In Vitro to In Vivo Extrapolation for Developmental Toxicity Potency of Valproic Acid Analogues

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The devTOX *quick*Predict assay (devTOX^{qP}) is a human induced pluripotent stem cell biomarker-based assay developed as an alternative to animal tests to screen for developmental toxicity potential. The developmental toxicity potential (dTP) concentration from the devTOX^{qP} assay indicates a chemical's developmental toxicity potency. Previous work showed that the potency ranking of dTP concentrations for valproic acid and its analogues was consistent with in vivo developmental toxicity. In this study, we applied in vitro to in vivo extrapolation (IVIVE) to address whether the devTOX^{qP} dTP concentrations could quantitatively predict the in vivo developmental toxicity lowest effect levels for these chemicals. We evaluated the impact of in vitro kinetics, pharmacokinetic (PK) parameters, and different PK models on IVIVE outcomes. To evaluate the effect of in vitro kinetics, an equilibrium distribution model was applied to devTOX^{qP} assay to translate nominal concentrations to free and cellular concentrations, which were used subsequently in IVIVE analyses. A one-compartment PK model including population variability, standard physiologically based pharmacokinetic (PBPK) models, and pregnancy-specific PBPK models were used for reverse dosimetry. The equivalent administered doses (EADs) that would result in maternal or fetal blood concentrations equivalent to in vitro activity concentrations were estimated by IVIVE. These EADs were compared to lowest effect levels in rat developmental toxicity studies and/or human therapeutic doses, and to EADs from a recent OECD case study publication derived using different sets of in vitro data. We also explored a chemical read-across approach incorporating structural similarity information in data interpretation. Our preliminary results showed close agreement between EADs and in vivo rat lowest effect levels, indicating that the devTOX^{qP} assay can quantitatively predict developmental toxicity potential of chemicals at relevant concentrations. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.