Abstract submitted for Society of Toxicology 2009 annual meeting
Baltimore, MD March 15-19

Biological Profiling of Endocrine Related Effects of Chemicals in ToxCast

RJ Kavlock, D Dix, K Houck, R Judson and M Martin.
National Center for Computational Toxicology, ORD, US EPA, RTP, NC.

The Food Quality Protection Act of 1996 mandates that EPA implement a validated screening program for detecting estrogenic chemicals, as well as other endocrine targets deemed appropriate by the Administrator. EPA's Endocrine Disruptor Screening Program (EDSP) has been developing and validating screening assays for disruption of estrogen (E), androgen (A) and thyroid (T) signaling pathways. The EDSP includes in vitro and in vivo assays for detecting E, A or T activity; and 73 chemicals have been proposed for initial screening. ToxCast is an EPA research program using a broad range of high-throughput screens to profile the bioactivity of chemicals and develop predictive signatures of toxicity, based on modeling in vitro assay data to in vivo toxicity phenotypes. ToxCast profiled 56 of the 73 EDSP chemicals using in vitro assays which characterized receptor binding, activation, inhibition and target gene regulation, providing biological fingerprints relevant to E, A, T and other endocrine related activities. Of the over 600 ToxCast assays, six assess E, and 5 each are related to A and T receptor signaling. In addition to E, A and T endpoints, ToxCast also measured interactions with progesterone, glucocorticoid and PPAR receptors, aromatase activity, and other nuclear receptors including AhR, CAR, FXR, LXR and PXR that may modulate endocrine metabolism. Many assay targets were human proteins, but in some cases rodent or other species were targeted, affording cross-species comparisons. Results for the prototypic xenoestrogen bisphenol A, and the anti-androgen vinclozolin support the ability of ToxCast to identify potential endocrine disruptors, while screening other endpoints beyond E, A and T offers broader insights into the bioactivity of the EDSP chemicals.
Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.