Predicting Human Oral Bioavailability

Results

- The extrapolation of Caco-2 data is a core step in the prediction of oral bioavailability. However, the extrapolation of Caco-2 data is a core step in the prediction of oral bioavailability.

- Data from high throughput screening assays describe potential toxicity to humans.

In this work, the Caco-2 permeability rate was measured for 310 ToxCast chemicals. Measured values and QSAR predicted results were used for the estimation of oral bioavailability. Caco-2 data may enable the use of Caco-2 data and literature to achieve improved predictions of oral bioavailability.

Potential improvements in toxicokinetics using more accurate estimates of oral bioavailability may be used to determine corresponding oral equivalent doses for oral dosing studies relative to Fbio,r = 1 for this limited set of chemicals.

Toxicokinetics in Rat with Fbio Estimates

- Do Fbio estimates based on measured values or literature estimates improve our prediction of toxicokinetics?

Using measured Fbio, a variety of toxicokinetic parameters were compared to measured data.

Using QSAR predicted Fbio, estimates based on measured data were compared to measured data.

Collectively, improved correlation of intravenous and oral dosing predictions with measured data was estimated Fbio using measured Fbio or QSAR predicted Fbio for oral dosing estimates relative to Fbio,r = 1 for this limited set of chemicals.

Summary

- PAB was measured for 310 ToxCast chemicals; 80 % have estimated Fbio,r = 1.

- Estimates for Fbio,h incorporating either Caco-2 measured PAB or QSAR predicted PAB seem reasonable for high throughput applications.

- Correlation of measured oral and i.v. dosing kinetics with predicted results was improved when dosing estimates incorporate predicted Fbio,h.

- Future work may evaluate models using collection of literature pharmacokinetic studies with oral dosing.