Toxicological Priority Index (ToxPi) as a Platform for Incorporation of Exposure Data for Chemical Prioritization

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This work was reviewed by EPA and approved for presentation but does not necessarily reflect Agency policy
Diversity of data from ToxCast™ *in vitro* HTS assays

**Cellular Assays**
- **Cell lines**
  - HepG2 human hepatoblastoma
  - A549 human lung carcinoma
  - HEK 293 human embryonic kidney
- **Primary cells**
  - Human endothelial cells
  - Human monocytes
  - Human keratinocytes
  - Human fibroblasts
  - Human proximal tubule kidney cells
  - Human small airway epithelial cells
- **Biotransformation competent cells**
  - Primary rat hepatocytes
  - Primary human hepatocytes
- **Assay formats**
  - Cytotoxicity
  - Reporter gene
  - Gene expression
  - Biomarker production
  - High-content imaging for cellular phenotype

**Biochemical Assays**
- **Protein families**
  - GPCR
  - NR
  - Kinase
  - Phosphatase
  - Protease
  - Other enzyme
  - Ion channel
  - Transporter
- **Assay formats**
  - Radioligand binding
  - Enzyme activity
  - Co-activator recruitment

Judson et al., 2010, Environ. Health Perspect. (doi: 10.1289/ehp.0901392)

http://www.epa.gov/ncct/toxcast/
A numerical index that can be used for ranking (instead of absolute thresholds) is more flexible for different prioritization tasks. Can better accommodate new data, new chemicals, data adjustments, etc.

- Integration over multiple domains of information
- Extensibility to incorporate additional types of data
- Transparency in score derivation and visualization
- Flexibility to customize components for diverse prioritization tasks

ToxPi (Toxicological Priority Index)

In vitro assays (ToxCast)

Chemical properties (descriptors)

Pathways (endocrine)
Rationale for an integrated chemical prioritization scheme

- Integration over multiple domains of information
- Extensibility to incorporate additional types of data
- Transparency in score derivation and visualization
- Flexibility to customize components for diverse prioritization tasks

A numerical index that can be used for ranking (instead of absolute thresholds) is more flexible for different prioritization tasks. Can better accommodate new data, new chemicals, data adjustments, etc.
Definitions & notation

Slice: “Pie” slices representing individual components or aggregations of multiple related components.

Component: Individual in-vitro assays, chemical properties/descriptors, etc.

\[ \text{ToxPi} = f(\text{In vitro assays} + \text{Chemical properties} + \text{Pathways}) \]

Domain: Domain/field of knowledge; represented by the slice(s) of a given color family.

Each chemical signature gives a score index (ToxPi) used for ranking chemicals fingerprint.
Interpreting ToxPis for individual chemicals

Example: Endocrine profiling and prioritization of environmental chemicals using ToxCast™

ToxPi = \sum_{i=1}^{I} w_i \ast \text{assay}_i + \sum_{c=1}^{C} w_c \ast \text{chemProp}_c + \sum_{p=1}^{P} w_p \ast \text{pathway}_p

Score for \text{In vitro assay}_{i=1}

Reif et al., 2010, submitted
Example of data sources

- **36 assays**
  - 1 technology

- **38 assays**
  - 4 technologies

- Calculated using LeadScope software

- Calculated using QikProp software

- **5 assays**
  - 3 technologies

- **6 assays**
  - 4 technologies

- **5 assays**
  - 4 technologies

- 27 specific pathway components used; data from external knowledgebases
Prioritization of ToxCast™ chemicals
(sorted by overall ToxPi endocrine score)
Example ToxPi scores for reference chemicals from ToxCast™ phase I

Ranks and scores consistent with published bioactivity
Alternative ToxPi implementations for different applications

A) Incorporate additional components (slices) from other domains

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

C) Adjust weighting schemes (e.g. Weights of In vitro assay slices AR, ER, and TR have been increased)
Source for preliminary exposure data

- Exposure data obtained from EPI Suite™ v4.00 (http://www.epa.gov/oppt/exposure/pubs/episuite.htm):
  - **Bioaccumulation/bioconcentration factor** (Log BCF, Log BAF) from BCFBAF program
  - **Persistence** (half life air, half life water, persistence time) from Level III fugacity model

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Source for preliminary exposure data: ToxCast Phase I
Source for preliminary exposure data

- Exposure data obtained from EPI Suite™ v4.00 (http://www.epa.gov/oppt/exposure/pubs/episuite.htm):
  - **Bioaccumulation/bioconcentration factor** (Log BCF, Log BAF) from BCFBAF program
  - **Persistence** (half life air, half life water, persistence time) from Level III fugacity model

- Ran EPI Suite™ in batch mode passing chemicals smiles/CAS

- From summary results, extracted data for 309 ToxCast Phase I chemicals

- Adjusted data range for negative values and removed null values

- Normalized data to incorporate exposure domain into ToxPi framework with other data domains
Incorporating exposure information: Preliminary ToxPi endocrine scores
(sorted by overall ToxPi score)
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Previous top 15 prioritized chemicals by overall ToxPi score

New top 15 prioritized chemicals with exposure domain

#22 #31 #33 #18 #26
Interpreting ToxPis with exposure domain for individual chemicals

Bisphenol A

Perfluorooctane sulfonic acid (PFOS)

AR
TR
LogP, TPSA
CaCO2
KEGG path
Ingenuity path

Other
XME/ADME
Other NR

ER
AR
Persistence
BCF/BAF
Disease classes

BCF/BAF
Persistence
Disease classes

Interpreting ToxPis with exposure domain for individual chemicals

Bisphenol A

Perfluorooctane sulfonic acid (PFOS)
Conclusions

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- Combining multiple data sources into an overall, weight-of-evidence ‘ToxPi’ score results in more robust conclusions than any single data source taken alone.

- Framework developed here provides graphical insight and transparent visualization of relative contribution of all sources of data.

- Amenable to incorporating extant prioritization schemes and relevant data from diverse sources.

- Because ToxPis are intended for relative ranking, particular implementations of this framework can be continually updated with new chemicals and future data.

- Adding exposure domain information changes ToxPi scores for ToxCast Phase I chemicals

- Future plans: Incorporate other exposure data (manufacturing volumes, usage, etc.)
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