High-throughput screening, predictive modeling and computational embryology

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High-throughput screening (HTS) studies are providing a rich source of data that can be applied to chemical profiling to address sensitivity and specificity of molecular targets, biological pathways, cellular and developmental processes. EPA's ToxCast project is testing 960 unique chemicals (drugs, pesticides, etc) in over 500 distinct assays, testing for diverse biochemical activities, receptor binding activities, reporter gene activation and gene expression profiles, stress-response indicators, and perturbation in cell state and cellular function. Also included are assays to monitor effects in zebrafish embryos and pathways of differentiation in mouse embryonic stem cells. In vitro profiles (AC50 in uM) are compared using machine-learning algorithms to identify patterns of biological activity and optimal feature selection for predictive modeling. Early findings suggest that developmental toxicity does not emerge from a simple molecular stream. Because many cells in a system interact to generate emergent properties (growth, patterning, homeostasis, robustness), computer models are needed to capture the complexity of multicellular networks and the key events leading to dysmorphogenesis. A predictive Virtual Embryo framework utilizes detailed knowledge to build computational models that run a morphogenetic series of events and can analyze the complexity of developmental processes. Potential regulatory applications are to inform and guide application QSAR models for predicting developmental effects; extract and organize literature for information relevant to developmental processes and defects; standardize in vitro and HTS data for predictive modeling of the disturbances to developmental processes; prioritize environmental chemicals for targeted testing; and systems modeling to analyze key pathways and mechanisms. [This abstract does not reflect EPA policy]