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High-Throughput Screening in ToxCast/Tox21

Abstract

Addressing safety aspects of drugs and environmental chemicals relies extensively on animal testing. However, the quantity of chemicals needing assessment and challenges of species extrapolation require development of alternative approaches. The EPA's ToxCast program addresses this through use of an extensive in vitro screening program to generate data on a large library of important environmental chemicals. The in vitro assays encompass both cell-free, biochemical assays targeting proteins that may be potential molecular initiating events as well as cellular assays that provide coverage of critical signaling pathways and cellular processes. A variety of computational approaches are used to analyze the resulting data sets to gain insight in to inherent biological activity of chemicals and possible mechanisms of toxicity. We describe several examples including identification of estrogen receptor and aromatic hydrocarbon receptor pathway modulators through effects in primary human cell systems. In addition, we used existing in vivo data from a subset of the chemicals to anchor generation of predictive models from the in vitro data for a number of adverse endpoints including reproductive and developmental toxicities. The strengths and weaknesses of this approach will be described. *This work does not necessarily reflect official Agency policy.*