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Project title: Data on *in vitro* metabolism and mechanisms of action in combination with kinetic modeling: integrating in risk assessment.

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Summary

In this study an approach was developed for the integration of in silico and in vitro derived toxicity data in human risk assessment. The first part of the project was focusing on selecting a set of compounds for which there are reliable in vivo toxicity data available. For these compounds we then used a number of in silico systems (DEREK, OECD-Toolbox, TOPKAT) to predict toxicity endpoints and targets in vivo. Furthermore, in silico systems to predict the formation of metabolites (METEOR, OECD-Toolbox) were used and added to the prediction for toxicity endpoints and targets. The outcomes were compared with known in vivo toxicity endpoints and targets. A main conclusion from this part was that a generally good qualitative prediction was possible, with some drawbacks that can be related to the underrepresentation of certain endpoints in the in silico systems (e.g. neurotoxicity). The addition of biotransformation predictions further improved the qualitative predictions.
Part 2 of the project used the qualitative predictions made in part 1 in selecting appropriate in vitro systems that could be used to obtain toxic concentrations for the endpoints and targets. This was mainly done on the basis of date derived from studies found in the literature, and preference was given to data derived from those studies that used well-established in vitro systems.
In part 3, kinetic modelling was used to evaluate steady-state blood concentrations of the compounds in this study, related to no-effect levels in vivo. This was done based on in vivo and on in vitro data. The results were very comparable in the majority of the cases.
In the final part 4 of the project we used the in vitro-obtained toxicity data (from part 2) as points of departure to predict in vivo toxic doses, making use of reverse dosimetry based on the kinetic modelling done in part 3. The outcome was then compared with known in vivo human safe doses. The result showed that in general the in vitro-derived evaluations for human risk underestimated the in vivo toxicity. In over half the cases studied here, however, the ratio between the in vitro and the in vivo derived risk estimates differed no more than two orders of magnitude.

Important reasons for the underestimations are the apparent lack of relevant biotransformation processes in the in vitro systems as well as the lack of detailed data on in vitro biokinetic behaviour of the compounds under study. Overall we conclude that the QIVIVE approach proposed here to integrate in silico- and in vitro-derived toxicity data needs refinements, mainly by improving our knowledge of the relevant biotransformation processes and how to incorporate them in in vitro systems. In general, however, qualitative predictions of endpoints was good; the quantification very much depends on the quality of the in vitro data for their relevance to qualitatively predict in vivo toxicity more precisely.

Key words: in silico predictions, in vitro toxicity, toxic endpoints and targets, kinetic modelling, reverse dosimetry, quantitative in vitro- in vivo extrapolation.

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