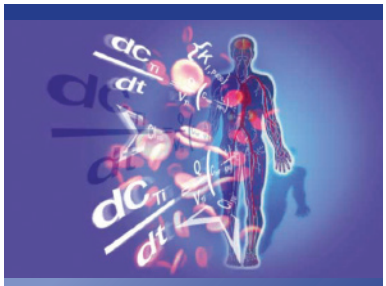
cyprotex AN EVOTEC COMPANY

In **Silico**

Cloe HIA

Human intestinal absorption prediction from Caco-2 permeability and simple phys-chem data



A tool for integrating *in vitro* ADME and phys-chem data to predict dose-dependent absorption

- Quantitatively predict human intestinal absorption from Caco-2 permeability and simple physicochemical data.
- Understand dose-dependent absorption and ascertain whether solubility or permeability is limiting poor absorption.
- Identify the main site of absorption within the gastrointestinal (GI) tract.
- Solve problems such as poor absorption in the GI tract.

Additional Features

- Simple and easy to use.
- Interactive sensitivity analysis to investigate the impact of altering compound properties on the predicted human intestinal absorption.
- Identifies the optimal pH values at which to measure the solubility of ionizable compounds.
- Accessible through our online web portal, Cloe Gateway, www.cloegateway.com, via pay per use or license agreement.
- Send your data to Cyprotex, and let us run predictions on your behalf.
- Provision of full consultancy service for interpretation of any predictions generated.

Cloe HIA Data Requirements

A simple set of early ADME and physicochemical data is required to run a Cloe HIA simulation as detailed below. Either measured or predicted values can be used.

- Aqueous solubility at one or more pH (a discrete value or solubility range can be provided at each pH)
- Caco-2 apparent permeability coefficient (P_{app}) at a measured pH (apical to basolateral only)
- pK_a log value(s)
- Log P

Cloe HIA Data Delivery

Predictions are generated in a downloadable pdf report and Excel spreadsheet with interactive sensitivity analysis capability.

The following parameters are reported.

- Predicted total absorption at several user-specified dose levels.
- Identification of factors (solubility and/or permeability) limiting absorption at any poorly absorbed dose level(s).
- Predicted dependence of the solubility on pH, over the range of the GI tract contents (pH 2-7.5).
- Predicted absorption from the different segments of the GI tract at each dose level.
- Predicted time course data representing absorption over time.
- Predicted solubility over the pH range of the gastrointestinal tract, and the peak concentration of compound achieved in the different parts of the tract.

To find out more contact **enquiries@cyprotex.com**

Cloe HIA uses physiological modelling to integrate Caco-2 permeability and phys-chem data. It models transit of fluid (containing dissolved and undissolved compound), gastric, biliary, and pancreatic secretion and absorption in five segments of the GI tract.

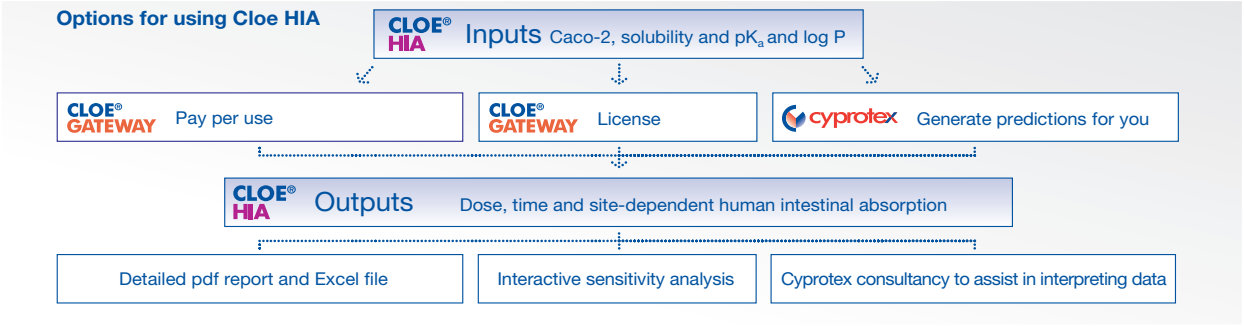
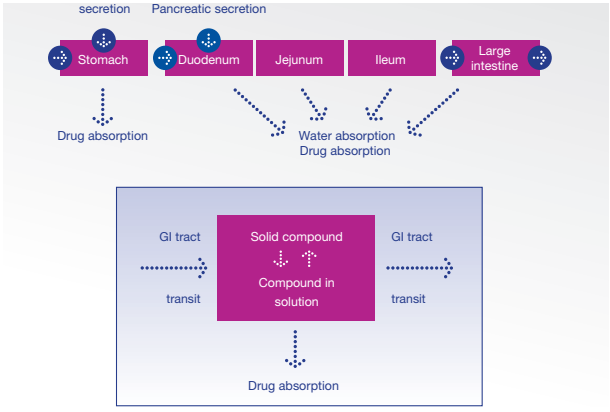


Figure 1

Schematic diagram of the intestinal absorption model.

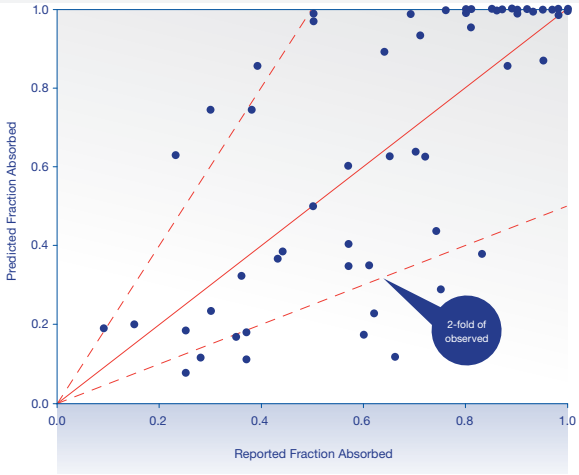


Nine compartments representing the five segments of the GI tract - stomach, duodenum, jejunum, ileum and colon - are represented. The fluid content, carrying dissolved and undissolved compound passes from one compartment to the next, simulating the action of peristaltic motion. Within each compartment the dynamic interconversion between dissolved and undissolved compound is modelled. Dissolved compound can be absorbed across the GI tract epithelium. The volume of each compartment - which represents the fluid content - is modelled dynamically, simulating the following processes:

- Transit of the fluid with characteristic rate constants through each compartment.
- Gastric secretion into the stomach, and biliary and pancreatic secretions into the duodenum.
- Absorption of fluid from duodenum, jejunum, ileum and large intestine.

Figure 2

Prediction of human intestinal absorption using Caco-2 permeability, turbidimetric solubility, pK_a and log P data combined with physiological modelling.



The solid line represents the line of unity and the dotted lines represent two fold of the reported fraction absorbed values. Data are for 122 combinations of dose and compound for 82 compounds. Reported values are from Thomas *et al* (2008). Cloe HIA provides a reliable quantitative prediction of human intestinal absorption from Caco-2 P_{app}, solubility, pK_a and log P data. Greater than 84% of the predictions are within two-fold of the reported *in vivo* value for an independent test set (Figure 2) and the Spearman rank correlation coefficient between predicted and reported faction absorbed in 0.76. It is a generic model which is applicable to a diverse set of chemistry. The model addresses dose-dependent absorption and the potential limitations of solubility on human intestinal absorption.

Three main options exist for gaining access to Cloe HIA

- **Pay per use** - You can pre-purchase credits online which can be used to access Cloe HIA through the Cloe Gateway web portal. This is a cost effective option for users who only require occasional use of Cloe HIA.
- **License** - This allows unlimited access to Cloe HIA via either a single user or site license. This is the most cost effective option if you use Cloe HIA regularly.
- **Consultancy** - Cyprotex can run the predictions on your behalf. You can either send us your data or we can generate data for you via our ADME and phys-chem experimental services. Assistance in interpreting the data is included in this service.

Contact **enquiries@cyprotex.com** for a demo

References

Thomas S *et al*., (2008) *J. Pharm Sci* 97; 4557-74