

Future Activities of the EDSP

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Priority Setting

Second List

- 2010 Appropriations requires EPA to issue a second list of no less than 100 chemicals by October 30, 2010
 - Issue 25 orders per year for these chemicals.
 - The goal is to begin issuing orders in late 2010.
 - These data would be due to the Agency in late 2012.

Future Prioritization for EDSP Tier 1 Screening

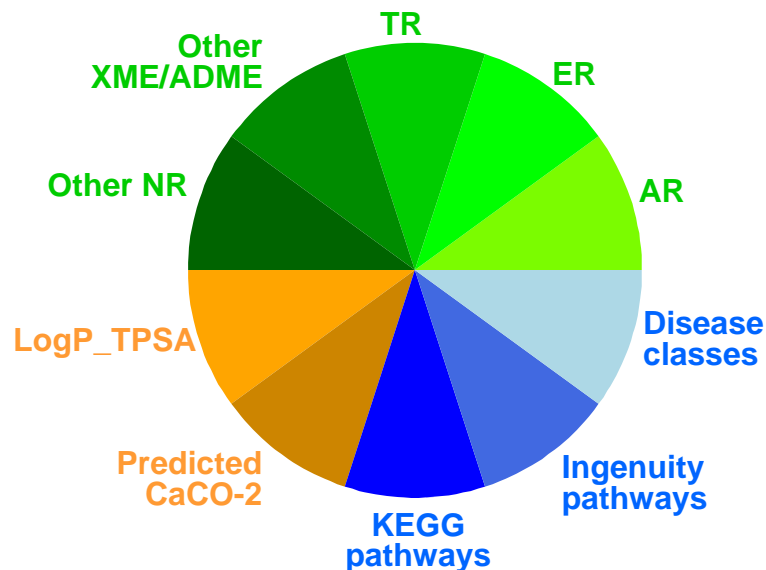
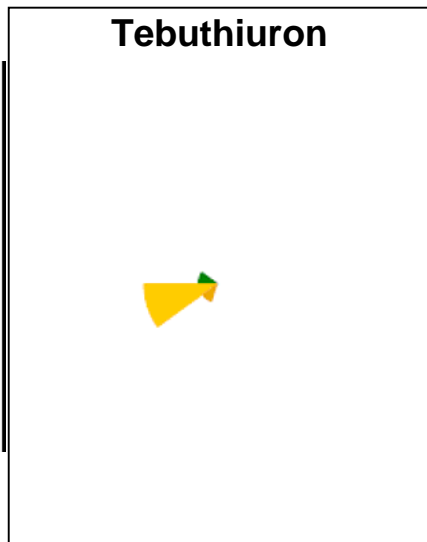
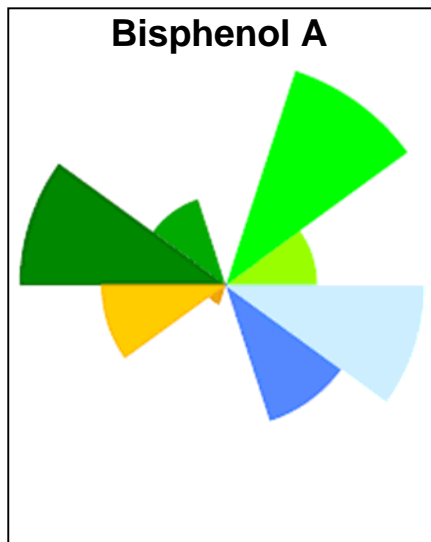
- Pesticide active ingredients – current plan is to use EPA’s schedule for re-evaluating registered active ingredients in the Registration Review program, consistent with EDSTAC and SAB/SAP recommendations

(http://www.epa.gov/oppsrrd1/registration_review/)

- Inert ingredients and other chemicals – develop *in vitro* and *in silico* tools that are integrated with exposure-based metrics

ToxPi: Prioritization Index for Endocrine Activity

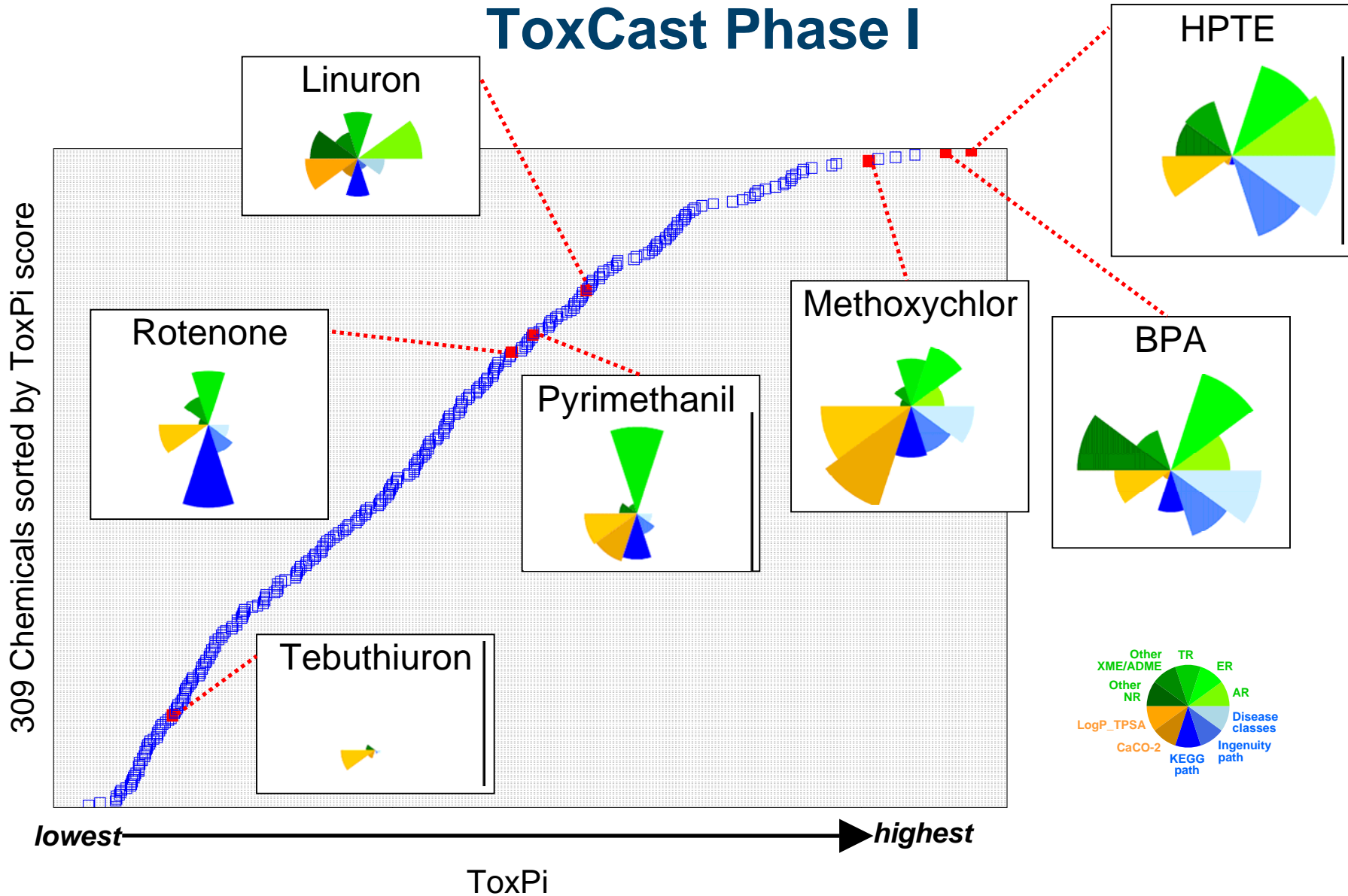
Prioritization Index = ToxPi = f(In vitro assays + Chemical properties + Pathways)



ToxPi is calculated from a weighted combination of all data sources for each chemical.

The size of each slice indicates relative rank or score for each chemical; the distance from the origin is proportional to the normalized value (e.g. **assay potency** or **predicted permeability**); the width indicates the relative weight of that slice in the overall ToxPi calculation.

Example ToxPi Rankings from ToxCast Phase I



ToxCast Website:

www.epa.gov/ncct/toxcast

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ToxCast™ Program

Predicting Hazard, Characterizing Toxicity Pathways, and Prioritizing the Toxicity Testing of Environmental Chemicals

Introduction

In 2007, EPA launched ToxCast™ in order to develop a cost-effective approach for prioritizing the toxicity testing of large numbers of chemicals in a short period of time. Using data from state-of-the-art high throughput screening (HTS) bioassays developed in the pharmaceutical industry, ToxCast™ is building computational models to forecast the potential human toxicity of chemicals. These hazard predictions will provide EPA regulatory programs with science-based information helpful in prioritizing chemicals for more detailed toxicological evaluations, and lead to more efficient use of animal testing.

In its first phase, ToxCast™ is profiling over 300 well-characterized chemicals (primarily pesticides) in over 400 HTS endpoints. These endpoints include biochemical assays of protein function, cell-based transcriptional reporter assays, multi-cell interaction assays, transcriptomics on primary cell cultures, and developmental assays in zebrafish embryos. Almost all of the compounds being examined in Phase 1 of ToxCast™ have been tested in traditional toxicology tests, including developmental toxicity, multi-generation studies, and sub-chronic and chronic rodent bioassays. ToxRefDB, a relational database being created to house this information, will contain nearly \$1B worth of toxicity studies in animals when completed. ToxRefDB is integrated into a more comprehensive data management system developed by NCCT called ACToR (Aggregated Computational Toxicology Resource), that manages the large-scale datasets of ToxCast™. ACToR is comprised of several independent data repositories linked to a common database of chemical structures and properties, and to tools for development of predictive HTS and genomic bioactivity signatures that strongly correlate with specific toxicity endpoints from ToxRefDB. These ToxCast™ signatures will be defined and evaluated by their ability to predict outcomes from existing mammalian toxicity testing, and identify toxicity pathways that are relevant to human health effects.

The second phase of ToxCast™ will screen additional compounds representing broader chemical structure and use classes, in order to evaluate the predictive bioactivity signatures developed in Phase I. Following successful conclusion of Phases I and II, ToxCast™ will provide EPA regulatory programs an efficient tool for rapidly and efficiently screening compounds and prioritizing further toxicity testing.

ToxCast™ Navigation

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Evaluation of Tier 1 Data

In 2012 EPA will review Tier 1 test data from the List 1 chemicals.

- Determine which chemicals need no further testing.
- Determine which chemicals need Tier 2 tests and which tests to require.
- Analyze performance of the battery and compare Tier 1 results with ToxCast predictions and with existing toxicological data used to support pesticide registrations.