

Application of High-Throughput In Vitro Assays for Risk-Based Chemical Safety Decisions of Environmental and Industrial Chemicals

Multiple drivers shape the types of human-health assessments performed on chemicals by U.S. EPA resulting in chemical assessments are “fit-for-purpose” ranging from prioritization for further testing to full risk assessments. Layered on top of the diverse assessment needs are the resource intensive nature of traditional toxicological studies used to test chemicals and the lack of toxicity information on many chemicals. To address these challenges, the Agency initiated the ToxCast program to screen thousands of chemicals across hundreds of high-throughput screening assays in concentrations-response format. One of the findings of the project has been that the majority of chemicals interact with multiple biological targets within a narrow concentration range and the extent of interactions increases rapidly near the concentration causing cytotoxicity. This means that application of high-throughput in vitro assays to chemical assessments will need to identify both the relative selectivity at which chemicals interact with biological targets and the concentration at which these interactions perturb signaling pathways. The integrated analyses will be used to both define a point-of-departure for comparison with human exposure estimates and identify which chemicals may benefit from further studies in a mode-of-action or adverse outcome pathway framework. The application of new technologies in a risk-based, tiered manner provides flexibility in matching throughput and cost considerations with the degree of certainty required for specific decision contexts ranging from prioritization to full risk assessments.