Biological profiling of the ToxCast Phase II Chemical Library in Primary Human Cell Co-Culture Systems

Kleinstreuer[1] N, Houck[1] K, Judson[1] R, Reif[1] D, Kothiya[1] P, Martin[1] M, Knudsen[1] T, Richard[1] A, Polokoff[2] M, Yang[2] J, Berg[2] E, Kavlock[1] R, Dix[1] D

[1]NCCT, ORD, U.S. EPA, RTP, NC

[2]BioSeek LLC, SAN FRANCISCO, CA

The U.S. EPA's ToxCast research project was developed to address the need for high-throughput testing of chemicals and a pathway-based approach to hazard screening. Phase I of ToxCast tested over 300 unique compounds (mostly pesticides and antimicrobials). With the addition of Phase II, the library contains 1060 unique compounds, including 135 failed pharmaceuticals donated by industry partners, reference compounds known to be endocrine disruptors, carcinogens or reproductive/developmental toxicants, high-production volume chemicals, food additives, cosmetic ingredients, and proposed alternatives to commonly used plasticizers and surfactants. The chemicals were tested in a panel of BioMAP® systems, using complex co-cultures of primary human cells to characterize heterogeneous interactions underlying angiogenic and inflammatory processes. All compounds were assayed in duplicate at 4 concentrations in 8 cell systems using combinations of endothelial cells, peripheral blood mononuclear cells, bronchial epithelial cells, fibroblasts, keratinocytes and coronary artery smooth muscle cells, under various endogenous stimuli, totaling 87 endpoints and over 450,000 data points. ToxCast compounds were classified based on their ability to cause overt cytotoxicity in various cell types and on their bioactivity profiles when compared to reference compounds. Chemicals were identified with activities similar to known inducers of mitochondrial dysfunction, microtubule disruptors, cAMP elevators and NFkB pathway inhibitors. Forty-nine alternative chemicals were compared to the corresponding-use compounds and in some cases found to have significantly lower bioactivity, or none at all, at the tested concentrations. In vitro signatures for disruption of embryonic vasculogenesis and induction of tumor angiogenesis derived from ToxCast Phase I data were forward-validated for the Phase II compounds with in vivo developmental toxicity or carcinogenicity data.

This abstract does not reflect U.S. EPA policy