Abstract 129 — Poster Presentation: Session II-13 "Endocrine Disruption"

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

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Abstract

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 doses that cause *in vivo* effects, mostly 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 effective *in vivo* doses for potential endocrine-active chemicals. Our TK models estimate the daily oral equivalent doses (OEDs) in laboratory animals and humans that would result in steady-state blood concentrations equivalent to the point of departure (POD) values identified from the Tox21 HTS *in vitro* estrogen receptor transactivation assay, BG1Luc. For most of the chemicals tested, OEDs estimated from POD values are lower than the lowest effective doses for rodent uterotrophic assays, suggesting that BG1Luc HTS provides a more conservative hazard estimate for use in risk assessment. In addition, we performed sensitivity analyses to evaluate the impact of different pharmacokinetic parameters on OED estimation. This modeling approach highlights the importance of PK considerations in 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.