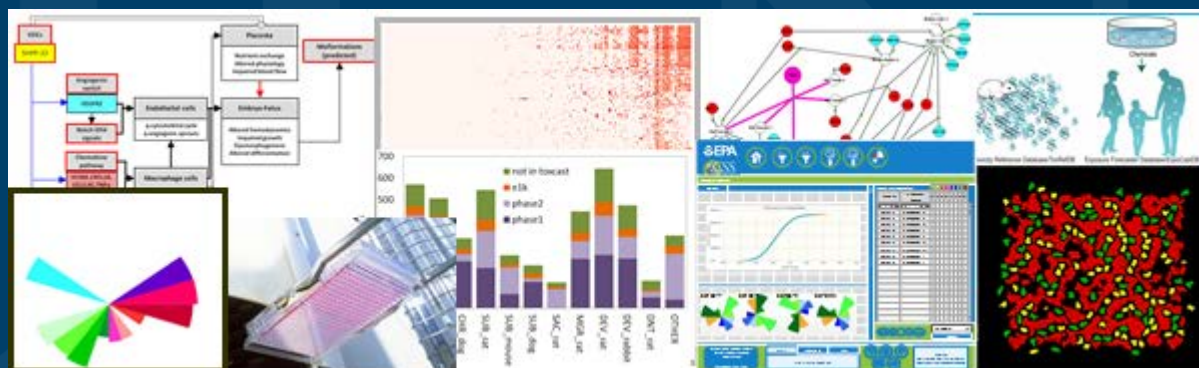


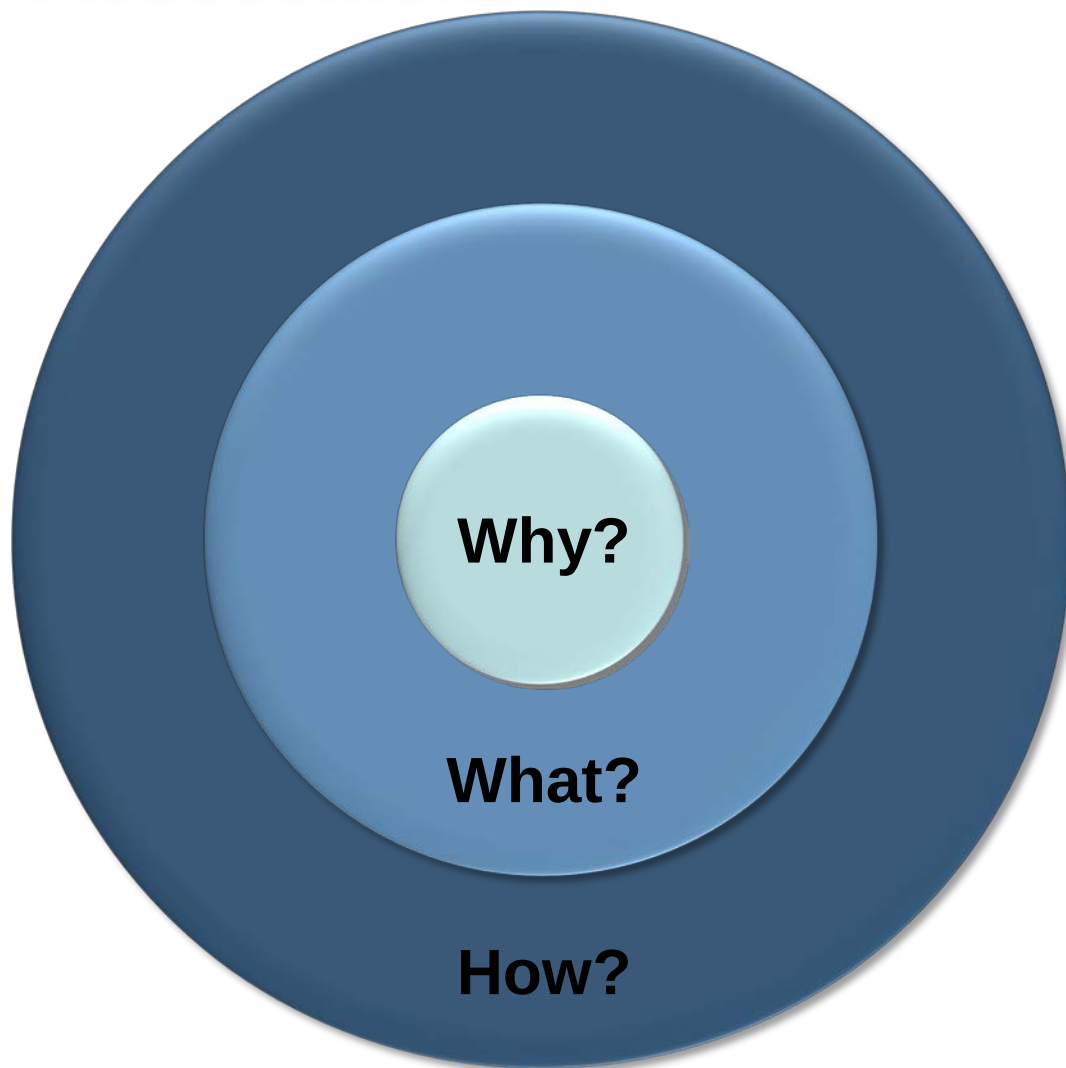
ToxCast and the Use of Human Relevant *In Vitro* Exposures: Incorporating high-throughput exposure and toxicity testing data for 21st century risk assessments



BTS
April 4, 2017

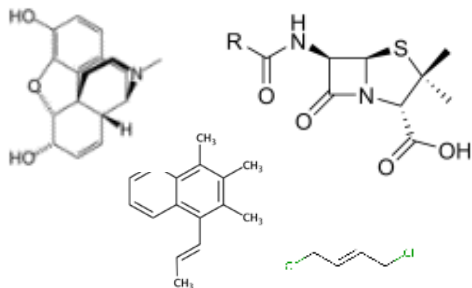
Russell Thomas
Director
National Center for Computational Toxicology

Using the 'Golden Circle' for the Transition to 21st Century Risk Assessment

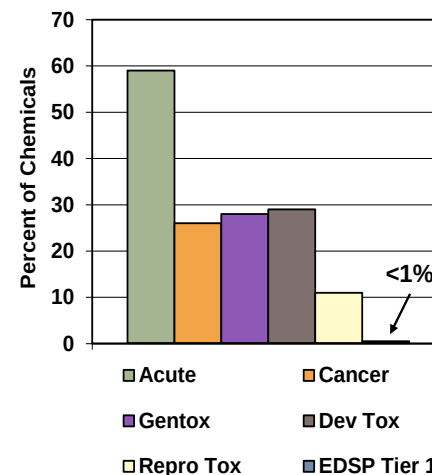


Understanding 'Why' We Need to Innovate In This Space...

Number of Chemicals /Combinations



Lack of Data



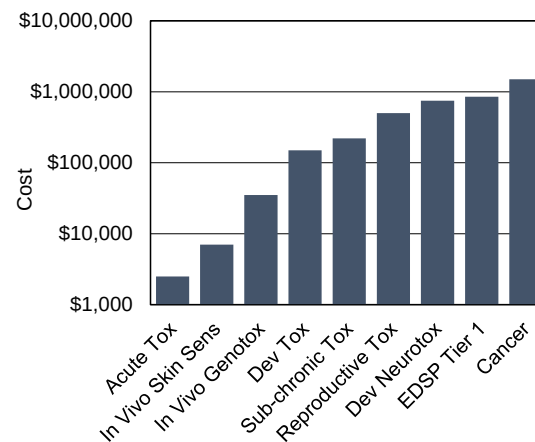
Modified from Judson *et al.*, EHP 2010

Why?

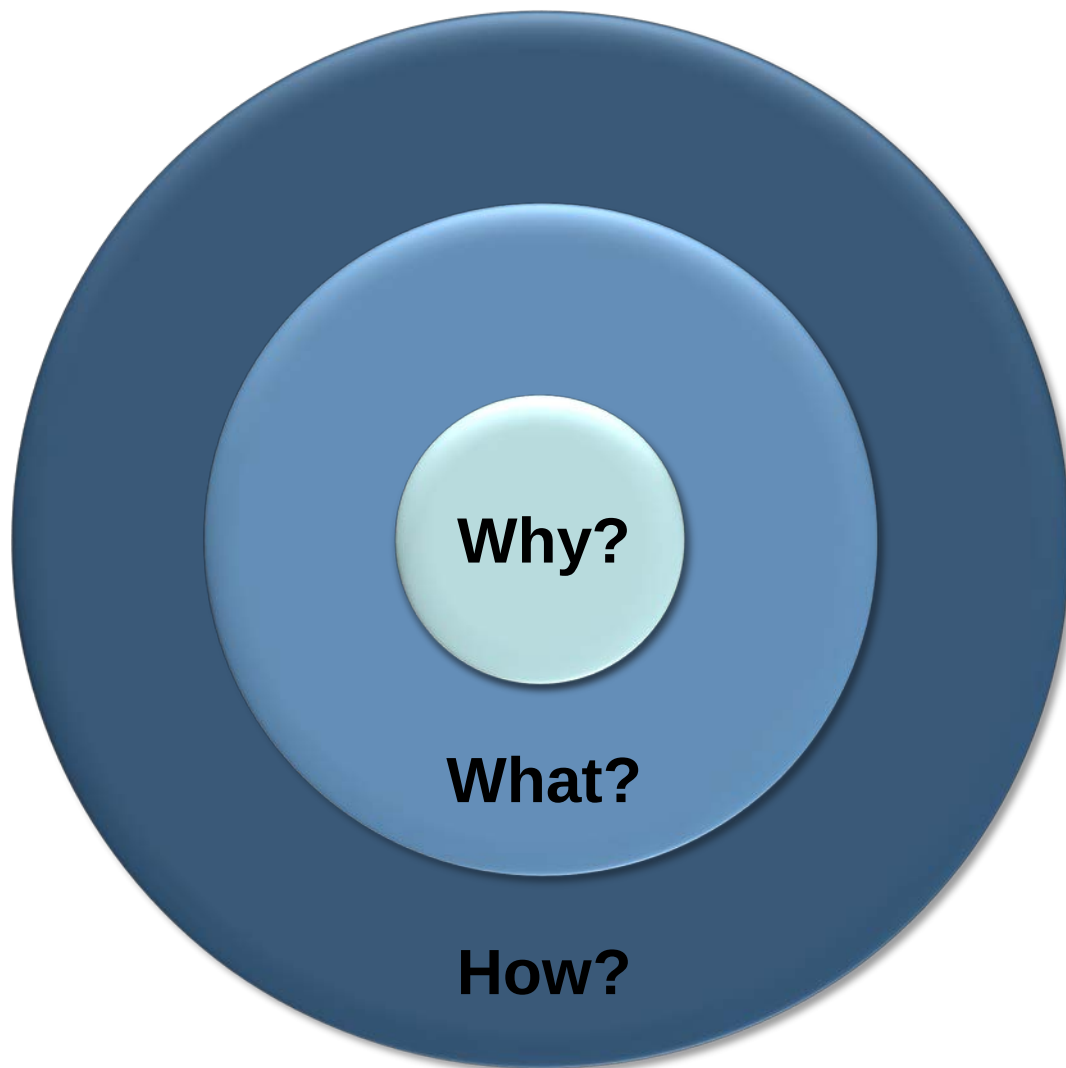
Ethics Concerns



Economics



'Golden Circle' of 21st Century Risk Assessment



Risk Assessments Generally Contain a Standard Set of Components



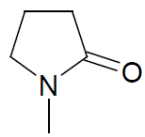
United States
Environmental Protection Agency

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

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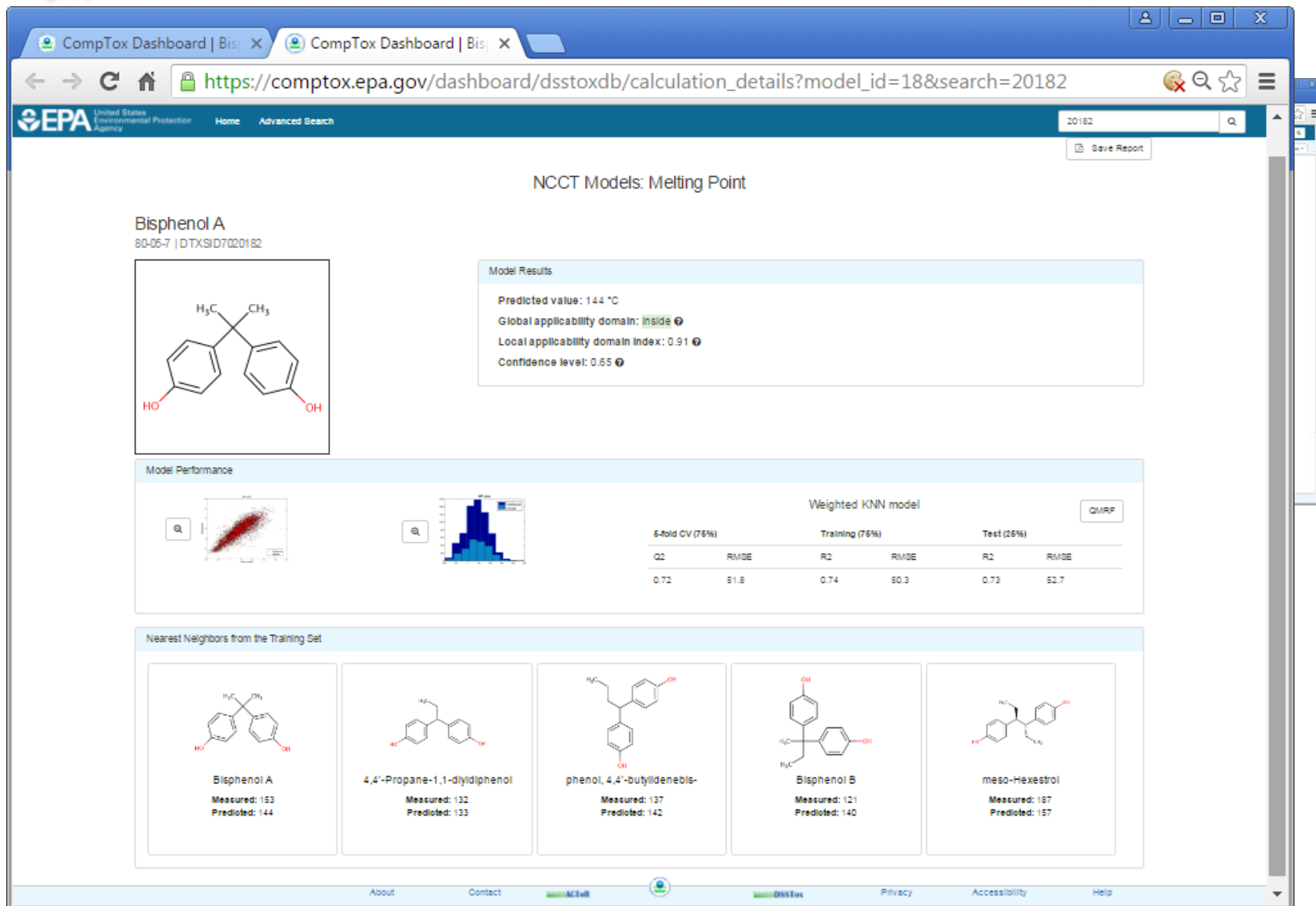
Phys Chem
Exposure
Hazard
Dose Response,
PK, and PODs

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Variability
Risk Summary
Uncertainty

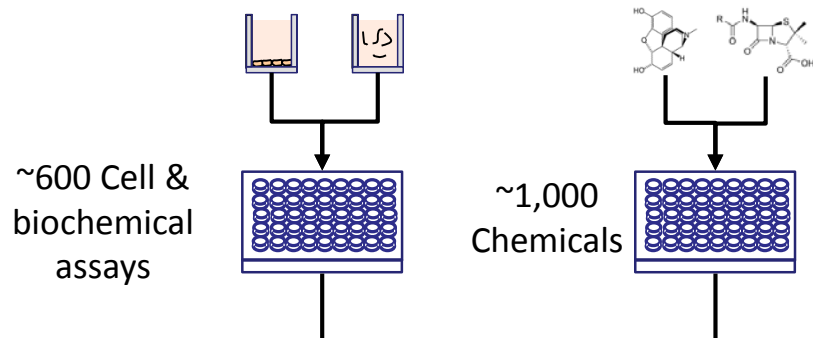
New technologies and approaches will also have to cover these basic components

It All Starts With Chemistry...

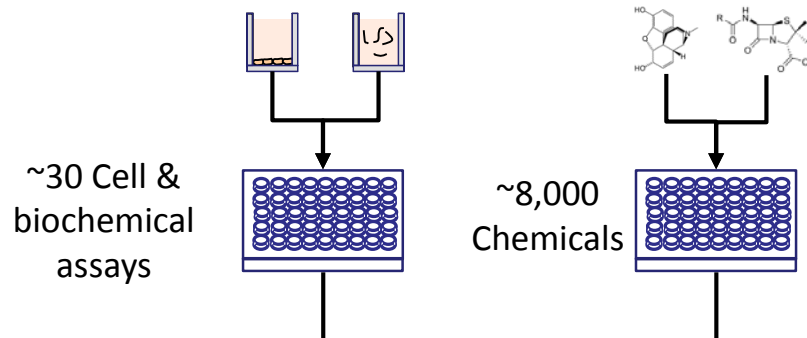


Adding the High-Throughput Hazard Screening Component

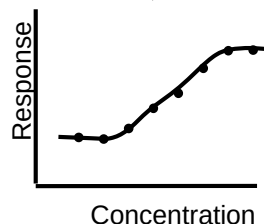
ToxCast



Tox21

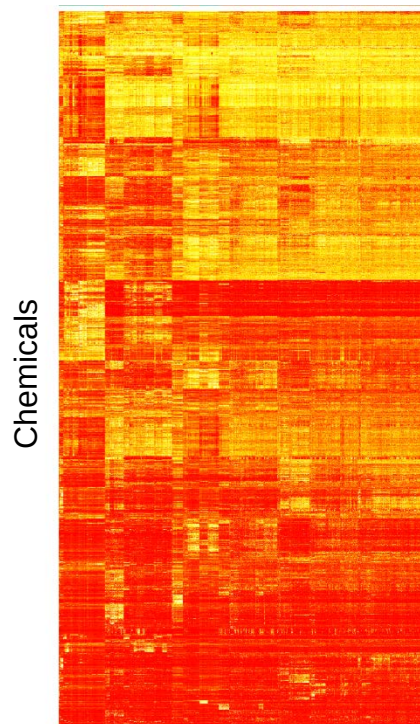


Set	Chemicals	Assays	Completion
ToxCast Phase I	293	~600	2011
ToxCast Phase II	767	~600	2013
ToxCast Phase III	1001	~100	Ongoing
E1K (endocrine)	880	~50	2013



Broad Success Derived from High-Throughput Screening Approaches

Group Chemicals by
Similar Bioactivity and
Predictive Modeling



Assays/Pathways

Provide Mechanistic
Support for Hazard ID



Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone

In June, 2014, 20 experts from nine countries met at the International Agency for Research on Cancer (IARC, Lyon, France) to assess the carcinogenicity of perfluorooctanoic acid (PFOA), tetrafluoroethylene (TFE), dichloromethane (DCM), 1,2-dichloropropane (1,2-DCP), and 1,3-propane sultone in this industry). The working group considered the rarity of cholangiocarcinoma, the very high relative risk, the young ages of the patients, the absence of non-occupational risk factors, and the intensity of the exposure as indications that the excess of metabolism of DCM does occur in

strong evidence that DCM metabolism via glutathione-S-transferase T1 (GSTT1) leads to the formation of reactive metabolites that GSTT1 activity is strongly associated with genotoxicity of DCM in vitro and in vivo, and that GSTT1-mediated metabolism of DCM does occur in



Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC, Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be cell proliferation (hyperplasia in rodents). Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on animals, including in pet flea collars. For parathion, associations with cancers in several tissues were observed in occupational studies. The insecticides malathion and diazinon were classified as "probably carcinogenic to humans" (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in

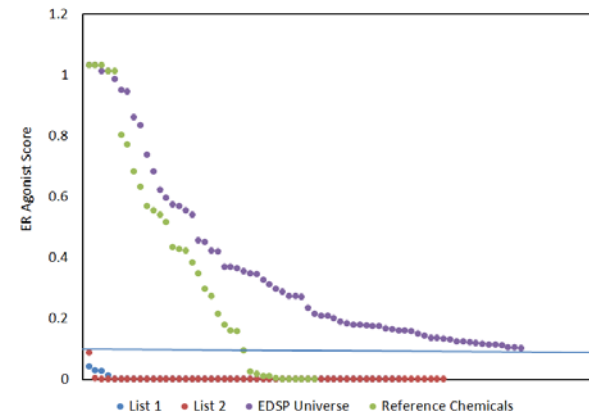


Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid

In June, 2015, 26 experts from 13 countries met at the International Agency for Research on Cancer (IARC, Lyon, France) to assess the carcinogenicity of the insecticides lindane and 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT), and the herbicide 2,4-dichlorophenoxyacetic acid. Immunosuppressive effects that can operate in humans. The insecticide DDT was classified as "probably carcinogenic to humans" (Group 2A). DDT was used for the control of insect-borne diseases during World War 2; subsequently it was widely applied to eradicate blood or adipose taken in adulthood; however, the possible importance of early-life exposure to DDT remains unresolved. Studies on non-Hodgkin lymphoma and cancers of the liver and testis provided limited evidence in humans for the carcinogenicity of DDT.

IARC Monographs 110, 112, 113

Prioritization of Chemicals
for Further Testing



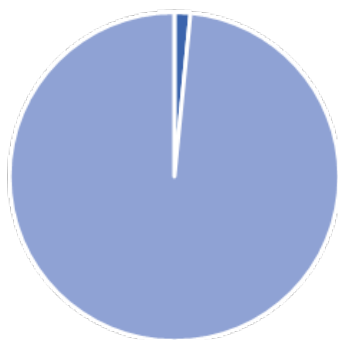
FIFRA SAP, Dec 2014

Selected Criticisms of ToxCast

- You don't include metabolism in your *in vitro* assays
- You don't measure my favorite endpoint
- You don't cover all of biological space
- *In vitro* assays are not normal biology
- Assay (x) in your battery did not get the right answer for my chemical
- My assay disagrees with your assay (x), so your approach is flawed
- You can't test my favorite chemicals because of limitations in your methods (e.g., solvents, high LogP)
- Your assay descriptions do not allow me to reproduce your results
- I get different answers when I analyze your data

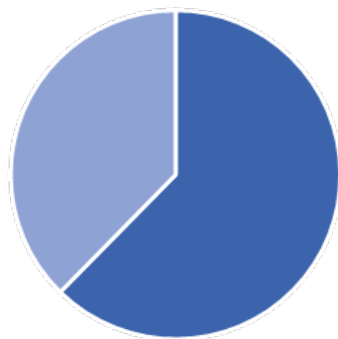
Beginning to Address Concerns for Increased Biological Coverage

Gene Coverage

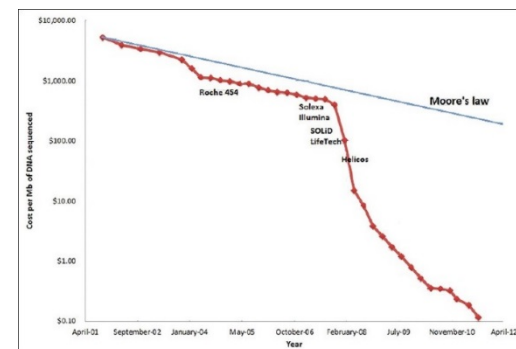


■ ToxCast
■ Not in ToxCast

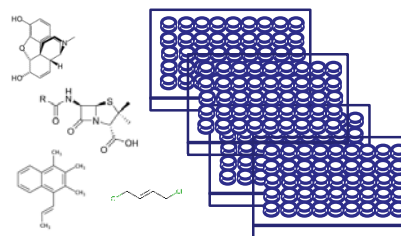
Pathway Coverage*



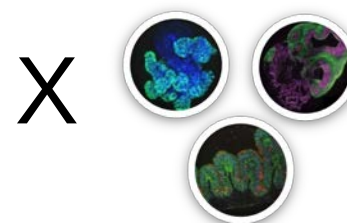
*At least one gene from pathway represented



Thousands of chemicals



Multiple Cell Types

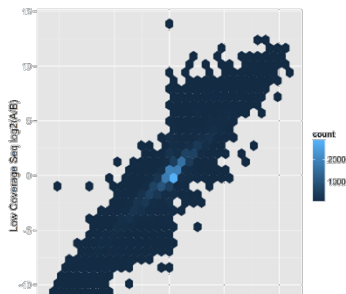


X

Requirements:

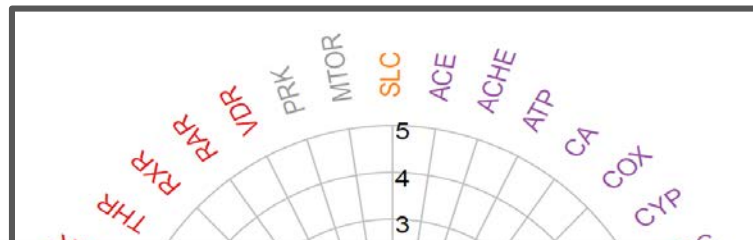
- Low cost
- Whole genome
- 384 well
- Automatable

Comparing Sequencing Platforms and Developing Analysis Approach



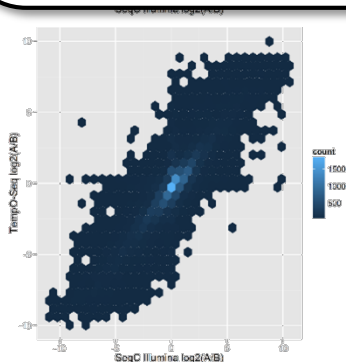
TruSeq
 r^2 0.74

MOA/MIE 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



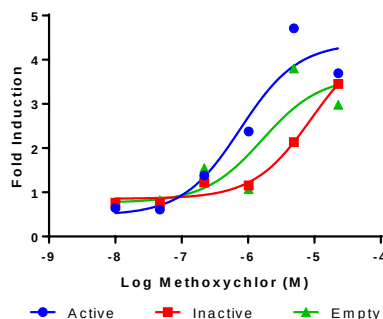
Currently capable of assigning to >40 MOAs/MIEs based on transcriptional responses

Beginning to Address Metabolic Competence

“Extracellular” Approach



Chemicals metabolism in the media or buffer of cell-based and cell-free assays

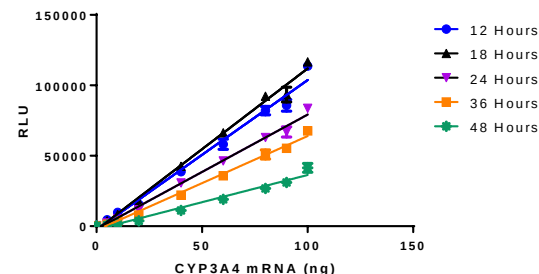
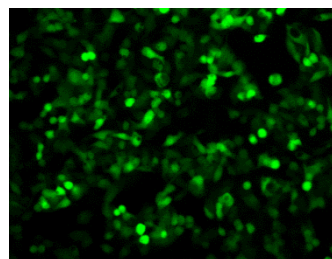


More closely models effects of hepatic metabolism and generation of circulating metabolites

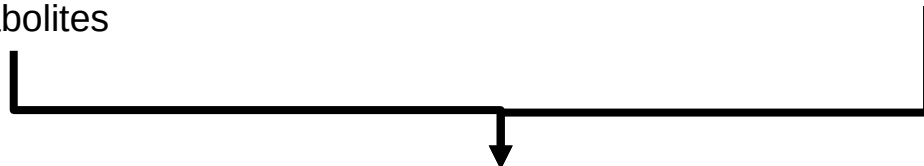
“Intracellular” Approach



Capable of metabolizing chemicals inside the cell in cell-based assays



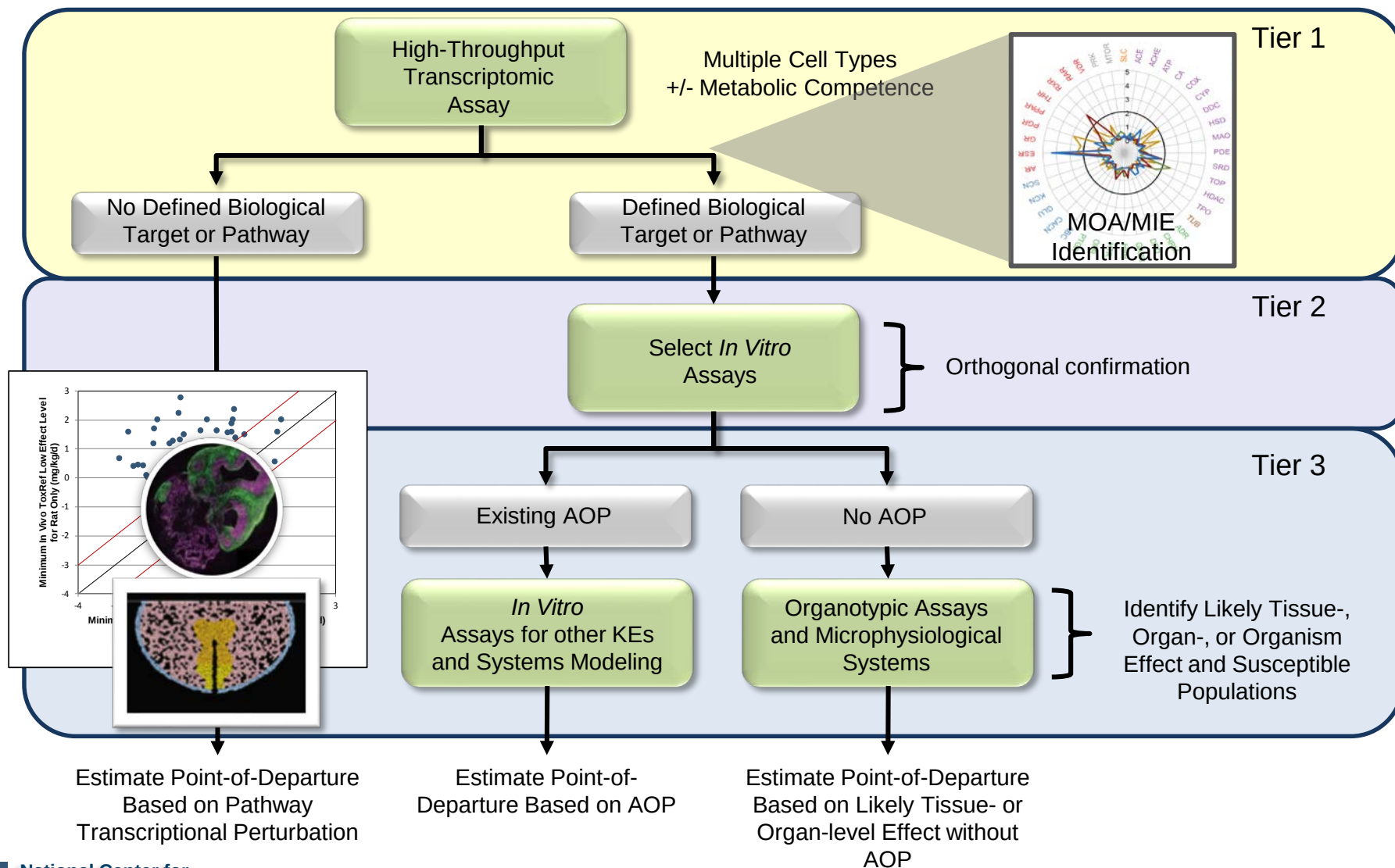
More closely models effects of target tissue metabolism



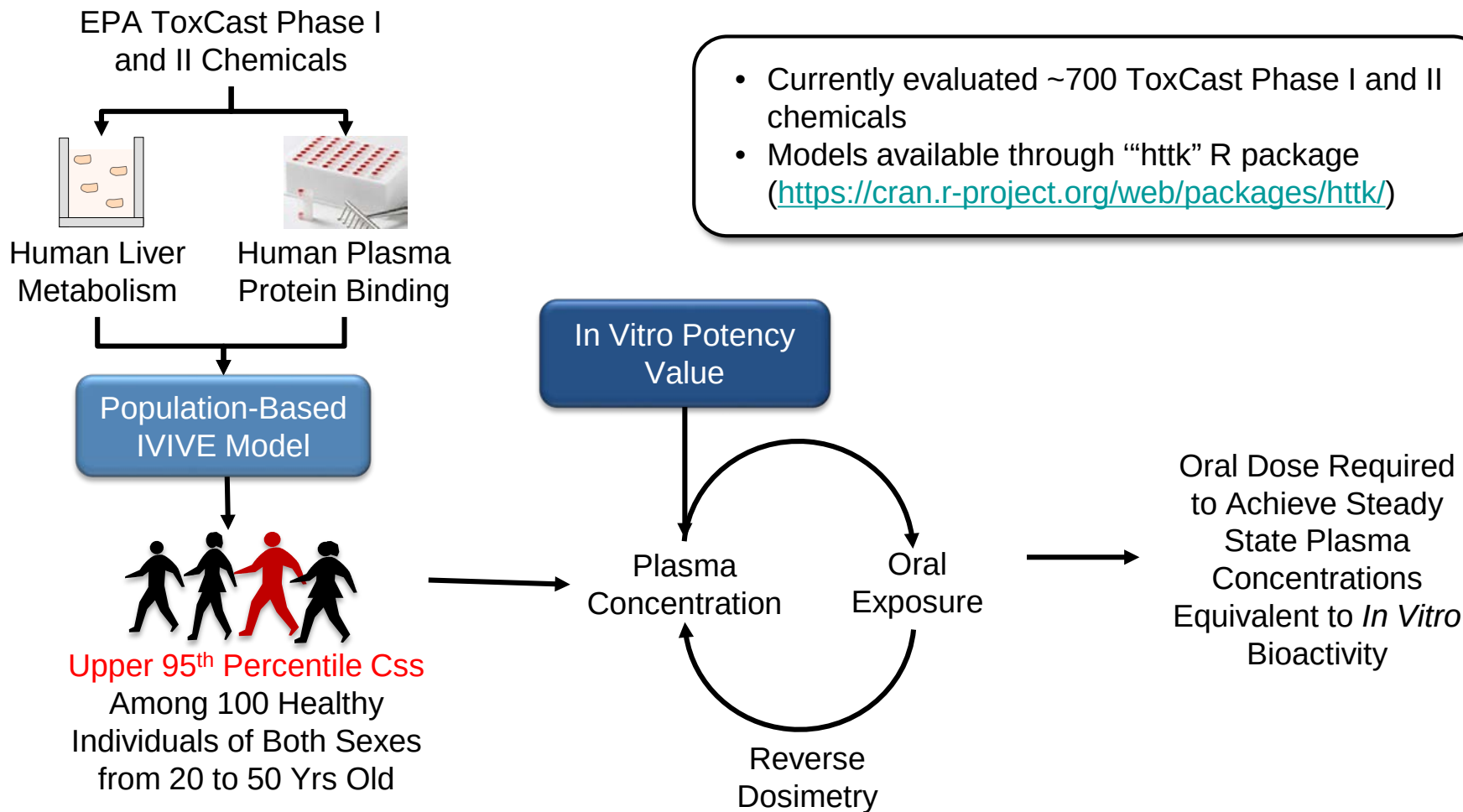
Integrated approach to model *in vivo* metabolic bioactivation and detoxification

Collaboration with Unilever

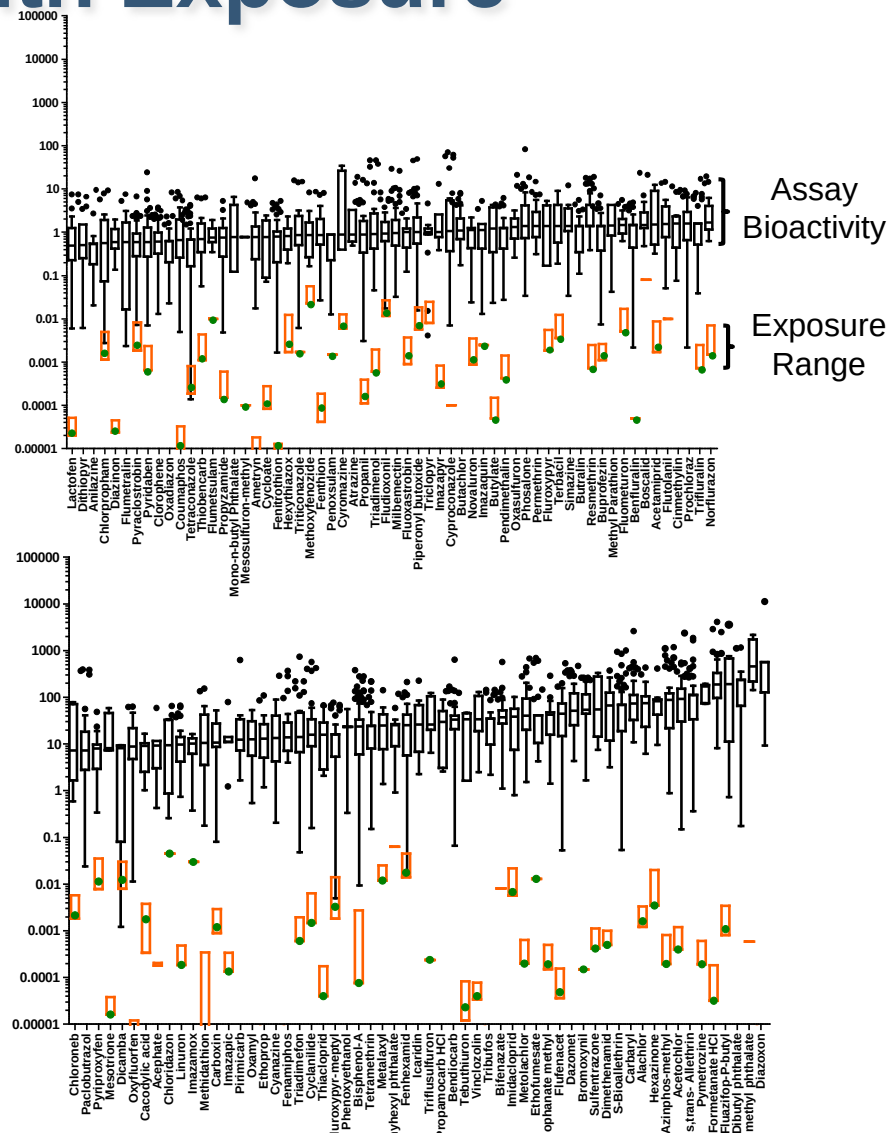
Framework for Integrating Hazard Components...

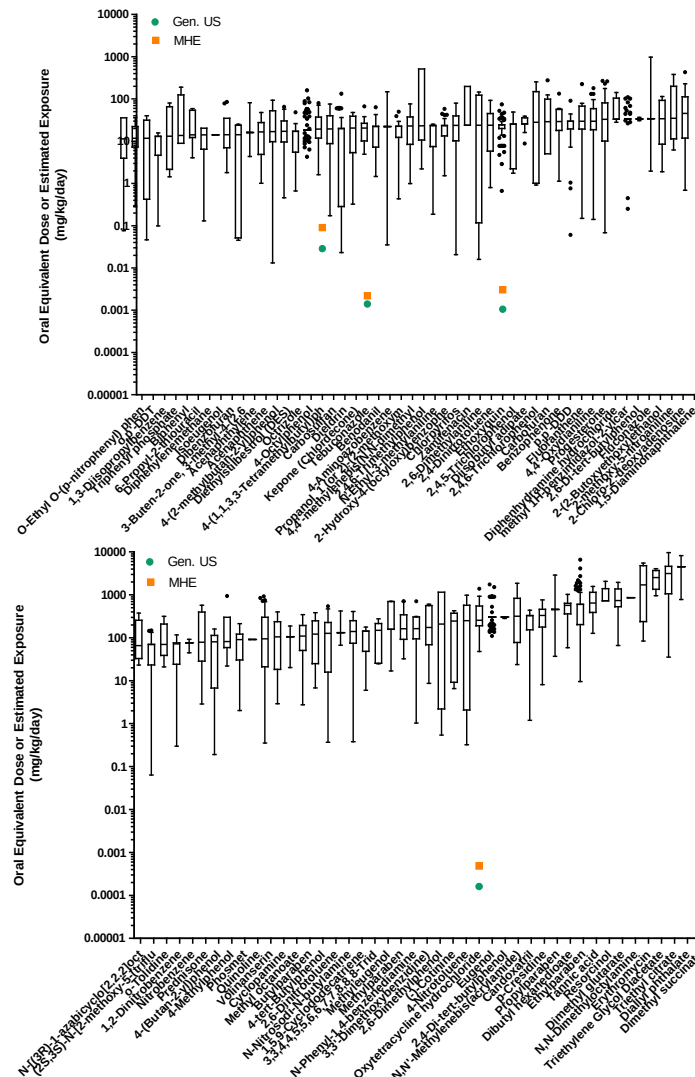


Adding the High-Throughput Toxicokinetic Component

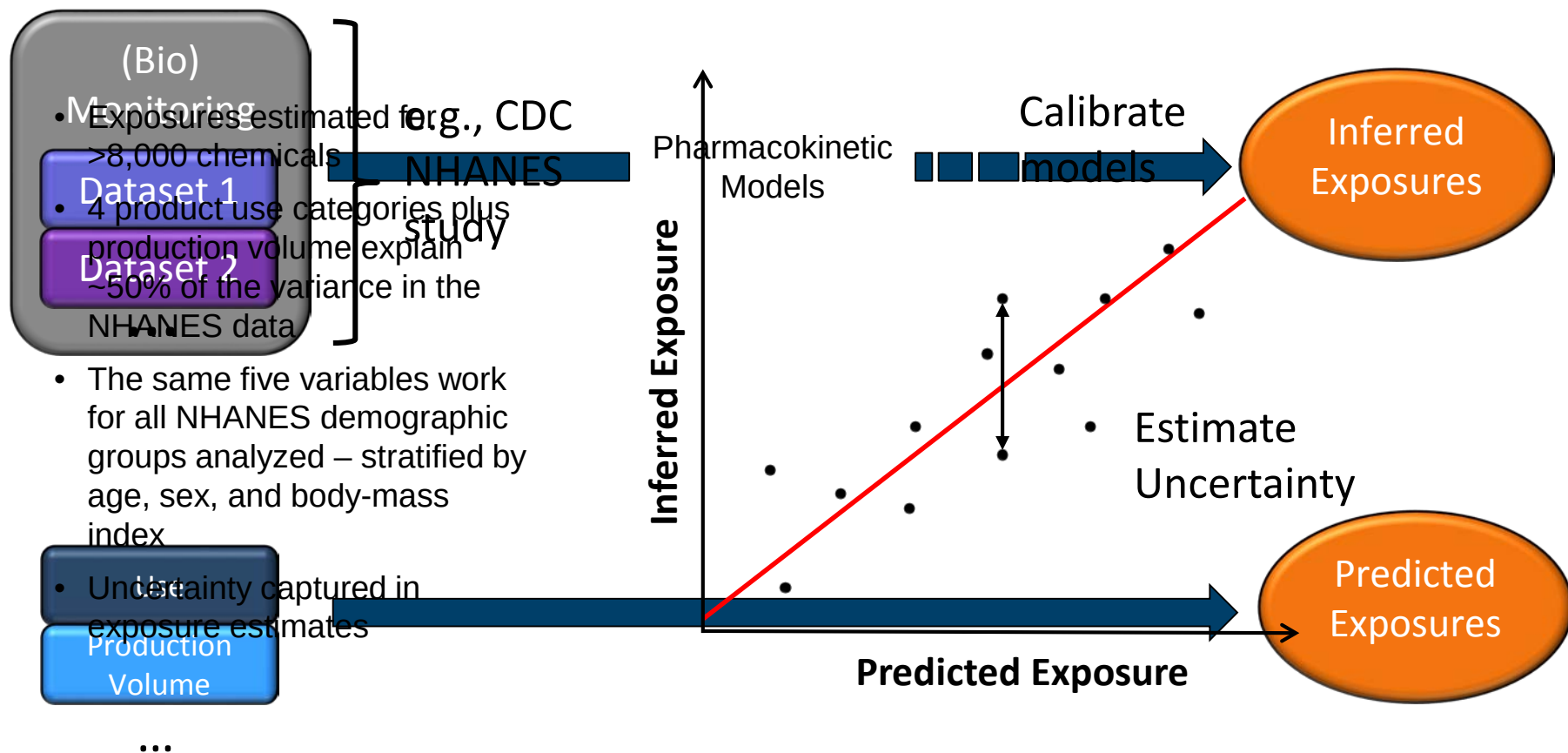


Retroff *et al.*, *Tox Sci.*, 2010
Wetmore *et al.*, *Tox Sci.*, 2012

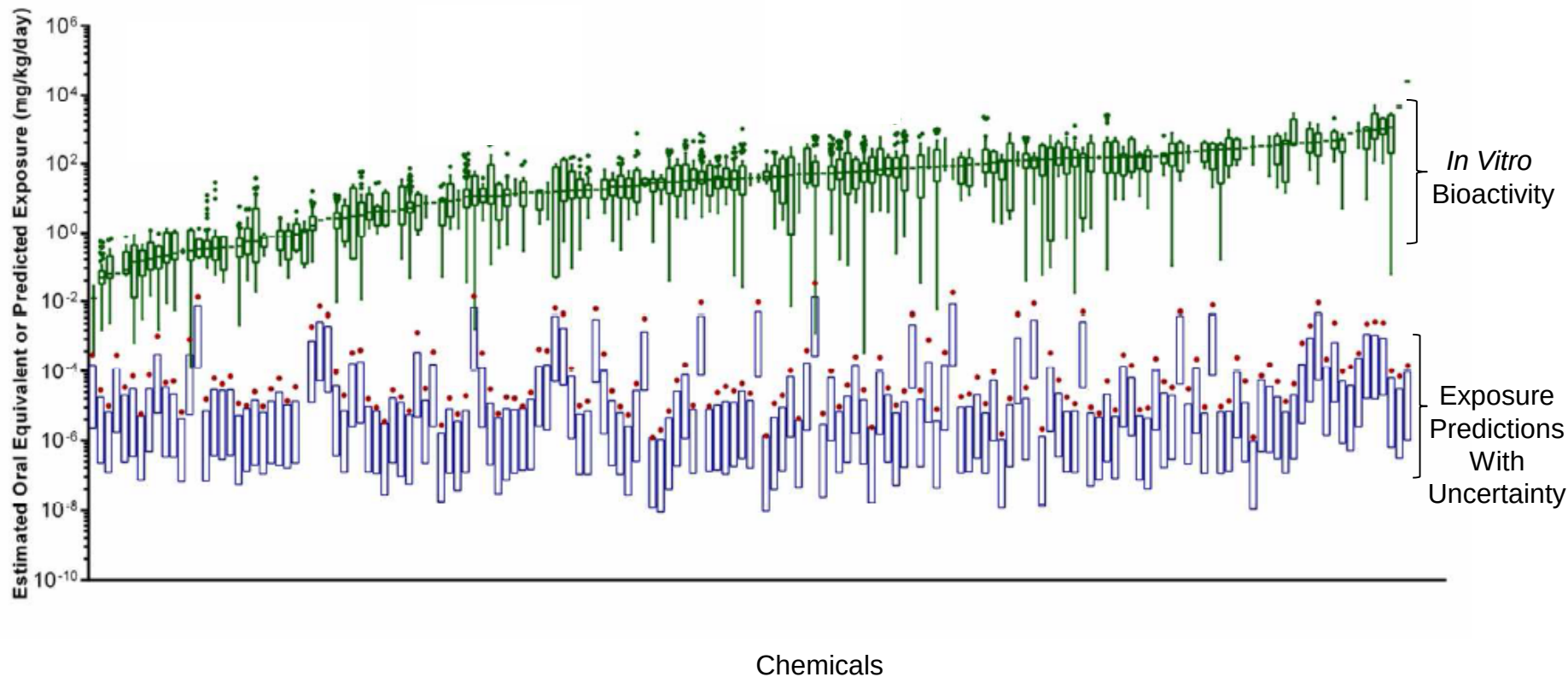




Adding the High-Throughput Exposure Component



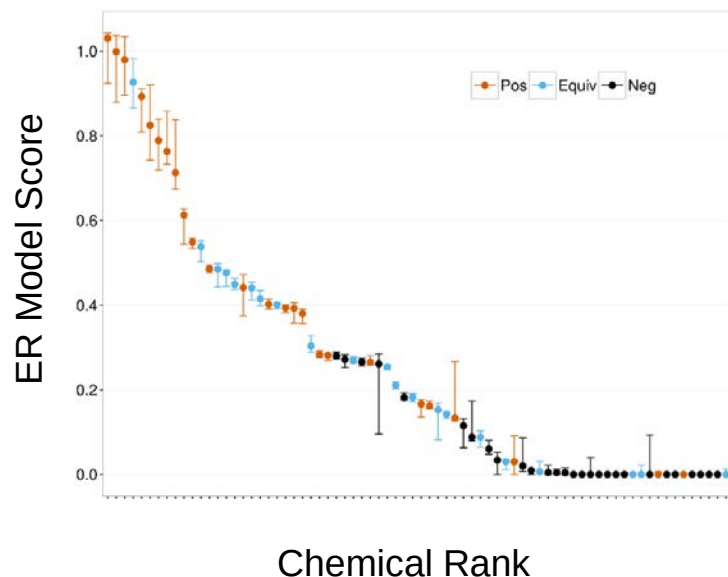
Comparing Bioactivity with Exposure Predictions for Risk Context



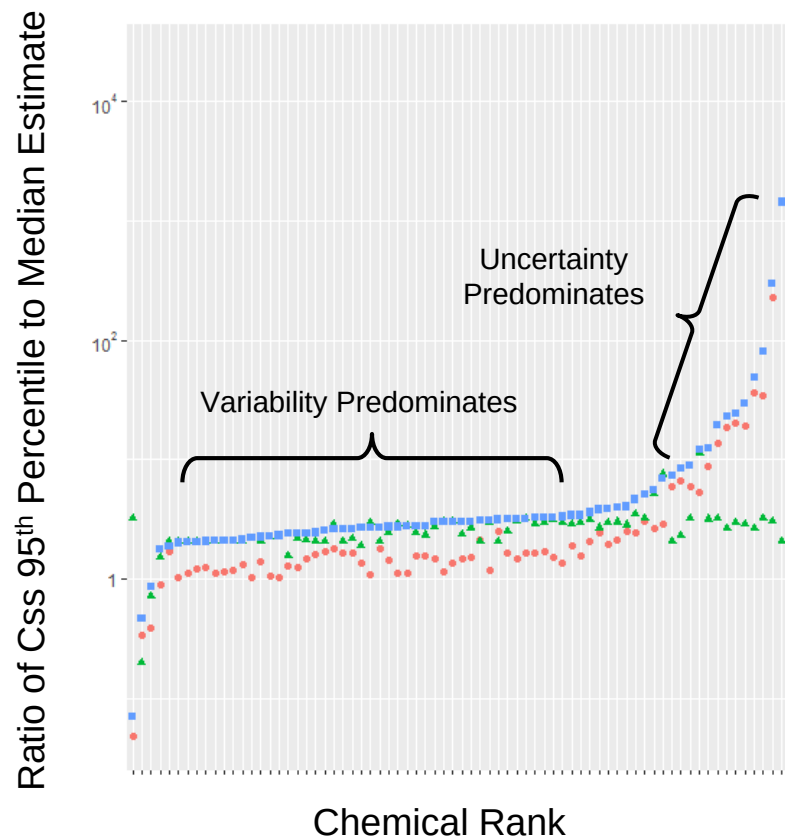
Wetmore *et al.*, *Tox Sci.*, 2015

Adding in Uncertainty and Variability for PD and PK

Propagation of Experimental Uncertainty in Models of ER Potency



Propagation of Experimental Uncertainty in High-Throughput Toxicokinetic Estimates



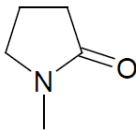
Covering All the Components of a 21st Century Risk Assessment

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



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Phys Chem

Exposure

Hazard

Dose Response,

PK, and PODs

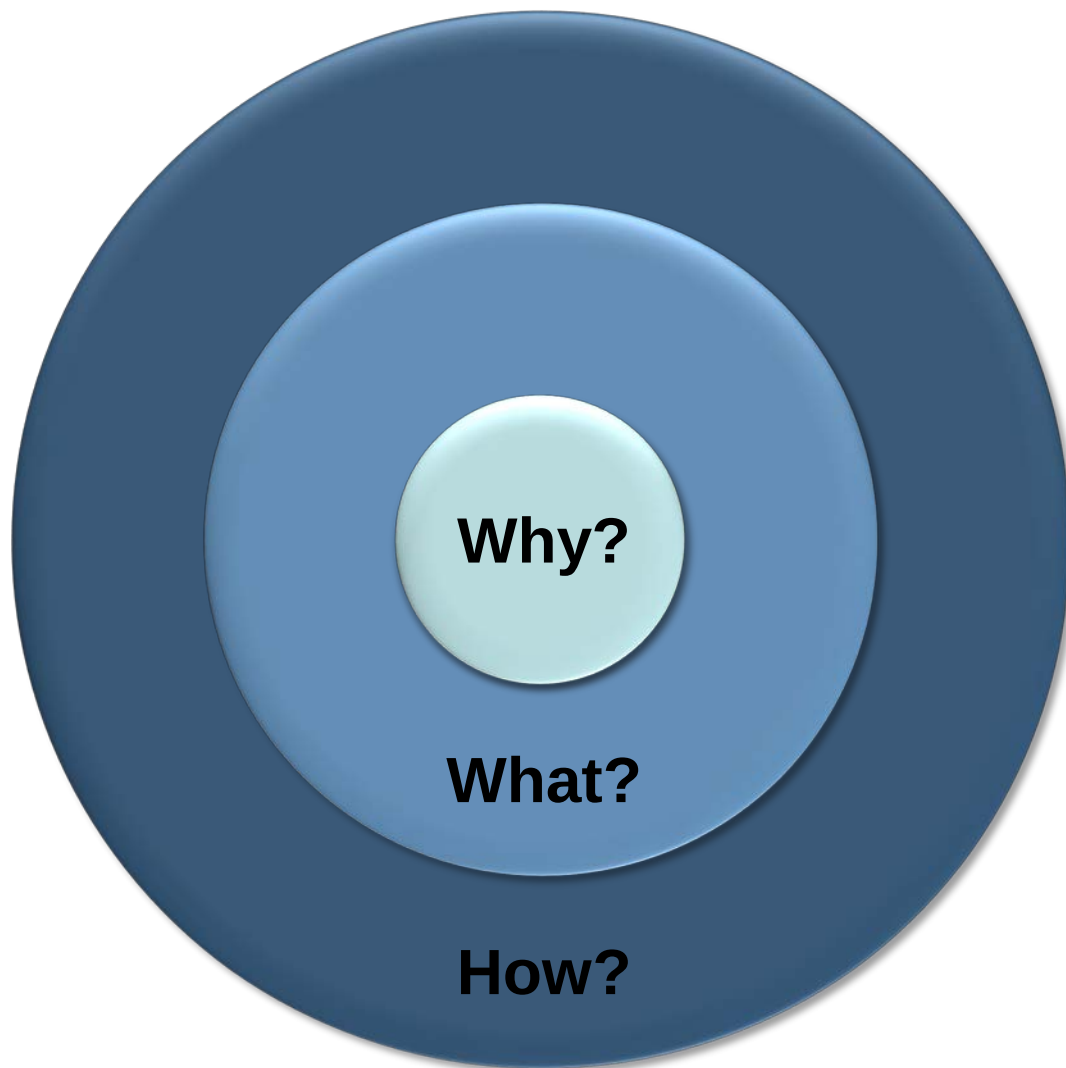
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Variability

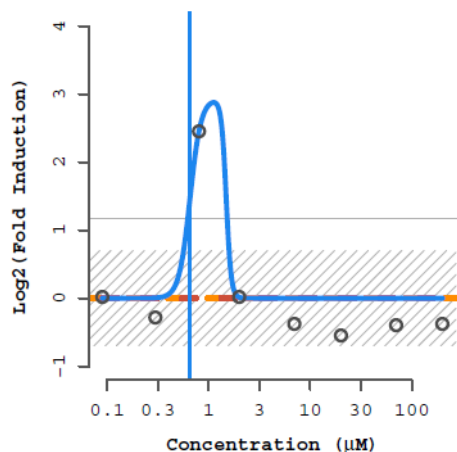
Risk Summary

Uncertainty

'Golden Circle' of 21st Century Risk Assessment



Regulatory Applications Require More Focus on Quality and Transparency



ASSAY: ARID117 (ATQ_Era_TRANS)

NAME: Thioglycolic acid
CHID: 26141 CASRN: 68-11-1
SPID(S): TX007664
L4ID: 420385

HILL MODEL (in red):
tp ga gw
val: 3.1e-11 -2.15 0.416
sd: NaN NaN NaN

GAIN-LOSS MODEL (in blue):
tp ga gw la lw
val: 2.93 -0.184 8 0.173 18
sd: 3.56 0.334 9.48 5.82 814

	CNST	HILL	GNLS
AIC:	20.14	26.14	17.79
PROB:	0.23	0.01	0.76
RMSE:	0.92	0.92	0.32

MAX_MEAN: 2.45 MAX_MED: 2.45 BMAD: 0.233

COFF: 1.17 HIT-CALL: 1 FITC: 50 ACTP: 0.77

FLAGS:

Only one conc above baseline, active
Borderline active

- Public release of Tox21 and ToxCast data on PubChem and EPA web site (raw and processed data)
- Publicly available ToxCast data analysis pipeline
 - Data quality flags to indicate concerns with chemical purity and identity, noisy data, and systematic assay errors
- Tox21 and ToxCast chemical libraries have undergone analytical QC and results publicly available
- Public posting of ToxCast procedures
 - Chemical Procurement and QC
 - Data Analysis
 - Assay Characteristics and Performance
- External audit on ToxCast data and data analysis pipeline
- Migrating ToxCast assay annotations to OECD 211 compliant format

Application to Regulatory Decisions for Endocrine Screening

Prioritization of the EDSP Universe of Chemicals

Integrated Bioactivity and Exposure Ranking

Prioritization of the Endocrine Program Universe of Chemicals: A Computational Approach for the Identification and Screening of Chemicals in the Endocrine Disruptor Screening Program

U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program

Jointly developed by:

Office of Chemical Safety and Pollution Prevention
Office of Science Coordination and Policy (OSCP)
Office of Pesticide Programs (OPP)
Office of Pollution Prevention and Toxics (OPPT)

Office of Water (OW)
Washington, DC 20460

Office of Research and Development (ORD)
National Environmental and Effects Health Research
Mid-Continent Ecology Division (MED), Duluth, MN
Toxicity Assessment Division (TAD), RTP, NC 27111

National Center for Computational Toxicology (NCCT)
Research Triangle Park, NC 27709

December 2012

Exposure SAP White Paper

New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

New High-throughput Methods to Estimate Chemical Exposure

1

Integrated Bioactivity and Exposure Ranking: A Computational Approach for the Identification and Screening of Chemicals in the Endocrine Disruptor Screening Program

Environmental Protection Agency
Endocrine Disruptor Screening Program

by:

Office of Chemical Safety and Pollution Prevention
Office of Research and Development (ORD)
Office of Water (OW)

Mid-Continent Ecology Division (MED), Duluth, MN
Toxicity Assessment Division (TAD), RTP, NC 27111

Exposure SAP December 2-5

35350

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may claim all or part of a response confidential. EPA will issue another Federal Register document pursuant to 5 CFR 1320.5(a)(1)(iv) to announce the submission of the ICR to OMB and the opportunity to submit additional comments to OMB. If you have any questions about this ICR or the approval process, please contact the technical person listed under FOR FURTHER INFORMATION CONTACT.

Authority: 44 U.S.C. 3501 et seq.

Dated: June 10, 2015.

Jane Jones,
Assistant Administrator, Office of Chemical Safety and Pollution Prevention.
[FR Doc. 2015-1488 Filed 06-19-15; 8:45 am]
BILING CODE 6950-10-P

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-OPPT-2015-0305; FRL-9028-08]

Use of High Throughput Assays and Computational Tools: Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This document describes how EPA is planning to incorporate an alternative scientific approach to screen chemicals for their ability to interact with the endocrine system. This will improve the Agency's ability to fulfill its statutory mandate to screen pesticide chemicals and other substances for their ability to cause adverse effects by their interaction with the endocrine system. The approach incorporates validated high throughput assays and a computational model and, based on current research, can serve as an alternative for some of the current assays in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery. EPA has partial screening results for over 1800 chemicals that have been evaluated using high throughput assays and a computational model for the estrogen receptor pathway. In the future, EPA anticipates that additional alternative methods will be available for EDSP chemical screening based on further advancements of high throughput assays and computational models for other endocrine pathways. Use of these alternative methods will accelerate the pace of screening, decrease costs, and reduce animal testing. In addition, this approach advances the goal of providing sensitive, specific, quantitative, and

efficient screening using alternative test methods to some assays in the Tier 1 battery to protect human health and the environment.

DATES: Comments must be received on or before August 18, 2015.

ADDRESSES: Submit your comments, identified by docket (identification ID) number EPA-HQ-OPPT-2015-0305, by one of the following methods:

- **Federal eRulemaking Portal:** <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- **Mail:** Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001.
- **Hand Delivery:** To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>. Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: For technical information contact: Jane Robbins, Office of Science Coordination and Policy (OSCP), Office of Chemical Safety and Pollution Prevention, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001; telephone number: (202) 564-6622; email address: robbins.jane@epa.gov.

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1404; email address: TSCA-Hotline@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

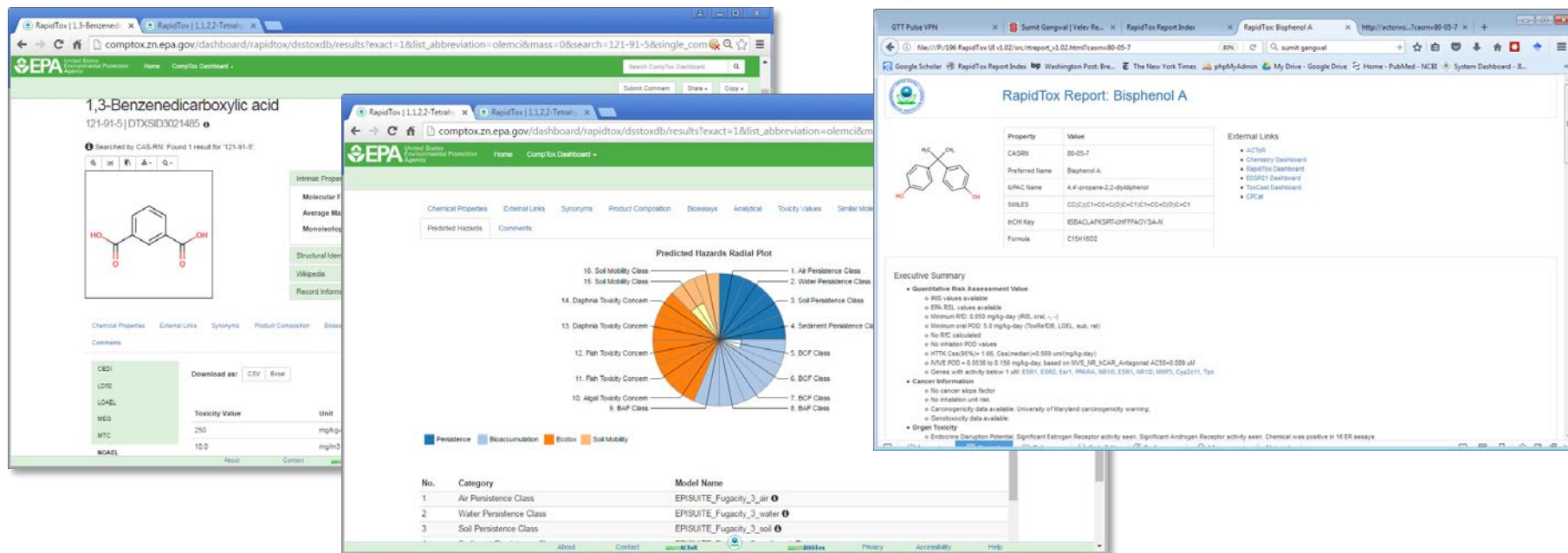
A. Does this action apply to me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including those interested in endocrine testing of chemicals (including pesticides), and the EDSP in general. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. What is the agency authority for taking this action?

The EDSP is established under section 400(p) of the Federal Food, Drug and

Beginning Application to Quantitative Risk Assessment Through New 'RapidTox' Dashboard



- 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

Collaborators:

Unilever



EPA's National Center for Computational Toxicology