

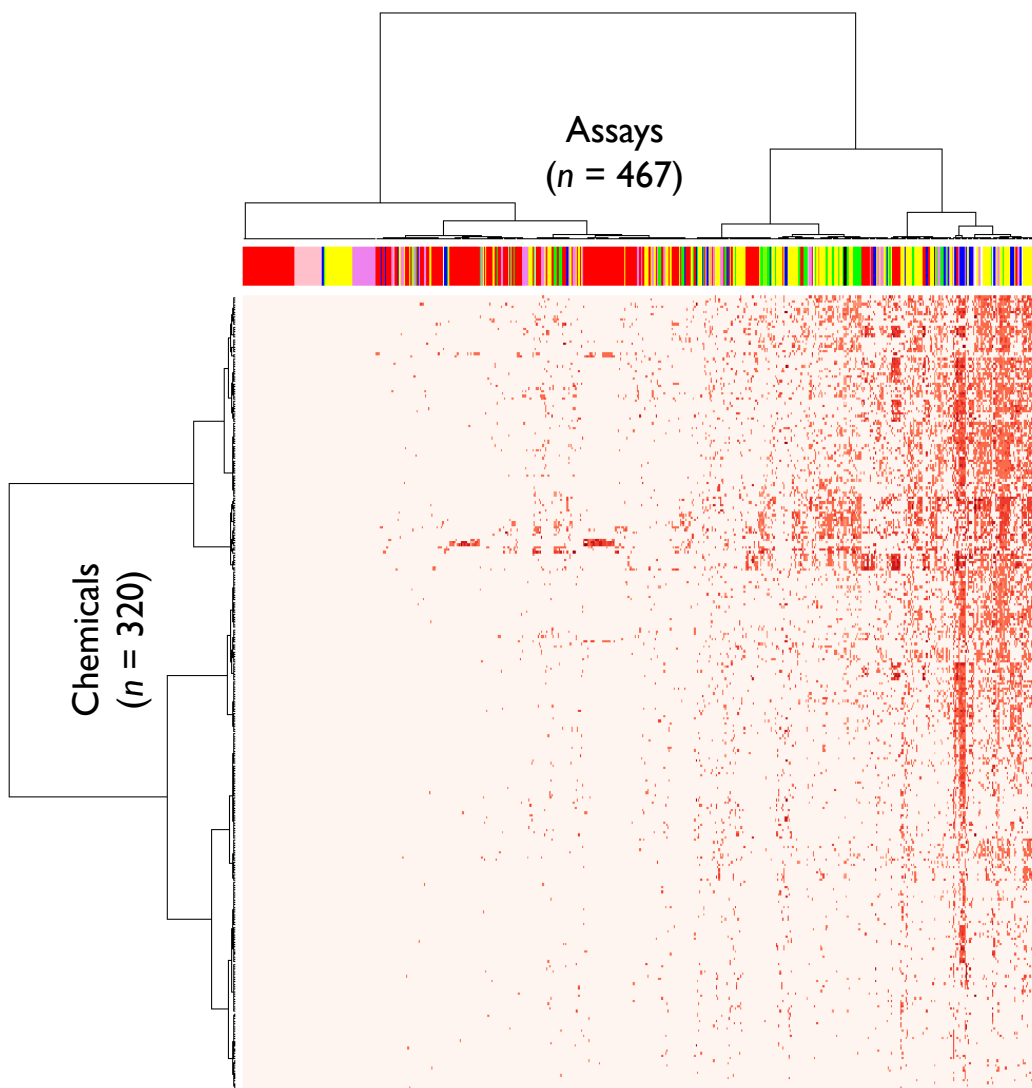
# Toxicological Priority Index (ToxPi) as a Platform for Incorporation of Exposure Data for Chemical Prioritization

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



**COMPUTATIONAL  
TOXICOLOGY**



## 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

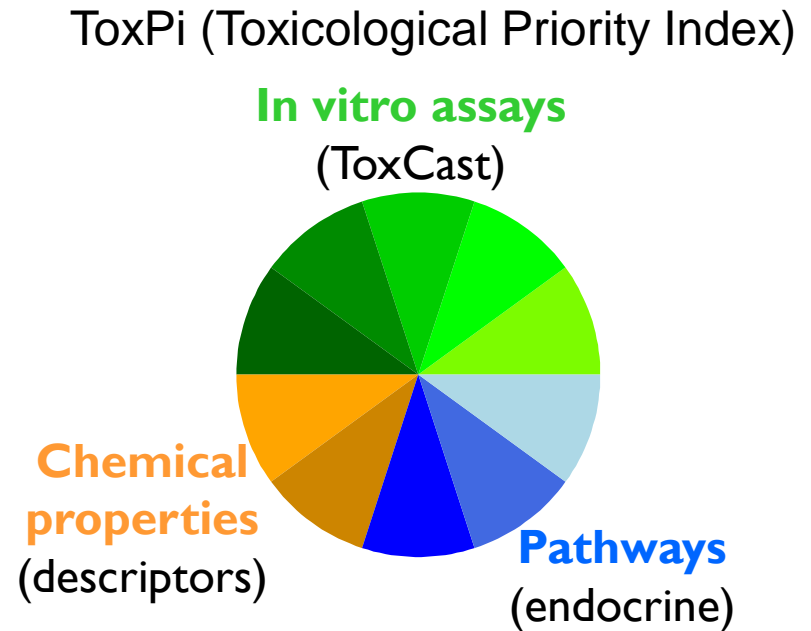
- **Protein families**
  - GPCR
  - NR
  - Kinase
  - Phosphatase
  - Protease
  - Other enzyme
  - Ion channel
  - Transporter
- **Assay formats**
  - Radioligand binding
  - Enzyme activity
  - Co-activator recruitment

<http://www.epa.gov/ncct/toxcast/>

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

# 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.

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# Definitions & notation



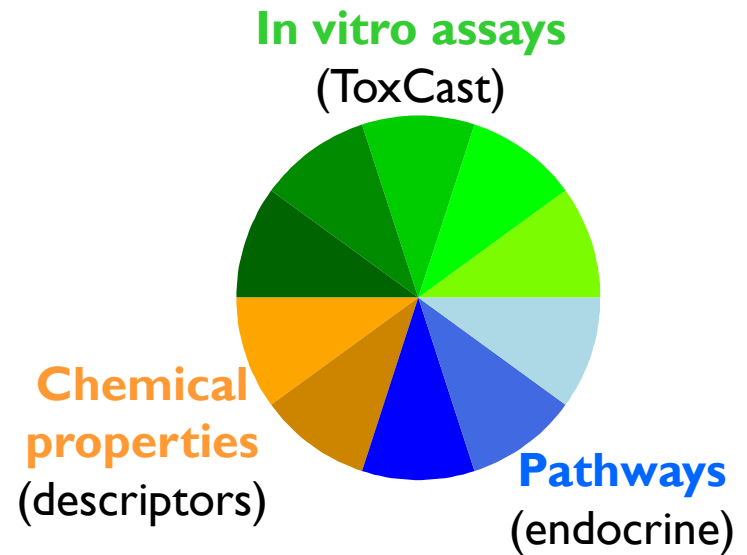
Each chemical *signature/profile/fingerprint* gives a score index (ToxPi) used for ranking chemicals

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

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

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

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



# Interpreting ToxPis for individual chemicals

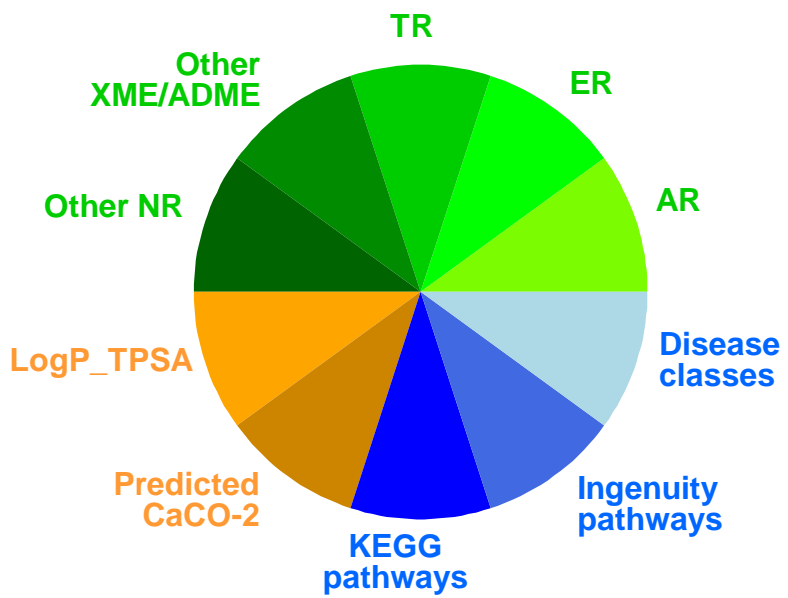
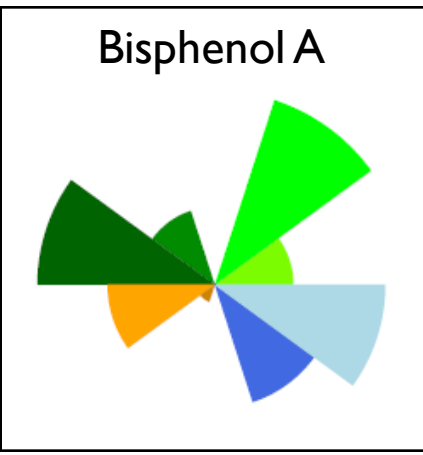
## Example: Endocrine profiling and prioritization of environmental chemicals using ToxCast™

$$\text{ToxPi} = \sum_1^I w_i * \text{assay}_i + \sum_1^C w_c * \text{chemProp}_c + \sum_1^P w_p * \text{pathway}_p$$



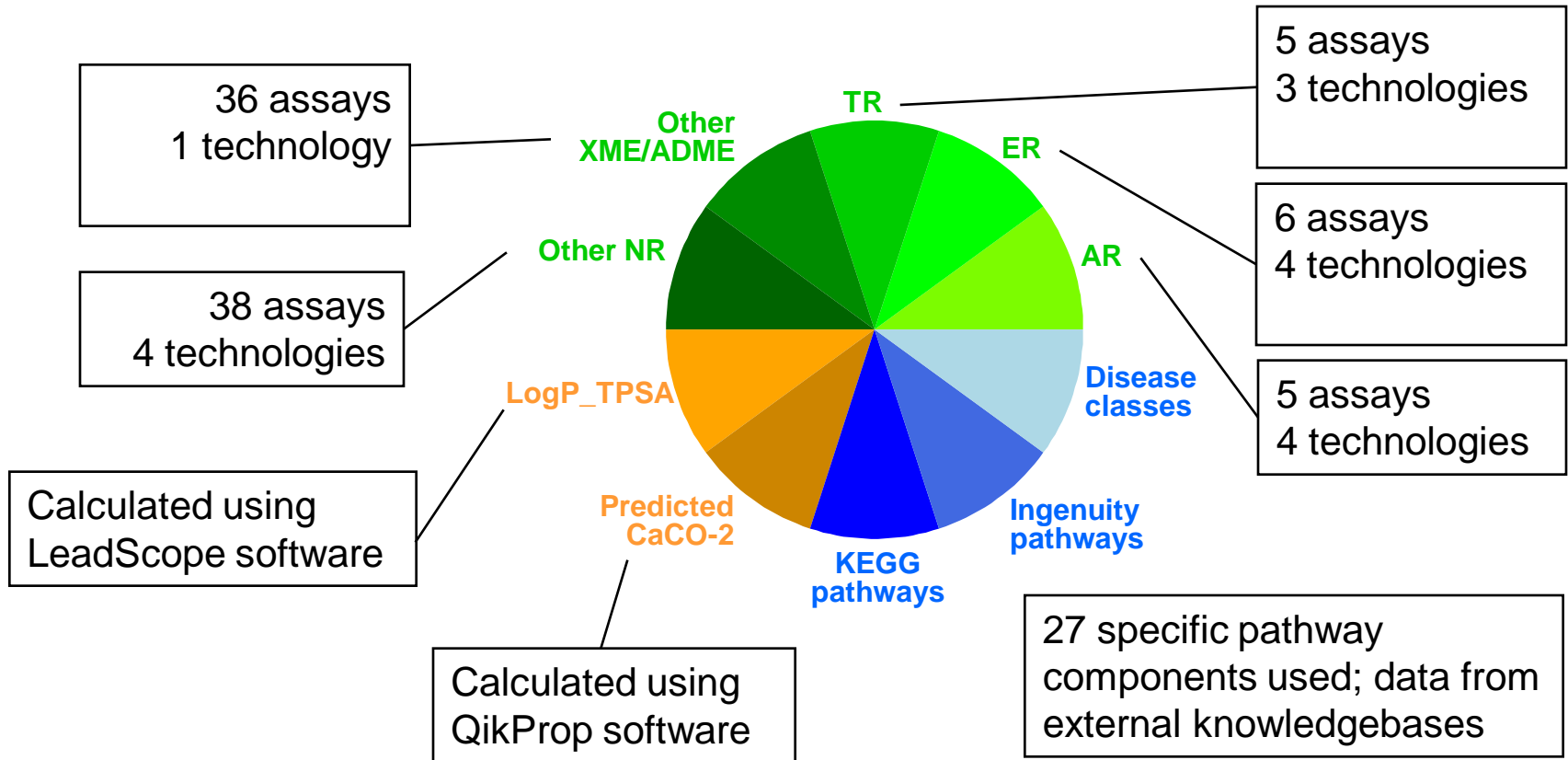
0                      .25                      .5                      .75                      1

Score for **In vitro assay**<sub>i=1</sub>

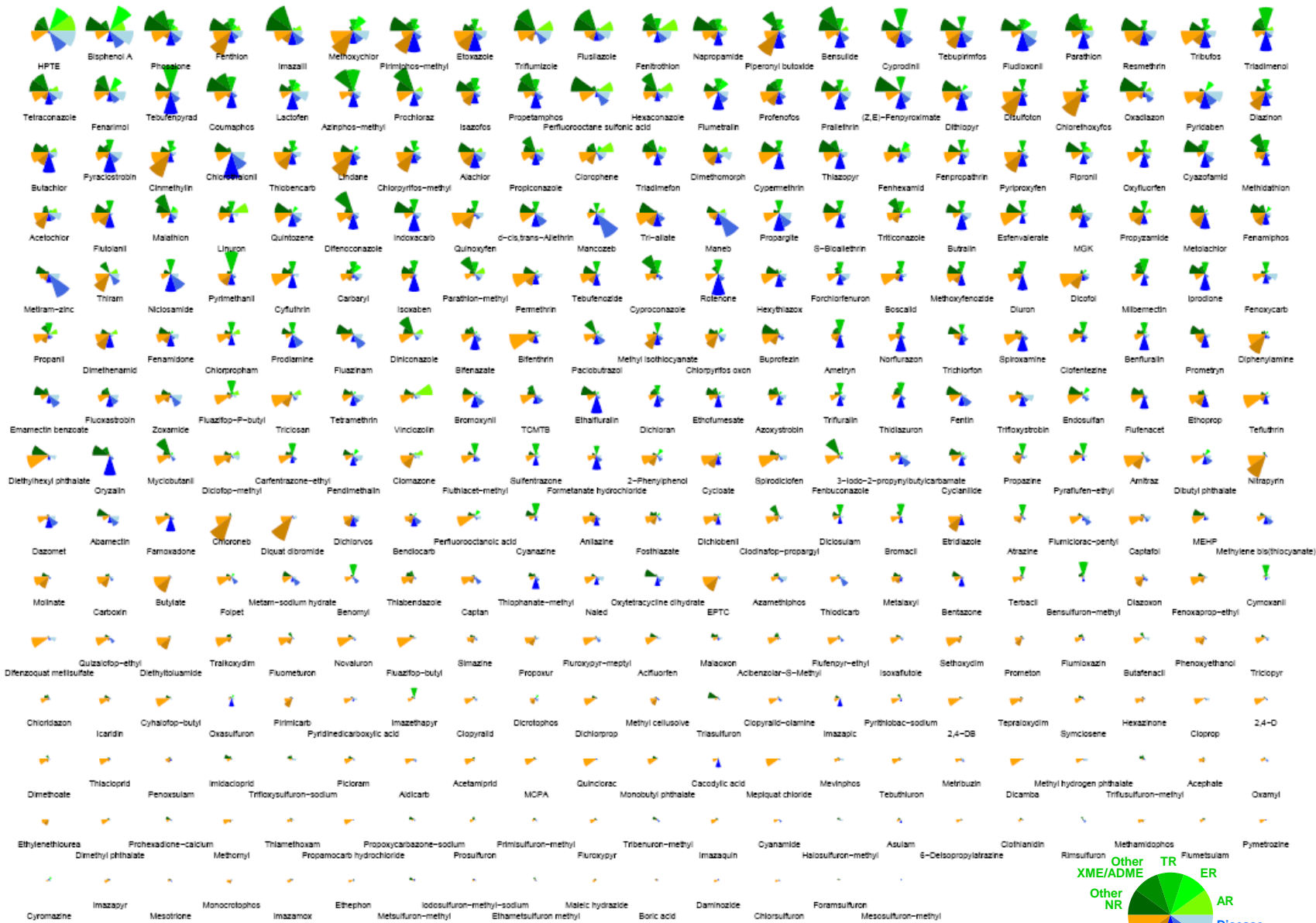


Reif et al., 2010, submitted

# Example of data sources

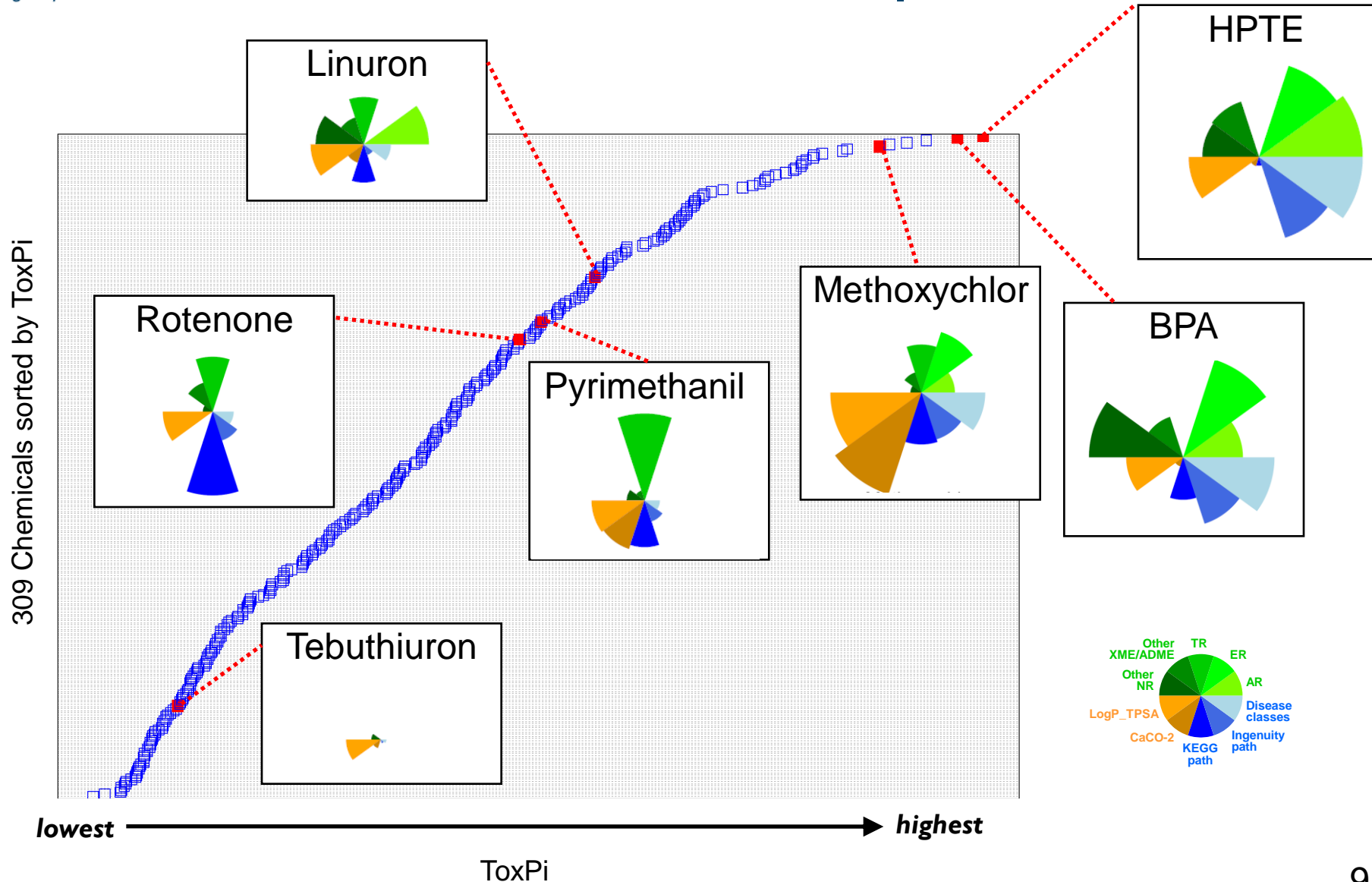


# Prioritization of ToxCast™ chemicals (sorted by overall ToxPi endocrine score)



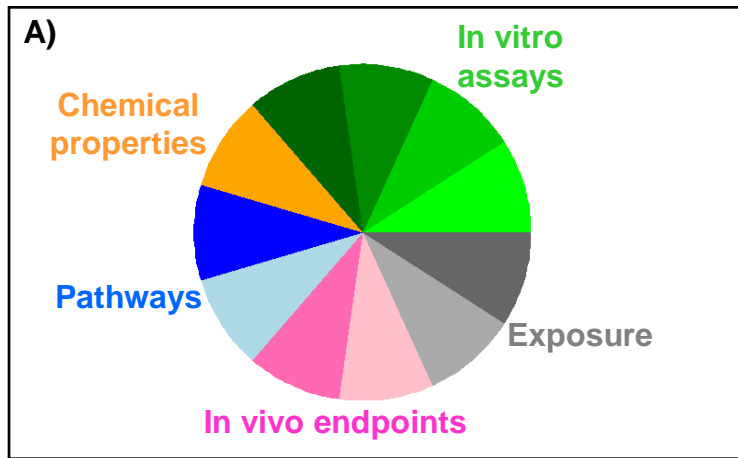


# Example ToxPi scores for reference chemicals from ToxCast™ phase I

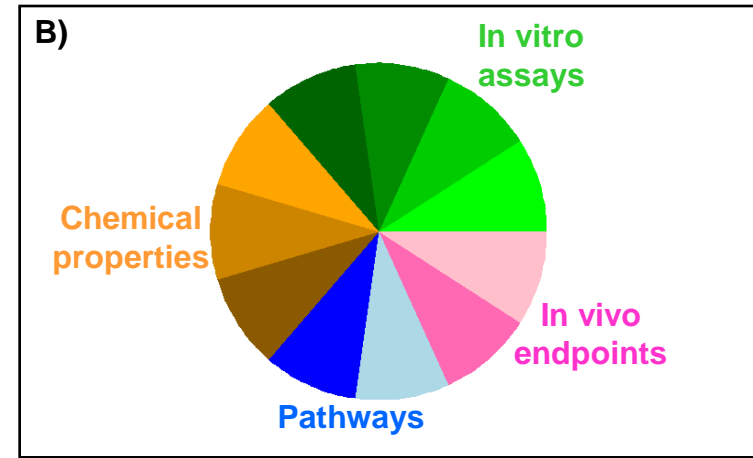


Ranks and scores consistent with published bioactivity

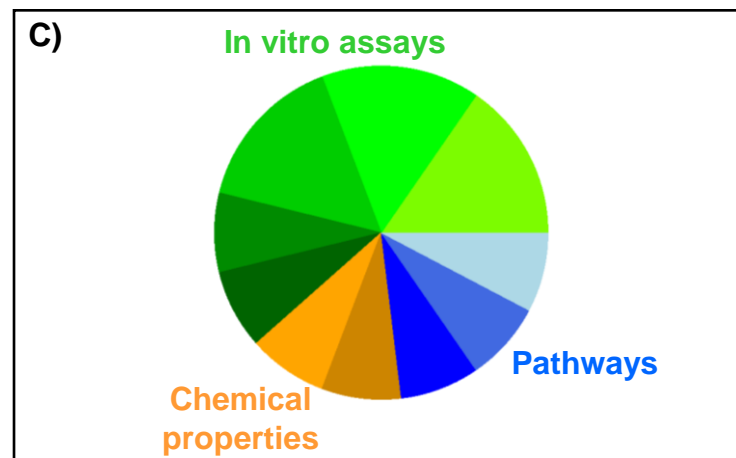
# Alternative ToxPi implementations for different applications



**A)** Incorporate additional components (slices) from other domains



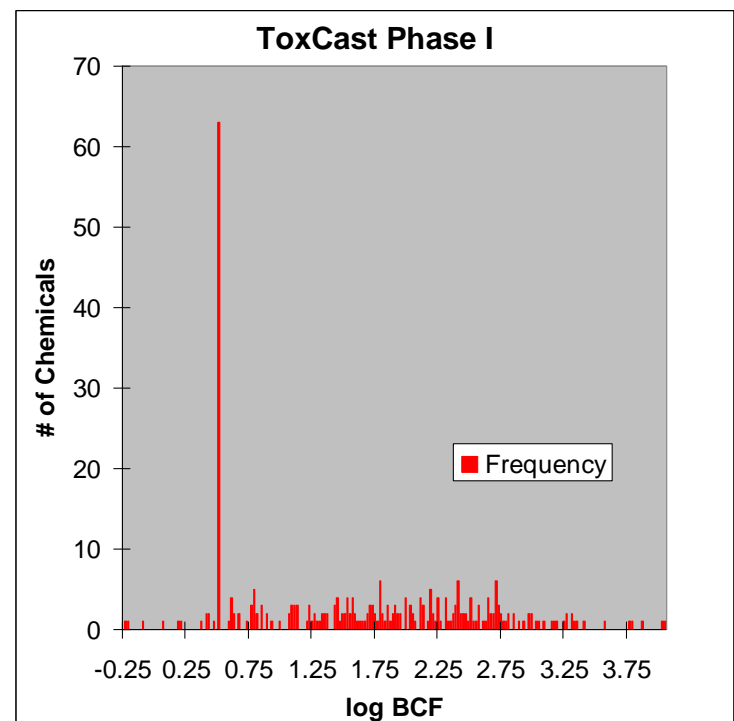
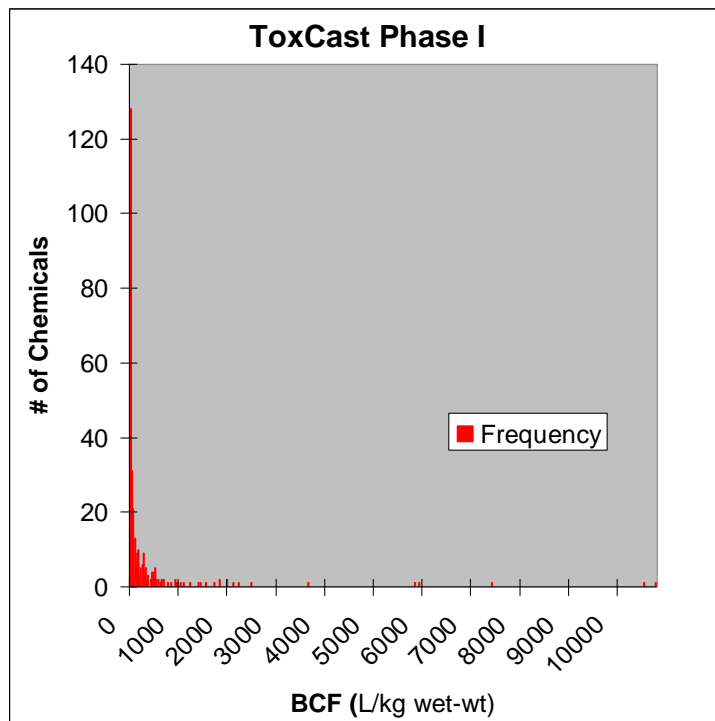
**B)** Customize individual domains (e.g. Add a targeted chemical descriptors)



**C)** Adjust weighting schemes (e.g. Weights of In vitro assay slices AR, ER, and TR have been increased)

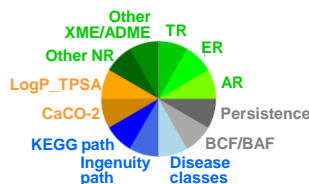
# Source for preliminary exposure data

- 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

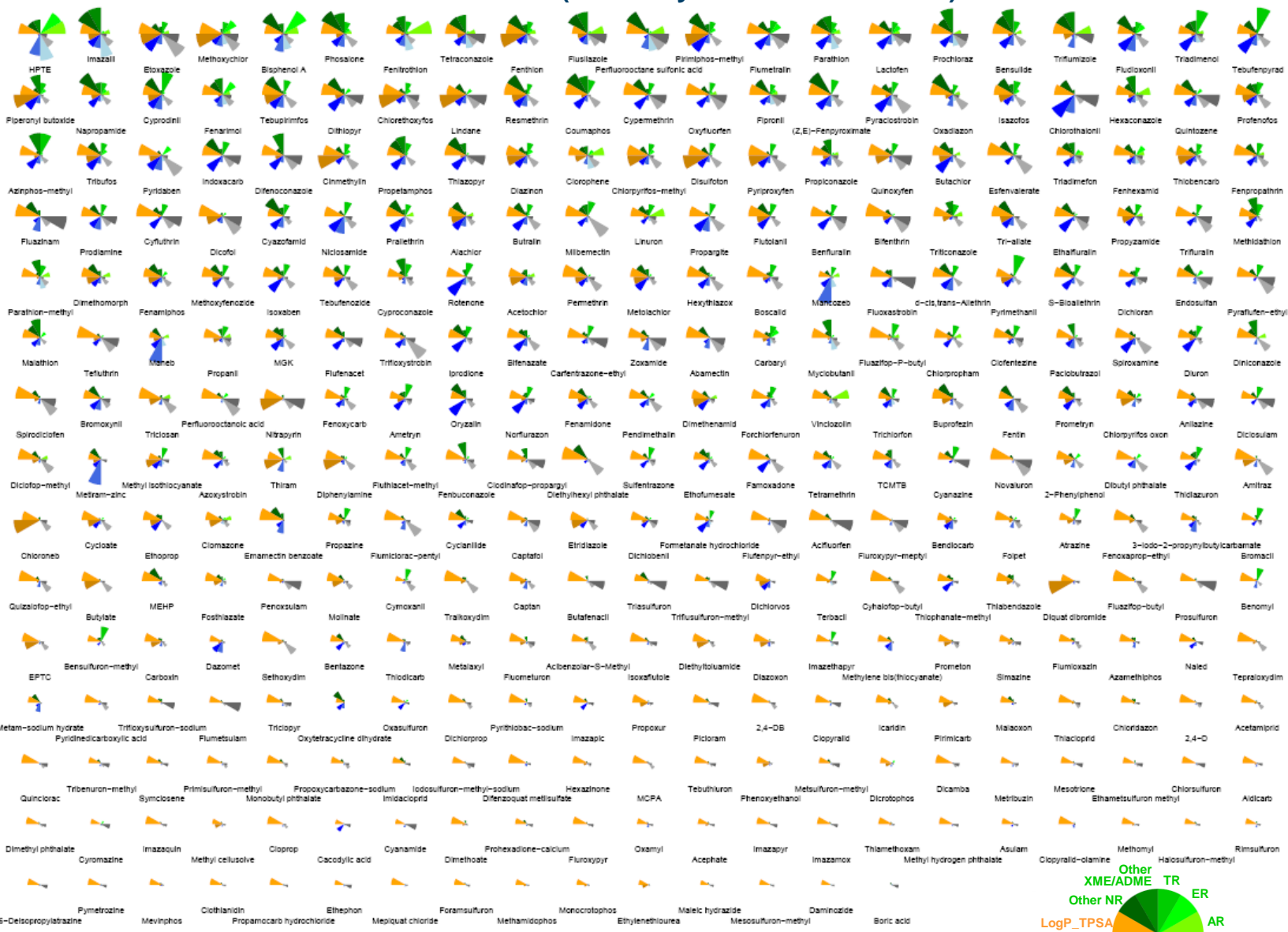


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  - **Bioaccumulation/bioconcentration factor** (Log BCF, Log BAF) from BCFBAF program
  - **Persistence** (half life air, half life water, persistence time) from Level III fugacity model
- Ran EPI Suite™ in batch mode passing chemicals smiles/CAS
- 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)



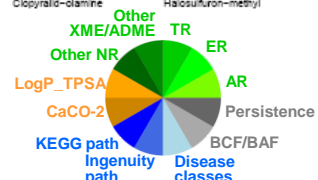
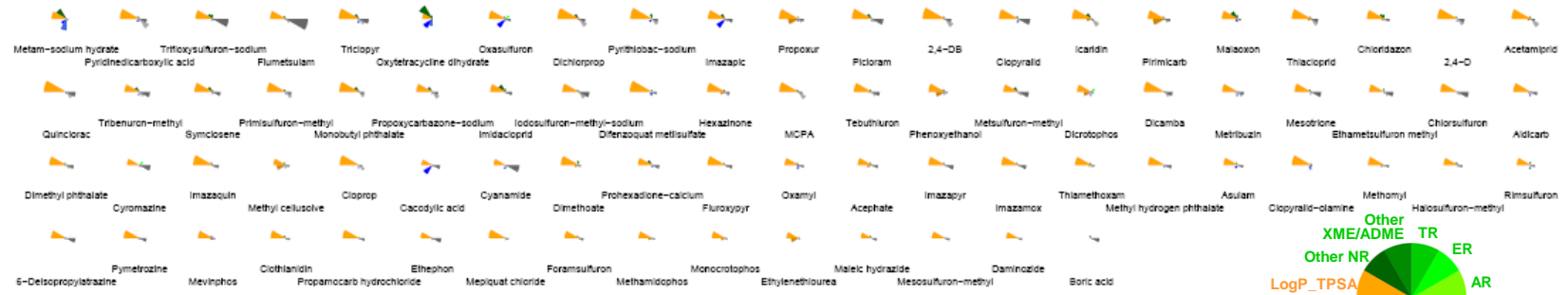
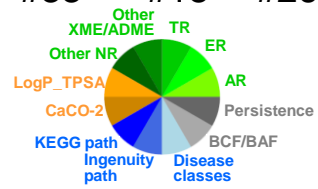
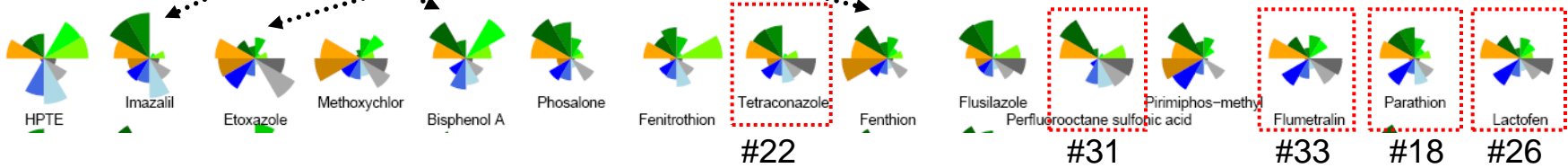
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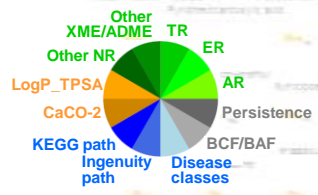
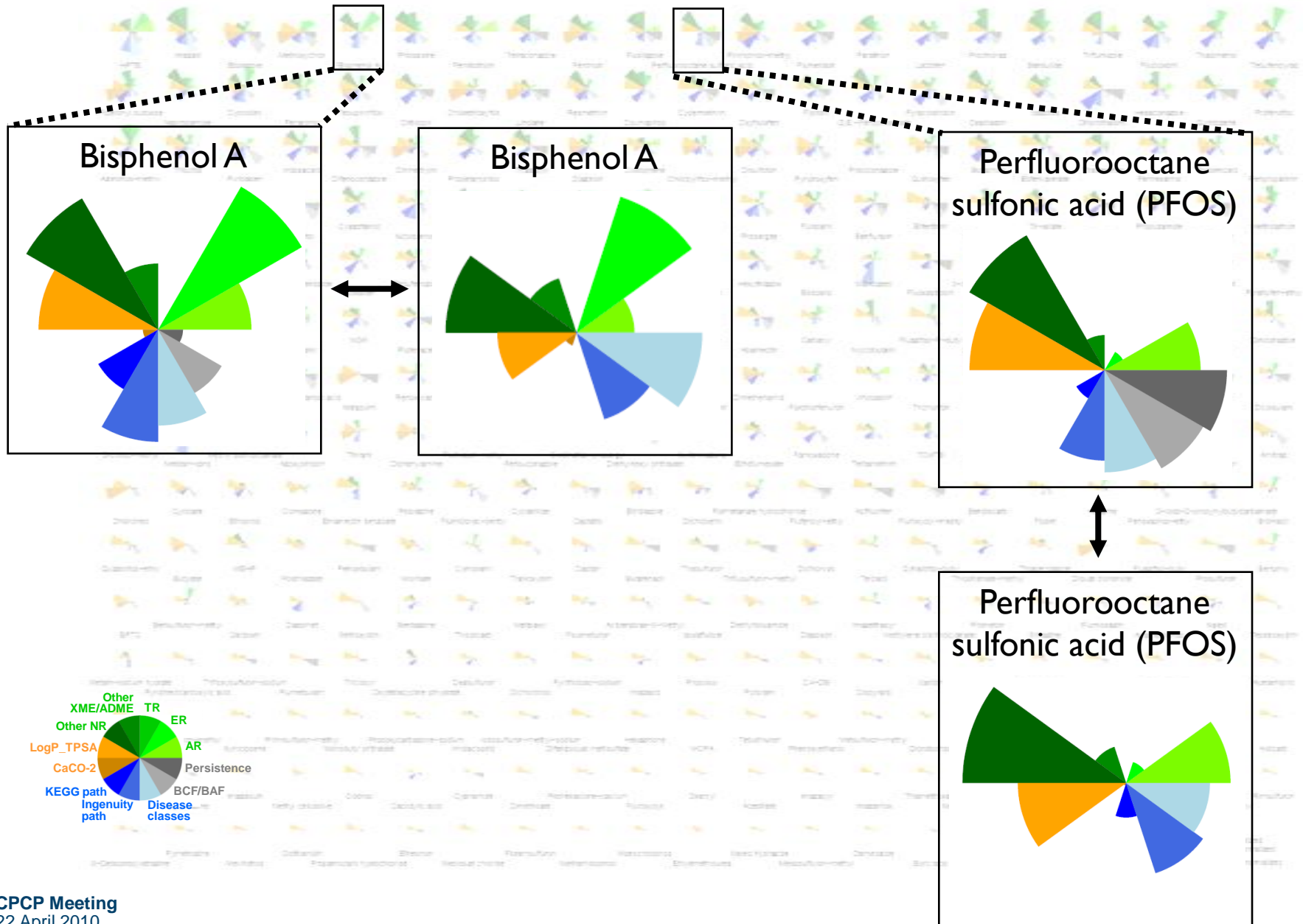
## Previous top 15 prioritized chemicals by overall ToxPi score



## New top 15 prioritized chemicals with exposure domain



# Interpreting ToxPis with exposure domain for individual chemicals





# Conclusions

***This work was reviewed by EPA and approved for presentation but does not necessarily reflect Agency policy***

- 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.)



# Acknowledgments

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**...**

**David Dix**

**Robert Kavlock**

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**National Center for Computational Toxicology  
Office of Research and Development**

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