Endocrine Profiling and Prioritization Using ToxCast Assays

David Reif[1], Matthew Martin[1], Keith Houck[1], Richard Judson[1], Thomas Knudsen[1], Shirlee Tan[2], Vicki Dellarco[3], David Dix[1] and Robert Kavlock[1]

[1]National Center for Computational Toxicology, USEPA, RTP, NC
[2]Office of Science Coordination and Policy, Washington, DC
[3]Office of Pesticide Programs; USEPA, Washington, DC

The U.S. EPA's Endocrine Disruptor Screening Program (EDSP) is charged with screening pesticide chemicals and environmental contaminants for their potential to affect the endocrine systems of humans and wildlife (http://www.epa.gov/endo/). The prioritization of chemicals for testing is a goal shared by both the EDSP and the U.S. EPA's ToxCast™ program (http://epa.gov/ncct/toxcast/), in which a battery of *in vitro*, high-throughput screening assays (467) have assessed a library of 309 environmental chemicals at a cost <1% of that required for full-scale animal testing. In order to aid the EDSP, we describe putative endocrine profiles for the entire ToxCast™ library of 309 unique chemicals by focusing on assays involving the estrogen (*n*=5), androgen (*n*=4) and thyroid (*n*=4) signaling pathways, as well as other nuclear receptors and xenobiotic metabolizing enzymes (*n*=70) that have potential relevance to endocrine signaling. Using these multi-assay profiles in combination with information on relevant chemical properties, toxicity pathways, and *in vivo* study results, we present a flexible ranking system by which chemicals can be prioritized for further screening. By incorporating multiple sources of information (*in vitro* assays + chemical descriptors + pathways + *in vivo* studies), this prioritization system offers a comprehensive look at a given chemical's toxicity signature. Importantly, the signatures provide a transparent look at the relative contribution of all information sources that determine an overall priority ranking. The results demonstrate that combining multiple data sources into an overall weight of evidence approach for prioritizing further chemical testing results in more robust conclusions than any single line of support taken alone. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*