Symposium: In vitro and In vivo alternative models of developmental toxicity of pharmaceutical compounds

VIRTUAL EMBRYO: SYSTEMS MODELING IN DEVELOPMENTAL TOXICITY.
TB Knudsen, US EPA, NCCT/ORD, RTP, NC, USA.

High-throughput screening (HTS) 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. Chemical profiling in ToxCast covered 965 drugs-chemicals in over 500 diverse assays testing 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 profiles (AC50 in uM) are compared with reference and in vivo data using machine-learning algorithms to identify patterns of biological activity and optimal feature selection for predictive modeling. Findings from Phase-I chemical library (309 compounds) reflect that developmental toxicity does not emerge from a simple molecular stream. Computer models are needed to capture the complexity of multicellular networks and the key events underlying dysmorphogenesis. EPA's Virtual Embryo project is building a framework for incorporating knowledge into computational systems models that integrate cellular and molecular dynamics with adverse outcome pathways across life stage and species. Cell-agent-based computer models that run a morphogenetic series of events with cell signaling networks and gradients can be used to analyze complex relationships and enhance predictive models relevant to key developmental key pathways and processes. Progress has been demonstrated for systems such as limb-bud morphogenesis and angiogenesis. *This abstract does not necessarily reflect US EPA policy.*