Physiologically Based Pharmacokinetic Modeling: An Introduction

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Outline

• What is pharmacokinetics (PK)?
• Why PK?
• PK Modeling Methods
• PBPK Model Components
• PBPK Model Structures

This presentation does not represent official US EPA policy.
Abbreviations

- **AUC**: area under the concentration-time curve (mg/L*hr)
- **Cl or Cl_d**: clearance (L/hr)
- **Cmax**: maximum concentration (mg/L or M)
- **ka**: absorption rate constant (1/hr)
- **Km**: Michaelis-Menten constant (M)
- **Vmax**: maximal metabolism rate
- **PD**: pharmacodynamics
- **PK**: pharmacokinetic
- **TD**: toxicodynamics
- **TK**: toxicokinetics
- **V or Vd**: volume of distribution (L) or tissue (L) (conversion of volume to mass assumes 1 g/mL, the density of water)
- **Q**: blood flow
What is Pharmacokinetics?

- What the body does to a chemical
- Absorption, Distribution, Metabolism, Excretion (ADME)
- Kinetics: rates of change,
- PK: chemical concentrations as a function of time
- Pharmacokinetics = Toxicokinetics
- Pharmacodynamics: What the chemical does to the body (PD=TD)
Why Use PK-based Analyses?

• Improved candidate selection during chemical or drug development
  – Cross-species comparisons of metabolism or absorption
  – Duration of action of different formulations
• Improved toxicity study design
  – Dose, species, dosing interval selection
• Improved toxicity study interpretation
  – Cross-species comparisons of metabolites or tissue distribution
  – Links to pharmacodynamics and effects
• Improved risk and safety assessments
  – Understanding interspecies, dose, route-to-route extrapolations
  – Evaluating population variability
    • Modeling populations (e.g., polymorphisms) versus individuals
    • Modeling life stages (e.g., children, elderly, ill)
  – Evaluating uncertainties
Dose-response Assessment

Exposure:
- external dose/concentration

Pharmacokinetics:
- internal tissue dose

Pharmacodynamics:
- action on target tissue

Response:
- measured toxicity

Low Information Default
Which Pharmacokinetic Analysis Method?

- Classical Compartmental Models
- Noncompartmental Models
- Population Pharmacokinetics
- PBPK Models
Classical Compartmental

- Fits equations to data to estimate PK parameters
- Requires *in vivo* data in relevant species
- Can be “physiological”, e.g., methanol distributes with total body water, but not a requirement
- Limitations:
  - Used for nonvolatiles, though adaptable for volatiles
  - PK changes with exposure difficult to address
  - Limited tissue distribution characterization
Noncompartmental/Regression Analysis

• Mathematical analysis of plasma time course data: trapezoid rule, nonlinear regression
  – Uses assumption of linear terminal phase to calculate AUC (zero to infinity) from data collected to final time point
• No model structure assumptions
• Requires *in vivo* chemical concentration data in relevant species

• Calculates pharmacokinetic outputs such as
  – AUC: area under curve
  – CL: clearance
  – Vss: steady state volume of distribution
  – Tmax: time of max. concentration
  – Cmax: max. conc.
Population Pharmacokinetics

- Statistical analyses to characterize pharmacokinetic parameters for populations of people
- Often focuses on issues of limited data (sparse data) for each individual within the population versus extensive time course data for an individual
Physiologically Based Pharmacokinetic (PBPK) Models

- PBPK models describe the organism as a set of tissue compartments interconnected by blood (plasma) flow
- Systems of differential equations based upon mass balance
PBPK Analysis

- Captures biological processes and hypotheses explicitly
  - Varying degrees of detail or biological realism
  - Flexibility to reflect biology
- Can incorporate changes in PK due to chemical (e.g. GSH depletion, protein induction), growth/aging
- Facilitates analyses across species, doses and human population subgroups
- Limitations:
  - Greater requirements for *in vitro* or *in vivo* data
  - Statistical evaluation of uncertainty and variability more challenging
  - Model development and implementation requires appropriate expertise
PBPK Model Components

• Model Purpose/Goal
• Deterministic Model
  – Biological Hypotheses
  – Exposure conditions
  – Desired outputs
• Non-deterministic Model
  – Statistical model
• Data
Model Purpose: Basic Questions

What do I need to know to carry out an analysis based upon internal dosimetry (i.e., applying pharmacokinetics)?

- What toxic effects at what life stages? (i.e., potential critical studies)
- What species (toxicity, PK, metabolism studies)?
  - Toxicity testing animals
  - Humans
- What is known about the mode of action for each toxicity of interest?
  - Parent chemical and/or metabolite(s) (reactive or not?)
  - Interactions with macromolecules, cells, tissues, systems?
  - Critical for PK model structure and selection of dose metrics.
- How will model be used in safety or risk assessment?
  - Route-to-route extrapolation (What routes?)
  - Cross-species extrapolation
  - Cross-chemical extrapolation
PBPK Model Components

Physiological/Anatomical
- Tissue volumes
- Blood flow rates
- Cardiac output
- Glomerular filtration rate
- Alveolar ventilation rate
- Hematocrit
- Glutathione concentration
- DNA concentration

Biochemical/Physicochemical
- Tissue: blood partition coefficient
- Blood: air partition coefficient
- Enzymatic rate constants
- Equilibrium or rate constants for protein binding
- Transporter rate constants

ADME
What Tissues (Compartments)?

- **Absorption**
- **Distribution**
  - Storage (e.g., fat, bone, serum protein binding)
  - Distributional kinetics (e.g., total body water)
- **Clearance**
  - Metabolism
  - Excretion (e.g., urine, bile, hair)
- **Target Tissues for Toxicity or surrogate (often blood)**
Description for a Single Well-mixed Tissue Compartment

TERMS

\[ Q_t = \text{tissue blood flow} \]
\[ C_{vt} = \text{venous blood concentration} \]
\[ P_t = \text{tissue blood partition coefficient} \]
\[ V_t = \text{volume of tissue} \]
\[ A_t = \text{amount of chemical in tissue} \]

mass-balance equation:

\[ \frac{dA_t}{dt} = V_t \frac{dC_t}{dt} = Q_t C_{art} - Q_t C_{vt} \]

venous equilibration assumption

\[ C_{vt} = \frac{C_t}{P_t} \]

\( C_{vt} \): free concentration in tissue available for clearance(s)
Diffusion Limited Distribution

TISSUE mass-balance equation:

\[
\frac{dA_t}{dt} = V_t \frac{dC_t}{dt} = PA_t \left( C_{tb} - C_t / P_t \right)
\]

TISSUE BLOOD mass-balance equation:

\[
\frac{dA_{tb}}{dt} = V_{tb} \frac{dC_{tb}}{dt} = Q_t \left( C_{art} - C_{vt} \right) + PA_t \left( C_t / P_t - C_{bt} \right)
\]

\(PA_T\): permeability area cross-product for tissue (L/hr)

Tissue: 33 L

Blood: 2 L RBC, 3 L plasma

Interstitial Fluid: 13 L

Capillary Wall

Intracellular Fluid: 33 L
Liver Compartment

rate of change of amount in liver = rate of uptake in arterial blood - rate of loss in venous blood - rate of loss by metabolism

\[
\frac{dA_l}{dt} = Q_l(C_a - C_{vl}) - \frac{V_m C_{vl}}{K_m + C_{vl}}
\]

When \( C_{vl} \ll K_m \), if \( V_m / K_m \ll Q_l \) (liver blood flow), then flow limited metabolism.

http://www.ncsu.edu/crsc/reports/ftp/pdf/crsc-tr02-17.pdf
Chemical-Specific Data

- **In vivo PK:** chemical levels over time and doses
  - Single or repeated exposures
  - Exposure (dosing) regimens: intravenous bolus or infusion, oral bolus, inhalation, dermal
  - Serial determinations in multiple animals (e.g., tissue or blood concentrations)
  - Repeated measures in same animal/human (e.g., serum, urine, feces, exhaled breath, closed chamber atmosphere)

- **In vitro or ex vivo**
  - Partition coefficients: analysis of equilibrium chemical distribution to blood and tissues
  - Protein binding rate or equilibrium constants
  - In vitro metabolism (e.g., estimates of Km and Vmax)
  - Changes in biochemistry following exposure (e.g., GSH depletion)
Examples of PBPK Models

- Pharmacological Agents
- Volatile Organic Compounds
- Mixtures
- Vapors with Nasal Toxicity
- Lifestages
Pharmacological
Agents:
All-Trans
Retinoic Acid

Clewell HJ 3rd, Andersen ME, Wills RJ, Latriano L.

A physiologically based pharmacokinetic model for retinoic acid and its metabolites.

Key Factors in Risk Assessment for all-trans-Retinoic Acid

- Species differences in metabolism
  - rodents: oxidation to active form
  - primates: glucuronidation to inactive form

- Exposure route differences in bioavailability
  - rapid oral uptake can exceed capacity of glucuronidation pathway
  - slow topical uptake subject to high affinity clearance

- Kinetic differences between isomers
  - all-trans: rapid glucuronidation/clearance
  - 13-cis: slow oxidation/clearance
Pharmacological Agents: Dichloroacetate

Water soluble model for dichloroacetate (Barton et al., 1999)
Pharmacological Agents: Diazepam

Wide range of mathematical analyses:


Volatile Organic Compounds: Vinyl Chloride

Clewell HJ, Gentry PR, Gearhart JM, Allen BC, Andersen ME.

Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model.

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

<table>
<thead>
<tr>
<th>Animal Bioassay Study</th>
<th>95% UCL Risk/million/ppb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>Maltoni - mouse inhalation</td>
<td>1.52</td>
</tr>
<tr>
<td>Maltoni - rat inhalation</td>
<td>5.17</td>
</tr>
<tr>
<td>Feron - rat diet</td>
<td>3.05</td>
</tr>
<tr>
<td>Maltoni - rat gavage</td>
<td>8.68</td>
</tr>
</tbody>
</table>

Human risk estimates (per million) for lifetime inhalation of 1 ppb vinyl chloride in air based on the incident of liver angiosarcoma in human epidemiological studies

<table>
<thead>
<tr>
<th>Epidemiological Study</th>
<th>95% UCL Risk/million/ppb</th>
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</thead>
<tbody>
<tr>
<td>Fox &amp; Collier</td>
<td>0.71 - 4.22</td>
</tr>
<tr>
<td>Jones et al.</td>
<td>0.97 - 3.60</td>
</tr>
<tr>
<td>Simonato et al.</td>
<td>0.40 - 0.79</td>
</tr>
</tbody>
</table>

Nasal Toxicity: Vinyl Acetate

Life Stage & Species Extrapolations

Neonatal Model
- Liver
  - Poorly Perfused
  - Richly Perfused
  - Lung

Maternal Model
- Liver
  - Poorly Perf.
  - Richly Perf.
- Mammary
  - Metabolism
  - Gut
  - Placenta
  - Lung
  - Body
  - Brain
Conclusion

• Model purpose
• Deterministic Biological Model
  – PK Determinants (ADME)
  – Target Tissues
  – Exposure Routes
• Non-deterministic Model
  – Often statistical (likelihood based)
  – Describes relationship between data and model
References Reviews


