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 profile thousands of chemical compounds for biological activity and potential toxicity. EPA's ToxCast™ project, and the broader Tox21 consortium, in addition to projects worldwide, are generating HTS data for thousands of chemical compounds. ToxCast phase-I tested 309 chemicals, mostly pesticides with rich in vivo animal testing data (ToxRefDB), in about 567 in vitro assays for 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 were assays to monitor effects in zebrafish embryos and pathways of differentiation in mouse embryonic stem cells. In vitro features were mined by machine learning approaches against for (ToxCastDB) to identify patterns and features for predictive modeling of developmental toxicity. This faces several challenges, such as correlating in vitro concentration-response with internal dose-response kinetics; understanding how in vitro bioactivity profiles extrapolate from one cell-type or technology platform to another; and linking targets of in vitro bioactivity into pathways of developmental toxicity and mechanistic models. The vision is an in silico platform that can help inform risk assessment decisions based on relevant scientific knowledge and cell-agent-based computer simulations of embryonic tissues. EPA's Virtual Embryo project is building computer models of the developing embryo to analyze chemical toxicity in silico, as an integrated platform to computationally assess the potential for developmental effects following a pregnant woman's exposure to environmental chemicals. [This abstract does not necessarily reflect US EPA policy].