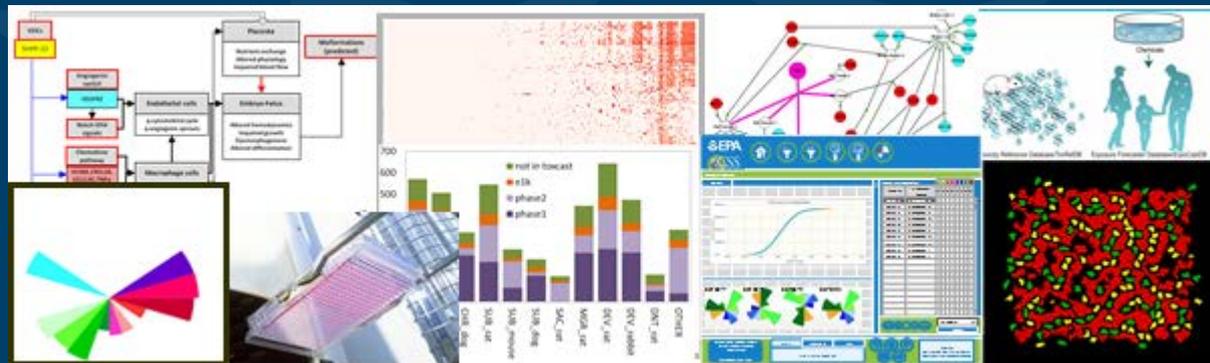


# High Throughput *in vitro* Assay Testing in Hazard Assessment

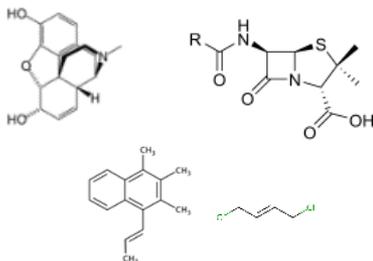


JOINT DOD TECHNICAL INTERCHANGE AND ROADMAP  
DEVELOPMENT TO PROMOTE THE USE OF NEW APPROACH  
METHODOLOGIES IN RAPID CHEMICAL HAZARD ASSESSMENT  
August 14, 2018

**Maureen R. Gwinn**  
National Center for Computational Toxicology  
Office of Research and Development  
US Environmental Protection Agency

# Regulatory Agencies Make a Broad Range of Decisions on Chemicals...

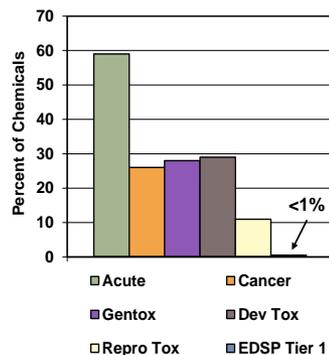
## Number of Chemicals /Combinations



## Ethics/Relevance Concerns

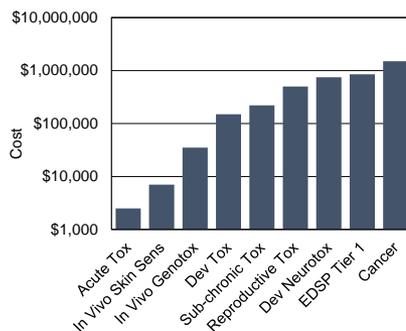


## Lack of Data



Modified from Judson *et al.*, EHP 2010

## Economics



- Number of chemicals and combinations of chemicals is extremely large (>20,000 substances on active TSCA inventory)
- Due to historical regulatory requirements, most chemicals lack traditional toxicity testing data
- Traditional toxicology testing is expensive and time consuming
- Traditional animal-based testing has issues related to ethics and relevance

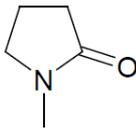
# Risk Assessments Generally Contain a Standard Set of Components

**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**

**Variability**

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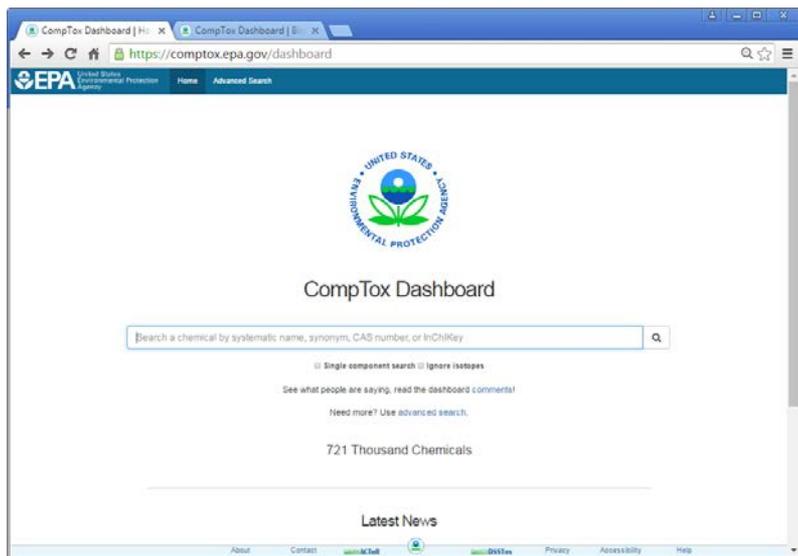
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New technologies and approaches will also have to cover these basic components

# It All Starts With Chemistry...



**Bisphenol A**  
80-05-7 | DTXSID7020182

Examined by Approval Name: Round 1 result for Bisphenol A.

**Physical Properties**

Molecular Formula: C<sub>15</sub>H<sub>16</sub>O<sub>2</sub>  
Average Mass: 228.261 g/mol  
Molecular Weight: 228.116330 g/mol

**Chemical Properties**

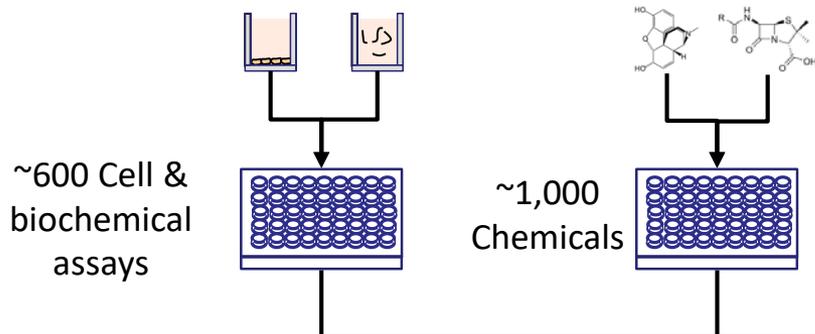
Octanol-water Partition Coefficient (logK <sub>ow</sub> )	Average	Median	Range
Experimental	3.33 (2)	3.43	3.43
Predicted	3.42 (2)	3.42	3.25 to 3.64

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

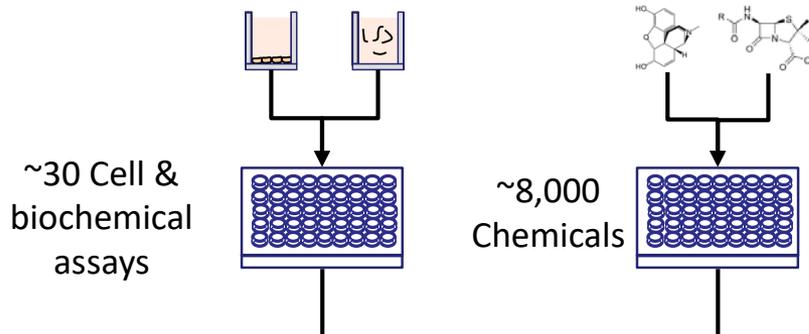
- Chemical structure database of >700,000 unique substances with QC flags to link chemical structure with names and identifiers
- Consensus QSAR models for a range of physical chemical properties, environmental fate, and hazard characteristics
- Comprehensive physical-chemical property database (experimental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

# ToxCast and Tox21: Adding the High-Throughput Hazard Screening Component

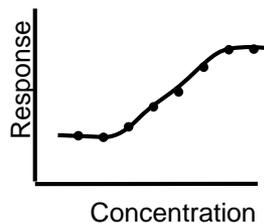
## ToxCast



## Tox21



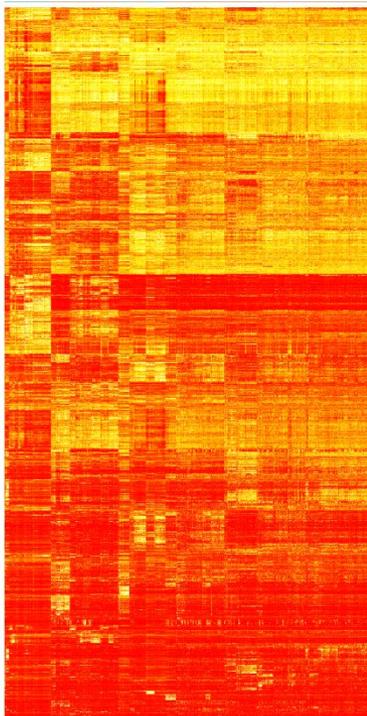
Set	Chemicals	Assays	Completion
ToxCast Phase I	293	~600	2011
ToxCast Phase II	767	~600	2013
ToxCast Phase III	1001	~100	Ongoing
E1K (endocrine)	880	~50	2013



# Broad Success Derived from High-Throughput Screening Approaches

## Group Chemicals by Similar Bioactivity and Predictive Modeling

Chemicals



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 with 1,2-DCP 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 strong evidence that DCM metabolism via glutathione-S-transferase T1 (GGT1) leads to the formation of reactive metabolites, that GGT1 activity is strongly associated with genotoxicity of DCM in vitro and in vivo, and that GGT1-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

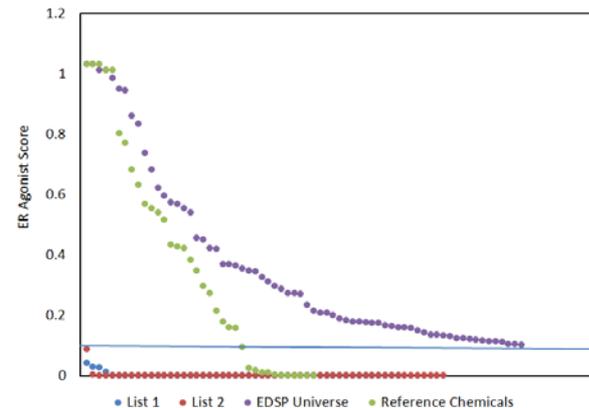
**Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid**



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

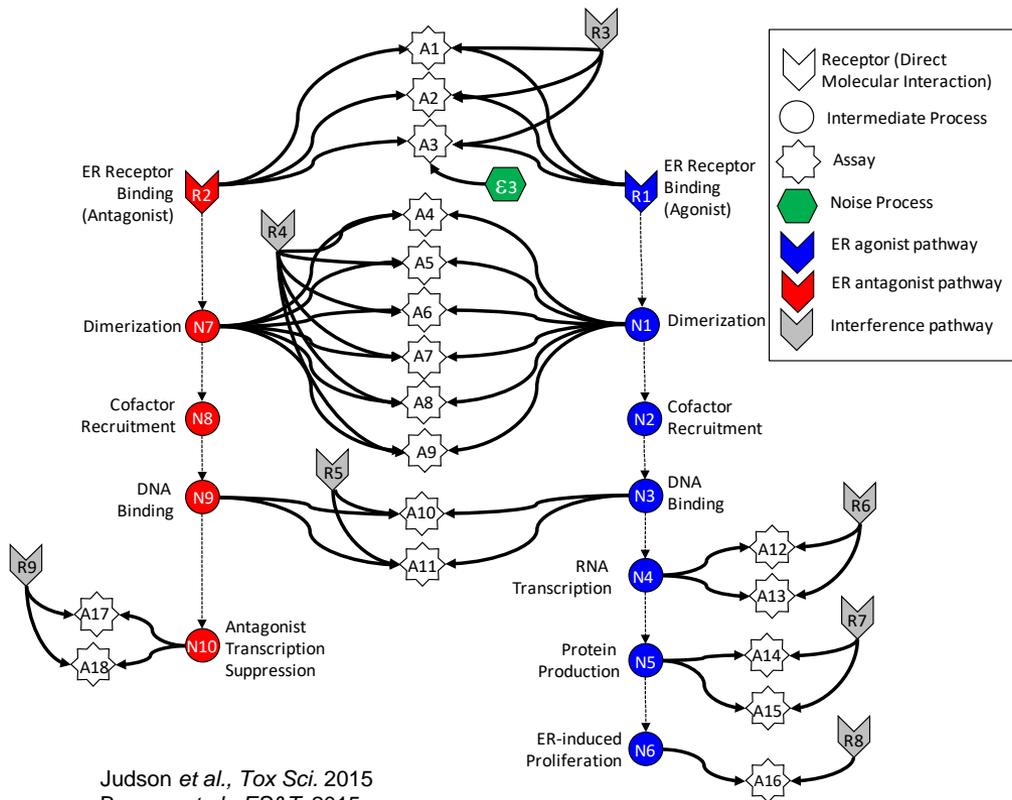
## Prioritization of Chemicals for Further Testing



FIFRA SAP, Dec 2014

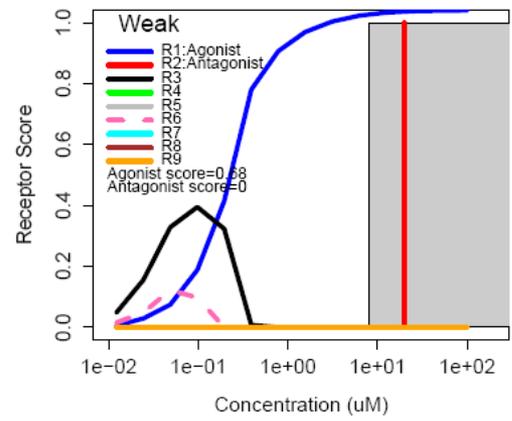
# Application of High-Throughput Assays to Identify Potential Endocrine Disrupting Chemicals

18 *In Vitro* Assays Measure ER-Related Activity

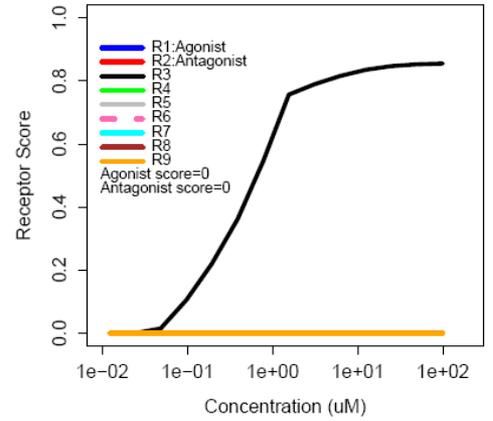


Judson *et al.*, *Tox Sci.* 2015  
 Browne *et al.*, *ES&T.* 2015  
 Kleinstreuer *et al.*, *EHP* 2016

80-05-7 : Bisphenol A



10016-20-3 : alpha-Cyclodextrin

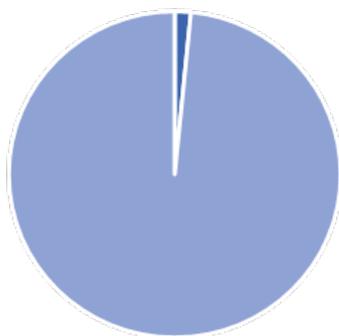


# Selected Criticisms of ToxCast

- 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

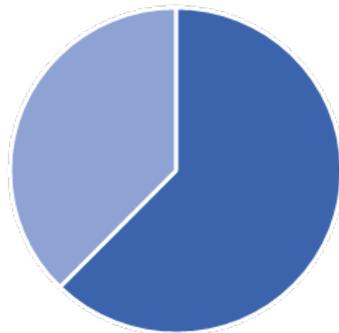
# Beginning to Address Concerns for Increased Biological Coverage

## Gene Coverage

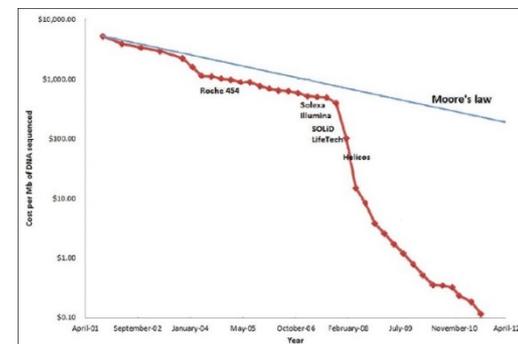


■ ToxCast  
■ Not in ToxCast

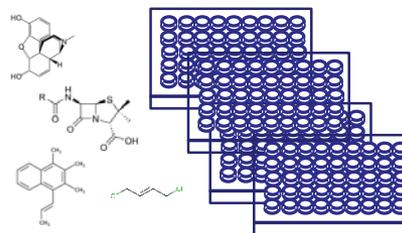
## Pathway Coverage\*



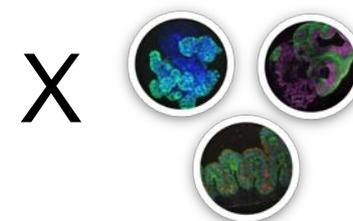
\*At least one gene from pathway represented



Thousands of chemicals



Multiple Cell Types



### Requirements:

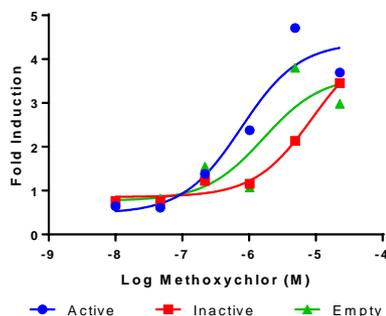
- Low cost
- Whole genome
- 384 well
- Automatable

# Beginning to Address Metabolic Competence

## “Extracellular” Approach



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

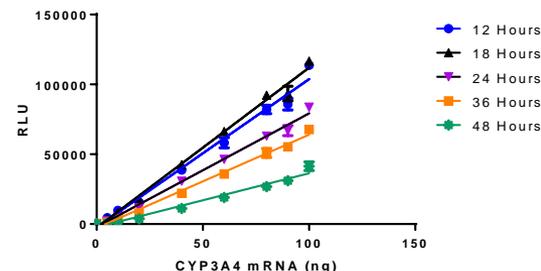
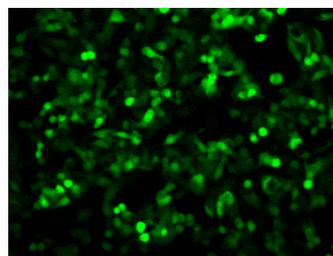


More closely models effects of hepatic metabolism and generation of circulating metabolites

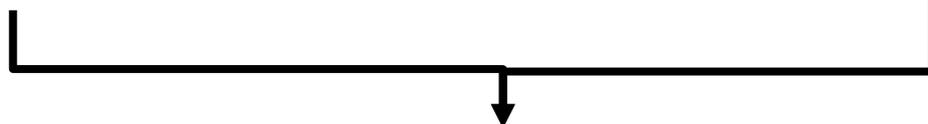
## “Intracellular” Approach



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



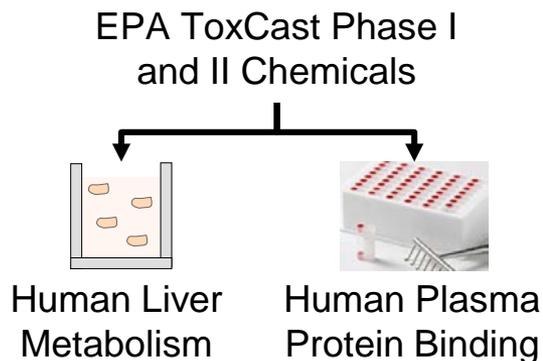
More closely models effects of target tissue metabolism



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

Collaboration with Unilever

# Adding the High-Throughput Toxicokinetic Component



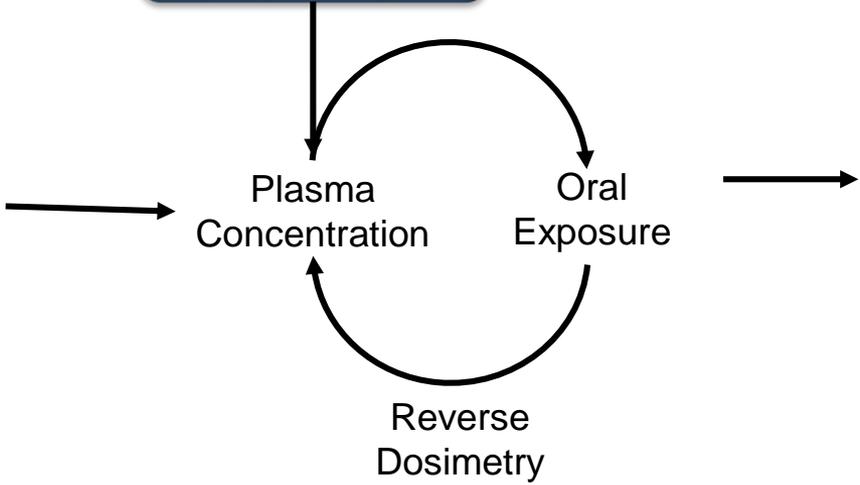
- Currently evaluated ~700 ToxCast Phase I and II chemicals
- Models available through “httk” R package (<https://cran.r-project.org/web/packages/httk/>)

Population-Based IVIVE Model



Upper 95<sup>th</sup> Percentile C<sub>ss</sub>  
Among 100 Healthy  
Individuals of Both Sexes  
from 20 to 50 Yrs Old

In Vitro Potency Value



Oral Dose Required to Achieve Steady State Plasma Concentrations Equivalent to *In Vitro* Bioactivity

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

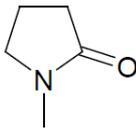
# Covering All the Components of a 21<sup>st</sup> Century Risk Assessment

**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



March 2015

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**Variability** ✓

**Risk Summary**

**Uncertainty** ✓

**Phys Chem** ✓

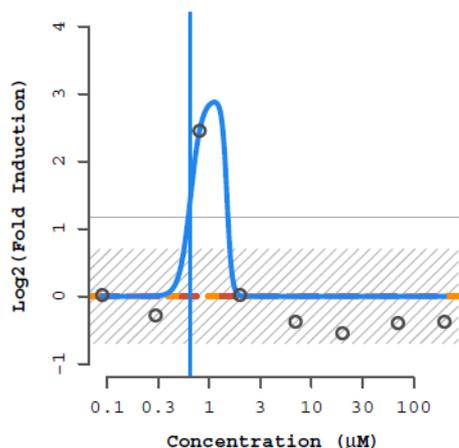
**Exposure** ✓

**Hazard** ✓

**Dose Response,**

**PK, and PODs** ✓

# Regulatory Applications Require More Focus on Quality and Transparency



ASSAY: AEID117 (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

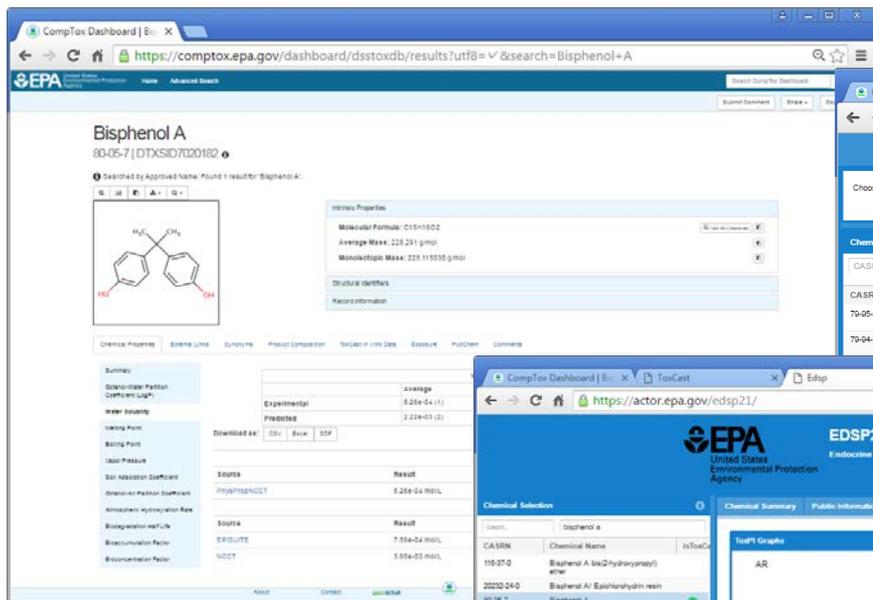
COFF: 1.17 HIT-CALL: 1 FITC: 50 ACTP: 0.77

#### 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

# Effort to Provide Data Through Display and Decision Support Dashboards



**Bisphenol A**  
00-05-7 | DTXSID7000102

Substances by Approved Name: Found 1 result for Bisphenol A:

Cc1ccc(cc1)C(C)(C)c2ccc(O)cc2

**Physical Properties**

- Molecular Formula: C<sub>15</sub>H<sub>16</sub>O<sub>2</sub>
- Average Mass: 228.291 g/mol
- Monoisotopic Mass: 228.11533 g/mol

**Structural Identifiers**

Record Information

**Summary**

Chemical Properties | Estrogen-Like | Subtypes | Product Composition | Toxicity-IRIS Data | Exposure | Pathways | Comments

**Experimental**

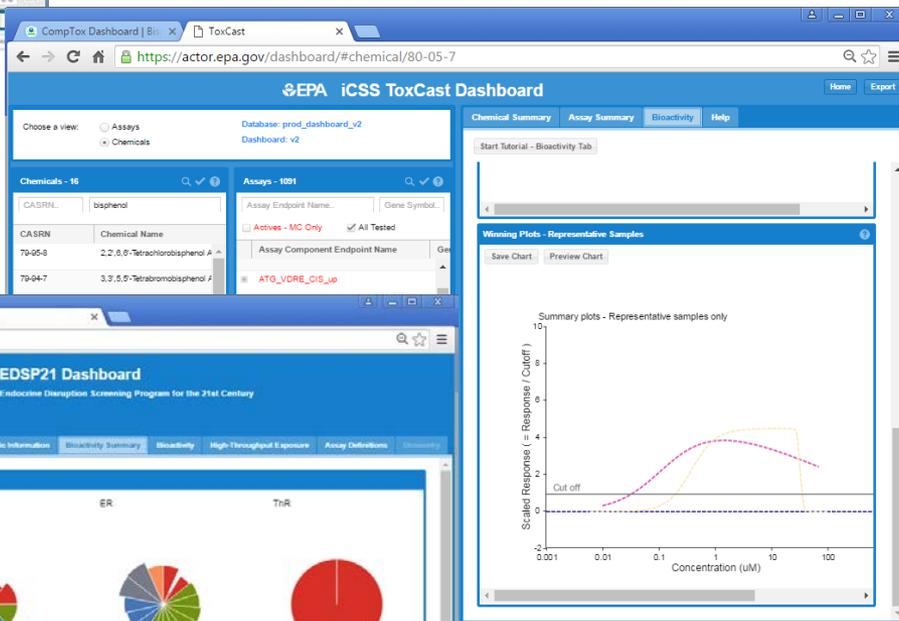
Parameter	Value
Water Solubility	0.264-04 (1)
Water Solubility	2.224-03 (2)

**Download as:** CSV | Excel | PDF

**Biological Activity**

Source	Result
PhysToxNCDT	5.2E-04 (MOL)
NCATS	Result
EPIDROUTE	7.55E-04 (MOL)
NCDT	3.85E-03 (MOL)

Enhanced Chemistry Dashboard  
(<https://comptox.epa.gov/dashboard>)



**EPA iCASS ToxCast Dashboard**

Choose a view:  Assays  Chemicals

Database: prof\_dashboard\_v2  
Dashboard: v2

**Chemicals - 16**

CASRN	Chemical Name
70-05-8	2,2',4,4'-Tetrachlorobisphenol A
70-04-7	3,3',5,5'-Tetrabromobisphenol A

**Assays - 1091**

Assay Endpoint Name... Gene Symbol...

Active - MC Only  All Tested

Assay Component Endpoint Name

ATQ\_VDRE\_CIS\_up

**Chemical Summary** | Assay Summary | Bioactivity | Help

Start Tutorial - Bioactivity Tab

**Winning Plots - Representative Samples**

Save Chart | Preview Chart

Summary plots - Representative samples only

Scalped Response (= Response / Cutoff)

Concentration (uM)

ToxCast Dashboard  
(<https://actor.epa.gov/dashboard>)



**EDSP21 Dashboard**  
Endocrine Disruption Screening Program for the 21st Century

**Chemical Selection**

CASRN	Chemical Name	iToxCast
103-37-0	Bisphenol A bis(2-hydroxypropyl) ether	
20230-24-0	Bisphenol A/ Epichlorohydrin resin	
80-05-7	Bisphenol A	
1875-54-3	Bisphenol A diglycidyl ether	
1555-94-2	Bisphenol A glycidyl methacrylate	
1473-01-1	Bisphenol AF	
2026-38-8	Bisphenol A/ Epichlorohydrin resin	
20230-25-3	Bisphenol A-bisphenol A diglycidyl ether polymer	

**ToxP Graphs**

AR | ER | TR

**ACSB Values - AR**

Assay Endpoint ID	ACSB
ATS_AR_TRA	Inactive
NVS_AR_HAR	10.7950
NVS_AR_HAR	7.5394
NVS_AR_HAR	10.0040
OT_AR_AREL	Inactive

**ACSB Values - ER**

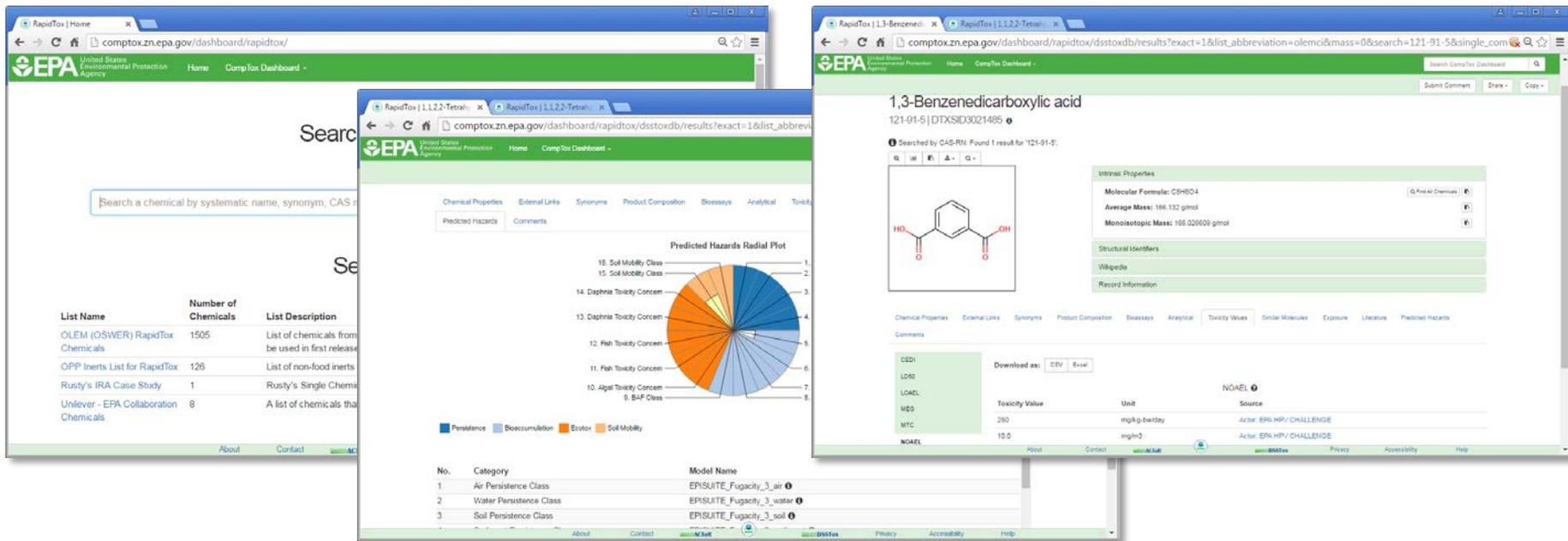
Assay Endpoint ID	ACSB
ACEA_ER_DS	0.3580
ATQ_VRE_CIS	0.0091
ATQ_VRE_TR	0.1104
NVS_ER_HER	0.421
NVS_ER_HER	0.6076

**ACSB Values - TR**

Assay Endpoint ID	ACSB
ATS_TR_VL3	Inactive
NVS_TR_HTR	Inactive
Tox21_TR_LUC	Inactive
Tox21_TR_LUC	85.7600

EDSP21 Dashboard  
(<https://actor.epa.gov/edsp1>)

# RapidTox Workflow as a Focal Point for Integrating Components



The image displays three overlapping screenshots of the RapidTox web application interface. The leftmost screenshot shows a search results page with a table of chemical lists. The middle screenshot shows a 'Predicted Hazards Radial Plot' for a search query. The rightmost screenshot shows a detailed profile for 1,3-benzenedicarboxylic acid, including its chemical structure and various toxicity values.

List Name	Number of Chemicals	List Description
OLEM (OSWER) RapidTox Chemicals	1505	List of chemicals from be used in first release
OPP Inerts List for RapidTox	126	List of non-food inerts
Rusty's IRA Case Study	1	Rusty's Single Chemi
Unilever - EPA Collaboration Chemicals	8	A list of chemicals that

**Predicted Hazards Radial Plot**

Legend: Persistence (Blue), Bioaccumulation (Light Blue), Ecotox (Orange), Soil Mobility (Yellow)

No.	Category	Model Name
1	Air Persistence Class	EPISLITE_Fugacity_3_air
2	Water Persistence Class	EPISLITE_Fugacity_3_water
3	Soil Persistence Class	EPISLITE_Fugacity_3_soil

**1,3-Benzenedicarboxylic acid**  
121-91-5 [DTXSID3021485]

Chemical Structure: O=C(O)c1ccc(O)cc1

**Intrinsic Properties**

- Molecular Formula: C<sub>8</sub>H<sub>6</sub>O<sub>4</sub>
- Average Mass: 166.132 g/mol
- Monoisotopic Mass: 166.020009 g/mol

**Toxicity Values**

Parameter	Toxicity Value	Unit	Source
LD50	250	mg/kg bodywt	Actel: EPA/HPV/CHALLENGE
MTC	10.0	mg/m <sup>3</sup>	Actel: EPA/HPV/CHALLENGE
NOAEL			

- 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

# Where do we go from here?

## **Barriers to progress**

- Different regulatory needs
- Inconsistent characterization of data, NAMs
- Low confidence in new methods due to lack of understanding
- Culture shift needed!

## **Opportunities for progress**

- Data sharing
- Classification systems for NAMs
- Collaborative case studies as proof of concept for use of NAMs in chemical risk assessment

# 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**