Integration of High-Throughput Screening Data with Dosimetry and Human Exposure in the Toxicity Assessment of Environmental Chemicals

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High-throughput *in vitro* screening and computational tools provide government an efficient way to identify those chemicals that warrant further testing while conserving limited testing resources. Incorporation of kinetic and exposure information should provide a more meaningful interpretation of *in vitro* findings. In this study, hepatic metabolic clearance and plasma protein binding were experimentally measured for 240 ToxCast Phase I chemicals. These data were used to parameterize a population-based *in vitro-to-in-vivo* extrapolation model for estimating the human oral equivalent dose necessary to produce a steady-state *in vivo* concentration equivalent to AC_{50}/LEC values from ToxCast *in vitro* data. These values were compared against chronic aggregate human oral exposure estimates to assess whether *in vitro* bioactivity occurred at the anticipated maximum level of human exposure. Of the 170 chemicals for which exposure estimates were available, 12 chemicals – 2-phenylphenol, chlorpropham, cyromazine, dicamba, difenoconazole, fludioxonil, piperonyl butoxide, pyrithiobac-sodium, quinclorac, tebuthiuron, triclopyr, and triclosan – had estimated human oral exposures greater than the predicted oral equivalent doses. If these chemicals were ranked based on AC_{50}/LEC values alone, they would not necessarily have been high priorities for further evaluation. *In vitro* assay endpoints with oral equivalent doses lower than the estimated human oral exposures included changes in cell growth kinetics, cytokine expression, and several cytochrome P450 isozymes. Incorporation of dosimetry and exposure information in the interpretation of *in vitro* screening data provides valuable information for use in determining chemical testing priorities. *This abstract does not necessarily reflect EPA policy.*

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