UFZ HELMHOLTZ Centre for Environmental Research

Biotransformation and blood flow: Does the well-stirred liver model underestimate *in vivo* clearance?

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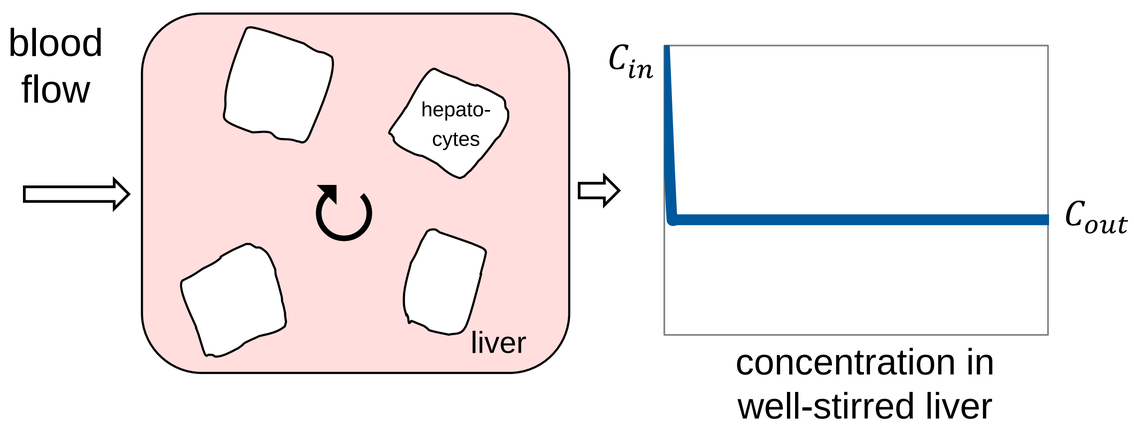
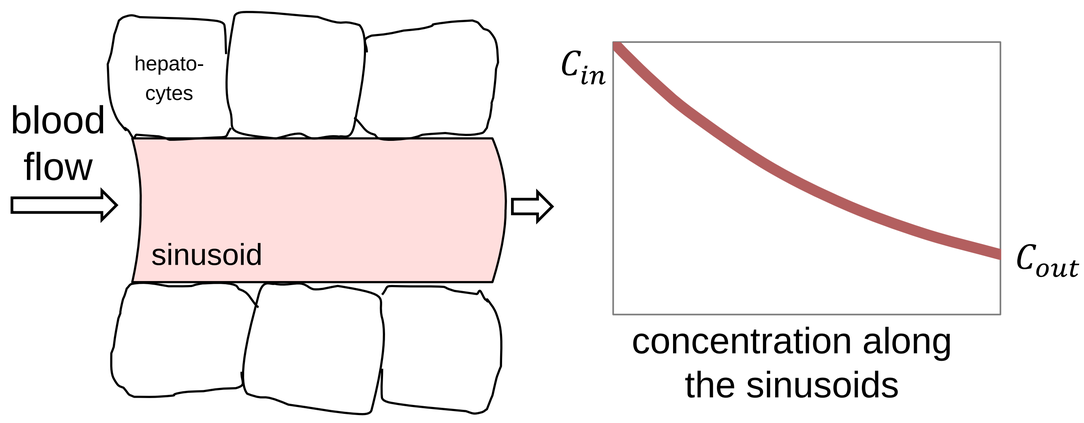
CONCEPTUAL OVERVIEW OF THE TWO COMMONLY USED TYPES OF LIVER MODELS

Well-stirred liver model („WS“):



- homogenous concentration within the liver
- mathematically simple, but rather far from reality

Parallel tube liver model („PT“):



- continuously decreasing concentration in the sinusoids
- mathematically more complex, but closer to reality

WHAT IS THE MAXIMUM DIFFERENCE BETWEEN THE MODELS AND WHEN DOES IT OCCUR?

- Prediction of the whole-body biotransformation rate constants k_B with both models from given intrinsic biotransformation activities:

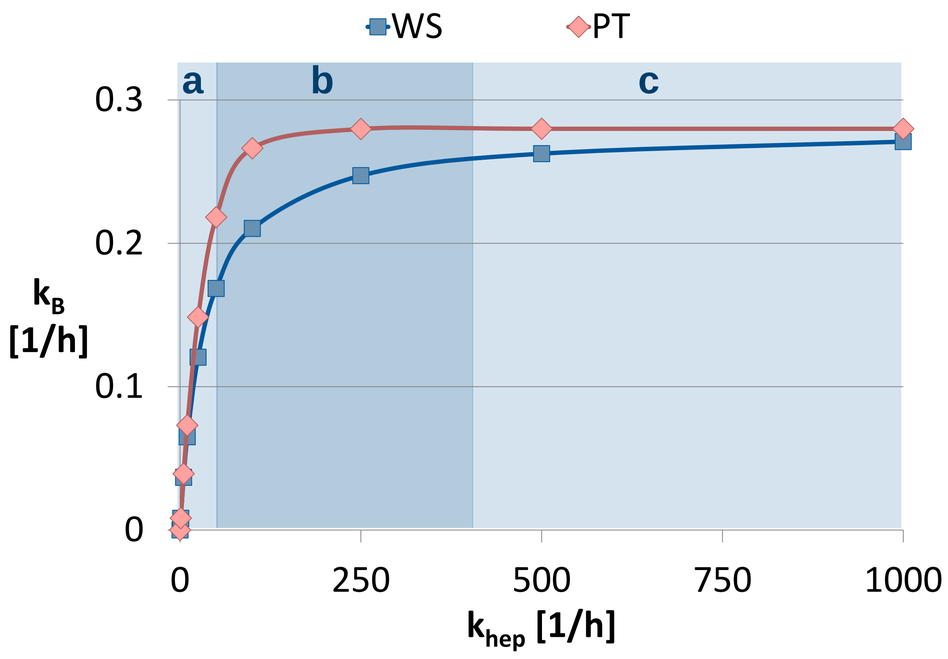
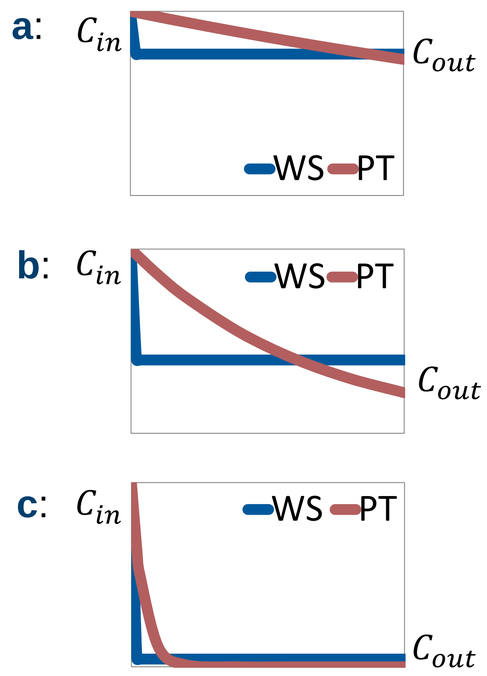


Fig. 1: Plot of the whole-body biotransformation rate constants k_B calculated with both models from hepatocyte biotransformation rate constants (k_{hep}) reflecting the intrinsic biotransformation kinetics in hepatocytes.

- Prediction of the outflowing blood concentrations C_{out} with both models from given inflowing concentration C_{in}:



concentration in liver or along sinusoids, respectively

a: slight reduction of C_{in}, i.e. low elimination efficiency (calculated as $E = \frac{C_{in} - C_{out}}{C_{in}}$)

b: notable reduction of C_{in}, i.e. intermediate to high elimination efficiency

c: almost complete depletion of C_{in}, i.e. high elimination efficiency

→ the maximum difference between both models occurs at intermediate to high elimination efficiencies (0.6<E<0.9, section b in fig. 1), i.e. for compounds that are unlikely to bioaccumulate because of strong biotransformation

→ even for those cases the difference between both liver models in terms of whole body rate constant k_B amounts to only 20%

CONCLUSION

The well-stirred liver model does not predict notably lower *in vivo* biotransformation than the parallel tube model. Accordingly, there seems to be no need for the use of the parallel tube liver model in regulatory context related to bioaccumulation assessment.

cefic ECETOC Acknowledgements: We acknowledge funding by Cefic (LRI-ECO 47).

Note: A third established liver model, the so called dispersion model, was not evaluated here. However, mechanistically the dispersion model can be seen as a hybrid of the WS and PT model with results lying between those of the WS and PT model.

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