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Biological profiling and dose-response modeling tools, characterizing uncertainty

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Through its ToxCast project, the U.S. EPA has developed a battery of *in vitro* high throughput screening (HTS) assays designed to assess the potential toxicity of environmental chemicals. At present, over 1800 chemicals have been tested in up to 600 assays, yielding a large number of concentration-response data sets. Standard processing of these data sets involves finding a best fitting mathematical model and set of model parameters that specify this model. The model parameters include quantities such as the half-maximal activity concentration (or "AC_{50}") that have biological significance and can be used to inform the efficacy or potency of a given chemical with respect to a given assay. All of this data is processed and stored in an online-accessible database and website: http://actor.epa.gov/dashboard2.

Results from these *in vitro* assays are used in a multitude of ways. New pathways and targets can be identified and incorporated into new or existing adverse outcome pathways (AOPs). Pharmacokinetic models such as those implemented EPA's HTTK R package can be used to translate an *in vitro* concentration into an *in vivo* dose; i.e., one can predict the oral equivalent dose that might be expected to activate a specific biological pathway. Such predicted values can then be compared with estimated actual human exposures prioritize chemicals for further testing.

Any quantitative examination should be accompanied by estimation of uncertainty. We are developing methods to estimate the confidence in model parameters obtained from HTS assays. We explore various mathematical models (constant, Hill, and gain-loss), methods to fit experimental concentration-response data to the models (least squares and maximum likelihood estimation), and multiple techniques to assess uncertainty in parameter estimates (asymptotic theory, bootstrapping, and Bayesian methods). We consider possible statistical error models that connect the mathematical models to the observed data and consider the applicability of each method based on possible error distributions in the types of data obtained with a large HTS library such as the one being produced by the ToxCast project. *The views expressed are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*