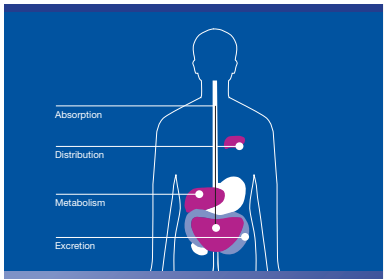
cyprotex AN EVOTEC COMPANY

In Silico Prediction

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

Background Information



'A virtual screening tool for predicting human pharmacokinetics from chemical structure alone.'

- 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.

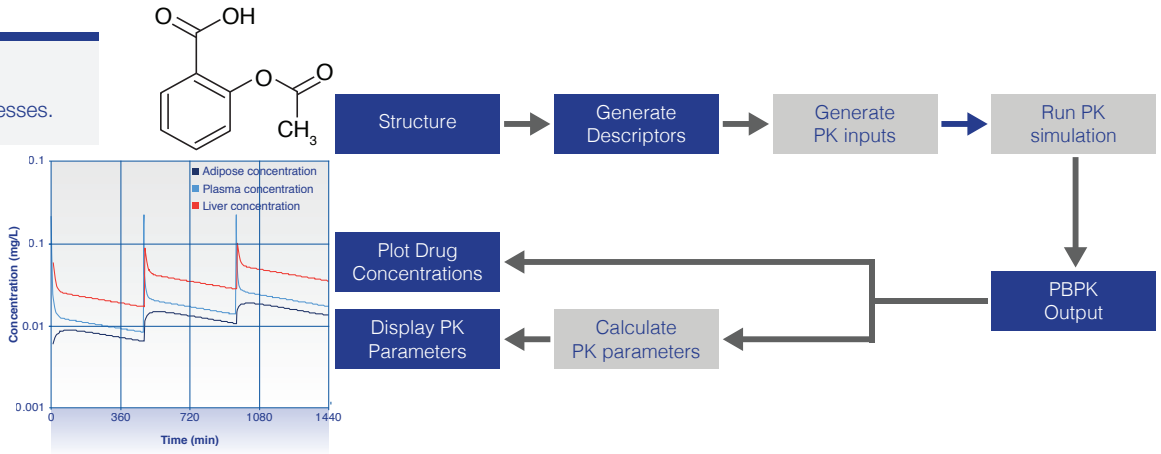
chemPK™ Data Delivery

- 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.



'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).

Table 1

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

PK parameter	MFE[a]	Rank
Total clearance (CL)	2.54	0.51
Half-life ($t_{1/2}$)	2.16	0.52
Mean time a molecule resides in the body (MRT)	2.26	0.47
Volume of distribution (V)	2.08	0.71
Volume of distribution at steady-state conditions (V_{SS})	2.03	0.69

[a] Mean fold error

Table 2

Oral PK parameters for an independent test set of 35 compounds[a].

PK parameter	MFE[b]	Rank
Highest drug concentration in plasma (C_{max})	3.30	0.72
Time at which highest concentration occurs (t_{max})	1.73	0.17
Area under the plasma drug concentration-time curve (AUC_{last})	3.46	0.71

[a] MW < 450 g/mol
[b] Mean fold error

The Run PK simulation node:

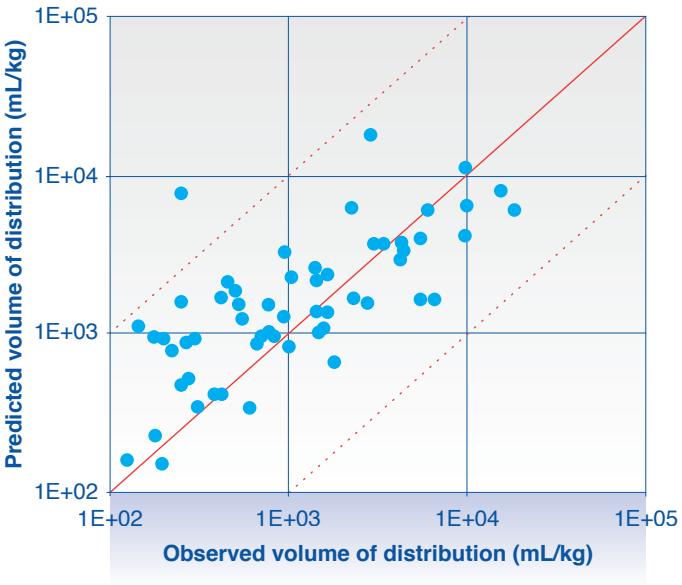
- Executes the PBPK model with intravenous and oral dosing including a repeat dose option.
- Requires the parameters generated by the Generate PK inputs node.
- Output is in KNIME table (data frame) format that can be processed in any way required, e.g.:
  - Converted to XLS
  - Converted to CSV
  -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

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

- CL, $t_{1/2}$, MRT, V, V_{SS}, AUC_{∞} and fraction absorbed to the last timepoint.
- C_{max}, t_{max} and AUC_{last} for all tissues/organs.

Figure 2

Plot of the predicted volume of distribution versus the observed volume of distribution for a test set of 62 compounds.



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.