The level 3 ab initio case study aims to determine the safe doses for a cosmetic ingredient in a consumer use scenario, by only using in vitro and in silico data.

PBPK models are physiologically relevant and are based on a compartmental approach which make predictions of the kinetics tissue concentration possible. These models are therefore a suitable tool to predict tissue concentrations within a realistic exposure scenario.

Consequently, PBPK models were developed for two SEURAT-1 reference compounds: valproic acid and methotrexate, to predict tissues concentrations.

Results – MTX single oral dose of 10 mg

The model PBPK models predicted quite well the in vivo data following an oral dose of 10mg [2]. The model was, as well, as predictive of the 7.5 mg and 15 mg doses.

Bioavailability (Frac) and unbound fractions in plasma (fup) are both significant parameters for venous and liver concentration predictions

Liver’s partition coefficient and liver’s clearance are significant parameters for liver’s concentration predictions

Results – VPA oral dose of 1000 mg once and twice daily

The PBPK model under-predicted the in vivo blood concentration data with an oral administration twice daily

Conclusions

In a context of an ab initio studies, although VPA model under-predicted the single dose administration, the PBPK models were able to predict the in vivo data (MTX single dose and VPA repeated dose) within a 90% confidence interval.

Supplementary in vitro data in order to reduce uncertainty of the most sensitive parameters (fup, PC Liver, CLH and Frac) may improve the predictions and more particularly the single dose of VPA.

References

[4] Perucca et al., 1978

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