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EPA's ToxCast Program for Predicting Hazard and Prioritizing Toxicity Testing of Environmental Chemicals

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EPA's National Center for Computational Toxicology is developing methods that apply computational chemistry, high-throughput screening (HTS) and genomic technologies to predict potential toxicity and prioritize the use of limited testing resources. The ToxCast research program is designed to forecast toxicity based on bioactivity profiling, and for proof-of-concept is focusing on environmental chemicals with extensive toxicity data to provide an interpretive context for these bioactivity profiles. Toxicity data from rodent *in vivo* studies are being captured into a relational database called ToxRefDB, allowing chemical groupings based on toxicities specific to study type, target organ, or effect categories. The ToxCast chemicals represent numerous structural classes and phenotypic outcomes, including tumorigens, developmental and reproductive toxicants, and neurotoxicants. ToxCast will include a broad spectrum of data on environmental chemicals: physical-chemical properties, computationally-predicted biological activities, biochemical and cell-based phenotypic characterization based on HTS assays, high-content screening assays, and *in vitro* gene expression analyses. At present we have gene expression profiles from rat and human hepatocytes exposed to a subset of ToxCast chemicals. In collaboration with the NIH Chemical Genomics Center HTS data for a variety of nuclear receptors (NR) potentially modulated by ToxCast chemicals is being generated. These complementary HTS and genomics data will be compared to *in vivo* toxicity data, in order to determine whether NR bioactivity profiles are predictive of hepatotoxicity. As the ToxCast proof-of-concept advances, it will expand to a broader range of data types that can be used to develop predictive models for multiple toxicities, useful for the prioritization of chemicals for further toxicological evaluation. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*