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Moving Towards Version 2.0 of Toxicity Testing in the 21st Century and Application to Regulatory Decision Making

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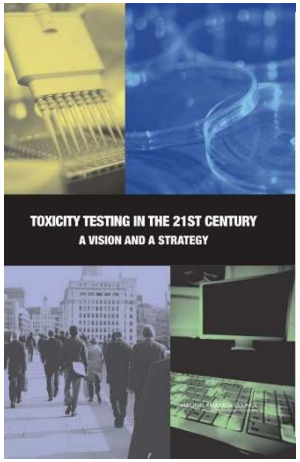
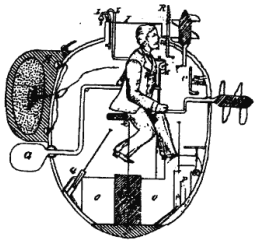
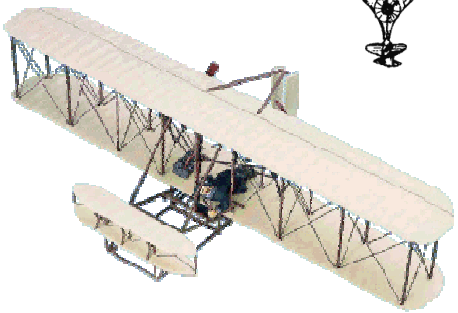
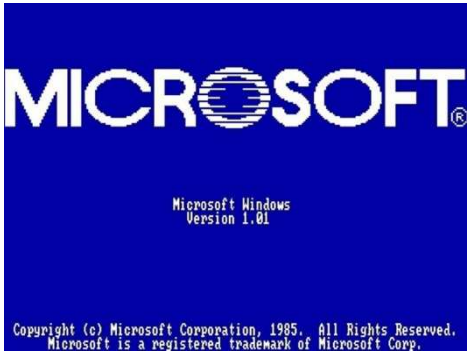
EPA United States Environmental Protection Agency

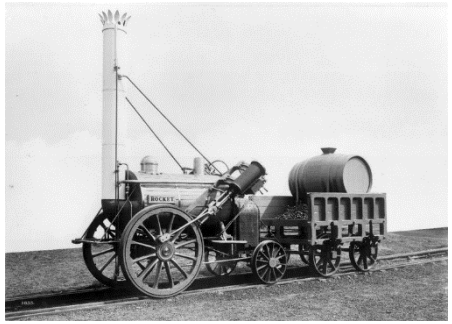
Version 1.0 is Never Perfect…

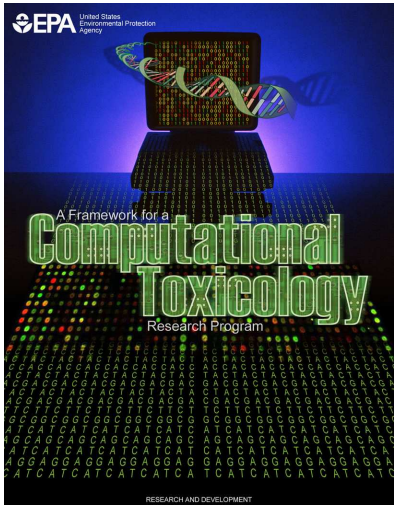












What Does Version 2.0 Look Like?

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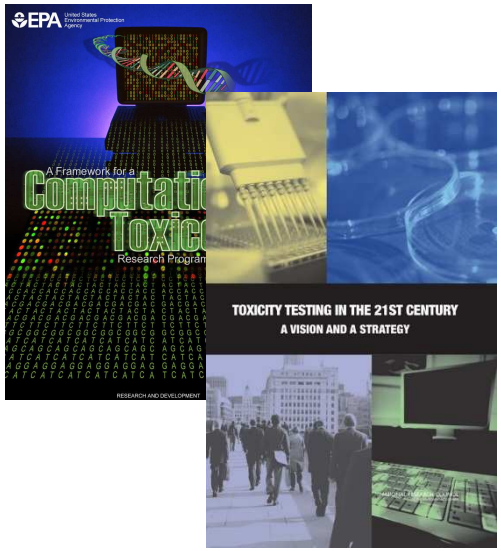

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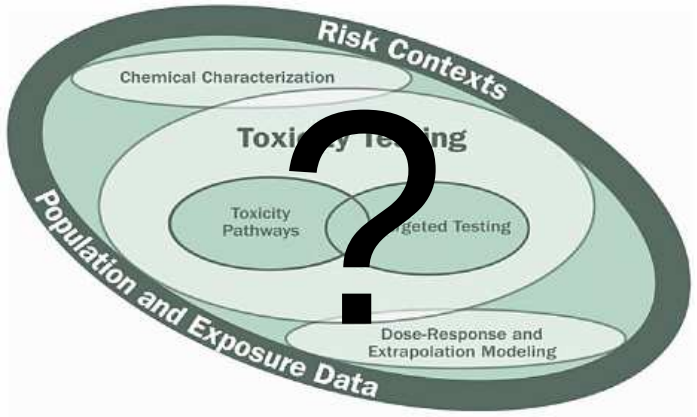
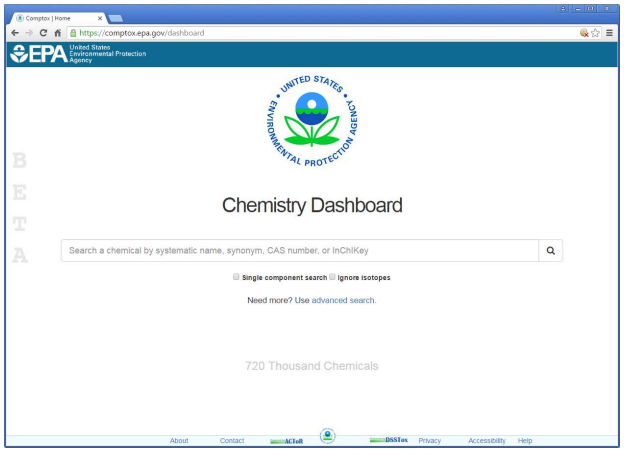


Are the new approaches ready for regulatory decision making?

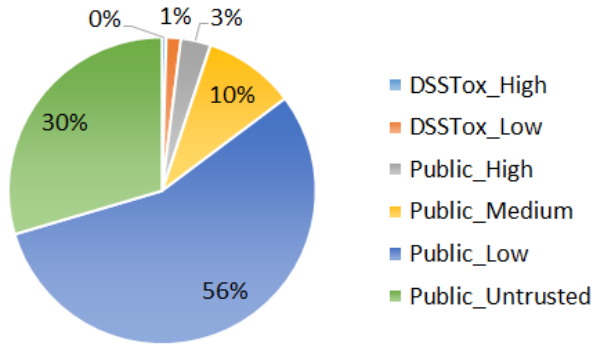
The scientific and knowledge base has evolved significantly over the past 8 – 10 years

Chemical Characterization

Quality Chemistry as the Foundation



https://comptox.epa.gov



- Developing a centralized resource for curated chemical structure, identifier, and physical chemical properties of >700K unique substances with data quality flags
- Expand and curate training sets for QSAR models for phys-chem, environmental fate, and toxicological properties
- Use the centralized chemical resource as the foundation for an integrated hazard, bioactivity, pharmacokinetics, and exposure knowledgebase

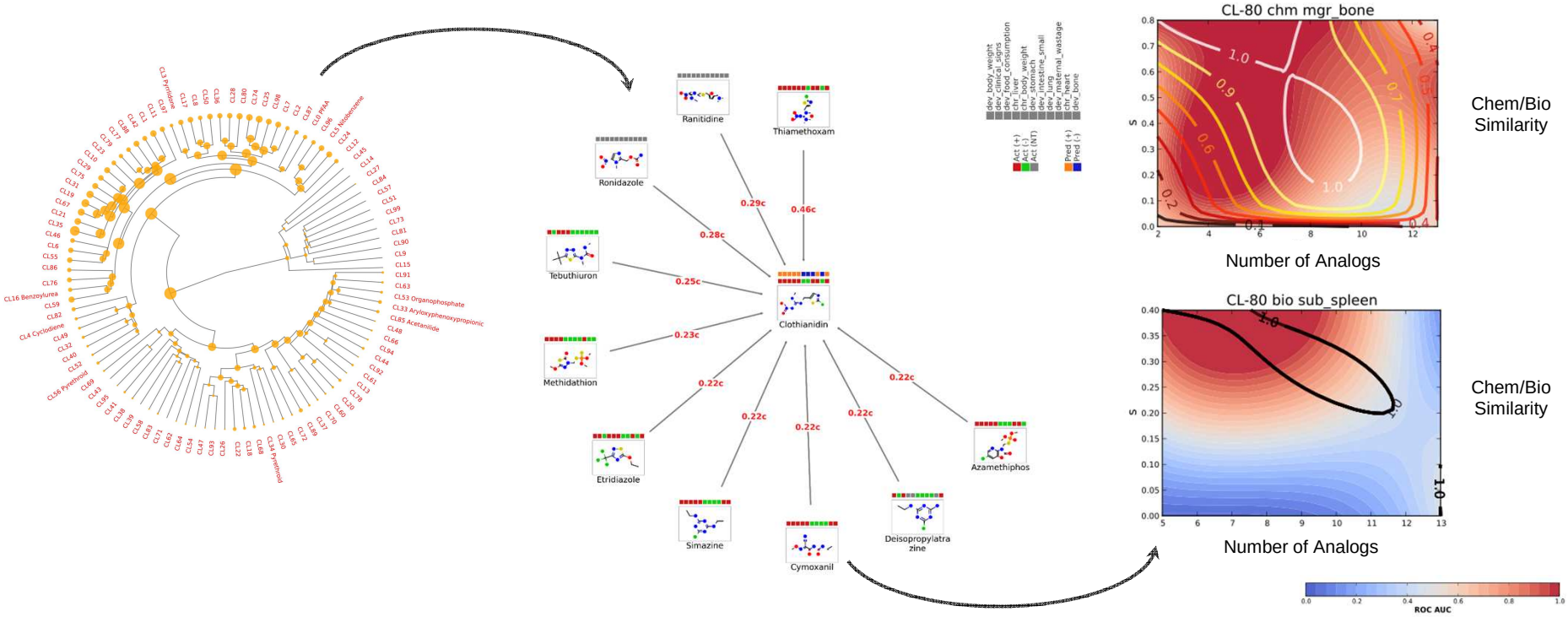
Chemical Characterization

Quantitatively Evaluating Read-Across Uncertainty

Chemicals Clustered Based on Chemotype, Structure, or Biological Descriptors

Read-across Analysis Based on Similarity-Weighted Activity of Nearest Neighbors

Uncertainty Analysis

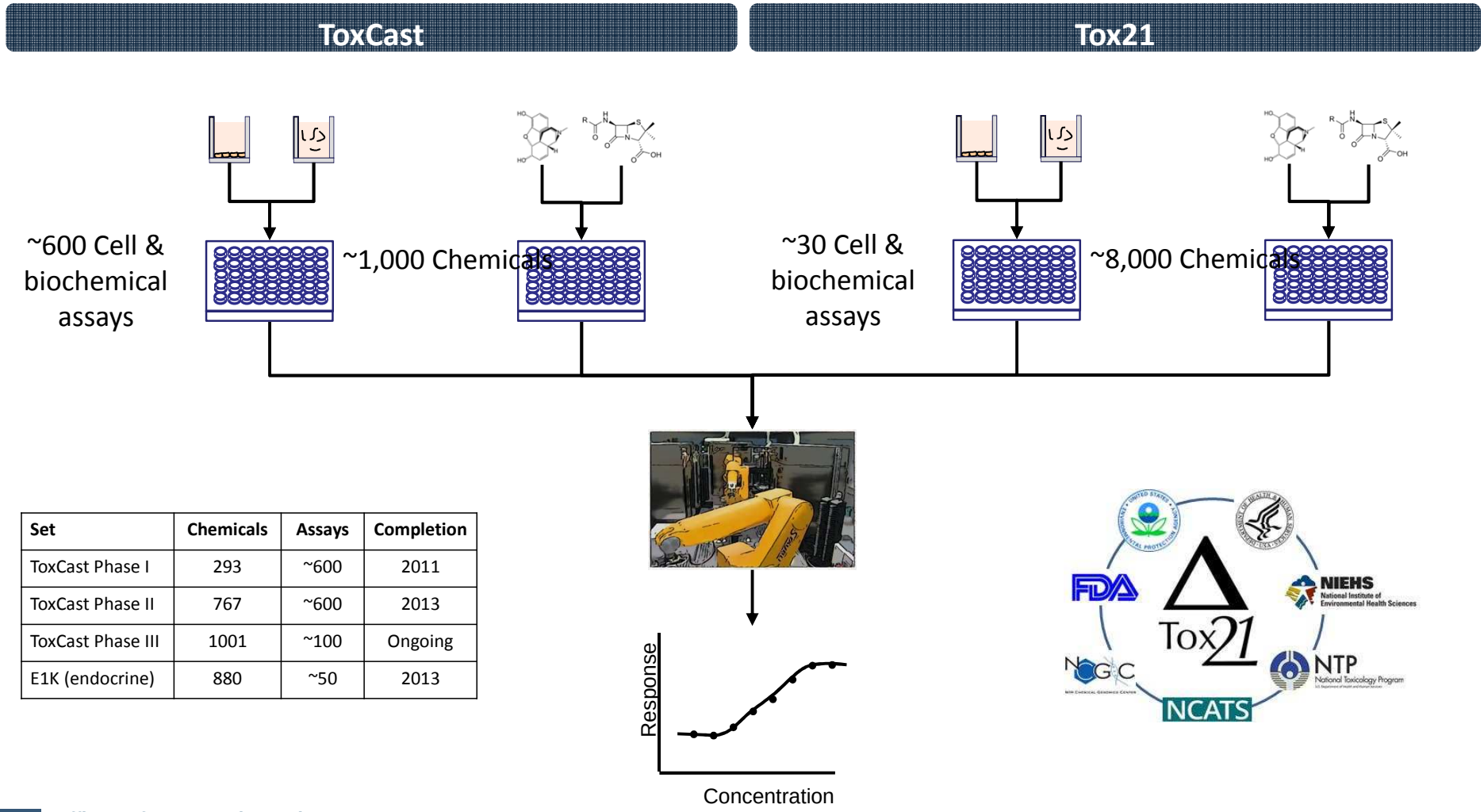


Read-across approach will allow users to define similarity and analog cut-offs while trading off uncertainty

Patlewicz *et al.*, In Review

Toxicity Testing

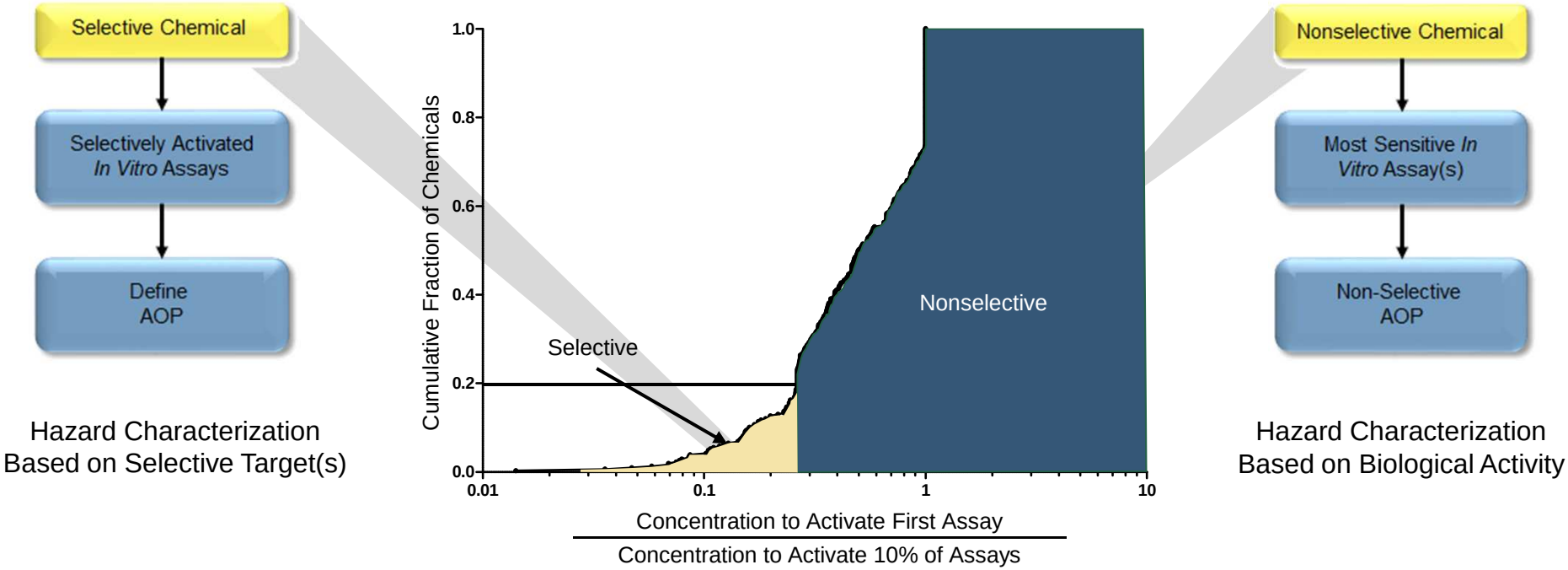
ToxCast and Tox21 High-Throughput Screening



Set	Chemicals	Assays	Completion
ToxCast Phase I	293	~600	2011
ToxCast Phase II	767	~600	2013
ToxCast Phase III	1001	~100	Ongoing
E1K (endocrine)	880	~50	2013

Toxicity Testing

Considering Biological Selectivity as a Starting Point for Safety Decisions

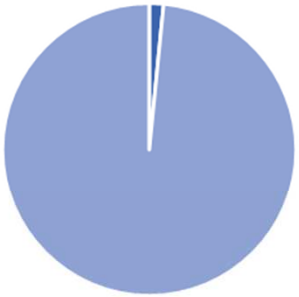


Thomas *et al.*, 2013

Toxicity Testing

New Approaches to Comprehensively Assess Potential Biological Effects

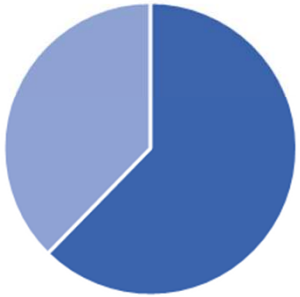
Gene Coverage



ToxCast

Not in ToxCast

Pathway Coverage*

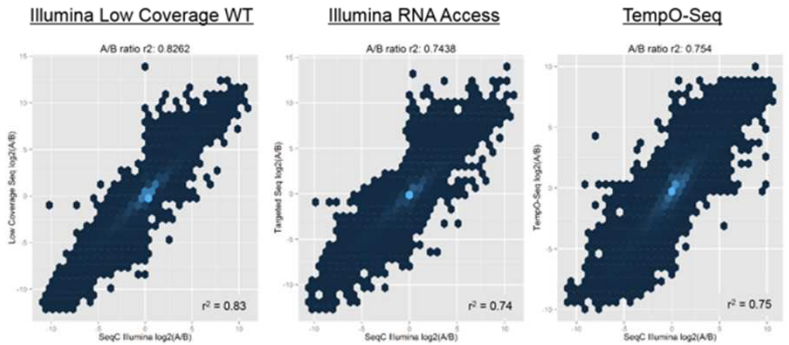


*At least one gene from pathway represented

High-Throughput Transcriptomic Platforms

- Low-cost
- Whole genome
- 384-well
- Automatable

Technical Comparison



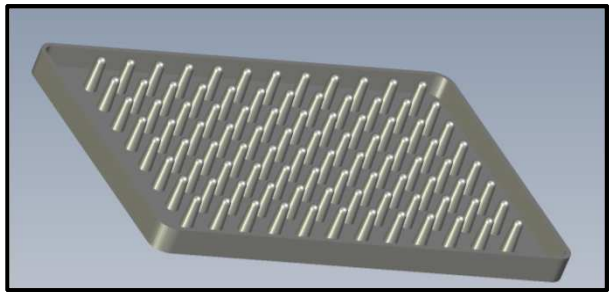
Functional Comparison

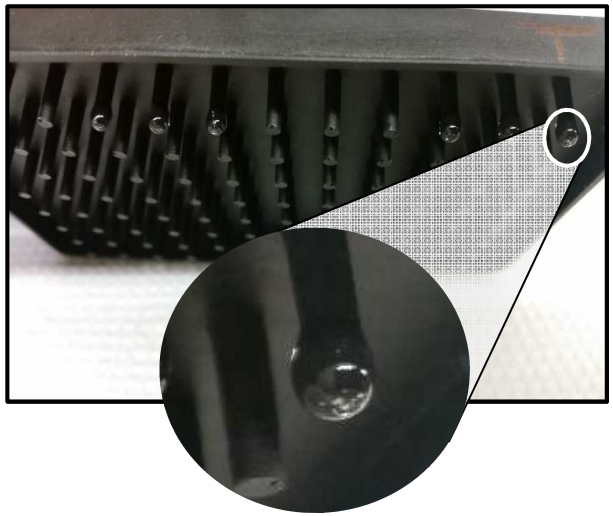
Correct Mechanistic Match		
2/5 (40%)	2/5 (40%)	5/5 (100%)

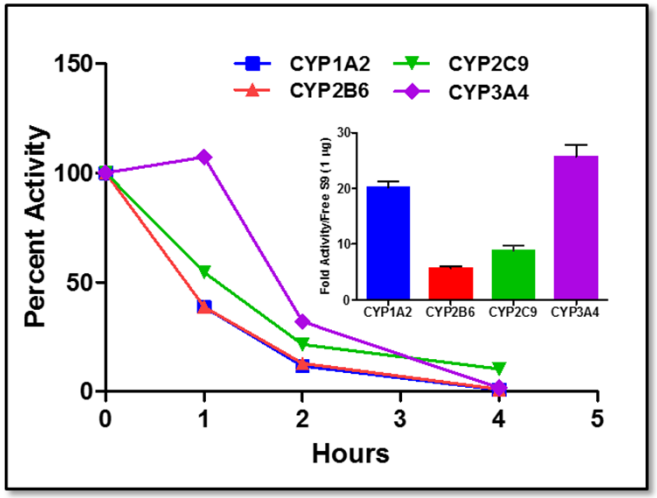
Karmus and Martin, Unpublished

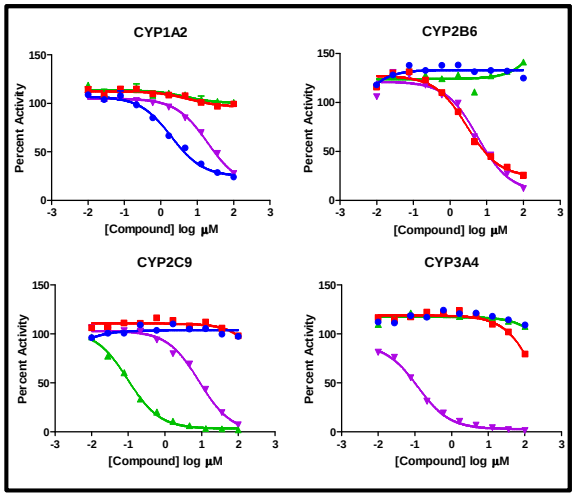
Toxicity Testing

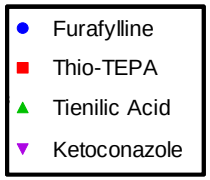
Incorporating Metabolic Competence into In Vitro Assays







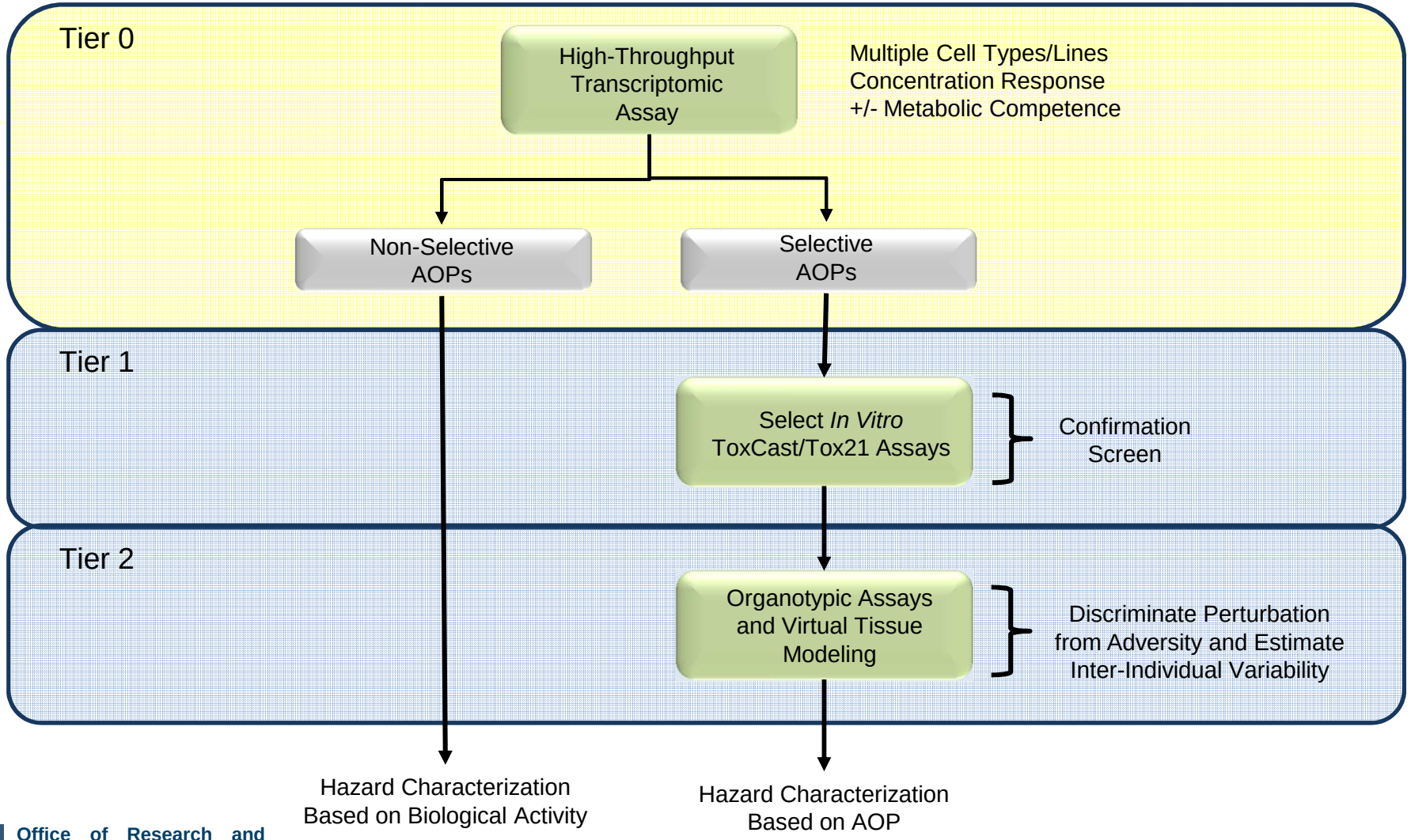




DeGroot and Simmons, Unpublished

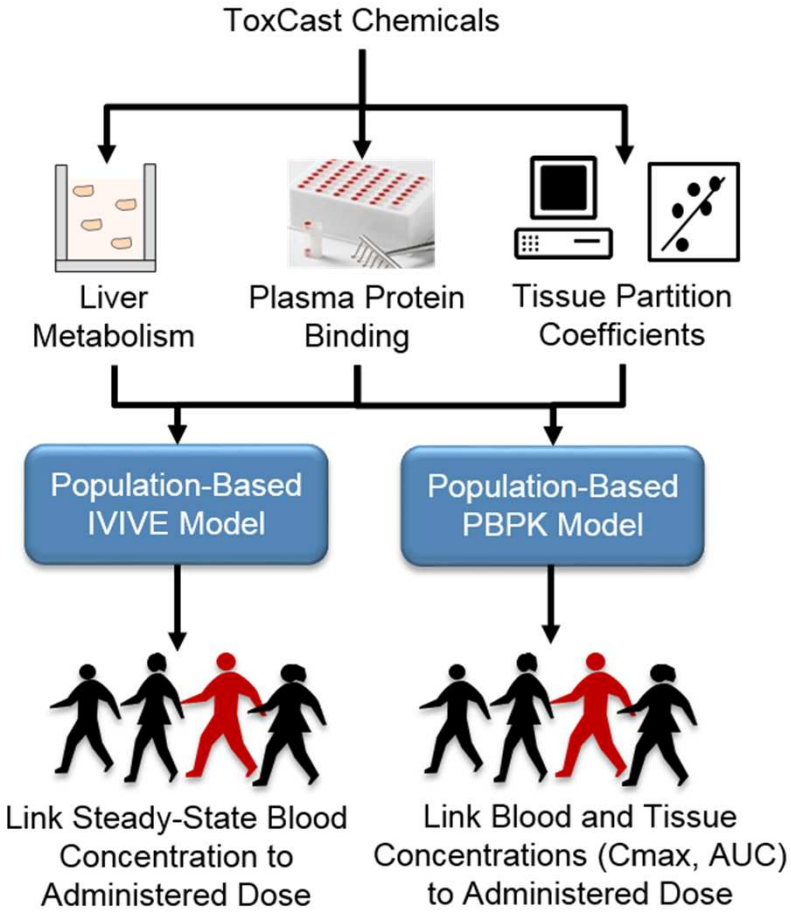
Toxicity Testing

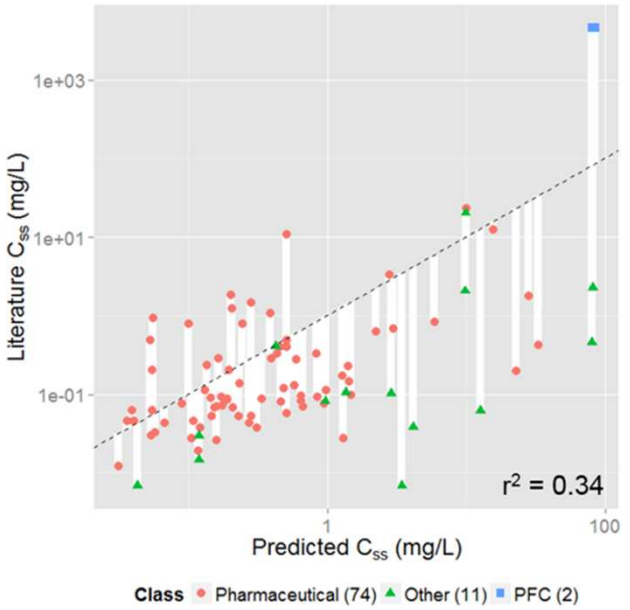
Integrating New Thinking Into a Tiered Testing Framework

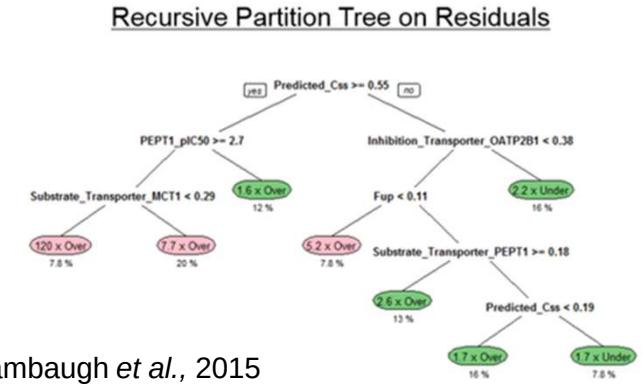


Dose and Systems Modeling

Incorporating Dosimetry and Uncertainty into In Vitro Screening



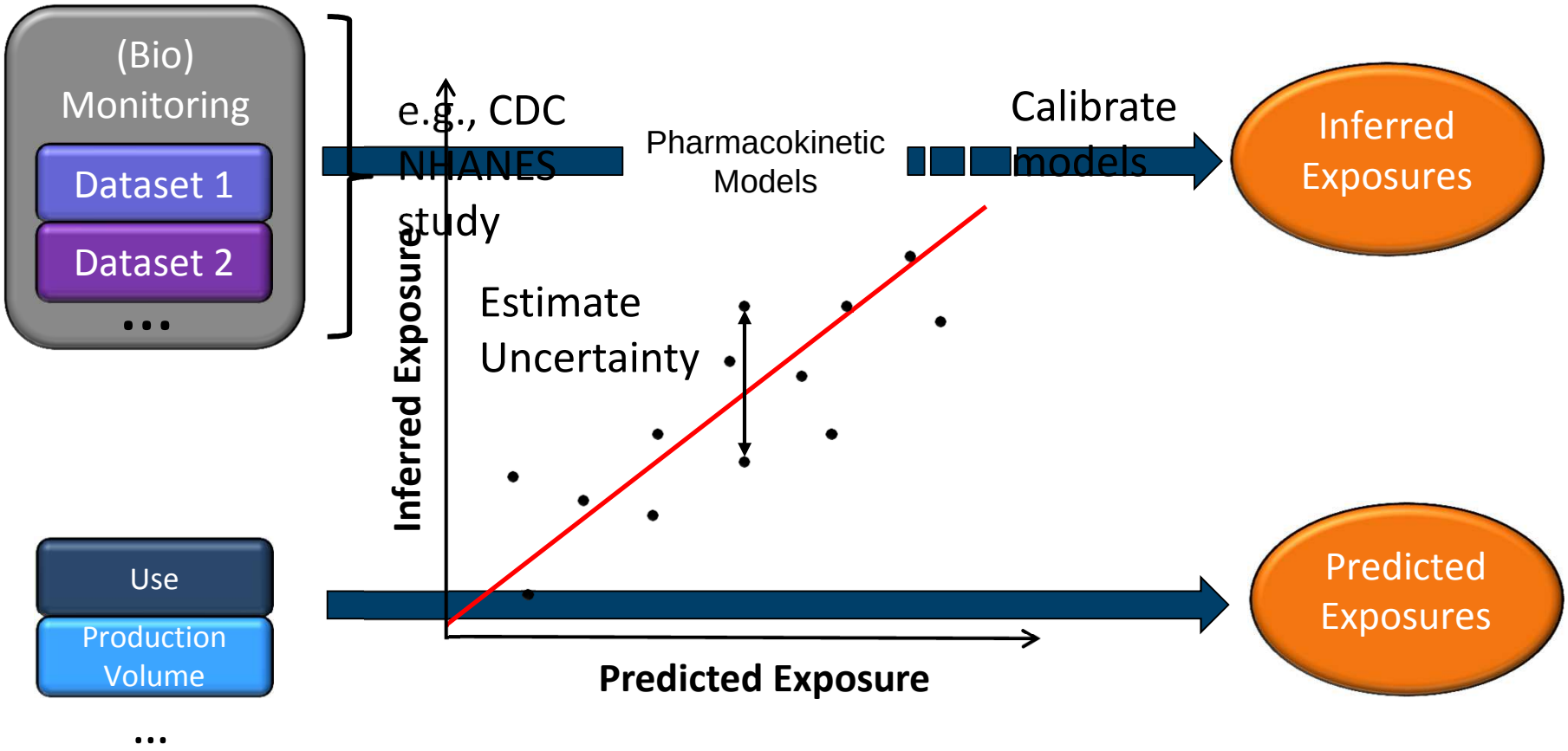




Wambaugh *et al.,* 2015

Population and Exposure Data

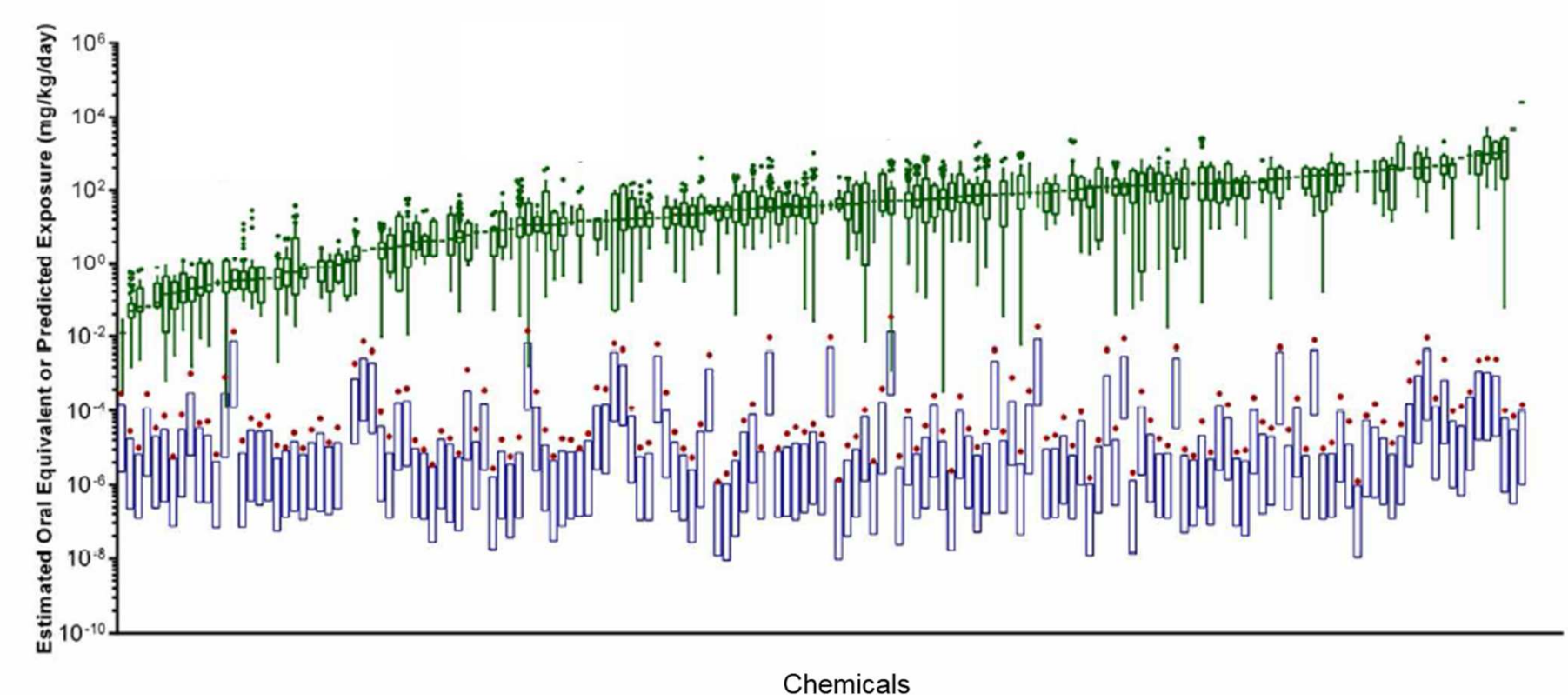
Estimating Exposure and Associated Uncertainty with Limited Data



Wambaugh *et al.*, 2014

Population and Exposure Data

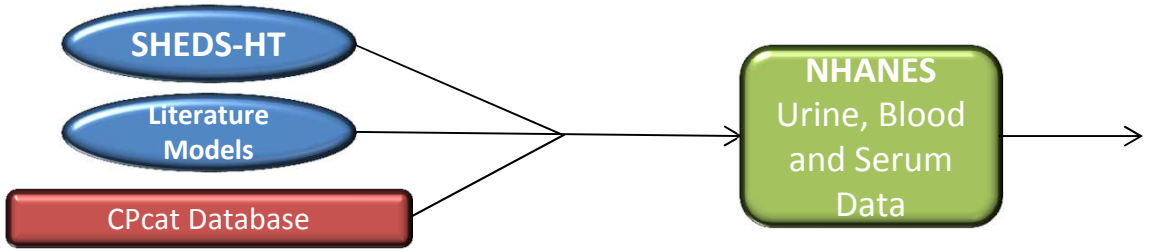
Enabling Risk-Based Chemical Safety Decisions



Wetmore *et al.*, *Tox Sci.*, 2015

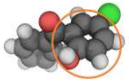
Population and Exposure Data

Reducing Uncertainty in Exposure Models



- Averaging multiple exposure models
- Exposure model determined by chemical use

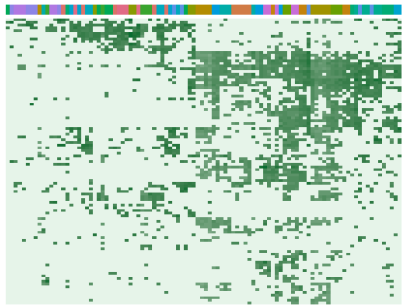
Use Database (FUSE)



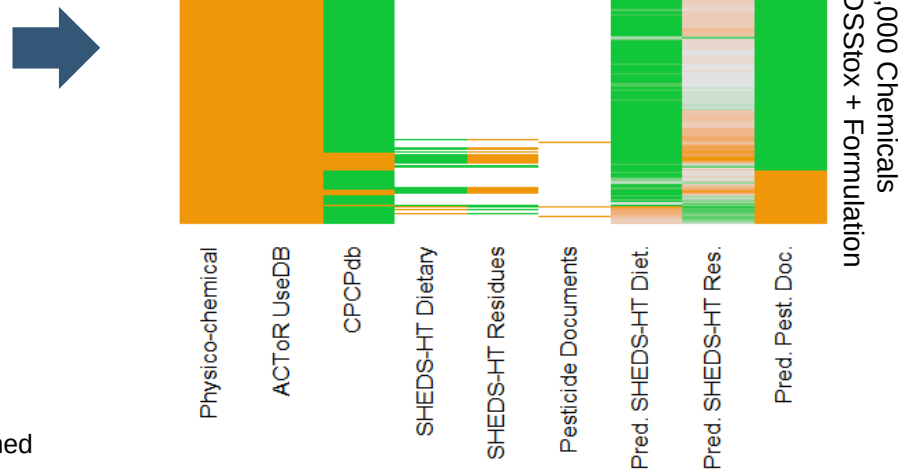
Machine Learning Approaches to Predict Chemical Use

Pilot Study

- 20 Product types x 5 products/type
- 2D GCxTOF/MS



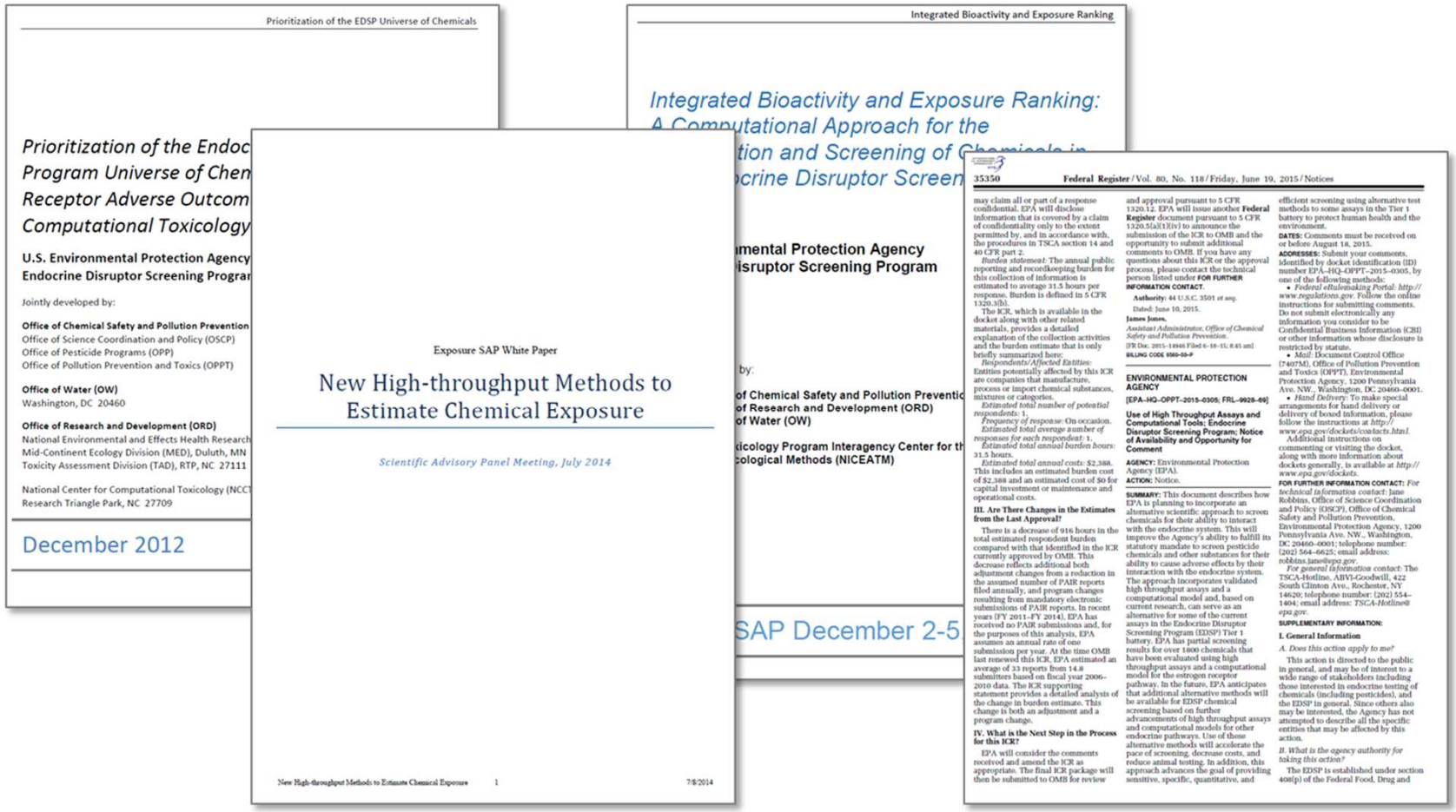
Non-Targeted Analytical Screening of Consumer Product Composition



Wambaugh, Isaacs, and Phillips, Unpublished

Risk Context

Initial Focus on Endocrine-Related Regulatory Application



Risk Context

Case Studies Applying NAMs to Chemical Assessments

OPP Case Study

Decision Context: Prioritize non-food use inert ingredients for additional study

Desired Components:

- Phys-Chem properties with environ fate and transport
- Hazard profile – GL and GL-like studies, RA, and QSAR
    - Chronic tox endpoints
- ToxCast data in AOP context
- Toxicokinetic data (*in vivo* and *in vitro*)
- Consumer and industrial use

OLEM-Region Case Study

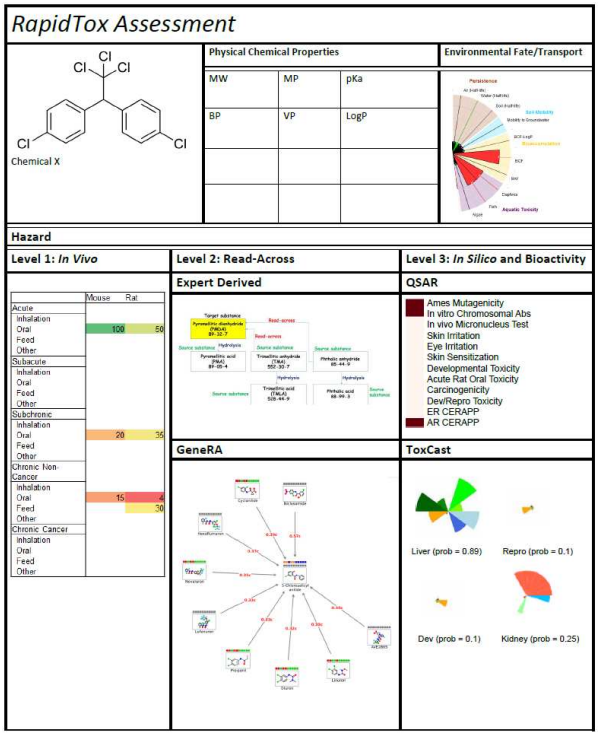
Decision Context: Estimate toxicity values with associated uncertainty for data poor chemicals at Superfund sites

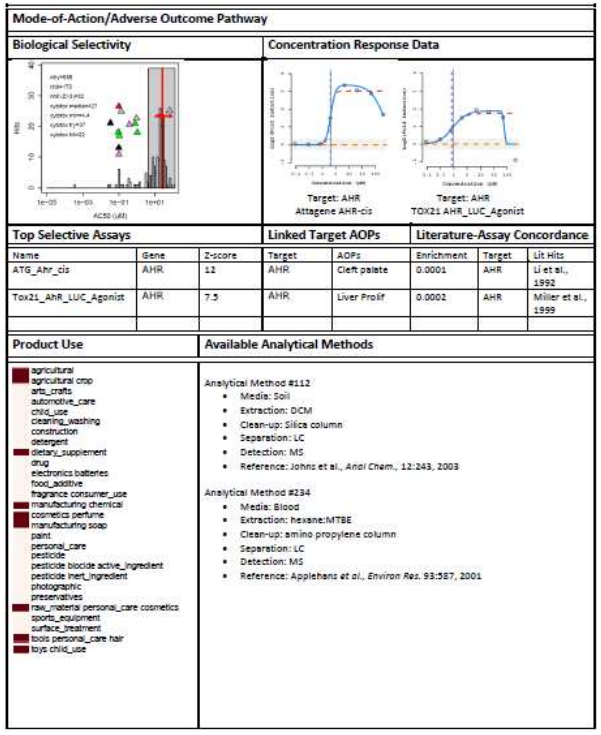
Desired Components:

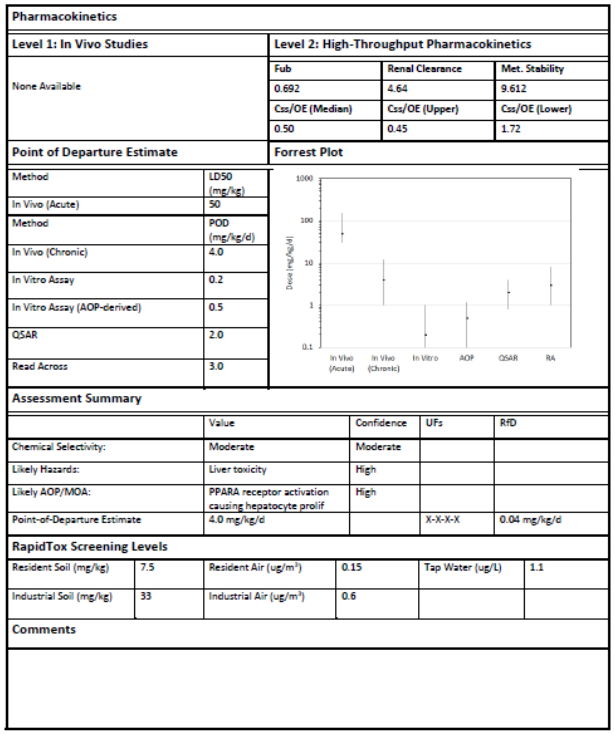
- Phys-Chem properties with environ fate and transport
- Hazard profile – GL and GL-like studies, RA, and QSAR
    - Acute and chronic tox endpoints
- ToxCast data in AOP context
- Toxicokinetic data (*in vivo* and *in vitro*)
- Bioavailability (sediment and Caco-2)
- Consumer and industrial use
- Screening level estimates with defined exposure scenarios
- Available analytical chemistry methods

Risk Context

Integrating Traditional and NAMs for Regulatory Decisions







Mock Up – Not real data

- Semi-automated decision support tool with dashboard interface
- Combining diverse data streams into quantitative toxicity values with associated uncertainty

Challenges

- Technical limitations/obstacles associated with each technology (e.g., metabolism, volatiles, etc.)
- Moving from an apical to a molecular paradigm and defining adversity
- Predicting human safety vs. toxicity
- Combining new approaches to have adequate throughput and sufficiently capture higher levels of biological organization
- Systematically integrating multiple data streams from the new approaches in a risk-based, weight of evidence assessment
- Quantifying and incorporating uncertainty and variability
- Dealing with the "V" word
  - Defining a fit-for-purpose framework(s) that is time and resource efficient
  - Performance-based technology standards vs. traditional validation
  - Role of *in vivo* rodent studies and understanding their inherent uncertainty
- Legal defensibility of new methods and assessment products

Acknowledgements and Questions

Tox21 Colleagues:
- NTP Crew
- FDA Collaborators
- NCATS Collaborators

ORD Colleagues:
- NERL
- NHEERL
- NCEA

EPA's National Center for Computational Toxicology