chemPK™ V.2 - Human PK Prediction Directly from Chemical Structure

Background Information

- Predicts key human oral and intravenous pharmacokinetic parameters directly from structure.
- No in vitro ADME or physicochemical data requirements.
- Save money and time by allowing pharmacokinetics to be characterised virtually (no synthesis required).
- Provides early stage filter for directing chemistry and prioritising screening.
- Superior approach which uses PBPK model optimised from human clinical (in vivo) data.

chemPK™ Input Requirements
- Chemical structure, e.g., SMILES, mol or sdf.
- Dosing regimen.

chemPK™ Data Delivery
- Predicted pharmacokinetic parameters following oral and intravenous dosing regimens (for single and repeat doses).
- Predicted time concentrations for plasma (or blood) and all tissues/organs with graphical representation.
- Predicted time series hepatic metabolism, renal elimination and faecal elimination.

How does it work?

chemPK™ utilises a KNIME workflow-based approach which executes the processes illustrated in Figure 1.

Figure 1
chemPK™ workflow processes.

To find out more contact enquiries@cyprotex.com
KNIME can be downloaded easily and for free. Cyprotex can then provide the bespoke KNIME nodes (chemPK™) for the workflow including Generate PK inputs, Run PK simulation and Calculate PK parameters nodes.

The Generate PK input node includes calculations of the following parameters:

- 10 Tissue partition coefficients (Kp) trained on in vivo data
  - Adipose, brain, heart, gut wall, kidney, liver, lung, muscle and skin.
  - Tissue partition coefficient for the remaining tissues and organs that are not explicitly represented in the PBPK model.
- Rate of renal clearance trained using in vivo plasma and urine profiles following intravenous (bolus and infusion), oral and subcutaneous dosing.
- Rate of metabolism in the liver trained using intravenous in vivo profiles (bolus and infusion).
- Rate of absorption from the gastrointestinal tract trained using oral in vivo profiles (rapid release).

The Run PK simulation node:

- Executes the PBPK model with intravenous and oral dosing including a repeat dose option.
- Requires the parameters generated by the Generate PK inputs node.
- Output is in KNIME table (data frame) format that can be processed in any way required, e.g.:
  - Converted to XLS
  - Converted to CSV
  - Plotted using Python, R, etc.
  - Written to a database using a connector

The Calculate PK parameters node reports the following predicted PK parameters:

- CL, t1/2, MRT, V, VSS, AUC, and fraction absorbed to the last timepoint.
- Cmax, tmax and AUClast for all tissues/organs.

Table 1
Intravenous PK parameters for an independent test set of 62 compounds.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>MFEa</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total clearance (CL)</td>
<td>2.54</td>
<td>0.51</td>
</tr>
<tr>
<td>Half-life (t1/2)</td>
<td>2.16</td>
<td>0.52</td>
</tr>
<tr>
<td>Mean time a molecule resides in the body (MRT)</td>
<td>2.26</td>
<td>0.47</td>
</tr>
<tr>
<td>Volume of distribution (V)</td>
<td>2.08</td>
<td>0.71</td>
</tr>
<tr>
<td>Volume of distribution at steady-state conditions (VSS)</td>
<td>2.03</td>
<td>0.69</td>
</tr>
</tbody>
</table>

* Mean fold error

Table 2
Oral PK parameters for an independent test set of 35 compounds.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>MFEa</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest drug concentration in plasma (Cmax)</td>
<td>3.30</td>
<td>0.72</td>
</tr>
<tr>
<td>Time at which highest concentration occurs (tmax)</td>
<td>1.73</td>
<td>0.17</td>
</tr>
<tr>
<td>Area under the plasma drug concentration-time curve (AUClast)</td>
<td>3.46</td>
<td>0.71</td>
</tr>
</tbody>
</table>

* MW < 450 g/mol

We are looking for partners with whom we can further develop the chemPK™ model. If you would like to be involved then please get in touch.

Contact enquiries@cyprotex.com for a demonstration.