Building Fit-for-purpose Pharmacokinetic Models

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In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making Webinar Series

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Introduction

- Toxicokinetics (TK) provide a bridge between hazard (e.g., what tissue concentration causes an effect?) and exposure (e.g., what dose do we get exposed to?)

- Traditional TK methods are resource intensive

- Relatively high throughput TK (HTTK) methods have been used by the pharmaceutical industry to prospectively evaluate success of planned clinical trials (Jamei, et al., 2009; Wang, 2010)
  - A key application of HTTK has been “reverse dosimetry” (also called Reverse TK or RTK) (Tan et al., 2006)
  - RTK can approximately convert in vitro HTS results to daily doses needed to produce similar levels in a human for comparison to exposure data (Wetmore, et al., 2012)
  - How accurate do predictions need to be?
“Among competing hypotheses, the one with the fewest assumptions should be selected.” William of Ockham

“…when you have eliminated the impossible, whatever remains, however improbable, must be the truth…” Sherlock Holmes (Arthur Conan Doyle)

“PBPK? My immediate response: Junk in, junk out. The take-home is that most of the models [are] only as good as your understanding of the complexity of the system.” Louis Guillette, Medical University of South Carolina

“As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality.” Albert Einstein

Orrin Pilkey & Olinda Pilkey-Jarvis (2007)
“Models can offer a means of avoiding the conclusions derived from actual experiments.” Kristin Shrader-Frechette, University of Notre Dame

“Essentially, all models are wrong, but some are useful.” George Box, University of Wisconsin

1. Think probabilistically: Evaluate model performance systematically across as many chemicals (and chemistries) as possible

2. Forecasts change: Today’s forecast reflects the best available data today but we must accept that new data and new models will cause predictions to be revised

3. Look for consensus: Evaluate as many models and predictors/predictions as possible
“Since all models are wrong the scientist cannot obtain a ‘correct’ one by excessive elaboration. On the contrary[,], following William of Occam[, they] should seek an economical description of natural phenomena.” George Box, University of Wisconsin
“Since all models are wrong the scientist cannot obtain a ‘correct’ one by excessive elaboration. On the contrary[,] following William of Occam[,] they] should seek an economical description of natural phenomena.”

George Box, University of Wisconsin

Complexity should fit the problem...
High-Throughput Bioactivity

- **Tox21**: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

- **ToxCast**: For a subset (>1000) of Tox21 chemicals ran >800 additional assay endpoints (Judson et al., 2010)

- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function)

- All data is public: http://actor.epa.gov/dashboard2
Pharmacokinetics Allows Context for High Throughput Screening

Endocrine disruption AOP (Judson et al., in prep.)

ToxCast Bioactivity Converted to mg/kg/day with HTTK (Wetmore et al., 2012)

ExpoCast Exposure Predictions (Wambaugh et al., 2014)

ToxCast Chemicals

December, 2014 Panel:
“Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening“

Studies like Wetmore et al. (2012) addressed the need for TK data using *in vitro* methods.
ToxCast *in vitro* Bioactive Concentrations

- One point for each chemical-*in vitro* assay combination with a systematic (Hill function) concentration response curve
- How can we use toxicokinetics to convert these to human doses?

Wetmore *et al.* (2012)
High Throughput Toxicokinetics (HTTK)

- *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.

\[
C_{ss} = \frac{\text{oral dose rate}}{(GFR \times F_{ub}) + \left( Q_{l} \times F_{ub} \times \frac{Cl_{int}}{Q_{l} + F_{ub} \times Cl_{int}} \right)}
\]

- Oral dose in (mg/kg/day)
- Sum of hepatic and renal clearance (mg/kg/day)

Jamei *et al.* (2009)
Steady-State is Linear with Dose

Steady-state Concentration (µM) vs. Daily Dose (mg/kg/day)

Prediction

\[ C_{ss} = \frac{\text{oral dose rate}}{\left( \frac{\text{GFR} \cdot F_{ub}}{Q_i \cdot F_{ub} \cdot \frac{Cl_{int}}{Q_i + F_{ub} \cdot Cl_{int}}} \right)} \]

- 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)
Steady-State is Linear with Dose

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

$$C_{ss} = \frac{\text{oral dose rate}}{(\text{GFR} \times F_{ub}) + \left( \frac{Q_i \times F_{ub} \times Cl_{int}}{Q_i + F_{ub} \times Cl_{int}} \right)}$$

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

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

Wetmore et al. (2012)
It appears harder to prioritize on bioactive *in vitro* concentration without *in vivo* context.
Translation from *in vitro* to steady-state oral equivalent doses allow greater discrimination between effective chemical potencies.

Wetmore *et al.* (2012)
Reverse Dosimetry with HTTK

High Throughput

In Vitro

Bioactive

Concentration

HTTK

in vitro

data

Simulated Human

In Vivo

Doses

Monte Carlo

Simulation of Biological

Variability

Combination of higher exposure and sensitivities

Populations that are More Sensitive

Images from Thinkstock
Variability in this Steady-State TK Model

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

- In vitro clearance (µL/min/10^6 hepatocytes) is scaled to a whole organ clearance using the density of hepatocytes per gram of liver and the volume of the liver (which varies between individuals)
- Glomerular filtration rate (GFR) and blood flow to the liver (Q_l) both vary from individual to individual
- Further assume that measured HTTK parameters have 30% coefficient of variation

Jamei et al. (2009)
Monte Carlo (MC) Approach to Variability: SimCYP (Pharma) Approach

\[ C_{ss} = \frac{\text{oral dose rate}}{(GFR \times F_{ub}) + \left( \frac{Q_{l} \times F_{ub} \times Cl_{int}}{Q_{l} + F_{ub} \times Cl_{int}} \right)} \]

\[ C_{ss} \]

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

- The higher the predicted $C_{ss}$, the lower the oral equivalent dose, so the upper 95% predicted $C_{ss}$ from the MC has a lower oral equivalent dose.

Environmental chemicals: Yoon *et al.* (2014)

Hepatocytes and passive GFR alone tend to underestimate clearance.
543 Chemicals with httk R Package

https://cran.r-project.org/web/packages/httk/
Can access this from the R GUI: “Packages” then “Install Packages”

443 with PBTK models

Lead developer Robert Peace
Comparison Between httk and SimCYP

- In the Rotroff et al. (2010) and Wetmore et al. (2012, 2013, 2014, 2015) papers SimCYP was used to predict distributions of \( C_{ss} \) from \textit{in vitro} data.

- We can reproduce the results from those publications for most chemicals using our implementation of Monte Carlo.

- Any one chemical’s median and quantiles are connected by a dotted line.

The RED assay for measuring protein binding fails in some cases because the amount of free chemical is below the limit of detection. For those chemicals a default value of 0.5% free was used. We have replaced the default value with random draws from a uniform distribution from 0 to 1%.
Using *in vivo* Data to Evaluate RTK

- 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)
Through comparison to *in vivo* data, a cross-validated (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.

Wambaugh et al. (2015)
New In Vivo PK Data Set

- Could the difference be related to inhomogeneous $C_{ss}$ data?
  - Initially relying on Obach (2008) data plus data curated by TNO (Sieto Bosgra lead) from literature
- Only 13 non-pharmaceuticals examined so far
- Cross lab study:
  - 20 chemicals examined by NHEERL (Mike Hughes lead)
  - 8 chemicals examined by RTI (Tim Fennell lead)
  - 2 overlap chemicals (Bensulide and Propyzamide)
An In Vivo Toxicokinetic Library

Work by Mike Hughes, Caroline Ring, Tim Fennell (RTI) and many more
Evaluating Steady-state Conc. (1 mg/kg/day exposure)

Similar to pharmaceuticals in Sohlenius-Sternbeck et al., 2010

Work by Mike Hughes, Caroline Ring, Tim Fennell (RTI) and many more
Three Compartment (SimCYP Steady-state) Model

Good enough for prioritizing chemicals...

\[ Q_{\text{iv}} = Q_{\text{ha}} + Q_{\text{pv}} \]

\[ Q_{\text{hepatic artery}}/R_{\text{blood:plasma}} \]

\[ Q_{\text{portal vein}}/R_{\text{blood:plasma}} \]
Pharmacokinetics Allows Context for High Throughput Screening

*Endocrine disruption AOP* (Judson et al., in prep.)

ToxCast Bioactivity Converted to mg/kg/day with HTTK (Wetmore et al., 2012)

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**ToxCast Chemicals**

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A General Physiologically-based Pharmacokinetic (PBPK) 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).
## Physiological Data

### Volumes and flows from Schmitt (2008) + Nisha Sipes (Rabbit)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Mouse</th>
<th>Rat</th>
<th>Dog</th>
<th>Human</th>
<th>Rabbit</th>
<th>Mouse</th>
<th>Rat</th>
<th>Dog</th>
<th>Human</th>
<th>Rabbit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>0.07</td>
<td>0.07</td>
<td>0.05</td>
<td>0.21</td>
<td>0.05</td>
<td>10.80</td>
<td>1.60</td>
<td>3.50</td>
<td>3.71</td>
<td>12.80</td>
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<tr>
<td>Bone</td>
<td>0.05</td>
<td>0.04</td>
<td>0.04</td>
<td>0.07</td>
<td>0.04</td>
<td>23.31</td>
<td>36.11</td>
<td>1.30</td>
<td>3.36</td>
<td>36.11</td>
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<tr>
<td>Brain</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>13.20</td>
<td>5.20</td>
<td>4.50</td>
<td>10.00</td>
<td>5.20</td>
</tr>
<tr>
<td>Gut</td>
<td>0.04</td>
<td>0.03</td>
<td>0.04</td>
<td>0.02</td>
<td>0.05</td>
<td>72.50</td>
<td>39.20</td>
<td>23.00</td>
<td>16.43</td>
<td>44.40</td>
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<tr>
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<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>14.00</td>
<td>15.60</td>
<td>5.40</td>
<td>3.43</td>
<td>6.40</td>
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<tr>
<td>Kidneys</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00</td>
<td>0.01</td>
<td>65.00</td>
<td>36.80</td>
<td>21.60</td>
<td>17.71</td>
<td>32.00</td>
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<td>0.05</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>0.04</td>
<td>90.00</td>
<td>47.20</td>
<td>30.90</td>
<td>20.71</td>
<td>70.80</td>
</tr>
<tr>
<td>Lung</td>
<td>0.01</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>2.00</td>
<td>6.22</td>
<td>10.56</td>
<td>2.00</td>
<td>6.22</td>
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<tr>
<td>Muscle</td>
<td>0.37</td>
<td>0.39</td>
<td>0.44</td>
<td>0.38</td>
<td>0.54</td>
<td>45.50</td>
<td>30.00</td>
<td>25.00</td>
<td>10.71</td>
<td>62.00</td>
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<tr>
<td>Skin</td>
<td>0.15</td>
<td>0.17</td>
<td>0.17</td>
<td>0.03</td>
<td>0.04</td>
<td>20.50</td>
<td>23.20</td>
<td>10.00</td>
<td>4.29</td>
<td>23.20</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>5.50</td>
<td>4.07</td>
<td>1.65</td>
<td>1.10</td>
<td>3.60</td>
</tr>
<tr>
<td>Rest</td>
<td>0.03</td>
<td>0.05</td>
<td>0.00</td>
<td>0.05</td>
<td>0.03</td>
<td>110.19</td>
<td>90.00</td>
<td>5.59</td>
<td>2.97</td>
<td>90.00</td>
</tr>
</tbody>
</table>

### Other parameters from Davies and Morris (1993) + Nisha Sipes (Rabbit)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Mouse</th>
<th>Rat</th>
<th>Dog</th>
<th>Human</th>
<th>Rabbit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Body Water</td>
<td>ml/kg</td>
<td>725.00</td>
<td>668.00</td>
<td>603.60</td>
<td>600.00</td>
<td>716.00</td>
</tr>
<tr>
<td>Plasma Volume</td>
<td>ml/kg</td>
<td>50.00</td>
<td>31.20</td>
<td>51.50</td>
<td>42.86</td>
<td>44.00</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>ml/min/kg</td>
<td>400.00</td>
<td>296.00</td>
<td>120.00</td>
<td>80.00</td>
<td>212.00</td>
</tr>
<tr>
<td>Average BW</td>
<td>kg</td>
<td>0.02</td>
<td>0.25</td>
<td>10.00</td>
<td>70.00</td>
<td>2.5</td>
</tr>
<tr>
<td>Total Plasma Protein</td>
<td>g/ml</td>
<td>0.06</td>
<td>0.07</td>
<td>0.09</td>
<td>0.07</td>
<td>0.057</td>
</tr>
<tr>
<td>Plasma albumin</td>
<td>g/ml</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.04</td>
<td>0.0387</td>
</tr>
<tr>
<td>Plasma a-1-AGP</td>
<td>g/ml</td>
<td>0.01</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.0013</td>
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<tr>
<td>Hematocrit</td>
<td>fraction</td>
<td>0.45</td>
<td>0.46</td>
<td>0.42</td>
<td>0.44</td>
<td>0.36</td>
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<tr>
<td>Urine</td>
<td>ml/min/kg</td>
<td>0.035</td>
<td>0.139</td>
<td>0.021</td>
<td>0.014</td>
<td>0.0417</td>
</tr>
<tr>
<td>Bile</td>
<td>ml/min/kg</td>
<td>0.069</td>
<td>0.063</td>
<td>0.008</td>
<td>0.003</td>
<td>0.0833</td>
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<tr>
<td>GFR</td>
<td>ml/min/kg</td>
<td>14.0</td>
<td>5.2</td>
<td>6.1</td>
<td>1.8</td>
<td>3.12</td>
</tr>
</tbody>
</table>
# Schmitt (2008) Tissue Composition Data

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Cells</th>
<th>Interstitium</th>
<th>Water</th>
<th>Lipid</th>
<th>Protein</th>
<th>Neutral Lipid&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Neutral Phospholipid&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Acidic Phospholipid&lt;sup&gt;c&lt;/sup&gt;</th>
<th>pH&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>0.86</td>
<td>0.14</td>
<td>0.03</td>
<td>0.92</td>
<td>0.06</td>
<td>1</td>
<td>0.0022</td>
<td>0.0006</td>
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<tr>
<td>Bone</td>
<td>0.9</td>
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<td>0.26</td>
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<tr>
<td>Brain</td>
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<td>0.79</td>
<td>0.11</td>
<td>0.08</td>
<td>0.39</td>
<td>0.48</td>
<td>0.13</td>
<td>7.10</td>
</tr>
<tr>
<td>Gut</td>
<td>0.9</td>
<td>0.096</td>
<td>0.78</td>
<td>0.07</td>
<td>0.15</td>
<td>0.69</td>
<td>0.26</td>
<td>0.05</td>
<td>7.00</td>
</tr>
<tr>
<td>Heart</td>
<td>0.86</td>
<td>0.14</td>
<td>0.7</td>
<td>0.11</td>
<td>0.19</td>
<td>0.48</td>
<td>0.43</td>
<td>0.09</td>
<td>7.10</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.78</td>
<td>0.22</td>
<td>0.73</td>
<td>0.06</td>
<td>0.21</td>
<td>0.26</td>
<td>0.61</td>
<td>0.13</td>
<td>7.22</td>
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<tr>
<td>Liver</td>
<td>0.82</td>
<td>0.18</td>
<td>0.68</td>
<td>0.08</td>
<td>0.21</td>
<td>0.29</td>
<td>0.59</td>
<td>0.11</td>
<td>7.23</td>
</tr>
<tr>
<td>Lung</td>
<td>0.5</td>
<td>0.5</td>
<td>0.74</td>
<td>0.04</td>
<td>0.11</td>
<td>0.51</td>
<td>0.38</td>
<td>0.11</td>
<td>6.60</td>
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<tr>
<td>Muscle</td>
<td>0.88</td>
<td>0.12</td>
<td>0.76</td>
<td>0.01</td>
<td>0.19</td>
<td>0.49</td>
<td>0.42</td>
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<td>0.08</td>
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<td>7.00</td>
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<tr>
<td>Spleen</td>
<td>0.79</td>
<td>0.21</td>
<td>0.75</td>
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<td>0.3</td>
<td>0.54</td>
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</tr>
<tr>
<td>Red blood cells</td>
<td>1–</td>
<td></td>
<td>0.63</td>
<td>0.01</td>
<td>0.33</td>
<td>0.3</td>
<td>0.59</td>
<td>0.1</td>
<td>7.20</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values taken from (Kawai et al., 1994). Original values given as fraction of total organ volume were rescaled to tissue volume by subtracting vascular volume.

<sup>b</sup> Values taken from (ICRP, 1975). Original values given as fraction of total tissue mass were rescaled to cellular volume as follows: Water fraction of total tissue reduced by interstitial volume and subsequently all values normalized by cellular fraction.

<sup>c</sup> Data taken from (Rodgers et al., 2005a).

<sup>d</sup> Values taken from ([Waddell and Bates, 1969], [Malan et al., 1985], [Wood and Schaefer, 1978], [Schanker and Less, 1977], [Harrison and Walker, 1979] and [Civelek et al., 1996]). Mean values were calculated when more than one value was found for the same tissue.

<sup>e</sup> Data taken from (Gomez et al., 2002).
Prediction of Ionization

- Neutral and ionized species of the same molecule will partition differently into environmental and biological media.
- Better models are needed for predicting pKa at different pH for chemicals.

![Diagram showing environmental and biological partitioning of chemical species.](image)

*Project lead Cory Strope (Hamner)*
Predicted PK Metrics

- Human hepatic concentration of various chemicals as a function of 28 daily doses (10 mg/kg/day)
- Can predict mean and peak concentration and time integrated area under the curve (AUC) for various tissues
Evaluating HTPBPK Predictions with In Vitro Data

- HTPBPK predictions for the AUC (time integrated plasma concentration or Area Under the Curve)
- in vivo measurements from the literature for various treatments (dose and route) of rat.
- Predictions are generally conservative – i.e., predicted AUC higher than measured
- Oral dose AUC ~6.4x higher than intravenous dose AUC

Wambaugh et al. (2015)
Evaluation Leads to Insight

Examining the impact of lumping – default is liver, kidney, rest of body
What if we separate rest of body into richly and slowly perfused?

Work by Robert Pearce
Evaluation Leads to Insight

Examining the impact of lumping – default is liver, kidney, rest of body
What if we separate rest of body into richly and slowly perfused?

Separate Slowly and Richly Perfused Compartments

Default “httk” Lumping

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Work by Robert Pearce
Evaluation Leads to Refined Models

Ongoing refinements of tissue-specific partition coefficient predictions: Handling high log P, better treatment of ionization (Pearce et al. manuscript)
Summary

- Toxicokinetics (TK) provides a bridge between hazard and exposure by predicting tissue concentrations due to exposure.
- We must keep in mind the purpose – simple models appear to allow meaningful prioritization of further research.
- A primary application of HTTK is “Reverse Dosimetry” or RTK:
  - Can infer daily doses that produce plasma concentrations equivalent to the bioactive concentrations.
- We can also use QSAR to build provisional PBTK models.

**But we must consider parsimony and domain of applicability:**

- Do not build beyond the evaluation data.
- Carefully determine whether, when, and why model errors are conservative.
- Collect PK data from *in vivo* studies to allow larger, systematic studies.

- R package “httk” freely available on CRAN allows statistical analyses.

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

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