vEmbryo *In Silico* Models: Predicting Vascular Developmental Toxicity

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The cardiovascular system is the first to function in the vertebrate embryo, reflecting the critical need for nutrient delivery and waste removal during organogenesis. Blood vessel development occurs by complex interacting signaling networks, including extra-cellular matrix remodeling, inflammatory chemokine pathways and growth factor signaling. The crosstalk among these signaling pathways necessitates systems-based models that incorporate detailed cellular and molecular behaviors to adequately recapitulate embryonic vascular development. Existing computational models incorporate dynamic imaging and experimentation to gain insight into angiogenic cell behavior and functional vascular patterning. Many complex *in vitro* systems and small model organisms such as zebrafish have been adapted and refined to study vascular network formation, a process that is largely conserved among species. The U.S. EPA's Virtual Embryo project has built an *in silico* agent based model (ABM) of vascular morphogenesis, based on the hypothesis that chemical disruption of embryonic vascular plexus formation represents a potentially significant adverse outcome pathway (AOP) leading to developmental toxicity. Critical molecular signals in this model have corresponding *in vitro* assay targets in the ToxCast data set, and vascular bioactivity scores across these targets were calculated for over a thousand chemicals to predict their potential to disrupt vascular development. The *in silico* ABM model can test cell signaling interactions and emergent vessel network topologies following disturbance of specified growth factors, cell-surface receptors, and breakdown of the extracellular matrix, informed by the ToxCast data. Various ToxCast compounds, including reference vascular disruptors and test environmental chemicals, have been simulated *in silico* and tested in functional vascular assays, including whole embryo culture, aortic explant assay, zebrafish, and angiogenesis co-cultures of endothelial cells and fibroblasts.
This abstract does not necessarily reflect US EPA policy.