www.epa.gov
science in ACTION
BUILDING A SCIENTIFIC FOUNDATION FOR SOUND ENVIRONMENTAL DECISIONS

Prioritizing Endocrine-Disruptor Screening Using ToxPi

Visually translating the integration of ToxCast data

July 6, 2010

Impact Statement

This research paper presents ToxPi (Toxicological Priority Index), a new weight-of-evidence framework for profiling and prioritizing chemicals. It numerically integrates various knowledge sources about chemical specific properties (biological and chemical). This numeric summation is displayed graphically in order to help further understand the chemical. ToxCast is a multi-year, multi-million dollar effort that uses advanced science tools to help efficiently ($20K per chemical) understand biological processes impacted by chemicals that may lead to adverse health effects. ToxCast currently includes 467 in vitro, high-throughput screening assays which have assessed over 300 environmental chemicals. This study applied ToxPi to ToxCast's 309 chemicals, which includes 52 of the chemicals currently undergoing screening in Tier 1 of the EDSP. In the future, ToxPi may be used to prioritize chemicals for screening in the EDSP Tier 1 battery.

Understanding which chemicals can cause endocrine disruption (ability of a chemical to interact with the body's hormonal systems and cause adverse health outcomes such as birth defects and cancer) is a high US EPA priority. EPA has developed a group of tests (the EDSP Tier I battery) capable of describing endocrine disruptor potential and is in the process of acquiring data on chemicals using these tests. EDSP assays are relatively expensive (~$0.5M per chemical) and tools are needed to help select which chemicals should be first in line for further testing. This study applied ToxPi to multiple potential endocrine disrupting measures and then ranked chemicals for additional screening. The knowledge sources used in this study included in vitro assays, chemical properties and pathways. For this study, 90 ToxCast assays relevant to endocrine activity were selected, and these assay results were then used to generate results in 27 endocrine pathways. Two chemical properties relevant to biological activity were also used. Results indicate that combining multiple ToxCast data sources into an overall, weight-of-evidence ToxPi for prioritizing further chemical screening is a robust prioritization method.

Study Description

ToxPi is shown visually as a circle with component slices making up the circle. Figure 1 visually represents ToxPi for endocrine activity and the circle's slices are color-coded with shades of three different colors to show the types of in vitro assays, chemical properties and pathways used in this study. The 90 selected ToxCast assays are represented by five green slices: Androgen Receptor (AR, 5 assays), Estrogen Receptor (ER, 6 assays), Thyroid Receptor (TR, 5 assays), Xenobiotic

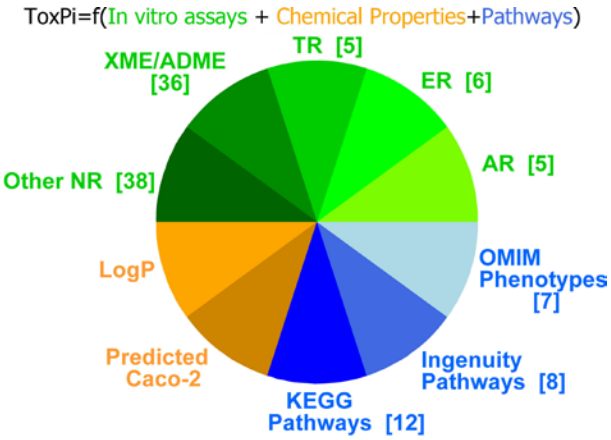


Figure 1 EDSP ToxPi Framework

Metabolizing Enzyme/ Absorption-Distribution-Metabolism-Excretion (XME/ADME, 36 assays), and Other Nuclear Receptor (NR, 38 assays).The three blue slices represent 27 pathway effects indicated from the assay results, and the orange slices represent the two chemical properties used.

Figure 2 shows individual ToxPi scores for two chemicals, Bisphenol A (BPA) and Tebuthiuron. BPA is commonly used in plastics and Tebuthiuron is a herbicide. The slice representing ER for BPA extends farther from the circle's center when compared to the Tebuthiuron indicating that BPA is more potent across ER assays when compared to Tebuthiuron. BPA also ranks above Tebuthiuron in all other ToxPi slices.

Figure 2 ToxPi Profiles for Two Reference Chemicals

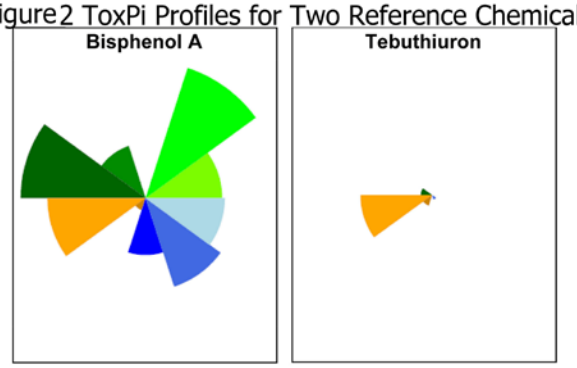
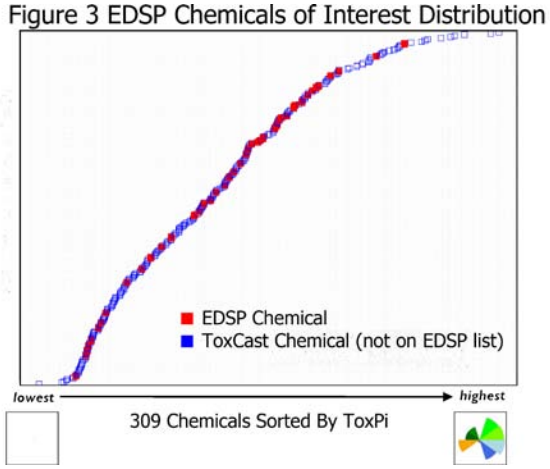


Figure 3 shows ToxPi results for all 309 ToxCast chemicals, including EDSP chemicals that are part of ToxCast. The blue boxes represent ToxCast chemicals that are not on the EDSP tier 1 list and the red boxes are

EDSP chemicals. ToxPi scores are on the horizontal axis (score from lowest to highest) and the individual chemicals run along the vertical axis. EDSP chemicals are represented throughout the ToxPi distribution. EDSP chemical distribution is not surprising since these were selected solely upon exposure considerations. In comparison, ToxPi takes into account biological information and provides a method for efficiently prioritizing chemicals for further testing.

Figure 3 EDSP Chemicals of Interest Distribution



Until data from EDSP screening is available, a good ToxPi validity evaluation for endocrine disruption is to select "reference" chemicals. The "reference" chemicals have substantial research on their toxicological activities. Therefore, there is an expectation about where these chemicals should fall along the ToxPi distribution. Figure 4 shows ToxPi for reference chemicals along the ToxPi distribution for all ToxCast chemicals. For assessing ToxPi, reference chemical scores should provide rankings that do not put known hazards near the bottom of the priority list. As Figure 4 shows, potent reference chemicals such as BPA, methoxychlor and its metabolite HPTE are at the top of the ToxPi distribution as expected.

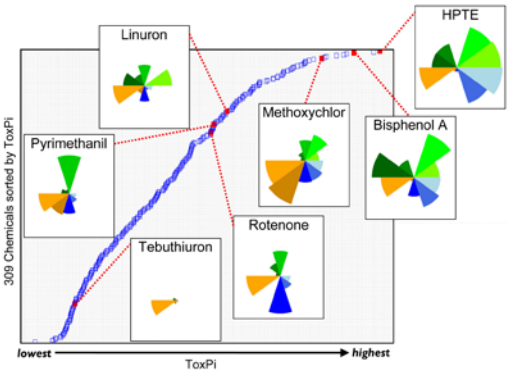


Figure 4 Guidepost (spike-in) Chemicals

In the future, ToxPi predictions will be compared to the EDSP Tier 1 screening results to test the validity of the approach.

Conclusions

Combining multiple ToxCast data sources into an overall, weight-of-evidence ToxPi resulted in a robust prioritization method. Benefits of ToxPi include its:

- **Efficiency:** ToxPi's advantage is that knowledge sources used to prioritize chemicals comes from more than one source which increases the likelihood of detecting true endocrine active chemicals. This improves efficiency by ensuring optimal use of costly animal and human resources.
- **Flexibility:** Because ToxPi is intended for relative ranking, particular implementations of this framework can be continually updated with new chemicals and future data. Other knowledge sources such as in vivo endpoints and exposure can be applied to this framework to assess other types of possible disruptions and chemicals
- **Collaborative Approach:** ToxPi is amenable to incorporating existing and emerging knowledge sources and data from diverse sources, thereby facilitating analysis across EPA resources and offices.
- **Potential:** Additional development of ToxPi based upon forthcoming ToxCast results will be focused on ranking chemicals for their potential to cause other types of health effects such as reproductive toxicity, birth defects, and cancer.

Background

The Food Quality and Protection Act (FQPA) and the Safe Drinking Water Act (SDWA) requires EPA to develop a screening program to assess the potential for chemicals to interact with the endocrine system. As a result, EPA's EDSP is responsible for screening pesticide chemicals and environmental contaminants for potential impacts to the endocrine systems of humans and wildlife. The prioritization of chemicals for testing is a goal shared by both EDSP and ORD.

References

Reif et al. (2010) "Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data." Environmental Health Perspectives.

More information: http://epa.gov/ncct/toxcast/

Originating Organization for Fact Sheet

EPA

Primary Author of Fact Sheet
Monica Linnenbrink
Secondary Authors of Fact Sheet
Robert Kavlock, David Dix and David Reif
First/Lead Author of Paper
David Reif