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Integrating toxicokinetics improves predictive value of primary rat hepatocytes

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The pharmacological as well as the potential toxicological effects are evoked by the effective dose of a drug at its site of action. Toxicokinetic (TK) properties are usually not characterised in in vitro toxicity models, which limits the use of these models. Thus, implementation of TK data into established in vitro systems holds great potential for improving the value of these systems. Here, TK data was integrated with multiple biological endpoints to characterise the long-term, repeat dose hepatocyte model for hepatotoxicity. For this purpose compounds with well described toxicities and kinetics in animals and humans were applied, namely Amiodarone, Chlorpromazine, Cyclosporine A and Ibuprofen. The long-term cell cultures were treated daily with two concentrations per compound for a period of 14 days. On day one, three and 14 sample collection was performed for global gene expression, metabonomic and proteomic analyses. Samples of supernatant, cells and plastic binding were collected at five different time points on the first and last day of treatment for kinetic analyses. Due to the metabolic competence of primary rat hepatocytes the amount of parent compound decreased continuously in the course of 24h after treatment start, notably to various extents on day 0 compared to day 13. Overall, valuable mechanistic information by comparing transcriptome, proteome and metabonome results was supported by TK knowledge. In conclusion, the primary rat hepatocyte model was improved involving TK data, hence the onset of pharmacological effects and the extrapolation of a NOEC (no observed effect concentration) for toxicity was facilitated.