Predictive Models and Computational Toxicology

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EPA's 'virtual embryo' project is building an integrative systems biology framework for predictive models of developmental toxicity. One schema involves a knowledge-driven adverse outcome pathway (AOP) framework utilizing information from public databases, standardized ontologies, semi-automated literature mining tools, and curated MeSH annotations to map relationships of adverse developmental outcomes to potential key events involving genes, proteins, molecular pathways, and chemicals. A data-driven approach identifies significant statistical linkages between molecular pathway targets (e.g., retinoic acid receptor and TGF-beta signaling) for distinct developmental features such as disruption of blood vessel development, cleft palate, male urogenital defects and limb abnormalities. Specifically, the target-feature associations are mined from 3.2 million *in vitro* data points in the high-throughput screening (HTS) and *in vivo* toxicity profiling data from EPA's ToxCast and ToxRefDB databases. Multicellular *in silico* computer models of the developing tissues are engineered with CompuCell3D. These small working prototype models can capture bioactivity profiles from HTS data, AOP framework information, and theoretical exposures to predict systems-level responses and dose effects. The capacity of these *in silico* models to engage the normal biology and simulate the behavior of a complex system steps us closer to *in vitro* profiling environmental chemicals for potential adverse effects on *in vivo* development and reproduction. *This abstract does not necessarily reflect US EPA policy.*