

EPA's ToxCast Program for Predicting Toxicity and Prioritizing Chemicals for Further Screening and Testing

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Testing of environmental and industrial chemicals for toxicity potential is a daunting task because of the wide range of possible toxicity mechanisms. Although animal testing is one means of achieving broad toxicity coverage, evaluation of large numbers of chemicals is challenging due to high monetary and ethical costs. As an alternative, we have evaluated the utility of bioactivity profiling using a broad suite of biochemical and cellular assays to predict toxicity potential. A set of 309 reference chemicals manifesting diverse animal toxicity endpoints was tested in a wide variety of biochemical, cellular and model organism assays. Over 200 biochemical assays drawn from major protein super-families including G-Protein coupled receptors, kinases, phosphatases, proteases, ion channels, nuclear receptors, and CYP450s, were used to evaluate potential molecular targets. Cellular assays determined effects of chemicals on cell growth kinetics, cell health parameters and in vivo human pharmacology models. Finally, effects on *C. elegans* reproduction and zebrafish development were examined. Results demonstrated good compatibility of the chemicals with all of the assay types. Active rates in the assays varied considerably among both the assays and the chemicals. Bioactivity profiles demonstrated patterns of activity consistent with known effects of specific chemicals as well as novel findings. These data are serving as the basis for correlation with the in vivo toxicity information captured in the EPA's ToxRef relational database, and ultimately should be useful in identifying key toxicity pathways and predicting human toxicity. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*