Quantitative Model of Systemic Toxicity Using ToxCast and ToxRefDB

Lisa Truong[1], Gladys Ouedraogo[2], Sophie Loisel-Joubert[2], and Matt Martin[1]

[1] US EPA- ORD – NCCT , RTP, NC 27711

[2] L'Oréal, Paris, France

EPA's ToxCast program profiles the bioactivity of chemicals in a diverse set of ~700 high throughput screening (HTS) assays. In collaboration with L'Oreal, a quantitative model of systemic toxicity was developed using no effect levels (NEL) from ToxRefDB for 633 chemicals with HTS data, chemical fingerprints, and a subset with reverse toxicokinetic (RtK) data. Floor and ceiling performance baselines (95% Confidence Intervals) were estimated to be 5 and 3 orders of magnitude uncertainty (OMU), respectively based on historical NEL distributions and reproducibility across study type and species. An initial read-across model was developed using chemical fingerprints to identify structurally similar neighbor NEL values resulting in 4.6 OMU, a $1/5^{th}$ reduction in model uncertainty based on our performance baselines. HTS data was then incorporated into the model using 74 groups of assays based on biology (ie: response data, gene families), technology annotation (assay mechanisms, signal directions), and assay confounders (oxidative stress, cytotoxicity). For each assay grouping, a mean activity value was computed and adjusted for confounders. Incorporating HTS data with read-across resulted in a 4.2 OMU, a total reduction in model uncertainty of $2/5^{th}$. RtK steady-state concentrations were then incorporated to adjust *in vitro* concentration (uM) to *in vivo* dose (mg/kg/day). Although RtK values were only available for a subset of the total chemical set (211), including RtK further lowered the overall model uncertainty to 3.7 OMU, roughly $3/5^{th}$ of the total model uncertainty we expect to be able to reduce. Herein, we have identified a model that incorporates HTS (dynamics), read-across (chemistry) and RtK (kinetics) to predict systemic NEL harnessing and incorporating the power of both new and existing data. *This abstract does not necessarily represent EPA policy.*

.