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Chemical and Biological Profiling Approaches for Exploring Mutagenicity & Carcinogenicity of EPA ToxCast™ Chemicals

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Phase I of U.S. Environmental Protection Agency's ToxCast™ research project is building on three rich data tiers: 309 unique, structurally diverse chemicals (predominantly pesticides), activity and concentration response data from approximately 500 in vitro (cell-based and cell-free) high-throughput screening (HTS) assays, and extensive in vivo rodent bioassay data extracted from EPA pesticide registration records (entered in EPA's ToxRefDB). Contained within these data tiers are chemicals with mutagenic and non-mutagenic mechanisms of carcinogenicity, a rich source of target-specific bioassay data for multiple rodent species pertaining to tumorigenicity, and HTS assay results that are potentially relevant to, and informative of mutagenic and carcinogenic mechanisms in rodents and humans. Results of a preliminary analysis of three HTS assays potentially pertaining to genotoxicity and carcinogenicity in the larger context of the ToxCast™ dataset will be presented [GreenScreen HC *GADD45a-GFP* (Gentronix Ltd.), CellCiphr p53 (Cellumen Inc.) and CellSensor p53RE-bla (Invitrogen Corp.], along with a preliminary toxicity signature for a non-genotoxic mechanism of liver tumorigenicity for a subset of ToxCast chemicals. In addition, a future course for broadening the ToxCast™ chemical test space, HTS assay coverage, and reference genotoxicity studies contained within ToxRefDB will be described. These efforts, combined with progress in expanding public genotoxicity databases and integrating structure-activity relationship (SAR) approaches, point to exciting prospects for computational toxicology impacting the field of mutagenesis and carcinogenesis. *This work was reviewed by EPA and approved for publication, but does not necessarily reflect EPA policy, nor does mention of trade names constitute endorsement.*

245 words (250 maximum)