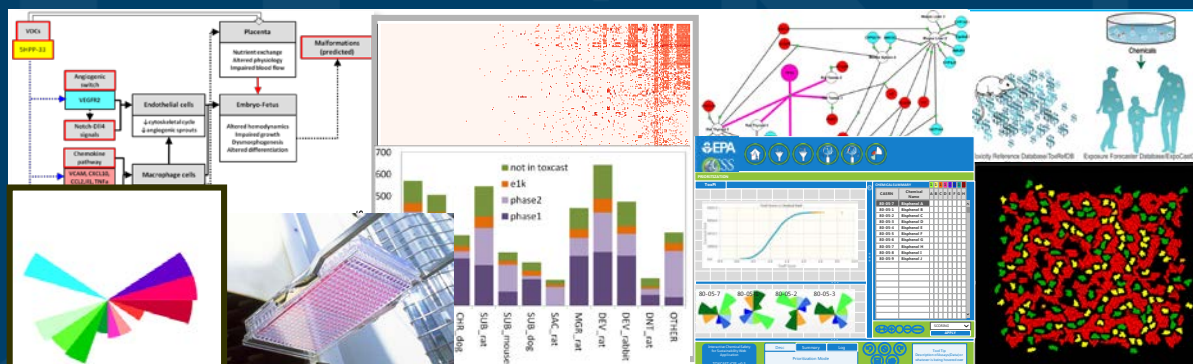


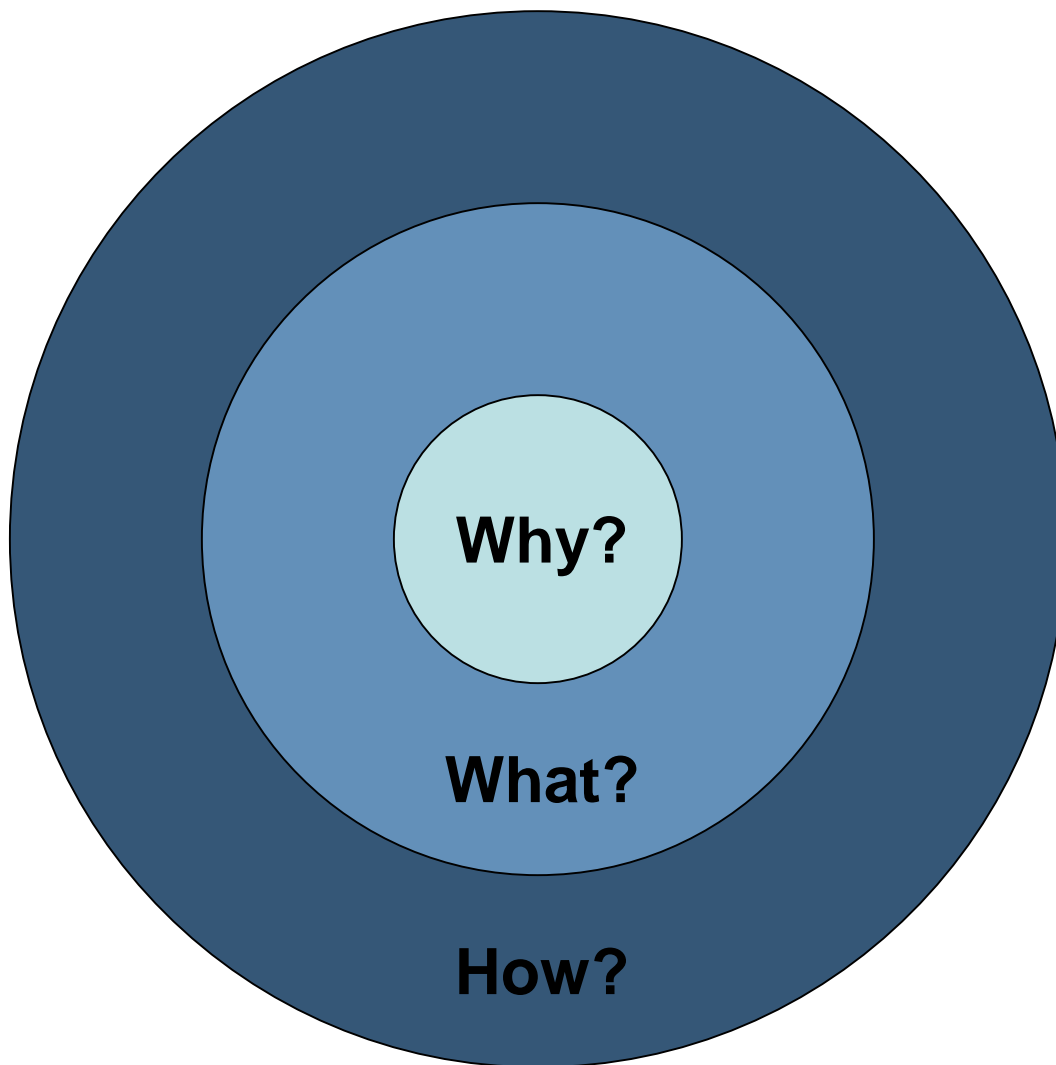
# Incorporating New Technologies for 21st Century Toxicity Testing and Risk Assessment



GlobalChem  
February 22, 2017

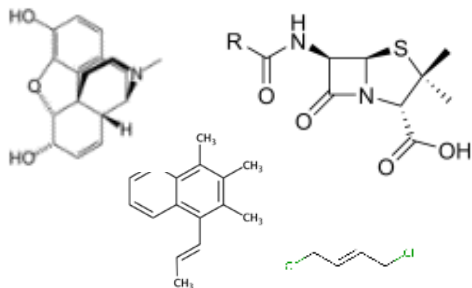
Russell Thomas  
Director  
National Center for Computational Toxicology

# Sinek's 'Golden Circle' of 21<sup>st</sup> Century Risk Assessment

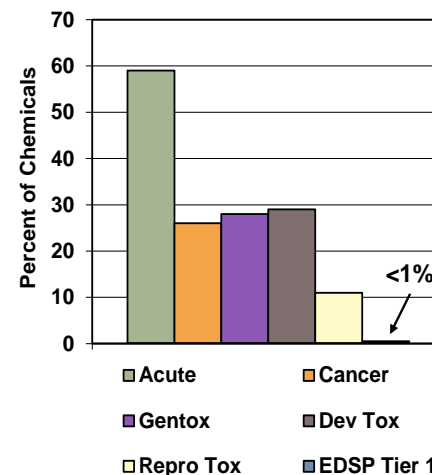


# All Understand 'Why' We Need to Innovate In This Space...

## Number of Chemicals /Combinations



## Lack of Data



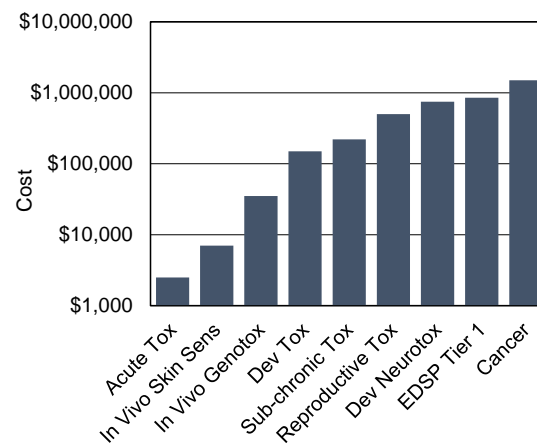
Modified from Judson *et al.*, EHP 2010

**Why?**

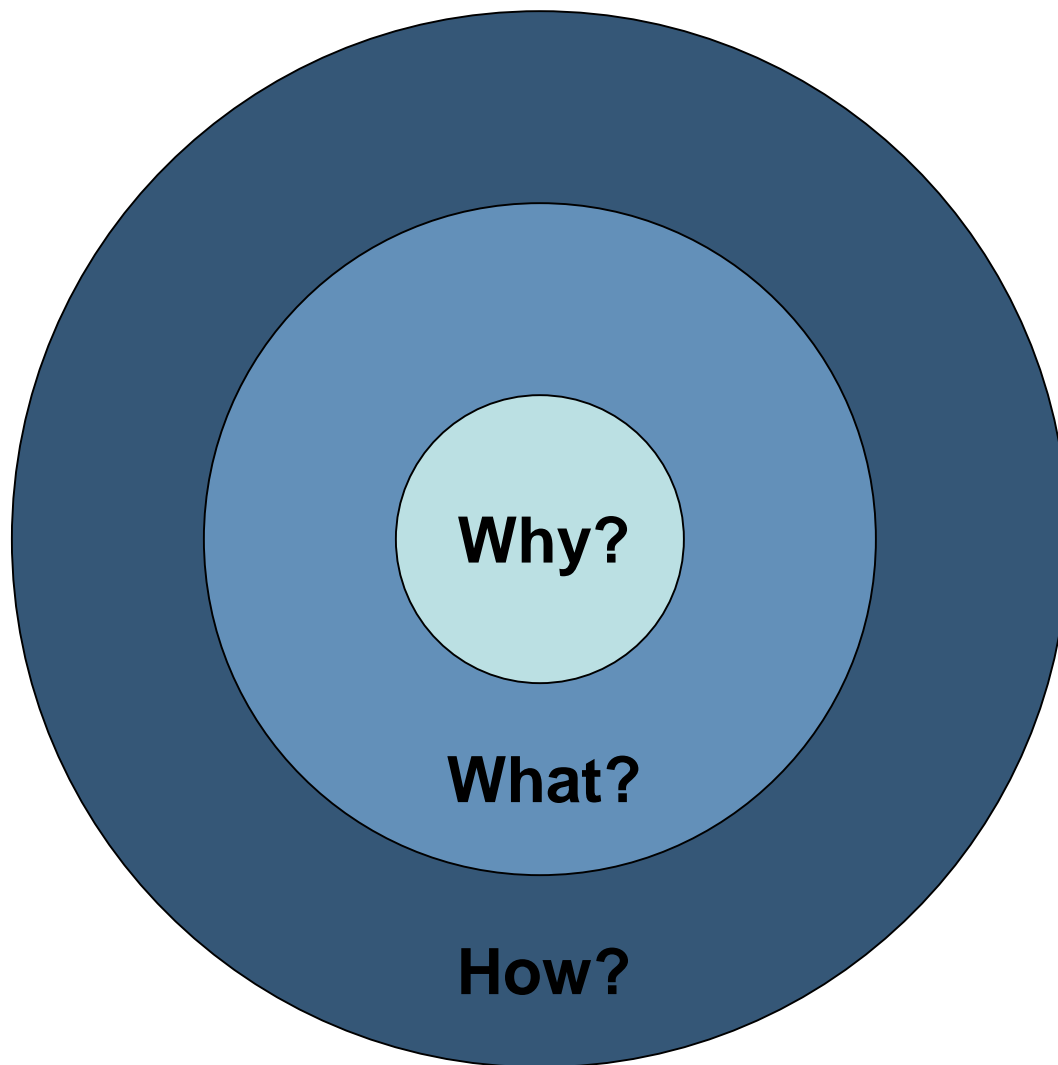
## Ethics Concerns



## Economics



# 'Golden Circle' of 21<sup>st</sup> Century Risk Assessment



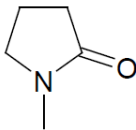
# Risk Assessments Generally Contain a Standard Set of Components

**EPA** 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

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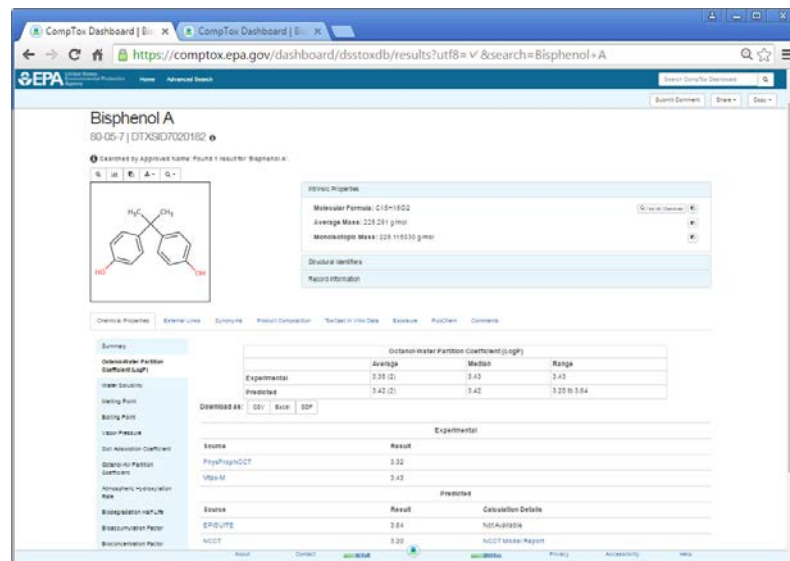
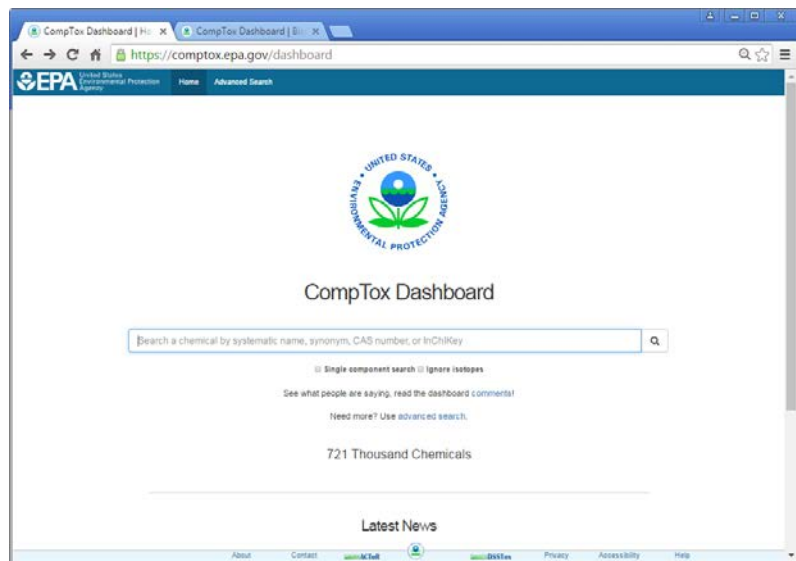
**Phys Chem**  
**Exposure**  
**Hazard**  
**Dose Response,**  
**PK, and PODs**

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**Variability**  
**Risk Summary**  
**Uncertainty**

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

# It All Starts With Chemistry...

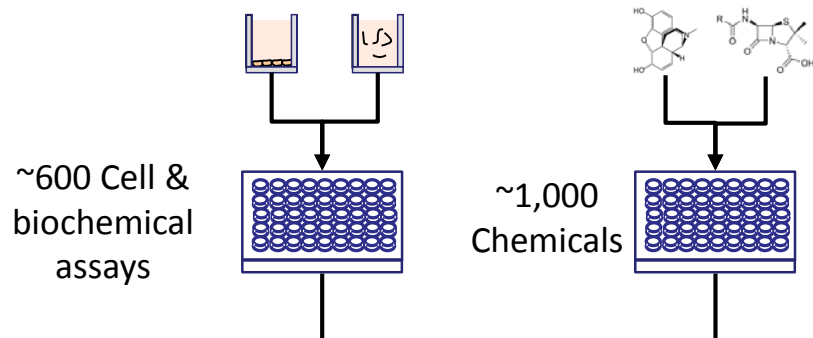


<https://comptox.epa.gov/dashboard>

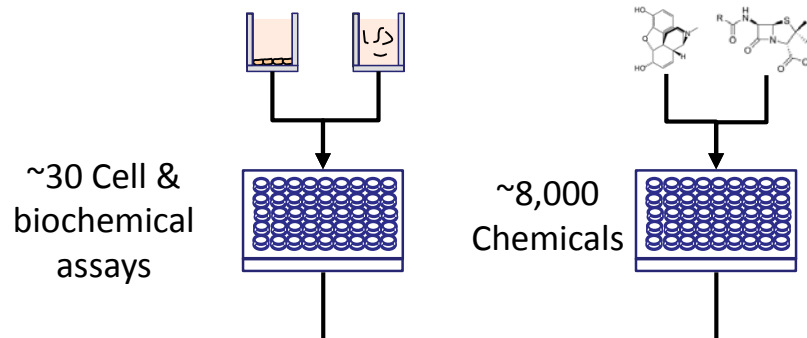
- Chemical structure database of >700,000 unique substances with QC flags to link chemical structure with names and identifiers
- Consensus QSAR models for a range of physical chemical properties, environmental fate, and hazard characteristics
- Comprehensive physical-chemical property database (experimental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

# Adding the High-Throughput Hazard Screening Component

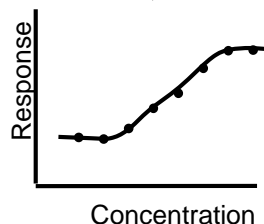
## ToxCast



## Tox21

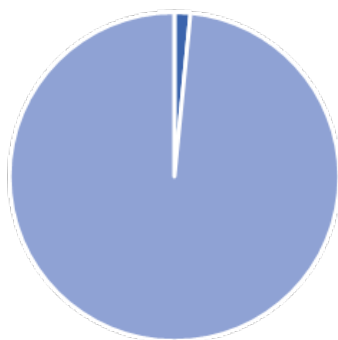


Set	Chemicals	Assays	Completion
ToxCast Phase I	293	~600	2011
ToxCast Phase II	767	~600	2013
ToxCast Phase III	1001	~100	Ongoing
E1K (endocrine)	880	~50	2013



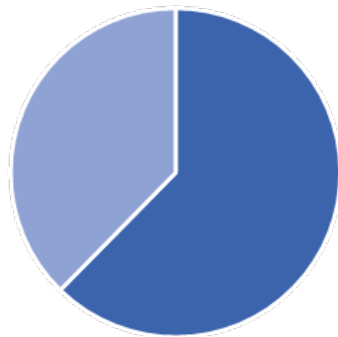
# Beginning to Address Concerns for Increased Biological Coverage

## Gene Coverage

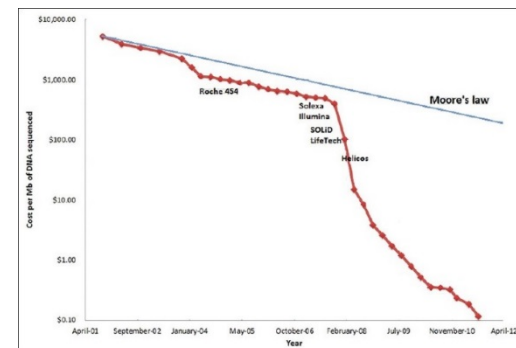


■ ToxCast  
■ Not in ToxCast

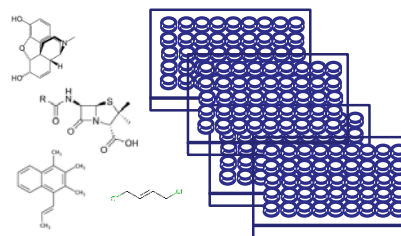
## Pathway Coverage\*



\*At least one gene from pathway represented

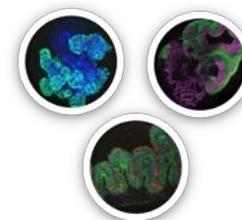


Thousands of chemicals



Multiple Cell Types

X

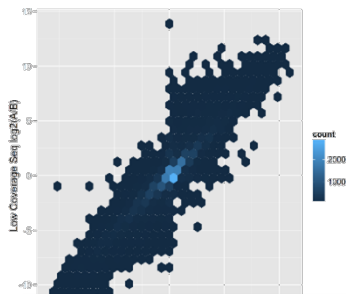


## Requirements:

- Low cost
- Whole genome
- 384 well
- Automatable

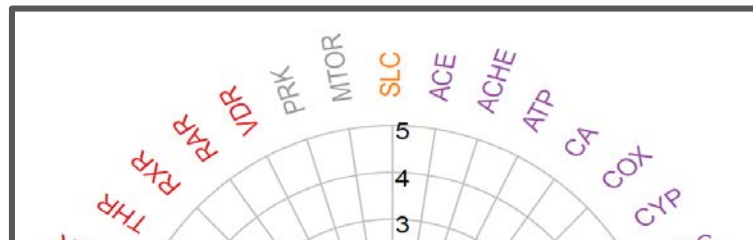


# Comparing Sequencing Platforms and Developing Analysis Approach



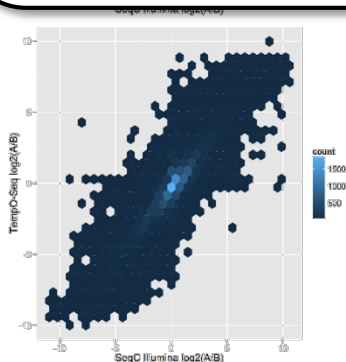
**TruSeq**  
 $r^2$  0.74

## MOA Analysis Pipeline

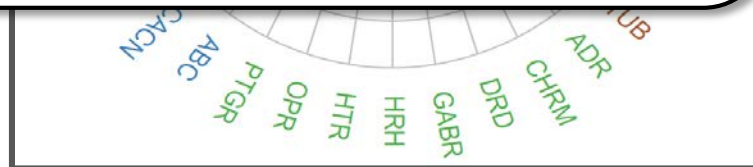


**COMING SOON!**

- 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)

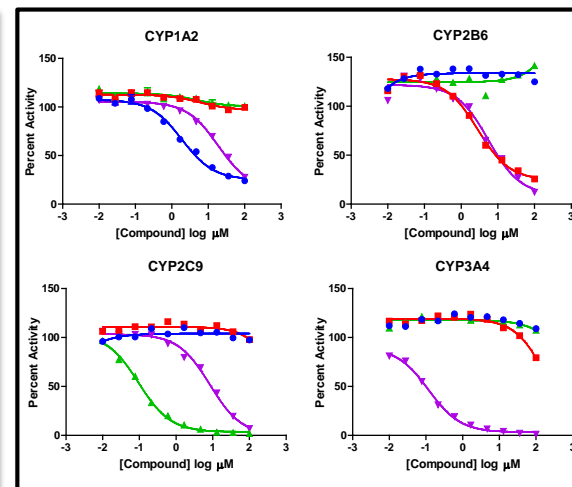
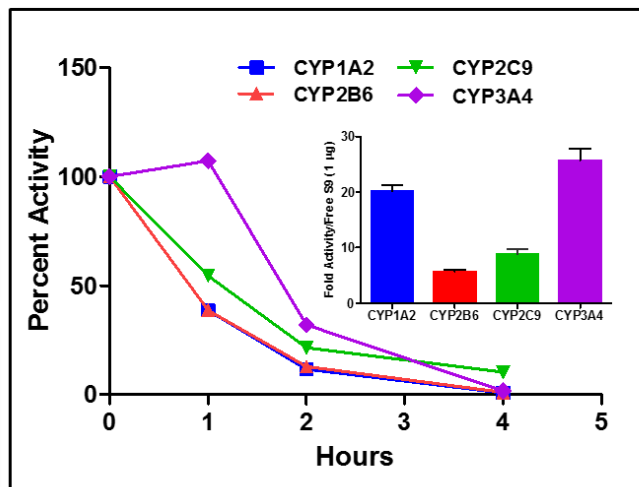
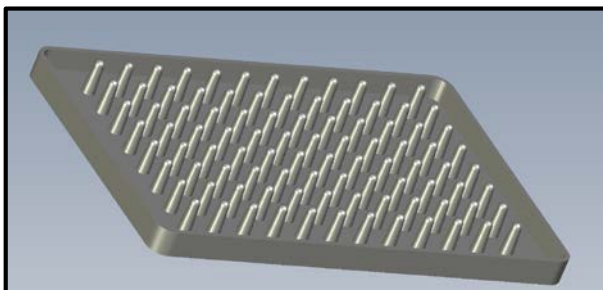


**Low Coverage**  
 $r^2$  0.83

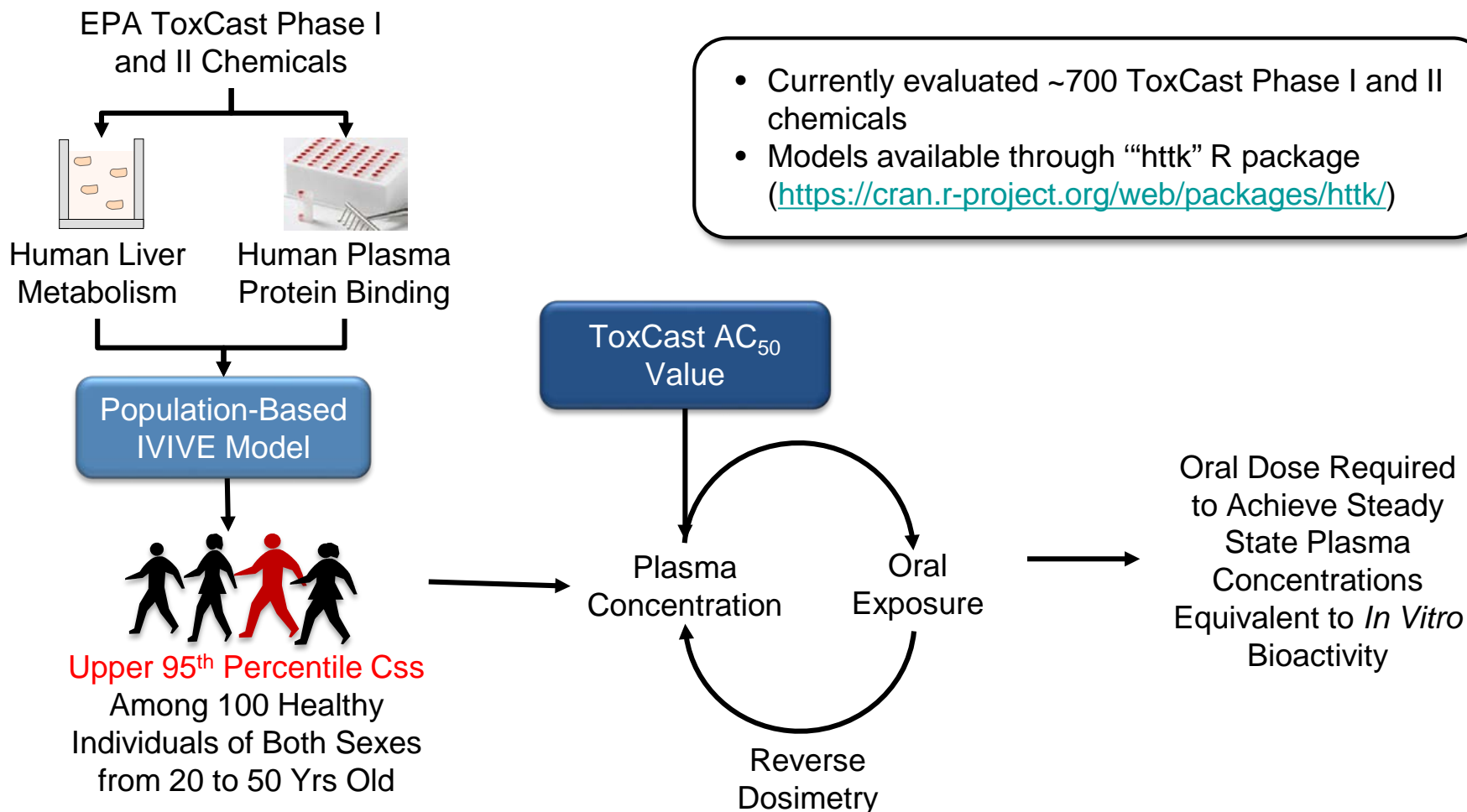


Currently capable of assigning to >40 MOAs based on transcriptional responses

# Beginning to Address Metabolic Competence



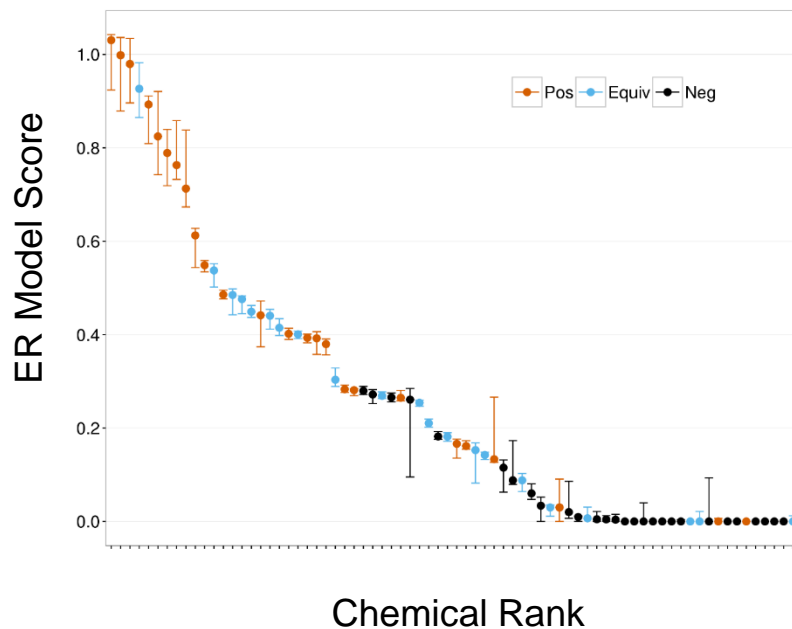
# Adding the High-Throughput Toxicokinetic Component



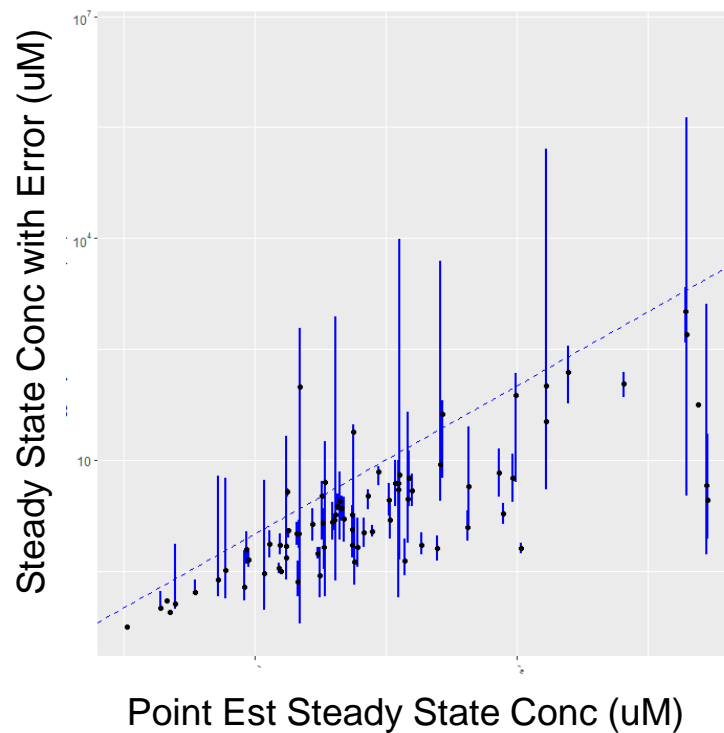
Retroff *et al.*, *Tox Sci.*, 2010  
Wetmore *et al.*, *Tox Sci.*, 2012

# Adding in Chemical-Specific Uncertainty

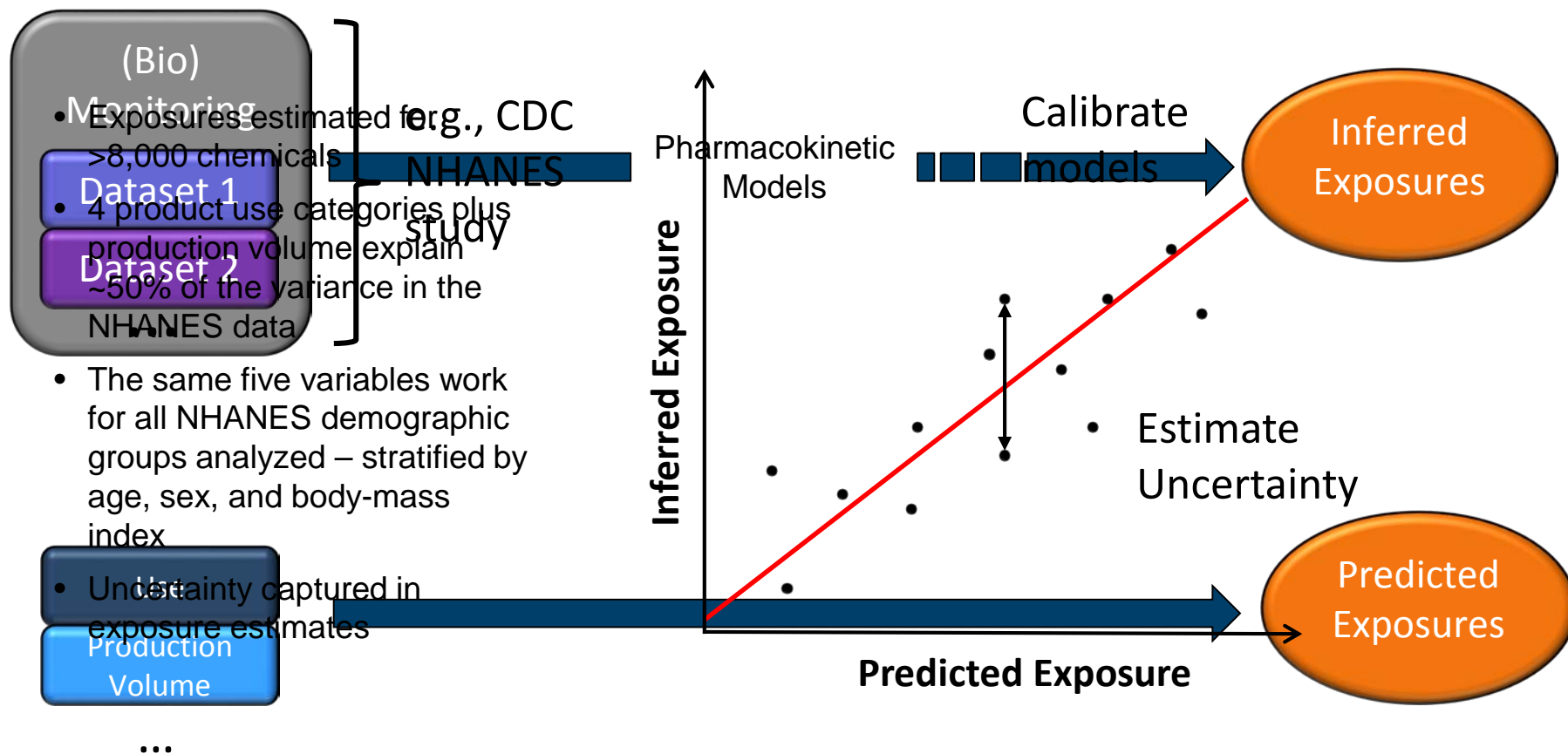
Propagation of Experimental Uncertainty in  
Models of ER Potency



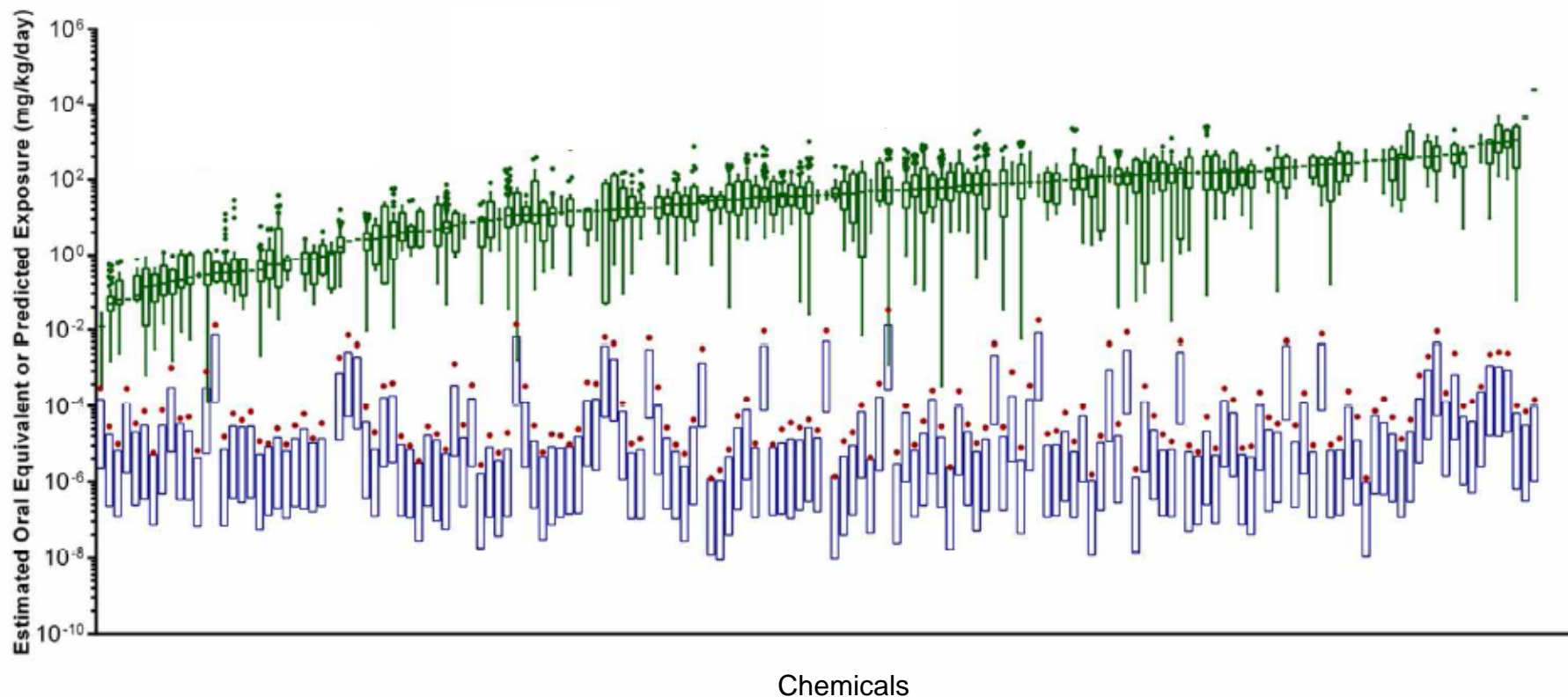
Propagation of Experimental Uncertainty in  
High-Throughput Toxicokinetic Estimates



# Adding the High-Throughput Exposure Component



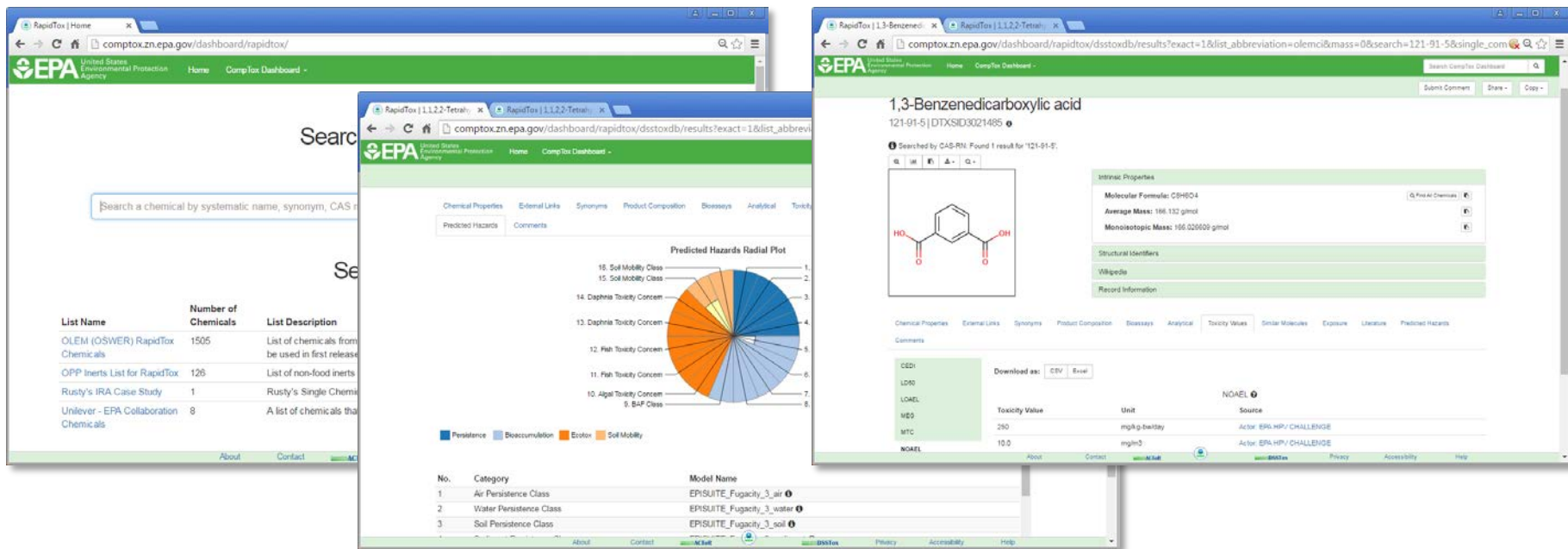
# Comparing Bioactivity with Exposure Predictions for Risk Context



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**