Development of a Tiered Set of Modeling Tools for Derivation of Biomonitoring Guidance Values

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Abstract

There are numerous programs ongoing to evaluate environmental exposure of humans to xenobiotic chemicals (eg: EU ESBIO; 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 suite of model tools would be the most appropriate method to facilitate forward- and reverse-dosimetry estimations of xenobiotic exposure to aid in interpretation of biomonitoring results. A tiered approach of simple, arithmetic pharmacokinetic (PK) models, as well as more standardized 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. In this project, three types of PK and PBPK models will be developed, utilizing the MEGen model generation application. QSAR estimations of chemical-specific parameters will be included, as well as accommodation of variations in urine production. Estimates of variability in human physiology will also be incorporated, to allow for Monte Carlo analysis of biomarker level concentrations. Validation of each of the model structures will be conducted with published datasets of representative biomarkers.

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Background

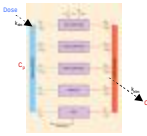
Risk assessments for chemicals based on known exposure level measured in workplace (BAT, BEI)
- passive dosimetry
- biomonitoring

population exposures
- biomonitoring programs (ESBIO, US CDC, Health Canada)

Biomonitoring data interpretation requires kinetic models to correlate biomarker levels with exposure

Simple PK model

Complex PBPK model



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
- Inclusion of Monte-Carlo simulations of population variance

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

Tier 2:
- Differential-equation based PBPK model
- ACSL version can be run from Excel
- Parameters can be modified from workbook

Tier 3:
- Core model from Tier 2
- Biomarker levels evaluated across population
- Reference physiology values from PopGen or P3M
- Crystal-Ball can be used for Monte-Carlo analysis

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:
- absorption/elimination rates
- volume of distribution (blood only)

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

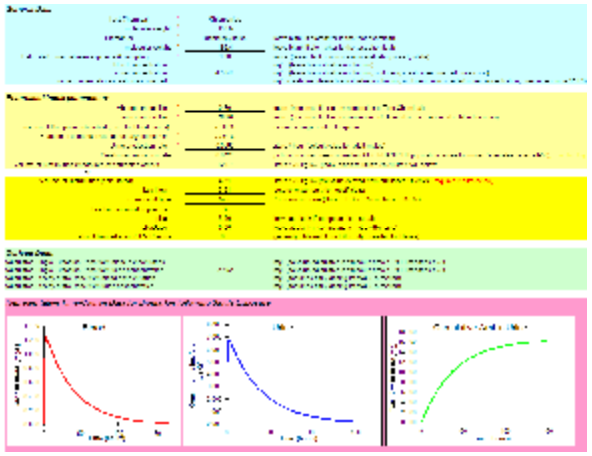
as per Poulin and Theil (2002)

PBPK models:
- absorption/elimination rates
- metabolism rate(s)
- blood:tissue partition coefficients

$$P_{t:P} = \frac{[K_{ab:w} * (V_{st} + 0.3\,V_{prd}) + (1 * V_{ac} + 0.7\,V_{pd})]}{[K_{ab:w} * (V_{st} + 0.3\,V_{prd}) + (1 * V_{ac} + 0.7\,V_{prd})]} * \frac{f_{up}}{f_{ut}}$$

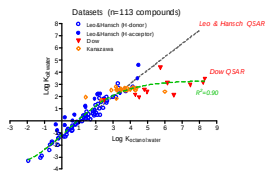
as per Poulin and Theil (2000)

User Interface for Excel-based Tier-1 Biomonitoring Model

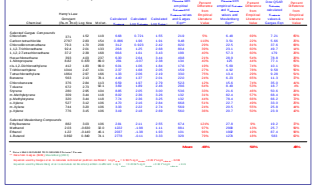


QSAR-derived Partition Coefficients

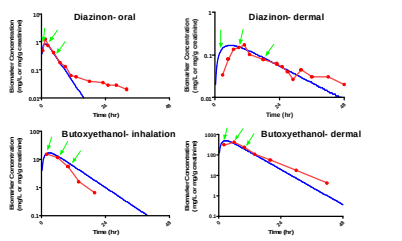
Extended QSAR for prediction of $K_{oil:water}$ from $K_{octanol:water}$



QSAR-derived blood:air partition coefficients (using Koil:water QSAR)



Tier-1 Model: Comparison of predicted vs. actual biomarker levels



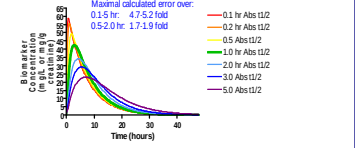
Refit of Reverse Dose Calculation (calculated from measured biomarker / actual amount administered) at time points X-fold the Elimination half-life

Test Material	Biomarker	Exposure Route	Sample Matrix	Abs. half-life (hr)	Elim. half-life (hr)	0.5x Mean	0.5x RSD	1.0x Mean	1.0x RSD	2.0x Mean	2.0x RSD
Chlorpyrifos *	TCP	Oral	Urine	0.5	26.9	**126%**	25%	**103%**	21%	**118%**	21%
Chlorpyrifos	TCP	Dermal	Urine	22.5	26.9	**82%**	92%	**88%**	74%	**82%**	48%
Chlorpyrifos	TCP	Oral	Blood	0.5	26.9	**82%**	24%	**88%**	32%	**100%**	45%
Chlorpyrifos	TCP	Dermal	Blood	22.5	26.9	**68%**	75%	**68%**	59%	**62%**	56%
Diazinon **	DAPs	Oral	Urine	0.5 **	2.13	**75%**	NA	**105%**	NA	**105%**	NA
Diazinon	DAPs	Dermal	Urine	9.12 **	2.13	**24%**	NA	**97%**	NA	**93%**	NA
Butoxyethanol	BAA	Inhalation	Urine	1.0 ***	4.75	**93%**	NA	**87%**	NA	**73%**	NA
Butoxyethanol	BAA	Dermal	Urine	1.0 ***	2.13	**53%**	NA	**114%**	NA	**123%**	NA

* Nolan et al., Toxicol Appl Pharm, 73, 8-15 (1984)
** Garfitt et al, Tox Lett, 124-105-113 (2002)
*** Kezic et al, Int Arch Occup Environ Health, 77:580-586 (2004)

Tier-1 Model Assumptions: Impact of absorption rate (k_{abs})

Butoxyethanol- inhalation



Output of Modeling tools

Tier 1:

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

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

Tier 3:

Dose ->	Day-1 Urine level	Day-2 Urine level	Day-3 Urine level	Day-4 Urine level
1	0.10 ± 0.03	0.05 ± 0.02	0.03 ± 0.02	0.01 ± 0.01
2	0.15 ± 0.03	0.08 ± 0.02	0.04 ± 0.02	0.02 ± 0.01
3	0.20 ± 0.03	0.10 ± 0.02	0.05 ± 0.02	0.03 ± 0.01
4	0.22 ± 0.03	0.11 ± 0.02	0.06 ± 0.02	0.03 ± 0.01
5	0.25 ± 0.03	0.13 ± 0.02	0.06 ± 0.02	0.03 ± 0.01
6	0.28 ± 0.03	0.14 ± 0.02	0.07 ± 0.02	0.04 ± 0.01
7	0.30 ± 0.03	0.15 ± 0.02	0.08 ± 0.02	0.04 ± 0.01
8	0.35 ± 0.03	0.18 ± 0.02	0.09 ± 0.02	0.04 ± 0.01
9	0.40 ± 0.03	0.20 ± 0.02	0.10 ± 0.02	0.05 ± 0.01
10	0.50 ± 0.03	0.25 ± 0.02	0.13 ± 0.02	0.06 ± 0.01

Multiple model runs at various doses + multiple Monte-Carlo runs at each dose..... Dose range "lookup" from array of biomarker conc. vs. time

Future Model Development Plans

Tier-2 Model: Additional parameters required

If biomarker = parent compound
- tissue:blood partition coefficients for parent compound
- metabolic rate constant (Km/Vmax) for loss of parent compound
- renal elimination rate for parent compound

If biomarker = metabolite
- metabolic rate constant (Km/Vmax) for parent -> biomarker
- tissue:blood partition coefficients for biomarker metabolite
- renal elimination rate for biomarker metabolite

Tier-3 Model: Additional parameters required
- variation in all compound-independent and -dependent parameters

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
- Estimates of variation in biomarker concentrations across population can be conducted, via Monte-Carlo analysis with the Tier-3 modeling tool
- Tools should be valuable in risk assessments of chemicals that are based on biomonitoring data