Development Of A Biologically Based Model To Describe Perfluorooctanoic Acid (PFOA) Kinetics

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Introduction

•Perfluorooctanoic acid (PFOA) is a fluoroorganic surfactant used in fluoropolymer processes.

•PFOA is reported to be metabolically inert.

•PFOA is a believed to be relatively biopersistent in humans.

•The recent removal of perfluorooctanyl sulfonate (PFOS) from the marketplace has brought attention to other fluoroorganic compounds

•Liver effects including peroxisome proliferation have been noted in rats.

•Sex differences have been shown in the rat. PFOA is cleared more rapidly in the female rat than in the male rat.

•Species differences have also been observed with the rat reportedly clearing PFOA more rapidly than the human.

•Protein binding has been reported in the rat. Target organs and proteins are not yet clearly identified.

•Preliminary modeling efforts are based on available literature data.

Perfluorinated Compounds:

•Steric hindrance by large fluorine C-F bonds forms a spiral structure in the carbon chain and causes a more rigid molecule than in hydrocarbons.

•Fluorine is highly electronegative and the carbon backbone is completely covered by the "electron cloud" of fluorine atoms presenting an even charge distribution.

•C-F bonds are very strong and short.

Materials and Methods

•All models were constructed using Advanced Continuous Simulation Language (ACSL).

•The preliminary models were tested against available laboratory and worker exposure data for acceptability.

•The initial model was a non-physiological, 2-compartment model (Figure 2).

•The lung and dermal compartments are included to accommodate potential exposure via these routes, but the primary focus of the work is on the oral route of exposure.

•While the liver is not a site of PFOA metabolism, it is described as a separate model compartment since it is a reported toxicity target in some animal species and may represent a source of significant protein binding.

•Physiological and chemical specific data input into the model are shown in Table 1.

•Blood data compared against model simulations in Figures 4 and 5 were obtained from the literature.

Figure 1 - Modeling Pathway

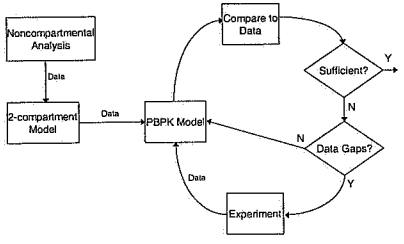
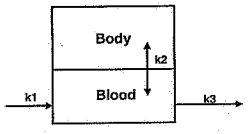


Table 1 - Input Parameters

Parameter	Variable	Rat	Human
Body Weight	BW (kg)	450	70
Alveolar Output	QP (L/hr)	6.6	290
Cardiac Output	QC (L/hr)	6.6	310
Blood Flow (% cardic output)			
Skin	QDC	5.8	5.8
Fat	QFC	7	5.2
Slowly Perfused	QSC	2.8	2.8
Rapidly Perfused	QRC	52	46
Kidney	QKC	14.1	17.5
Liver	QLC	18.3	22.7
Tissue Volume (% body weight)			
Skin	VDC	3.4	19
Fat	VFC	30	7
Slowly Perfused	VSC	47	51
Rapidly Perfused	VRC	5	6
Kidney	VKC	0.4	0.7
Liver	VLC	2.6	3.4
Partition Coefficients			
Blood : Air	PB	10	10
Skin : Blood	PD	10	10
Fat : Blood	PF	10	10
Slow: Blood	PS	10	10
Rapid : Blood	PR	10	10
Kidney : Blood	PK	10	10
Liver : Blood	PL	10	10
Metabolic Constants			
Maximum Rate	VMAX (umol/hr)	0	0
Michaelis Constant	KM (umol/L)	0	0
Protein Binding Constants			
Maximum Rate	VMAX (umol/hr)	1	1
Michaelis Constant	KM (umol/L)	0.1	0.1

Figure 2 - Two-Compartment Model



Body lumped into single storage compartment

Figure 3 - PBPK Model

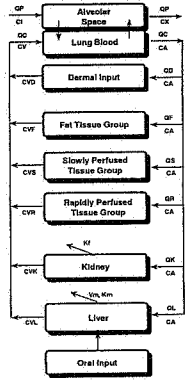


Figure 4 - Two-Compartment Results

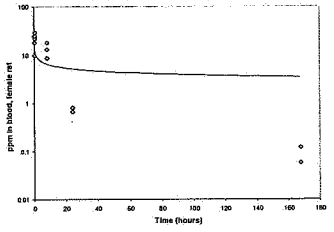
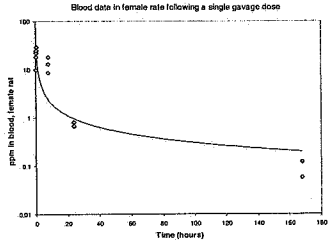


Figure 5 - PBPK Results



Discussion

•The two-compartment model simulates the general trends in the rat data. It is not satisfactory, however, for predictive uses.

•The preliminary PBPK model performs better than the two-compartment model, but includes many estimated or "fit" parameter values. One function of this investigation was to identify the data gaps in the existing literature. Table 2 lists the relevant areas and their relative importance to the modeling effort.

•The human data in the literature at this time are not complete enough for modeling purposes. Most of the human data are taken from monitoring of production workers and thereby lacks any exposure information. In addition, there is no associated 'event' on which to base a time scale. The reported human blood concentrations of PFOA are generally below 35 ppm.

•While protein binding has been noted in the literature, there is no information available to quantify the binding parameters. A binding term is included in the preliminary PBPK model but the values used have no physical significance at this point.

Table 2 - Data Gaps

Information Type	Available?	Optimal for Kinetic Model Use?	Acceptable for Kinetic Model Use with Caveats and/or Restrictions?	Additional Work Important for Use in Kinetic Model ?	Can Estimates be Made and Used With Restriction ?	Priority
Dermal Permeability Coefficient	Y	Y	Y	N	na	na
Skin:Vehicle Partition Coefficient	N	na	na	Y	Y	Medium
Skin Compartment Description	N	na	na	Y	Y	Medium
Rate and Extent of Absorption (Oral) Rat	Y	N	Y	Y	Y	Low
Rate and Extent of Absorption (Oral) Human	N	na	na	Y	N	High
Concentration Dependent Kinetics (Oral)	Y	N	N	Y	Y	High
Vehicle Effects (Oral)	N	na	na	Y	Y	Low
Inhalation Uptake Kinetics	Y	N	N	Y	Y	Low
Physiological Compartment Definition	N	na	N	Y	Y	High
Tissue:Blood Partition Coefficients	N	na	na	Y	Y	High
Qualitative Description of Binding	Y	N	N	Y	N	High
Species Specific Binding	N	na	na	Y	N	High
Quantitative Description of Binding	N	na	na	Y	N	High
Definition of Elimination Routes	Y	N	Y	Y	Y	High
Elimination Kinetics	Y	N	Y	Y	Y	High
Bioactivation	Y	N	Y	Y	Y	High
Biological Half-life in Humans	Y/N	N	N	Y	Y	High
Mass Balance	Y	N	Y	Y	Y	High
Branched vs. Straight Chain Kinetics	N	na	na	Y	N	Medium
Quantitative Structure/Activity Relationship	N	na	na	Y	N	High
Biologically Based Kinetic Model	N	na	na	Y	N	High
Metabolism	Y	Y	Y	N	na	na

Protein Binding

Qualitative Binding Determination

- Determine key tissues from mass balance data and literature.
- Identify target proteins in key tissues.
- Determine branched chain effects.
- Check for the presence of non-protein (*e. g.* lipid) interactions.

Quantitation of Model Parameters

- Calculate stability, stoichiometry and kinetic parameters of PFOA interaction with applicable proteins and biomolecules.
- Determine differences in binding of proteins with linear and branched PFOA.

Conclusions and Future Direction

•Classical compartmental modeling was not sufficient to describe PFOA kinetics in mammalian systems.

•A preliminary rat PBPK model was developed.

•Data gaps were identified and a pathway for further model development presented.

Future Directions:

•Conduct Mass Balance, Adsorption, Distribution and Elimination studies in male and female rats.

•Characterize the rate, extent and type of PFOA binding in rats and human systems.

•Develop model descriptions for the human.

•Include quantitative protein binding terms into rat and human PBPK models.

•Use model to simulate the plasma kinetics, uptake, distribution and elimination of PFOA in humans.