

# Model Documentation and Evaluation

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

April 6-10, 2009

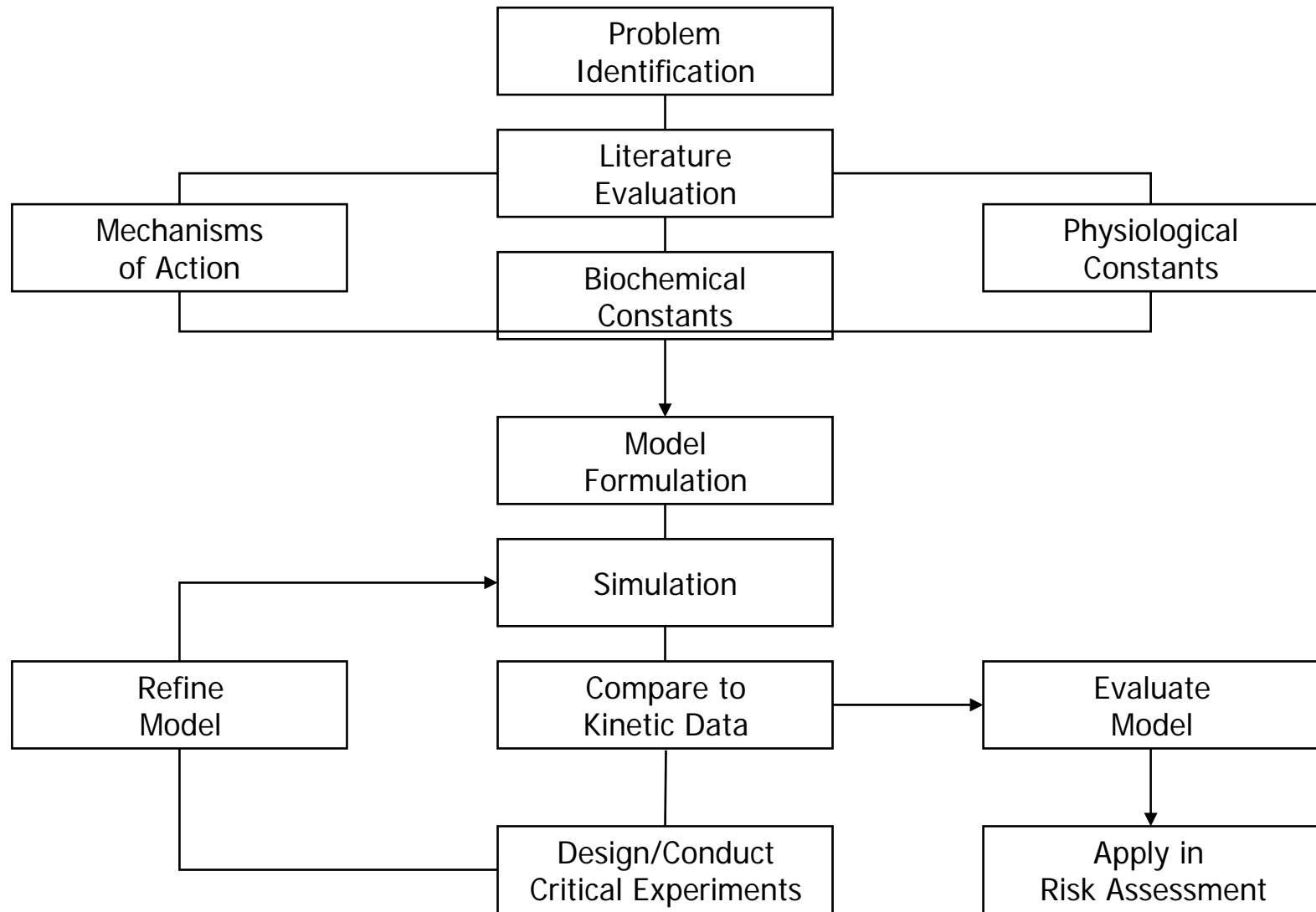
Center for Human Health Assessment  
Center for Drug Safety Sciences



# Purpose-specific model validation

- Are we sufficiently confident in the simulations of dose metrics obtained with a PBPK model for a specific application?
- What are the relative uncertainties associated with alternative(s) to PBPK modeling ?

# Is the Model Suited to the Problem?



# Elements of Problem Formulation

- What is the critical effect?
  - Acute/chronic/developmental
  - Target tissue, dose range
- What is the mode of action for the effect?
  - Parent chemical/circulating metabolite/reactive metabolite
  - Reactivity/receptor activation/physical interaction
- What is the basis for the quantitative assessment?
  - Nonclinical or clinical data
- What dosing regimens are of concern?
  - Route, duration, lifestage
- What is the model needed for?
  - Cross-species/cross-route/alternative dosing
  - In vitro to in vivo extrapolation
- What data are available for developing the model?
  - In vivo kinetics/in vitro metabolism
  - Animal/human

# Evaluation of PBPK models

- Verification
  - Does the model code implement the model described in the documentation?
- Validation
  - Does the model adequately reproduce the data sets used in its development?

# Evaluation of PBPK models

- Reality check (simulations vs data)
- Model robustness
- Biological plausibility
- Extrapolation uncertainty

# Elements of Modeler/Risk Assessor Interaction

- What are we trusting the model for?
  - Basis of extrapolation
    - Physiology
      - blood flow to liver
    - Biochemistry
      - Michaelis-Menten kinetics
    - Incorporation of vitro data
      - target tissue metabolism
  - Nature of mode-of-action driven dose metric
    - Measurable
      - blood concentration vs. reactive metabolite
    - Calibratable
      - liver metabolism vs. nasal metabolism
  - Extent of kinetic data
    - Validation data
    - Calibration data

# Documentation of Model

## 1. Background

### 1.1 Efficacy/Toxicity overview

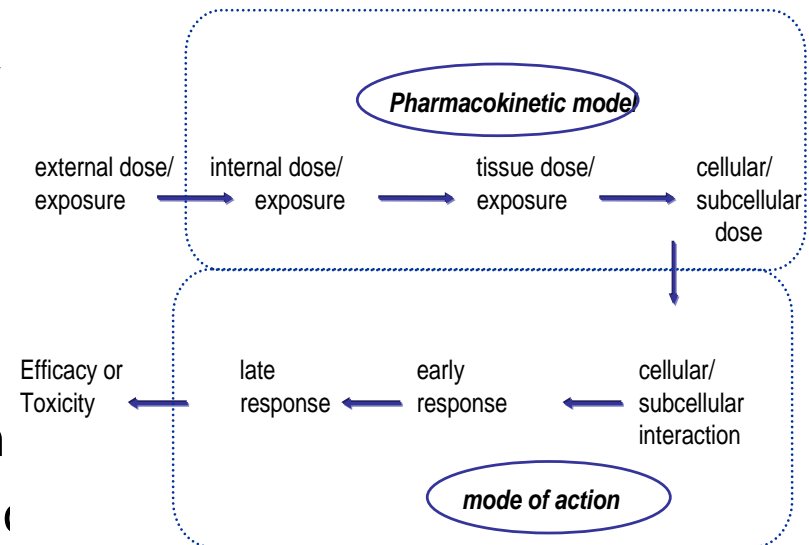
### 1.2 Pharmacokinetics overview

### 1.3 Modes of action overview

### 1.4 Purpose of analysis

### 1.5 Role of PBPK modeling

- Route-to-route extrapolation
- Animal to human extrapolation
- Extrapolating dosing regimen
- Evaluating human variability
- Drug-drug interactions
- etc.



# Documentation of Model

## 2. PBPK Model Characterization and Evaluation

2.1 Model capability and selection

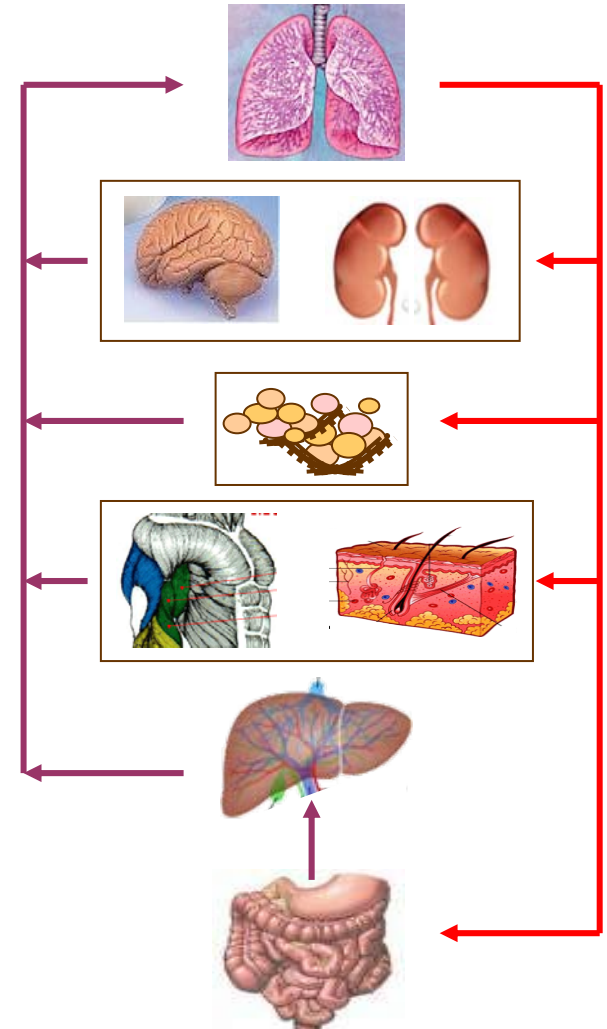
2.2 Model structure and biological characterization

2.3 Parameter estimation and analysis

2.4 Purpose-specific model evaluation

2.5 Model documentation

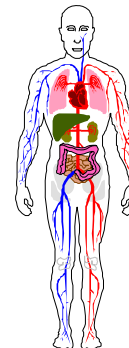
2.6 Model reviews



# Documentation of Model

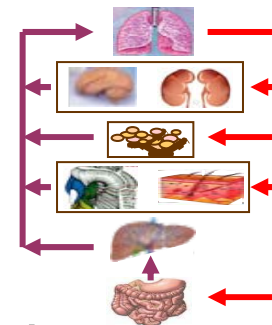
## 2.1 Model capability and selection

- Drug(s) modeled
- Species (strains), life stages, ages, population variations to which model applies
- Exposures addressed: routes, matrices
- Dose metrics modeled



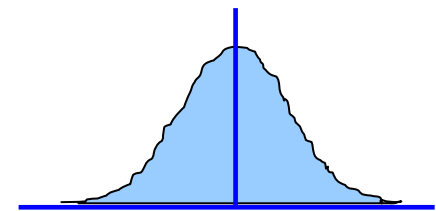
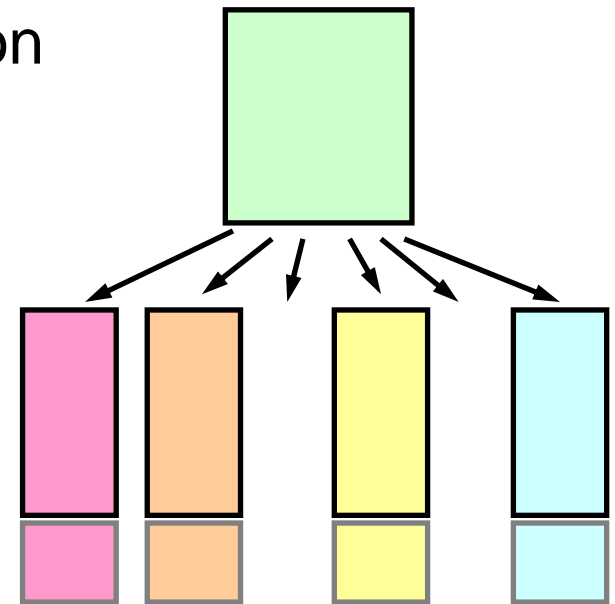
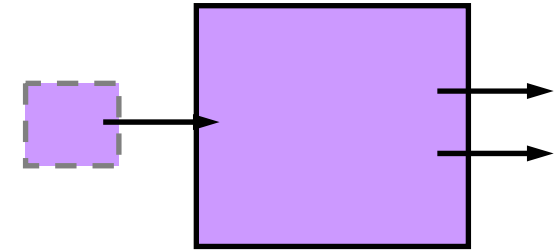
## 2.2 Model structure and biological characterization

- Absorption processes (exposure routes)
- Distribution – tissues
- Metabolism
- Excretion
- Summary of modeling approach (e.g., perfusion limited compartments) and biological basis of model

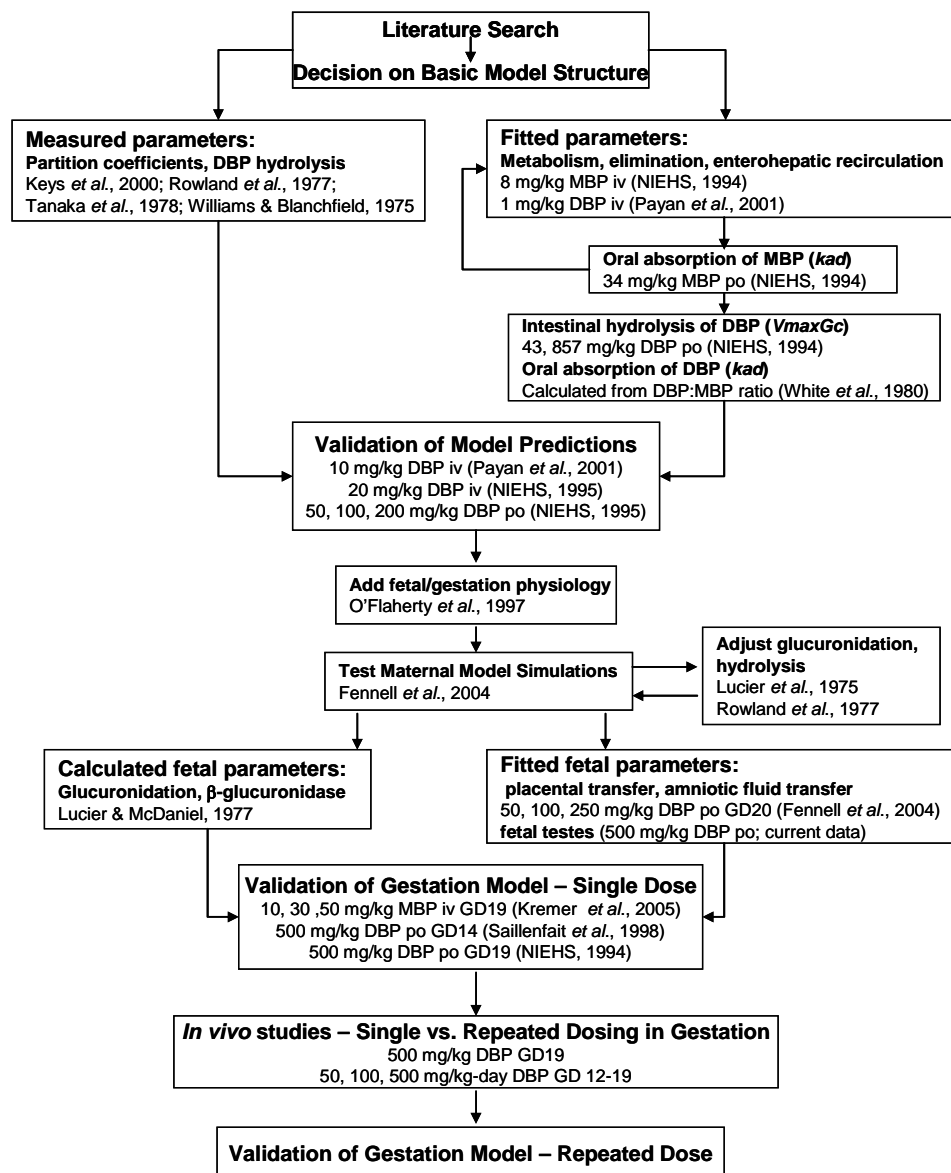


# Documentation of Model

- 2.3 Parameter estimation and analysis
  - From where and how were model parameters obtained
- 2.4 Purpose-specific model evaluation
  - Performance (model compared to data), Robustness, Plausibility, Extrapolation uncertainty
- 2.5 Model documentation
  - Sources, availability, forms
- 2.6 Model reviews
  - Peer-reviewed literature (limited independent review)
  - Independent review by scientific panel, Agency
  - Summarize kind of review and findings



# Model Parameterization Flowchart



(Clewell et al. 2008)

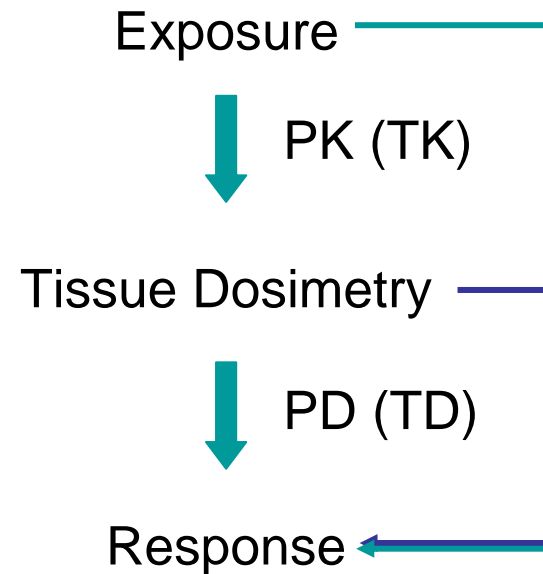
# Documentation of Model

## 3. Evaluation of Dose Metrics

- Characterization of dose-response for the internal dose metrics
- Sensitivity and uncertainty analysis

## 4. PBPK Model Application

- Description of internal exposure-response analysis
- Characterization of confidence in results



# ***IPCS Project on Good PBPK Modelling Practice***

- International Coordinating Planning Group
- October 2006: NIEHS/EPA Workshop on Uncertainty & Variability in PBPK models
  - Statistical methods (modellers/statisticians)
  - **Ref: Barton et al., Tox. Sci. 99:395 (2007)**
- April 2007: EU (UK HSE) hosted workshop on good modelling practice (modellers, risk assessors)
  - Practice for modellers; transparent documentation for users
  - **Ref: Loizou et al., Regul. Toxicol. Pharmacol. 50: 400 (2008).**

# ***IPCS Project on Good PBPK Modelling Practice***

- Draft guidance document with case studies posted for public comment in Autumn/08
- July 2009: IPCS Workshop
  - July 6-8 in Berlin, Germany
  - Development of guidance through application to case studies (modellers, risk assessors)

# Discussion

- Is “validation” of PBPK platforms feasible?
  - Similar to “validation” of Winnonlin?
- Is there a need for FDA guidance on PBPK modeling ?
- Should FDA participate in the IPCS activity?