In silico Testing of Environmental Impact on Embryonic Vascular Development

Kleinstreuer[1] N, Rountree[1] M, Sipes[1] N, Chandler[1,3] K, DeWoskin[2] R, Singh[4] A, Spencer[4] R, Kavlock[1] R, Dix[1] D, and Knudsen[1] T

[1]NCCT, [2]NCEA, and [3]NHEERL, ORD, U.S. EPA and [4]Lockheed Martin, RTP, NC, USA 27711

Understanding risks to embryonic development from exposure to environmental chemicals is a significant challenge given the diverse chemical landscape and paucity of data for most of these compounds. EPA's Virtual Embryo project is building *in silico* models of morphogenesis to test mechanistic hypotheses by simulating chemical perturbations on complex developing systems. ToxCast™ Phase-I generated data on 309 unique compounds, majority pesticides, across over 500 *in vitro* high-throughput screening (HTS) assays and can be used to evaluate concentration-dependent effects on many diverse biological targets. The present study examined environmental chemicals that are developmentally toxic *in vivo,* that also disrupt ToxCast assay targets related to blood vessel development. We hypothesized that embryonic microvascular networks are targets for putative Vascular Disruptor Compounds (VDCs) with teratogenic potential. To test this hypothesis, we ran computer simulations using cellular-agent-based models of vascular development. The models test signaling pathway interactions and emergent vessel topologies following disturbance of specified growth factors, cell-surface receptors, and breakdown of the extracellular matrix. The vascular model was developed in CompuCell3D software and supplemented through semi-automatic knowledgebase creation. Altering critical pathways in the model, consistent with ToxCast bioactivity for chemical teratogens, caused *in silico* teratogenic effects and disruption of normal vascular network formation. VDCs exhibited target- and dose-dependent vascular network changes *in silico*, including an anti-angiogenic specific thalidomide analog run as a positive control to demonstrate reproducibility of experimental results. [This abstract does not necessarily reflect US EPA policy]