

TERATOLOGY SOCIETY 2011

SYMPOSIUM 3 “Determining the Risk of Chemicals in Our Environment – Challenges and Opportunities for Advancement”

Use of High-Throughput Testing and Approaches for Evaluating Chemical Risk – Relevance to Humans. TB Knudsen, USEPA/ORD/ NCCT, Research Triangle Park, NC.

ToxCast is profiling the bioactivity of thousands of chemicals based on high-throughput screening (HTS) and computational models that integrate knowledge of biological systems and *in vivo* toxicities. Many of these assays probe signaling pathways and cellular processes critical to development, creating the opportunity for models that predict these effects in the embryo. ToxCast Phase-I profiled 309 data-rich environmental chemicals in well over 500 assays. Phase-II is profiling another ~700 chemicals that include ~100 drugs that failed for various reasons in human trials, some reference compounds known to adversely impact human development, and untested environmental compounds of interest due to potential health risks. The assays assess diverse biochemical activities, receptor binding activities, reporter gene activation and gene expression profiles, stress-response indicators, and perturbation in cell state and cellular function. Also included were zebrafish embryogenesis, and mouse embryonic stem cell differentiation and cell number assays. *In vitro* profiles (AC50 in uM) and *in vivo* endpoints (mg/kg/day dosage) are compared for each chemical in the ToxCastDB database, with machine-learning algorithms used to identify patterns of biological activity and optimal feature selection for predictive modeling. Applying this approach to human developmental toxicity faces several challenges and uncertainties for *in vitro* to *in vivo* extrapolation, including: exposure metrics; correlating *in vitro* concentration-response with internal dose-response kinetics; predicting across tissues and developmental stages; and linking targets of *in vitro* bioactivity into pathways of developmental toxicity. [This abstract does not necessarily reflect EPA policy.]