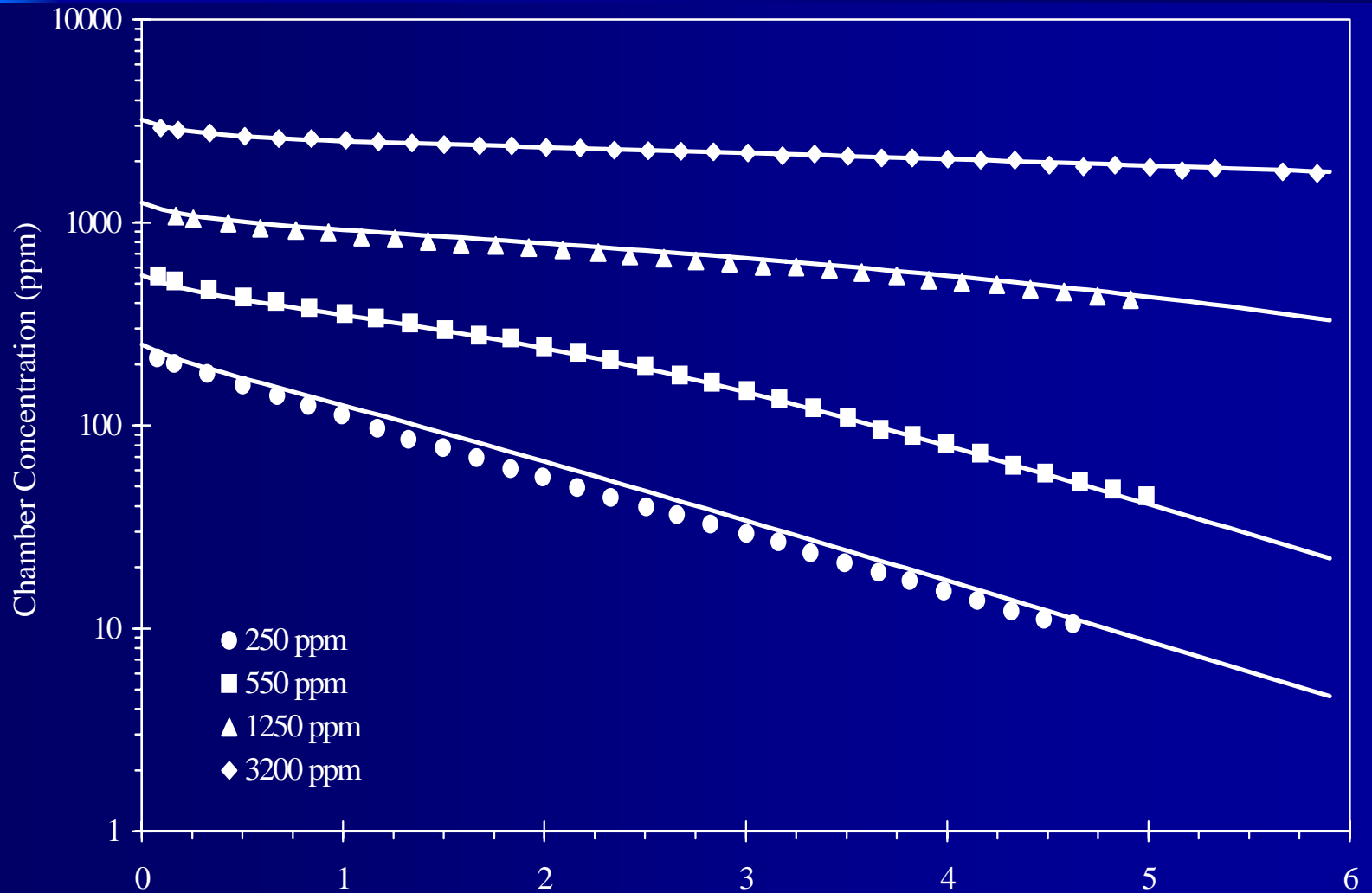


Model Parameterization

- Physiological Parameters (from literature)
 - tissue volumes, blood flows
 - alveolar ventilation, cardiac output
- Partition coefficients (measured in vitro)
 - Rodent: blood:air and tissue:air
 - Human: blood:air
- Metabolism (estimated by fitting in vivo data)
 - Rodent: closed chamber gas uptake, disposition studies
 - Human: closed chamber gas uptake

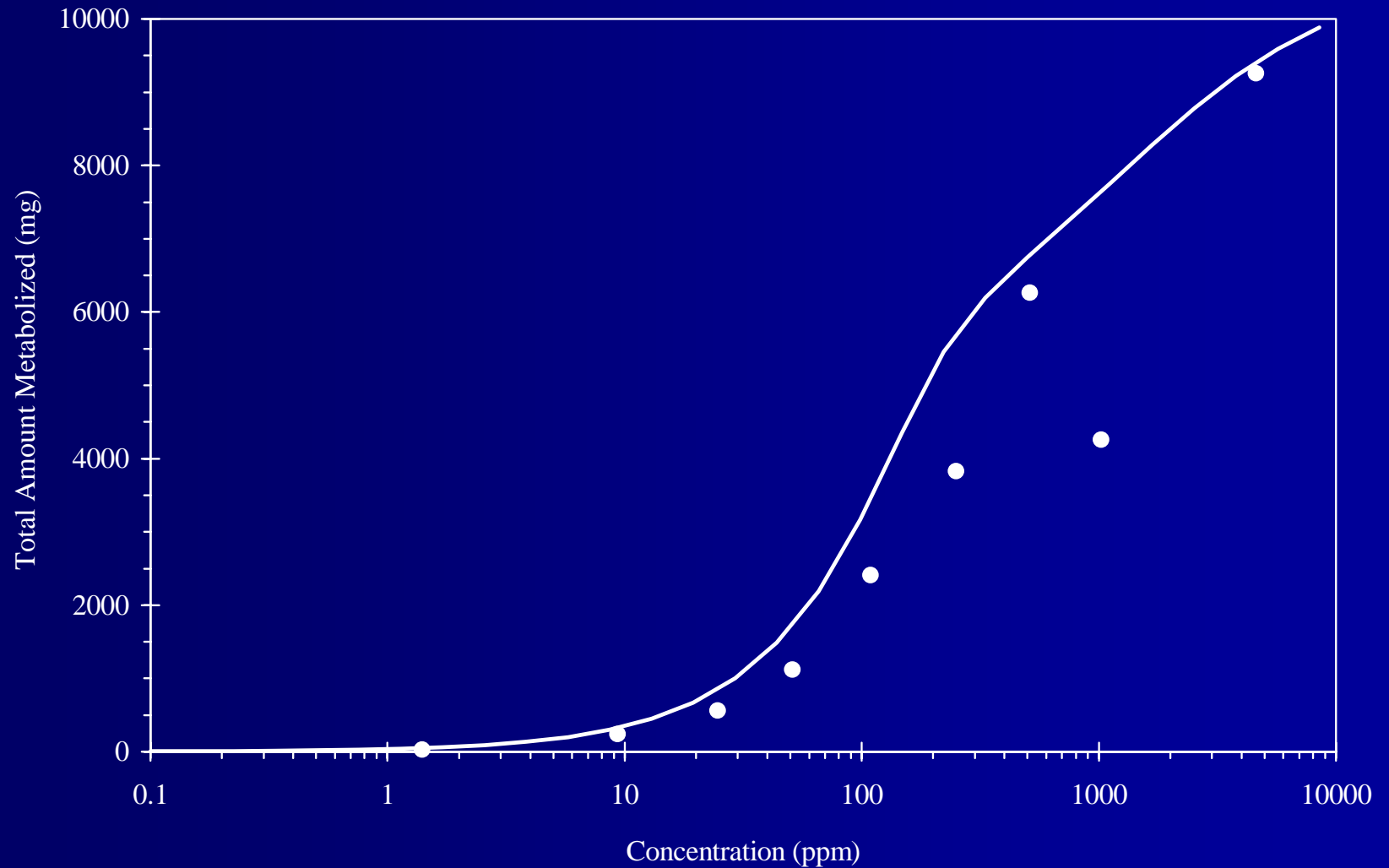
Estimation of Metabolism Parameters

Gas Uptake Studies in Male F344 Rats



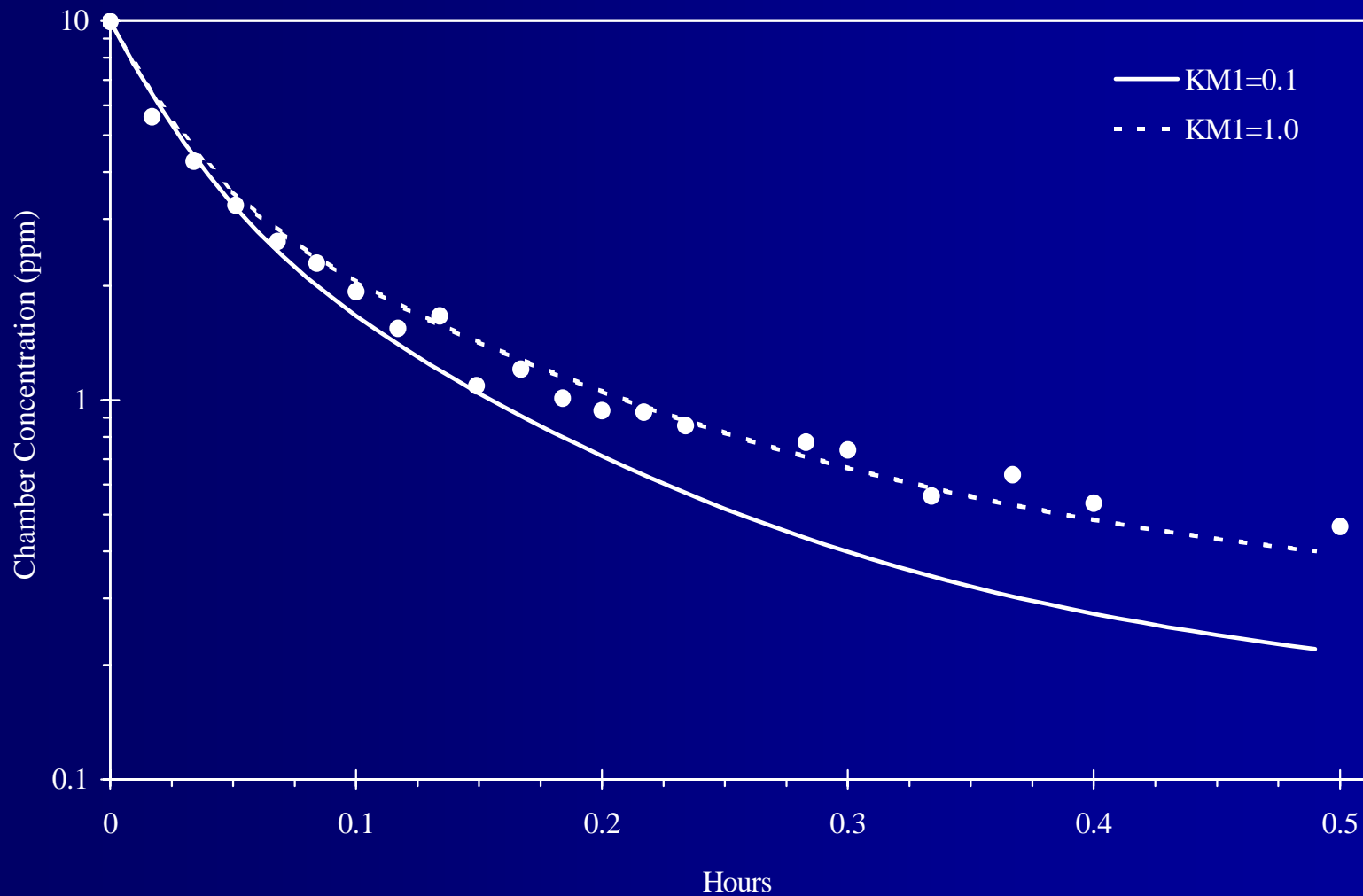
Estimation of Metabolism Parameters

Radiolabel Studies in Male Sprague-Dawley Rats



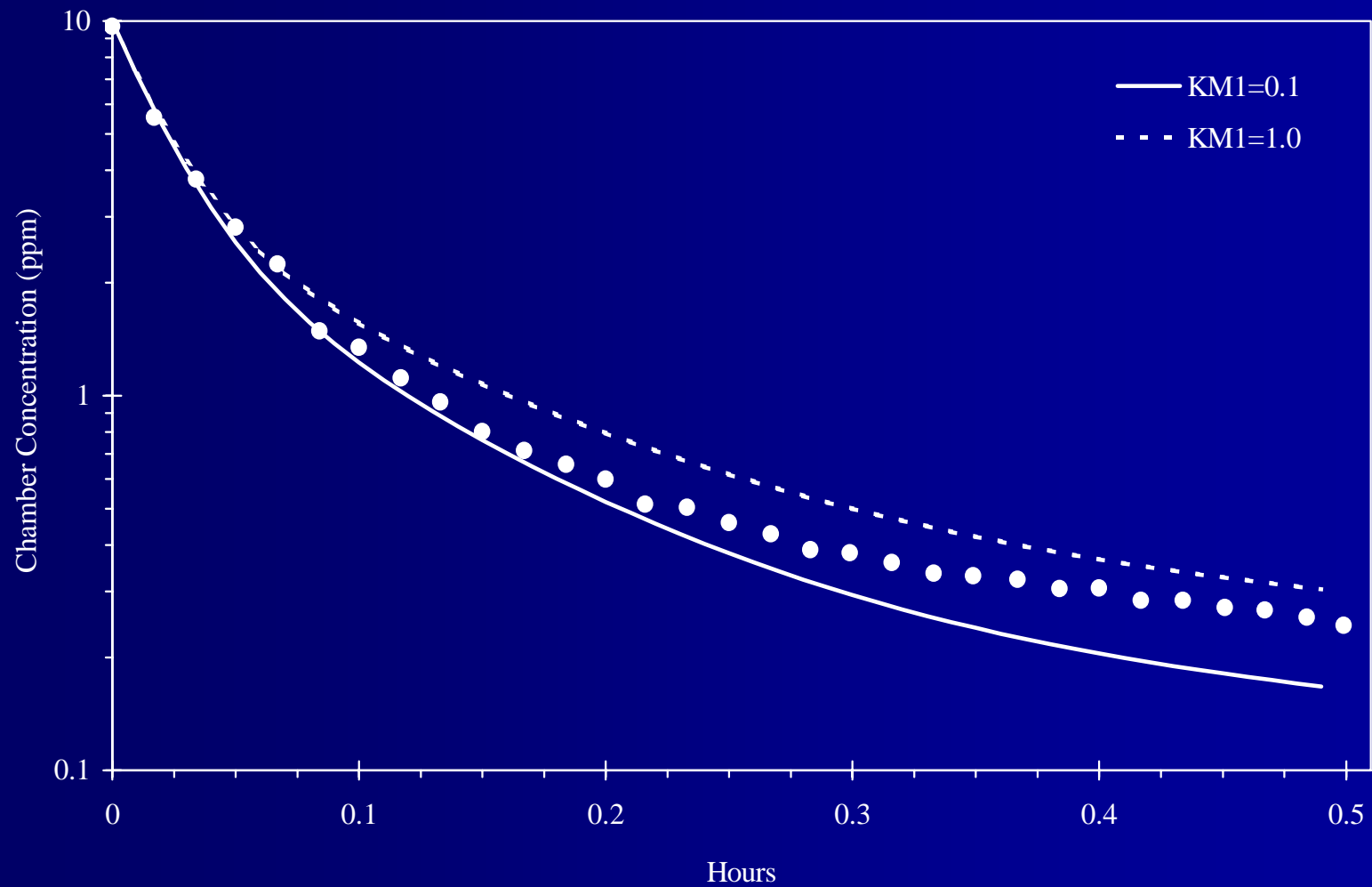
Estimation of Metabolism Parameters

Human Inhalation Study – Subject A



Estimation of Metabolism Parameters

Human Inhalation Study – Subject B



Cross-Species and Cross-Route Correspondence Using PBPK Dose Metric

Human risk estimates (per million) for lifetime exposure to 1 ppb vinyl chloride in air based on the incidence of liver angiosarcoma in animal bioassays

Animal Bioassay Study	95% UCL Risk / million / ppb	
	Males	Females
Maltoni - Mouse Inhalation	1.52	3.27
Maltoni - Rat Inhalation	5.17	2.24
Feron - Rat Diet	3.05	1.10
Maltoni - Rat Gavage	8.68	15.70

Comparison of Cancer Risk Estimates for Vinyl Chloride

<u>Basis</u>	<u>Inhalation</u> (1 ug/m ³)	<u>Drinking Water</u> (1 ug/m ³)
Old EPA -- Animal (mg/kg/day -- BSA)	84.0 x 10 ⁻⁶	54.0 x 10 ⁻⁶
PBPK -- Animal	2.7 x 10 ⁻⁶	1.1 x 10 ⁻⁶
PBPK -- Human (Epidemiology)	1.7 x 10 ⁻⁶	

Levels of Model Uncertainty

- Uncertainty Regarding Model Parameters
 - The tip of the iceberg
- Uncertainty Regarding the Mode of Action
 - Appropriateness of dose metric
- Uncertainty Regarding the Biology
 - Deficiencies in model structure

Uncertainty in TCE Lung Tumor Dose Metrics

Using Alternative Possibilities for Cross-Species Scaling of Alcohol Dehydrogenase in lung

Species / Exposure	Chloral in Lung Tracheobronchial Region	
	AUC	C _{MAX}
mouse / 600 ppm*	9.4	2.6
rat / 600 ppm	2.8 ^a (28) ^b	0.3 (3.4)
human / 100 ppm	0.016 (10.5)	0.003 (2.2)
human / 1 mg/L	0.00002 (0.01)	--

* Significantly increased lung tumors

^a Assuming ADH scales by body weight to the $\frac{3}{4}$ power

^b Assuming ADH scales similarly to lung P450

Models in Perspective

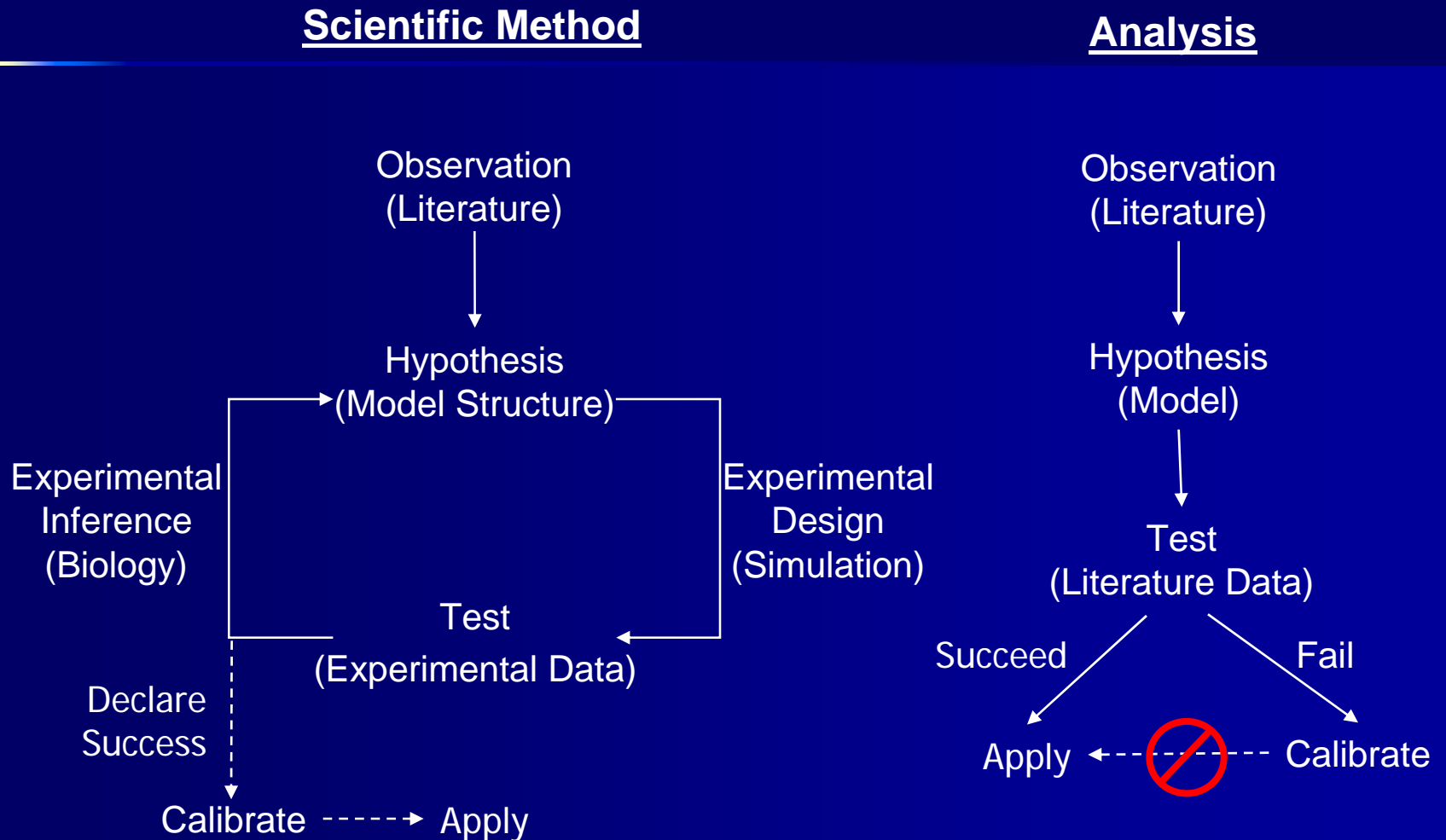
“...no model can be said to be ‘correct’. The role of any model is to provide a framework for viewing known facts and to suggest experiments.”

-- Suresh Moolgavkar

“All models are wrong and some are useful.”

-- George Box

Summary: Alternative PBPK Model Development Approaches



Calibrating a deficient model does not overcome its deficiency