United States Environmental Protection Agency

# OMICS FOR ENVIRONMENTAL SCIENTISTS, ENGINEERS, AND REGULATORS: AN INTRODUCTION

# LABORATORY-BASED CASE STUDIES

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# Current issues common across regulations

- Occurrence vs. exposure
  - Chemical in water or tissue
  - Interactions - Mixtures
  - Nonchemical stressors e.g. DO
- Lamp post
  - Look for what you can look for
- Apical endpoints
  - Uninformative
- Practical limitations
  - Extrapolation
    - In vitro → In vivo
    - Chemical → chemical
    - Models → Non model

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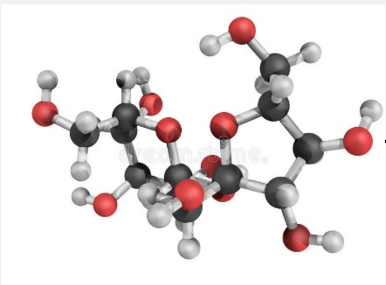
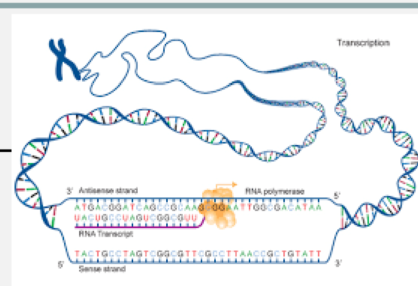
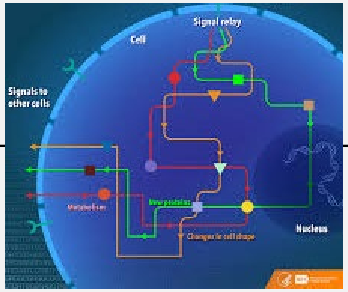
# Linkage of exposure to apical effect

Occurrence | Exposure

Apical Effect





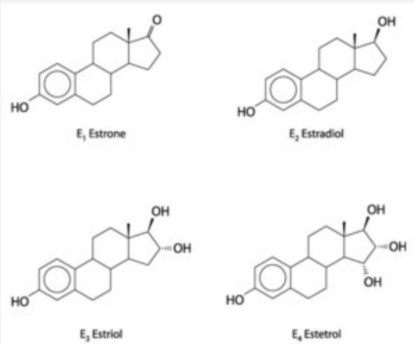

Develop classifie

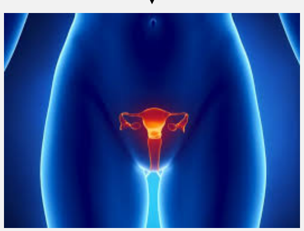
| Toxicant | Macro-Molecular Interactions | Cellular Responses | Organ Responses | Organism Responses | Population Responses |
|---|---|---|---|---|---|
| Chemical Properties | Receptor/Ligand Interaction | Gene activation | Altered Physiology | Lethality | Structure |
| | DBA Binding | Protein Production | Disrupted Homeostasis | Impaired Development | Extinction |
| | Protein Oxidation | Altered Signaling | Altered tissue development/ function | Impaired Reproduction | |


Patterns of up and down regulation of gene expression

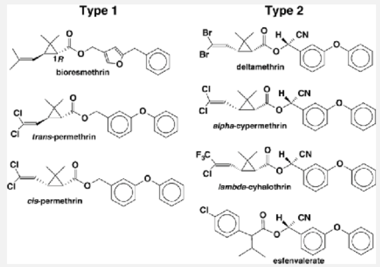
- Fingerprint
- Relate exposure to activated MOA
- Predictive of apical effect

# Create panel of biomarkers capable of discriminating MOA

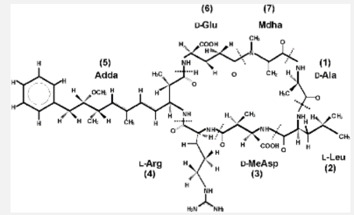


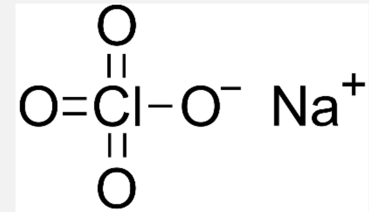
Estrogenic




Neurotoxic

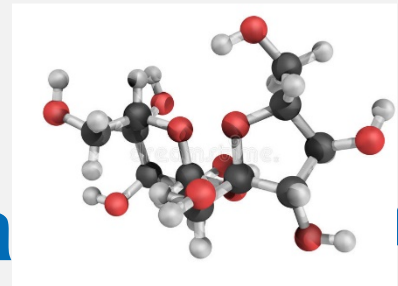



Hepatotoxic

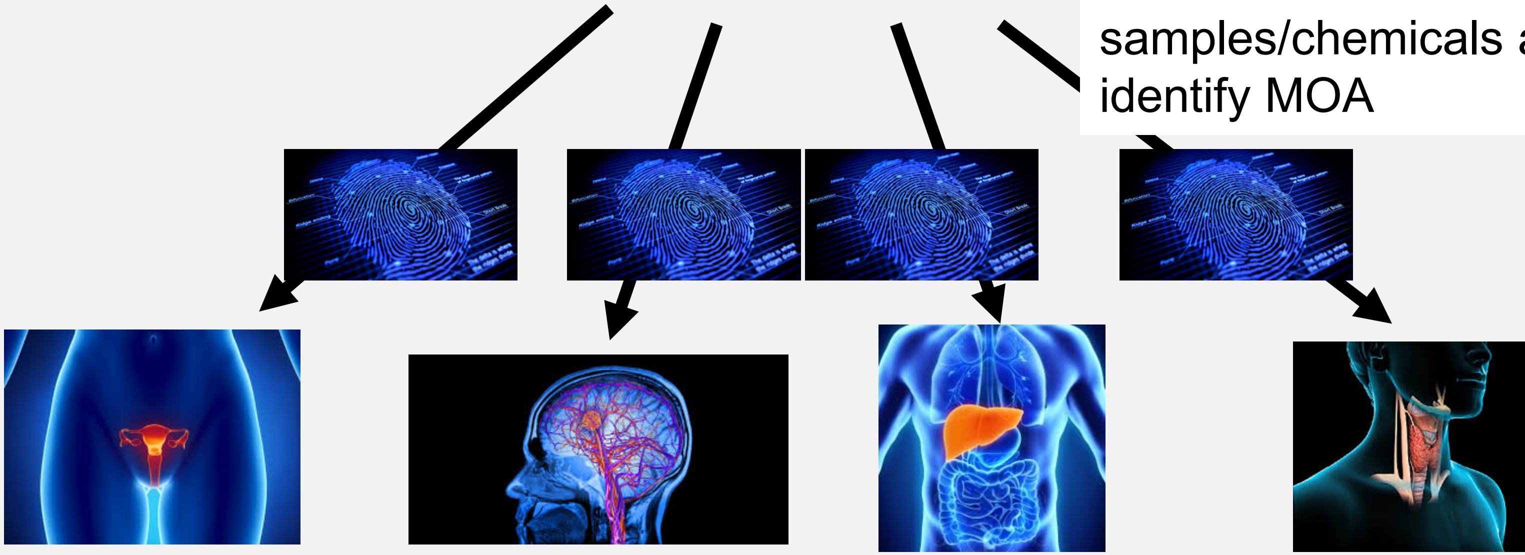



Thyroid active

# Create panel rkers capable of discrimina A



Able to screen unknown or uncharacterized samples/chemicals and identify MOA



Estrogenic

Neurotoxic

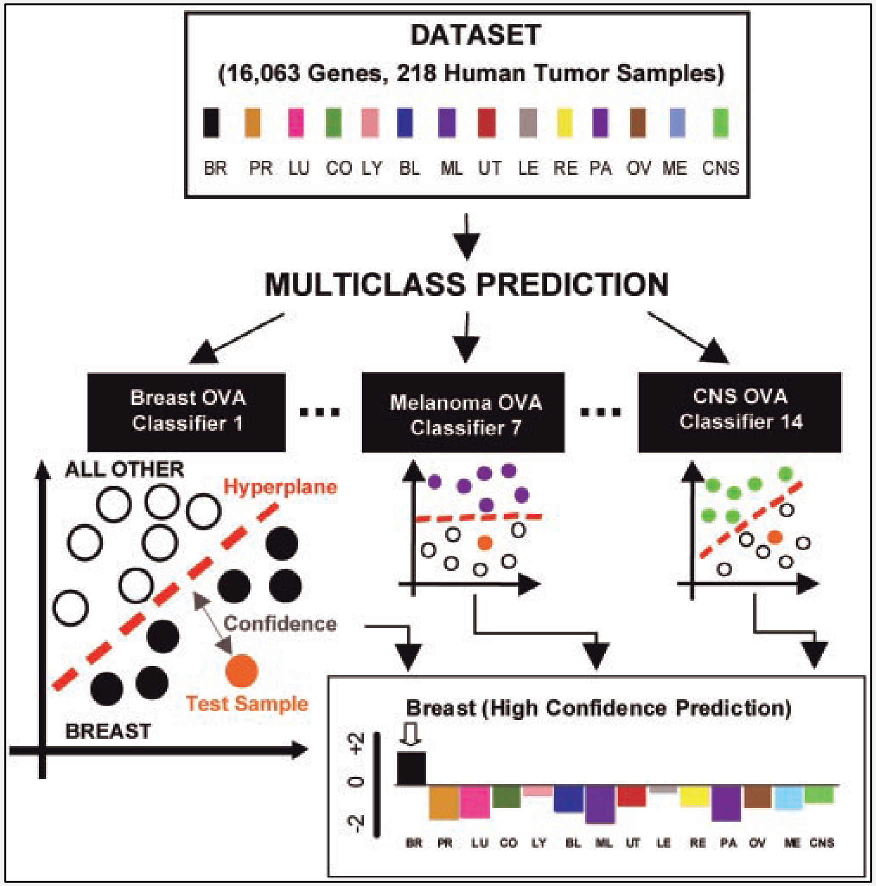
hepatotoxic

Thyroid active

# Conceptual example

Tissue of origin test

- Metastatic cancer
- No gold standard
- Histological different from tissue of origin

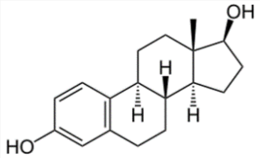



Ramaswamy, S., et al. 2001. Multiclass cancer diagnosis using tumor gene expression signatures. Proceedings of the National Academy of Sciences of the United States of America 98, 15149-15154.

# Forensics ID cause of impairment – TMDL - CWA


MOA

Collect water samples
Conduct in-lab exposures

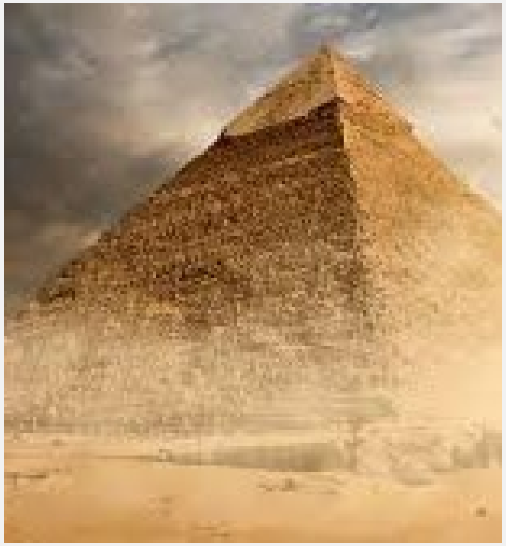



# Current research

- User interactions
  - Data driven outreach
  - Clear definitions of use and end-user needs
    - Performance criteria
  - Demonstration of added benefit – comparison to current approaches
    - Effort to minimize disruption to end-user (same species - FHM, test systems, etc.)
- Focus on specific applications
- Real-world validation

# Historical drivers of current research direction

- Initial promise of omics technologies
  - Immature technology/data analysis
- Limited interaction with POs
- Initial work were very broad ill-defined case studies.
  - **Can** we do this instead of **how well** can we do this.
  - Little consideration for experimental design
    - Underpowered
  - No consideration for current approaches



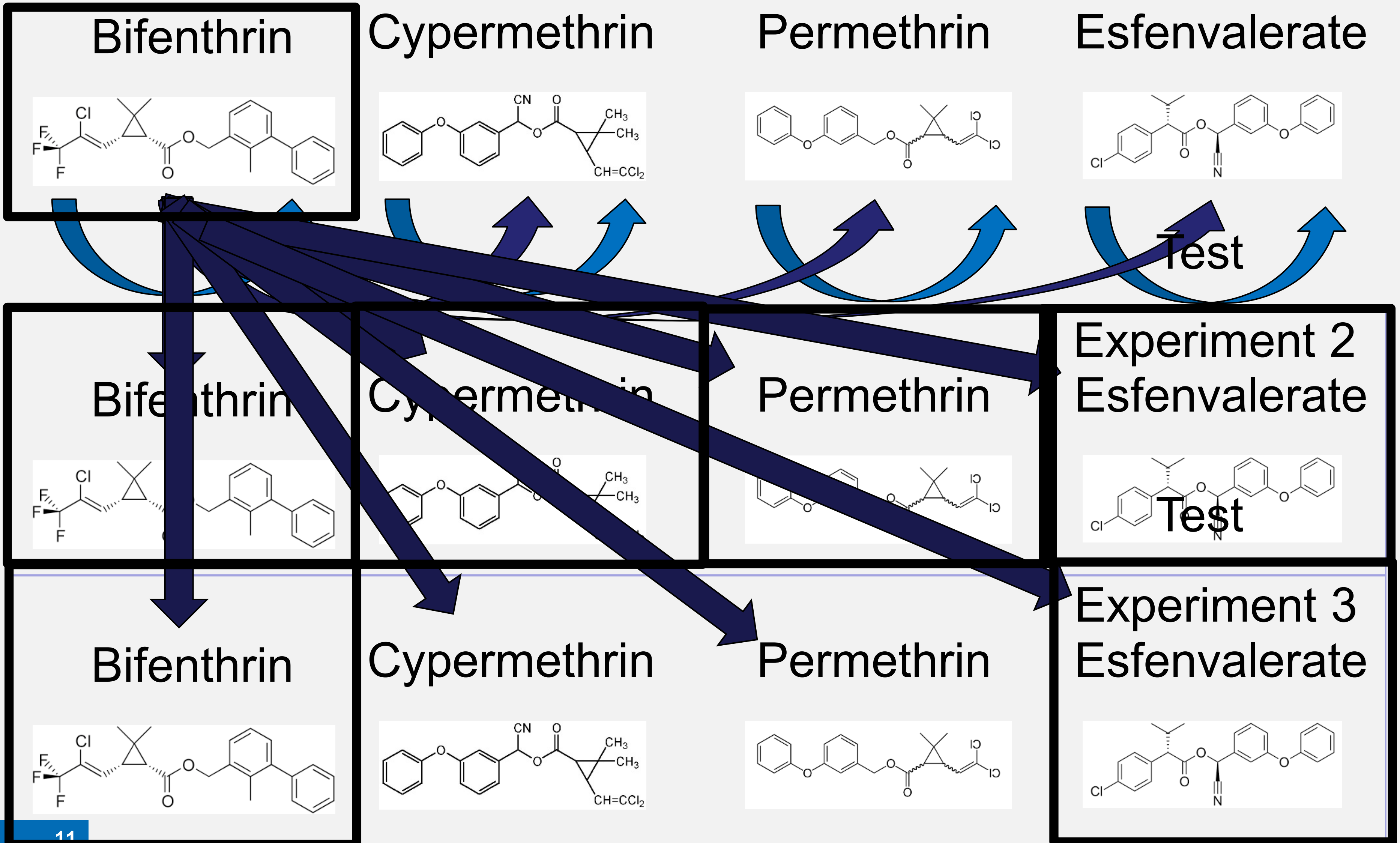
# Current research - Biomarkers

- Identify optimal test conditions
  - *Pimephales promelas* – Fathead minnow
    - Commonly used aquatic model system
    - Native to much of the U.S.
    - Huge toxicity database
  - Maximize test for chemical space
    - Age and duration of exposure
- Performance
  - Stability of gene expression over time
  - Stability of gene expression under differing water quality conditions (pH, TDS)
  - Stability of gene expression in space – targeting sources

# Can we do it

- Pyrethroid case study
  - 4 model pyrethroids
    - Type 1: Permethrin, Bifenthrin
    - Type 2: Esfenvalerate, Cypermethrin
  - FHM larvae
  - Dose response
  - 48 h exposure – Transcriptomic response

# Pyrethroid biomarker development



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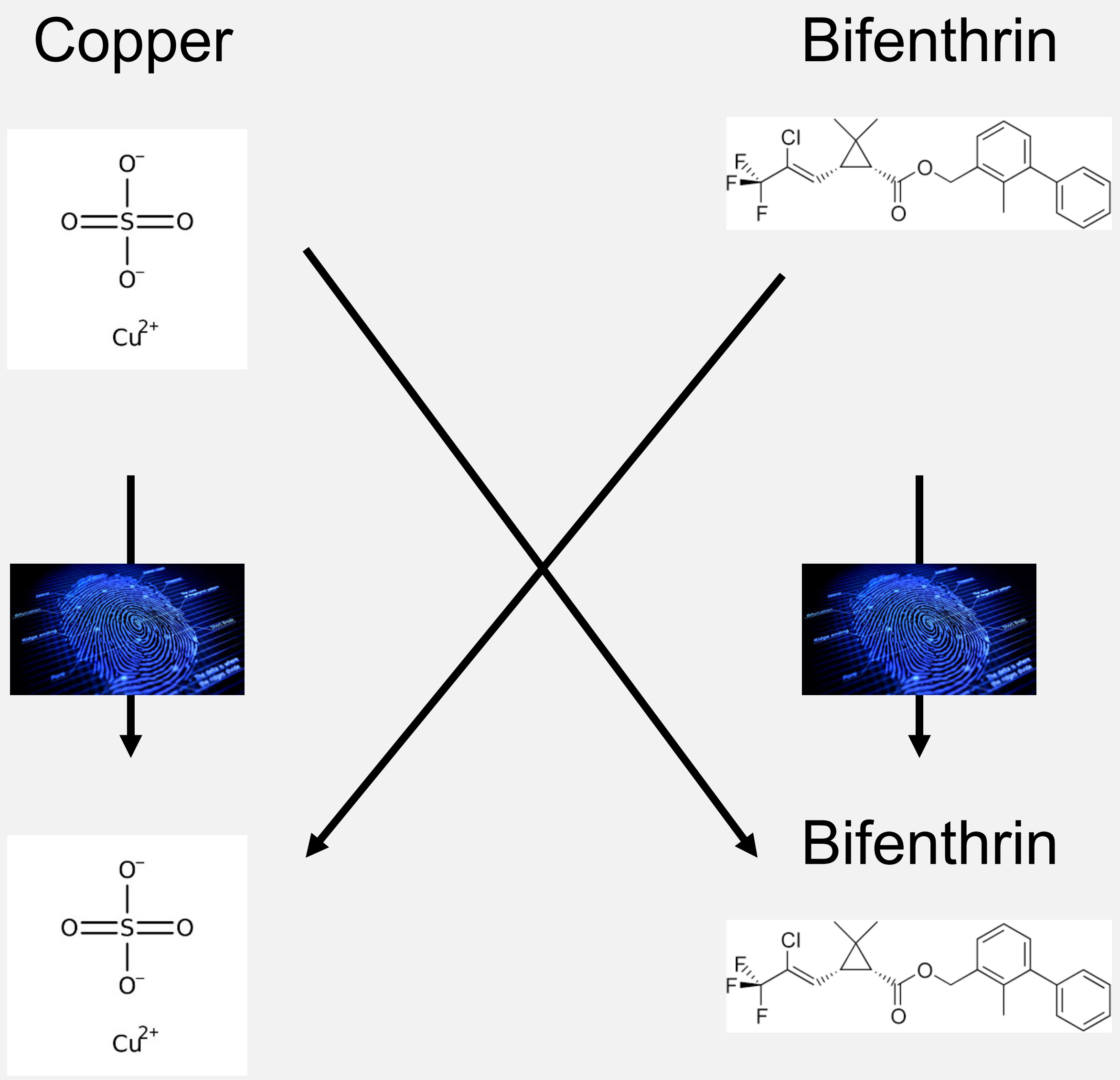
# Performance - specificity



# Conclusions

- Able to develop omics based fingerprints
  - Sensitive at ranges that are protective
  - General enough to classify across related chemicals (MOA)
  - Specific enough to avoid misclassifying unrelated chemicals (MOA)