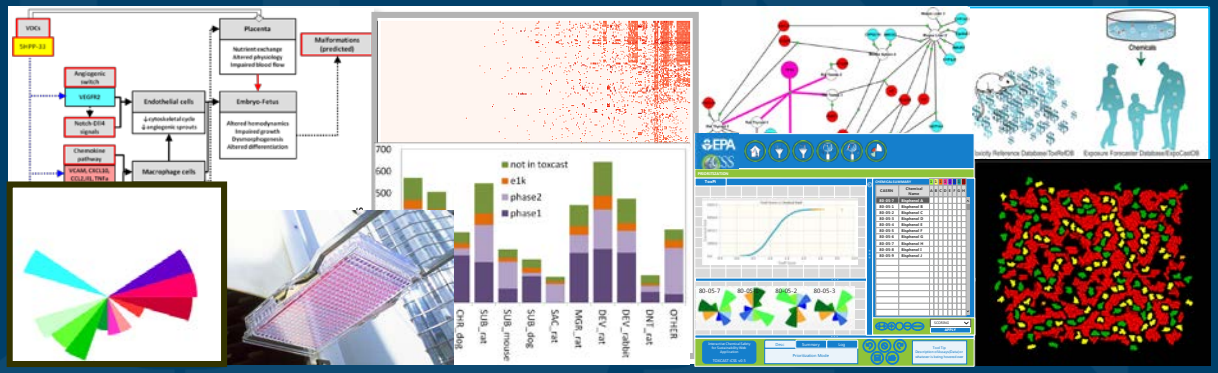
United States
Environmental Protection
Agency

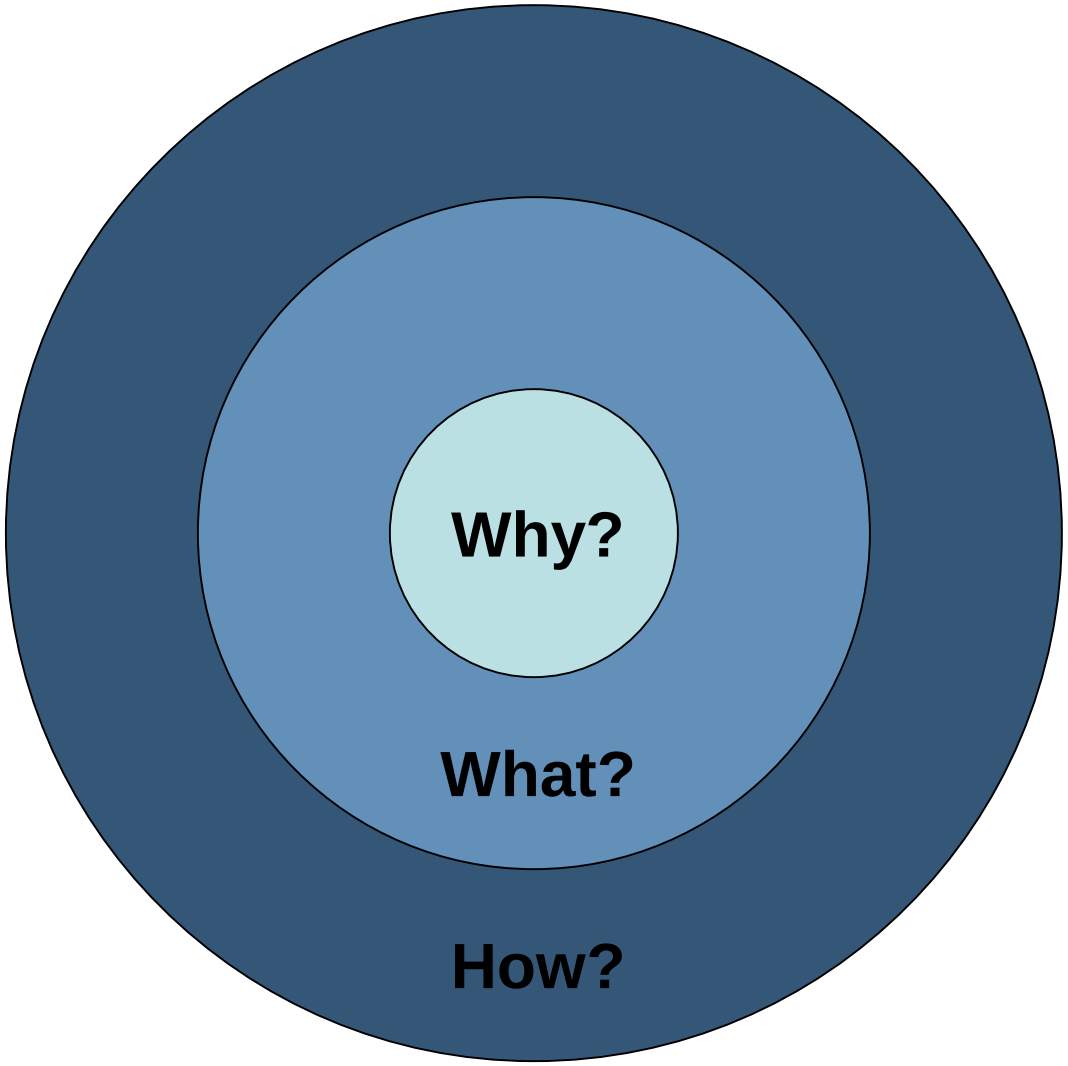
# Incorporating New Technologies for 21st Century Toxicity Testing and Risk Assessment




**GlobalChem**
**February 22, 2017**

**Russell Thomas**
**Director**
**National Center for Computational Toxicology**

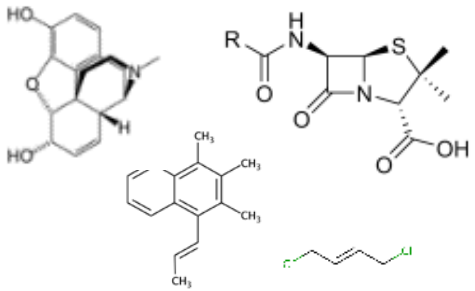
# Sinek's 'Golden Circle' of 21st Century Risk Assessment



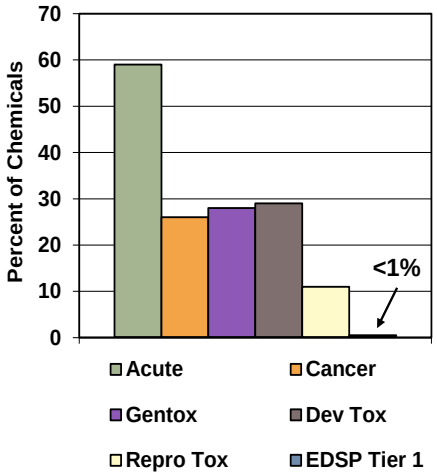
# All Understand 'Why' We Need to Innovate In This Space…

United States Environmental Protection Agency

## Number of Chemicals /Combinations



## Lack of Data

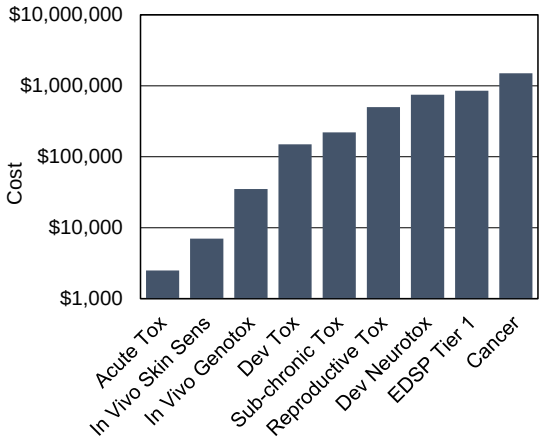



Modified from Judson *et al.*, EHP 2010

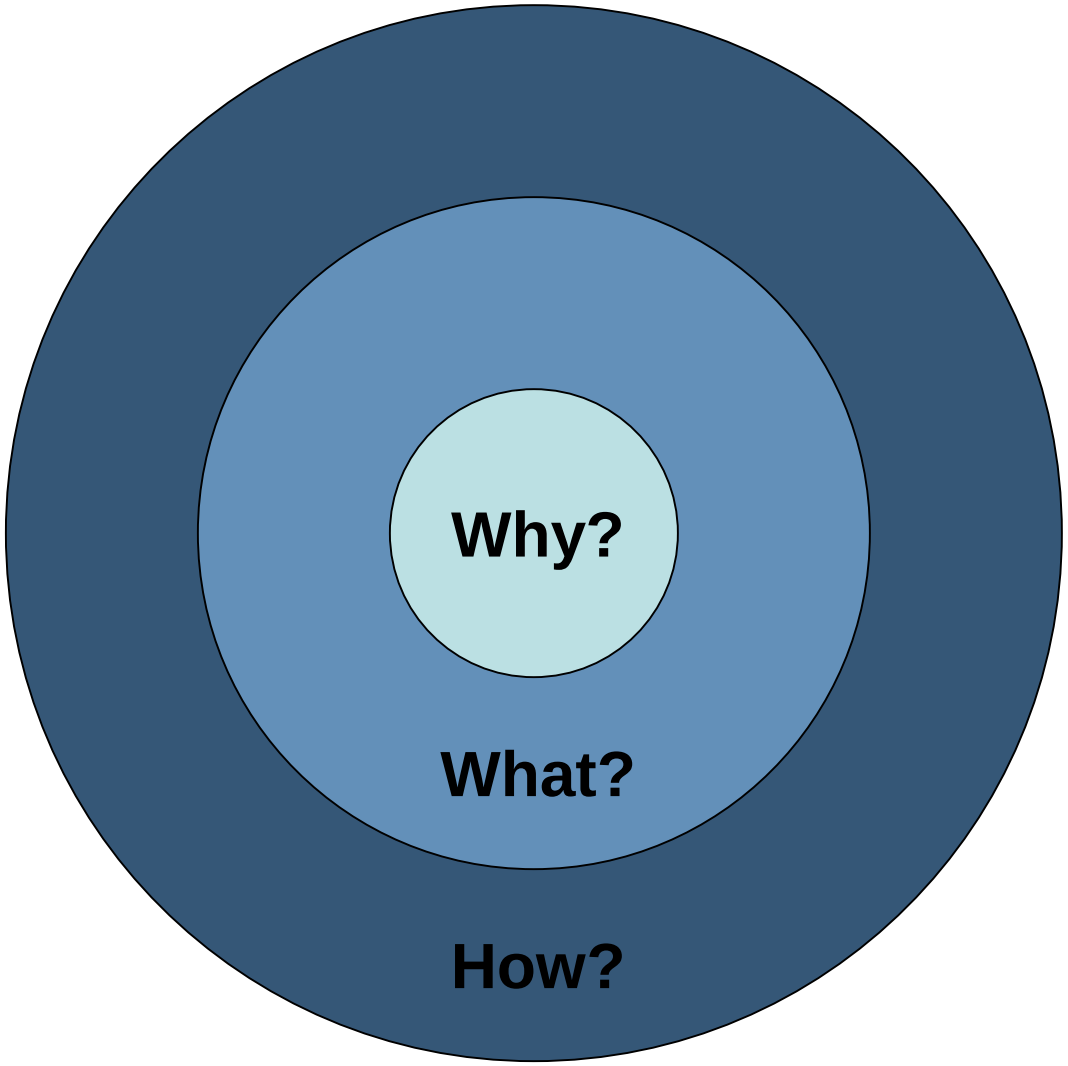
**Why?**

## Ethics Concerns

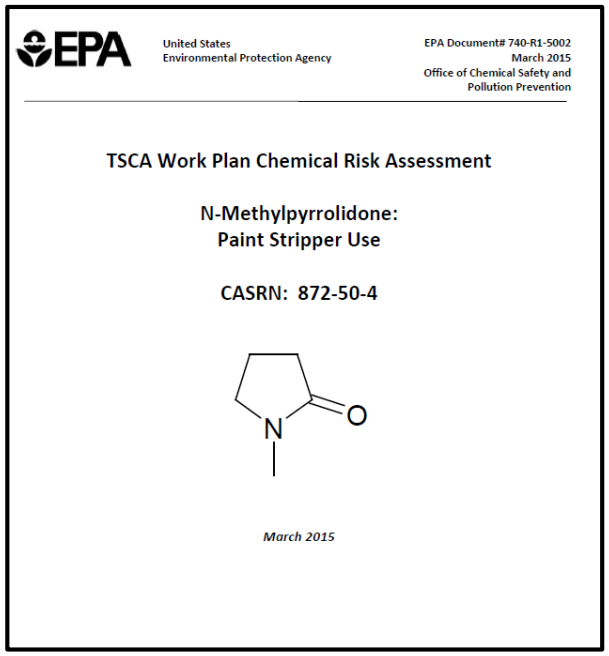
## Economics



# ‘Golden Circle’ of 21st Century Risk Assessment



# Risk Assessments Generally Contain a Standard Set of Components



United States Environmental Protection Agency

EPA Document# 740-R1-5002
March 2015
Office of Chemical Safety and Pollution Prevention

**TSCA Work Plan Chemical Risk Assessment**

**N-Methylpyrrolidone: Paint Stripper Use**

**CASRN: 872-50-4**




*March 2015*

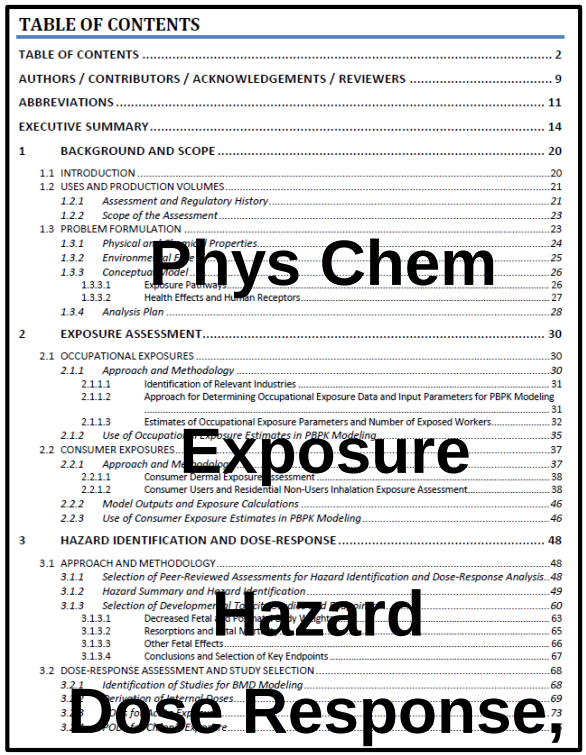
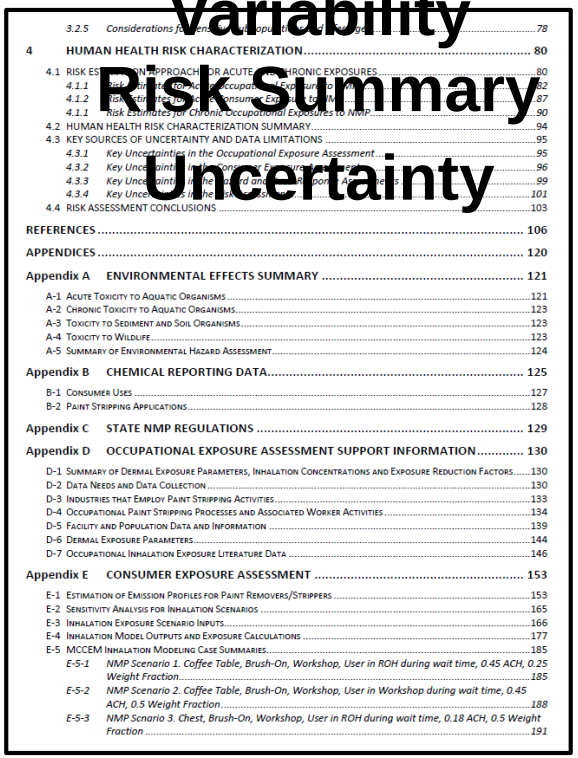


**TABLE OF CONTENTS**







**Variability**

**Risk Summary**

**Uncertainty**

**Phys Chem**

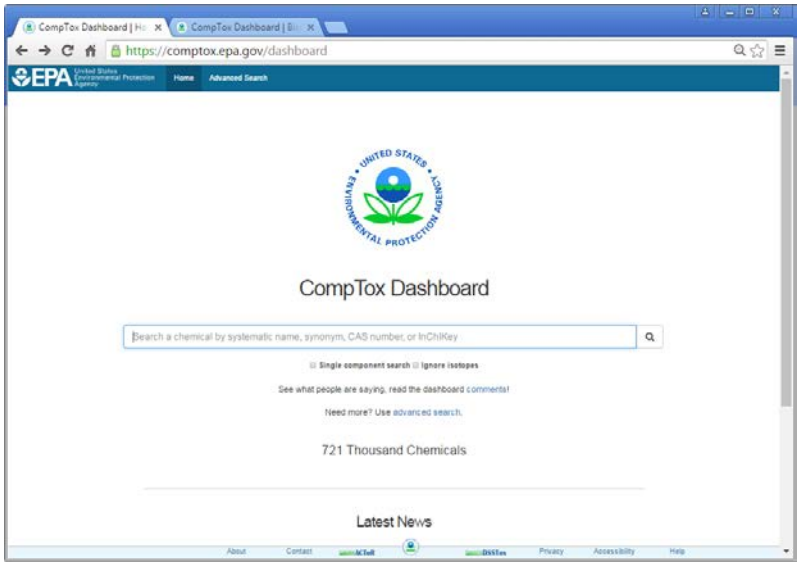
**Exposure**

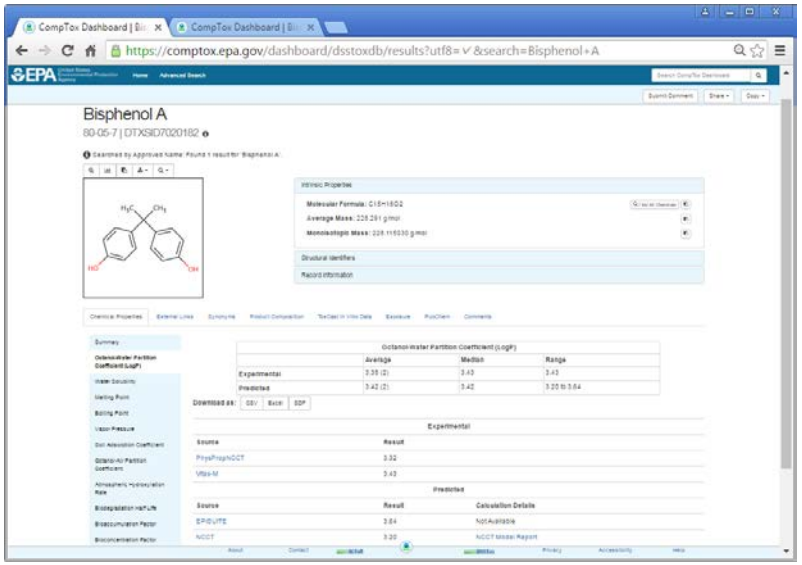
**Hazard**

**Dose Response, PK, and PODs**

New technologies and approaches will also have to cover these basic components

# It All Starts With Chemistry…




https://comptox.epa.gov/dashboard

- Chemical structure database of >700,000 unique substances with QC flags to link chemical structure with names and identifiers
- Consensus QSAR models for a range of physical chemical properties, environmental fate, and hazard characteristics
- Comprehensive physical-chemical property database (experimental and predicted)

# Adding the High-Throughput Hazard Screening Component

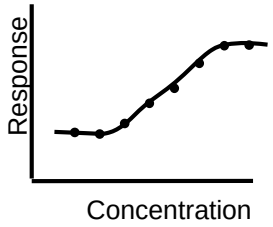
**ToxCast** | **Tox21**

~600 Cell & biochemical assays

~1,000 Chemicals

~30 Cell & biochemical assays

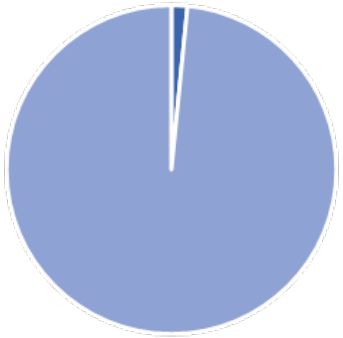
~8,000 Chemicals



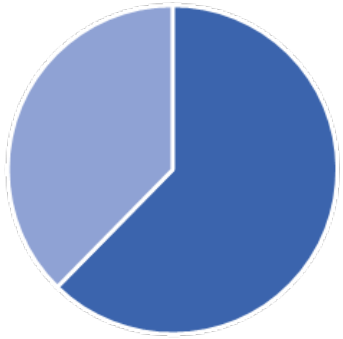

| Set | Chemicals | Assays | Completion |
|---|---|---|---|
| ToxCast Phase I | 293 | ~600 | 2011 |
| ToxCast Phase II | 767 | ~600 | 2013 |
| ToxCast Phase III | 1001 | ~100 | Ongoing |
| E1K (endocrine) | 880 | ~50 | 2013 |

# Beginning to Address Concerns for Increased Biological Coverage

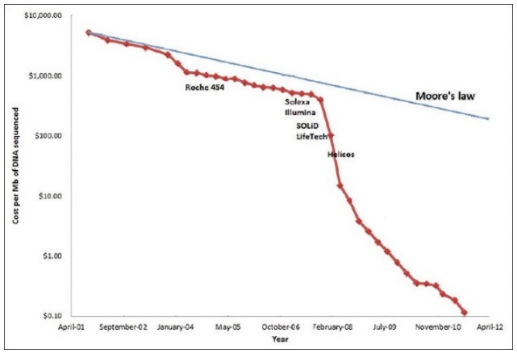
## Gene Coverage



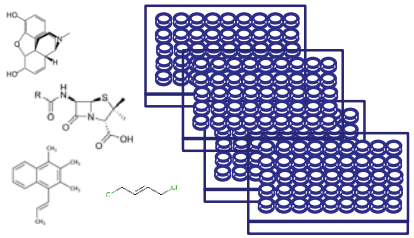

## Pathway Coverage*



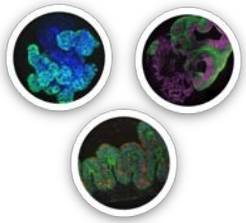
*At least one gene from pathway represented




Thousands of chemicals



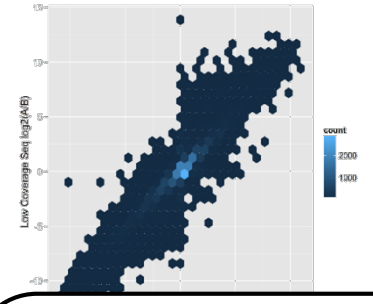
Multiple Cell Types



**Requirements:**

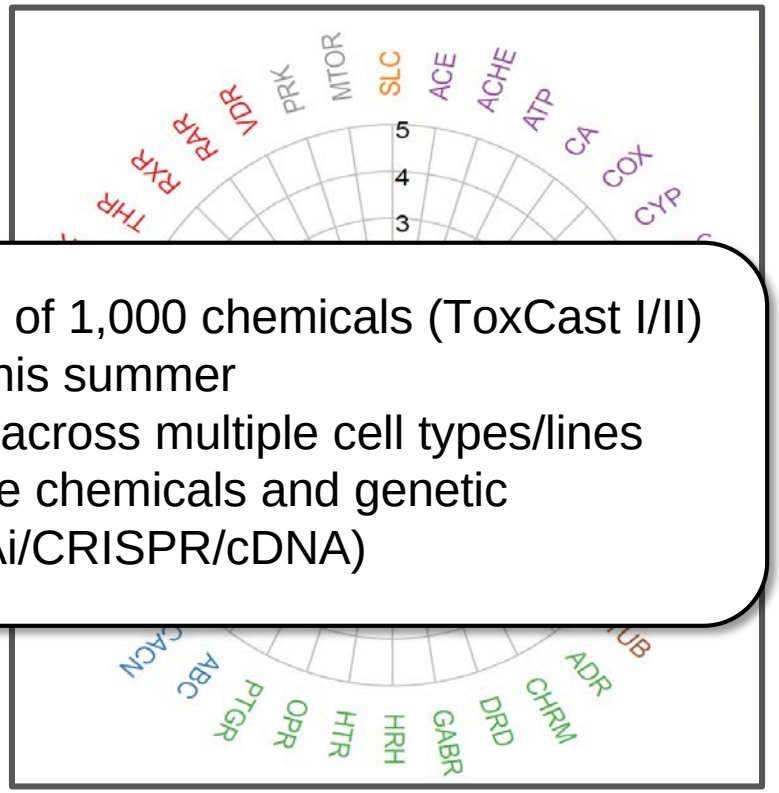
- Low cost
- Whole genome
- 384 well
- Automatable

# Comparing Sequencing Platforms and Developing Analysis Approach



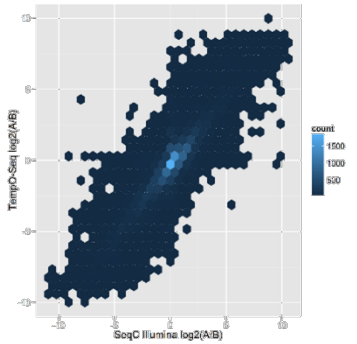
**TruSeq**
$r^2$ 0.74

MOA Analysis Pipeline





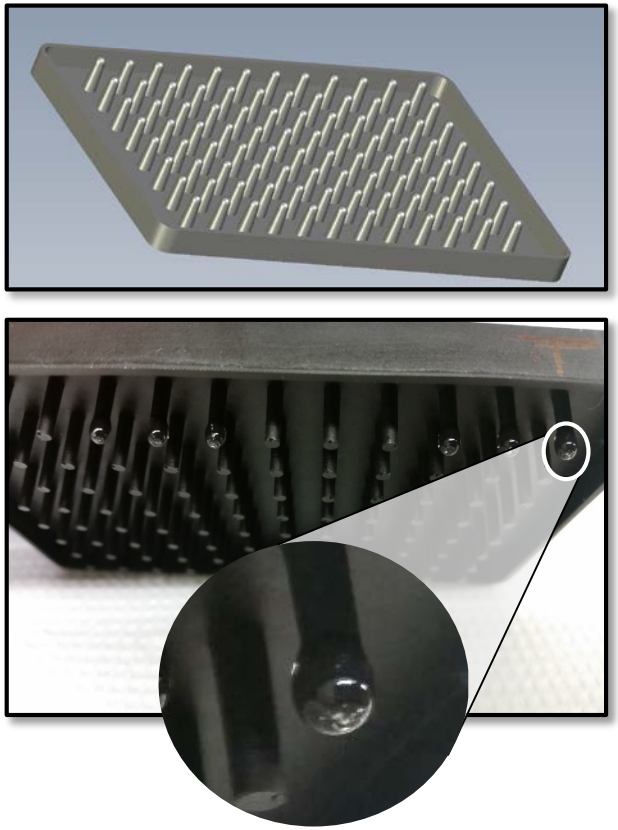
- Large scale screen of 1,000 chemicals (ToxCast I/II) in single cell type this summer
- Additional screens across multiple cell types/lines
- Additional reference chemicals and genetic perturbations (RNAi/CRISPR/cDNA)

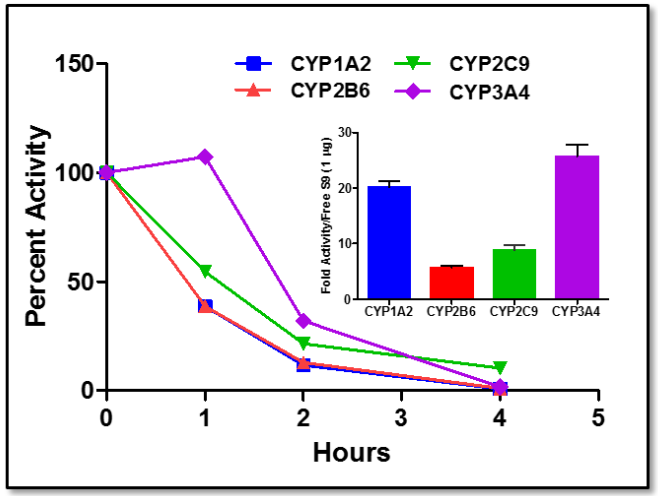


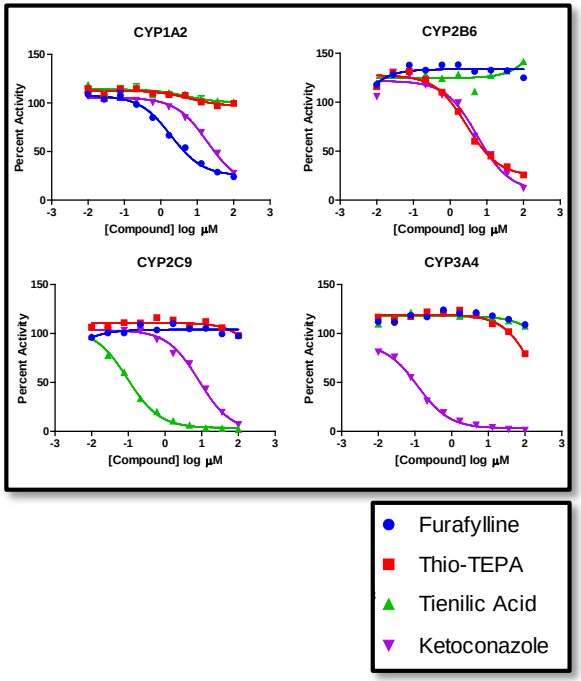
**Low Coverage**
$r^2$ 0.83

Currently capable of assigning to >40 MOAs based on transcriptional responses

# Beginning to Address Metabolic Competence

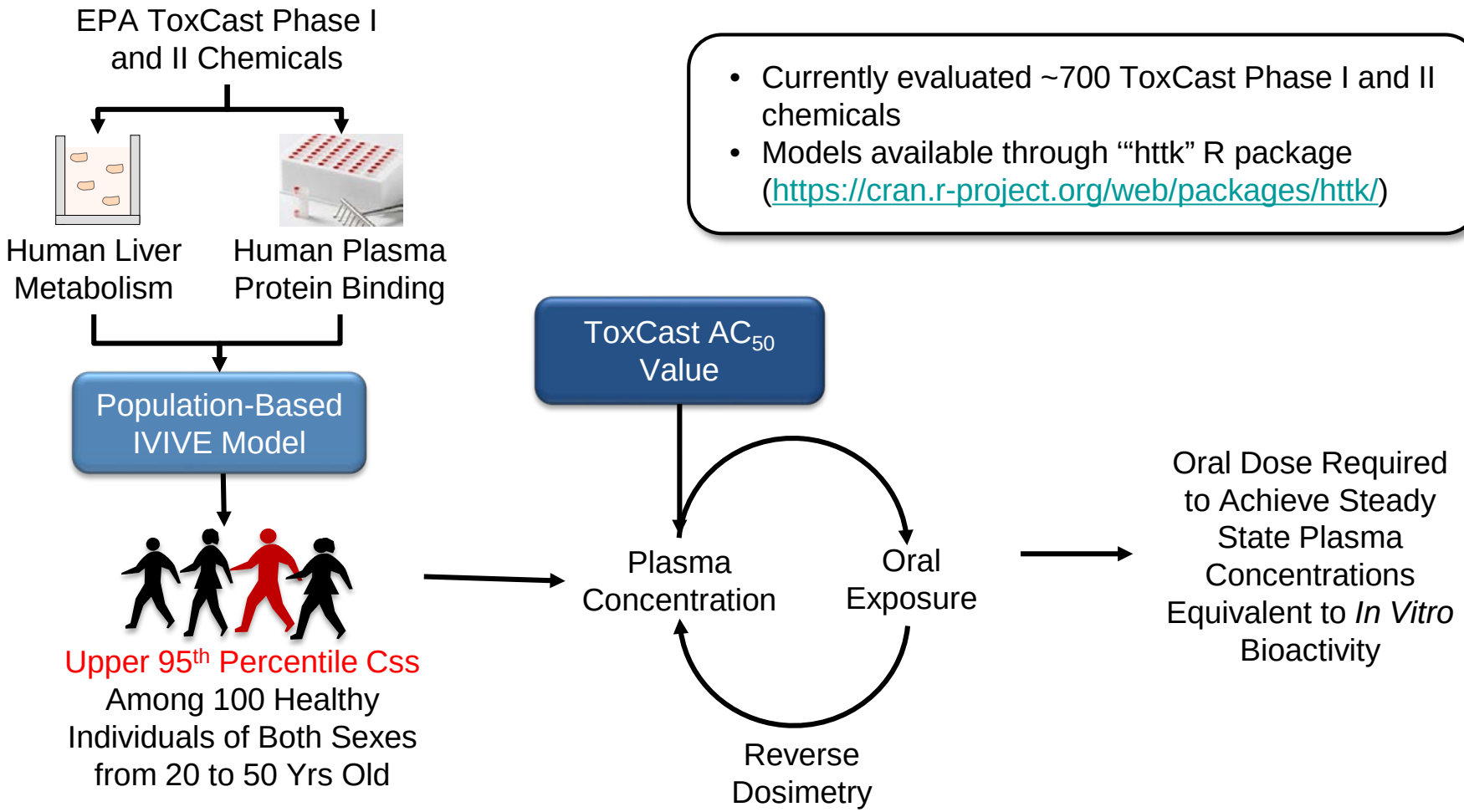





DeGroot and Simmons, Unpublished

# Adding the High-Throughput Toxicokinetic Component

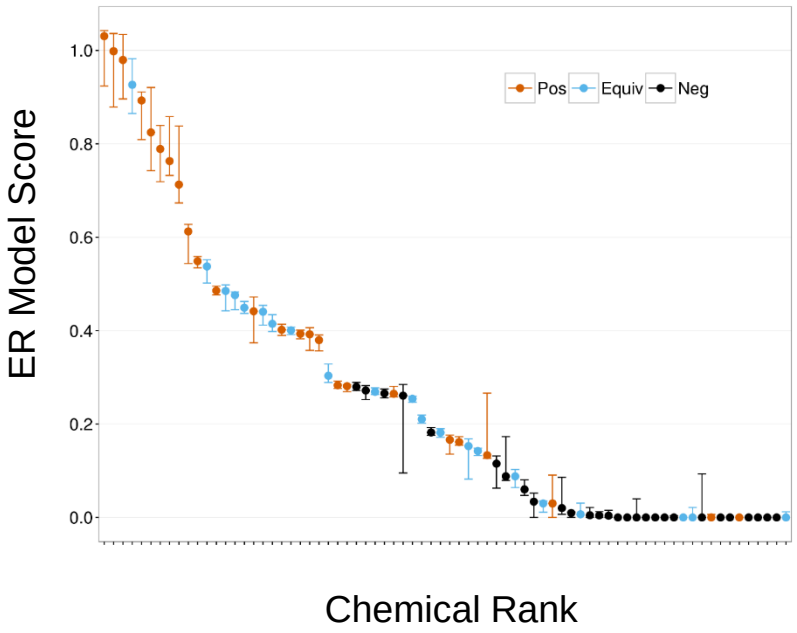



- Currently evaluated ~700 ToxCast Phase I and II chemicals
- Models available through "'httk" R package (https://cran.r-project.org/web/packages/httk/)

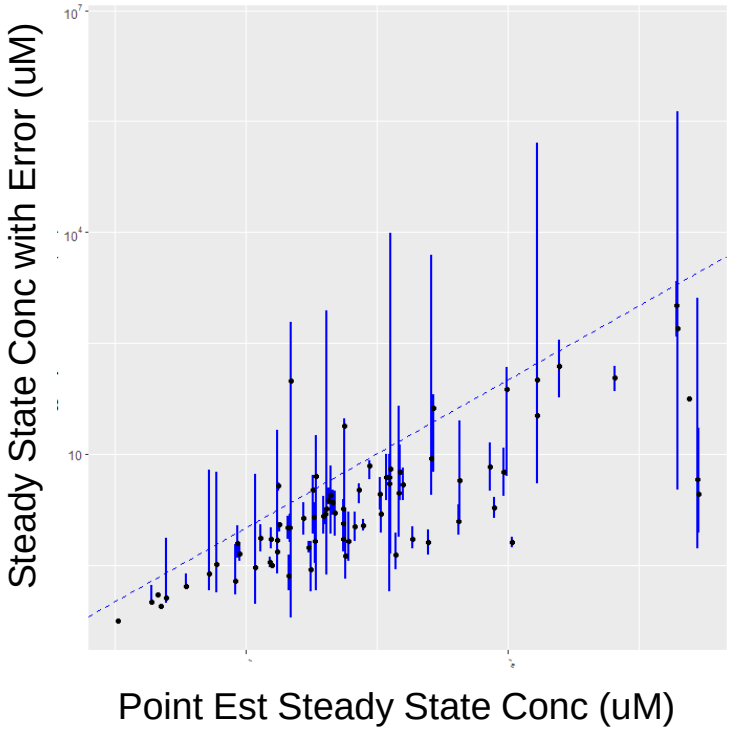
Rotroff *et al., Tox Sci.*, 2010
Wetmore *et al., Tox Sci.,* 2012

# Adding in Chemical-Specific Uncertainty

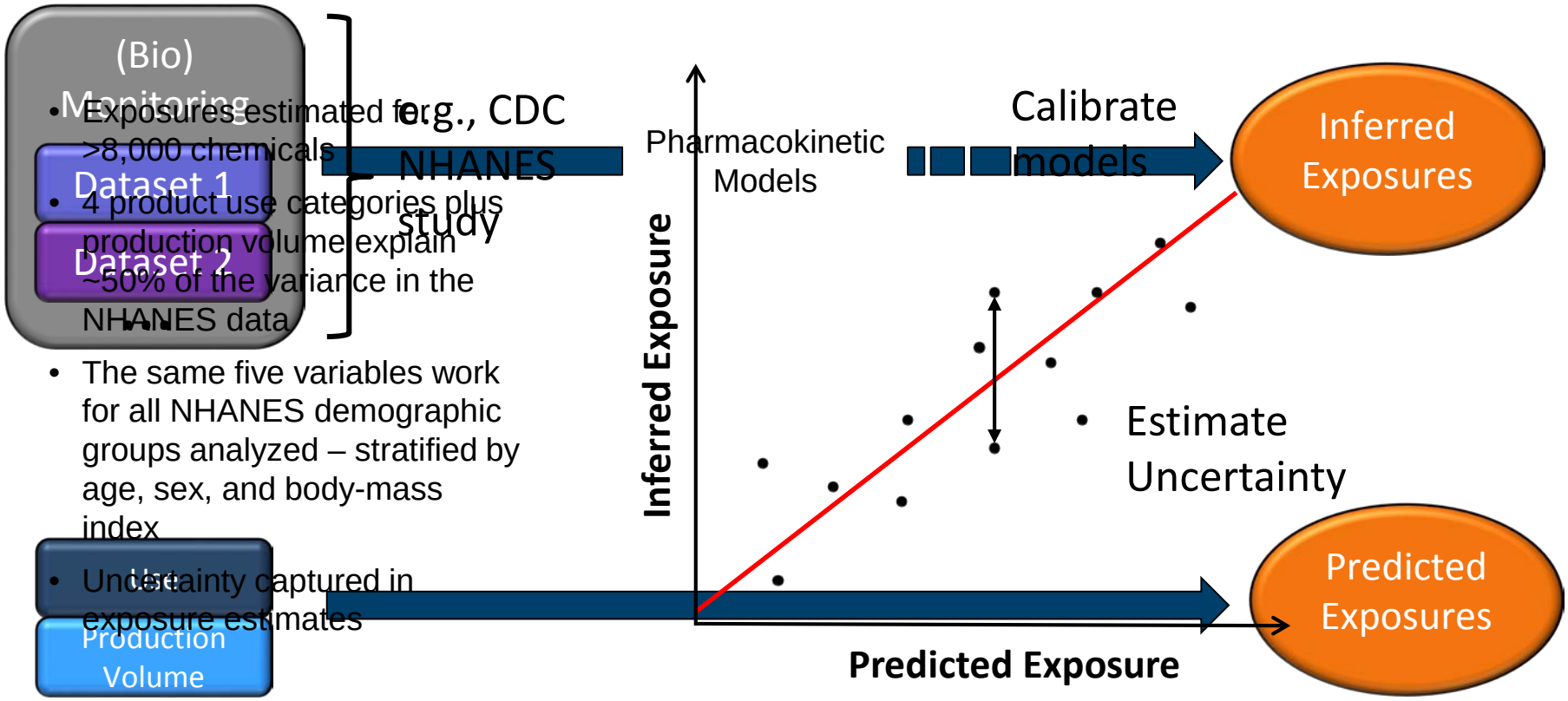
Propagation of Experimental Uncertainty in Models of ER Potency




Propagation of Experimental Uncertainty in High-Throughput Toxicokinetic Estimates



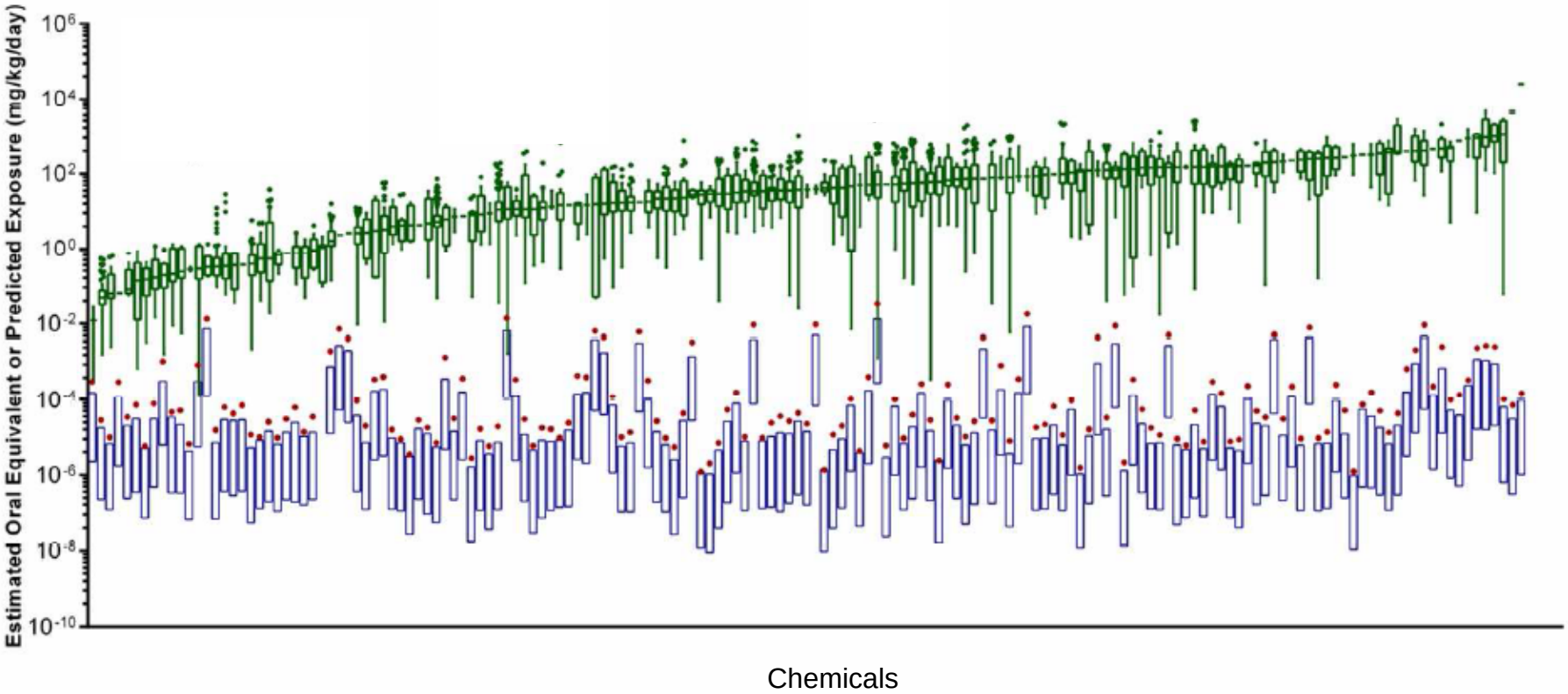
# Adding the High-Throughput Exposure Component




- Exposures estimated for >8,000 chemicals
- 4 product use categories plus production volume explain ~50% of the variance in the NHANES data
- The same five variables work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index
- Uncertainty captured in exposure estimates

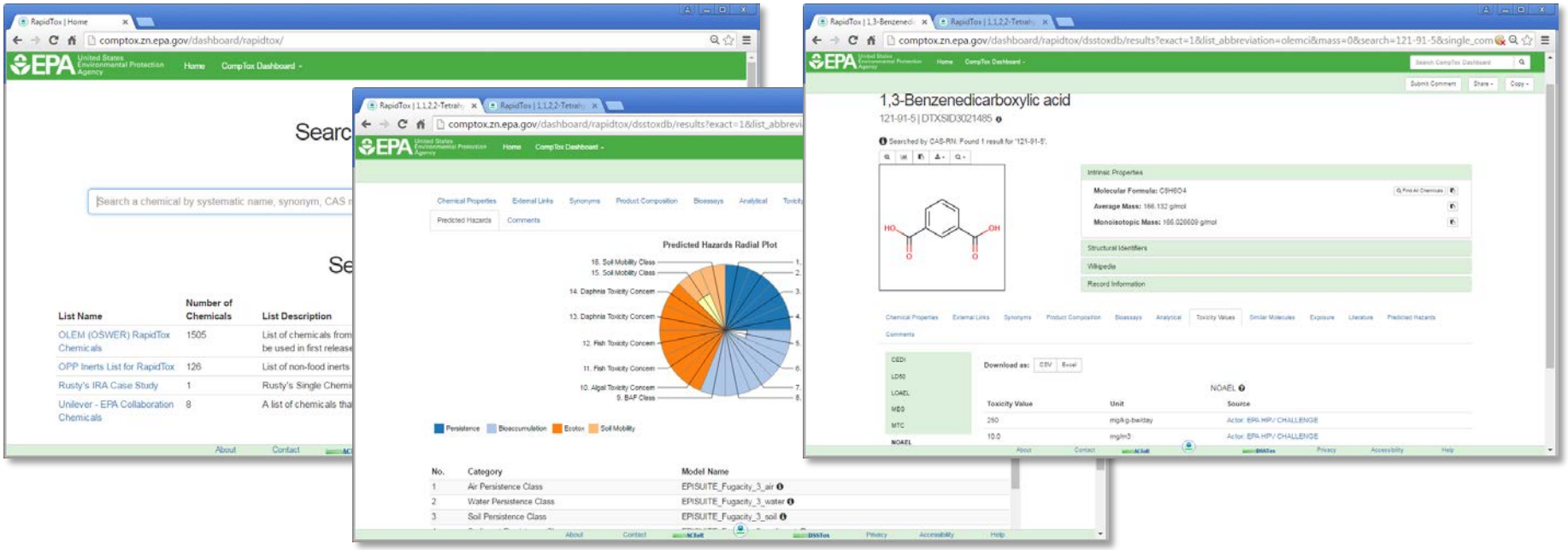
Wambaugh *et al.*, 2014

# Comparing Bioactivity with Exposure Predictions for Risk Context




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

# RapidTox Dashboard as a Focal Point for Integrating Components




- Semi-automated decision support tool with dashboard interface for high-throughput risk assessments
- Integrate a range of information related to chemical properties, fate and transport, hazard, and exposure
- Transparent and interactive enough to enable expert users to review the assumptions made and refine the predictions
- Deliver quantitative toxicity values with associated estimates of uncertainty

# Thank You for Your Attention!

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

EPA Colleagues:
- NERL
- NHEERL
- NCEA

**EPA's National Center for Computational Toxicology**