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High Throughput Prioritization for Integrated Toxicity Testing Based on ToxCast Chemical Profiling

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The rational prioritization of chemicals for integrated toxicity testing is a central goal of the U.S. EPA's ToxCast™ program (http://epa.gov/ncct/toxcast/). ToxCast includes a wide-ranging battery of over 500 *in vitro* high-throughput screening assays which in Phase I was used to screen a library of 309 environmental chemicals at a cost <1% of that required for extensive animal testing. Various statistical and biological models have been employed to make associations between Phase I *in vitro* bioactivity and other data domains. We have now developed a flexible prioritization support software tool incorporating ToxCast *in vitro* bioactivity profiles, inferred toxicity pathways, *in vitro* to *in vivo* dosimetry estimates, and chemical structural descriptors. This approach calculates a comprehensive toxicity potential and provides multivariate visualizations representing the relative contribution of each data domain to an overall priority score. We demonstrate custom implementations for four prioritization tasks relating to systemic, cancer, developmental or reproductive toxicity testing. ToxCast scores are calculated as a function of specific chemical properties, *in vitro* assays, pathways and dosimetry features selected for each prioritization and type of toxicity testing. Features can be customized to a wide range of specific prioritization tasks (e.g. MOA-specific features relating to endocrine disruption); domains can be added to represent additional data (e.g. exposure potential); and domains can be up- or down-weighted to reflect relative value and give extra emphasis to specific features. Initial results indicate that combining multiple data domains into an overall weight of evidence approach for prioritization produces more robust conclusions than any single type of data taken alone. *This abstract does not necessarily reflect Agency policy.*