

Applying Physiologically-Based Pharmacokinetic Modeling to Predict Relative Tissue Distribution and Excretion Capacities in Infants, Children, and the Unborn

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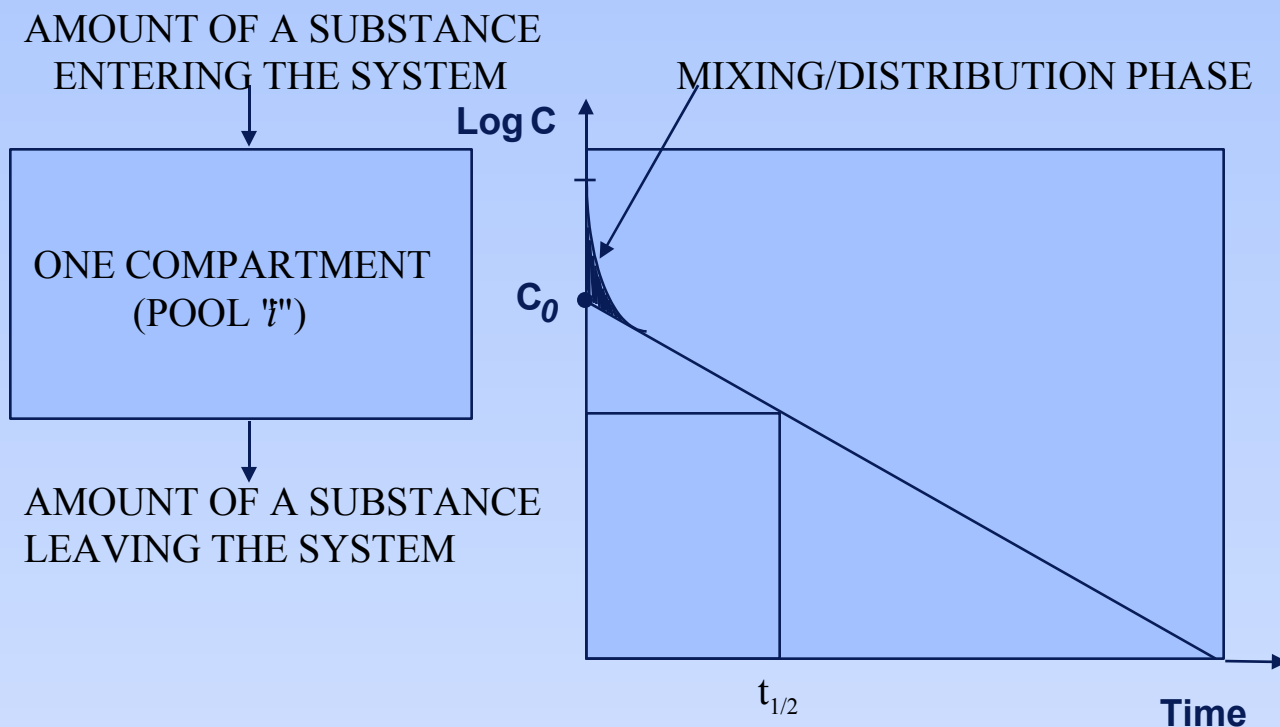
Based on the Following Publications:

Byczkowski, J.Z.: Linked PBPK model and cancer risk assessment for breast fed infants. Drug Inf. J. 30: 401-412, 1996.

Byczkowski, J.Z., and Lipscomb, J.C.: Physiologically based pharmacokinetic modeling of the lactational transfer of methylmercury. Risk Analysis 21: 869-882, 2001.

Dorman, D.C., Allen, S.L., Byczkowski, J.Z., Claudio, L., Fisher, J.W., Harry, G.J., Li, A.A., Makris, S.L., Padilla, S., Sultatos, L.G., and Mileson, B.E.: Methods to Identify and Characterize Developmental Neurotoxicity for Human Health Risk Assessment: III. Pharmacokinetic and Pharmacodynamic Considerations. Environmental Health Perspectives. 109 (Suppl 1) 101-111, 2001.

- While several "ready made" computer-aided pharmacokinetic (PK) models are being more or less successfully used in clinical trials and routine clinical practice, they do not have a predictive power and usually fail in pre-clinical extrapolations of PK data from animals to human subjects, particularly to infants, children and the unborn.



$$-dA_i/dt = \text{const} * A_{i0}$$

$$\text{if } V_i = V_{i0}$$

$$-dC_i/dt = k * C_{i0}$$

$$C_{i(t)} = C_{i0} * \exp(-k * t)$$

$$\log C_{i(t)} = \log C_{i0} - k * t / 2.303$$

$$t_{1/2} = 0.693 / k$$

Where: C_i - concentration of a substance in "i-th" compartment at time t ;
 C_{i0} - theoretical concentration at $t = 0$;
 k - the rate constant of a substance elimination;
 $t_{1/2}$ - half-life.

$$C_i = C_{i0} * e^{-k * t} + \dots$$

- **Mathematical methods used in pharmacokinetic modeling can be sub-divided into: (1) descriptive and (2) predictive.**

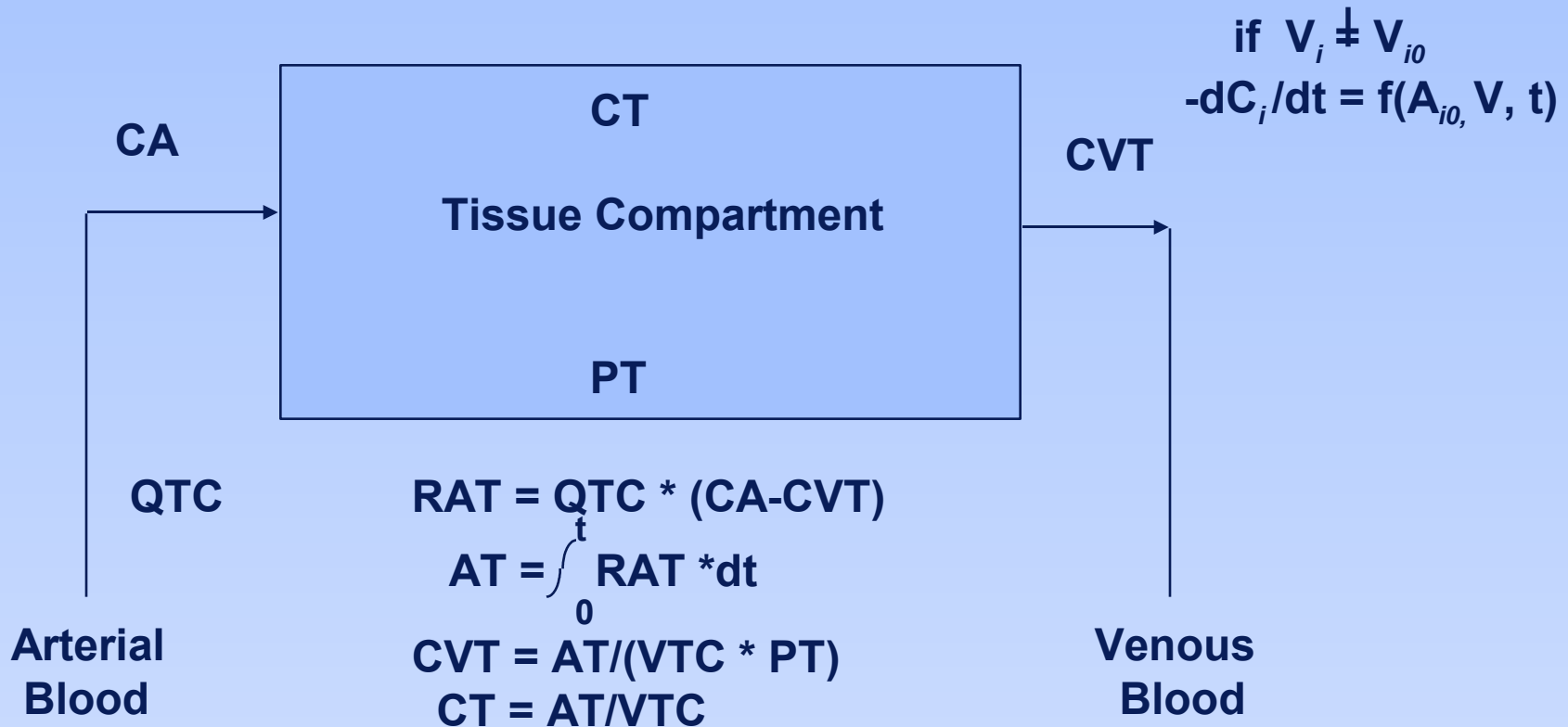
(1) A nonlinear regression analysis is an example of the descriptive mathematical method, in which parameters of the equation for a continuous curve are fit into the experimental data points. Descriptive models may be valuable for mimicking the system variables between the experimental data points but they often fail in extrapolations beyond the range of experimental calibrations.

(2) A physiologically based pharmacokinetic (PBPK) modeling is an example of the predictive method, in which parameters of the PBPK model quantitatively describe relations between the internal workings and correspond to the physicochemical and physiological properties of the PK system. The PBPK model provides insight into the mechanism of disposition of the chemical within the organism, and reflects as well as describes the real physiological phenomena of interactions between the chemical and the organism. Properly calibrated and validated predictive models may be used beyond the range of experimental data points, and thus they can still reliably predict the behavior of PK systems in regions where no information is available.

- **The PBPK models can predict the dose delivered to the fetus/child: peak concentration, concentration at the critical time point, integrated dose (AUC), etc.**

- Quantification of the developmental non-linearities and discontinuities are well handled only by the physiologically based PK/PD (PBPK/PD) models.

Basic Concepts of PBPK Modeling

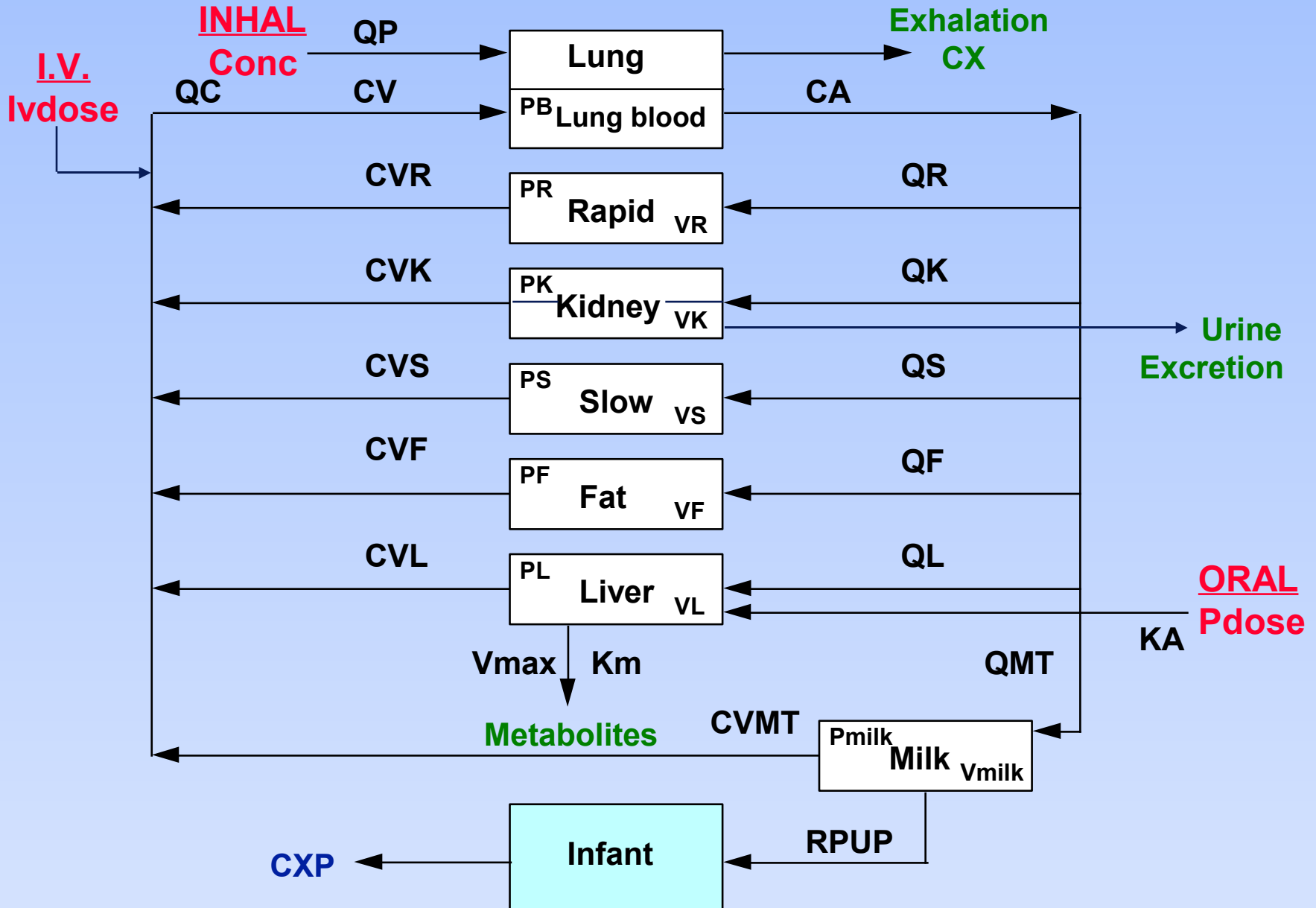


Where: CA - concentration in arterial blood; CVT - concentration in blood leaving the tissue; CT - concentration in tissue; PT - partition coefficient tissue/blood; QTC - fractional blood flow to tissue; RAT - rate of change of amount in tissue; AT - amount in tissue; VTC - volume of tissue.

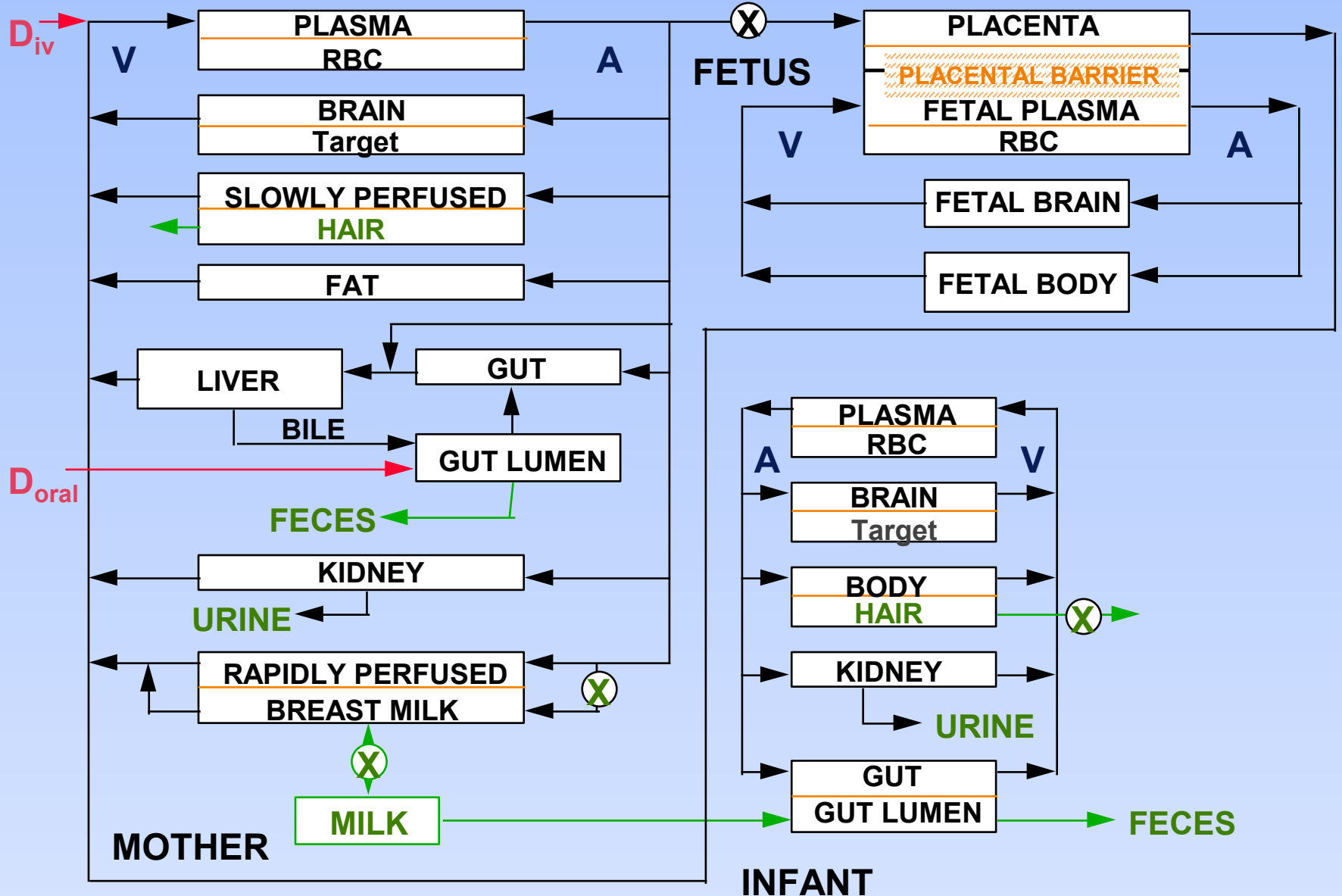
The basic assumption in PBPK modeling is that either blood flow to the tissue or diffusion are limiting the drug delivery.

- The mathematical basis for PBPK modeling was established by Torsten Teorell (Arch. Intern. Pharmacodyn. 57:205-225; 226-240, 1937) but simultaneous solutions of several interlinked differential equations were not feasible before the invention of the digital computer.
- Kenneth Bischoff (Chem. Eng. Prog. Symp. Ser. 62:33-45, 1966) applied digital solution of a physiologically realistic description of drug distribution in mammals.
- Initially, sets of interlinked differential equations had to be coded in a programming language (e.g., Fortran), linked to commercial subroutines, solved and interfaced with commercial display programs.
- When computer hardware became sufficiently fast and a specialized simulation software made it easier to construct PBPK models, several successful models were developed, at first for toxic chemicals in adult animals (Ramsey and Andersen, Toxicol. Appl. Pharmacol. 73:159-175, 1984; Leung, J. Toxicol. Environ. Health. 32:247-267, 1991).
- Eventually, PBPK models were developed to describe distribution of chemicals in pregnant and lactating animals and humans (Fisher et al. Toxicol. Appl. Pharmacol. 99:395-414, 1989).

Schematic representation of chemical mass flow in the PBPK model for lactating mother



Schematic representation of chemical mass flow in the PBPK model for a child during pregnancy and lactation



- In a fully developed organism, ADME kinetics of drugs is governed mainly by chemical-specific physicochemical parameters (e.g., partition coefficients, tissue protein binding, metabolism constants, etc).
- In developing child the uptake and distribution of chemicals within the target tissue are affected by the rapid and pronounced anatomical and physiological changes that take place during pregnancy and maturation.
- Both tissue distribution and the internal dose of chemicals change over time, often in a nonlinear fashion. PBPK models for developing child must take into account changes in physiological parameters occurring during pregnancy, lactation and fetal/neonatal development.
- The parameters that are most affected by these changes are:
 - (1) maternal body weight,
 - (2) maternal tissue and fluid volumes,
 - (3) weight of the embryo/fetus/infant and volume of its developing organs,
 - (4) metabolic clearance,
 - (5) pulmonary ventilation,
 - (6) cardiac output,
 - (7) renal function, and
 - (8) maternal intestinal motility.

- **PBPK models for fetus and developing child are inherently more complex than conventional PBPK models and require:**
 - **Extensive parametrization that includes:**
 - (1) **Maternal physiological parameters changing during gestation and lactation;**
 - (2) **Embryo/fetal/infant physiological parameters changing during development.**
 - **Powerful computational tools:**
 - (1) **Contemporary PCs have sufficient power to run simulations which required mainframe or VAX microcomputers less than a decade ago.**
 - (2) **Specialized software (e.g., ACSL, SCoP, etc) provide user-friendly interface for simultaneous solution of multiple nonlinear differential equations and transfer functions.**
 - **Experimental validation:**
 - (1) **While human embryo/fetal/infant growth has been relatively well described in quantitative terms, very little data is available for the laboratory animals.**
 - (2) **Allometric scaling offers a reasonable choice to extrapolate between humans and animals. However, validation is usually confined to comparisons with limited data during the late embryonic and fetal periods of development (e.g., after gestation d 11 in the rat and mouse).**

- **Examples of successful PBPK models for pregnancy and/or lactation:**

(1) A flow-limited PBPK model of tetracycline in the pregnant rat (Olanoff and Anderson, J. Pharmacokinet. Biopharm. 8: 599-620, 1980).

(2) A PBPK model of morphine disposition in the rat during d 18-20 of gestation (Gabrielsson and Paazlow, J. Pharmacokinet. Biopharm. 11: 147-163, 1983), extended later for teophylline and methadone (J.P.B. 12: 149-165, 1984; 13: 355-372, 1985; 16: 183-201, 1988).

(3) A flow-limited PBPK model of trichloroethylene and its acidic metabolite, TCA, in the rat during d 13-22 of gestation (Fisher et al., Toxicol. Appl. Pharmacol. 99: 395-414, 1989).

(4) A PBPK model of weak acids distribution to the mouse and rat fetus, depending on pH of body fluids (O'Flaherty et al., Toxicol. Appl. Pharmacol. 112: 245-256, 1992).

(5) A flow-limited PBPK model of lactational transfer of inhaled perchloroethylene in the rat and human (Byczkowski, Drug Inf. J. 30: 401-412, 1996).

(6) A PBPK model of lead in children and adults (O'Flaherty, Environ. Health Perspect. 106(Suppl. 6):1495-1503, 1998).

(7) A comprehensive PBPK model of gestational and lactational transfer of methylmercury from the exposed mother to her fetus and nursing infant (Byczkowski and Lipscomb, Risk Analysis 21: 869-882, 2001; Clewell, et al., Risk Analysis 19: 547-558, 1999).

- **Structure of a successful PBPK model describing pregnancy and lactation.**

(1) The volume of the placenta and placental blood flow were described by the following growth function:

$$\mathbf{VPI = VPIA * \exp(VPIB * (\exp(VPIC * Time))); \quad QPI = QPIM * VPI}$$

where: VPI is the volume of placenta (kg), VPIA = 0.85, VPIB = -9.434, and VPIC = -5.23e-4 are placental weight logistic constants, and Time is the time that elapsed from the moment of conception (hrs), QPI is the blood flow through placental tissue (L/hr), and QPIM = 58.5 is the allometric placental blood flow constant (L/hr/kg^{3/4}), * is multiplication (Clewel et al., Risk Analysis 19:547-558, 1999).

(2) All tissue volumes and blood flow rates were linked to body weights by means of growth functions that reproduced physiological measurements, e.g., volume of fetus:

$$\mathbf{VFe = BWP * \exp(VFeB * (\exp(VFeC * Time))) + VFeD * \exp(VFeE * (\exp(VFeF * Time)))}$$

where: VFe is the volume of the fetus (kg), BWP is the final fetal weight, equal to the neonatal body weight at birth, VFeB = -16.081, VFeC = -5.67e-4, VFeD = 3.50, VFeE = -140.178, and VFeF = -7.01e-4 are all fetal weight logistic constants, and Time is the time that elapsed from the moment of conception (hrs) (Clewel et al., Risk Analysis 19:547-558, 1999).

(3) Infant breast milk intake was expressed as a function of the age-dependent, growing body weight:

$$\mathbf{OUTI = INTAKE * ((PNO * (WBODY - BWP)) ** 0.2) / (1.15 * 24)}$$

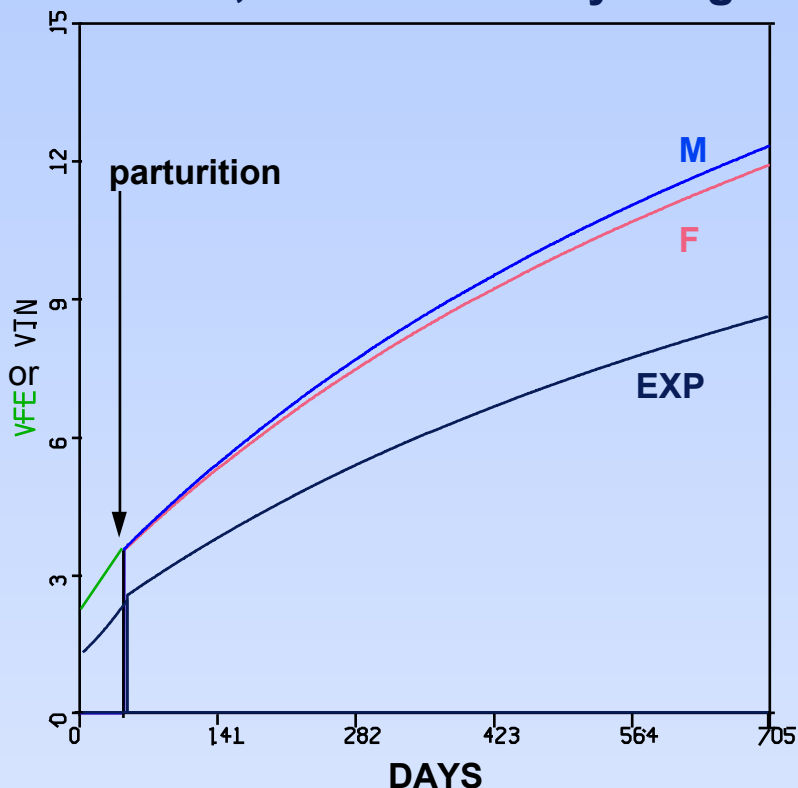
where: OUTI is the rate of consumption of breast milk by a human infant (L/hrs), INTAKE is a fraction of milk yield (default = 1.), PNO is the number of simultaneously nursed infants, WBODY is the body weight of human as a function of age (kg), BWP is the neonatal body weight at birth (kg), ** is exponent. On average, the rate of consumption of breast milk by a human infant is 0.67 L/day, at age 10.5 days (WBODY=3.78 kg), and 0.98 L/day, at age 97.5 days (WBODY=5.36) (O'Flaherty, Toxicol. Appl. Pharmacol. 111:332-341, 1991).

(4) Different body weight growth curves were used for male and female infants:

$$WBODY = BWP + WCHILD * AGE * FAIG / (HALF + AGE) + WADULT / (1.0 + KAPPA * EXP(-LAMBDA * WADULT * AGE))$$

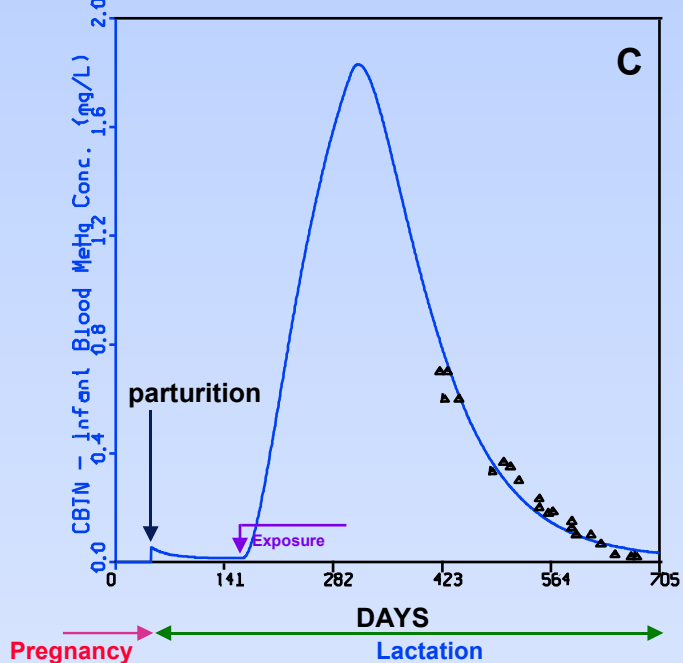
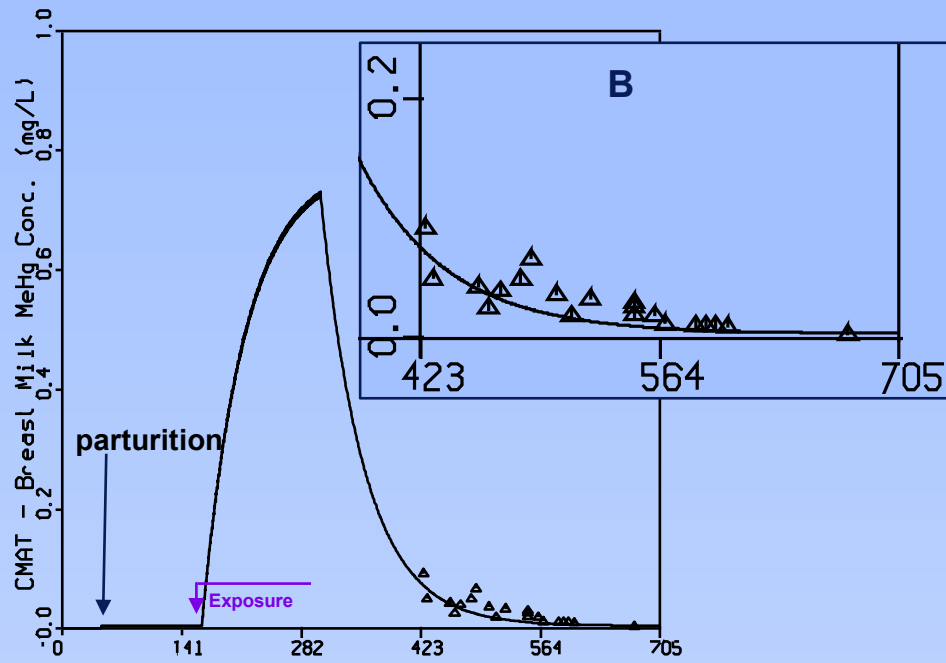
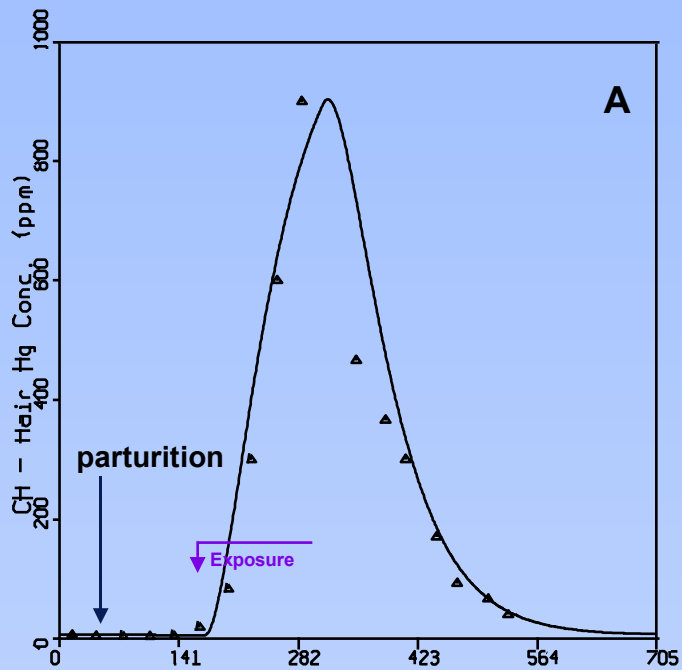
where: WBODY is body weight of a human as a function of age (kg), BWP is the neonatal body weight at birth (kg), WCHILD is the maximum weight for early hyperbolic section of growth curve (kg) for female or male, AGE is the age of the child at which the simulation begins (yr), FAIG is the fraction of average infant growth (default = 1.0), HALF is the age at which weight is half WCHILD (yr), WADULT is the maximum weight for later logistic section of growth curve (kg) for female or male, KAPPA is the logistic constant kappa, and LAMBDA is the logistic constant lambda (1/(kg-yr)) for female or male (O'Flaherty, Toxicol. Appl. Pharmacol. 111:332-341, 1991).

(5) Some other physiological functions also required different scaling in males and females, even after body weight has been taken into account.



Reconstruction of the female infant body growth curve for an exclusively breast-fed daughter of the lactating woman exposed to 0.12 mg of MeHg/kg/day for over 4 months during lactation period (it was estimated that BW increased from 2.5 kg at birth to 6.5 kg at 1 year; Amin-Zaki et al. Am. J. Dis. Child. 130:1070-1076, 1976). Normal average infant body weight growth curve for female (F) and male (M), compared to lactationally exposed female infant (EXP).

(From: Byczkowski and Lipscomb, Risk Analysis 21: 869-882, 2001)



Comparison of the MeHg_{Lac} PBPK model predictions with clinical data from a lactating woman, exposed to 0.12 mg of MeHg/kg/day for over 4 months during the lactation period, and from her nursing infant. Curves are the result of computer-aided simulations of MeHg concentration in: A. maternal hair (CH in ppm), B. breast milk (CMAT in mg/L; the inset shows the end of curve magnified x 2), and C. infant blood (CBIn in mg/L). Reported maternal body weight was BW = 38 kg (assumed VFC=0.01), female infant body weight at birth was estimated as BWP = 2.5 kg (Amin-Zaki et al. Am. J. Dis. Child. 130: 1070-1076, 1976). (From: Byczkowski and Lipscomb, Risk Analysis 21: 869-882, 2001)

Table I. MeHgLac PBPK Model Simulation Parameters for Humans

Input Parameter					
	Value	Description	(Units)	Simulation Scenario	Source
Original gestational model ⁽¹⁾					
Blood Flows					
QCC	20.0	Cardiac output	(L/hr/kg^{3/4})	default	(2)
QFeC	54.0	Fetal	(L/hr/kg^{3/4})	default	(1)
QPIM	58.5	Placenta	(L/hr/kg^{3/4})	default	(1)
Plasma Flows (fraction of QCC)					
QBrBC	0.114	Brain plasma	(ratio)	default	(1)
QFC	0.052	Fat	(ratio)	default	(1)
QGC	0.181	Gut	(ratio)	default	(1)
QKC	0.175	Kidney	(ratio)	default	(1)
QLC	0.046	Liver	(ratio)	default	(1)
QRC	0.183	Rapidly perfused	(ratio)	default	(1)
QSC	0.249	Slowly perfused	(ratio)	default	(1)
Body Weights					
BW	67.77	Body weight mother	(kg)	default	(1)
BWP	3.5	Initial body weight Infant	(kg)	default	(1)

Table I. Cont.

Tissue Volume (fraction of BW)

VBrC	0.02	Brain	(ratio)	default	(1)
VBrBC	0.007	Brain plasma	(ratio)	default	(1)
VFC	0.273	Fat	(ratio)	default	(1)
	0.01	Fat	(ratio)	Case specific	(3)
VGC	0.017	Gut	(ratio)	default	(1)
VHC	0.002	Hair	(ratio)	default	(1)
VIC	0.014	Intestine	(ratio)	default	(1)
VKC	0.004	Kidney	(ratio)	default	(1)
VLC	0.026	Liver	(ratio)	default	(1)
VPC	0.041	Plasma	(ratio)	default	(1)
VRBCC	0.024	Red blood cells	(ratio)	default	(1)
VRC	0.10	Rapidly perfused tissues	(ratio)	default	(1)
VSC	0.35	Slowly perfused tissues	(ratio)	default	(1)
VRemain	0.122	Remainder of body	(ratio)	default	(1)

Lactational module

Plasma Flows (fraction of QCC)

fQMT	0.1	Mammary tissue (fraction of QRC)		default	(4)
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Body Weights

BW	38.	Body weight mother	(kg)	Case specific	(3)
	58.	Body weight mother	(kg)	default	(5)
BWP	2.5	Initial body weight Infant	(kg)	Case specific	(3)

Table I. Cont.

Infant Growth

(default=female)

WCHILD	22.	Max. weight for early section of growth curve	(kg)	default	(6)
	23.	Max. weight, Male			(6)
HALF	3.	Age at which weight is half WCHILD	(yr)	default	(6)
WADULT	34.	Max. weight for later section of growth curve	(kg)	default	(6)
	50.	Max. weight, Male			(6)
KAPPA	600.	Logistic constant kappa		default	(6)
LAMBDA	0.017	Logistic constant lambda	(1/(kg-yr))	default	(6)
	0.0095	Logistic constant, Male			(6)

Tissue Volume (fraction of BW)

VGI	0.0836	GI tract infant	(ratio)	default	(4)
VHIn	0.333	of VHC	(ratio)	default	*
VMILKC	0.0014	Initial volume of milk	(L/kg/PNO)	default	(4)
OUTX = OUTI		Milk intake = milk yield (from growth curve F)		default	(7)
	0.02917	Milk yield	(L/hr)	Case specific	(3)

* - initial estimate, optimized by the model over available data.⁽³⁾; ⁽¹⁾Clewell et al. Risk Anal. 19, 547-558 (1999); ⁽²⁾Brown et al. Toxicol. Ind. Health. 13, 407-484 (1997); ⁽³⁾Amin-Zaki et al. Am. J. Dis. Child. 130, 1070-1076 (1976); ⁽⁴⁾Byczkowski. Drug Inf. J. 30, 401-412 (1996); ⁽⁵⁾Fujita. Bull. Environ. Contam. Toxicol. 18, 205-209 (1977); ⁽⁶⁾O'Flaherty et al. Toxicol. Sci. 60, 196-213 (2001); ⁽⁷⁾Byczkowski et al. Toxicol. Appl. Pharmacol. 125, 228-236 (1994).

- **PBPK modeling of tissue distributions of chemical compounds gave realistic results when either tissue:blood partitioning has been measured experimentally or tissue composition along with chemical solubility were taken into account.**

(1) Partitioning may be measured either by the method of Gargas et al. (Toxicol. Appl. Pharmacol. 97:87-99, 1989) for volatile chemicals, or by the method of Jepson et al. (Fund. Appl. Toxicol. 22:519-524, 1994) for non-volatile chemicals.

(2) Solubility of chemicals in blood and other tissues may be predicted from physicochemical properties of the compound and tissue composition. The solubility of chemicals in blood and tissue was adequately described by equations provided by Poulin and Krishnan (Toxicol. Appl. Pharmacol. 136: 126-130.1996).

(3) Even though tissues of very young children contain more water than in adults, Pelekis et al. (Regulat. Toxicol. Pharmacol. J. 33:12-20, 2001) suggested that no significant adult-child differences in the chemical concentrations of the non-metabolized volatile chemicals are likely to be observed during inhalation exposures.

Table II. PBPK Model Simulation Parameters for Child
 (defaults for 1 year and older, after Pelekis et al. Regulat. Toxicol. Pharmacol. J. 33:12-20, 2001)

Input Parameter	Value	Description	(Units)
QPC	31.3	Pulmonary ventilation rate	(L/h/kg)
Blood Flows			
QCC	22.6	Cardiac output	(L/h/kg)
Tissue Blood Flows (fraction of QCC)			
QFC	0.1	Fat	(ratio)
QSC	0.22	Slowly perfused	(ratio)
QLC	0.24	Liver	(ratio)
QRC	0.44	Rapidly perfused, determined from difference in the total body volume (QRC=1.0 - S Qi)	(ratio)
Body Weight			
BW	10.0	Body weight	(kg)
Tissue Volume (fraction of BW)			
VFC	0.167	Fat	(ratio)
VSC	0.46	Slowly perfused tissues, determined from difference in the total body volume (VSC=0.91 - S Vi)	(ratio)
VLC	0.025	Liver	(ratio)
VRC	0.178	Rapidly perfused tissues	(ratio)

Table III. Water and Lipid Composition of Human Tissues
 (defaults for 1 year and older, after Pelekis et al. Regulat. Toxicol. Pharmacol. J. 33:12-20, 2001)

Tissue Compartment	Fraction of tissue weight		
	Water	Neutral lipids	Phospholipids
Liver	0.720	0.039	0.0280
Fat	0.150	0.798	0.00200
Richly perfused	0.720	0.039	0.00280
Slowly perfused	0.750	0.035	0.0100

- **All predictive models must be validated or at least confirmed in living organisms, preferentially in humans.**

(1) Typically, PBPK models are first developed experimentally in rodents.

(2) The decision whether or not to develop a PB/PK model for a particular chemical should be based on the availability of clinical data from pregnant or lactating mother and her infant, and data collected from laboratory animals. For many chemicals and drugs there is simply not enough information available to justify the construction and calibration of a PB/PK model. In these cases, a classical pharmacokinetic (PK) description of the available data or a qualitative evaluation may be the only feasible approach.

Paradigm for PBPK study in pregnancy and lactation

DRUG OR CHEMICAL OF CONCERN

