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Pathway Profiling and Tissue Modeling Using ToxCast HTS Data

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High-throughput screening (HTS) and high-content screening (HCS) assays are providing data-rich studies to probe and profile the direct cellular effects of thousands of chemical compounds in commerce or potentially entering the environment. *In vitro* profiling may compare unknown bioactivities against reference compounds of well-characterized activity or else be interrogated in different ways, looking for novel and predictive signatures of *in vivo* toxicities. EPA's ToxCast™ project has generated HTS and HCS data on 309 environmental chemicals across 467 *in vitro* assays. Proof-of principle (Phase-I) addressed mostly pesticidal and anti-microbial chemicals with rich *in vivo* animal testing data culled from EPA's ToxRefDB database. The assays cover diverse biochemical activities, receptor binding activities, reporter gene activation and gene expression profiles, stress-response indicators, and perturbation in cell state and cellular function. In addition, the Phase-I assay space was expanded to monitor susceptibility in zebrafish embryos and pathways of differentiation in mouse embryonic stem cells. Machine-learning is used to identify patterns of biological activity and build predictive signatures of toxicity for chemical prioritization. A key aspect to this strategy is the integration of HTS/HCS data into canonical pathways for developmental signaling and cellular regulation. Several challenges face technology development such as correlating *in vitro* concentration-response with internal dose-response kinetics *in vivo*, understanding how *in vitro* bioactivity profiles extrapolate from one cell-type or technology platform to another, and linking individual targets of *in vitro* bioactivity into pathways of developmental toxicity. Computer simulators that reconstruct an emergent morphogenetic series of events can help extrapolate predictive signatures to different tissues, stages, doses, species, and exposures. Such multicellular models are a goal of EPA's Virtual Embryo. The project aligns with the federal Tox21c consortium ramping up to test ~10,000 chemical compounds by *in vitro* profiling. [*This work is approved by EPA but does not reflect official Agency policy*].