A toxicity signature for species-specific disruption of embryonic vasculogenesis derived from ToxCast *in vitro* profiling data.

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Blood vessel formation is crucial for normal embryo development and is sensitive to disruption by diverse teratogens. Recent studies have begun to reveal the cell signaling networks underlying vasculogenesis and angiogenesis and how these pathways might be perturbed by specific chemicals. For example, vascular endothelial growth factor (VEGF) and platelet-derived growth-factor receptor (PDGFRβ) pathways are sensitive to thalidomide and perturbation may disrupt vascular cell recruitment and proliferation at key stages of embryogenesis. An initial analysis of ToxCast™ high-throughput screening (HTS) data from 467 assays and 309 environmental chemicals revealed measureable effects on multiple *in vitro* assays for molecular targets or cellular processes important to vasculogenesis and angiogenesis. A predictive signature was built around statistical associations to *in vivo* developmental endpoints derived from EPA's ToxRefDB database. This analysis revealed a strong connection between developmental defects and a network of pathways consisting of pro-inflammatory / anti-angiogenic cytokine signaling, VEGF signaling, the plasminogen activating system (PAS) network of enzymes and growth factors mediating matrix remodeling and local signaling during blood vessel growth. From these inferred associations, we hypothesize that embryonic microvascular networks are targets for the teratogenic activity of a number of environmental chemicals. Furthermore, relatively robust patterns emerge from the *in vitro* profiling data linked to species-specific *in vivo* developmental toxicity in either rats or rabbits. The strongest pattern reflects a differential response in the up- or down- regulation of specific elements in the proposed vascular signature. This implies a systematic response that foreshadows perturbations with species-specific impacts on developmental toxicity.
[*This work is approved by EPA but does not reflect official Agency policy*].