In Vitro to In Vivo Extrapolation to Facilitate Animal-free Risk Assessment of Potential Developmental Toxicants

Xiaoqing Chang[1], Jessica Palmer[2], Elizabeth Donley[2], Emily Reinke[1], David Allen[1], and Nicole Kleinstreuer[3]

[1]Inotiv, Research Triangle Park, NC, USA; [2]Stemina Biomarker Discovery Inc., Cambridge, MA, USA; and [3]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, USA

In vitro systems can be used for toxicity screening in a cheaper and more rapid manner than animal tests. In vitro assays can also provide insight on safe exposure levels when combined with in vitro to in vivo extrapolation (IVIVE). IVIVE uses pharmacokinetic models to relate concentrations of substances that induce in vitro responses to in vivo exposure levels that could result in human or animal adverse effects. In this study, a group of 186 potential developmental toxicants were selected and tested in a human induced pluripotent stem cell-based assay, devTOX quickPredict (devTOXqP). IVIVE was performed to translate the developmental toxicity potential (dTP) concentration of each chemical tested in the devTOXqP assay to a corresponding equivalent administered dose (EAD). EADs were then compared to lowest effect levels (LELs) in rat developmental toxicity studies. For each chemical, the impact of in vitro kinetics, pharmacokinetic parameters, and different types of pharmacokinetic models on EAD estimates was evaluated. The pharmacokinetic model that most closely approximated the rat pharmacokinetic data was also identified. Our preliminary results showed that the EADs estimated from devTOXqP assay data are lower than the rat LELs for the majority of assessed chemicals, suggesting that the devTOXqP assay can provide conservative toxicity estimates for use in risk assessment. This presentation demonstrates an optimized approach for using in vitro data to support the implementation of new approach methodologies for animal-free risk assessment. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.