Toxicokinetics in Risk Assessment: From Predictive Evaluations to Regulatory Testing

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Outline

• Product Development and Registration Timeline
  • Empirical and Predictive Toxicokinetics
• GastroPlus Validations
• High-Throughput applications of GastroPlus for IVIVE
**Product Development Timeline**

**Discovery**
- **Pre-Development**
- **Development**
- **Post Registration**
- **Re-Registration**

**Toxicokinetic activities**

**In silico**
- Toxicokinetic modeling

**In vitro**
- Comparative metabolism study (EU)

**ADME study (OECD 417)**
- Probe AME *in vivo* study (4 species)
- *In vivo* Toxicokinetics Endpoint
- Preliminary PBPK model (interspecies)

**High-end PBPK models (interspecies & multiple routes)**
- *In silico* High throughput PBPK models (IVIVE)
Product Development Timeline

Discovery

Pre-Development

Development

Post Registration

Re-Registration

Opportunity: Standardize modeling approaches

In silico Toxico-kinetic modeling

High-end PBPK models (interspecies & multiple routes)

Preliminary PBPK model (interspecies)

In silico High throughput PBPK models (IVIVE)
Modeling software criteria:

Support for multiple exposure routes and regimens
  - Oral, Inhalation, Dermal (critical for relevant Risk Assessments)
  - Acute, steady-state

Incorporates critical QSARs for:
  - Absorption rates and amounts
  - Metabolic clearance
  - Plasma protein binding
  - Tissue distribution

Based on Compartmental PK or PBPK designs

Provides model predictions of parent compound and metabolite(s)

Supports various species and lifestages

Minimal to no coding required
  - Best option for regulatory buy-in

Batch modeling feature

Selected: GastroPlus™ from Simulations Plus
Modeling software criteria:
  GastroPlus validated primarily with pharmaceutical compounds
delivered via the oral route
Needed to validate QSAR and PK / PBPK predictions for:
  Broad range of chemistries for non-pharmaceuticals
  Oral, Inhalation, Dermal exposure routes
    Inhalation modeling for non-volatile compounds only
    Multiple dermal formulation types
Multi-step validation plan
  Accuracy of physical-chemical property predictions
    pKa, LogP
  Accuracy of pharmacokinetic parameter predictions
    Metabolic clearance, plasma protein binding, Fa%, F%
  Accuracy of systemic exposure predictions
    Cmax, AUC
Accommodates multiple formulation types
Contains species-specific portal of entry physiologies
Experimental vs. Predicted pKa Values

from ADMET Predictor model of GastroPlus™ (ADMET) or Pipeline Pilot™ (PP)

The predicted pKa values from ADMET correlated well with the literature data and were better than those predicted by PP.
Experimental vs. Predicted LogP Values

The predicted LogP values from ADMET correlated well with the literature data and were comparable to those predicted by EpiSuite.
Accuracy of PK parameter predictions

<table>
<thead>
<tr>
<th>$C_{l_{int}}$</th>
<th>Fraction Unbound in Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fold difference from empirical data</td>
<td>Percent of the total compounds $^*$</td>
</tr>
<tr>
<td>1 to 3</td>
<td>38%</td>
</tr>
<tr>
<td>3 to 10</td>
<td>29%</td>
</tr>
<tr>
<td>10 to 100</td>
<td>29%</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>7%</td>
</tr>
</tbody>
</table>

* $n=463$ ** $n=441$

Empirical data for Clint and Fup via personal communication (J. Wambaugh, 2015)

Metabolic clearance and Fup predictions by GastroPlus are quite acceptable:
- 67% of predicted Clint values within 10x of empirical data
- 87% of predicted Fup values within 30% of empirical data
### Accuracy of Steady-State Systemic Exposure predictions

Comparison of GastroPlus Prediction Results with Published IVIVE Modeling Results (oral route)

*Data from Wetmore, et al. 2012 (Toxicol Sci 125(1): 157-174)*

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Reference PK or PBPK derived (Css µM) *</th>
<th>Restrictive hepatic clearance (Css µM) *</th>
<th>GastroPlus Predicted (Css µM)</th>
<th>GastroPlus Predicted with Empirical Clint* and Fup* (Css µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-D</td>
<td>9.05-90.05</td>
<td>43.27</td>
<td>64.56</td>
<td>57.95</td>
</tr>
<tr>
<td>Cacodylic acid</td>
<td>1.8</td>
<td>3.06</td>
<td>9.53</td>
<td>7.37</td>
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<tr>
<td>Carbaryl</td>
<td>0.03</td>
<td>0.07</td>
<td>1.13</td>
<td>0.47</td>
</tr>
<tr>
<td>Fenitrothion</td>
<td>0.03</td>
<td>17.92</td>
<td>0.84</td>
<td>15.7</td>
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<tr>
<td>Lindane</td>
<td>0.46</td>
<td>13.21</td>
<td>7.96</td>
<td>6.68</td>
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<tr>
<td>Parathion</td>
<td>0.17</td>
<td>24.64</td>
<td>1.66</td>
<td>17.28</td>
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<tr>
<td>Perfluorooctane sulfonic acid</td>
<td>19,990</td>
<td>153.23</td>
<td>143.68</td>
<td>155.42</td>
</tr>
<tr>
<td>Perfluorooctanoic acid</td>
<td>20,120</td>
<td>53.16</td>
<td>89.57</td>
<td>61.34</td>
</tr>
<tr>
<td>Picloram</td>
<td>0.27</td>
<td>57.63</td>
<td>39.27</td>
<td>67.96</td>
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<tr>
<td>Thiabendazole</td>
<td>0.45</td>
<td>13.76</td>
<td>11.76</td>
<td>15.8</td>
</tr>
<tr>
<td>Triclosan</td>
<td>2 to 10</td>
<td>1.56</td>
<td>7.67</td>
<td>1.36</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>&lt;0.13</td>
<td>0.35</td>
<td>2.60</td>
<td>2.49</td>
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</tbody>
</table>

- Steady state blood level predictions from GastroPlus consistent with those obtained with SimCYP and overall conservative vs. Reference data
- PredictedCss values generally improve with inclusion of measured Clint and Fup
Oral Acute Exposures

The predicted pharmacokinetic values from GastroPlus correlated well with the literature data:
- **Cmax**: 69% within 3-fold, and 88% within 10-fold of experimental data.
- **AUC**: 54% within 3-fold, and 85% within 10-fold of experimental data.
Inhalation Acute Exposures

The predicted pharmacokinetic values correlated acceptably with the literature data:

- **Cmax**: 50% within 3-fold, and 63% within 10-fold of experimental data
- **AUC**: 50% within 3-fold, and 63% within 10-fold of experimental data

- Generally over-predicted (conservative)
Dermal Acute Exposures

The predicted pharmacokinetic values correlated acceptably with the literature data
Cmax: 44% within 3-fold, and 89% within 10-fold of experimental data
- generally over-predicted (conservative)
Methods for High Throughput Exposure assessment Tool (HEAT)

- Determine external exposures for Dow products
  - Using formulation data and validated Occupational or Consumer exposure models
- Pre-define predictions of blood levels across a range of external exposures (0.001-1000 mg/kg)
  - Oral, Inhalation and Dermal routes
  - Select most conservative formulation types and exposure conditions for each route
Trends in Systemic Exposure Predictions with GastroPlus

Bioaccumulation after 28 days oral exposure

Saturation of oral absorption
Trends in Systemic Exposure Predictions with GastroPlus

Trends towards lower uptake of inhaled chemicals through pulmonary tissue
- trend enhanced for solid formulations vs. solutions
Selection of Optimal Exposure time for \textit{de novo} Inhalation modeling

**Ethylene Glycol Cmax vs. Exposure Time**

- **Y-axis:** Plasma Concentrations (ug/mL)
- **X-axis:** Exposure Time (1 mg/kg/hr inhaled) (h)
Selection of Optimal Exposure time for *de novo* Inhalation modeling

**Predicted Linearity of Absorption Estimates**

- **Single Dose**
  - Ethylene Glycol
  - Biohelly
  - Phenoxethanol

- **Repeat Dose**
  - Biphenyl
  - Ethylene Glycol
  - Phenoxethanol

**Cmax/Dose vs Time**

- **Single Dose**
  - Ethylene Glycol
  - Phenoxethanol
  - Biphenyl

- **Repeat Dose**
  - Biphenyl
  - Ethylene Glycol
  - Phenoxethanol

*Optimal Exposure time for Inhalation Exposures set to 0.25 hr*
Impact of metabolism on systemic bioavailability via inhalation

Time to steady state dependent on metabolic stability of compound:
- isomers with two CYP-metabolizable moieties more rapidly cleared than analogs with one moiety
Conclusions

- GastroPlus has been shown to provide adequate predictions of PhysChem properties, pharmacokinetic parameters and systemic blood levels, compared to literature values and/or other validated QSAR programs.

- Predicted systemic blood levels are being generated for a test data set (~ 60 compounds) by the oral, inhalation and dermal exposure routes for the HEAT exposure model.
  - Formulation types and exposure scenarios chosen to provide conservative blood level predictions.

- Future research work
  - Refine model predictions with empirical Clint and Fup values.
  - Note: GastroPlus provides estimates of CYP metabolism only.
  - Derive correlations for pulmonary clearance of unmetabolized volatile compounds.

- Proper understanding of the benefits and limitations of predictive modeling tools such as GastroPlus™ will allow for optimum implementation of animal alternatives in novel high throughput safety assessment programs.
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