Development of Reverse Toxicokinetic Models to Correlate *In Vitro* and *In Vivo* Estrogen Receptor Activity

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High-throughput screening (HTS) assays provide an efficient way to identify chemicals with the potential to interfere with estrogen receptor (ER) pathways. However, nominal *in vitro* assay concentrations may not accurately reflect potential *in vivo* effects of these chemicals due to differences in bioavailability and clearance between the two systems. Therefore, we developed reverse toxicokinetic (TK) models to more accurately correlate *in vitro* concentrations with potential *in vivo* effects for two ER reference chemicals, 17β-estradiol (E2) and bisphenol A (BPA). Our TK models estimate the daily oral equivalent doses (OEDs) in laboratory animals and humans that would result in a steady-state *in vivo* blood concentration equivalent to the *in vitro* POD (point of departure) values from an ER-targeted HTS assay. We compared the estimated OEDs to human exposures and the *in vivo* dose range reported to elicit uterotrophic effects in laboratory animals. For both chemicals, we used published experimental data for hepatic clearance and unbound plasma protein fraction (Fub) to populate our models. We performed sensitivity analyses to evaluate the impact of both hepatic clearance and Fub on OED estimations. This modeling approach highlights the importance of TK considerations in ranking ER active chemicals based on *in vitro* HTS ER assays.

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