In Vitro to In Vivo Extrapolation for Developmental Toxicity Potency of Selected Tox21 Chemicals

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To support implementation of new approach methodologies for regulatory decision-making on developmental toxicity, 186 chemicals were tested in a human induced pluripotent stem cell-based assay, devTOX *quick*Predict (devTOX^{qP}). In this study, we evaluated the performance of the devTOX^{qP} assay for predicting the lowest effect level (LEL) in rat developmental toxicity studies. We performed *in vitro* to *in vivo* extrapolation (IVIVE) using the developmental toxicity potential (dTP) concentration from the devTOX^{qP} assay to estimate equivalent administered doses (EADs) that would result in the maximum plasma concentrations equivalent to dTP concentrations. The resulting EADs were compared to *in vivo* LELs. Additionally, we evaluated the impact of *in vitro* kinetics, pharmacokinetic parameters, and different physiologically based pharmacokinetic (PBPK) models on EAD estimates. Our preliminary results showed that the EAD estimates using an open-source, generalized PBPK model are lower than the rat developmental toxicity LELs for approximately 70% of chemicals, suggesting that human cells are more sensitive and devTOXqP assay may provide a more conservative hazard estimate for use in risk assessment. The fold differences between EAD estimates and rat LELs vary among chemicals. For over half of chemicals tested, EAD estimates are within an order of magnitude of the lowest LELs. Adjusting for *in vitro* kinetics can improve prediction for rat LELs for some, but not all chemicals, indicating a need for further characterization of conditions when this adjustment should be applied. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.