Predictive modeling of developmental toxicity using EPA's Virtual Embryo

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Standard practice in prenatal developmental toxicology involves testing chemicals in pregnant laboratory animals of two species, typically rats and rabbits, exposed during organogenesis and evaluating for fetal growth retardation, structural malformations, and prenatal death just prior to term. Phenotypic heterogeneity that often follows from disruption of molecular function, cellular processes and signaling pathways in the embryo poses a major challenge to understanding mechanisms. The compendium of biological signatures mined from EPA's ToxCast™ high-throughput screening assays can be mapped to *in vivo* endpoints in prenatal developmental toxicity studies (ToxRefDB). An initial evaluation on ~300 chemicals and ~500 assays returned well-over 400 significant associations with developmental endpoints. We observed an increase in the number of predictive associations for developmental endpoints in the general rank order: fetal weight reduction to skeletal defects to soft tissue abnormalities to prenatal losses. These associations included 75-80 canonical pathways (Ingenuity, KEGG) having at least 5 significant ($P \leq 0.05$) assay-endpoint predictors within a pathway. The associative pattern was evident despite the fact that initial ToxCast™ *in vitro* assays were not run on embryonic systems. Furthermore, the diversity of perturbed pathways signifies complex downstream sequelae that must be connected to embryogenesis. EPA's new Virtual Embryo project (v-Embryo™) is providing this framework using cell-based computational models of morphogenesis that accept data on biological pathways, together with relevant knowledge of the developing system to simulate dysmorphogenesis. Successful computational (*in silico*) models will eventually be useful to explore which of the diverse biological pathways, signaling networks, and morphogenetic processes best characterize sensitive systems at susceptible stages of pregnancy. [This work has been reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy].