Sipes NS[1], Wambaugh JF[2], Pearce R[2], Kapraun D[2], Wetmore BA[3], DeVito MJ[1], Auerbach SS[1], Ferguson SS[1].[1]NTP/NIEHS, RTP, NC, [2]NCCT/USEPA, RTP, NC, [3]NERL/USEPA, RTP, NC, United States. Estimating Likelihood of Fetal *In Vivo* Interactions Using In Vitro HTS Data

Tox21/ToxCast efforts provide *in vitro* concentration-response data for thousands of compounds. Predicting whether chemical-biological interactions observed *in vitro* will occur *in vivo* is challenging. We hypothesize that using a modified model from the FDA guidance for drug interaction studies, C_{max}/AC_{50} (*i.e.*, maximal *in vivo* blood concentration over the half-maximal in *in vitro* activity concentration), will give a useful approximation for concentrations where *in vivo* interactions are likely. Further, for doses where maternal blood concentrations are likely to elicit an interaction ($C_{max}/AC_{50}>0.1$), where do the compounds accumulate in fetal tissues? In order to estimate these doses based on Tox21 data, *in silico* parameters of chemical fraction unbound in plasma and intrinsic hepatic clearance were estimated from ADMET predictor (Simulations-Plus Inc.) and used in the HTTK R-package to obtain C_{max} values from a physiologically-based toxicokinetics model. *In silico* estimated C_{max} values predicted *in vivo* human C_{max} with median absolute error of 0.81 for 93 chemicals, giving confidence in the R-package and *in silico* estimates. A case example evaluating C_{max}/AC_{50} values for peroxisome proliferator-activated receptor gamma (PPARγ) and glucocorticoid receptor revealed known compounds (glitazones and corticosteroids, respectively) highest on the list at pharmacological doses. Doses required to elicit likely interactions across all Tox21/ToxCast assays were compared to estimated daily exposures (Wambaugh *et. al*., 2014). 199 compounds were estimated to have likely interactions across 1-32 assays for the most conservative 95^{th} % population at doses lower than estimated daily environmental exposures. The major chemical use-categories included pharmaceuticals, chemical intermediates and dyes. Maximum fetal tissue accumulation (2^{nd} trimester-birth) ranged from the most to least accumulated tissue: rest of body, gut, kidney, lung, brain, and thyroid. 3,3',5,5'-Tetrabromobisphenol A and Triphenyltin acetate were among the top affecters across tissues (excluding thyroid) at concentrations disrupting nuclear receptors (PPARγ and retinoid X receptor, respectively). This approach can prioritize compounds and biological pathways quickly when no experimental data exists. Out of domain compounds, passive transport, and later developmental stage are present and need to be evaluated. This approach has shown promise toward estimating *in vivo* interaction concentrations for HTS data. *This abstract does not reflect official NTP or EPA views.*