In Vitro to In Vivo Extrapolation for Developmental Toxicity Potency of Valproate Analogues

X. Chang[1], A. Lumen[2], J. Palmer[3], U.J. Lee[2], P. Ceger[1], B. Donley[3], S. Bell[1], D.G. Allen[1], W. Casey[4], N. Kleinstreuer[4]

[1]ILS, RTP, NC, United States; [2]DHHS/FDA/NCTR/OCS/NCTR/OR/DBT, Jefferson, AR, United States; [3]Stemina Biomarker Discovery, Inc., Cambridge, MA, United States; [4]NIH/NIEHS/DNTP/NICEATM, RTP, NC, United States

To support implementation of alternatives to animal testing for regulatory decision-making for developmental toxicity, several case studies have been developed under the European Union ToxRisk project. In one case study, the teratogenic potency of ten valproate (VPA) analogues was investigated using an in vitro human induced pluripotent stem cell (iPSC)-based assay, the devTOX quick Predict assay (devTOX^{qP}). Previous work showed that the potency ranking from devTOX^{qP} was consistent with observed developmental toxicity potency in vivo. In this study, we applied in vitro to in vivo extrapolation (IVIVE) to evaluate the impact of pharmacokinetics and different modeling approaches on predicting relevant external exposure from in vitro developmental toxicity potential concentrations derived from the iPSC devTOX^{qP} assay. We used several pharmacokinetic models, including an open-source one-compartment model and both open-source and commercial physiologically-based pharmacokinetic pregnancy models. The IVIVE analysis estimated equivalent administered doses (EADs) that would result in maternal blood concentrations equivalent to the developmental toxicity potential and cytotoxic in vitro concentrations. The estimated EADs were compared to published lowest effect levels (LELs) from in vivo developmental toxicity studies. Our preliminary results showed close agreement between EADs and in vivo rat LELs for two VPA analogues (within 3.5-fold), suggesting that the devTOX^{qP} assay and IVIVE approaches are suitable for quantitatively predicting in vivo developmental toxicity potential. 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.

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