High Throughput Exposure Estimation Using NHANES Data

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Abstract

In the ExpoCast project, high throughput (HT) exposure models enable rapid screening of large numbers of chemicals for exposure potential. Evaluation of these models requires empirical exposure data and due to the paucity of human metabolism/exposure data such evaluations include large uncertainty. Wambaugh et al. (2013; ES&T) used CDC National Health and Nutrition Examination Survey (NHANES) as a data source for urinary biomarkers of human chemical exposure and developed an exposure prediction model that had large uncertainties. To reduce the uncertainties, we developed a one-compartment pharmacokinetic (PK) model for relating both serum and urine biomarkers to probable chemical exposures. The PK model was parameterized with metabolic clearance and volume of distribution data compiled from literature sources. This expanded the chemical space explored beyond the urine evaluation chemicals by incorporating serum and blood biomarker concentrations to include environmentally persistent chemicals such as perfluorinated and polychlorinated biphenyl chemicals. Exposures were inferred probabilistically, using Markov Chain Monte Carlo (MCMC) to estimate the distribution of parent chemical exposures consistent with the biomarker data. By incorporating up to 50 additional metabolites from the NHANES data, we reduced the uncertainty in the parent chemical exposure inferences. The incorporation of a more diverse set of metabolites and corresponding reduction in uncertainty in ExpoCast predictions will play a key role in the confident application of exposure models in prioritization and risk assessment contexts. *This abstract does not necessarily reflect EPA policy.*

Objective

Develop a PK model for relating serum and urinary biomarkers to probable chemical exposures.

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Methods

- We used urine and serum biomarker data from NHANES
- A database was developed and curated for:
  - i. Parent to product metabolism pathways and
  - ii. PK parameters for the NHANES environmental chemical from literature sources.
- For 13 NHANES chemicals with serum concentrations
  - i. Uncertainties were computed for oral equivalent doses in ug/kg/day
  - ii. Steady state concentrations were calculated from oral equivalent doses and available PK data

Urinary Compound	logP	fu_p	Cl_{total} (L/h)	Vd_{ss}
Bisphenol A	3.3	0.257	0.197	23.22
Carbaryl	2.4	0.692	0.970	26.11
Acetochlor	3.0	0.135	0.824	27.92
Acephate	-3.3	0.868	0.094	0.498
Foramsulfuron	-0.8	0.065	0.007	0.116
ortho-Phenylphenol	3.1	0.041	0.019	8.29
Oxasulfuron	1.1	0.061	0.038	0.237
Dimethoate	0.8	0.965	0.510	1.464
N,N-Diethyl-3-methylbenzamide	2.2	0.356	0.232	8.98
Methidathion	2.2	0.268	0.185	7.11
Azinphos methyl	2.8	0.214	0.629	19.66

Table 1: PK parameters and parameters for a selection of NHANES urinary chemicals (Tonnelier *et al.*, 2012; Wetmore *et al.*, 2012).

Serum Compound	logP	fu_p	Cl_{total} (L/h)	Vd_{ss}
Mirex	7.6	0.015	0.002	18982
Aldrin	4.7	0.013	0.001	6868.6
Perfluorodecanoic acid	6.5	0.005	<0.001	1145.1
Perfluoroheptanoic acid	4.4	0.002	<0.001	3.84
Perfluorononanoic acid	5.8	0.001	<0.001	48.64
Dieldrin	3.9	0.009	0.008	381.90
Endrin	3.9	0.006	<0.001	165.12
Perfluorooctane sulfonamide	4.8	0.002	0.003	155.03
Perfluorooctane sulfonic acid	6.2	0.005	<0.001	85.17
Perfluorooctanoic acid	6.3	0.005	0.002	5.86

Table 2: PK parameters for the NHANES serum chemicals (Wetmore, unpublished).

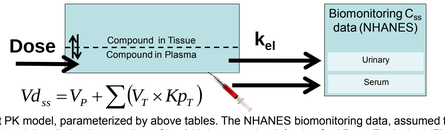


Figure 1. One compartment PK model, parameterized by above tables. The NHANES biomonitoring data, assumed to be the concentration of chemical at steady state (C_{ss}) and the elimination rate ($k_{el} = Cl_{total}/Vd_{ss}$) are used to infer the Oral Dose Equivalent (Figure 3). Adding the tissue volumes (V_T) partition coefficients for each tissue (Kp_T; calculated using Schmitt (2008)), volume of plasma (V_P), we calculate the volume of distribution at steady state (Vd_{ss}) to model the dose-response curves and steady state assumption for our chemicals, presented in Figure 6.

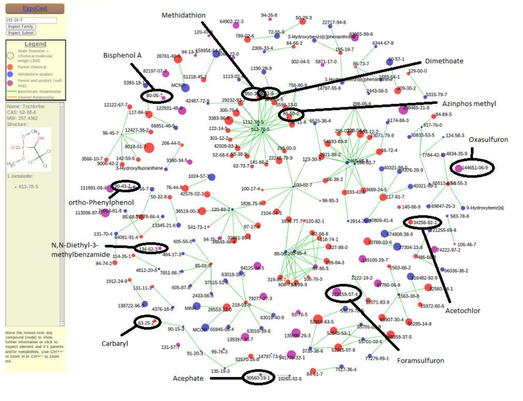


Figure 2: A visualization of the NHANES parent (red) to metabolite (blue) mappings for urinary chemicals. Green lines represent the metabolism pathway from parent to product chemicals. Compounds colored in purple are assumed to be both the parent and metabolite compound. The diameter of the circle is scaled to represent the molecular weight of the chemical compound it represents.

Urinary compounds for which we have PK data in Table 1 are circled.

Results

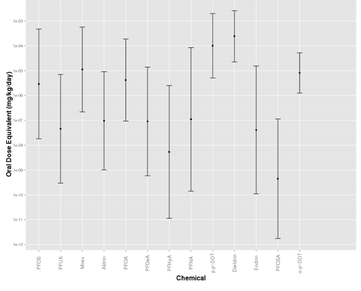


Figure 3: The oral dose equivalent (ODE) of 13 chemicals calculated from the geometric mean of the serum concentration reported for the total population in the NHANES survey. We calculated this analytically using the PK model (Figure 1) and the daily clearance (Cl_{total} in L/day; Tables 1,2) predictions, the NHANES reported geometric mean concentration ($\hat{\mu}$; mg/kg),

$$\log(ODE) = \log(\hat{\mu}) + \log(CL_{total}).$$

The uncertainties associated with the ODE are determined by the standard error of the NHANES data along with the coefficient of variation of the error of the predictions of whole-animal clearance from *in vitro* estimates. Due to insufficient data for environmental chemical clearance rates, we used an approximation for the standard deviation:

$$\log(sd(CL_{total})) = \log(CL_{total}) + \log(0.5)$$

yielding the confidence intervals:

$$CI(ODE) = \sqrt{\hat{u}_{se}^2 + sd(CL_{total})^2}$$

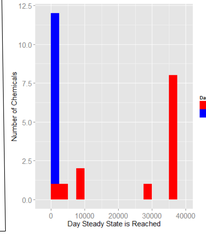
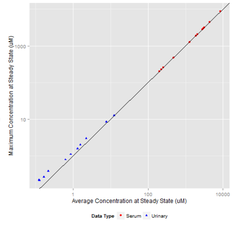


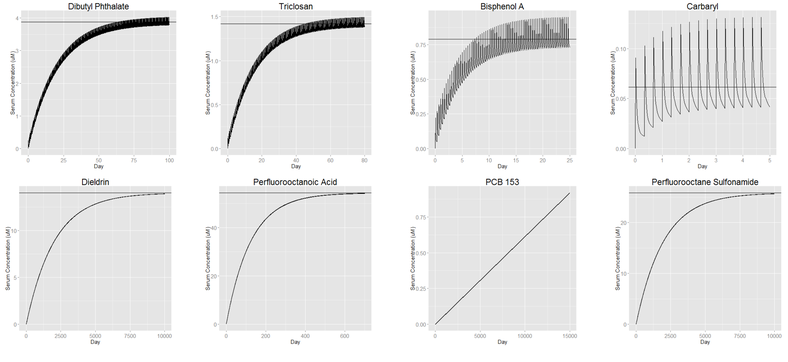
Figure 4: Time required for serum and urinary chemicals to reach steady state (SS) concentrations, where SS is reached when the response to additional doses change the curve by less than 1%.

Figure 5: Plot of the average concentration (Figure 6 horizontal line) versus the maximum concentration (Figure 6 peaks) reached by chemicals in the PK model.



Expansion of Chemical Space: Using a PK model (Figure 1) and assuming a dosing regimen of 1 mg/kg BW/day 3 times daily, we inspected the steady state concentration profile for each of the 13 serum chemicals and a number of urinary chemicals from the ToxCast project for which we had PK data.

Figure 6: Test of the steady state assumption: Below are the PK predictions of the concentration obtained from the dosing regimen, using a PK model with partition coefficients estimated from Schmitt (2008), compared to the inferred C_{ss}.

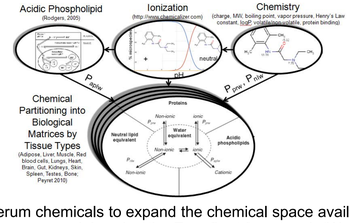


Conclusions

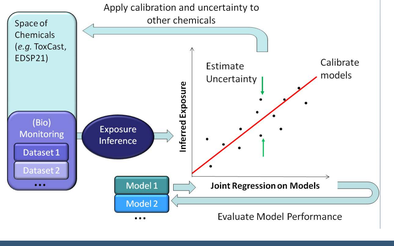
Serum chemicals present a challenge for current high throughput exposure estimation, and simplifying assumptions, such as the steady state assumption used for urinary chemicals, are not valid.

Future Work

- Expand model by identification and use of available PK parameters for serum chemicals e.g., PCBs, PBDEs.
- Improve computational estimation of parameter values for the calculation of partition coefficients for environmental chemicals with very high $P_{o:w}$ using the unified algorithm for calculating partition coefficients (Peyret *et al.*, 2010; below).



- Incorporate serum chemicals to expand the chemical space available to evaluate high-throughput exposure models using the ExpoCast framework (Wambaugh *et al.*, 2013).



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