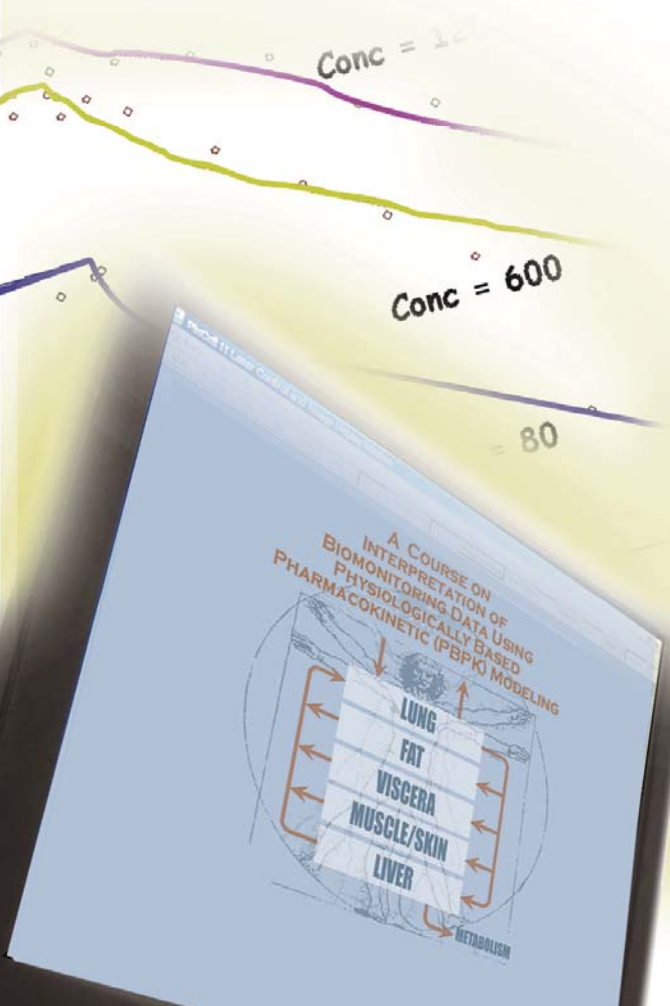


Clearance in PBPK Models

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

February 11 – February 15, 2008



Clearance Concepts in Physiology and Pharmacokinetics

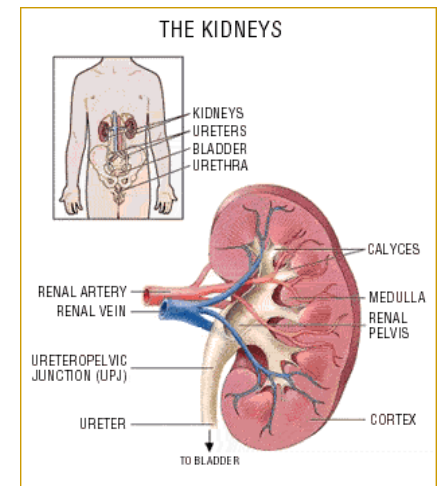
Background: Clearance terminology has a long history in describing both the physiology of specific organs and compartmental pharmacokinetics. These concepts also underlie most of the equations used in PBPK models.

The kidney removes chemicals from circulating blood by filtration. The liver removes chemicals from the circulating blood by metabolism. With each of these organs, we can describe the function of the organ in terms of "clearances". In this usage, clearance is a volumetric flow of blood (for instance, liters/hour) from which all chemical is removed.

Kidney Clearance: For the kidney, urinary clearance (Cl_{urine}) is estimated by the ratio of the total amount of chemical excreted in the urine over a given time interval divided by the blood concentration and duration of collection.

$$Cl_{urine} = ((C_{urine} * \text{Urine Volume}) / C_{blood}) / \text{Collection Duration}$$
$$\text{Amount Removed} = Cl_{urine} * \text{Cart}$$

Thus, urinary clearance becomes the volumetric flow of blood from which the chemical would have to be completely removed to account for the observed excretion into the urine. Compare renal clearances with renal blood flow and glomerular filtration to assess mechanisms of clearance - passive filtration versus active transport.



Extraction of Chemical from Renal Blood Flow:

Another useful concept is extraction, i.e., the proportion of blood flow from which all chemical is removed during a single pass through the organ. From the example with the kidney, extraction can be related to clearance and blood flow to the kidney (Q_{kidney}).

$$\text{Extraction (E)} = Cl_{\text{urine}} / Q_{\text{kidney}}$$

Hepatic Clearance: A great deal of work and analysis has been conducted to describe the removal of drugs and toxicants by metabolism in the liver in relation to extraction and clearance. The major relationships are similar to those for the kidney.

$$Cl_{\text{liver}} = Q_{\text{liver}} * \text{Extraction}$$

$$Cl_{\text{liver}} = Q_{\text{liver}} * (C_{\text{ART}} - C_{\text{VEN}}) / C_{\text{ART}}$$

$$Cl_{\text{liver}} = Q_{\text{liver}} * (C_{\text{IN}} - C_{\text{OUT}}) / C_{\text{IN}}$$

$$\text{Amount Removed} = Cl_{\text{liver}} * C_{\text{art}}$$

Hepatic metabolism: For the case where extraction is due to metabolism, the clearance at low substrate concentrations is readily expressed in relation to liver blood flow and the kinetic parameters for metabolism, V_{max} and K_m .

$$Cl_{liver} = (Q_{liver} * V_{max} / K_m) / (Q_{liver} + V_{max} / K_m)$$

As with the kidney, the interpretation of the liver clearance is the volumetric flow which the chemical has to be removed to account for the extraction.

Clearance Concepts in Data Based Compartmental PK Models

In deriving the parameters from compartmental pharmacokinetic models, we also talk about clearance of compounds from the central compartment by the liver metabolism. A one-compartment model with metabolic elimination in the liver is expressed in terms of the



Amount in the compartment (A_1), the Volume of distribution ($V_{d,1}$), and the Concentration in the compartment (C_1).

Clearances are Related to Volumes and Flows

The mass balance equation for the change in amount in the compartment can be written in several equivalent forms.

$$dA_1/dt = - k_{elim} * A_1$$

$$dA_1/dt = - k_{elim} * V_{d,1} * C_1$$

$$dA_1/dt = - Cl_{liver} * C_1$$

So, Clearance is the volume of distribution times the elimination rate constant

Some Advantages to Assessing Clearances in Compartmental Models

In the last formulation, the loss of chemical from the system over time is liver clearance multiplied by the concentration in the central compartment. If there are other organs that are involved in removal, i.e., in filtration by the kidney or in exhalation by the lungs, the equation is simply altered to account for the sum of all the clearances.

$$dA_1/dt = - (Cl_{liver} + Cl_{kidney} + Cl_{exhalation}) * C_1$$

Clearance Relationships as the Foundation of PBPK Models

When writing the mass balance equations for PBPK models, the individual terms on the right side of the equation, i.e., the arrows in the schematics, are generally written in relation to compartmental concentrations, not amounts as done with the compartmental descriptions. The concentration terms in the equation represent "free" concentrations within the compartments.

What do these Equations Represent?

This structure for the models is equivalent to calculating the activity of chemical available for diffusion, reaction, binding, or any other chemical interaction that should be based on the free concentration of the compound in the compartments.

Some representative equations we use in this course are:

$$dA_{\text{liver}}/dt = Q_{\text{liver}} * (C_{\text{ART}} - C_{\text{L}}/P_{\text{L}}) - (k * V_{\text{liver}}) * C_{\text{L}}/P_{\text{L}}$$

$$dA_{\text{fat}} / dt = PA_{\text{fat}} * (C_{\text{VF}} - C_{\text{F}}/P_{\text{F}})$$

$$dA_{\text{fat blood}}/dt = Q_{\text{fat}} * (C_{\text{ART}} - C_{\text{VF}}) + PA_{\text{fat}} * (C_{\text{F}}/P_{\text{F}} - C_{\text{VF}})$$

All the proportionality constants in these equations have units of flow (volume/time).

- $Q_{\text{liver}} ; Q_{\text{fat}}$ are blood flows (l/hr)
- V_{max}/K_m has units of mg/hr divided by mg/l (i.e., liters/hour)
- PA_{fat} has units of a permeation coefficient (cm/hr) times an area (cm²) - vol/time
- $k * V_{\text{liver}}$ has units of inverse time multiplied by volume (volume/time)

How do we interpret these proportionality constants in the equations?

- They represent inter- and intra-compartmental clearances.
- Each clearance term represents the net volume of the compartment cleared of chemical by the individual processes, i.e., flow, diffusion, and first-order or saturable metabolism.
- It is perfectly reasonable to think of these mass balance equations as clearance equations that calculate net mass fluxes between and within compartments.
- The net organ clearances are determined by the interrelationship of these individual microscopic clearance terms for any particular compartment in the PBPK model.

Simple PBPK Models for Lipophilic Compounds

Some general questions to consider are:

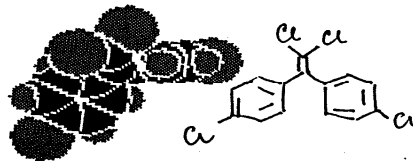
- What chemicals are included in this class of “lipophilic compounds”?
- How do we create a simulation model for one of these compounds from the component parts we developed in the earlier computer exercises?
- What kinds of generic behavior should we expect from these kinds of chemicals?

Some Lipophilic Compounds

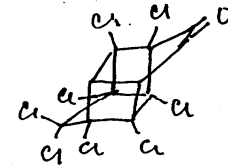
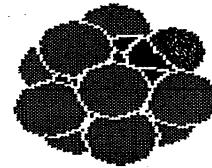
- DDT/DDE - an insecticide and its metabolite
- Mirex - an insecticide used for fire ants
- Kepone - chlordecone; an insecticide similar to Mirex
- Hexachlorobenzene - a fungicide
- Polychlorinated and polybrominated biphenyls PCBs and PBBs - used as dielectrics, fire retardants
- Polyhalogenated dibenzo-p-dioxins and furans - found as contaminants in other synthetic processes, in chlorine bleaching activities, and in incineration

Let's Look at Some Structures

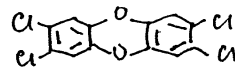
1. DDE:



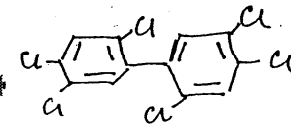
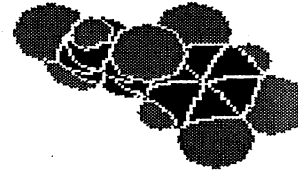
2. Kepone:



3. 2,3,7,8-TCDD



4. 2,4,5,2',4',5'-HCB

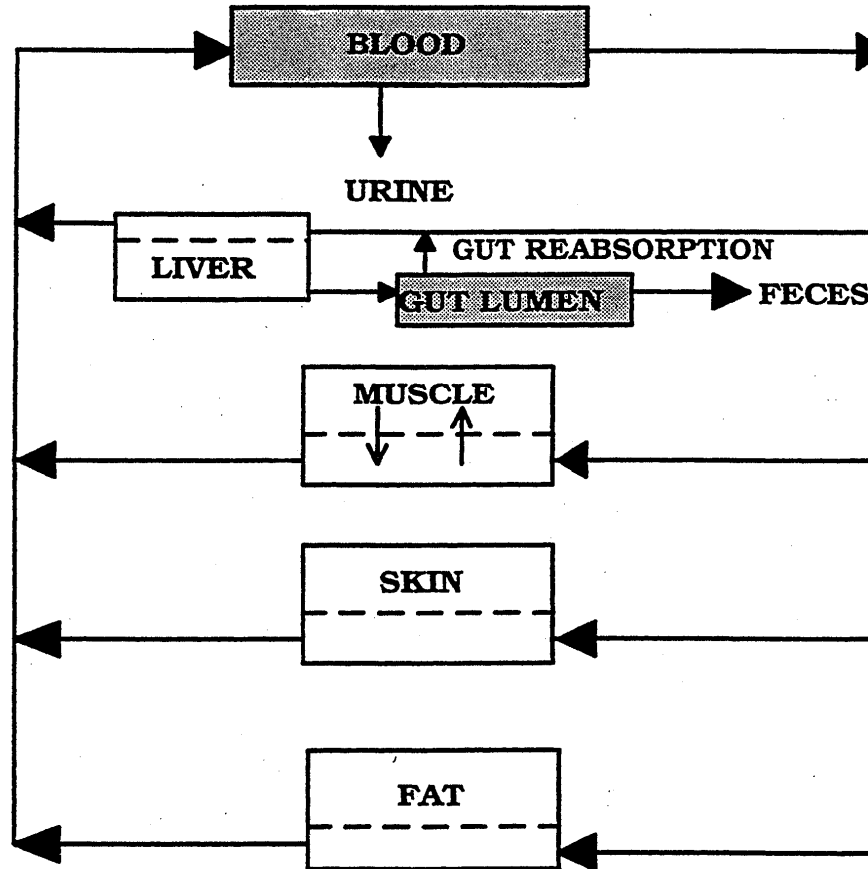


Properties: poorly water soluble, high octanol-water partition behavior, few accessible sites for metabolism. Provides an example of the role of physical chemical/biochemical properties in distributional and kinetic behavior of a class of compounds.

Why are these Compounds of Interest Environmentally?

- Direct biological activities
- Estrogenic actions (DDT and DDE)
- Fat seeking (i.e. lipophilic)
- Relatively resistant to metabolism
- Accumulate in the food chain
raptors, fish, marine mammals, people!!
- Very long persistence

PCB MODEL LUTZ ET AL. (1977)



* Metabolism in the liver; fat storage; diffusion-limited tissue uptake.

Compounds Examined:

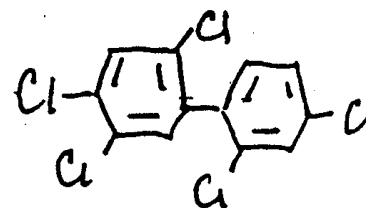
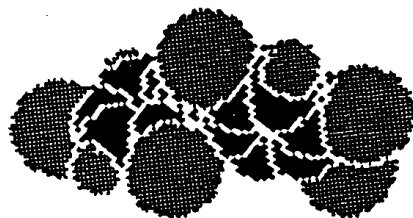
4-Chlorobiphenyl



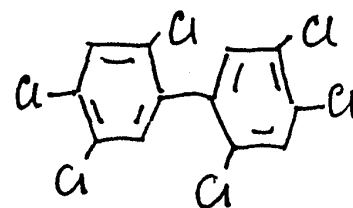
4,4'-Dichlorobiphenyl



2,2',4,4',5-Pentachlorobiphenyl



2,2',4,4',5,5'-Hexachlorobiphenyl



*Compartment sizes and perfusion rates for a standard
250-g rat*

Compartment	Volume	Blood Flow
	<i>ml</i>	<i>ml/min</i>
Blood	22.5	
Gut lumen	14	
Muscle	125	7.5
Liver	10	16
Skin	40	(0.5) ^a
Adipose tissue	17.5	0.4

^a Effective blood flow; see text.

Tissue/blood distribution ratios

Compartment	Parent				Metabolite			
	1-CB	2-CB	5-CB	6-CB	1-CB	2-CB	5-CB	6-CB
Blood	1	1	1	1	1	1	1	1
Gut lumen	1	1	1	1	1	1	1	1
Muscle	1	.2	1	4	0.14	0.40	0.10	0.30
Liver	1	3	6	12	2	5	2	4
Skin	10	10	7	30	0.25	0.30	0.10	2
Adipose	30	70	70	400	0.40	0.60	0.40	2

Kinetic Parameters

Rate Constant	1-CB	2-CB	5-CB	6-CB
Metabolism constant, k_m , ml/min	10.0	2.0	0.39	0.045
Kidney clearance, k_K , ml/min	0.20	0.133	0.033	0.030
Biliary clearance, k_B , ml/min	0.20	0.35	0.30	0.30
Gut reabsorption, k_G , min ⁻¹	0.00016	0.00016	0.00016	0.00016
Fecal transport, k_F , min ⁻¹	0.0008	0.0008	0.0008	0.0008

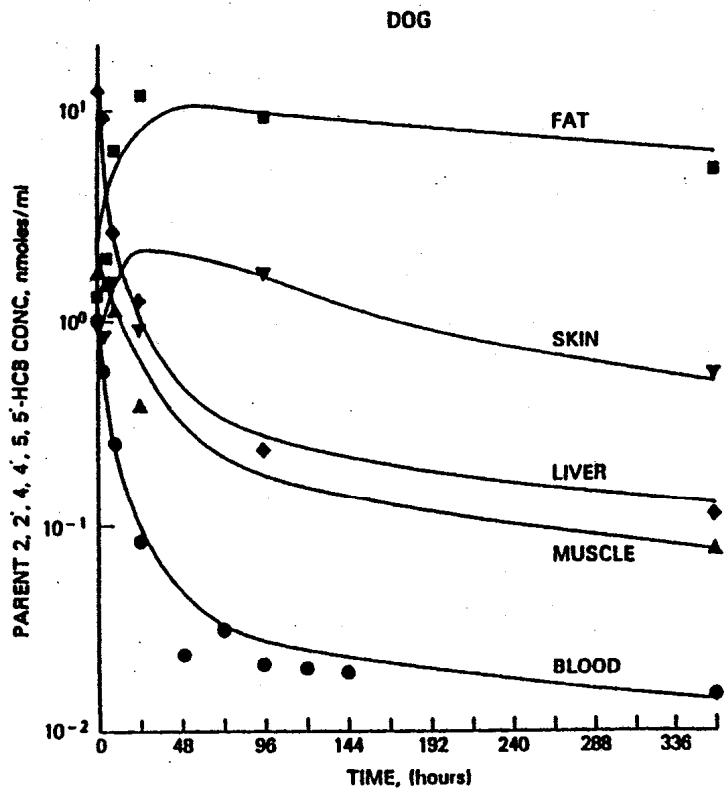


FIG. 6. Tissue concentration as a function of time for parent 2,2',4,4',5,5'-HCB in the dog.

Fat (■), skin (▼), liver (◆), muscle (▲), blood (●).

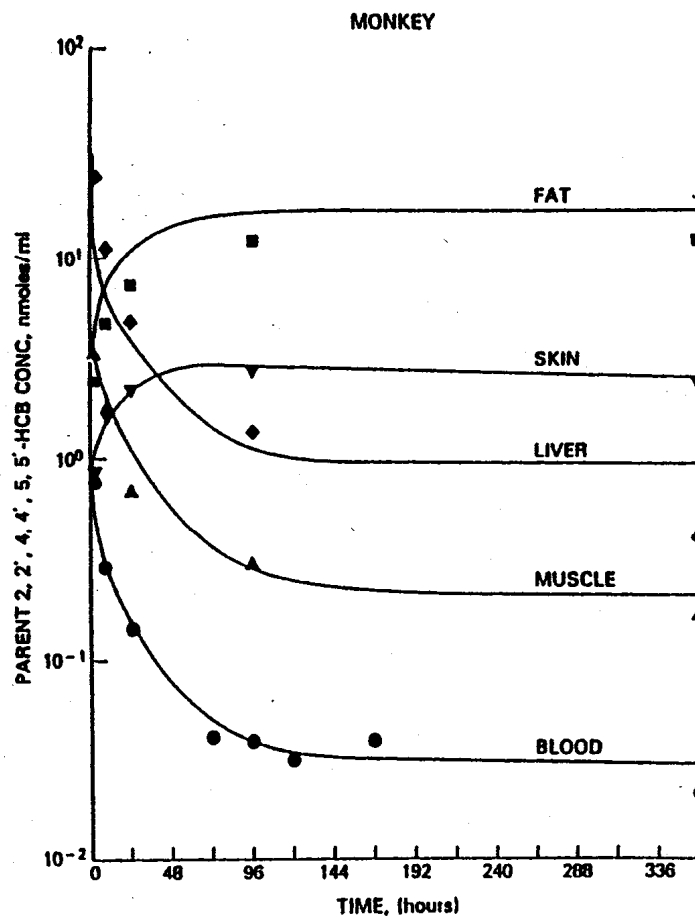


FIG. 3. Tissue concentration as a function of time for parent 2,2',4,4',5,5'-HCB in the monkey.

Fat (■), skin (▼), liver (◆), muscle (▲), blood (●).

What are the Elimination Routes for these Lipophilic Compounds?

- Metabolism - highly structure dependent
- Passive diffusion across intestines to lumen
- Exfoliation of cells lining intestines (HCB; Freeman et al.)
- Enterohepatic entrainment and fecal elimination
- Other ?????? Can you think of any?

Query: Why has cholestyramine been used to hasten elimination of Kepone from exposed people?

What Determines the Long Half-Life with These Chemicals?

- Hexachlorobiphenyl compound has the highest fat partitioning, $P_f = 400$.
- With this compound the half-life of elimination is greater than 60 days.
- What role does the fat storage play in determining the observed half-life?
- **Hint:** Determine the fat tissue intrinsic half-life given:
 $P_f = 400$
 $Q_f = 0.4 \text{ ml/min (0.024 l/hr)}$
 $V_f = 0.01751$
 $t_{12} \text{ (days)} = 0.693 * V_f * P_f / Q_f / 24$
- When do we expect the elimination behavior to be most sensitive to the fat tissue characteristics, i.e., when are the fat characteristics rate-limiting?

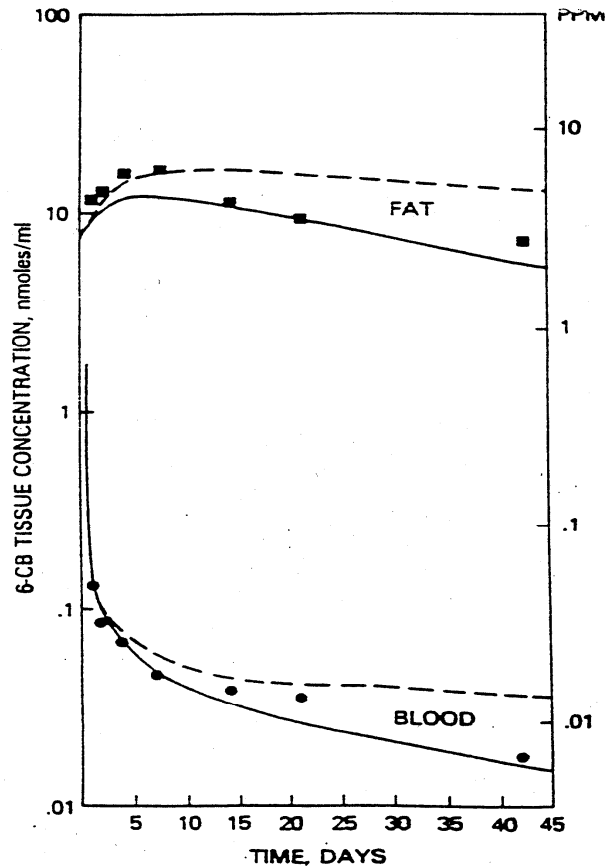
Incorporating Time-Dependent Physiological Parameters in Models for Lipophilic Compounds

Two Approaches for Implementation:

Dataset Functions (page 40) or Equations

Include explicit equations accounting for changing volumes, flows, partition coefficients, etc. These equations are placed in the derivative section and evaluated throughout the integration. For example,

$$\begin{aligned} BW_+ &\sim BW_0 + f(\text{time}) \\ V_{\text{tissue}} &\sim f(\text{time, lean body weight}) \\ Q_{\text{tissue}} &\sim f(V_{\text{tissue}}) \end{aligned}$$



HCB concentrations in fat and blood as a function of time for 42 days after a single iv dose of 0.6 mg/kg in the rat in models with and without accounting for changing body composition during the period of observation. **WHAT'S GOING ON HERE?**

Points to Emphasize from our Examination of these Lipophilic Compounds

- Complex models are created from relatively simple constituent parts.
- Slow elimination from the body does not tell us anything about the rates of movement of the chemical from one tissue to another in the body.
- Growth can lead to non-linear kinetic behavior for studies where elimination is very slow, or for cases where we examine kinetics in chronic, lifetime dosing situations.