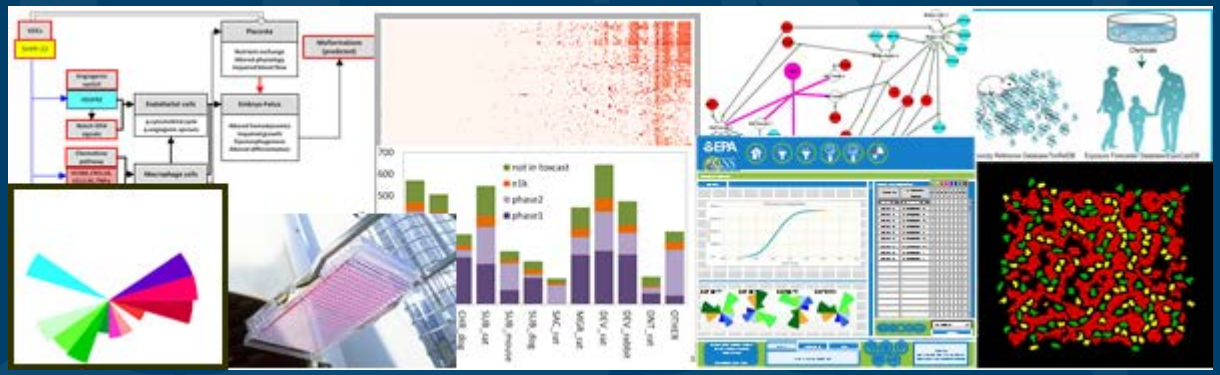
ORCID ID: 0000-0002-2340-0301

EPA United States Environmental Protection Agency

ToxCast/CompTox Update

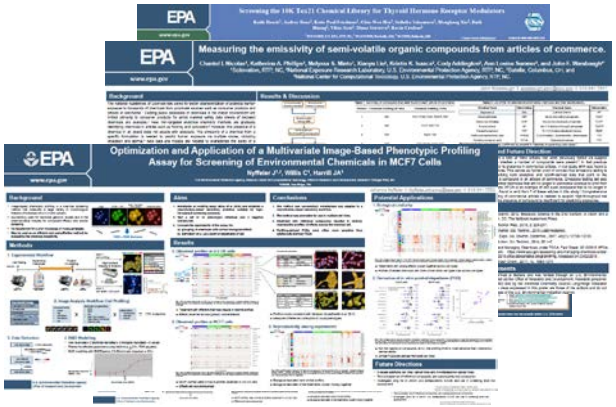


SOT 21st Century Toxicology Satellite Meeting

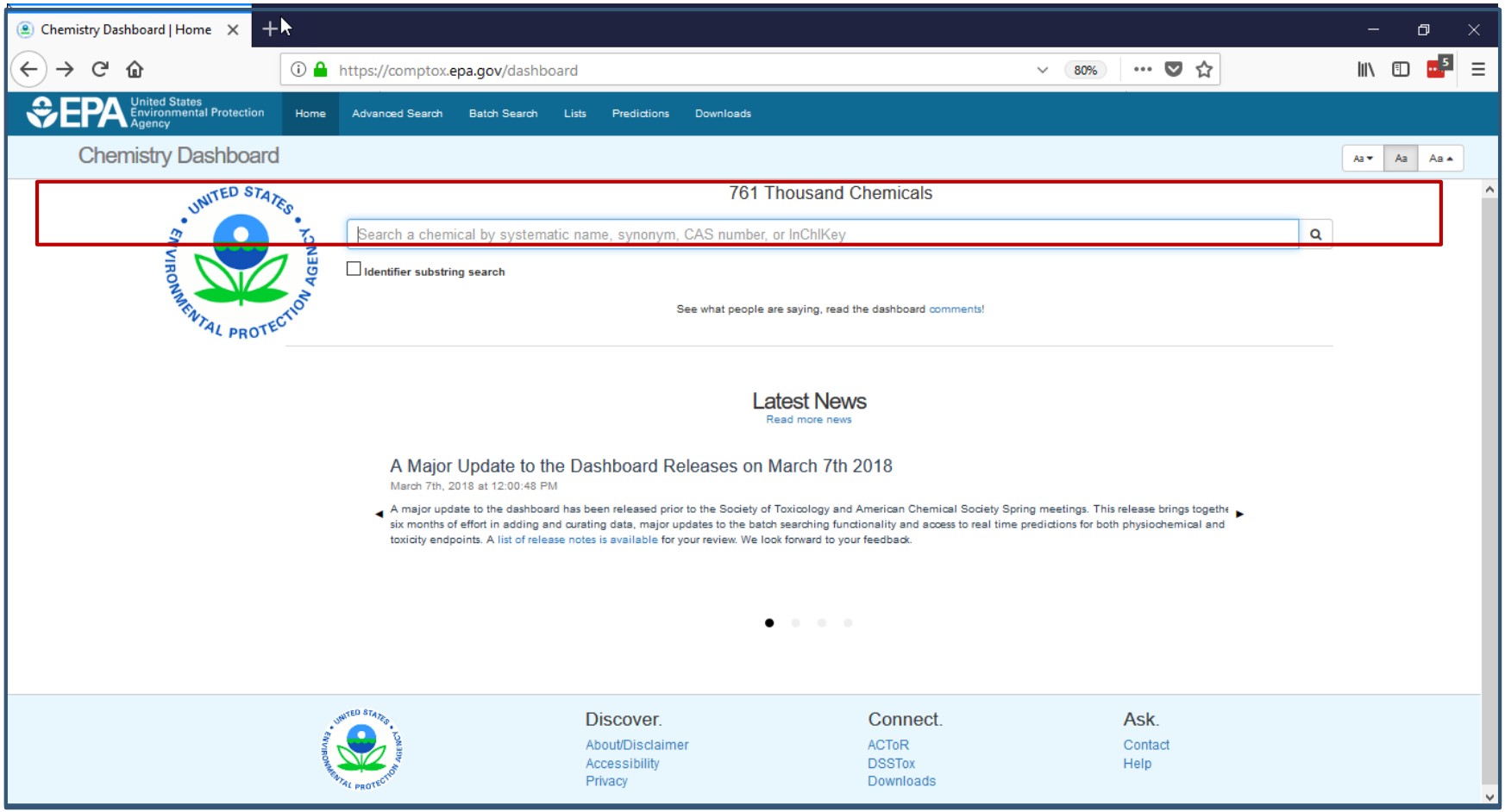
March 15, 2018

Rusty Thomas
Director
National Center for Computational Toxicology

A 10 min Update of the Program Would Require Johnny Mnemonic

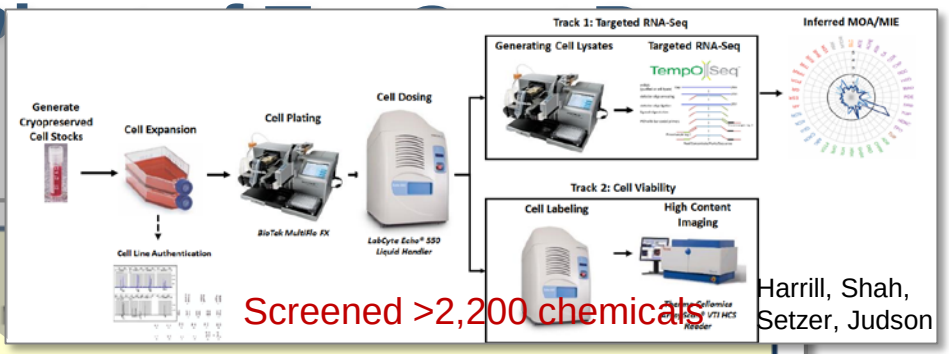


New Version of the Chemistry Dashboard – One Stop Shop



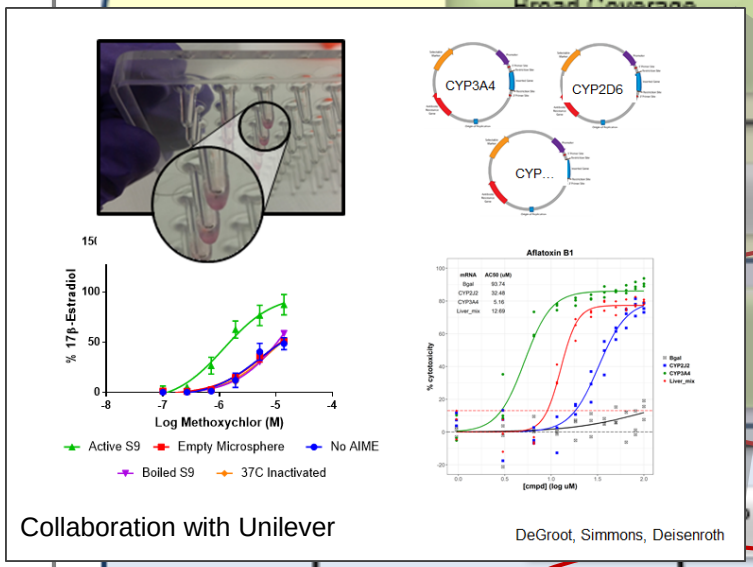
United States Environmental Protection Agency

Completing P



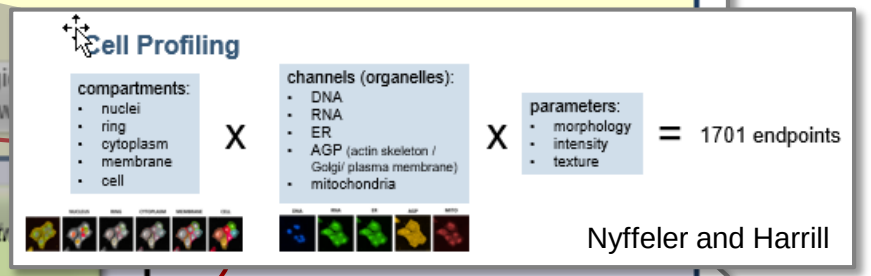
Screened >2,200 chemicals

Harrill, Shah, Setzer, Judson

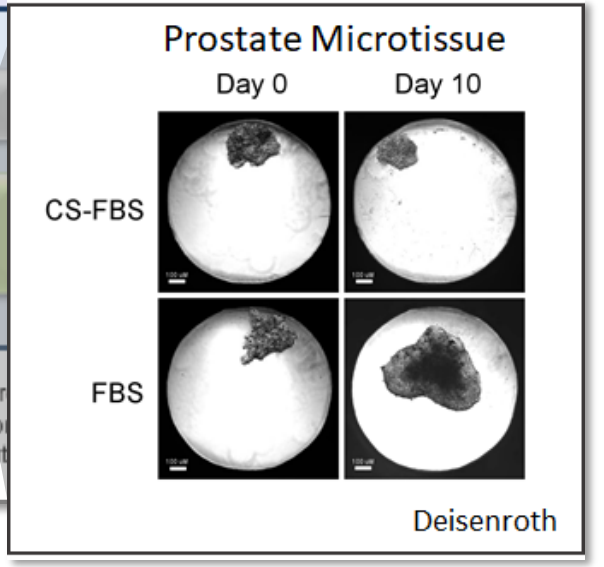


Collaboration with Unilever

DeGroot, Simmons, Deisenroth



Nyffeler and Harrill



Deisenroth

Select *In Vitro* Assays

No AOP

In Vitro Assays for other KEs and Systems Modeling

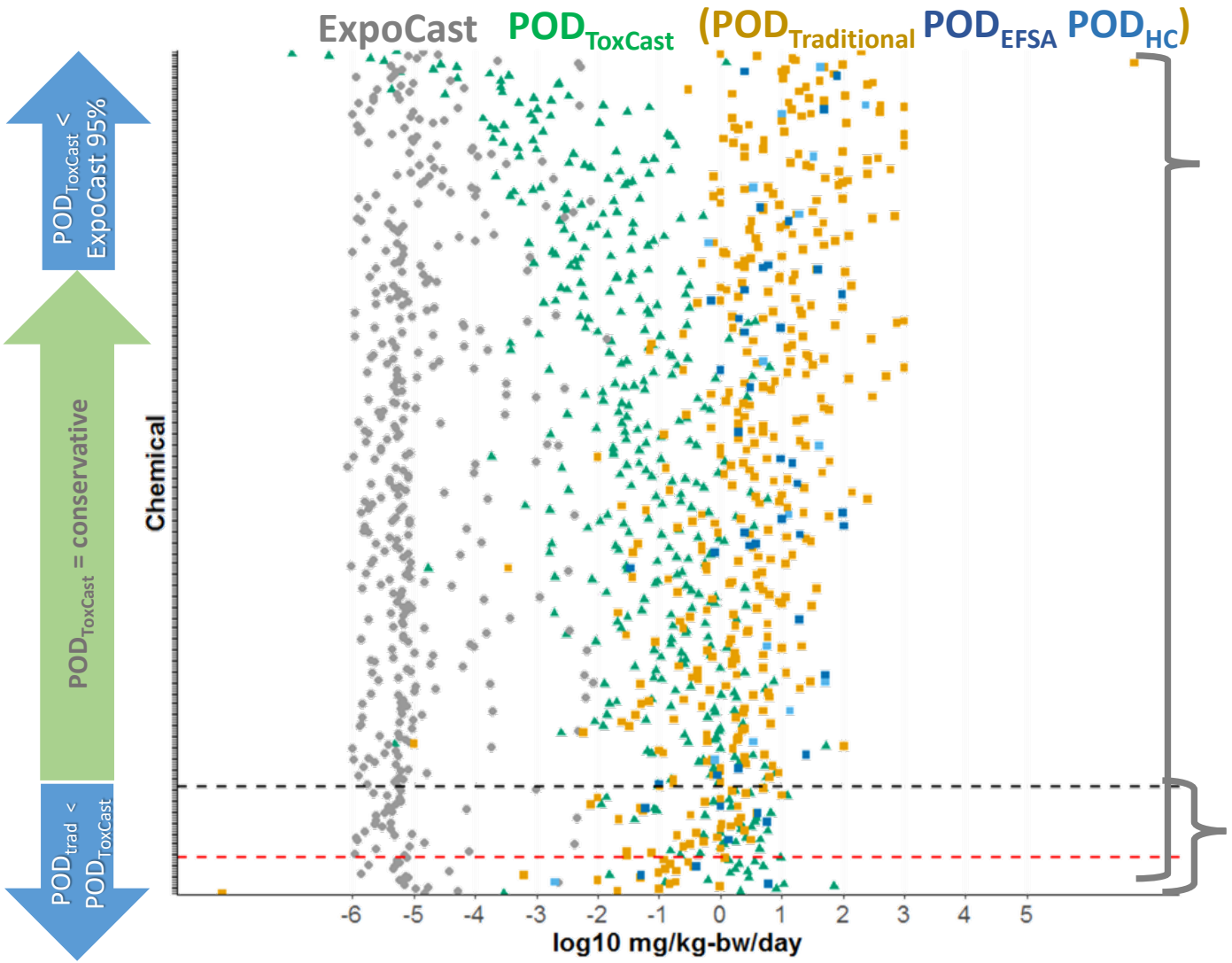
Organotypic Assays and Microphysiological Systems

Estimate Point-of-Departure Based on Pathway Transcriptional Perturbation

Estimate Point-of-Departure Based on AOP

Estimate Point-of-Departure Based on Likely Tissue- or Organ-level Effect without AOP

Completing Pivot of ToxCast Program



Total =

380 chemicals

httk, ToxCast data, and POD value(s) currently available

For ~91.3% of the chemicals, $POD_{ToxCast}$ was conservative.

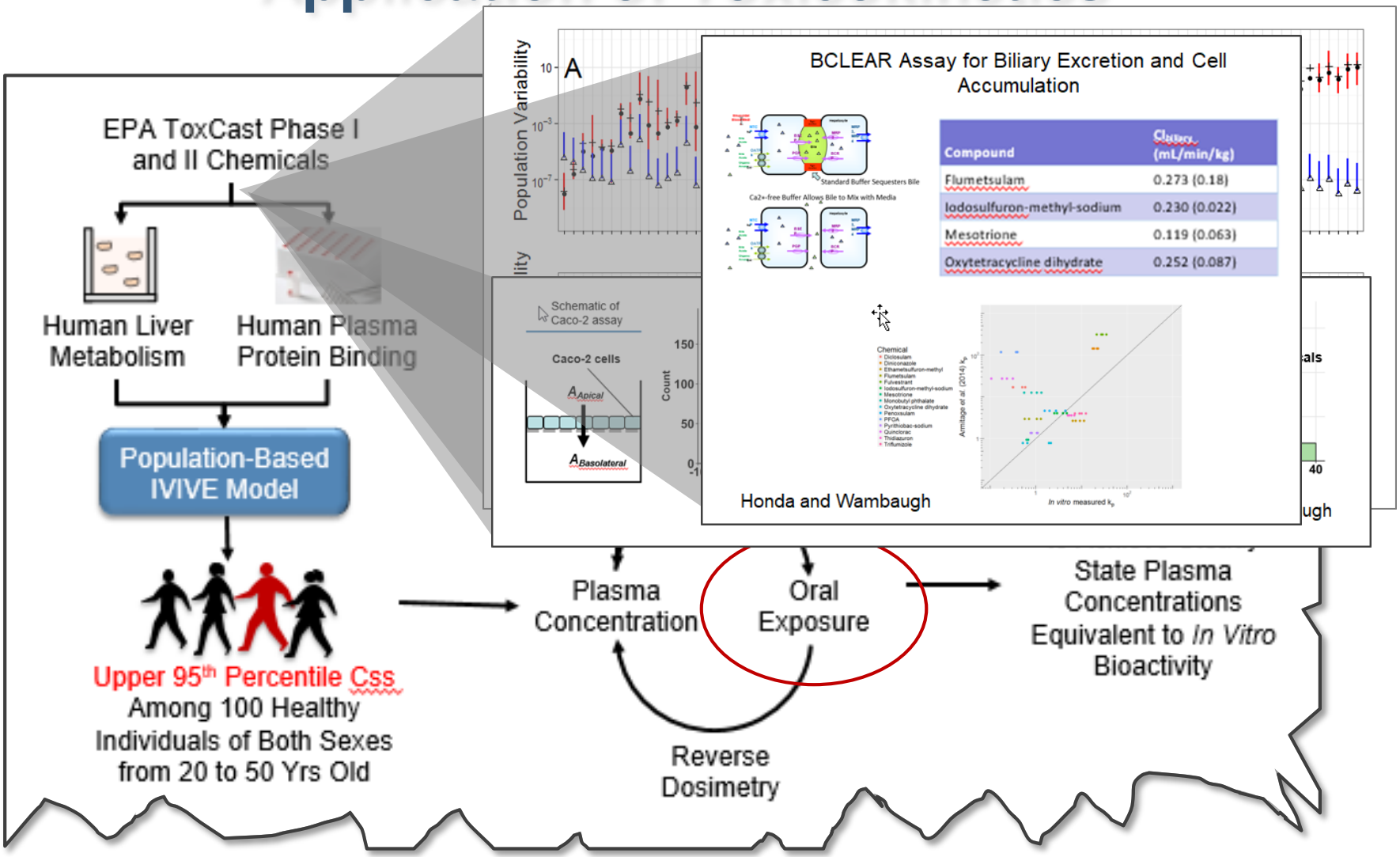
(~100-fold with human HTTK

~50-fold with rat HTTK)

Missing an important component of biology?

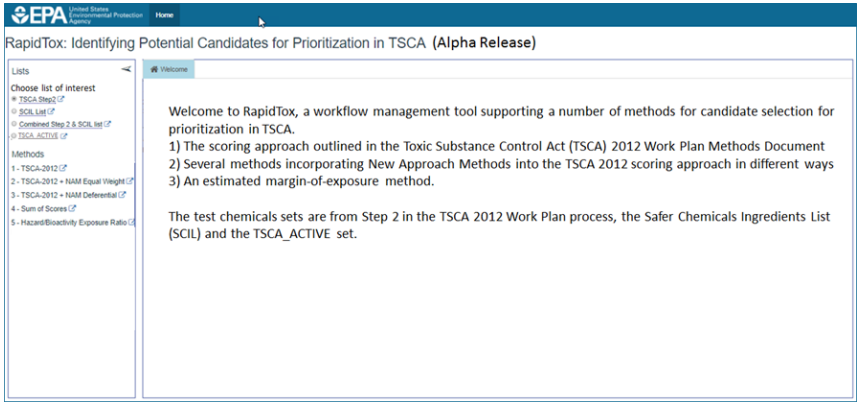
International case study with EPA, ASTAR, ECHA, Health Canada, and EFSA

Advancing Development and Application of Toxicokinetics



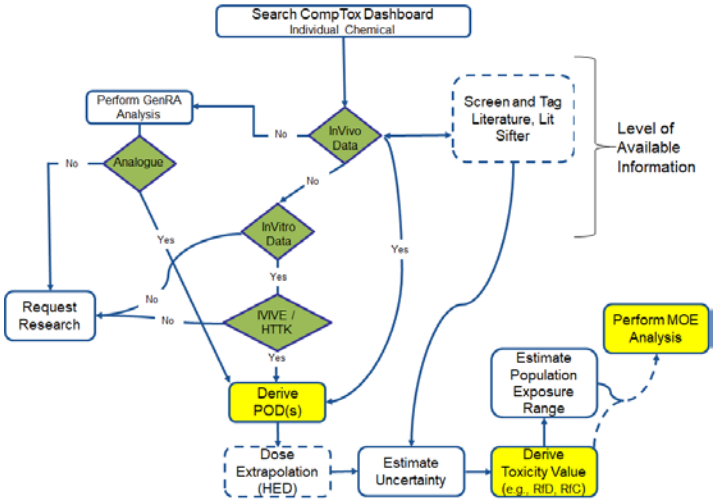
Working With Regulatory Partners to Incorporate Data into Decision Making

RapidTox Prioritization Workflow



- Decision support tool for prioritization with dashboard interface
- Integrate a range of information related to chemical properties, fate and transport, hazard, and exposure
- Transparent and interactive
- Working with EPA Office of Chemical Safety and Pollution Prevention

RapidTox Screening Level Assessment Workflow



- Decision support tool for screening level chemical assessments
- Integrate a range of traditional and NAM data related to hazard, and exposure
- Transparent and interactive
- Derive screening level points of departure and margins-of-exposure
- Working with EPA Office of Land and Emergency Management

Tox21 Update

SOT 21st Century Toxicology Satellite Meeting
March 15, 2017

Russell Thomas
National Center for Computational Toxicology
U.S. EPA

The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of any of the Federal agencies represented.

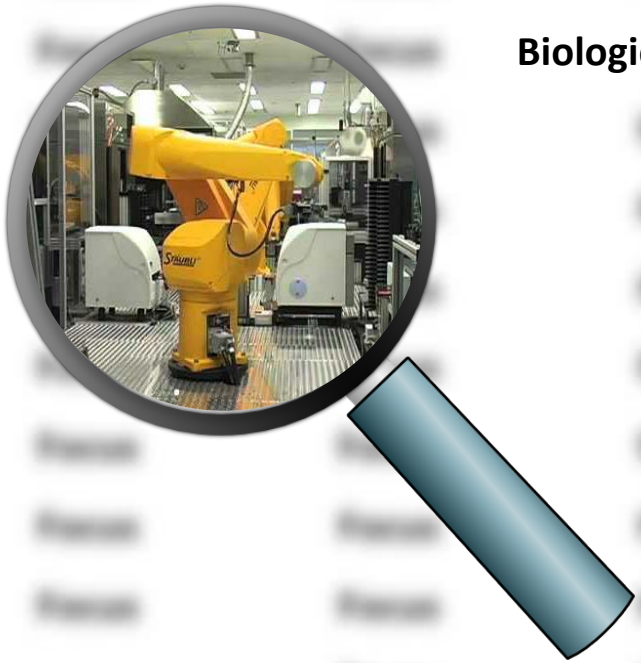
EPA NIH National Institute of Environmental Health Sciences NIH National Center for Advancing Translational Sciences FDA NTP National Toxicology Program U.S. Department of Health and Human Services

The Focus of Tox21 has been Predominantly on HTS

New Vision Expands the Scope to Move Toxicity Testing into 21st Century

Validation

Biokinetics

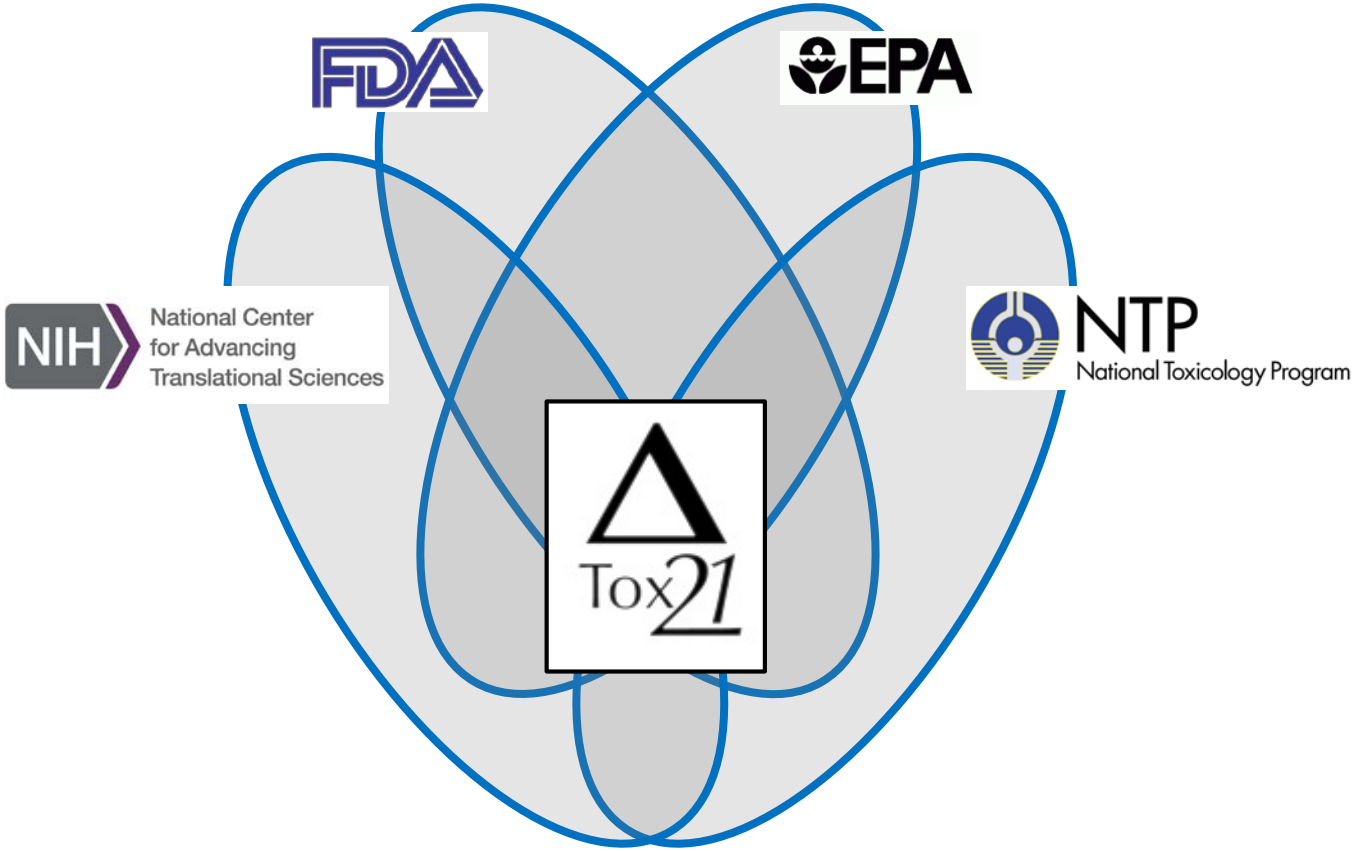


Organotypic Assays

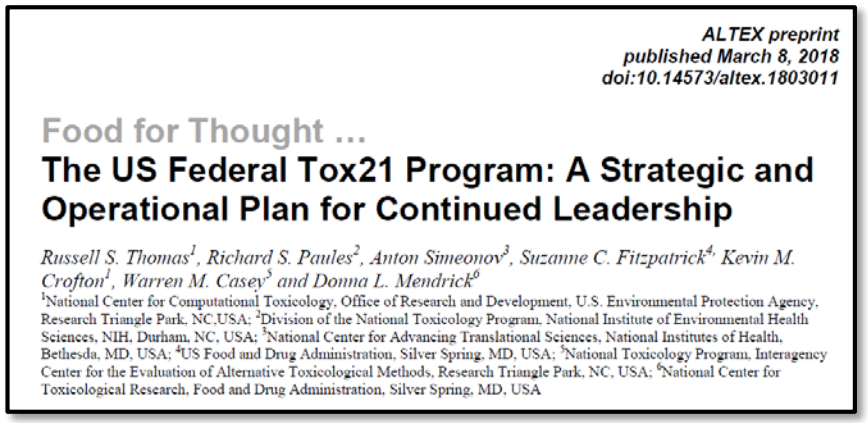
Biological Coverage

Metabolic Competence

The Challenge



New Tox21 Strategic and Operational Plan



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Food for Thought …

The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership

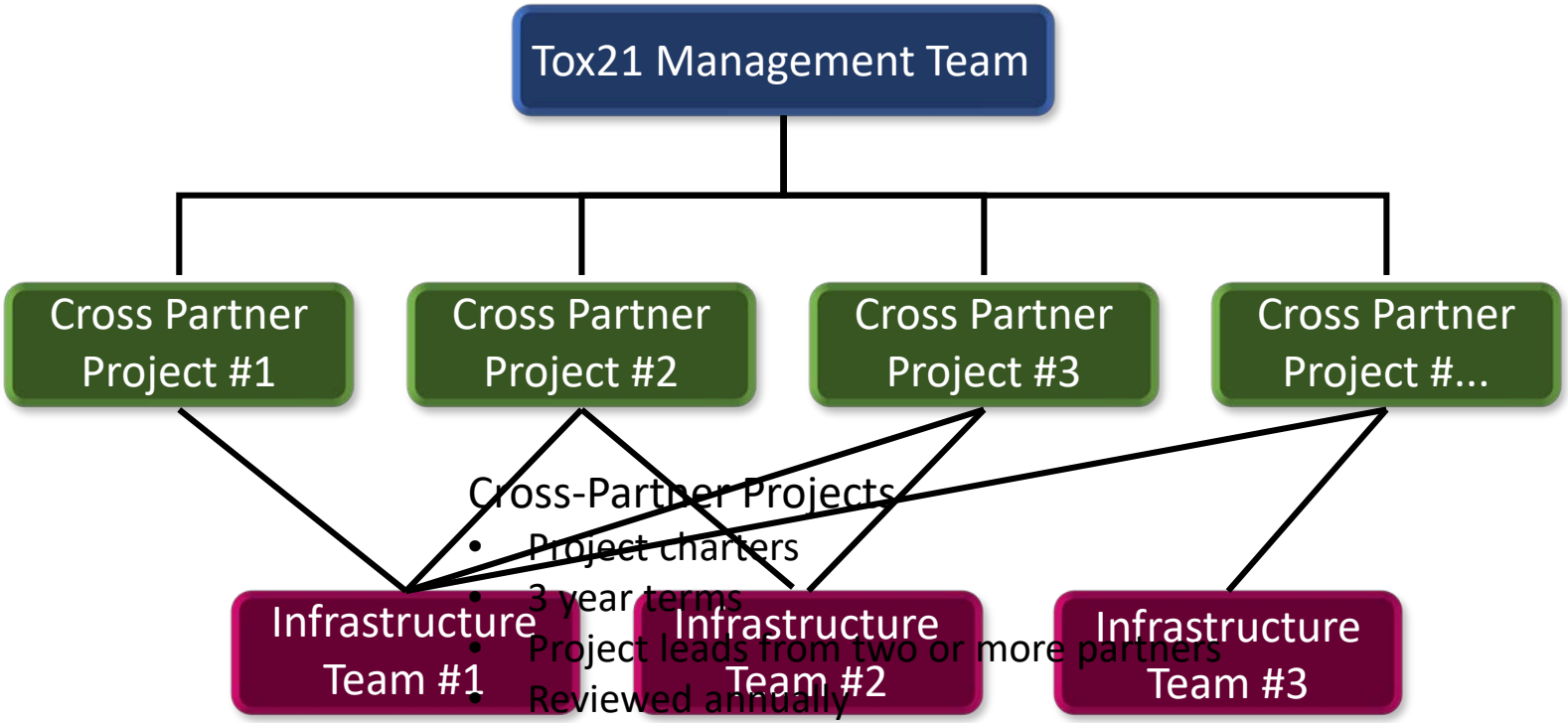
Russell S. Thomas[1], Richard S. Paules[2], Anton Simeonov[3], Suzanne C. Fitzpatrick[4], Kevin M. Crofton[1], Warren M. Casey[5] and Donna L. Mendrick[6]

[1]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC,USA; [2]Division of the National Toxicology Program, National Institute of Environmental Health Sciences, NIH, Durham, NC, USA; [3]National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA; [4]US Food and Drug Administration, Silver Spring, MD, USA; [5]National Toxicology Program, Interagency Center for the Evaluation of Alternative Toxicological Methods, Research Triangle Park, NC, USA; [6]National Center for Toxicological Research, Food and Drug Administration, Silver Spring, MD, USA

Areas of Focus

1. Develop and deploy alternative test systems that are predictive of human toxicity and dose response
2. Address key technical limitations of current *in vitro* test systems
3. Curate and characterize legacy *in vivo* toxicity studies to serve as a resource for interpreting Tox21 data
4. Develop framework for efficient validation of Tox21 approaches
5. Refine and deploy *in vitro* methods for characterizing pharmacokinetics to increase predictivity and reduce uncertainty

New Tox21 Structure



Initial Infrastructure Teams and Example Cross Partner Projects

Infrastructure Teams

- Chemical Library Management
- Communications
- Assay Evaluation and Screening

Cross-Partner Projects

- *In Vitro* Disposition of Tox21 Chemicals
- Performance Based Validation of Tox21 Assays
- Development of a Reference Chemical Dataset for Interpretation of High-Throughput Transcriptomic Screening Data
- Incorporating Genetic Susceptibility into Developmental Neurotoxicity Screening
- Development of a High-Throughput Assay to Identify 5-α Reductase Inhibitors for Orthogonal Evaluation in an Androgen-dependent Human 3D Prostate Tissue
- Cell Line Selection for High-Throughput Transcriptomic Screening
- Predictive Modeling of Developmental Toxicity with Human Pluripotent Stem Cells
- Development of a High-Throughput Assay to Identify Acetylcholinesterase Inhibitors