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Priority Setting: Using new predictive computer models and *in vitro* tools

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Initial Steps (1-3 yrs) Case Study

Case Study: Expert and *In Vitro* Predictive Systems for Hazard Potential

- **Role:** Use for priority setting
- **Goal:** Significantly accelerate screening and effectively determine whether higher tiered animal testing is needed to inform risk management decisions
- **Benefit:** Save resources, save time and maximally draw on all data to ensure those chemicals of greatest hazard potential are given priority for follow-up

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Use new computational toxicology tools to enhance priority setting/screening

Some reduction in animal studies

Tailor data generation

Use understanding of toxicity pathways

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Example: Future EPA Endocrine Screening Disruptor Program Prioritization

- Federal Food, Drug, and Cosmetic Act (FFDCA)
  - Requires EPA to:
    - Develop screening using validated assays to identify pesticides that may have human effects similar to effect produced by naturally occurring estrogen
  - Authorizes EPA to include:
    - Other endocrine effects, as designated by EPA Administrator
    - Other non-pesticide chemicals:
      - Have “an effect cumulative to that of a pesticide”
      - To which a substantial human population may be exposed safe
- Safe Drinking Water Act (SDWA) Amendments
  - Allows EPA to require chemical substances testing found in drinking water sources, if substantial human population may be exposed

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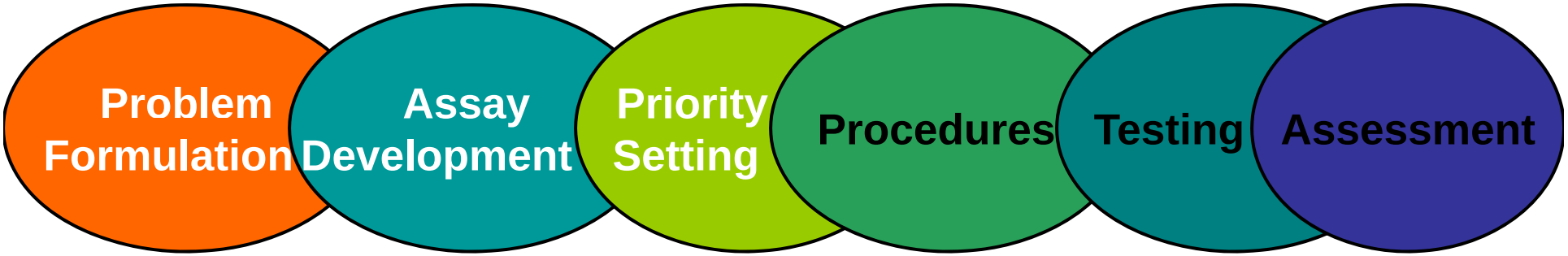

- Problem Formulation: Define nature of stressor, receptor and attribute (assessment endpoints)
- Assay Development : Develop and validate test assays
- **Priority Setting:** Select chemicals to screen
- Procedures: Develop more policies and procedures for testing
- Testing: Tiers 1 and 2
- Assessment : Weight-of-evidence evaluation of results

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Endocrine Disruptor Screening Program Basis

- Broad Chemical Universe Screening and Priority Setting
  Estrogen, androgen and thyroid
  - Human and ecological effects
- 2-Tiered Approach
  - Tier 1
    - *In vitro* and *in vivo* screens
    - Detect potential to interact with endocrine system
  - Tier 2
    - Multi-generation studies covering a broad range
    - Provide data for hazard assessment
- Hazard and Risk Assessment

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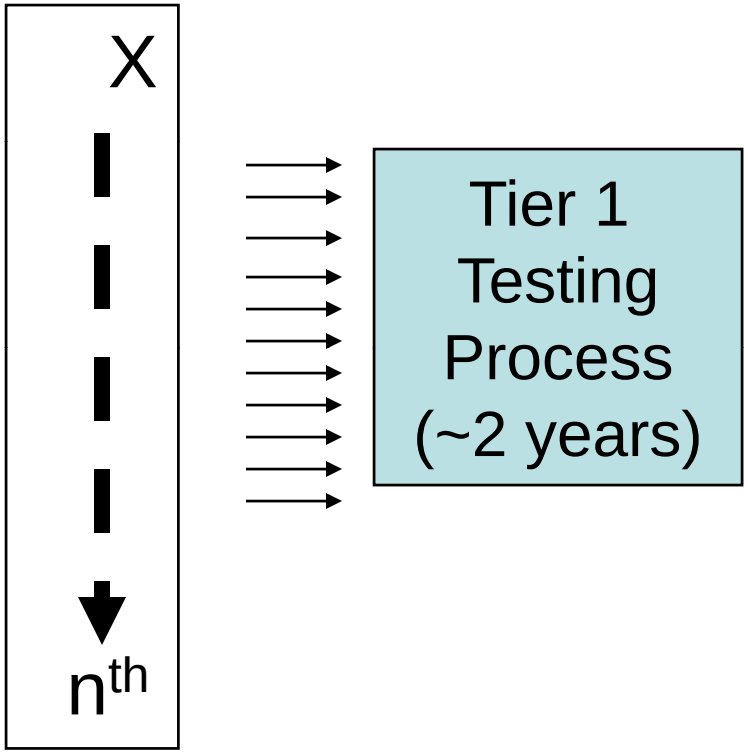
Priority Setting: EDSP Tier 1 Screen

1000's of chemicals

Determine which chemicals should be evaluated early in EDSP program



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Prioritizing Chemicals for Endocrine Disruptor Screening & Testing

- Chemicals without sufficient existing data:
  - Considered by the EDSTAC (USEPA 1998) to have largest number of chemicals and greatest prioritization need
  - EDSTAC (USEPA, 1998) and the SAB/SAP (USEPA, 1999) strongly recommended prioritization that included effects & exposure

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Prioritizing Chemicals for Endocrine Disruptor Tier 1 Screening: Effects

- EDSTAC (USEPA, 1998) recommends use of measured or predicted receptor binding and/or transcriptional activation data derived through *in vitro* assays/High Throughput Screening (HTS) and [Quantitative] Structure-Activity Relationships ([Q]SARs),
- SAB/SAP (USEPA, 1999) agreed but concluded HTS and [Q]SARs were not sufficiently developed at that time and encouraged continued research
- EPA's computational toxicology and endocrine disruptor research programs have been developing *in vitro* assays, HTS applications & [Q]SARs

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Tools: [Q]SAR-Based Expert System to Predict Estrogen Receptor Binding and Thyroid Inhibition

- ORD/OPP collaborative effort
- Focused on chemicals without sufficient data to determine if Tier 2 testing required
- Model's applicability domain – Structures associated with pesticide food use inert ingredients & antimicrobial pesticides

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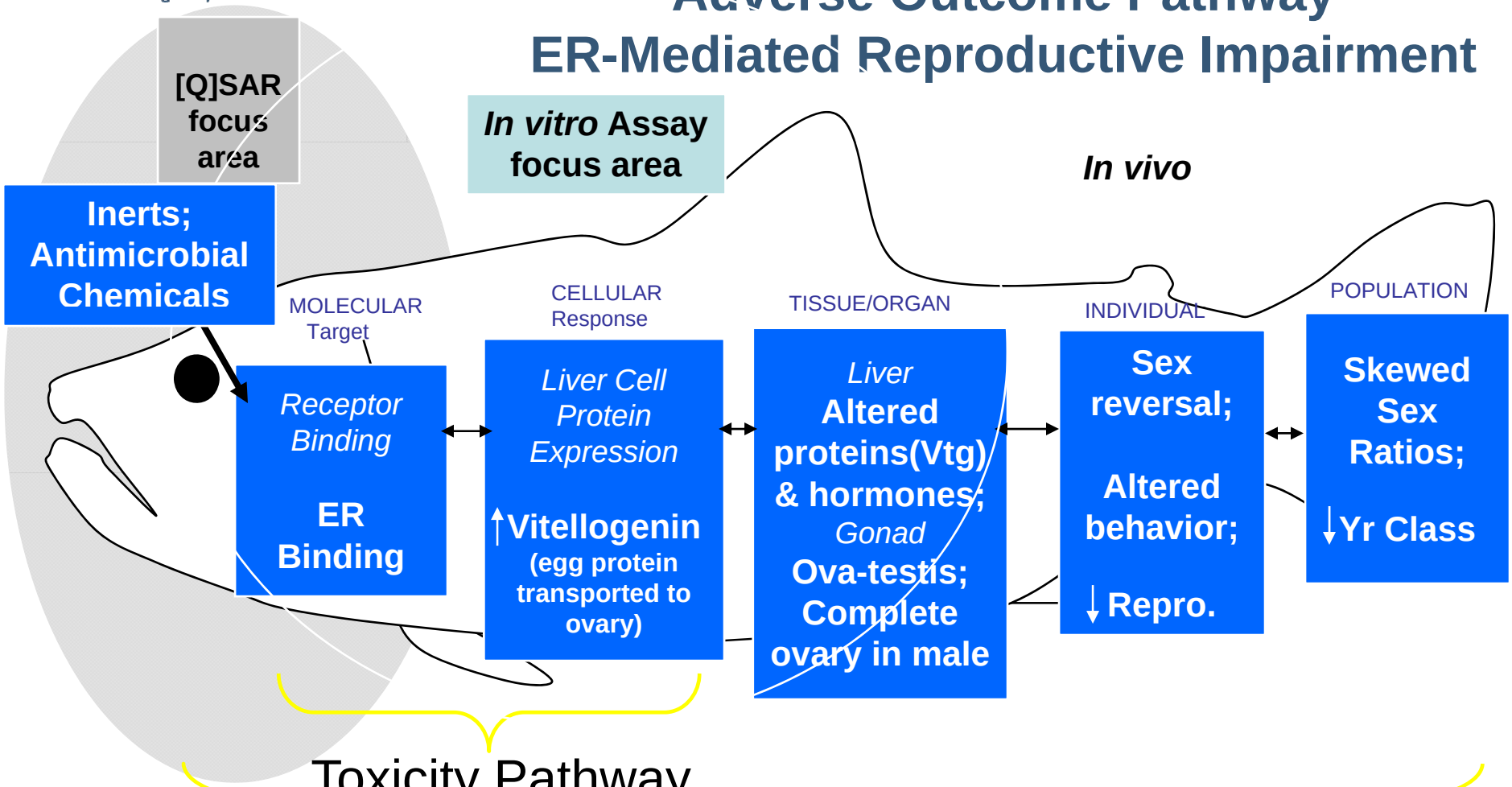
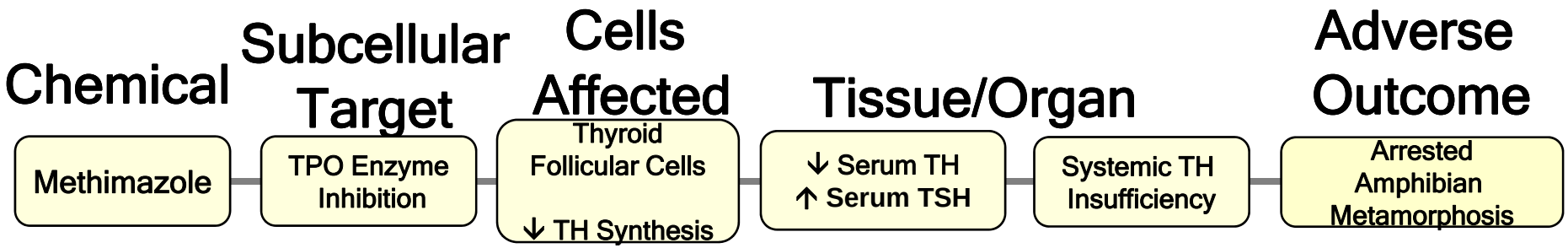
Adverse Outcome Pathway
ER-Mediated Reproductive Impairment

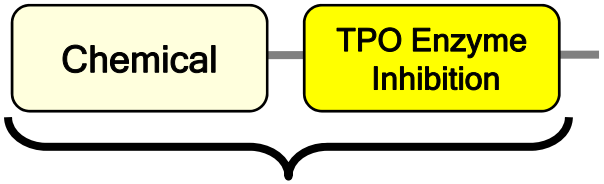


Greater Toxicological Understanding ⟷ Greater Risk Relevance

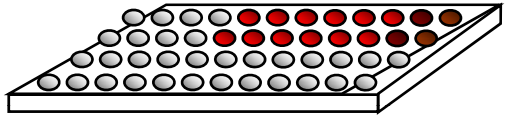
Tools: [Q]SAR-Based Approach to Predict Thyroid disruption – TPO inhibition AOP



***In Vitro* TPO Inhibition Assay**

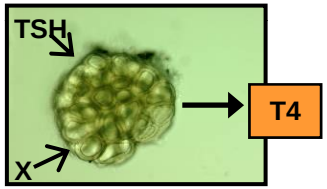


Molecular Initiating Event
Chemical + Cellular Target



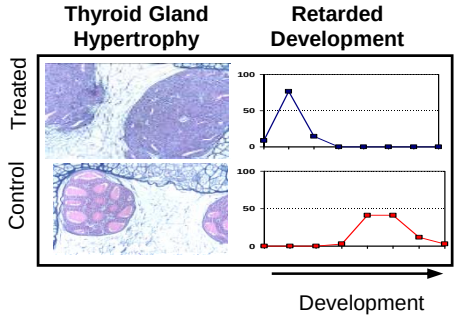
Develop [Q]SAR

Thyroid Gland Culture Assay:



Verify TH Synthesis Inhibition

Amphibian Metamorphosis Assay



***In Vivo* Verification of Adverse Outcome**

Adverse Outcome Pathway for Thyroid Peroxidase (TPO) Inhibition

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

- Purpose: Develop a cost-effective approach for efficiently prioritizing the toxicity testing of thousands of chemicals
- Uses data from high-throughput screening (HTS) bioassays
- Builds statistical and computational models to forecast potential chemical toxicity [in humans]
- Screened over 300 chemicals (primarily pesticides) in over 500 endpoints
- Currently screening a more diverse group of 700 additional chemicals

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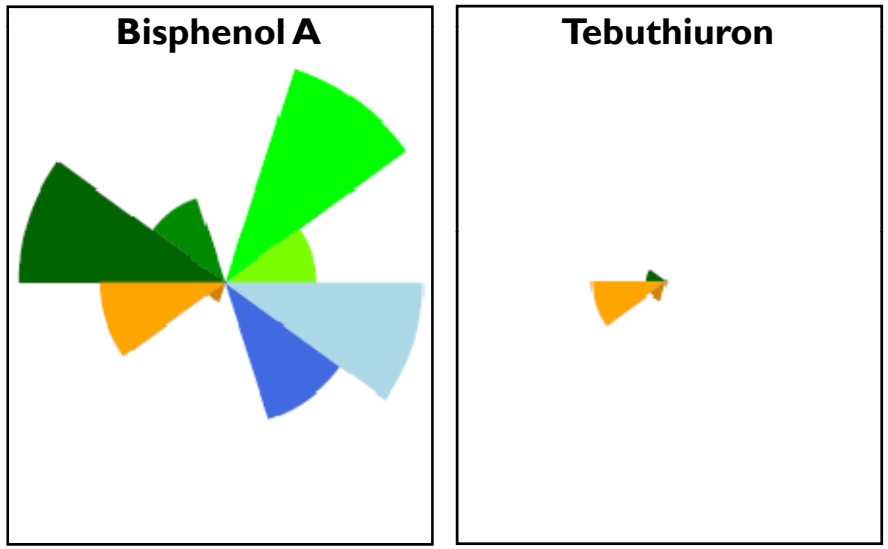
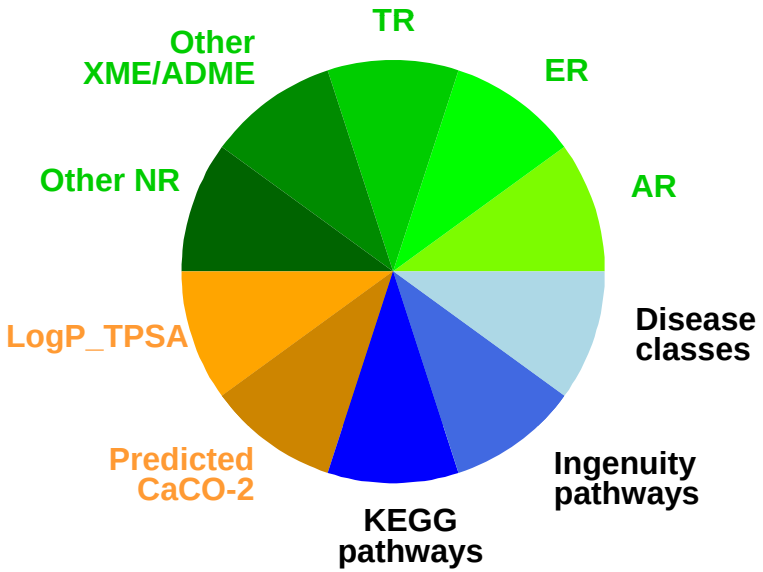
Prioritization Index = ToxPi = f(*In vitro* assays + Chemical properties + Pathways)





- ToxPi calculated from weighted combination of all data sources for a chemical
- Slice size indicates relative rank or score for each chemical
- Distance from origin is proportional to normalized value (*e.g.* assay potency or predicted permeability)
- Width indicates the relative weight of slice in overall ToxPi calculation

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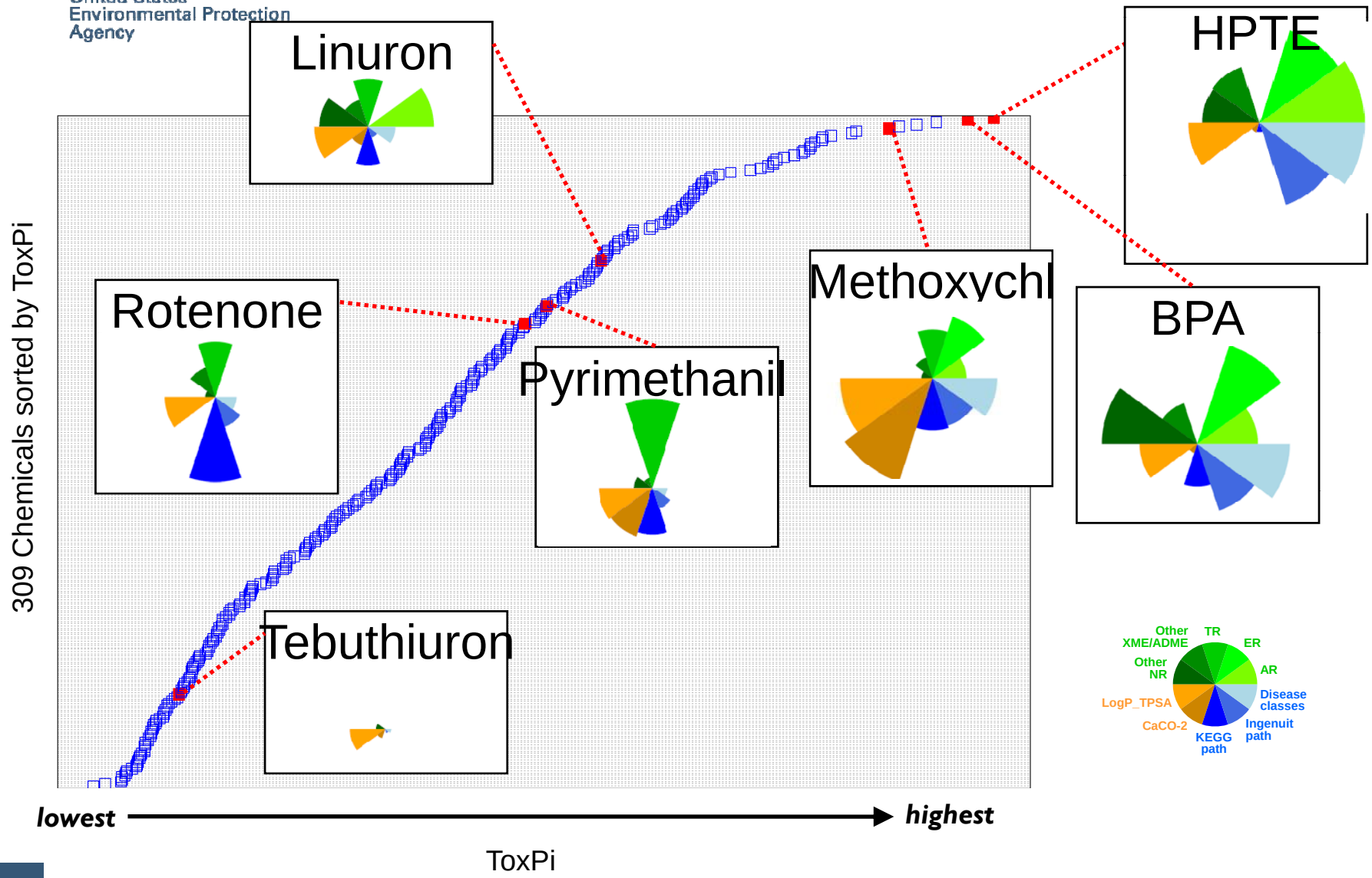

Example ToxPi Rankings from ToxCast Phase I

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Future Prioritization for EDSP Tier 1 Screening

- Inert ingredients & other chemicals
  - Develop *in vitro & in silico* tools that are integrated with exposure-based metrics
- Pesticide active ingredients
  - Plan is to use EPA's schedule for re-evaluating registered active ingredients in the Registration Review program (http://www.epa.gov/oppsrrd1/registration_review/)
- Consistent with EDSTAC & SAB/SAP recommendations

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Integrative Approaches to Testing and Assessment