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An integrated approach to improved toxicity prediction for the safety assessment during preclinical drug development using Hep G2 cells

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Abstract:

Efficient and accurate safety assessment of compounds is extremely important in the preclinical development of drugs especially when hepatotoxicity is in question. Multiparameter and time resolved assays are expected to greatly improve the prediction of toxicity by assessing complex mechanisms of toxicity. An integrated approach is presented in which Hep G2 cells and primary rat hepatocytes are compared in frequently used cytotoxicity assays for parent compound toxicity. The interassay variability was determined. The cytotoxicity assays were also compared with a reliable alternative time resolved respirometric assay. The set of training compounds consisted of well known hepatotoxins; amiodarone, carbamazepine, clozapine, diclofenac, tacrine, troglitazone and verapamil. The sensitivity of both cell systems in each tested assay was determined. Results show that careful selection of assay parameters and inclusion of a kinetic time resolved assay improves prediction for non-metabolism mediated toxicity using Hep G2 cells as indicated by a sensitivity ratio of 1. The drugs with EC₅₀ values 100 µM or lower were considered toxic. The difference in the sensitivity of the two cell systems to carbamazepine which causes toxicity via reactive metabolites emphasizes the importance of human cell based in-vitro assays. Using the described system, primary rat hepatocytes do not offer advantage over the Hep G2 cells in parent compound toxicity evaluation. Moreover, respiration method is non invasive, highly sensitive and allows following the time course of toxicity. Respiration assay could serve as early indicator of changes that subsequently lead to toxicity.

Key-words: Toxicity screening, preclinical drug development, in-vitro assays, HepG2, respiration, toxicodynamics