Pathway Profiling and Tissue Modeling of Developmental Toxicity

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High-throughput and high-content screening (HTS-HCS) studies are providing a rich source of data that can be applied to in vitro profiling 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-HCS data to construct in vitro cellular bioactivity profiles for thousands of chemical compounds in commerce or potentially entering the environment. EPA's ToxCast™ project generated HTS- HCS data on 309 environmental chemicals in more than 500 in vitro assays. Phase-I focused mostly on pesticidal and anti-microbial chemicals with rich in vivo animal testing data culled from the ToxRefDB database. The assays covered 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 were assays to monitor effects in zebrafish embryos and pathways of differentiation in mouse embryonic stem cells. In vitro profiles (AC50 in uM) and in vivo endpoints (mg/kg/day dosage) are compared for each chemical in the ToxMiner™ database, with machine-learning algorithms used to identify patterns of biological activity and optimal feature selection for predictive modeling. Applying this approach to predictive modeling and mechanistic understanding of developmental toxicity faces several challenges: 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 individual targets of in vitro bioactivity to complex signatures associated with pathways of developmental toxicity. Addressing these challenges will require innovative computer models that simulate kinetics (ADME) and multicellular dynamics. EPAs virtual embryo project (v-Embryo™) is building a framework for incorporating knowledge gained from these projects into computational (in silico) models that execute morphogenetic programs to simulate developmental toxicity. [This abstract does not necessarily reflect US EPA policy].