Nisha S. Sipes
National Center for Computational Toxicology, Office of Research and Development, US EPA, RTP, NC, USA

Profiling 976 ToxCast chemicals across 331 enzymatic and receptor signaling assays

Understanding potential health risks is a significant challenge for large numbers of diverse chemicals with poorly characterized exposures and mechanisms of toxicities. The present study analyzes chemical-target activity profiles of 976 chemicals (including failed pharmaceuticals, alternative plasticizers, food additives, and pesticides) in Phase I and II of the U.S. EPA's ToxCast™ project. The chemical inventory was profiled across 331 cell-free enzymatic and ligand-binding high-throughput screening (HTS) assays, including multiple G-protein-coupled and nuclear receptors, kinases, phosphatases, CYPs, histone deacetylases, ion channels and transporters. Over 14,000 chemical-assay pairs were tested in 8-point concentration series from 0.023 to 50 μM (or 0.009–20 μM for CYPs). Half-maximal activity concentrations (AC50) were identified for 7,135 active chemical-assay pairs for 729 unique chemicals in 256 assays. Chemicals varied in relative specificity or promiscuity toward assay types, and assays varied by sensitivity to chemical classes. In many cases, novel findings for previously unreported chemical-target combinations were associated with known chemical-target interactions through similarity analyses. Results from this large inventory of chemical-biological interactions can inform read-across methods as well as to link potential targets to molecular initiating events in adverse outcome pathways for diverse toxicities.

This abstract does not necessarily reflect U.S. EPA policy.