

Prioritizing ToxCast Chemicals Across Multiple Sectors of Toxicity Using ToxPi

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The Toxicological Prioritization Index (ToxPi™) framework was developed as a decision-support tool to aid in the rational prioritization of chemicals for integrated toxicity testing. ToxPi consolidates information from multiple domains—including ToxCast™ *in vitro* bioactivity profiles (a wide-ranging battery of over 500 high-throughput screening assays), inferred toxicity pathways, exposure predictions, and chemical properties/descriptors—into comprehensive toxicity scores and multivariate visualizations representing the contribution of each data domain to overall priority rankings. Here, we develop a generalizable methodology for aligning ToxCast assay data with diverse prioritization tasks and demonstrate an implementation for profiling and prioritizing chemicals according to four sectors of toxicological concern: systemic (non-cancer), cancer, developmental, and reproductive. The methodology draws upon the wealth of knowledge in existing knowledgebases to link biological pathways with relevant *in vitro* assay results. The multi-sector ToxPi profiles developed here can be viewed as an overall prioritization or decomposed into individual sectors for targeted evaluation. Unsupervised clustering of the ToxPi profiles segregated chemicals into sector-specific groups of toxicological concern, which revealed previously unrecognized clusters of chemicals having similar patterns of bioactivity. Exploring these chemical clusters in the context of *in vivo* data from ToxRefDB™ suggested testable hypotheses about the potential toxicity of chemicals without *in vivo* data. These results indicate that an overall weight-of-evidence approach that retains transparency as to the contribution of individual data sources can be useful in supporting prioritization decisions across diverse areas of toxicological concern. *This abstract does not necessarily reflect Agency policy.*