Predictive Modeling of Developmental Toxicity

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The use of alternative methods in conjunction with traditional *in vivo* developmental toxicity testing has the potential to (1) reduce cost and increase throughput of testing the chemical universe, (2) prioritize chemicals for further targeted toxicity testing and risk assessment, (3) generate predictive models of developmental toxicants useful as initial screens, and (4) understand mechanistic pathways leading to adverse impacts on embryonic and postnatal development. EPA's ToxCast™ project is focused on profiling the *in vitro* bioactivity of environmental chemicals to identify pathway-level and cell-based signatures that correlate with *in vivo* animal toxicity. Phase-I of ToxCast screened 309 chemicals in well over 500 *in vitro* assays for a range of molecular and cellular consequences including nuclear receptor signaling, pro-inflammatory response, and protein inactivation and activation. Phase-II is profiling another ~700 chemicals that include ~100 drugs that failed for various reasons in human trials, some reference compounds known to adversely impact human development, and untested environmental compounds of interest due to potential health risks. The assay platforms range from cell-free, to cell-based and multicellular platforms, including mouse embryonic stem cells (MESCs) and zebrafish embryogenesis models. From this dataset a predictive model of developmental toxicity was developed that identifies a battery of assays affected in a majority of developmental toxicants, including TGFβ and retinoid acid receptor signaling. Additionally, we explore the use of MESCs and zebrafish for their predictiveness of mammalian developmental toxicity in general, and across specific endpoints. [*This abstract does not necessarily reflect U.S. EPA policy*.]