Predictive Signatures of Developmental Toxicity Modeled with HTS Data from ToxCast™ Bioactivity Profiles

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The EPA ToxCast™ research program uses a high-throughput screening (HTS) approach for predicting the toxicity of large numbers of chemicals. Phase-I contains 309 well-characterized chemicals which are mostly pesticides tested in over 600 assays of different molecular targets, cellular responses and cell-states. The goal of the present study was to build multivariate predictive signatures of prenatal developmental toxicity. We used EPA's ToxMiner™ v12 to integrate *in vitro* data with *in vivo* toxicity data from ToxRefDB and run several different machine learning techniques (stepwise logistic regression, linear discriminant analysis, neural networks, support vector machines). Preliminary analysis revealed 70 non-redundant molecular targets and 12 cellular effects that mapped to 24 Ingenuity pathways, 28 KEGG pathways, and 48 OMIM disease phenotypes. Further analysis linked 35 molecular targets with developmental toxicity in the rabbit and 48 in the rat; the strongest linkages were to defects of the eye, kidney ureter, and palate. Predictive associations could be further sorted by species and several of the *in vitro* assays could discriminate between chemicals that had differential activity in rat or rabbit bioassays. Computational (*in silico*) models are being built to implement these predictive signatures in EPA's Virtual Embryo (v-Embryo™) for systems modeling and chemical prioritization. [*This work has been reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy*].