Towards Improving In Vitro–In Vivo Toxicity Extrapolation Using Multi-Scale Modeling: A Proof of Concept on Paracetamol Hepatotoxicity

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Background: In vivo tests for toxicity assessment of drugs are increasingly replaced by in vitro approaches. However, the translation of in vitro results to in vivo conclusions is challenging and currently relies on PBPK/PD models. Yet, by considering the ADME processes within homogeneous compartments, classical PBPK/PD models do not properly represent some differences between the in vitro and in vivo situations that may be critical.

Objectives: We propose to take into account additional aspects, in particular (i) spatial inhomogeneities within organs [1], (ii) expression level differences of metabolic enzymes between cells in vivo and in vitro, and (iii) the possible influence of the time-dependent concentration experienced by the cells. We used paracetamol toxicity in mice as prototypical example.

Methods: Toxicity of paracetamol was determined experimentally by measuring the fraction of dead cells in vitro for several concentrations and in vivo for several doses. The in vitro–in vivo differences were explored using a multi-scale model that represents (i) each individual cell in a monolayer or liver lobule architecture, (ii) the intracellular metabolism of paracetamol in each cell, and (iii) paracetamol transport within the blood vessel network in vivo.

Results: To compare the in vitro and in vivo toxicity, we first used a classical PBPK model to convert the in vivo dose-toxicity relationship into a concentration-toxicity relationship. Results show cells in vivo to be more susceptible to paracetamol than in vitro. Preliminary simulations indicate that the difference might be due to a down-regulation of CYP enzymes in vitro or to hypoxia due to liver congestion in vivo.

Conclusions: For paracetamol, simulations results of models refined beyond classical PBPK/PD show a better extrapolation of toxicity from in vitro to in vivo. Further simulations are being performed to better characterize the improvement obtained using the multi-scale model.

References: