Application of Reverse Dosimetry to Compare *In Vitro* and *In Vivo* Estrogen Receptor Activity

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High-throughput screening (HTS) assays provide an efficient way to identify endocrine-active chemicals. However, nominal *in vitro* assay concentrations of a chemical may not accurately reflect the blood or tissue levels that cause *in vivo* effects, mostly due to differences in bioavailability and clearance between the two systems. In this study, we developed and applied physiological based pharmacokinetic (PBPK) models to quantitatively correlate *in vitro* and *in vivo* dosimetry for a list of estrogen receptor (ER) reference chemicals. All the chemicals were tested in a HTS estrogen receptor transactivation assay, BG1Luc, from which we derived the point-of-departure (POD) values for each chemical. Using PBPK models built using GastroPlus software, we estimated the daily oral equivalent doses (OEDs) that would result in a Cmax value equivalent to the POD values. Critical model parameters (e.g. metabolic clearance, fraction of plasma protein binding) were derived from published experimental data or predicted from quantitative structure–activity relationship models. Where available, the daily OEDs were compared to the lowest effective doses (LEDs) in rat uterotrophic assays, rat multigenerational studies, or human exposure values. Our preliminary results showed that OED estimated using BG1Luc HTS assay data for bisphenol A, a highly studied and environmentally relevant ER reference chemical, was far lower than the oral LED for this chemical in rat uterotrophic assays, suggesting that the BG1Luc HTS assay may provide a more conservative hazard estimate for use in risk assessment. Our modeling approach highlights the importance of pharmacokinetic considerations in assessing and ranking endocrine-active chemicals based on *in vitro* HTS assays. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN27320140003C.*