Prediction of Plasma, Tissue and *in vitro* Cell Exposure of CS4 Chemicals Using IVIVE-PBPK and Biokinetic Models

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INTRODUCTION

In vitro data describing the human metabolism, protein binding and blood:plasma partitioning were generated for the CS4 compounds by Cyprotex. This data was used to build compound files and PBPK models in the human to predict human systemic clearance.
The predicted human clearance was scaled to predict clearance in rats using an *in silico* allometric approach. The exposure of the chemicals *in vivo* in rat plasma and tissue were also simulated. The predicted plasma and tissue concentrations were compared against previously published pharmacokinetic data for flutolanil and deguelin.

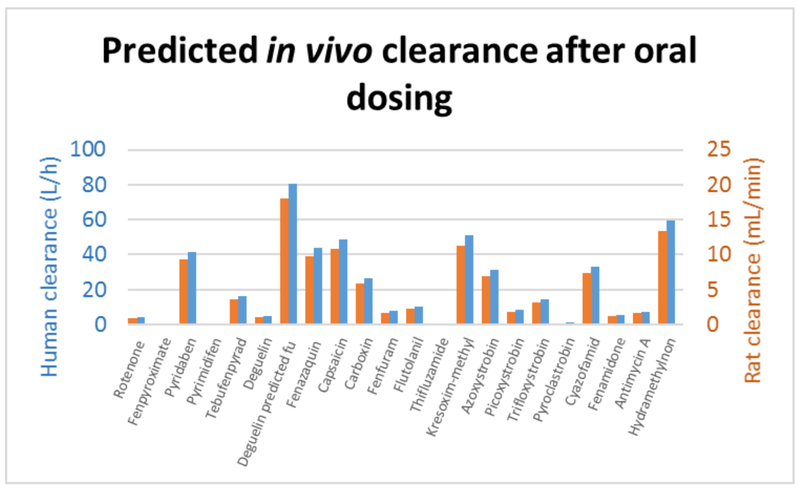
METHODS

Human hepatocyte *in vitro* intrinsic clearances, blood to plasma ratio and plasma protein binding data for CS4 compounds were provided by Cyprotex. The fraction unbound in hepatocyte incubations was determined from the compound lipophilicity (Kilford *et al*, 2008).
Physical/chemical and drug elimination data was used as an input for a full PBPK model (Simcyp v16) to predict human systemic clearance. Rat systemic clearance was then determined using allometric scaling:

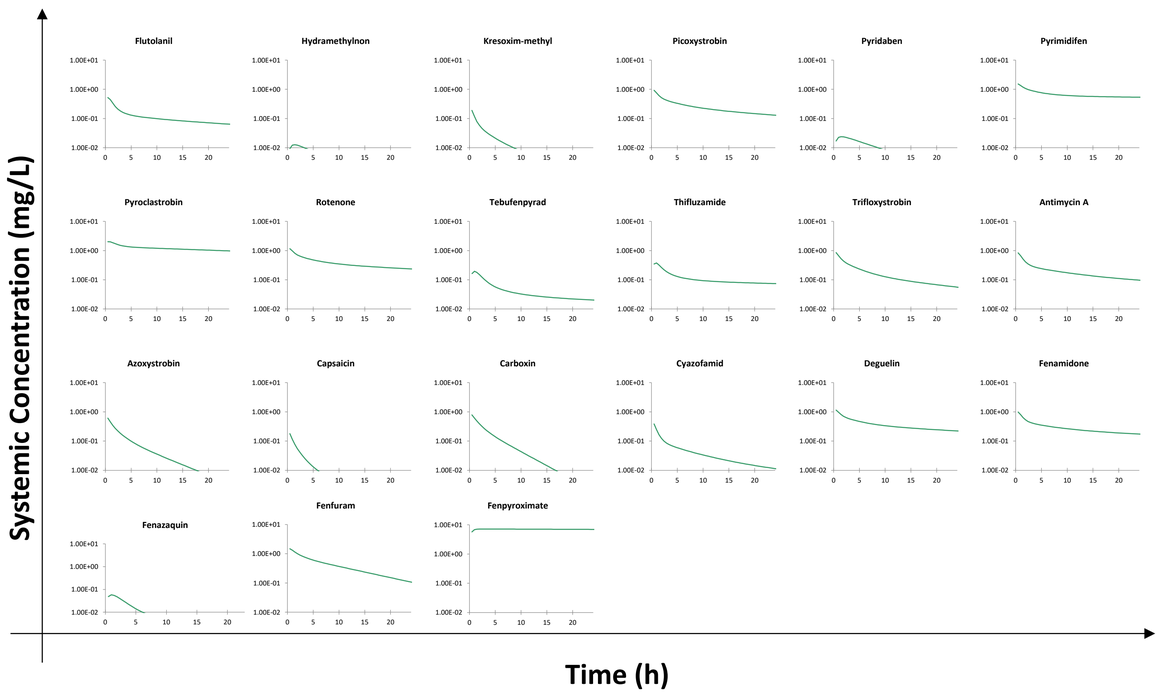
$$CL_{human} x \left(\frac{BW_{rat}}{BW_{human}}^{0.75} \right)$$

considering a mean bodyweight, BW, of 250 g for rat and 78.7 kg for human. *In vivo* clearance in rat was subsequently used in a full PBPK model (Simcyp v16) to predict rat plasma and tissue exposures.

RESULTS

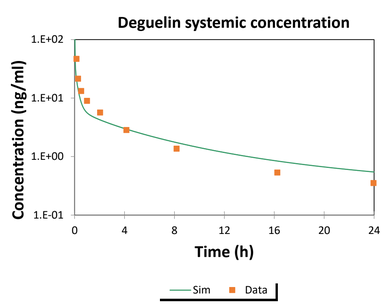


Simcyp prediction of human (blue, scale on left hand axis) and rat (orange, scale on right hand axis) systemic clearance for all CS4 compounds after oral dosing.

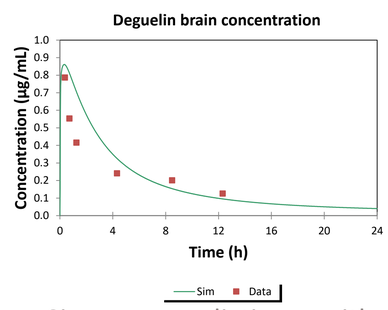


Simulation of systemic concentration vs. time for all CS4 compounds, using a 100mg oral dose in the human simulator

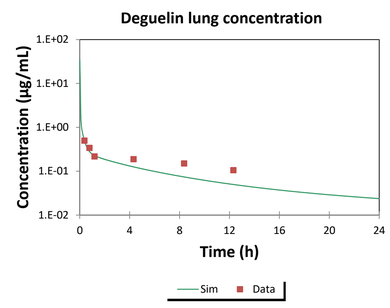
Deguelin and flutolanil rat exposure



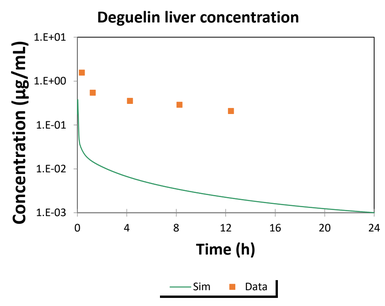
Simcyp prediction with predicted fu vs. data from Udeani 2001 for rats for IV administered Deguelin.



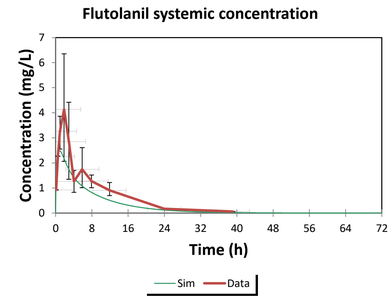
Simcyp prediction with predicted fu vs. data from Udeani 2001 for brain concentration in rats for IV administered Deguelin.



Simcyp prediction with predicted fu vs. data from Udeani 2001 for lung concentration in rats for IV administered Deguelin.

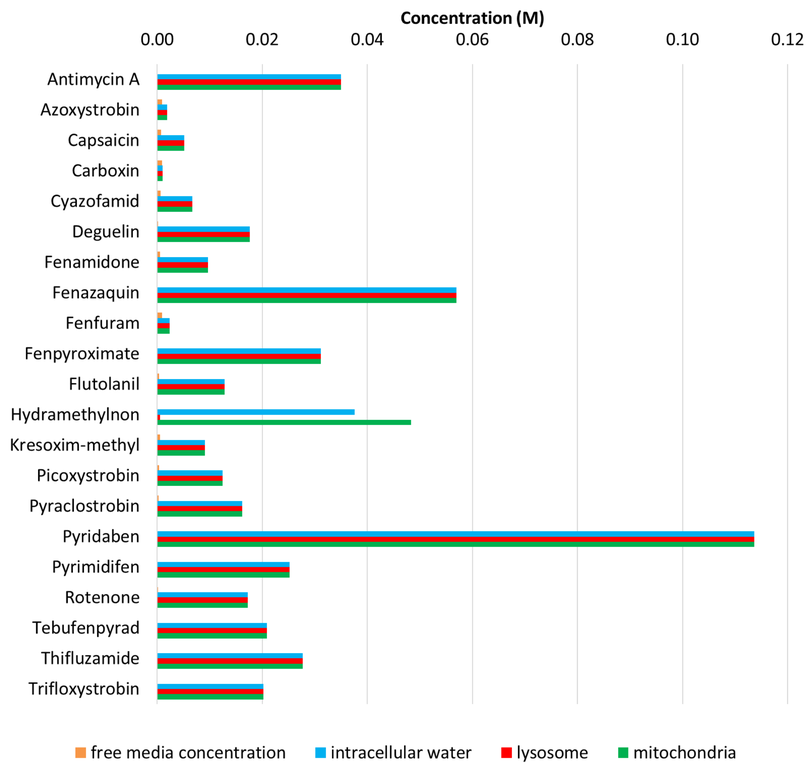


Simcyp prediction with predicted fu vs. data from Udeani 2001 for liver concentration in rats for IV administered Deguelin.



Simcyp prediction after fitting ka (green) vs. data from Murakami 1983 (orange) for an oral dose of 20 mg/kg of Flutolanil administered to rats.

Biokinetics



Predictions of *in vitro* distribution in U2OS cell reporter assays treated with 1mM of CS4 test compounds. Compounds distribute extensively into cells, primarily driven by their lipophilic nature. For most compounds the intracellular distribution is uniform however, hydramethynon shows preferential distribution into mitochondria. Predictions were generated for all *in vitro* cells assays employed in the case study.

CONCLUSIONS

We have made predictions for all CS4 compounds using the available data.

The results demonstrate that for the rat where data is available for comparison, the predicted and observed exposures for these chemicals showed an acceptable level of accuracy.

Good predictions were obtained for plasma concentrations of deguelin and flutolanil as well as some tissues. However, it is obvious that the concentration in the liver for deguelin is not well reproduced, suggesting that there are perhaps other processes that need to be considered.

REFERENCES

Kilford *et al* (2008), 'Hepatocellular Binding of Drugs: Correction for Unbound Fraction in Hepatocyte Incubations Using Microsomal Binding or Drug Lipophilicity Data'
Udeani *et al (2001),* 'Pharmacokinetics of deguelin, a cancer chemopreventive agent in rats'
Murakami *et al* (1983), ' Metabolism of flutolanil in rats'

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