In Vitro to In Vivo Extrapolation for Developmental Neurotoxicity: A Comparison of Physiologically Based Pharmacokinetic Models

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Background and Purpose

An extensive battery of assays has been developed for assessing developmental neurotoxicity (DNT), with the aim of replacing traditional in vivo guideline studies for risk assessment. These in vitro assays hold many advantages over costly, lengthy, in vivo studies. However, at present, there is no standardized approach to translate in vitro bioactive concentrations into in vivo dosages. In prior work, we developed an in vitro to in vivo extrapolation (IVIVE) approach for DNT using the Simcyp™ physiologically based pharmacokinetic (PBPK) model. As access to Simcyp is somewhat limited, in this project we applied this approach using two other PBPK modeling platforms—GastroPlus® and the U.S. Environmental Protection Agency's (EPA's) open-source high-throughput toxicokinetics (httk) package—to evaluate the transferability of the approach and potential for greater adherence to FAIR (Findable, Accessible, Interoperable, Reusable) principles.

Methods

Compounds evaluated here were previously found to elicit bioactivity in DNT new approach methodologies (NAMs) conducted at the EPA, for which in vitro toxicokinetic data had also been generated. PBPK modeling for an oral exposure of 1 mg/kg/day was conducted on these compounds at four stages spanning critical periods of neurodevelopment in Simcyp™, GastroPlus®, and httk to derive plasma concentrations, as well as concentrations at the site of brain development (fetoplacental and fetal brain) concentrations, where available. Postnatal brain concentrations for httk were derived using our preliminary httk-brain model. IVIVE was performed to determine human equivalent administered dosages (EADs) corresponding to bioactive concentrations from the DNT assays. To evaluate model performance, EADs were compared against doses shown to elicit DNT in vivo. EADs were also compared against human exposure estimates, including breastmilk exposures as applicable, to derive metrics that could be employed for risk assessment.

Results

Maximal concentrations (C_{max}) and area under the curve (AUC) values were obtained for 92 compounds in the three PBPK modeling platforms. Plasma and fetoplacental compartment concentrations were derived for all three, along with fetal brain for both Simcyp™ and httk, but not GastroPlus®, which cannot predict individual fetal tissue concentrations. In the pregnancy models, plasma C_{max} values fell within a median of two-fold across all three models, fetal brain within two-fold between Simcyp™ and httk, and the fetoplacental compartment within two-fold between Simcyp™ and GastroPlus®. The three programs also performed similarly at postnatal ages, with median plasma and brain C_{max} values falling within two-fold of one another across the three platforms. Notably, median fetoplacental compartment C_{max} values exceeded those in

maternal plasma. This suggests that using modeled maternal plasma concentrations as a surrogate to predict adverse effective concentrations may not provide sufficient protection to the developing fetus. In vivo DNT points of departure (PODs) fell within the range of EADs for bioactive endpoints, showing the concordance of NAM-derived DNT-IVIVE predictions with in vivo data. Moreover, the minimum EADs fell below in vivo DNT PODs, suggesting that using in vitro metrics may be more conservative than using in vivo data for risk evaluation.

Conclusions

This predictive toxicology DNT-IVIVE approach incorporates the intricacies of brain development and allows for life-stage, chemical, and endpoint-specific estimations of in vivo exposures that could elicit bioactivity at the site of brain development. The concordance between our DNT-IVIVE predictions and in vivo-derived DNT PODs supports the predictive ability of this approach and suggests that this method might be useful in employing DNT NAMs for risk assessment. This DNT-IVIVE approach can be integrated with bioactivity and toxicokinetic data and allows for varying degrees of complexity based on chemical risk evaluation and availability of in vitro data. This DNT-IVIVE approach is readily transferable across modeling platforms, albeit with varying limitations regarding model accessibility and complexity, which must be considered for the end goal. Indeed, model transparency and accessibility are critical considerations to allow sufficient evaluation by risk assessors. A more thorough evaluation of this approach is limited by the lack of in vivo and human DNT data. Overall, our DNT-IVIVE results suggest that bioactivity data from in vitro DNT NAMs may be more sensitive than using PODs from traditional in vivo DNT guideline studies. It also suggests that employing this DNT-IVIVE approach to derive metrics at the site of brain development may be more conservative for risk assessment practices than using plasma concentrations or in vivo DNT guideline studies.
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