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

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The devTOX^{qP} assay, a human induced pluripotent stem cell-based assay, was developed as an alternative method to animal-based developmental toxicity tests to provide a human-relevant system to screen chemicals for teratogenic potential. Potency rankings of valproic acid (VPA) analogues tested in the devTOX^{qP} assay were shown to be consistent with those from in vivo toxicity studies. However, it remains to be seen whether the devTOX^{qP} assay can quantitatively predict relevant in vivo exposures that would result in developmental toxicity. Accordingly, we performed in vitro to in vivo extrapolation (IVIVE) using various pharmacokinetic models to estimate equivalent administered doses (EADs) that would result in maternal or fetal plasma concentrations equivalent to the in vitro developmental toxicity potential concentrations identified in the devTOX^{qP} assay. We compared EADs to the lowest effect levels (LELs) obtained from in vivo rat developmental toxicity studies and human clinical doses, where available. For five VPA analogues with developmental LEL data, at least one model produced an EAD within 1.5-fold of the rat LEL range. For three of five analogues, all the modeled EADs were within 4-fold of the rat LEL range. The close agreement between EADs and in vivo rat LELs suggests that IVIVE using devTOX^{qP} assay input data can quantitatively predict in vivo developmental toxicity potential at relevant concentrations. This study highlights the importance of pharmacokinetic considerations in assessing a chemical's developmental toxicity potency based on in vitro assays. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.