The High Throughput Toxicokinetic (HTTK) R Package

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Chemical Risk = Hazard x Exposure

- The U.S. National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure.

- To address the thousands of chemicals in commerce and the environment, we need new approach methodologies (NAMs) that can inform prioritization of chemicals most worthy of additional study.

- High throughput risk prioritization needs:
  1. High throughput hazard characterization (Dix et al., 2007, Collins et al., 2008)
  2. High throughput exposure forecasts (Wambaugh et al., 2013, 2014)
  3. High throughput toxicokinetics (i.e., dose-response relationship) linking hazard and exposure (Wetmore et al., 2012, 2015)
High throughput screening (HTS) for *in vitro* bioactivity potentially allows characterization of thousands of chemicals for which no other testing has occurred.
In Vitro - In Vivo Extrapolation (IVIVE)

Utilization of *in vitro* experimental data to predict phenomena *in vivo*

- **IVIVE-PK/TK (Pharmacokinetics/Toxicokinetics):**
  - Fate of molecules/chemicals in body
  - Considers absorption, distribution, metabolism, excretion (ADME)
  - Uses empirical PK and physiologically-based (PBPK) modeling

- **IVIVE-PD/TD (Pharmacodynamics/Toxicodynamics):**
  - Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important
  - Perturbation as adverse/therapeutic effect, reversible/irreversible effects

- Both contribute to *in vivo* effect prediction
New Exposure Data and Models

High throughput screening + \textit{in vitro-in vivo} extrapolation (IVIVE) can predict a dose (mg/kg bw/day) that might be adverse.

Wetmore et al. (2012, 2015)
New Exposure Data and Models

High throughput screening + *in vitro-in vivo* extrapolation (IVIVE) can predict a dose (mg/kg bw/day) that might be adverse.

High throughput models exist to make predictions of exposure via specific, important pathways such as residential product use and diet.

NRC (2012)
High Throughput Toxicokinetics (HTTK)

- Most chemicals do not have TK data
- In order to address greater numbers of chemicals we collect *in vitro*, high throughput toxicokinetic (HTTK) data (Rotroff et al., 2010, Wetmore et al., 2012, 2015)
- HTTK methods have been used by the pharmaceutical industry to determine range of efficacious doses and to prospectively evaluate success of planned clinical trials (Jamei, *et al.*, 2009; Wang, 2010)
- The primary goal of HTTK is to provide a human dose context for bioactive *in vitro* concentrations from HTS (*i.e.*, *in vitro*-in *vivo* extrapolation, or IVIVE) (*e.g.*, Wetmore et al., 2015)
- Secondary goal is to provide open source data and models for evaluation and use by the broader scientific community (Pearce *et al.*, 2017a)
Most chemicals do not have TK data – we use *in vitro* HTTK methods adapted from pharma to fill gaps.

In drug development, HTTK methods allow IVIVE to estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010).

The rate of disappearance of parent compound (slope of line) is the **hepatic clearance** ($\mu$L/min/10$^6$ hepatocytes).

We perform the assay at 1 and 10 $\mu$M to check for saturation of metabolizing enzymes.
Most chemicals do not have TK data – we use in vitro HTTK methods adapted from pharma to fill gaps.

In drug development, HTTK methods allow IVIVE to estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010).

\[ F_{ub,p} = \frac{C_{\text{well}1}}{C_{\text{well}2}} \]
In Vitro Data for HTTK

- Most chemicals do not have TK data – we use *in vitro* HTTK methods adapted from pharma to fill gaps

- Environmental chemicals:
  - Rotroff et al. (2010) 35 chemicals
  - Wetmore et al. (2012) +204 chemicals
  - Wetmore et al. (2015) +163 chemicals
  - Wambaugh et al. (submitted) +389 chemicals

Cryopreserved hepatocyte suspension
Shibata et al. (2002)

Rapid Equilibrium Dialysis (RED)
Waters et al. (2008)

Formula:

\[ F_{ub,p} = \frac{C_{well1}}{C_{well2}} \]
Simple Model for Steady-State Plasma Concentration ($C_{ss}$)

$$C_{ss} = \frac{\text{oral dose rate}}{(GFR \times f_{up}) + \left(Q_l \times f_{up} \times \frac{Cl_{int}}{Q_l + f_{up} \times Cl_{int}}\right)}$$

Wilkinson and Shand (1975)

- **Passive Renal Clearance**
  - (GFR: Glomerular filtration rate
  - $f_{up}$: fraction unbound in plasma)

- **Hepatic Metabolism**
  - ($Cl_{int}$: Scaled hepatic clearance
  - $Q_l$: Blood flow to liver)
Assume that Steady-State is Linear with Dose

\[ C_{ss} = \frac{\text{oral dose rate}}{(GFR \times f_{up}) + (Q_i \times f_{up} \times \frac{Cl_{int}}{Q_i + f_{up} \times Cl_{int}})} \]
Assume that Steady-State is Linear with Dose

\[ C_{ss} = \frac{\text{oral dose rate}}{(GFR \times f_{uw}) + \left(\frac{Q_l \times f_{uw} \times Cl_{int}}{Q_l + f_{uw} \times Cl_{int}}\right)} \]

- Can calculate predicted steady-state concentration \( (C_{ss}) \) for a 1 mg/kg/day dose and multiply to get concentrations for other doses

Wetmore et al. (2012)
Assume that Steady-State is Linear with Dose

\[ C_{ss} = \frac{\text{oral dose rate}}{GFR \times f_{up}} + \left( \frac{Q_i \times f_{up} \times Cl_{int}}{Q_i + f_{up} \times Cl_{int}} \right) \]

- Can calculate predicted steady-state concentration \((C_{ss})\) for a 1 mg/kg/day dose and multiply to get concentrations for other doses

\[ \text{Prediction Slope} = C_{ss} \text{ for 1 mg/kg/day} \]

\[ \text{Daily Dose (mg/kg/day)} \]

\[ \text{Steady-state Concentration (µM)} \]

Wetmore et al. (2012)
HTTK Allows Steady-State In Vitro-In Vivo Extrapolation (IVIVE)

\[ C_{ss} = \frac{\text{oral dose rate}}{GFR \ast f_{up}} + \left( \frac{Q_l \ast f_{up} \ast Cl_{int}}{Q_l + f_{up} \ast Cl_{int}} \right) \]

- Can calculate predicted steady-state concentration \( C_{ss} \) for a 1 mg/kg/day dose and multiply to get concentrations for other doses

\[ \text{Slope} = \text{mg/kg/day per } C_{ss} \]

\( C_{ss} \) = \( \text{oral dose rate} \) \( GFR \ast f_{up} \) + \( \frac{Q_l \ast f_{up} \ast Cl_{int}}{Q_l + f_{up} \ast Cl_{int}} \)

\[ C_{ss} = \text{in vitro AC50} \]

\text{Prediction}

\( C_{ss} \) = \text{oral dose rate} \( GFR \ast f_{up} \) + \( \frac{Q_l \ast f_{up} \ast Cl_{int}}{Q_l + f_{up} \ast Cl_{int}} \)

\[ C_{ss} = \text{in vitro AC50} \]

\( C_{ss} \) = \text{oral dose rate} \( GFR \ast f_{up} \) + \( \frac{Q_l \ast f_{up} \ast Cl_{int}}{Q_l + f_{up} \ast Cl_{int}} \)

\[ C_{ss} = \text{in vitro AC50} \]
High-Throughput Toxicokinetics (HTTK) for *In Vitro-In Vivo* Extrapolation (IVIVE)

Using the generic HTTK physiologically based toxicokinetics model to inform IVIVE...

Selecting the appropriate *in vitro* and *in vivo* concentrations for extrapolation

Honda et al. (2019)
Using PBTK Models Improves IVIVE

Various Combinations of IVIVE Assumptions

Honda et al. (2019)
High throughput screening + *in vitro*-*in vivo* extrapolation (IVIVE) can predict a dose (mg/kg bw/day) that might be adverse.
ToxCast-derived Receptor Bioactivity Converted to mg/kg/day with HTTK Exposure Predictions

ToxCast Chemicals Near Field Far Field

mg/kg bw/day

High Throughput Risk Prioritization in Practice

December, 2014 Panel: “Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening”
High Throughput Risk Prioritization in Practice

ToxCast-derived Receptor Bioactivity Converted to mg/kg/day with HTTK

ExpoCast Exposure Predictions

Near Field
Far Field

Higher priority chemicals

ToxCast Chemicals

December, 2014 Panel: "Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"
Nearly eight orders of magnitude between estimated intake rate and bioactive equivalent dose.
Open Source Tools and Data for HTTK

https://CRAN.R-project.org/package=httk

R package “httk”

- Open source, transparent, and peer-reviewed tools and data for high throughput toxicokinetics (httk)
- Available publicly for free statistical software R
- Allows in vitro-in vivo extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
What you can do with R Package “httk”?

- Allows one compartment, three-compartment, and PBTK modeling
- Allows conversion of *in vitro* concentration to *in vivo* doses
- Allows prediction of internal tissue concentrations from dose regimen (oral and intravenous)
- A peer-reviewed paper in the Journal of Statistical software provides a how-to guide (Pearce et al., 2017a)
- You can use the built in chemical library or add more chemical information (examples provided in JSS paper)
- You can load specific (older) versions of the package
- You can use specific demographics in the population simulator (Ring et al., 2017)
- You can control the built in random number generator to reproduce the same random sequence (function set.seed())
A General Physiologically-based Toxicokinetic (PBTK) Model

- “httk” includes a generic 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.
- The only ways chemicals “leave” 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).
## Why Build Another Generic PBTK Tool?

<table>
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<th></th>
<th>SimCYP</th>
<th>ADMET Predictor / GastroPlus</th>
<th>MEGen</th>
<th>IndusChemFate</th>
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We want to do a statistical analysis (using R) for as many chemicals as possible.
Oral Equivalent Dose Examples

# State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95 quantile, for Acetochlor (published value):
get_wetmore_oral_equiv(0.1,chem.cas="34256-82-1")

# State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95 quantile, for Acetochlor (calculated value):
calc_mc_oral_equiv(0.1,chem.cas="34256-82-1")

# State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantile, for Acetochlor (published values):
get_wetmore_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))

# State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantiles, for Acetochlor (calculated value):
calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))

# State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for rat, 0.95 quantile, for Acetochlor (calculated value):
calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",species="Rat")
#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for human for Acetochlor (calculated value):
\[
calc_{mc\_css}(chem\.cas="34256-82-1")
\]

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (should produce errors since there is no published value, 0.5 quantile only):
\[
\text{get\_wetmore\_css(chem\.cas="34256-82-1",species="Rat")}
\]

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (calculated value):
\[
calc_{mc\_css}(chem\.cas="34256-82-1",species="Rat")
\]

#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (published value):
\[
\text{get\_wetmore\_css(chem\.cas="34256-82-1",species="Rat",which.quantile=0.5)}
\]

#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (calculated value):
\[
calc_{mc\_css}(chem\.cas="34256-82-1",species="Rat",which.quantile=0.5)
\]

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for mouse for Acetochlor (should produce error since there is no published value, human and rat only):
\[
\text{get\_wetmore\_css(chem\.cas="34256-82-1",species="Mouse")}
\]

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for mouse for Acetochlor (calculated value):
\[
calc_{mc\_css}(chem\.cas="34256-82-1",species="Mouse")
\]
\[
calc_{mc\_css}(chem\.cas="34256-82-1",species="Mouse",default.to.human=T)
\]
Generic PBTK Models

There is nothing new about the idea of generic PBTK models...
Generic PBTK Models

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There is nothing new about the idea of generic PBTK models...
“Although publication of a PBPK model in a peer-reviewed journal is a mark of good science, subsequent evaluation of published models and the supporting computer code is necessary for their consideration for use in [Human Health Risk Assessments]”

“...the default state of new and modernized Government information resources shall be open and machine readable.”
Doing Statistical Analysis with HTTK

- If we are to use HTTK, we need confidence in predictive ability

- 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 most compounds in the environment there will be no clinical trials

- Uncertainty must be well characterized
  - We compare to *in vivo* data to get **empirical estimates of HTTK uncertainty**
  - ORD has both compiled existing (literature) TK data (Wambaugh *et al.*, 2015) and conducted new experiments in rats on chemicals with HTTK *in vitro* data (Wambaugh *et al.*, 2018)
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals
• In order to evaluate a **chemical-specific TK model** for “chemical x” you can compare the predictions to *in vivo* measured data
  • Can estimate bias
  • Can estimate uncertainty
  • Can consider using model to extrapolate to other situations (dose, route, physiology) where you don’t have data
Building Confidence in TK Models

• In order to evaluate a chemical-specific TK model for “chemical x” you can compare the predictions to in vivo measured data
  • Can estimate bias
  • Can estimate uncertainty
  • Can consider using model to extrapolate to other situations (dose, route, physiology) where you don’t have data

• However, we do not typically have TK data
• In order to evaluate a chemical-specific TK model for “chemical x” you can compare the predictions to in vivo measured data
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  • Can estimate uncertainty
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• However, we do not typically have TK data

• We can parameterize a generic TK model, and evaluate that model for as many chemicals as we do have data
  • We do expect larger uncertainty, but also greater confidence in model implementation
  • Estimate bias and uncertainty, and try to correlate with chemical-specific properties

Cohen Hubal et al. (2018)
In order to evaluate a chemical-specific TK model for “chemical x” you can compare the predictions to in vivo measured data:
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- Can consider using model to extrapolate to other situations (chemicals without in vivo data)

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Cohen Hubal et al. (2018)
EPA is developing a public database of concentration vs. time data for building, calibrating, and evaluating TK models.

Curation and development ongoing, but to date includes:
- 198 analytes (EPA, National Toxicology Program, literature)
- Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure

Database will be made available through web interface and through the “httk” R package.

Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data:
https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit
We estimate clearance from two processes – hepatic metabolism (liver) and passive glomerular filtration (kidney).

This appears to work better for pharmaceuticals than other chemicals:
- ToxCast chemicals are overestimated
- Non-pharmaceuticals may be subject to extrahepatic metabolism and/or active transport.

Wambaugh et al. (2018)
Different crayons have different colors...
Different crayons have different colors, and none of them are the “average” color.
Population simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters built into R “httk” package (Pearce et al., 2017):

*Sample* NHANES biometrics for actual individuals:

- Sex
- Race/ethnicity
- Age
- Height
- Weight
- Serum creatinine

Slide from Caroline Ring (ToxStrategies)
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Regression equations from literature (McNally et al., 2014)
(+ residual marginal variability)


Slide from Caroline Ring (ToxStrategies)

Ring et al. (2017)
Population simulator for HTTK

Correlated Monte Carlo sampling of physiological model parameters built into R “httk” package (Pearce et al., 2017):

*Sample* NHANES biometrics for actual individuals:

- Sex
- Race/ethnicity
- Age
- Height
- Weight
- Serum creatinine

*Predict* physiological quantities

- Tissue masses
- Tissue blood flows
- GFR (kidney function)
- Hepatocellularity

Regression equations from literature (McNally et al., 2014)

(+ residual marginal variability)


Slide from Caroline Ring (ToxStrategies)

Ring et al. (2017)
Until I open the box, I don’t know what colors I have...

...especially if my six-year-old has been around.
Analytical Chemistry is an HTTK Bottleneck

- For HTTK we always need to develop a chemical-specific method for quantitating amount of chemical *in vitro*
  - This is very different from HTS where the same readout (e.g., bioluminescence) can be used for most chemicals

- In Wetmore et al. (2012), the rapid equilibrium dialysis (RED) assay (Waters et al. 2008) failed for fraction unbound in plasma ($f_{up}$) 38% of the chemicals.

**Figure from Chantel Nicolas**

1. Aliquots drawn after RED equilibration
2. Chemical isolated for further analysis
3. $f_{up}$ determined from response ratios

\[
\frac{\text{Analyte Peak Area Ratio (PBS-Side)}}{\text{Blank Peak Area Ratio}} - \frac{\text{Analyte Peak Area Ratio (Plasma-Side)}}{\text{Blank Peak Area Ratio}} = f_{up}
\]
The HTTK *in vitro* assays need to measure differences in chemical concentration

- Area of the internal standard (ITSD) at a known, fixed concentration fluctuates with time

- Find a peak that corresponds to chemical of interest, and then follow the ratio $R$ of the chemical peak to the ITSD
The HTTK *in vitro* assays need to measure differences in chemical concentration:

- Area of the internal standard (ITSD) at a known, fixed concentration fluctuates with time.
- Find a peak that corresponds to chemical of interest, and then follow the ratio $R$ of the chemical peak to the ITSD.
- For new measurements HTTK (>200 compounds to data) performed by Cyprotex, we have modified RED protocol to use a titration of plasma protein (10%, 30%, 100%) of physiological concentration.
  - Keeps chemical concentration in the same range.
  - Analyzed data in Bayesian framework that included a model for analytical chemistry.
  - Bayesian approach gives a credible interval (range of values that would be consistent with the data) – quantitative uncertainty.
New Plasma Binding Protocol Reduces Uncertainty

- New protocol performs assay at 100%, 30%, and 10% of physiologic protein concentration
- Median uncertainty for 100% physiological concentration only: +-5.5%

Wambaugh et al. (submitted)
• New protocol performs assay at 100%, 30%, and 10% of physiologic protein concentration

• Median uncertainty for 100% physiological concentration only: +5.5%

• Median uncertainty for three-point assay: +-1.4%

Wambaugh et al. (submitted)
New Data!

New experimental measurements of $f_{up}$ and $Cl_{int}$ are reported for 418 and 467 chemicals, respectively. These data raise the HTTK chemical coverage of the ToxCast Phase I and II libraries to 57%.
Quantifying the Impact of Uncertainty

Median Ratio for Uncertainty: 2.32
Median Ratio for Variability: 6.27
Median Ratio for Both: 7.13
Including chemical-specific uncertainty only caused changes in whether or not exposure and bioactivity overlapped in a small region

Wambaugh et al. (submitted)
The Impact of Measurement Uncertainty

Only six more chemicals overlap Wambaugh et al. (submitted)
We are working to augment the basic HT-PBPTK model with new PBTK models:

- For example, inhalation PBTK will allow for calculation of “inhalation equivalent doses” instead of oral equivalents.

Each model will be released publicly upon peer-reviewed publication.

Pre-publication models can be shared under a MTA.

We assume there will be coding errors and over-simplifications, so each publication involves curation of evaluation data from the scientific literature and through statistical analysis.
New HT-PBTK Models
New HT-PBTK Models

Gas Inhalation Exposure Route
EPA, USAF

Dermal Exposure Route
EPA, Unilever, INERIS
Generic Gas Inhalation Model

In Vivo TK database allowed rapid development and evaluation.
Generic Gas Inhalation Model

Generic model also helped data curation (units on axis in paper were wrong)

Linakis et al. (in preparation)
Figure from Matt Linakis (USAFSAM)

**Generic Gas Inhalation Model**

- Inhaled Air
- Exhaled Breath
- Mucous
- Alveolar Space
- Lung Blood
- Lung Tissue
- Gut Blood
- Gut Tissue
- Gut Lumen
- Liver Blood
- Liver Tissue
- Body Blood
- Body Tissue
- Kidney Blood
- Kidney Tissue

- $Q_{\text{alv}}$
- $Q_{\text{ulv}}$
- $Q_{\text{gut}}$
- $k_{\text{gutabs}}$
- $Q_{\text{cardiac}}$
- $Q_{\text{gfr}}$
- $Q_{\text{v}}$
- $Q_{\text{kidney}}$
- $Q_{\text{rest}}$

1,3-Butadiene (Human, 5ppm for 2h in EB)

- Correct
- Used 4h exposure instead of 2h
- Used mg/m3 dose units instead of ppm

(EMT Elim)
New HT-PBTK Models

Gas Inhalation Exposure Route
EPA, USAF

Aerosol Inhalation Exposure Route (with APEX model)
EPA, USAF

Dermal Exposure Route
EPA, Unilever, INERIS
New HT-PBTK Models

Gas Inhalation Exposure Route
EPA, USAFSAM

Aerosol Inhalation Exposure Route (with APEX model)
EPA, USAFSAM

Human Gestational Model
EPA, FDA

Dermal Exposure Route
EPA, Unilever, INERIS

Office of Research and Development
New HT-PBTK Models

Gas Inhalation Exposure Route
EPA, USAFSAM

Aerosol Inhalation Exposure Route
(with APEX model)
EPA, USAFSAM

Dermal Exposure Route
EPA, Unilever, INERIS

RESEARCH ARTICLE
Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation

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Maternal dosimetry
- Decrease in maternal plasma concentrations for retinoid analogues ranged from 8-15%

Fetal dosimetry
- Decrease in Fetal plasma concentrations for retinoid analogues ranged from 4-9%
HTTK is (mostly) Documented

Within R: type “help(httk)”
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Within R: type "help(httk)"
### Does My Chemical Have HTTK Data?

> library(httk)
> get_cheminfo()

```r
[1] "2971-36-0"   "94-75-7"     "94-82-6"     "90-43-7"     "1007-28-9"
[6] "71751-41-2"  "30560-19-1" "135410-20-7" "34256-82-1" "50594-66-6"
[11] "15972-60-8"  "116-06-3"   "834-12-8"    "33089-61-1" "101-05-3"
[16] "1912-24-9"   "86-50-0"     "131860-33-8" "22781-23-3" "1861-40-1" ...
```

> get_cheminfo(info="all")

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th>logP</th>
<th>pK&lt;sub&gt;A&lt;/sub&gt;</th>
<th>pK&lt;sub&gt;Donor&lt;/sub&gt;</th>
<th>MW</th>
<th>Human.Clint.p</th>
<th>Human.Clint.p Value</th>
<th>Human.Funbouch DSSTox_Substance_ID</th>
<th>Structure_Formula</th>
<th>Substance_Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-d</td>
<td>94-75-7</td>
<td>2.81</td>
<td>&lt;NA&gt;</td>
<td>2.81</td>
<td>221.03</td>
<td>0</td>
<td>0.149</td>
<td>DTXSID0020442</td>
<td>C8H6Cl2O3</td>
<td>Single</td>
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<tr>
<td>2,4-db</td>
<td>94-82-6</td>
<td>3.53</td>
<td>&lt;NA&gt;</td>
<td>4.5</td>
<td>249.09</td>
<td>0</td>
<td>0.104</td>
<td>DTXSID7024035</td>
<td>C10H10Cl2O3</td>
<td>Single</td>
</tr>
<tr>
<td>2-phenylphenol</td>
<td>90-43-7</td>
<td>3.09</td>
<td>&lt;NA&gt;</td>
<td>10.6</td>
<td>170.211</td>
<td>2.08</td>
<td>0.164</td>
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<td>C12H10O</td>
<td>Single</td>
</tr>
<tr>
<td>6-desisopropylatrazine</td>
<td>1007-28-9</td>
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<td>1.59</td>
<td>&lt;NA&gt;</td>
<td>173.6</td>
<td>0</td>
<td>0.539</td>
<td>DTXSID0037495</td>
<td>C5H8ClN5</td>
<td>Single</td>
</tr>
</tbody>
</table>

> "80-05-7" %in% get_cheminfo()

[1] TRUE

### Is a chemical available?

All data on chemicals A, B, C

subset(get_cheminfo(info="all"), Compound %in% c("A", "B", "C"))
• HTTK allows dosimetric adjustment of high-throughput screening (HTS) data across thousands of chemicals.

• New, chemical-specific *in vitro* experiments have been conducted by Cyprotex, using a revised protocol for measuring protein binding.

• Overall, variability contributed more significantly to $C_{ss}$ estimations of the 95th percentile.

• Comparison between high throughput toxicokinetics (HTTK) predicted concentrations and in vivo data is a valuable approach for evaluation and establishing confidence.

• Recent analyses indicate that some properties (e.g. average and maximum concentration) can be predicted with confidence.
  • A new database of in vivo concentration vs. time data is being developed (Sayre, in preparation).

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA.
ExpoCast Project
(Exposure Forecasting)

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