A Brief History of Physiologically Based Modeling

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

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Exposure - Dose - Response Relationships

Exposure
- absorption, distribution; metabolism

Tissue Dose
- chemical actions; receptor binding

Molecular Interactions
- receptor activation; tissue reactivity

Early Cellular Interactions
- functional changes: i.e., enhanced contractility, hepatic failure

Toxic Responses
- cancer; tissue disease; reproductive - neurologic effects
PBPK Modeling

Pharmacokinetic modeling is a valuable tool for evaluating tissue dose under various exposure conditions in different animal species.

To develop a full understanding of the biological responses caused by exposure to toxic chemicals, it is necessary to understand the processes that determine tissue dose and the interactions of chemical with tissues.

Physiological modeling approaches are used to uncover the biological determinants of chemical disposition.
Pharmacokinetics

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

Collect Data → Select Model → Fit Model to Data

\[ C_t = A e^{-k_a t} + B e^{-k_b t} \]
Physiologically Based Pharmacokinetics

\[
\begin{align*}
Q_p & \quad C_i \quad C_x \\
Q_c & \quad C_{vl} \quad C_{vf} \\
C_{vr} & \quad C_{vs} \\
Q_r & \quad Q_s \\
Q_{f} & \quad Q_{L} \\
Q_{c} & \quad C_{a}
\end{align*}
\]

Liver

Rapidly perfused (brain, kidney, etc.)

Slowly perfused (muscle, bone, etc.)
Why have so many Scientists Been Interested in PBPK Modeling?

Haggard/Kety - Efficacy of anesthetic gases/vapors
Teorell - Drug pharmacokinetics
Mapleson - Inhaled gases & analog computation
Fiserova-Bergerova - Metabolized vapors in workplace
Rowland/Wilkinson - Clearance Concepts in PKs
Bischoff and Dedrick - Engineering approach for PBPK
Physiological Modeling Of Volatiles

Haggard (1924)
Mapleson (1961)
Riggs (1963)
Fiserova-Bergerova (1974)

Physiological Modeling Of Drugs

Teorell (1937)

Kety (1951)

Bischoff (1971)
Dedrick (1973)
Rowland and Wilkinson (1975)

Volatile Organic Compounds

Ramsey and Andersen (1984)

CH₂Cl₂
Dioxin
VCM & TCE
ESTERS

More widespread interest for use in Risk Assessment and Drug Industry
Diethyl Ether – Uptake into the Body

From: Hagaard (1924)
Pulmonary Equilibration

Terms:

- \( Q_c \) = cardiac output
- \( Q_p \) = alveolar ventilation
- \( C_{inh} \) = inhaled concentration
- \( C_{exh} \) = exhaled concentration
- \( C_{art} \) = arterial concentration
- \( C_{ven} \) = venous concentration
- \( P_b \) = blood/air partition coefficient

Problem: Estimate amount taken up in first few breaths.

Rate of uptake = \( Q_c C_{art} \)
In the first few breaths, we can estimate uptake in relation to these physiological characteristics:

\[ Q_p \cdot (C_{inh} - C_{exh}) = Q_c \cdot (C_{art} - C_{ven}) \]

In first few breaths, \( C_{ven} = 0 \). By the equilibration assumption \( C_{exh} = C_{art}/P_b \), so

\[ Q_p \cdot C_{inh} = Q_c \cdot C_{art} + Q_p \cdot C_{art}/P_b \]

\[ C_{art} = Q_p \cdot C_{inh} \cdot P_b / (P_b \cdot Q_c + Q_p) \]

\[ \text{Uptake} = Q_c \cdot C_{art} = P_b \cdot Q_c \cdot Q_p \cdot C_{inh} / (P_b \cdot Q_c + Q_p) \]

Limiting conditions of solubility....
Pulmonary Uptake (1924)

Evaluate for limiting conditions:

\[ P_b \ll 1; \quad \text{rate} = P_b Q_c C_{inh} \quad \text{(poorly soluble)} \]
\[ P_b \gg 1; \quad \text{rate} = Q_p C_{inh} \quad \text{(very soluble)} \]

Former is blood flow limited; latter is ventilation limited.

Provided physiological insight in behavior, but no available techniques could solve equations for more complete biological description of mammalian system.
The System of Interest has a group of Parallel Physiological Compartments

Kety (1951)
Description for a Single Tissue Compartment

**Terms**
- $Q_t$: tissue blood flow
- $C_{vt}$: venous blood concentration
- $P_t$: tissue blood partition coefficient
- $V_t$: volume of tissue
- $A_t$: amount of chemical in tissue

**Mass-balance equation:**

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

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

*(venous equilibration assumption)*
Kety (1951)

• The kinetic behavior of the tissues is related to three tissue characteristics - volume, blood flow and partition coefficient. For infusion into a tissue at constant concentration, we have a simple exponential for filling:

$$C_t = P_t \times C_{art} \left(1 - e^{-\left(\frac{Q_t}{P_t \times V_t} \right) t}\right)$$

Tissue filling or elimination occurs with a rate constant $Q_t/(P_t \times V_t)$
Input Concentration Invariant ($C_{art}$ constant)

\[ Ct = Pt \times \text{Cart} \left(1 - e^{-\frac{Qt}{Pt \times Vt} \times t}\right) \]

Unrealistic physiologically, but shows general dependence of rate parameters on physiological and chemical specific parameters
Compartmental and Physiological Modeling of Drugs

Teorell (1937)

Blood circulation

Tissue boundaries

\[ \begin{align*}
\text{Symbol} & \quad D \quad B \quad K \quad T \quad I \\
\text{Amount} & \quad x \quad y \quad u \quad z \quad w \\
\text{Volume} & \quad V_1 \quad V_2 \quad - \quad V_3 \quad - \\
\text{Concentration} & \quad x/V_1 \quad y/V_2 \quad - \quad z/V_3 \quad - \\
\text{Perm. Coeff.} & \quad k_1' \quad - \quad k_4' \quad k_2' \quad - \\
\text{Velocity} & \quad K_1 = k_1'/V_1 \quad - \quad K_4 = k_4'/V_2 \quad k_3 = k_2'/V_3 \quad k_5 \\
\text{Constant} & \quad \text{neglected} \quad - \quad \text{not existing} \quad k_2 = k_2'/V_2 \quad - \\
\text{Name of process} & \quad \text{Resorption} \quad - \quad \text{Elimination} \quad \text{Tissue take up as output} \quad \text{Inactivation}
\end{align*} \]
Teorell (1937)

Provided a clear physiological description of determinants of drug disposition.

Lacked the ability to solve the series of equations and simplified the systems. Over the years so-called compartmental PK analysis was developed to examine pharmacokinetic behavior. These simplified models give equations that have exact solutions and have provided many useful insights despite their very much simplified depiction of animal physiology.

PK, more as study of systems of equations with exact solutions, rather than the study of PK processes.
Blood Flow Characteristics in Animals & Digital Computation

Bischoff and Brown (1961)
Modeling Tissue Accumulation of Methotrexate Due to Its Interaction with a Critical Enzyme

Methotrexate (tissue blood)  
Dihygrofolatereductase (DHFR)  
Methotrexate Complex  
MTX-DHFR Complex  
MTX-Tissue

R(t) - tissue partition  
Kd - MTX-DHFR dissociation constant

arterial blood  
venous blood
Compartmental model for Methotrexate

Plasma ---> Liver

Liver ---> G.I. Tract

G.I. Tract ---> Gut Lumen ---> Feces

Gut Lumen ---> Kidney

Kidney ---> Muscle

QL - QG

QG

Gut absorption

QK

QM

Bischoff et al. (1971)
Methotrexate - Bischoff et al. (1971)
Then used in toxicology......
Is any of this really new?

Ramsey and Andersen (1984)
Styrene & Saturable metabolism

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

- Equations solved by numerical integration to simulate kinetic behavior.
- With venous equilibration, flow limited assumptions.
Dose Extrapolation – Styrene

How does it work?

![Graph showing venous concentration over time for different concentrations of Styrene.](image)

- **Conc = 600 ppm**
- **Conc = 1200 ppm**
- **Conc = 80 ppm**

TIME - hours

Venous Concentration - mg/lier blood
What do we need to add/change in the models to incorporate another dose route – iv or oral?
Styrene - Dose Route Extrapolation

What do we need to add/change in the models to incorporate these dose routes?

**IV**

Styrene Concentration (mg/l) vs. Hours

**Oral**

Styrene Concentration (mg/l) vs. Hours
What do we need to add/change in the models to describe another animal species?

- Sizes
- Flows
- Metabolic Constants
Styrene - Interspecies Extrapolation

What do we need to add/change in the models to change animal species?

Graphs showing the concentration of styrene in blood and exhaled air over time.
ADVANTAGES OF SIMULATION MODELING IN
PHYSIOLOGY AND ALSO IN
PHARMACOKINETICS & RISK ASSESSMENT

- 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


Learning from PBPK Models

Haggard, 1924
Kety, 1951
Mapelson, 1963
Fiserova-Bergerova, 1974
Ramsey & Andersen, 1984
Reitz et al., 1990

Metabolism (Vmax; Km)

Elimination

Cinh

Cexh

Venous Blood

Lung

Fat

Viscera

Muscle/Skin

Liver

Vd
**Initial Fits - Some Good, some not so good**

- **Fat Concentration**
  - Male Rat - Single Exposure
  - **Time (hours)**
  - **Fat Concentration (g/ml)**
    - 700 ppm
    - 70 ppm
    - 7 ppm

- **Plasma Concentration**
  - Male Rat - Single Dose
  - **Time (hours)**
  - **Plasma Concentration (g/ml)**
    - 700 ppm

- **Excretion Rate**
  - Male Rat - Single Dose
  - **Time (hours)**
  - **Excretion Rate (mg/hr)**
    - 700 ppm
    - 70 ppm
    - 7 ppm

- **Exhaled D4**
  - Male Rate - Multiple Exposures
  - **Time (hours)**
  - **D4 Exhalation Rate (mg/hr)**
    - 700 ppm
    - 7 ppm
Revise the Model:

- Account for lipid storage compartments within tissues

- Account for lipid compartment to blood that transport compound from liver-peripheral tissue transport of chylomicrons, etc.

![Diagram showing liver lipid compartment and blood lipid compartment with lipid removal and carrier processes.](image)
• Revised Model Structure:

- Lipid storage in tissues
  • Liver
  • Lung
- Chylomicron-like lipid blood transport
- Second fat compartment
New Fits with Lipid Components in Blood

Then some experiments..... examine lipids in blood
Physiologically Based Pharmacokinetic (PBPK) Modeling

Define Realistic Model

Collect Needed Data

Make Predictions

Refine Model Structure

Metabolic Constants
Tissue Solubility
Tissue Volumes
Blood and Air Flows
Experimental System

Model Equations

You can be wrong!
Dose-Dependent Distribution of Dioxin

Abraham et al. (1989)

Concentration (% dose/gm tissue) vs. Dioxin Dose (nanograms/kg)

Liver and Fat concentrations are shown as a function of increasing dioxin dose.
Induction is Non-Uniform in Liver

The PBPK model for dioxin protein induction must account for regional differences in response.

How was this be accomplished?
Creating a Multi-Compartment Liver Acinus:

**Induction Equations:**

\[
d[P_r]/dt = k_0 + \frac{k(max) [Ah-dioxin]^n}{K_{b1}^n + [Ah-dioxin]^n} - k(\text{elim}) [P_r]
\]

**Liver Bulk Structure:**

[Diagram of liver structure with compartments and flow]
Visualization and Comparison with Immunohistochemistry

- Simulation of geometric organization is necessary. The predicted induction in the various sub-compartments was used to 'paint' regions in a two-dimensional acinus.
Modeling Regional Induction in the Liver

- Requires high \( n \)-values, i.e., the response is highly non-linear.
- Binding constants between adjacent zones vary by threefold.
- Induction is equivalent to switching cells.
- Raises questions about the actual mechanism of induction and how uncertainties in the 'mechanism' influence current risk assessments.

Protein induction visualized by painting the acinar structures according to extent of induction.
Comparing the pathologist's view with the modeler's predictions....
A 'Systems' Approach for Dose Response

- Uptake
- Absorption
- Distribution
- Metabolism
- Interaction w/ cellular networks
- Excretion
- Effects

Other Stimulus

RTK

TCDD Ligand

Ah Receptor

Adaptor

MAPK

Transcription

DRE
Physiological Pharmacokinetic Modeling and its Applications in Safety & Risk Assessments

References:


Haggard, H.W. (1924). The absorption, distribution, and elimination of ethyl ether. II. Analysis of the mechanism of the absorption and elimination of such a gas or vapor as ethyl ether. J. Biol. Chem., 59: 753


