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

X Chang[1], N Kleinstreuer[1], P Ceger[1], J Hamm[1], B Jones[1], L Rinckel[1], W Casey[2]

[1]ILS, RTP, NC, USA; [2]NICEATM/DNTP/NIEHS/NIH/HHS, RTP, NC, USA

Through the U.S. Tox21 high-throughput screening (HTS) program, efforts are underway to use quantitative high-throughput *in vitro* assays to assess chemical effects across multiple cellular pathways, including the estrogen receptor (ER) pathway. HTS assays provide an efficient way of identifying potential biological targets for chemicals. However, the nominal *in vitro* assay concentrations may not accurately reflect the potential *in vivo* effects of these chemicals due to the differences in bioavailability and clearance. A set of pharmacokinetic models was developed to correlate *in vitro* concentrations with potential *in vivo* effects for Tox21 chemicals with potential to interact with the ER. These models estimate the daily oral doses in laboratory animals and humans for Tox21 ER active chemicals that would result in a steady-state *in vivo* blood concentration equivalent to the *in vitro* AC_{50} (concentration at 50% maximum activity) values identified using HTS assays that specifically target the ER pathway. These models were built using published experimental data and quantitative structure–activity relationship predictions for hepatic metabolic clearance and unbound plasma protein fraction for tested chemicals. The models were also adapted to incorporate infant physiology to include this most vulnerable human population. Using daily oral doses estimated from the model, Tox21 ER active chemicals were ranked, with chemicals having the lowest effective dose in these models being considered the most likely to interact with the ER *in vivo*, either as agonists or antagonists. The estimated oral dose for a subset of chemicals was also compared to the in vivo dose range reported to elicit ER-related effects.

The Intramural Research Program of the National Institute of Environmental Health Sciences (NIEHS) supported this poster. Technical support was provided by ILS under NIEHS contracts N01-ES-35504 and HHSN27320140003C.