Inter-individual variability in high-throughput risk prioritization of environmental chemicals

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References provided on separate handout

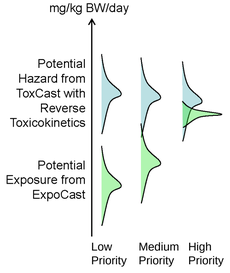
Background: High-throughput risk prioritization

Prioritize large numbers of environmental chemicals by comparing potential exposure to potential hazard

Exposure: ExpoCast high-throughput model framework[1,2]
Inferred based on urine biomonitoring data
Hazard: ToxCast *in vitro* high-throughput screening bioactivity assays[3]
Dose-response data on >1800 chemicals for >800 assays

Relate *in vitro* bioactivity to *in vivo* toxicity and risk:
***In vitro-in vivo* extrapolation** (IVIVE) [4,5,6]
using **reverse toxicokinetics** (TK) [5,7,8,9]

Reverse TK: Convert body concentrations equal to ToxCast bioactive concentrations to oral equivalent doses (OEDs)



Aim: Prioritization for modern US population groups

Previous work: reverse TK, prioritization for N. European Caucasian population[5] and for average Caucasian male[11]

Our goal: **Prioritization for a modern U.S. population**, including potentially sensitive demographic subgroups →

For 10 U.S. demographic groups with ExpoCast exposure inferences:

1. Total
2. Age 6-11
3. Age 12-19
4. Age 20-65
5. Age GT 65
6. BMI LE 30
7. BMI GT 30
8. Males
9. Females
10. Reproductive-Age Females (age 16-49)

Methods: Reverse toxicokinetics

TK model:

$$C_{ss} = \frac{\text{dose} \times F_a}{(GFR \times F_{ub}) + \frac{Q_{liver} \times F_{ub} \times CL_{int,h}}{Q_{liver} + F_{ub} \times CL_{int,h}}}$$

- General model (equivalent to 1-compartment model with oral infusion dosing)
- Can be parameterized for many chemicals using *in vitro* measurements of F_{ub} and CL_{int}[5]
- Implemented in open-source R package `httk`[10]

Parameters of TK model

Name	Description	Units
C_{ss}	Steady-state plasma concentration of chemical	mg/L
Dose	Oral infusion dose of chemical	mg/kg/day
F_a	Fraction absorbed	assumed 100%
GFR	Glomerular filtration rate (passive renal clearance)	L/h/kg bodyweight
Q_{liver}	Hepatic portal vein flow	L/h/kg bodyweight
F_{ub}	Fraction of chemical unbound in blood, scaled from *in vitro* fraction unbound in plasma[5] using *in silico* predicted blood:plasma ratio[10]	Unitless fraction (amt unbound in blood/total amt in blood)
$CL_{int,h}$	Whole-organ intrinsic hepatic clearance, scaled from *in vitro* measurements in human hepatocytes using well-stirred model[5] (incl. liver volume, hepatocellularity)	L/h/kg bodyweight

- Simulate inter-individual variability using Monte Carlo sampling of model parameters
- Apply fixed dose, 1 mg/kg/day
- Take 95th percentile C_{ss}

With assumption of first-order metabolism[5]:

$$\text{Oral Equiv. Dose} = \text{Fixed dose} \times \frac{\text{ToxCast AC}_{50}}{C_{ss} \text{ from fixed dose}}$$

Prioritize using **activity-exposure ratio** (**AER**)[5]

$$\text{AER} = \frac{\text{Oral Equiv. Dose}}{\text{Estimated exposure}}$$

HTTK-Pop: Population physiology simulator

- Open-source correlated Monte Carlo approach
- Simulates modern US population physiology
- Based on data from Centers for Disease Control National Health and Nutrition Examination Survey (CDC NHANES): representative sample of US population; data from 2007-2012 used

Sample NHANES-measured quantities

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

→ Regression equations from literature (+ residual marginal variability)

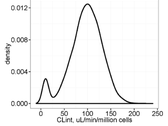
Predict physiological TK parameters

Tissue masses
Tissue blood flows
Glomerular filtration rate
Hepatocellularity

Captures correlation structure of NHANES-measured quantities
Simulates correlation structure of TK model parameters representing physiology

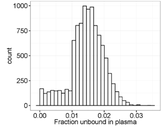
Chemical-specific TK parameters: Assume independent distributions

Intrinsic clearance



Normal distribution: mean = value measured *in vitro* in pooled adult human hepatocytes[5];
30% CV (main peak)
Assume 5% of population are poor metabolizers: mean = 10% of *in vitro* measured value, 30% CV (secondary peak)

Fraction unbound in plasma



Normal distribution: mean = value measured *in vitro* in pooled adult human plasma samples by rapid equilibrium dialysis[5]; 30% CV
Censored below average LOD (0.01)

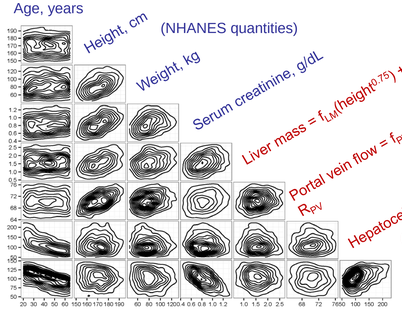
HTTK-Pop allows population specifications: samples NHANES quantities from appropriate *conditional* distribution

Population specification	Default
Age limits	0-79 years, NHANES distribution
Gender (# males/females)	NHANES proportions
BMI/weight category	NHANES proportions

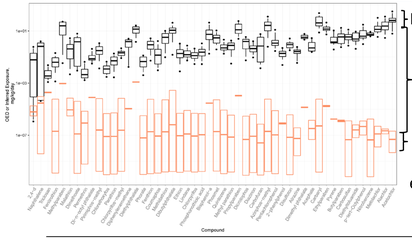
Used HTTK-Pop to simulate the 10 ExpoCast demographic groups (N=1000 in each group)

Performed reverse toxicokinetics for each group, for 50 compounds in ToxCast, ExpoCast, and `httk`

Pairwise joint distributions (contour plots) of HTTK-Pop outputs: sampled NHANES quantities (blue labels) and predicted TK model parameters (red labels), for a simulated population Age 20-65 (N=1000)



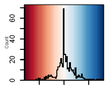
Results: Activity-exposure ratio (AER) prioritization



For Total US population: Range of oral equiv. doses (OEDs) across ToxCast assays (black boxes/whiskers) and inferred exposures (orange boxes: median and 95% CI on median). Log_{10} scale; distance from lower OED whisker (10th pctile) to upper bound of exposure 95% CI corresponds to activity-exposure ratio (AER)[5]

(B) Oral equiv. dose

Differences between demographic groups (number of orders of magnitude) in (A) AER; (B) Inferred exposure; (C) oral equivalent dose



Left colorbar:
AER for Total population (order of magnitude)

(C) Inferred exposure

Conclusions

- Extended open-source toxicokinetic modeling package `httk` to include inter-individual variability by developing population physiology simulator HTTK-Pop
- High-throughput prioritization based on activity-exposure ratio (AER) for demographic subgroups of modern US population
- AER differences from Total pop. may be driven by differences in exposure or in oral equiv. dose (*i.e.*, physiology), depending on demographic group