# Identifying Biological Hazards of Contaminants of Emerging Concern

## State of the Science

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**The contents of this presentation neither represent nor necessarily reflect official US EPA policy.*

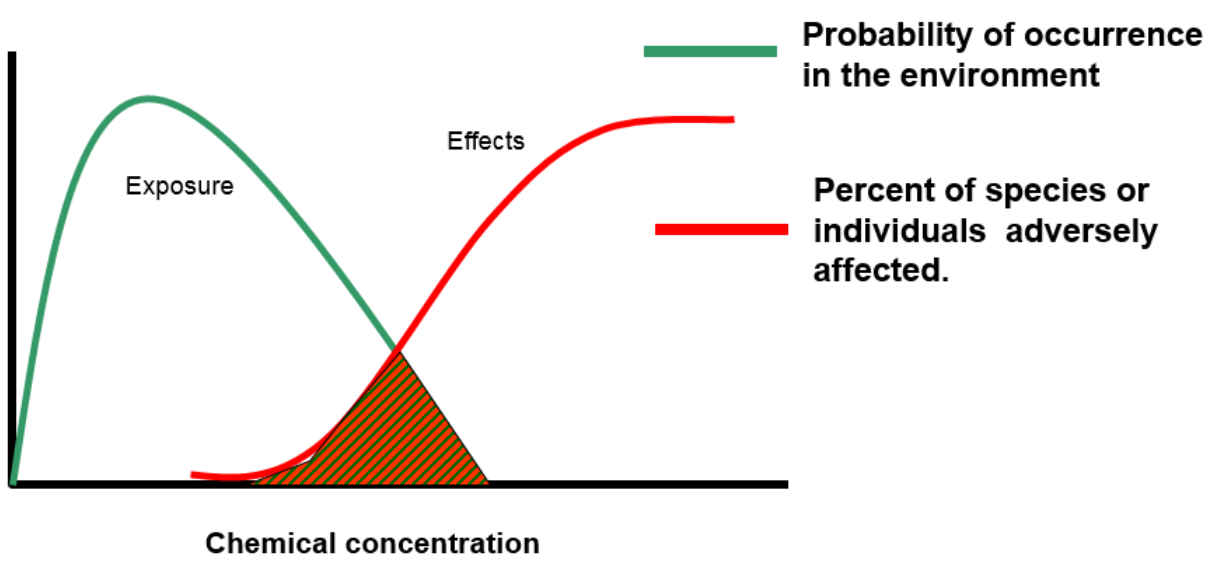
# Key Science Question:

1. Which classes of CECs**, including those with data gaps**, have the potential to impact adversely marine, estuarine, and freshwater wildlife, ecosystems, and beneficial uses of these aquatic environments?

- Monitoring is expensive and challenging, where can we best allocate the limited resources that are available?
- How can we take full advantage of the range of toxicity data sources available to set priorities and/or eliminate concerns?

# Challenge:

- Continually expanding the list of analytes monitored and/or detected in the environment
- Traditionally compare measure/predicted environmental concentrations (MEC/PECs)[a] with "monitoring trigger levels" (MTLs)[a] based on adverse effect concentrations from animal-based toxicity tests.

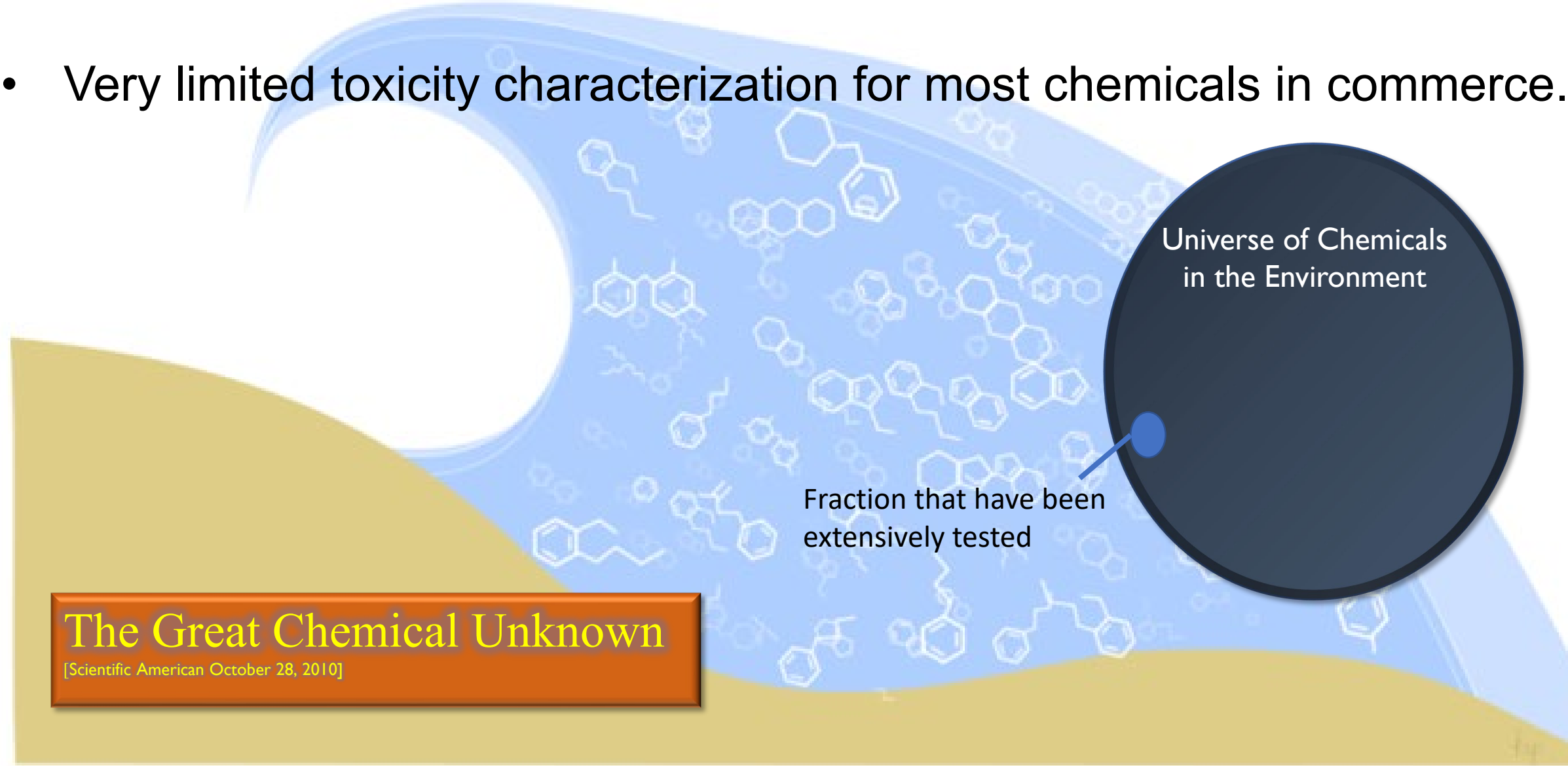



$$\text{Monitoring trigger quotient} = \frac{\text{MEC or PEC}}{\text{MTL}}$$

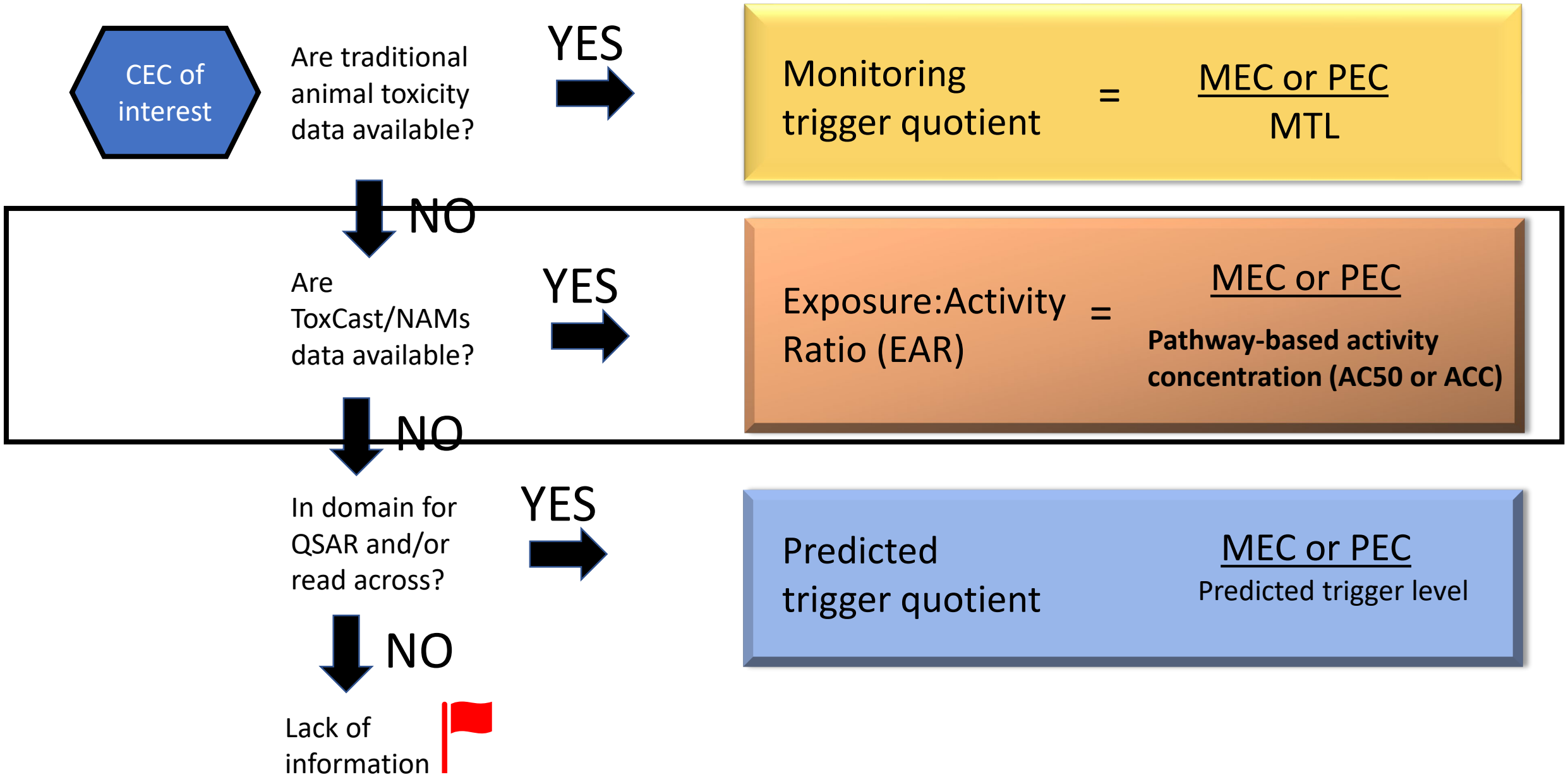
[a] *Southern California Coastal Water Research Project (SCCWRP). 2012. Technical Report 692 – Monitoring strategies for chemicals of emerging concern (CECs) in California's aquatic ecosystems – recommendations of a scientific advisory panel.*

# Challenge:

- Very limited toxicity characterization for most chemicals in commerce.



# CECs with Data Gaps

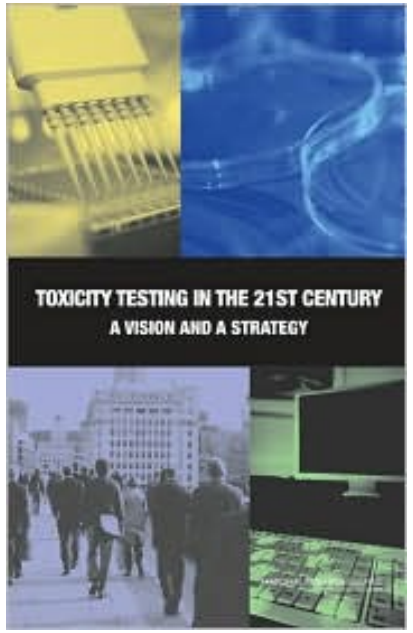


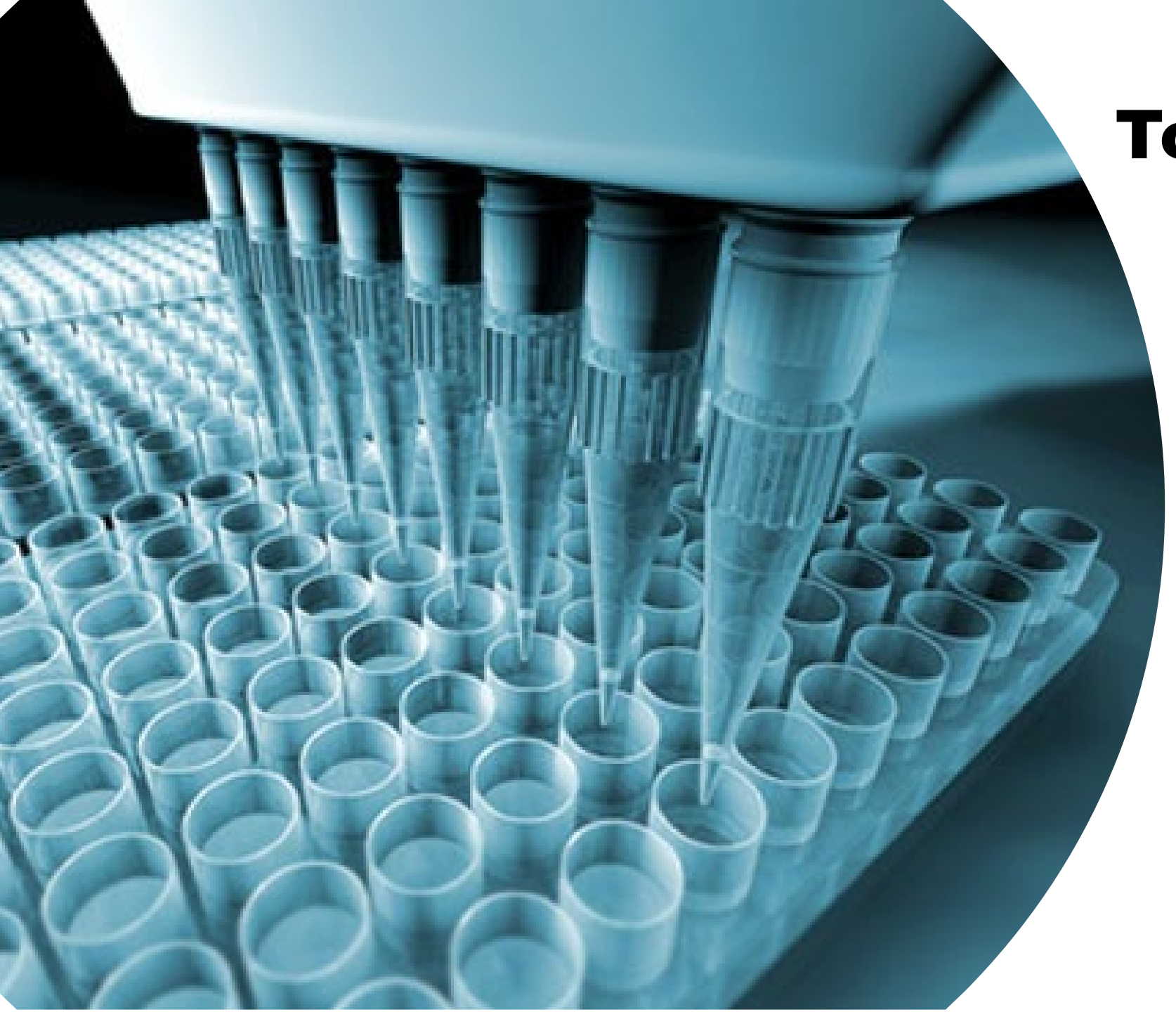
# New approach methods – high throughput screening

"Transform toxicity testing from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin"

"The vision emphasizes the development of suites of predictive, high-throughput assays ….."

"The mix of tests in the vision include tests that assess critical mechanistic endpoints involved in the induction of overt toxic effects rather than the effects themselves."



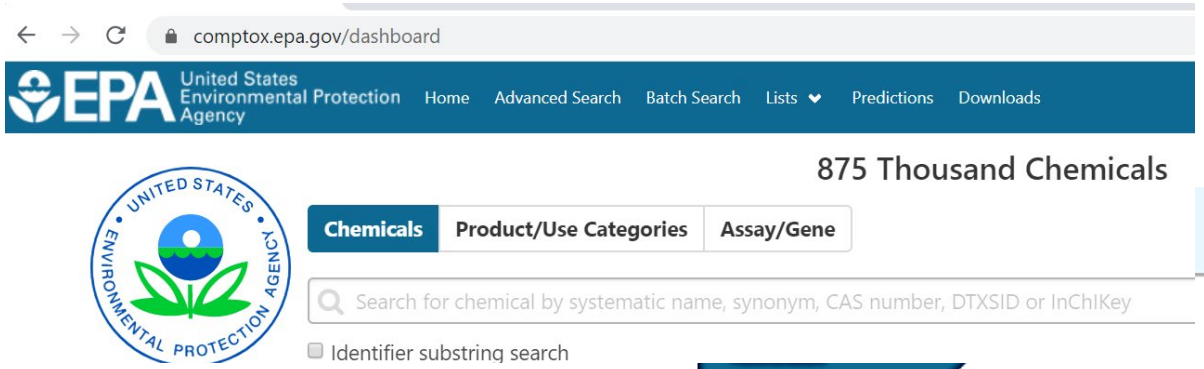


# ToxCast™

Tox21

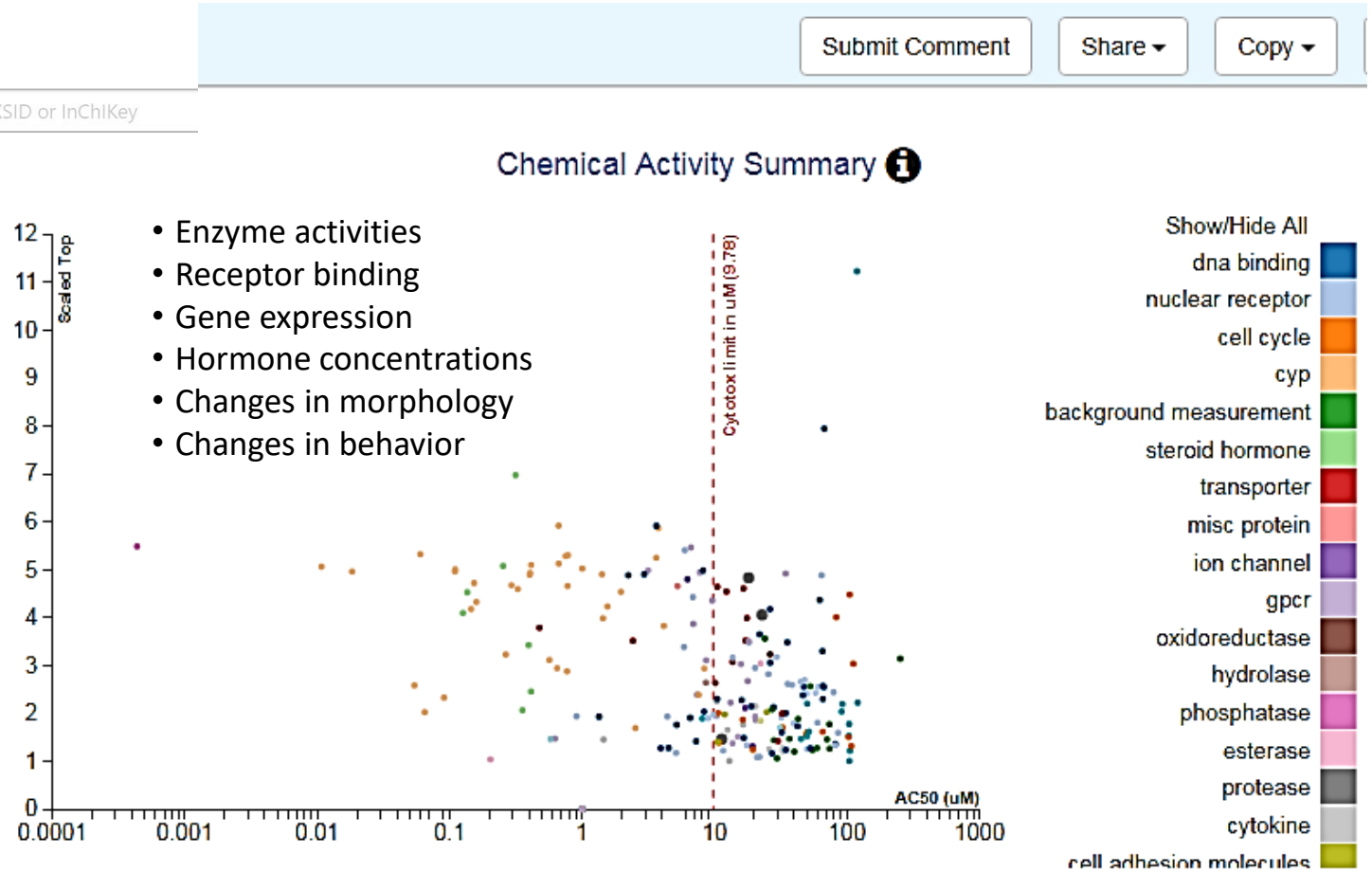
- 1570 assay endpoints
  - Enzyme activities
  - Receptor binding
  - Gene expression
  - Hormone concentrations
  - Changes in morphology
  - Changes in behavior
- Over 10,000 chemicals tested

# Publicly accessible source of information




## Comptox.epa.gov/dashboard

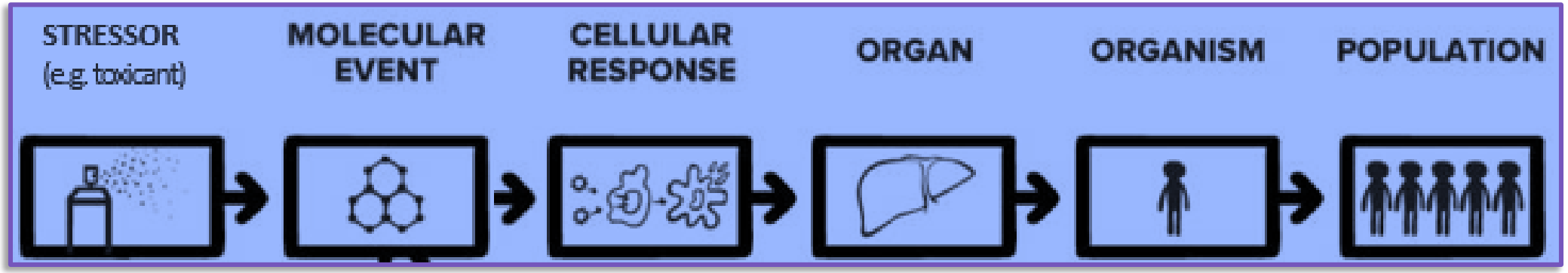
- What chemicals can do biologically (mode of action)
- Grouping by MOA
- At what concentrations (potency)

Medical diagnostic tests

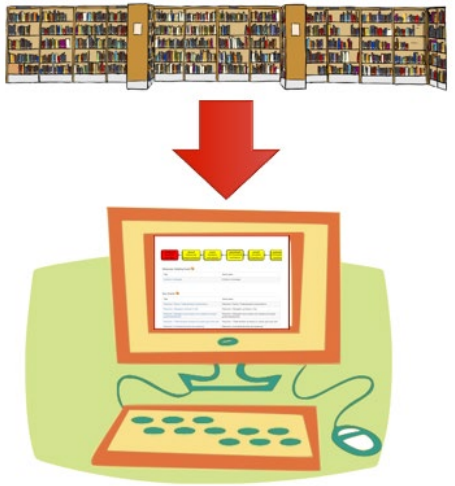
Doctors explain to patients, what the results of those tests mean relative to health.


# Adverse Outcome Pathways




- **Organize and assemble the specialized scientific knowledge required to interpret results from new approach methodologies (NAMs).**

- Present it in a simple to follow graphical and narrative format
  - Supported by scientific literature and evidence
  - Searchable, globally accessible, and transparent

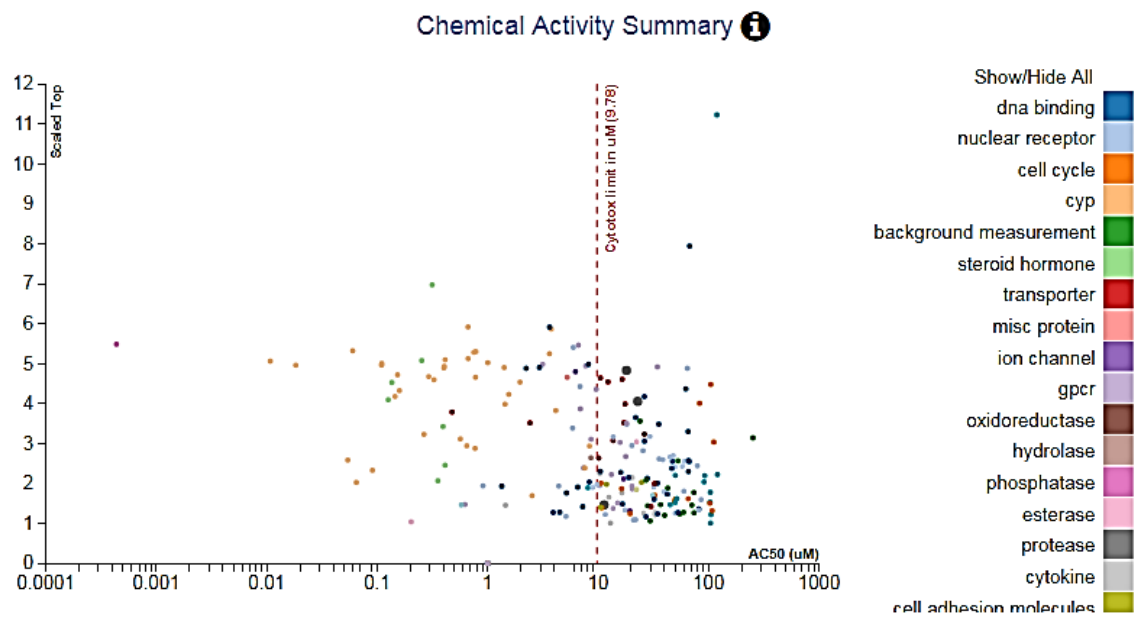


AOP-Wiki.org

# New Approach Methodologies

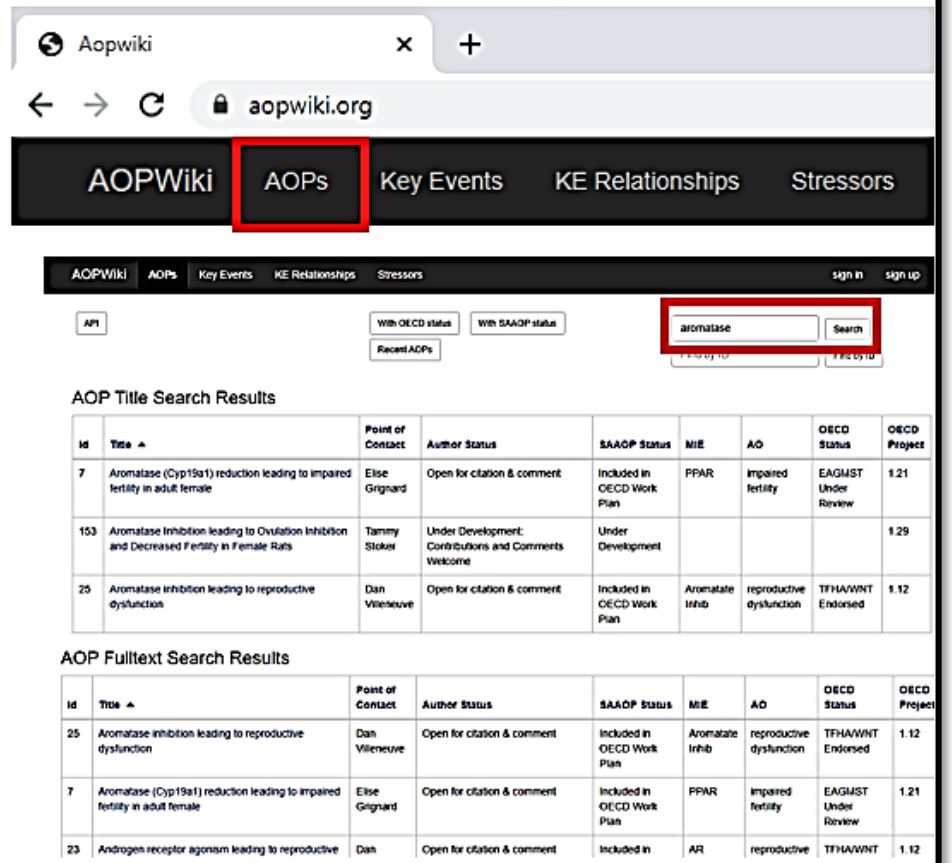
**What can this chemical do biologically?**

**Comptox.epa.gov/dashboard**

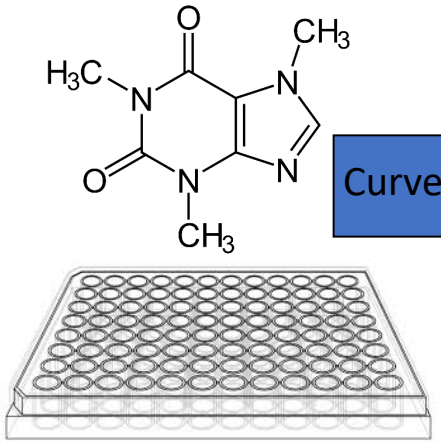



**Why does that matter?**

AOPwiki.org

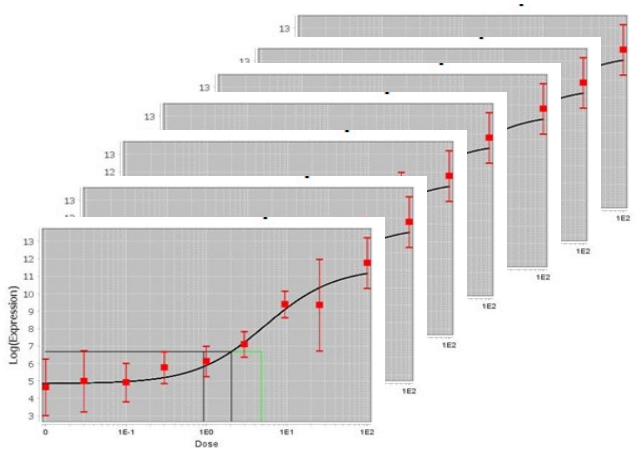


# New Approach Methodologies






Curve fitting




Dose-response in many assays

Exposure:Activity Ratio (EAR) = MEC or PEC

**Pathway-based activity concentration (AC50 or ACC)**

# Tool to Aid Calculation of MTLs/EARs

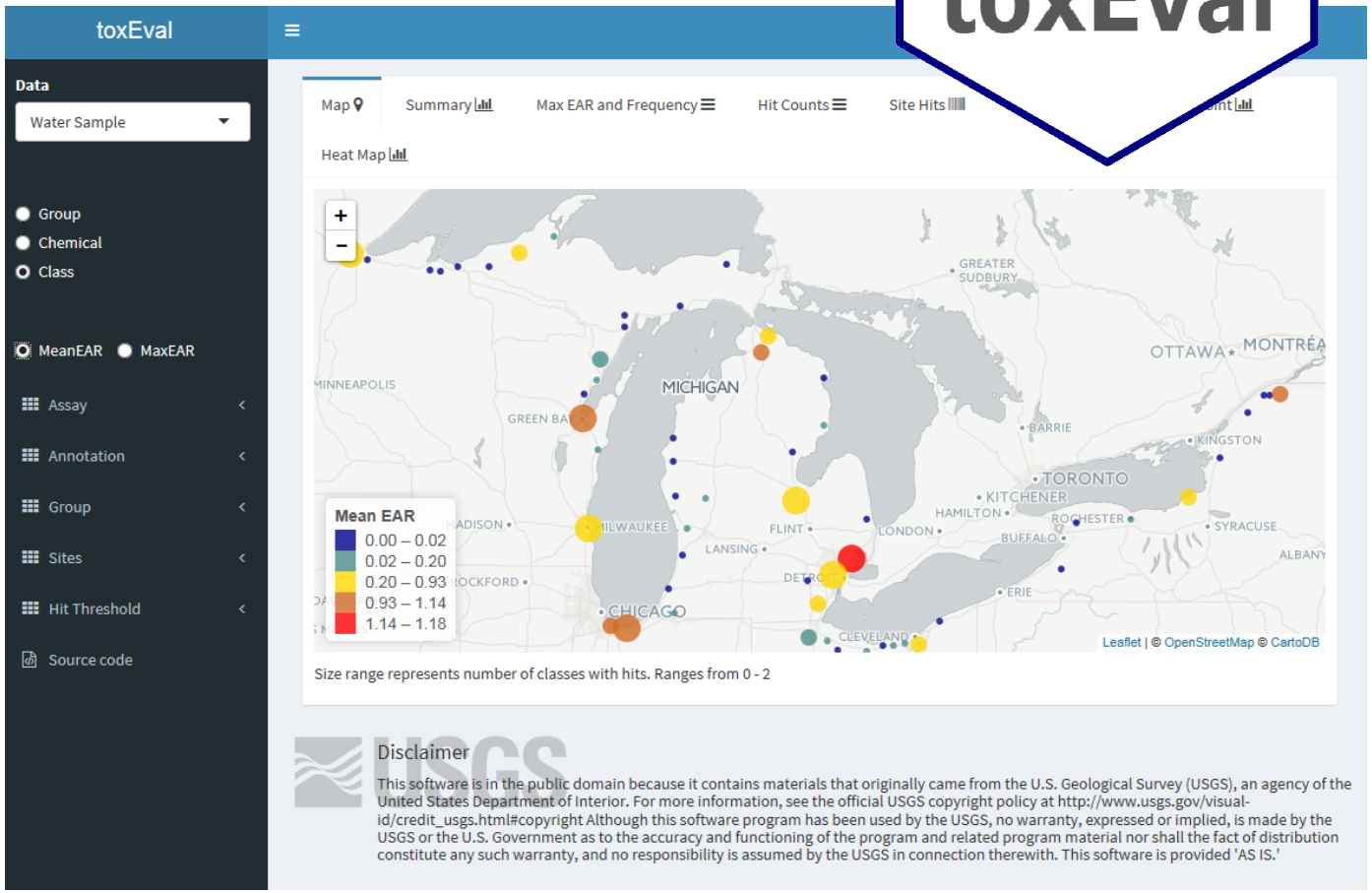
- EARs rapidly calculated and visualized using toxEval

  - Simple concept, simple calculations
  - Not as simple for a matrix of 300 chemicals x 1570 assay endpoints
  - Compute and visualize

Intended audience:

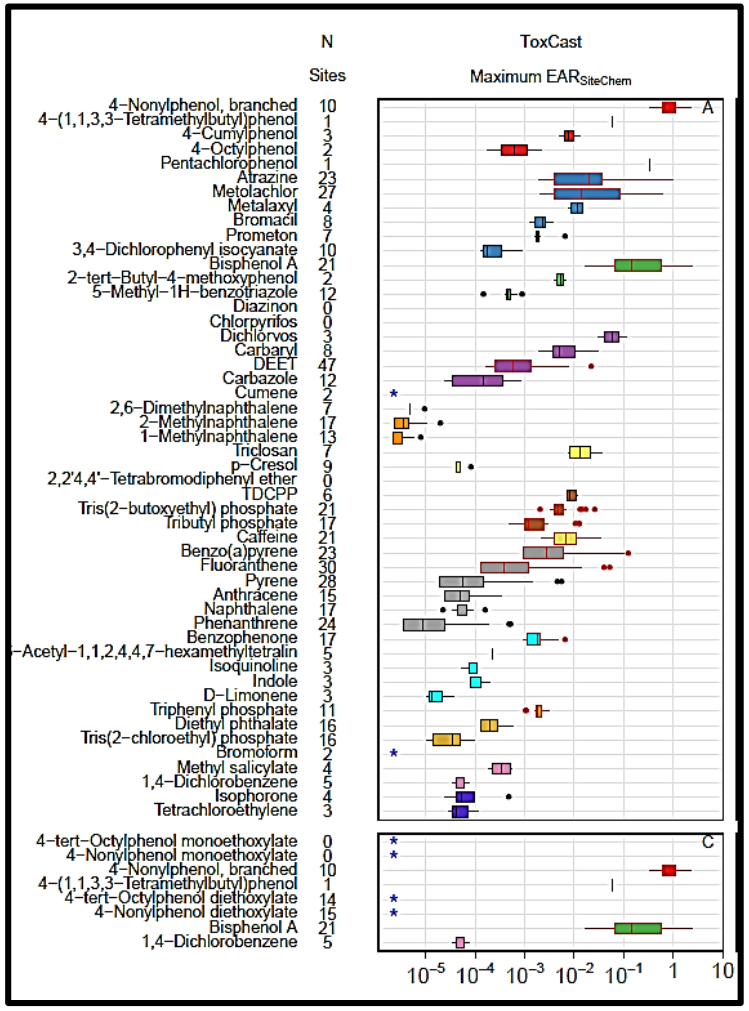
Regulators and resource managers (federal, state, local)
Researchers (government, academia, industry, NGO)

https://github.com/USGS-R/toxEval



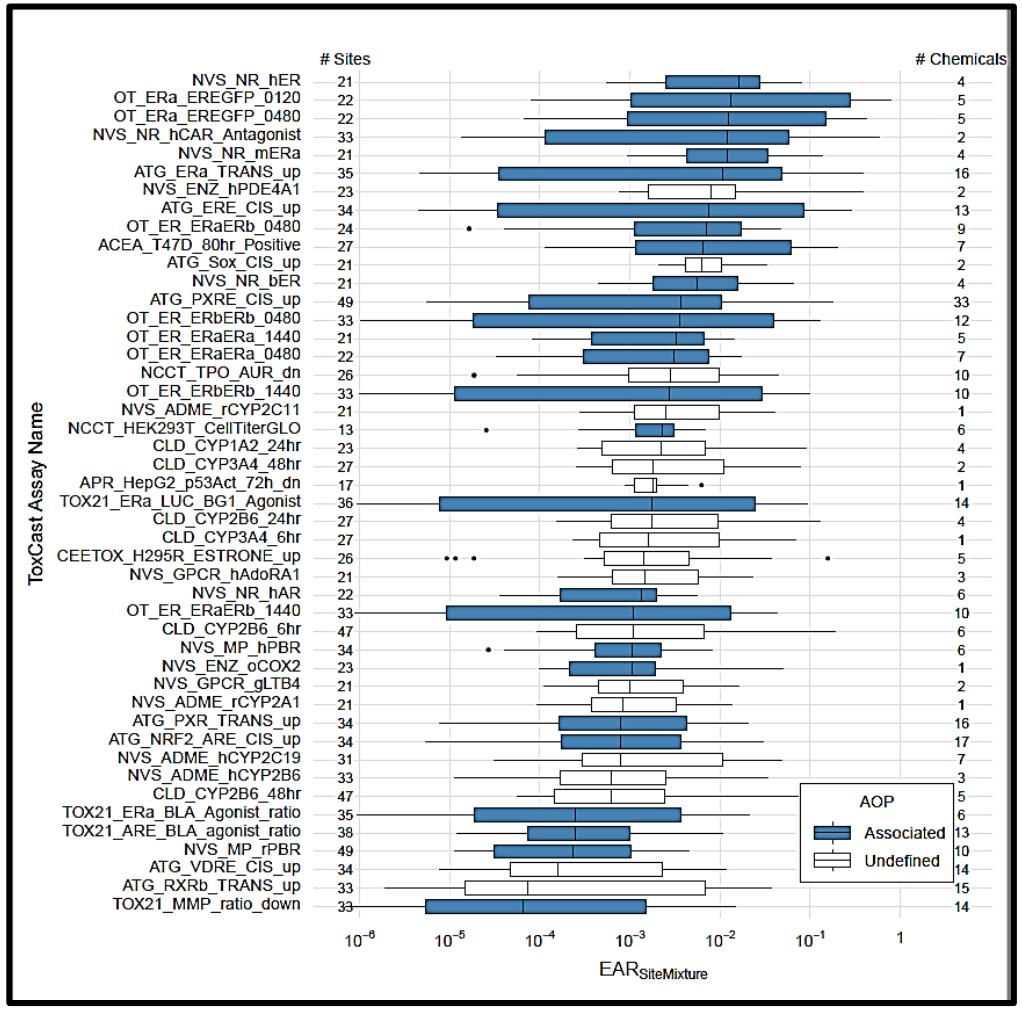
# Risk-based screening & prioritization – detected CECs

## Which chemicals?



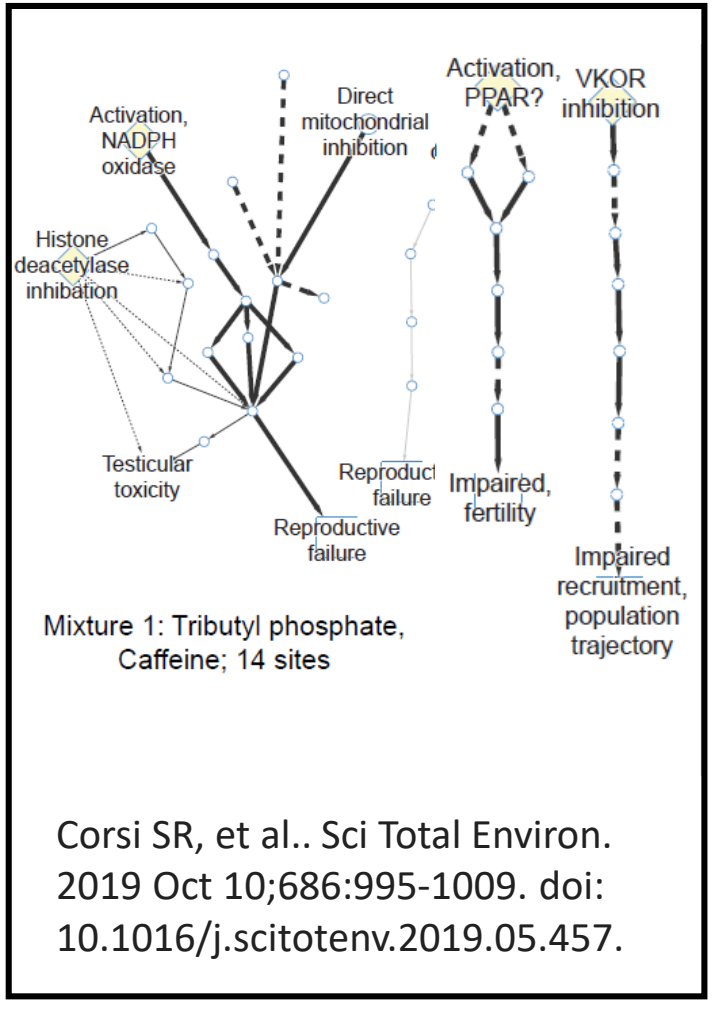

*Nominating as CMCs*

## Which biological pathways?




*Which bioassays to use for effects-based monitoring*

## What adverse effects might occur?



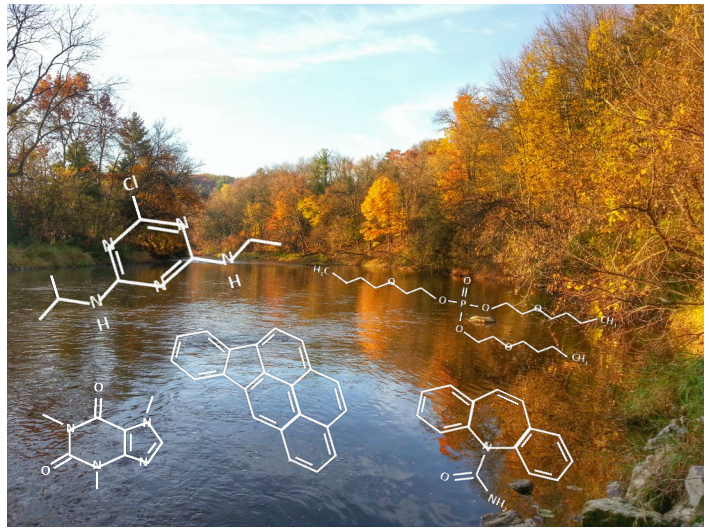

Corsi SR, et al.. Sci Total Environ. 2019 Oct 10;686:995-1009. doi: 10.1016/j.scitotenv.2019.05.457.

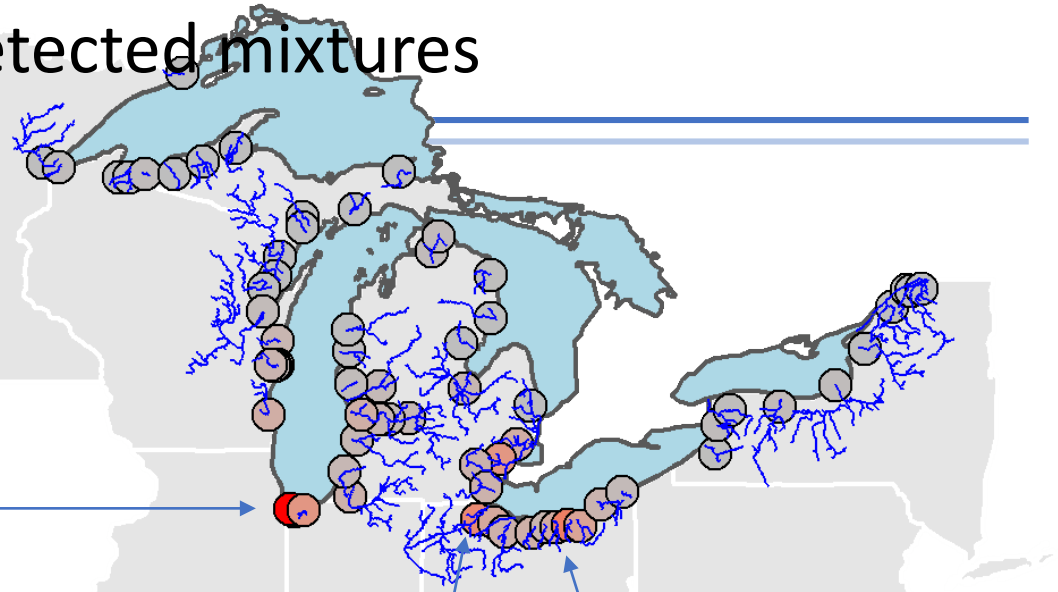
*Effects in resident organisms*

# Risk-based screening and prioritization – detected mixtures

## Summed EAR for mixtures

- Chemicals detected and evaluated in ToxCast







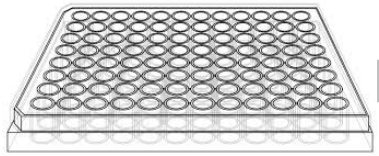

Alvarez et al. 2020 (in prep.)

# Effects-based screening and prioritization – accounting for unknowns

**Known components**

**Unknown components**

**Chemical Mixture**



Laboratory bioassay
(Concentration-response)

Most sensitive effect to set trigger level

Sensitive pathway(s) to infer dominant mode(s) of action

**Integrated potency estimate (non-specific)**

**Integrated potency estimate[s] (pathway-specific)**

**AOP-based hazard inference**

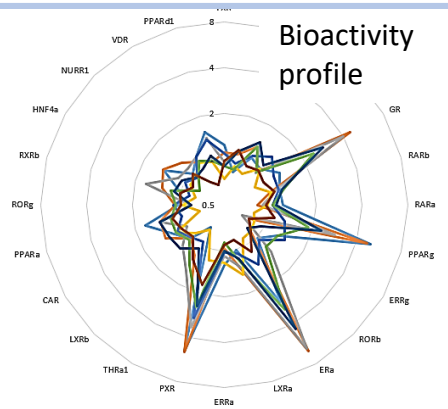
**$BEQ_{bioassay}$ vs. $BEQ_{analytical}$**

Apical hazard(s) that may be associated with exposure to the mixture

Inferring whether known constituent are the drivers.

# Effects-based screening and prioritization: Example

sample




Adverse Outcome Pathway Wiki

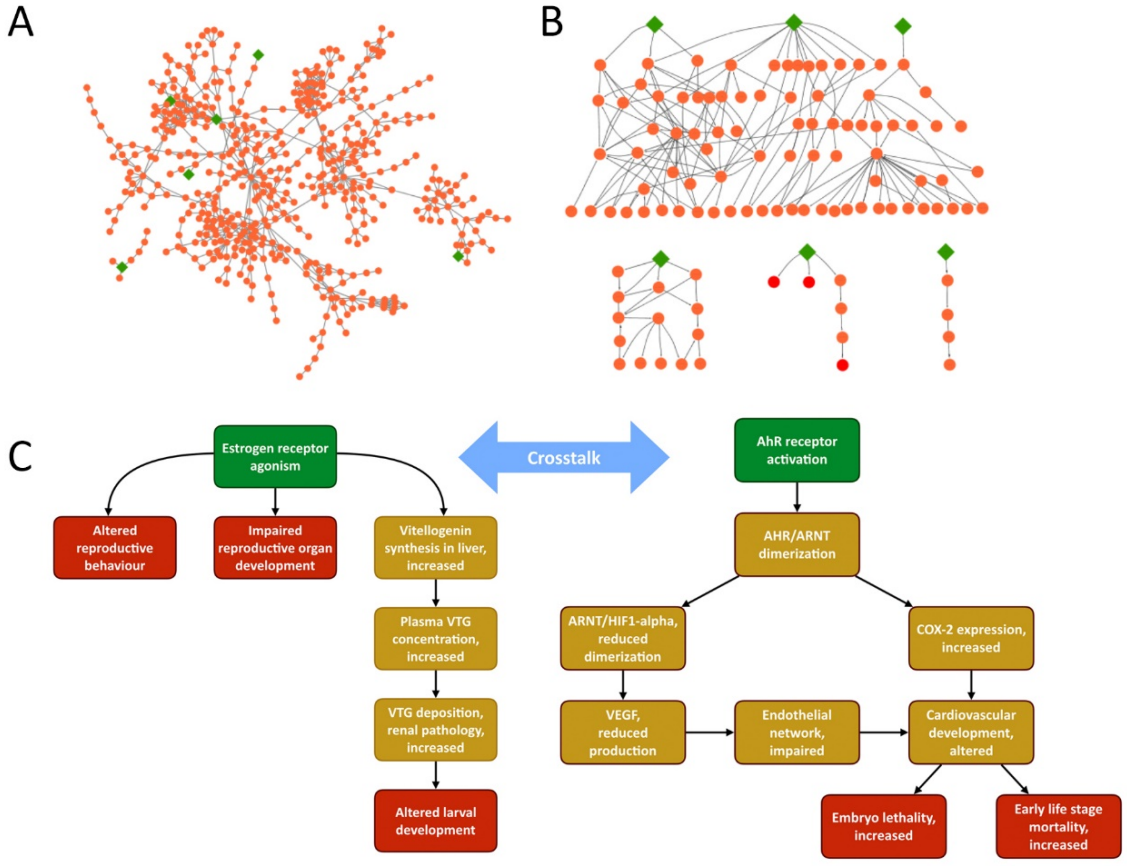
Knapen D, et al. Adverse outcome pathway networks I: Development and applications. *Environ Toxicol Chem*. 2018;37(6):1723-1733. doi:10.1002/etc.4125

**A.** 6 MIEs identified as hits by Attagene assay are KEs in global AOP network.

**B.** Network filtered to subset of AOPs directly linked to the 6 MIEs

**C.** Further filtered by taxonomic applicability.

Embryolethality
Reproductive hazard



# Conclusions

1. Which classes of CECs**, including those with data gaps**, have the **potential to impact adversely** marine, estuarine, and freshwater wildlife, ecosystems, and beneficial uses of these aquatic environments

- Data from new approach methodologies can support a risk-based prioritization when traditional toxicity data are lacking.
    - Considering relative concentrations and potency

- Scientific knowledge organized as adverse outcome pathways can aid interpretation/translation of pathway-based data into potential adverse effects

# Conclusions

- Pathway-based data can aid evaluation of mixtures of detected contaminants as well as mixtures of unknown composition.

- Can be used to prioritize (or deprioritize) chemicals and/or sites/sources for research, monitoring, or management activities.

- These data sources and approaches, while evolving, are sufficiently developed to be integrated into CEC monitoring strategies – many are conducted in a highly standardized manner.

# Post-doctoral opportunities

1. **Ecological Effects of Per- and Poly-Fluorinated Alkyl Substances (PFAS)**
   - Contact: Villeneuve.dan@epa.gov
   - URL: https://zintellect.com/Opportunity/Details/EPA-ORD-CCTE-GLTED-2020-08-A

2. **Analytical methods for evaluating toxicokinetics of per- and poly-fluorinated alkyl substances (PFAS) in challenging sample matrices.**
   - Contact: Blackwell.Brett@epa.gov
   - URL: https://zintellect.com/Opportunity/Details/EPA-ORD-CCTE-GLTED-2020-11-A

3. **University of Wisconsin-Madison – U.S. Environmental Protection Agency Fellowship with a focus on PFAS toxicology**
   - Contact: jennifer.hauxwell@aqua.wisc.edu