Development of PK- and PBPK-Based Modeling Tools for Derivation of Biomonitoring Guidance

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Abstract

There are numerous programs ongoing to evaluate environmental exposure of humans to xenobiotic chemicals (eg: EU ESBIO, COPHES; US CDC NHANES; Canadian Health Measures Survey). The goal of these projects is to determine relative trends in exposure to chemicals, across time and subpopulations. Due to the lack of data, there is little information correlating biomarker levels with exposure concentrations, and as a result, difficulty in utilizing biomonitoring data for biological guidance values. A tiered approach of simple, arithmetic pharmacokinetic (PK) models, as well as more standardized mean-value and probabilistic PBPK models, would promote the use of human biomonitoring data in the development of appropriate biomonitoring guidance values (BGVs). The output of these evaluations will be potentially useful in setting hazard/exposure criteria, such as the Derived No- Effect Level values under the EU REACH program. Both arithmetic PK and mean-value PBPK models have been developed and validated for this project, which utilize a user-friendly Excel spreadsheet interface. QSAR estimations of chemical-specific parameters have been included, as well as accommodation of variations in urine production. Validation of each model's structure and the impact of assumptions of major model parameters will be presented.

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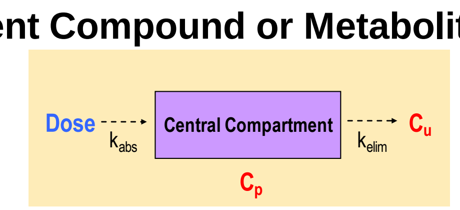
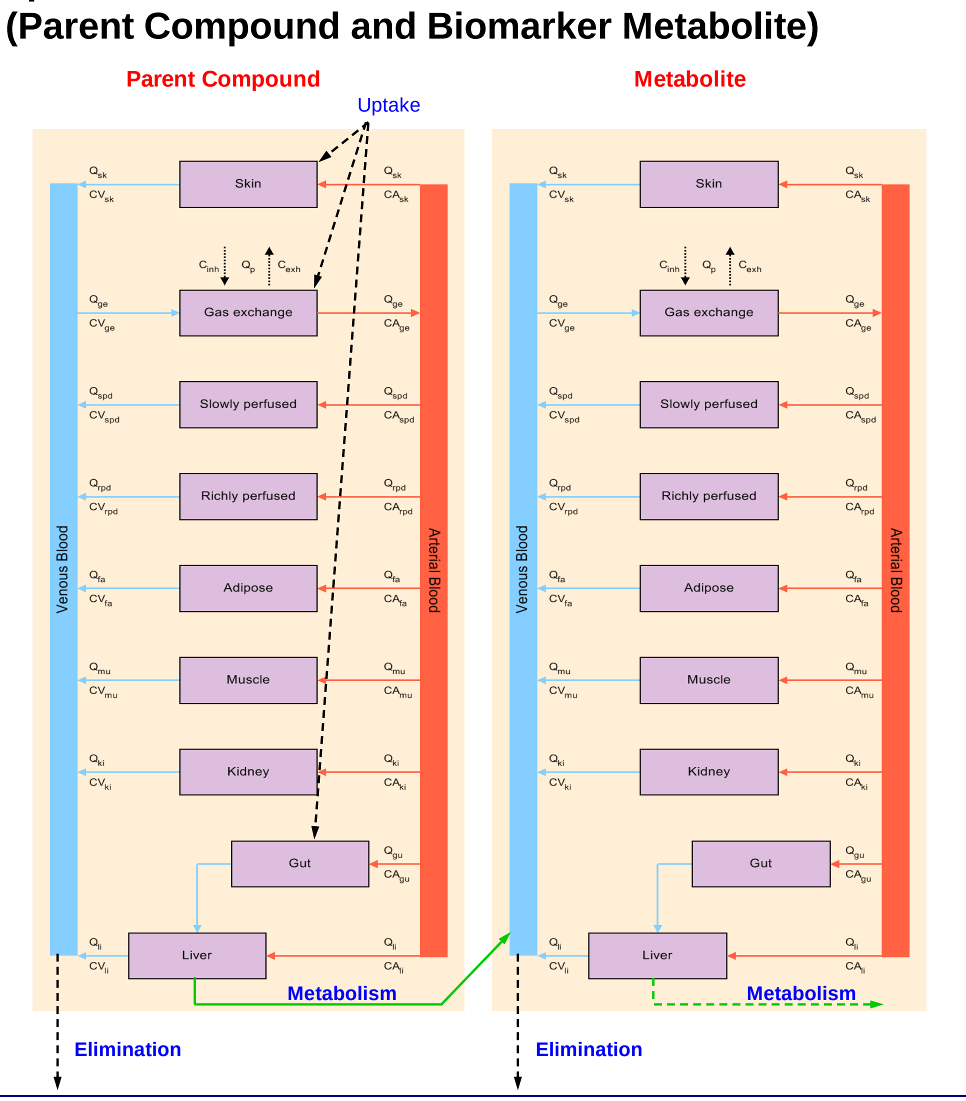
Model Structures

Simple PK model (Parent Compound or Metabolite)



Complex PBPK model (Parent Compound and Biomarker Metabolite)



Program Goal

Build a tiered set of modeling tools
- allowing reliable interpretation of human biomonitoring data
- validated with data for several biomarkers

Tools will be developed that are standardized and user-friendly
- Microsoft-Excel interface for PK and PBPK models
- Outline of base PBPK models with MeGEN application
- QSAR-derivations of Vd and blood:tissue PCs
- Inclusion of bladder compartment to account for micturition
- Reverse dosimetry "lookups" for PBPK tools

Tier 1:
- Excel-based PK model
- Screening tool for estimates of exposures
- QSAR prediction of Vd

Tier 2:
- Differential-equation based PBPK model
- ACSL version can be run from Excel
- Parameters can be modified from workbook
- QSAR prediction of blood:tissue partition coefficients

Parameters required for kinetic models

Chemical-independent
- PK model:
  - urine/creatinine production rates
- PBPK models:
  - urine/creatinine production rates
  - relative cardiac output to organs
  - relative body weight of organs

Chemical-dependent
- PK model:
  - first-order absorption/elimination rates
  - fraction of dose as biomarker
  - volume of distribution (blood only):

$$Vd_{ss} = (\Sigma V_t * P_{t:p}) + (V_e * E{:}P) + V_p$$

as per Poulin and Theil (2002)

- PBPK models:
  - first-order absorption/elimination rates
  - saturable metabolism rate(s) (K_m, V_{max})
  - blood:tissue partition coefficients:

$$P_{tp} = \frac{[K_{oil:w} * (V_{nlt} + 0.3\,V_{pht}) + (1 * V_{wt} + 0.7\,V_{pht})]}{[K_{oil:w} * (V_{npl} + 0.3\,V_{php}) + (1 * V_{wp} + 0.7\,V_{php})]} * \frac{f_{up}}{f_{ut}}$$

as per Poulin and Theil (2000)

Outputs modeled

PK: parent compound or one metabolite in blood or urine

PBPK: parent compound and one metabolite in blood or urine (with miturition times)

User Interface for Excel-based Tier-2 PBPK Biomonitoring Model

General Data:

	Test Chemical	Metabolite	
Chemical Name	AlcoholParent	AcidMetabolite	(leave blank if biomarker is the test chemical)
molecular weight	116	134	(leave blank if biomarker is the test chemical)
Estimated Time between exposure & sampling	4.00		hours (for urine: start of collection interval)
Exposure route	Oral		**Pull-down menu**
Exposure duration (dermal and inhalation only)			hours (leave blank for oral exposure)
Low dose for array (mg)	10.00		
High dose for array (mg)	1000.00		
Biomarker Concentration	Enter one value only, in one of the 8 boxes below		
whole blood concentration	300.0000	35.0000	mg/L (leave blank if value not known)
plasma concentration	300.0000	35.0000	mg/L (leave blank if value not known)
urine concentration	15000.0000	300.0000	mg/L (leave blank if value not known, or if using creatinine-corrected urine conc)
urine concentration- creatinine corrected	10000.0000	310.0000	mg/g creatinine (leave blank if value not known, or if using un-corrected urine concentration; creatinine mwt = 113.1)

Pharmacokinetic parameters:

	Test Chemical	Metabolite	
Absorption half-life	0.50		hours (assumed first-order absorption of Test Chemical)
Plasma elimination half-life	26.90	26.90	hours (assumed first-order elimination of Biomarker, as measured in blood or plasma)
Metabolism rates			
Vmax	250.000	0.000	mg / hr
Km	0.100	1.000	mg / L
Body weight	70.0		kg
Urine production rate	0.0583		Liters / hour (default value for 70 kg adult males)
Creatinine production rate	0.0729		g / hour in urine (mean of median CDC NHANES III population values for males & females, ages 20-59), in units of g Cr/L urine x Urine Productio
Urine micturition times	1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0 20.0		hours Mean Micturition Time Interval = 1.18 hours (will be used for all times after last value. If no values entered, will be set to 4 hours

Tissue:blood or Tissue:plasma partition coefficients

	Test Chemical	Metabolite	
Brain	0.93	0.70	Note: Tissue:plasma partition coefficient values are used, unless a Biomarker value entered for Parent Compound or Metabolite in Whole Blood
Kidney	0.83	0.68	
GI Tract	0.82	0.63	
Liver	0.84	0.66	
Lung	0.82	0.69	
Remaining richly perfused tisssues	0.93	0.70	(used brain:plasma)
Fat	1.29	0.08	
Muscle	0.81	0.65	
Skin	0.78	0.62	
Remaining slowly perfused tisssues	0.58	0.38	(used bone)
Blood:air	109896.00	109896.00	

\- or -

PhysChem Properties (for partition coefficient derivations)

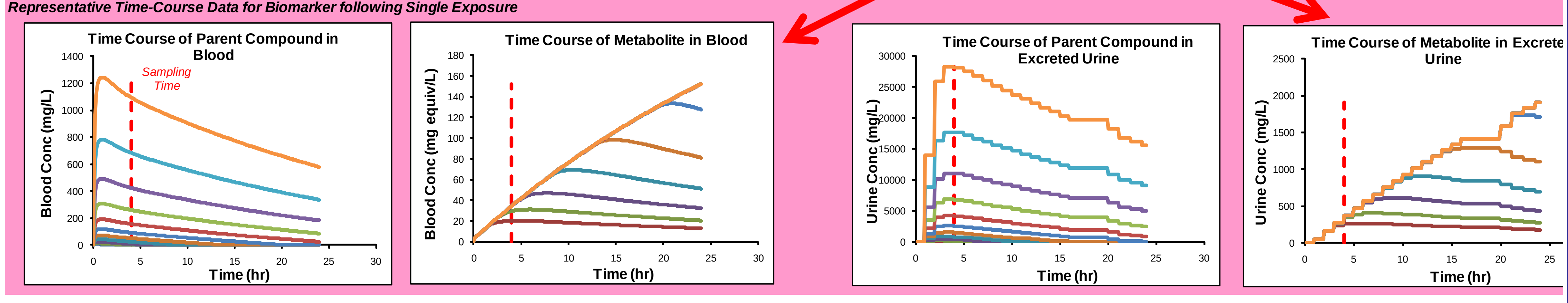
	Test Chemical	Metabolite	
Compound type	**Neutral**	**Acid**	**Pull-down menu** (Base=pKa≥7; Weak base=pKa<7)
Log Koctanol:water	1.16	0.34	**(Note: Log Kow and Henry's law constant can be estimated with US EPA EpiSuite-HenryWin QSAR: http://www.epa.gov/oppt/expo**
Henry's Law Constant	4.78E-03	4.68E-03	(Pa-m^3/mol) (1 atm = 101325 Pa)
Fraction unbound in plasma	61%	37%	**(Note: fraction unbound in plasma and pKa can be estimated with QSARs such as ADME boxes and ACD/pKa: http://www.acdlabs.**
pKa		4.00	(leave at blank if compound is neutral)

Derived Data:

	Test Chemical	Metabolite	
Calculated Single-Exposure Dose from blood conc.	287.0295	26.8627	mg
Calculated Single-Exposure Dose from plasma conc.	287.0295	26.8627	mg
Calculated Single-Exposure Dose from urine conc.	538.8163	12.8263	mg
Calculated Single-Exposure Dose from urine conc. - Cr corrected	451.1976	18.4789	mg

PBPK model accommodates saturable metabolism

Representative Time-Course Data for Biomarker following Single Exposure



Output of Modeling tools

Tier 1:

$$\text{Dose} = \frac{Cp * Vd * (k_{abs} - k_{elim})}{(k_{abs} * FrxAbs) * (e^{-kelim*t} - e^{-kabs*t})}$$

*Direct calculation of dose from biomarker level at time **t** after exposure*

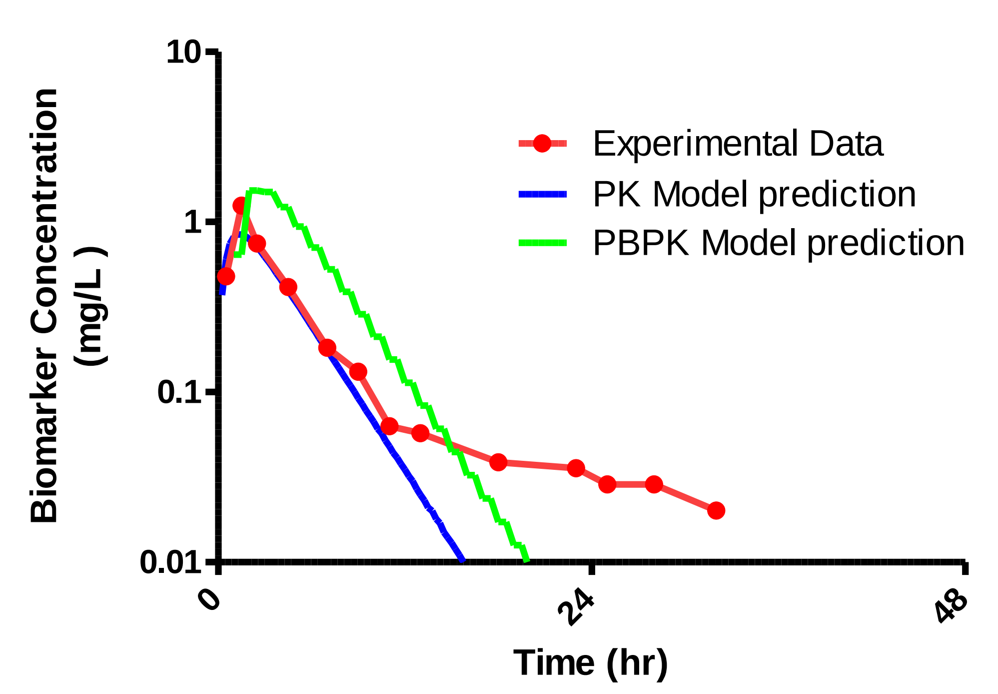
Tier 2:

Dose ->	Day-1 Urine level	Day-2 Urine level	Day-3 Urine level	Day-4 Urine level
1	0.100	0.0500	0.0250	0.0125
2	0.150	0.0750	0.0375	0.0188
3	0.200	0.100	0.0500	0.0250
4	0.220	0.110	0.0550	0.0275
5	0.250	0.125	0.0625	0.0313
6	0.280	0.140	0.0700	0.0350
7	0.300	0.150	0.0750	0.0375
8	0.350	0.175	0.0875	0.0438
9	0.400	0.200	0.100	0.0500
10	0.500	0.250	0.125	0.0625

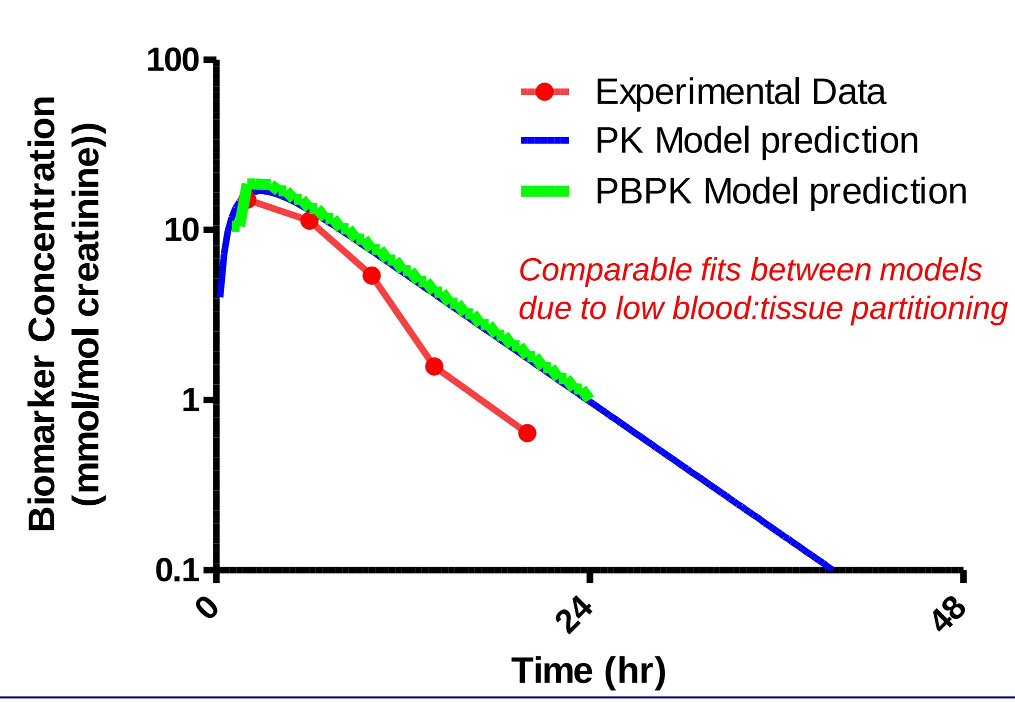
Multiple model runs at various doses...... Dose "lookup" from array of biomarker conc. vs. time

Comparison of PK and PBPK model fits to data

Diazinon: Urinary DEP metabolites following oral administration to human volunteers (0.011 mg/kg; Garfitt 2002)



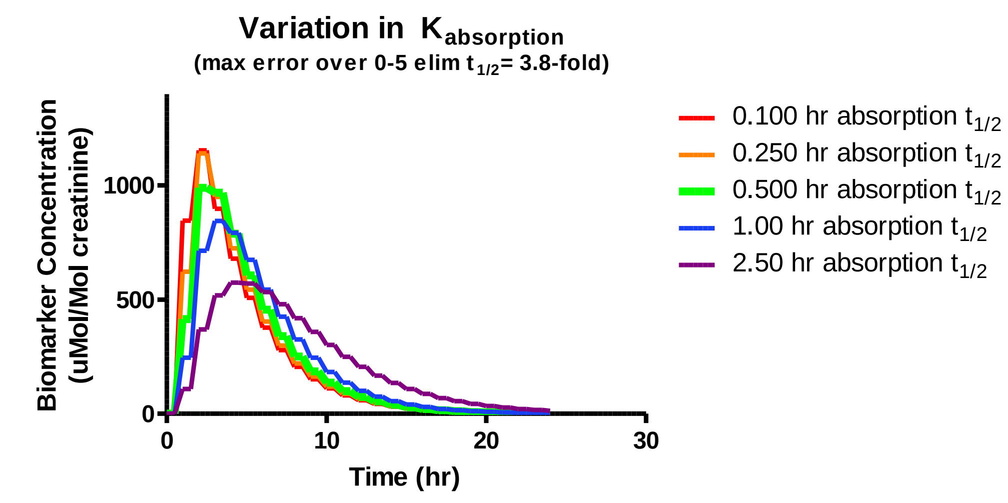
Butoxyethanol: Urinary BAA metabolite following inhalation exposure to human volunteers (19.3ppm x 0.5hr; Kezic 2004)

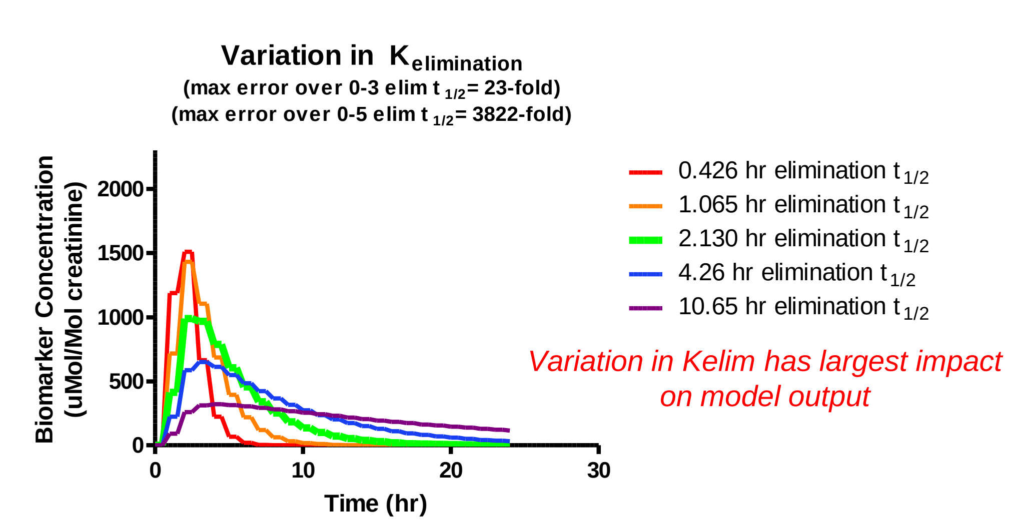


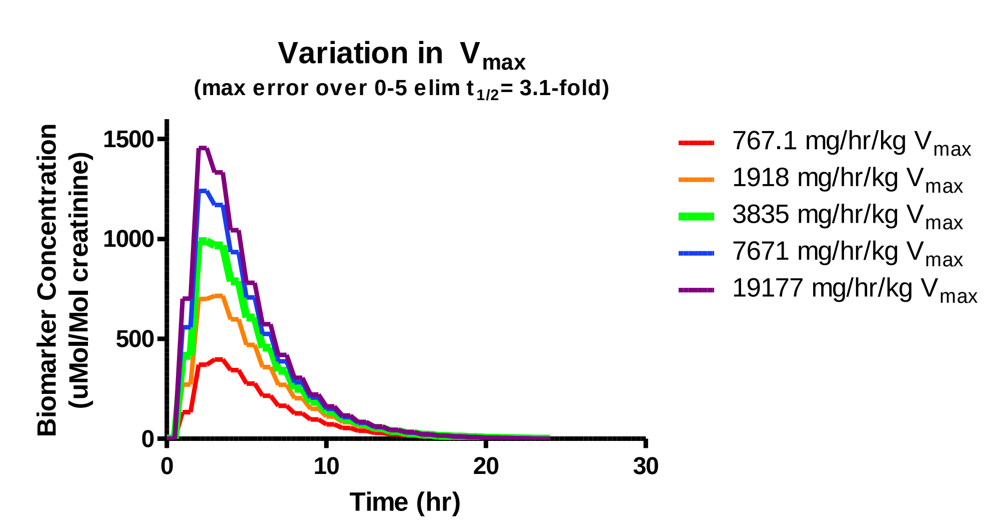
Comparable fits between models due to low blood:tissue partitioning

Impact of Model Parameter Assumptions

(Diazinon urinary DEP metabolite data)







Summary

- A program of tiered modeling tools has been developed for interpretation of human biomonitoring data
- -- Specific tools will be standardized and accessible via a user-friendly interface
- Minimal data is required for the simple PK tool
- Additional parameters, needed for Tier-2 PBPK tool, should provide more accurate dosimetry calculations
  - can model saturable metabolic processes
- Estimates of variation in biomarker concentrations across population can be conducted, via Monte-Carlo analysis with the upcoming Tier-3 modeling tool
- -- Tools should be valuable in risk assessments of chemicals that are based on biomonitoring data