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EPA's ToxCast Project: Lessons learned and future directions for use of HTS in predicting in vivo toxicology -- A Chemical Perspective

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U.S. EPA's ToxCast and the related Tox21 projects are employing high-throughput screening (HTS) technologies to profile thousands of chemicals, which in turn serve as probes of a wide diversity of targets, pathways and mechanisms related to toxicity. Initial models relating ToxCast Phase I HTS results to *in vivo* outcomes have been published, guided by biological mechanism and pathway organizing principles, but such models have yet to incorporate chemical reactivity or QSAR considerations. The expanded ToxCast and Tox21 chemical libraries (more than 1800 and 8300 substances, respectively) are unprecedented in size, diversity, and use-case coverage (pesticides, industrial, drugs, food-additives, cosmetics, etc.), offering significantly greater opportunities for cheminformatics and QSAR contributions to toxicity modeling. However, the nature of these libraries and HTS data sets, as well as the weight-of-evidence requirements for chemical safety assessments, continue to present major challenges for statistically-based biological or QSAR modeling approaches to the toxicity prediction problem. Cheminformatics approaches and toxicity-informed feature sets, proposed for use in conjunction with biological knowledge and adverse-outcome pathway hypotheses, are being developed as a means to focus and constrain modeling efforts into potentially productive areas of chemical and biological space, thereby improving modeling success and interpretability.

Abstract does not represent EPA policy.

(200 words)