

Higher Throughput Toxicokinetics to Allow Extrapolation

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Introduction

- In order to address greater numbers of chemicals we collect *in vitro*, high throughput toxicokinetic (HTTK) data
- The goal of HTTK is to provide a human dose context for in vitro concentrations from HTS
 - This allows direct comparisons with exposure
- A key application of HTTK has been reverse dosimetry
 - Allows in vitro in vivo extrapolation (What dose causes a bioactive concentration?)
 - Allows exposure reconstruction (What dose is consistent with a biomarker?)





The Need for *In Vitro* Toxicokinetics





High Throughput Toxicokinetics (HTTK) Jamei et al. (2009)

Minimal Model: Lumped Single Distribution Volume

- *In vitro* plasma protein binding and metabolic clearance assays allow approximate hepatic and renal clearances to be calculated
- At steady state this allows conversion from concentration to administered dose
- 100% bioavailability assumed









- Swap the axes (this is the "reverse" part of reverse dosimetry)
- Can divide bioactive concentration by C_{ss} for for a 1 mg/kg/day dose to get oral equivalent dose

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Wetmore et al. (2012)



Integrated Bioactivity:Exposure Ratio

(Wetmore et al. 2012, 2014, 2015)

 $IBER = \frac{Bioactive Dose}{Estimated exposure}$ IBER <= 1 : Exposurepotentially highenough to cause

bioactivity IBER >> 1: Exposure less likely to be high enough to cause bioactivity





In vivo Predictive Ability and Domain of Applicability

- In drug development, HTTK methods estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)
- For environmental compounds, there will be no clinical trials
- Uncertainty must be well characterized ideally with rigorous statistical methodology
 - We will use direct comparison to *in vivo* data in order to get an empirical estimate of our uncertainty
 - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals



Using in vivo Data to Evaluate HTTK



- When we compare the C_{ss} predicted from *in vitro* HTTK with *in vivo* C_{ss} values determined from the literature we find limited correlation ($R^2 \sim 0.34$)
- The dashed line
 indicates the identity
 (perfect predictor) line:
 - Over-predict for 65
 - Under-predict for 22
- The white lines indicate the discrepancy between measured and predicted values (the residual)



Wambaugh et al. (2015)



- Through comparison to *in* vivo data, a crossvalidated (random forest) predictor of success or failure of HTTK has been constructed
- Add categories for chemicals that do not reach steady-state or for which plasma binding assay fails
- All chemicals can be placed into one of seven confidence categories

Toxicokinetic Triage

140 150⁻ Number of HTTK Chemicals 00 80 66 36 19 6 0 Plasma Binding Assay Failed -3.27 Overest mated -3.2X Underest meted DoesNotRead Steady State >10x Underestinated -10X OVEREST MENE on the Order Triage Category

Wambaugh et al. (2015)



A General Physiologically-based Toxicokinetic (PBTK) Model

- Some tissues (e.g. arterial blood) are simple compartments, while others (e.g. kidney) are compound compartments consisting of separate blood and tissue sections with constant partitioning (i.e., tissue specific partition coefficients)
- Exposures are absorbed from reservoirs (gut lumen)
- Some specific tissues (lung, kidney, gut, and liver) are modeled explicitly, others (e.g. fat, brain, bones) are lumped into the "Rest of Body" compartment.
- Blood flows move the chemical throughout the body. The total blood flow to all tissues equals the cardiac output.
- The only ways chemicals "leaves" the body are through metabolism (change into a metabolite) in the liver or excretion by glomerular filtration into the proximal tubules of the kidney (which filter into the lumen of the kidney).



Evaluating In Vitro PBTK Predictions with In Vivo Data



- PBTK predictions for the AUC (time integrated plasma concentration or Area Under the Curve)
- Oral and *iv* studies for 26 ToxCast compounds
 - Collaboration with NHEERL (Mike Hughes and Jane Ellen Simmons)
 - Additional work by Research Triangle Institute (Tim Fennell)
- Can estimate
 - Fraction absorbed
 - Absorption Rate
 - Elimination Rate
 - Volume of Distribution



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Cyprotex is now measuring bioavailability (CACO2) for all HTTK chemicals



httk:An Up-to-Date Tool

Old versions are archived

<pre>Image: C C C C C C C C C C C C C C C C C C C</pre>	_		Inhaled Gas
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<pre>tensor @ Distributer @ Nourie Handwick. @ Bandwick @ Context and Statistical analysis of chemical toxicokinetics physiologically-based (PBTK.") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved fficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability and measurement limitations. Functions are also provided for exporting "PBTK" models is C SBML" and "JARANC" for use with other simulation solves (also known as "RTK").</pre>	← → C fi 🔒 htt	ps://cran.r-project.org/web/packages/httk/index.html Q 🏠 🚺 🗮	
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- "httk" R Package for reverse dosimetry and PBTK
- 543 Chemicals to date

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Aaencv

- 100's of additional chemicals being studied
- Pearce et al. package documentation manuscript accepted at Journal of Statistical Software

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https://cran.r-project.org/web/packages/httk/

Can access this from the R GUI: "Packages" then "Install Packages"

1e-01

1e-01

1e+01

Predicted K

1e+03



Application to High Throughput Risk Prioritization



ToxCast Chemicals

December, 2014 Panel:

"Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

DOCKET NUMBER: EPA-HQ-OPP-2014-0614





- Toxicokinetics (TK) provides a bridge between HTS and HTE by predicting tissue concentrations due to exposure
- HTTK methods developed for pharmaceuticals have been adapted to environmental testing
- A primary application of HTTK is "Reverse Dosimetry" or RTK
 - Can infer daily doses that produce plasma concentrations equivalent to the bioactive concentrations, **but**:
- We must consider domain of applicability
 - Collected new PK data from *in vivo* studies (EPA/NHEERL and Research Triangle Institute)
 - Organizing data from larger, systematic studies (e.g., National Toxicology Program) into computable format
- New R package "httk" freely available on CRAN allows statistical analyses
 - Analysis has been submitted



Chemical Safety for Sustainability (CSS) Rapid Exposure and Dosimetry (RED) Project

NCCT

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