In Vitro to In Vivo Extrapolation for Estrogenic Activity of Environmental Chemicals

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In vitro high-throughput screening (HTS) assays provide an efficient way to identify potential estrogen-active chemicals. To best utilize in vitro HTS assay data in prioritization and regulatory decision making, in vitro to in vivo extrapolation (IVIVE) is necessary. In this study, we evaluated the impact of critical pharmacokinetic parameters, dosimetry, and modeling approaches on IVIVE of estrogenic activity. In vitro lowest effective concentrations (LECs) for ten chemicals positive for estrogen receptor (ER) agonist activity were obtained from each of 16 ToxCast and/or Tox21 HTS assays mapping to various key events along the ER pathway. One-compartment and multi-compartment physiologically based pharmacokinetic models were used to estimate daily equivalent administered dose (EAD) that would result in blood concentrations equivalent to the in vitro LECs. The estimated lowest or median EADs were compared to the lowest or median lowest effect level (LEL) from in vivo uterotrophic assays for each chemical. The influence of fraction of unbound chemical (Fub) and hepatic clearance on EAD estimates was evaluated by systematically varying these parameters across a range of observed values. In addition, we applied a Fub adjustment method to better estimate the free fraction of a chemical available for tissue/cell uptake. We observed close agreement between EADs and *in vivo* LELs for the majority of chemicals tested, particularly after Fub adjustment. This study demonstrates an optimized approach for using in vitro data to quantitatively predict in vivo effects. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.*

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