Endocrine Profiling and Prioritization Using ToxCast Assays

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research&development

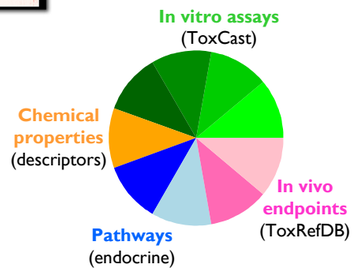
Research Objective

Develop a prioritization framework for potential endocrine disruptors that provides:

- Integration over multiple domains of information
- Extensibility to incorporate existing knowledge, prioritization schemes, and different types of data (e.g. measures of biotransformation, exposure, dosimetry)
- Multivariate assessment of toxicity relative to any set of chemicals
- Transparency in relative score for each chemical
- Flexibility to customize components for diverse prioritization tasks

Abstract

The U.S. EPA's Endocrine Disruptor Screening Program (EDSP) is charged with screening pesticide chemicals and environmental contaminants for their potential to affect the endocrine systems of humans and wildlife (http://www.epa.gov/endo/). The prioritization of chemicals for testing is a goal shared by both the EDSP and the U.S. EPA's ToxCast program (http://epa.gov/ncct/toxcast/), in which a battery of in vitro, high-throughput screening assays (467) have assessed a library of 309 environmental chemicals at a cost <1% of that required for full-scale animal testing. In order to aid the EDSP, we describe putative endocrine profiles for the entire ToxCast library of 309 unique chemicals by focusing on assays involving the estrogen (n=5), androgen (n=4) and thyroid (n=4) signaling pathways, as well as other nuclear receptors and xenobiotic metabolizing enzymes (n=70) that have potential relevance to endocrine signaling. Using these multi-assay profiles in combination with information on relevant chemical properties, toxicity pathways, and in vivo study results, we present a flexible ranking system by which chemicals can be prioritized for further screening. By incorporating multiple sources of information (in vitro assays + chemical descriptors + pathways + in vivo studies), this prioritization system offers a comprehensive look at a given chemical's toxicity signature. Importantly, the signatures provide a transparent look at the relative contribution of all information sources that determine an overall priority ranking. The results demonstrate that combining multiple data sources into an overall weight of evidence approach for prioritizing further chemical testing may result in more robust conclusions than any single line of support taken alone.



Prioritization Framework

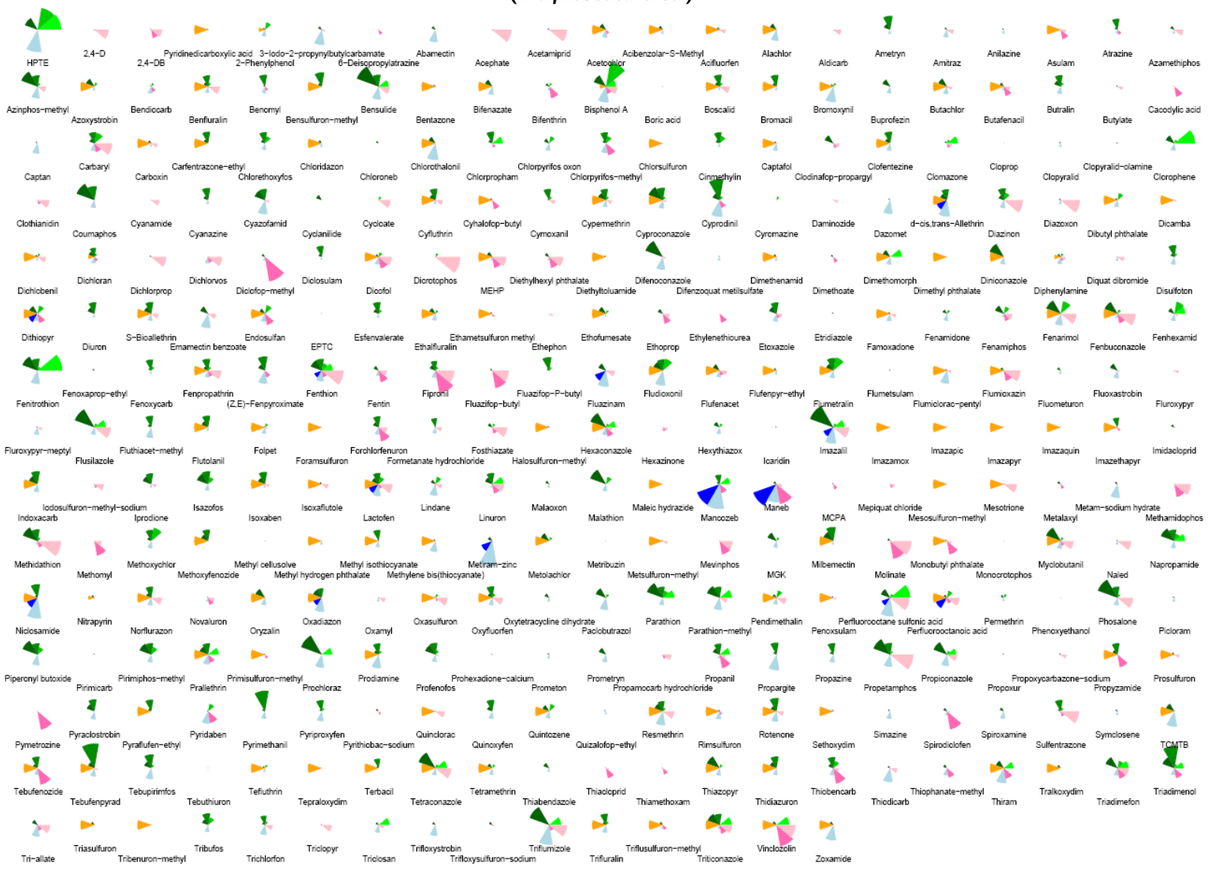
profile/ signature/ fingerprint

Each chemical gives a priority score (ToxScore) that can be ranked along any domain

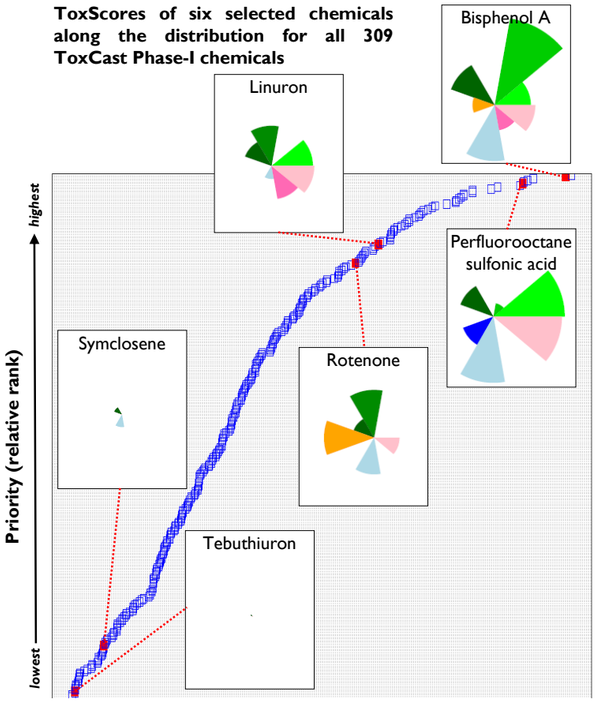
ToxScore = f(In vitro assays + Chemical properties + Pathways + In vivo endpoints)

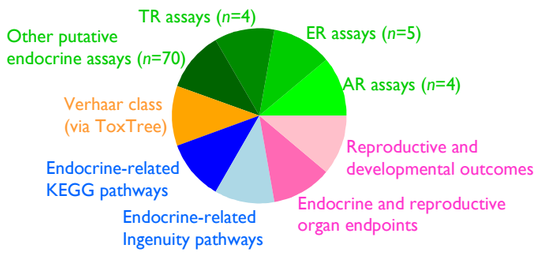
$$\text{ToxScore} = \sum_{I} w_i * \text{assay}_i + \sum_{C} w_c * \text{chemProp}_c + \sum_{P} w_p * \text{pathway}_p + \sum_{E} w_e * \text{endpoint}_e$$

ToxScore for each of the 309 ToxCast Phase-I Chemicals (*In alphabetical order*)



ToxScores of six selected chemicals along the distribution for all 309 ToxCast Phase-I chemicals





Results/Conclusions

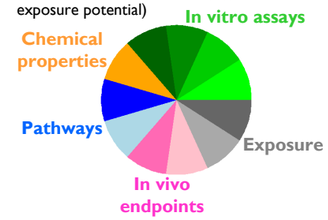
This implementation indicates that an integrated approach, wherein multiple domains of toxicological knowledge are simultaneously incorporated into chemical prioritization, can appropriately rank the ToxCast Phase-I chemicals for observed and/or potential toxicity. The inclusion of benchmark chemicals (akin to a "spike-in" set) as internal controls reduces the probability that potentially hazardous chemicals will be improperly assigned low priority for further testing and makes this a promising approach for diverse chemical prioritization tasks.

Impact and Outcomes

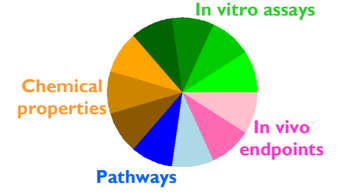
The framework developed here provides graphical insight into the multiple domains considered in chemical profiling and prioritization. It is amenable to incorporating extant prioritization schemes and relevant data from diverse sources, thereby facilitating meta-analysis across Agency resources. Because ToxScores are intended for relative ranking, particular implementations of this framework can be continually updated with new chemicals and future data.

Future Directions

Incorporate additional components (slices) that may be from other domains (e.g. Consideration of exposure potential)



Customize individual domains (e.g. Add a targeted set of chemical descriptors)



Adjust weighting schemes according to specific prioritization tasks or component (slice) meaning (e.g. In this example, the weight ($w_{i=4}$) of **In vitro assay$_{i=4}$** has been increased)

Integrate with existing prioritization schemes and toxicological knowledge (Endocrine Disruptor Priority Setting Database, Mid-Continent Ecology Division's system for ER binding potential, etc.)

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