

# Incorporating new technologies and high-throughput approaches in the design and selection of chemical alternatives

***Antony Williams***

*U.S. Environmental Protection Agency, RTP, NC*

*This work was reviewed by the U.S. EPA and approved for presentation but does not necessarily reflect official Agency policy.*

*June 15th, 2017*

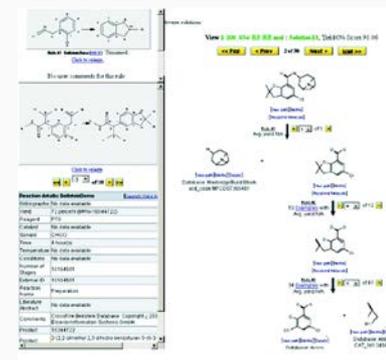
*21st Annual Green Chemistry & Engineering Conference, Reston, VA*

# Paradigm Shift in Chemical Design (especially in regards to toxicology)

- Chemical Design in the future
  - High-throughput modeling
  - SAR/QSAR/QSTR models
  - Retrosynthetic analysis algorithms for synthesis



- Toxicology
  - FEWER animal studies. Maybe NONE??
  - Openness in data sharing
  - More confidence in computational predictive models that link chemical structures to adverse outcomes



# It will depend on lots of DATA



Chemistry International  
The News Magazine of IUPAC

☰ **Volume 39, Issue 3 (Jul 2017)**

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## The Future of Chemical Information Is Now

Antony J. Williams ✉ / Harry E. Pence ✉

Published Online: 2017-05-24 | DOI: <https://doi.org/10.1515/ci-2017-0304>

# The Future of Chemical Information Is Now

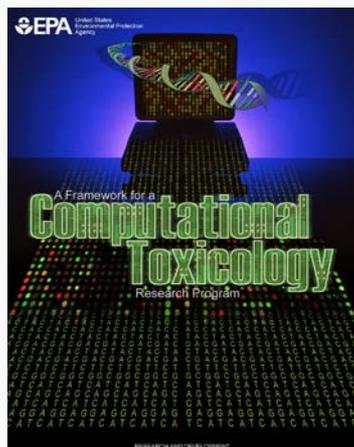
*by Antony J. Williams and Harry E. Pence*

**S**earch and retrieval of chemical information has been dramatically changed by the application of “Big Data” techniques. This development continues to be driven by the massive growth of chemical scientific literature and of online data and databases. Not only is there an expansion of the traditional avenues of publication, but many new contributing resources, such as open access journals, MOOCs (Massive Open Online Courses), Wikis, and blogs



- Adequate information on potential bioactivity for as many chemicals as possible
- Read-across, QSAR and QSTR models from large high-quality curated datasets

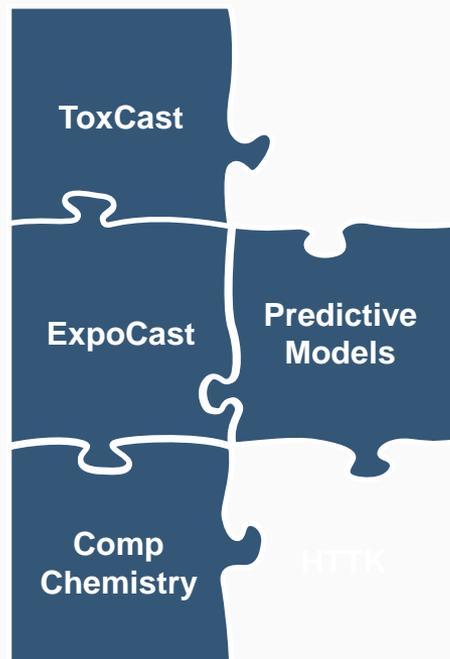
# National Center for Computational Toxicology



- National Center for Computational Toxicology established in 2005 to integrate:
  - High-throughput and high-content technologies
  - Modern molecular biology
  - Data mining and statistical modeling
  - Computational biology and chemistry
- Currently staffed by ~60 employees as part of EPA's Office of Research and Development
- Home of ToxCast & ExpoCast research efforts
- Key partner in U.S. Tox21 federal consortium
- Multiple cross-division collaborations

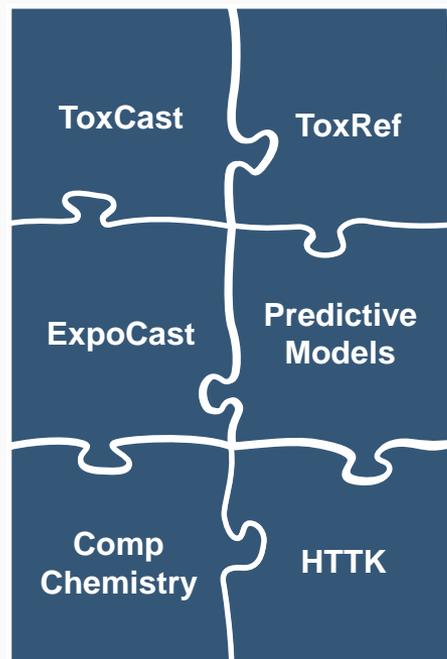
- Adequate information on potential bioactivity for as many chemicals as possible
- **High Throughput Screening** ToxCast/Tox21 generating and making available bioactivity data
- GREAT progress to date – more to come!
  
- Read-across, QSAR and QSTR models from large high-quality curated datasets
- **Chemistry data** gathering and high-throughput bioassays are providing the necessary data to generate these **models**

# Data and Modeling Efforts to Date



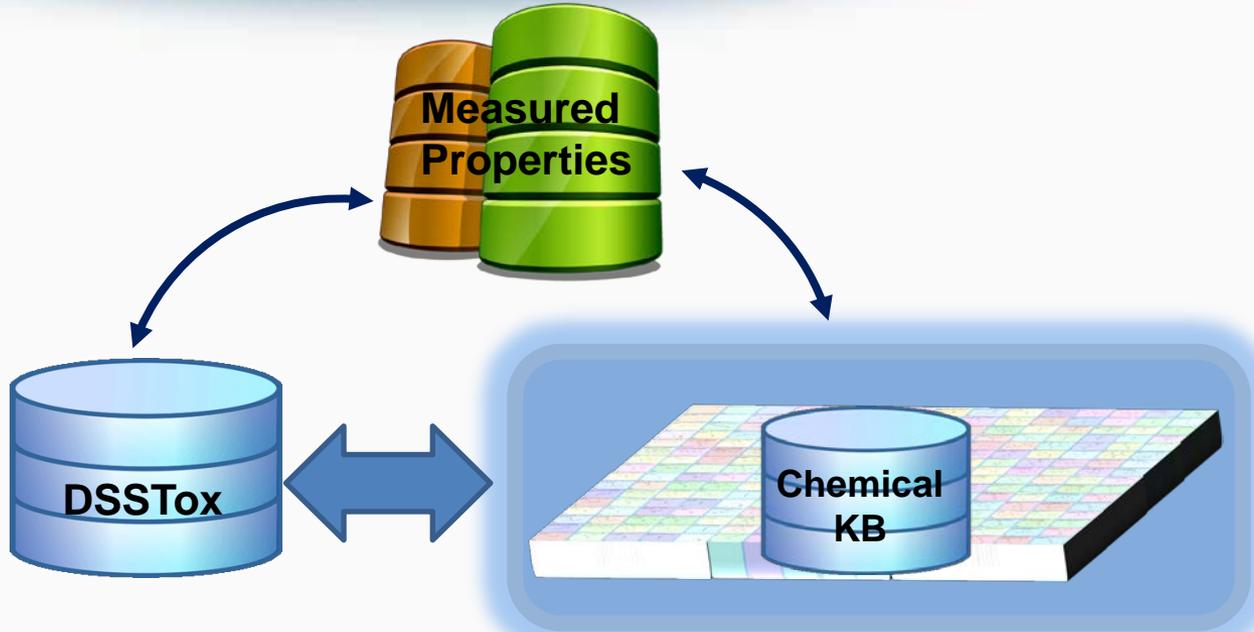
- High-throughput *in vitro* screening of ~4,000 chemicals across ~1200 assay endpoints (ToxCast) and ~8,000 chemicals in ~60 assay endpoints (Tox21)
- High quality, curated chemical structure and physical chemical properties database of ~750,000 chemicals
- High-throughput exposure estimates with uncertainty for ~ 7,000 chemicals based on production volume and chemical use

# Data and Modeling Efforts to Date

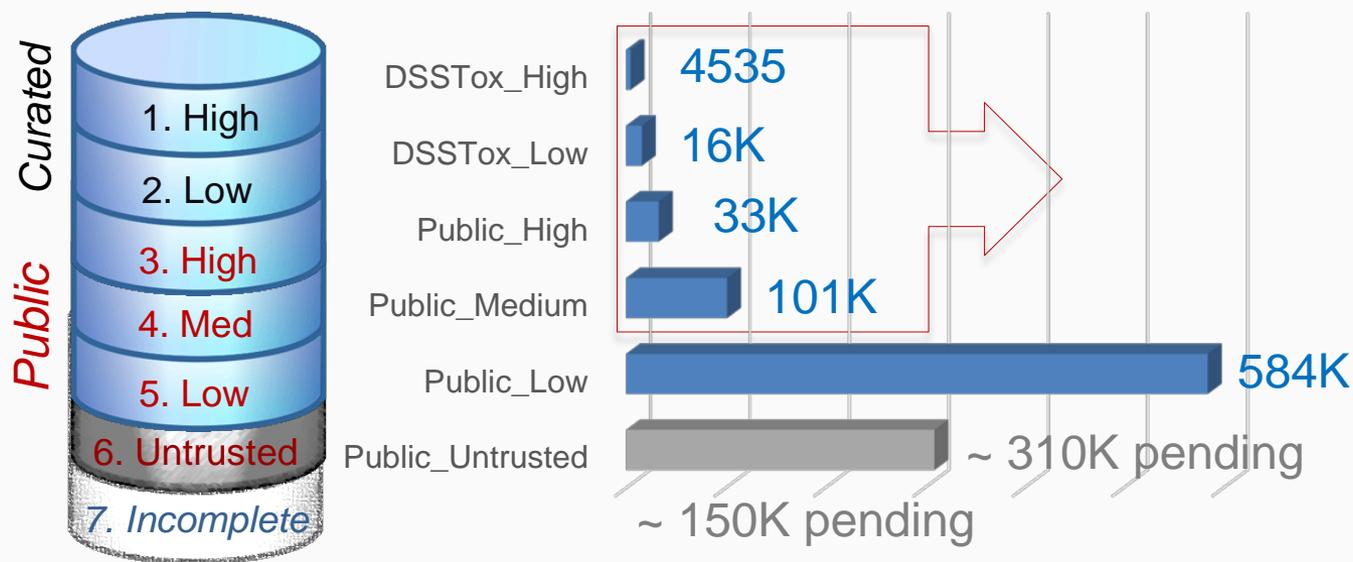


- High-throughput *in vitro* screening of ~4,000 chemicals across ~1200 assay endpoints (ToxCast) and ~8,000 chemicals in ~60 assay endpoints (Tox21)
- High quality, curated chemical structure and physical chemical properties database of ~750,000 chemicals
- High-throughput exposure estimates with uncertainty for ~7,000 chemicals based on production volume and chemical use
- Legacy *in vivo* data from ~6,000 animal toxicology studies on ~1,110 unique chemicals
- High-throughput toxicokinetic (HHTK) models for ~700 chemicals based on *in vitro* measurements
- AOPs and virtual tissue models for broad range of developmental toxicities

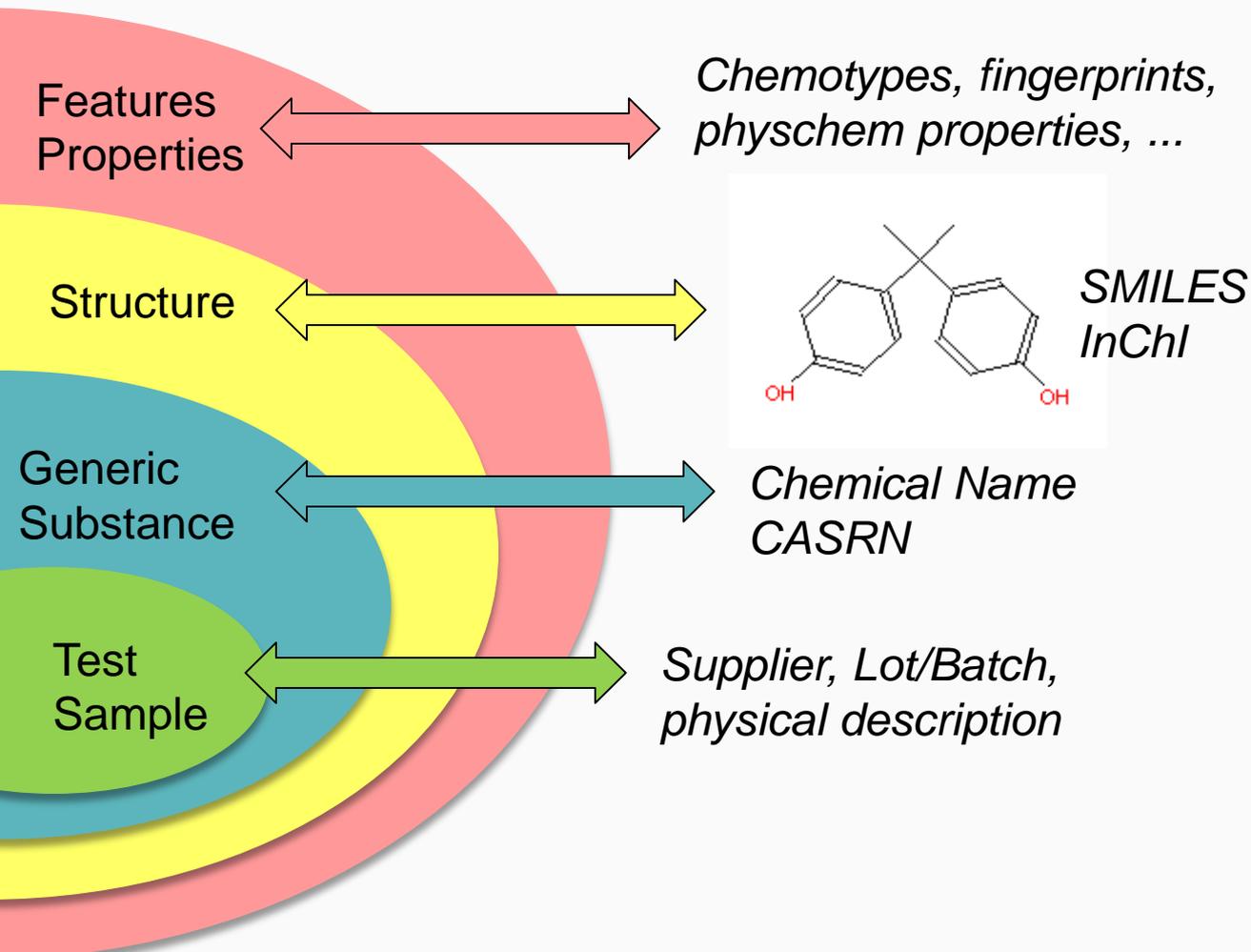
# Underpinning with chemicals



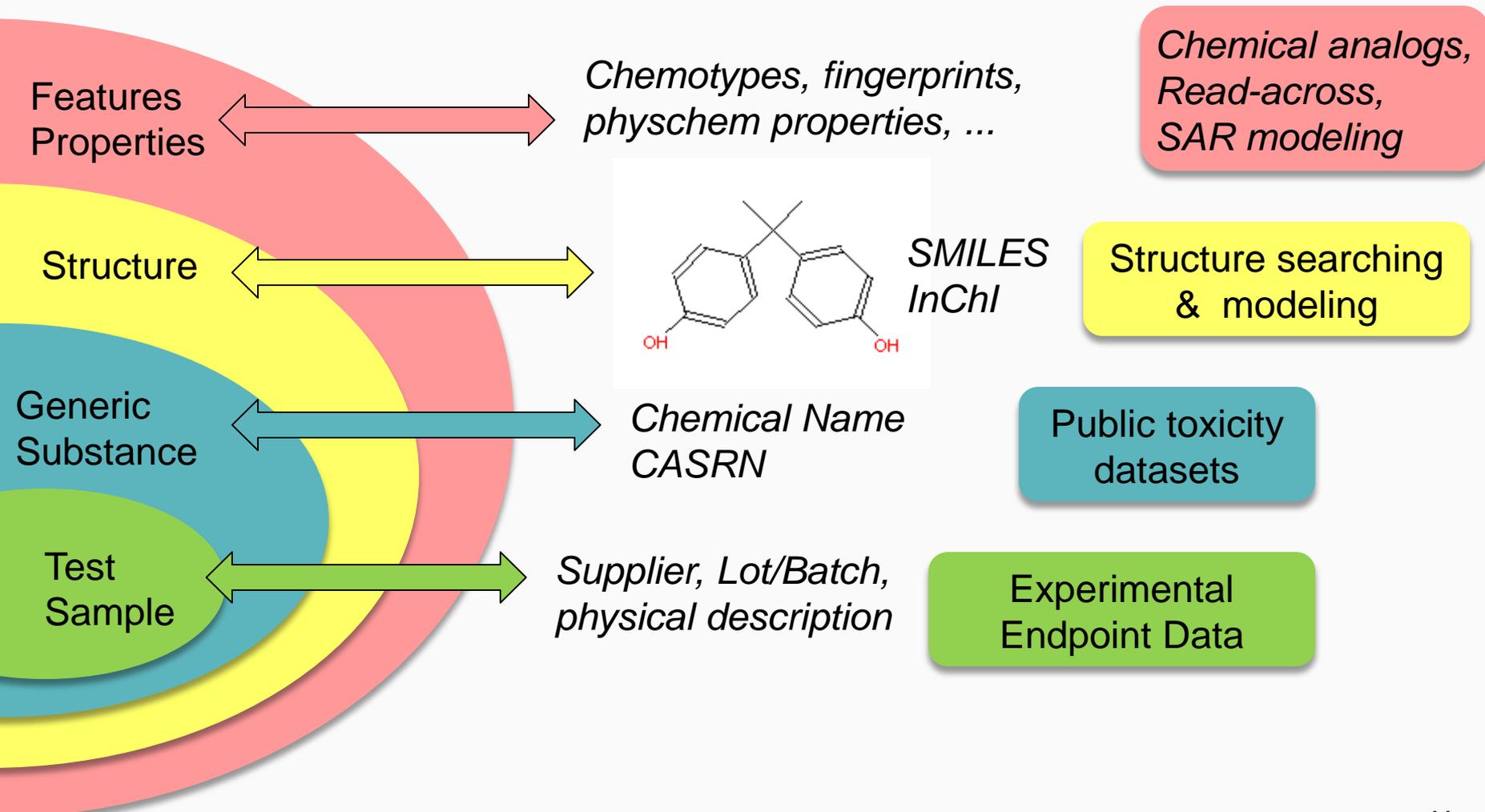
# Approximately 15 Years of Data... Growing with daily curation



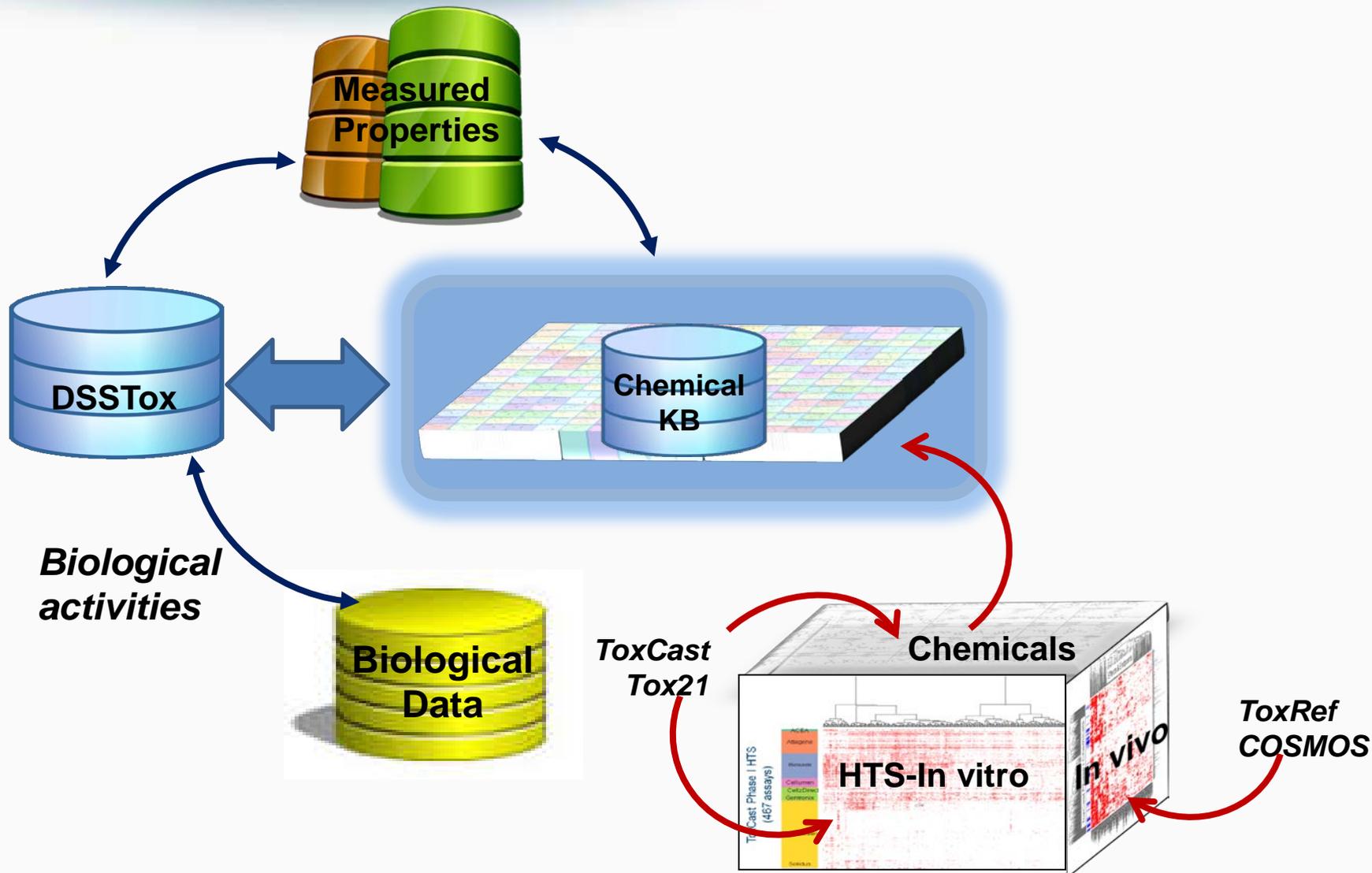
# Chemical representation levels supporting data integration



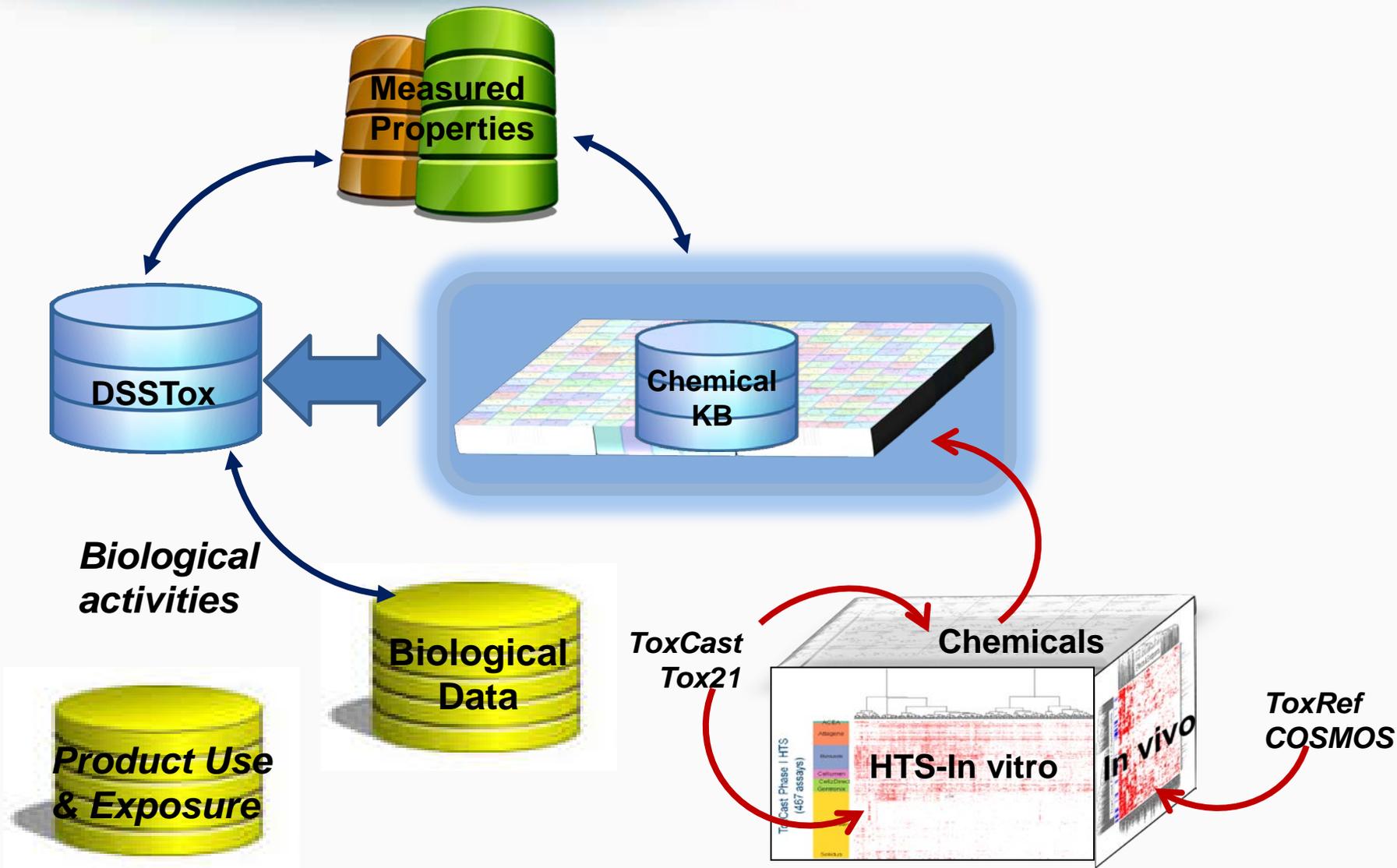
# Chemical representation levels supporting data integration



# Integrating *in vitro* and *in vivo* data



# Adding Product Use and Exposure



# High Throughput Measurement to Characterize Exposure

## Rapid Chemical Exposure and Dose Research

EPA is responsible for ensuring the safety of thousands of chemicals. Quantitative exposure data are available for only a small fraction of registered chemicals. This type of exposure data is needed to thoroughly evaluate chemicals for potential risks to humans, wildlife and ecosystems. EPA is developing innovative methods to develop exposure estimates for thousands of chemicals to better protect human health and the environment. These innovative methods are called rapid exposure and dose assessments.

### Rapid Exposure Predictions

Rapid, also called high-throughput, exposure predictions or ExpoCast provide rapid exposure estimates for thousands of chemicals. ExpoCast quickly and efficiently looks at multiple routes of exposure to provide exposure estimates. ExpoCast uses and enhances two well-known exposure models to estimate chemical exposure.

- [Farfield Exposure Models](#)
- [Nearfield Exposure Models](#)

### Evaluating High-throughput Exposure Predictions

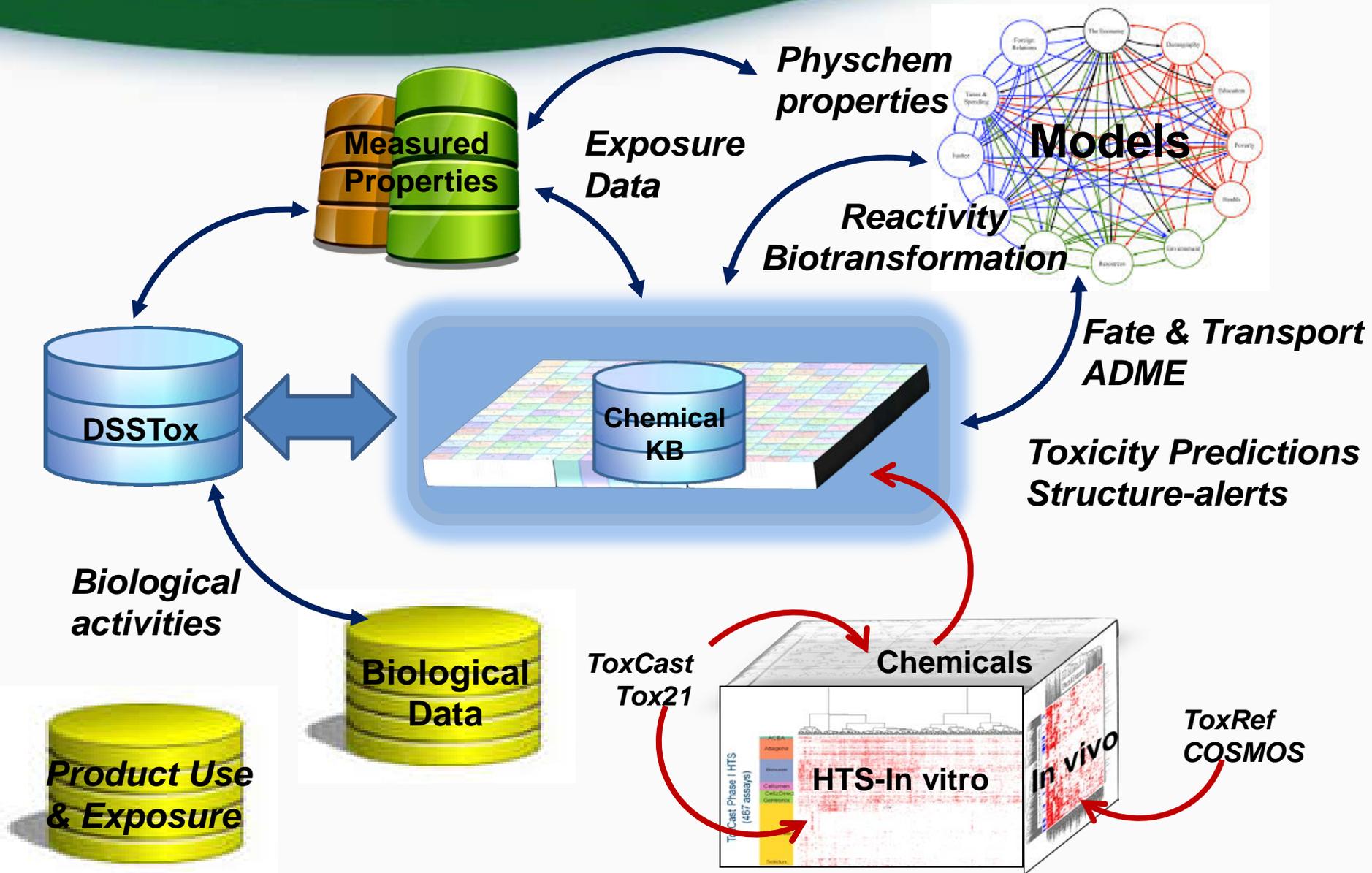
EPA is currently evaluating the effectiveness of high-throughput exposure models



*Pictured Above: Farfield Exposure Examples*



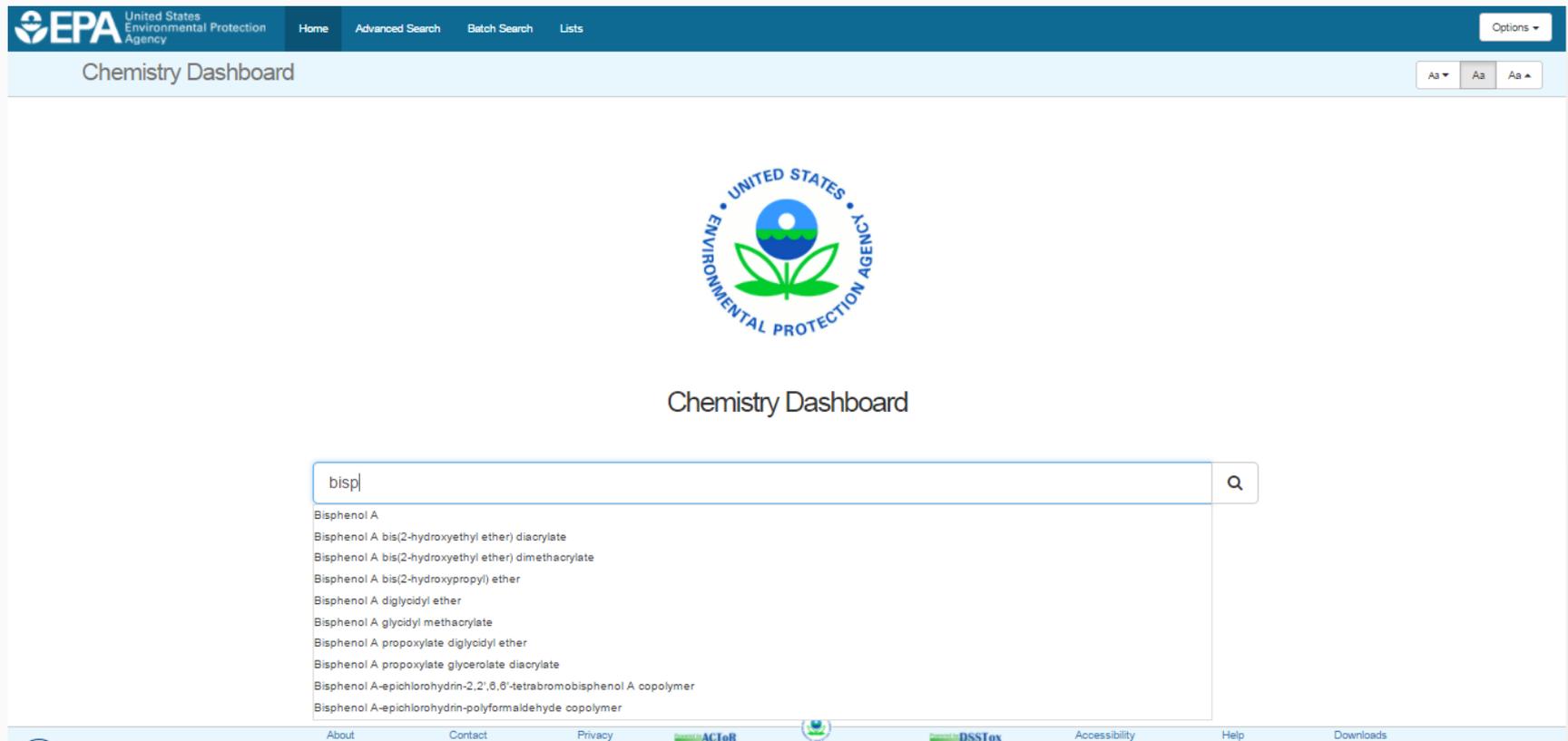
# Building Models from the data





- Data **curation**, standardization and versioning is essential
- Prototype application development suffices for research projects but **production development requires managed processes**
- **ODOSOS** (Open Data, Open Source and Open Standards) endows many benefits
- With this in mind...

# Our INTEGRATION Dashboard: <https://comptox.epa.gov>



United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Options

## Chemistry Dashboard

Aa Aa Aa



### Chemistry Dashboard

bisp|

- Bisphenol A
- Bisphenol A bis(2-hydroxyethyl ether) diacrylate
- Bisphenol A bis(2-hydroxyethyl ether) dimethacrylate
- Bisphenol A bis(2-hydroxypropyl) ether
- Bisphenol A diglycidyl ether
- Bisphenol A glycidyl methacrylate
- Bisphenol A propoxylate diglycidyl ether
- Bisphenol A propoxylate glycerolate diacrylate
- Bisphenol A-epichlorohydrin-2,2',6,6'-tetrabromobisphenol A copolymer
- Bisphenol A-epichlorohydrin-polyformaldehyde copolymer

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# Bisphenol A

## Chemistry Dashboard

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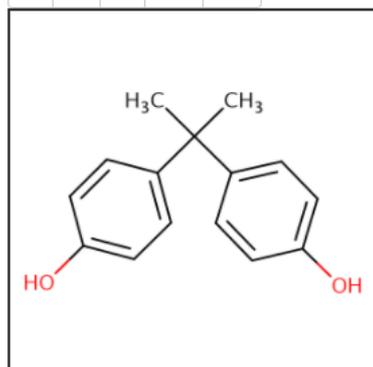
Aa

Aa

### Bisphenol A

80-057 |DTXSID7020182

Searched by Approved Name: Found 1 result for 'bisphenol A'.



#### Wikipedia

Bisphenol A (BPA) is an organic synthetic compound with the chemical formula  $(\text{CH}_3)_2\text{C}(\text{C}_6\text{H}_4\text{OH})_2$  belonging to the group of diphenylmethane derivatives and bisphenols, with two hydroxyphenyl groups. It is a colorless solid that is soluble in organic solvents, but poorly soluble in water. It has been in commercial use since 1957. BPA is employed to make certain plastics and epoxy resins. BPA-based plastic is clear and tough... [Read more](#)

#### Intrinsic Properties

#### Structural Identifiers

#### Related Compounds (Beta)

#### Presence in Lists

#### Record Information

Chemical Properties

Env. Fate/Transport

Synonyms

External Links

Toxicity Values (Beta)

Exposure

Bioassays

Similar Molecules (Beta)

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# Chemical Properties

## Chemistry Dashboard

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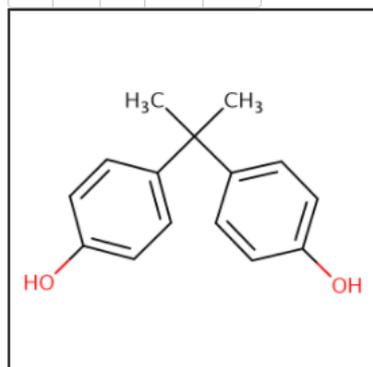
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- Consuming and producing open data

**Summary**

LogP: Octanol-Water

Water Solubility

Density

Melting Point

Boiling Point

Surface Tension

Vapor Pressure

LogKoa: Octanol-Air

Henry's Law

Index of Refraction

Molar Refractivity

pKa Acidic Apparent

Download as: TSV Excel SDF

Property	Average		Median		Range		Unit
	Experimental	Predicted	Experimental	Predicted	Experimental	Predicted	
LogP: Octanol-Water	3.32 (1)	3.24 (4)	3.32	3.24	3.32	2.40 to 3.73	-
Water Solubility	5.26e-04 (1)	1.58e-03 (4)	5.26e-04	1.58e-03	5.26e-04	5.70e-04 to 3.68e-03	mol/L
Density	-	1.14 (1)	-	1.14	-	-	g/cm <sup>3</sup>
Melting Point	155 (7)	144 (3)	156	144	153 to 158	132 to 157	°C
Boiling Point	200 (1)	349 (3)	200	349	200	334 to 364	°C
Surface Tension	-	46.0 (1)	-	46.0	-	-	dyn/cm
Vapor Pressure	-	2.52e-07 (3)	-	2.52e-07	-	7.01e-08 to 5.34e-07	mmHg
LogKoa: Octanol-Air	-	8.38 (1)	-	8.38	-	-	-
Henry's Law	-	6.96e-07 (1)	-	6.96e-07	-	-	atm-m <sup>3</sup> /mole
Index of Refraction	-	1.60 (1)	-	1.60	-	-	-
Molar Refractivity	-	68.2 (1)	-	68.2	-	-	cm <sup>3</sup>
pKa Acidic Apparent	-	10.3 (1)	-	10.3	-	-	-
Molar Volume	-	200 (1)	-	200	-	-	cm <sup>3</sup>
Polarizability	-	27.0 (1)	-	27.0	-	-	Å <sup>3</sup>

# Data Distribution

- Consuming and producing open data

**Summary**

LogP: Octanol-Water

Water Solubility

Density

Melting Point

Boiling Point

Surface Tension

Vapor Pressure

LogKoa: Octanol-Air

Henry's Law

Index of Refraction

Molar Refractivity

pKa Acidic Apparent

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Property	Median		Range		Unit
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LogP: Octanol-Water	3.32	3.24	3.32	2.40 to 3.73	-
Water Solubility	5.26e-04	1.58e-03	5.26e-04	5.70e-04 to 3.68e-03	mol/L
Density		1.14	-	-	g/cm <sup>3</sup>
Melting Point	56	144	153 to 158	132 to 157	°C
Boiling Point	200	349	200	334 to 364	°C
Surface Tension		46.0	-	-	dyn/cm
Vapor Pressure		2.52e-07	-	7.01e-08 to 5.34e-07	mmHg
LogKoa: Octanol-Air		8.38	-	-	-
Henry's Law		6.96e-07	-	-	atm-m <sup>3</sup> /mole
Index of Refraction		1.60	-	-	-
Molar Refractivity		68.2	-	-	cm <sup>3</sup>
pKa Acidic Apparent	-	10.3 (1)	-	10.3	-
Molar Volume	-	200 (1)	-	200	cm <sup>3</sup>
Polarizability	-	27.0 (1)	-	27.0	Å <sup>3</sup>

- Select/Deselect All
- LogP: Octanol-Water
- Water Solubility
- Density
- Melting Point
- Boiling Point
- Surface Tension
- Vapor Pressure
- LogKoa: Octanol-Air
- Henry's Law
- Index of Refraction
- Molar Refractivity
- pKa Acidic Apparent
- Molar Volume
- Polarizability

Download

# Data Distribution

	A	B	C	D	E	F	G	H
1	Property	Average		Median		Range		Unit
2		Experimental	Predicted	Experimental	Predicted	Experimental	Predicted	
3	LogP: Octanol-Water	3.32 (1)	3.24 (4)	3.32	3.24	3.32	2.40 to 3.73	-
4	Water Solubility	5.26e-04 (1)	1.58e-03 (4)	0.000526	0.00158	0.000526	5.70e-04 to 3.68e-03	mol/L
5	Density	-	1.14 (1)	-	1.14	-	-	g/cm <sup>3</sup>
6	Melting Point	155 (7)	144 (3)	156	144	153 to 158	132 to 157	°C
7	Boiling Point	200 (1)	349 (3)	200	349	200	334 to 364	°C
8	Surface Tension	-	46.0 (1)	-	46	-	-	dyn/cm
9	Vapor Pressure	-	2.52e-07 (3)	-	0.000000252	-	7.01e-08 to 5.34e-07	mmHg
10	LogKoa: Octanol-Air	-	8.38 (1)	-	8.38	-	-	-
11	Henry's Law	-	6.96e-07 (1)	-	0.000000696	-	-	atm-m <sup>3</sup> /mole
12	Index of Refraction	-	1.60 (1)	-	1.6	-	-	-
13	Molar Refractivity	-	68.2 (1)	-	68.2	-	-	cm <sup>3</sup>
14	pKa Acidic Apparent	-	10.3 (1)	-	10.3	-	-	-
15	Molar Volume	-	200 (1)	-	200	-	-	cm <sup>3</sup>
16	Polarizability	-	27.0 (1)	-	27	-	-	Å <sup>3</sup>
17								

# Modeling Details

United States Environmental Protection Agency Home Advanced Search 20182

### NCCT Models: Melting Point

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

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

**Model Results**  
Predicted value: 144 °C  
Global applicability domain: Inside  
Local applicability domain index: 0.91  
Confidence level: 0.65

## Calculation Result for a chemical

**Model Performance**  
Weighted KNN model **QMRP**  
5-fold CV (75%) Training (75%) Test (25%)  

Q2	RMSE	R2	RMSE	R2	RMSE
0.72	51.8	0.74	50.3	0.73	52.7

**Nearest Neighbors from the Training Set**

Chemical	Measured	Predicted
<chem>Cc1ccc(cc1)C(C)(C)c2ccc(O)cc2</chem> Bisphenol A	153	144
<chem>Cc1ccc(cc1)C(C)Cc2ccc(O)cc2</chem> 4,4'-Propane-1,1-diyldiphenol	132	133
<chem>Cc1ccc(cc1)C(C)Cc2ccc(O)cc2</chem> phenol, 4,4'-butylidenebis-	137	142
<chem>Cc1ccc(O)cc1C(C)(C)c2ccc(O)cc2</chem> Bisphenol B	121	140
<chem>Cc1ccc(O)cc1C(C)Cc2ccc(O)cc2</chem> meso-Hexestrol	187	157

Model Performance with full QMRF

Nearest Neighbors from Training Set

Chemical Properties

Env. Fate/Transport

Synonyms

External Links

Toxicity Values (Beta)

Exposure

Bioassays

Similar Molecules (Beta)

Literature

Comments

# Prediction Details and QMRF Report

## Model Results

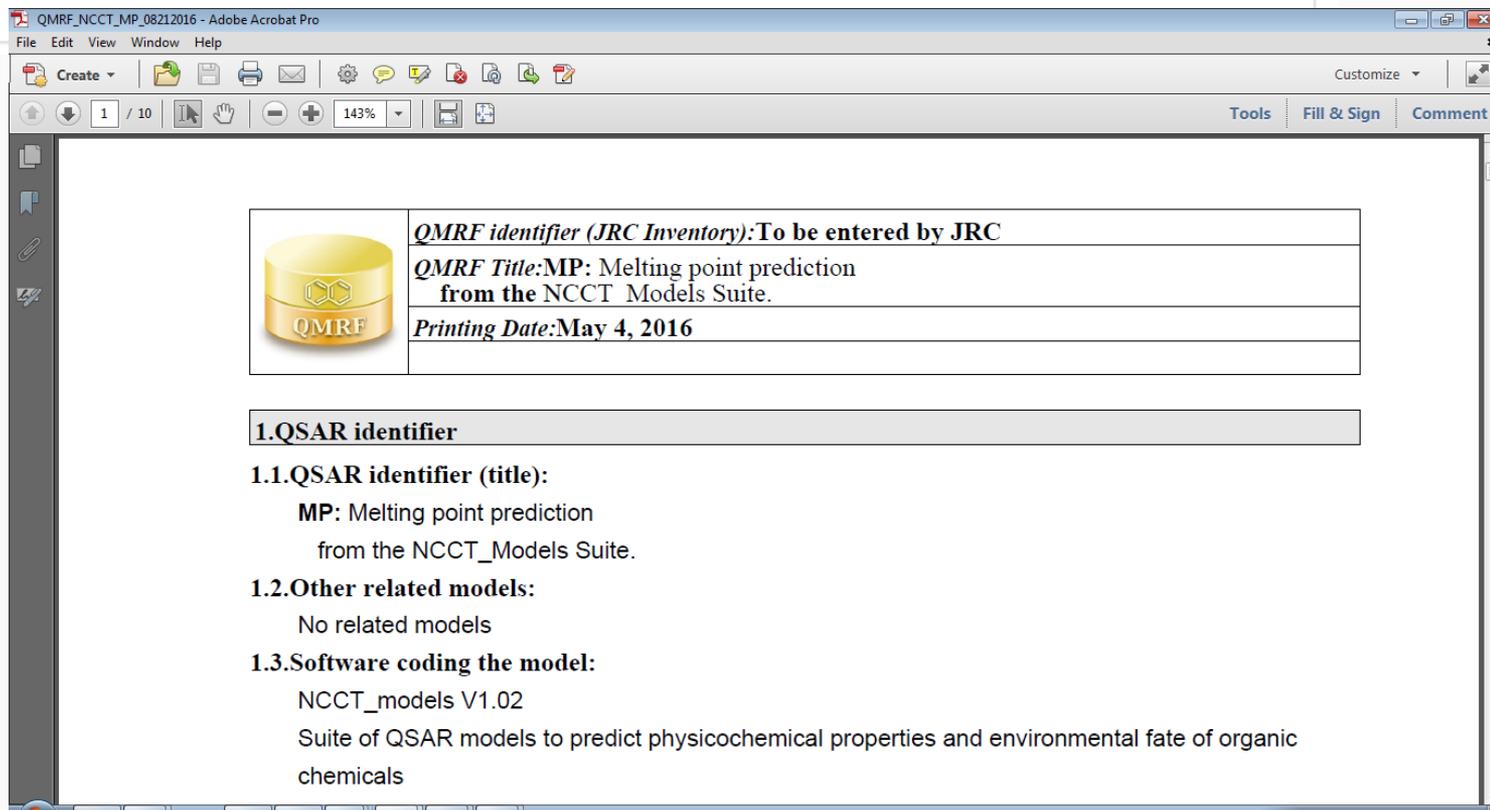
Predicted value: 144 °C

Global applicability domain: **Inside** ?

Applicability domain using the leverage approach. All training set space considered. More details in QMRF.

Local applicability domain index: 0.91 ?

Confidence level: 0.65 ?



The screenshot shows the Adobe Acrobat Pro interface with a QMRF report document open. The report content is as follows:

	<b>QMRF identifier (JRC Inventory): To be entered by JRC</b>
	<b>QMRF Title:</b> MP: Melting point prediction from the NCCT Models Suite.
	<b>Printing Date:</b> May 4, 2016

**1. QSAR identifier**

**1.1. QSAR identifier (title):**  
MP: Melting point prediction  
from the NCCT\_Models Suite.

**1.2. Other related models:**  
No related models

**1.3. Software coding the model:**  
NCCT\_models V1.02  
Suite of QSAR models to predict physicochemical properties and environmental fate of organic chemicals

- Our approach to modeling:
  - Obtain **high quality** training sets
  - Apply appropriate modeling approaches
  - **Validate** performance of models
  - Define the applicability domain and model limitations
  - Use models to predict properties across our full datasets
- Release as **Open Data and Open Models**



Journal

**SAR and QSAR in Environmental Research** >

Volume 27, 2016 - Issue 11: 17th International Conference on QSAR in Environmental and Health Sciences (QSAR 2016) - Part II. Guest Editors: C.G. Barber and G.J. Myatt

258

Views

4

CrossRef citations

16

Altmetric

Articles

## An automated curation procedure for addressing chemical errors and inconsistencies in public datasets used in QSAR modelling<sup>\$</sup>

K. Mansouri, C. M. Grulke, A. M. Richard, R. S. Judson & A. J. Williams 

Pages 911-937 | Received 03 Sep 2016, Accepted 24 Oct 2016, Published online: 25 Nov 2016

 Download citation

 <http://dx.doi.org/10.1080/1062936X.2016.1253611>

 Check for updates

OPERA Models: <https://github.com/kmansouri/OPERA>

# Making Toxicity Value Data available

Chemical Properties   Env. Fate/Transport   Synonyms   External Links   **Toxicity Values (Beta)**   Exposure   Bioassays   Similar Molecules (Beta)   Literature   Comments

Bioavailability Metric

Exposure Limit

Point Of Departure

**Regulatory Toxicity V...**

Exposure Descriptor

Effect Level

Misc Hazard Informa

Screening Level

Uncertainty Factor

Download as:   TSV   Excel

## Regulatory Toxicity Value

Grouping ID	Priority	Type	Subtype	Value	Units	Study Type	Exposure Route	Study Duration	Species	Media	Details	Source
49234	2	RfDo	-	0.05	mg/kg-d...	-	-	-	-	-	RSL de...	RSL
61404	5	RfD	-	0.05	mg/kg-d...	-	oral	chronic	-	-	RSEI d...	RSEI
...	...	...	...	...	...	...	oral	-	-	-	EPA Ris...	ACToR
...	...	...	...	...	...	...	oral	-	-	-	EPA Ris...	ACToR
...	...	...	...	...	...	...	oral	-	-	-	Pennsyl...	ACToR
...	...	...	...	...	...	...	oral	-	-	-	Pennsyl...	ACToR
253004	5	RfD	inhalation	0.0	mg/kg-d...	-	inhalation	-	-	-	Pennsyl...	ACToR
253005	5	unit risk	inhalation	0.0	(g/m3)-1	-	inhalation	-	-	-	Pennsyl...	ACToR
253020	4	RfD	oral	0.05	mg/kg-d...	-	oral	-	-	-	Detailed...	ACToR

An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or BMD, with UFs generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments

Chemical Properties   Env. Fate/Transport   Synonyms   External Links   **Toxicity Values (Beta)**   Exposure   Bioassays   Similar Molecules (Beta)   Literature   Comments

- Chemical Properties
- Env. Fate/Transport
- Synonyms
- External Links
- Toxicity Values (Beta)
- Exposure
- Bioassays
- Similar Molecules (Beta)
- Literature
- Comments

## Product & Use Categ...

- Chemical Weight Fraction
- Chemical Functional Use
- Monitoring Data
- Exposure Predictions

### Product & Use Categories (PUCs)

Download as:

<u>Product or Use Categorization</u>	<u>Categorization type</u>	<u>Number of Unique Products</u>
adhesive	CPCat Cassette	17
manufacturing metals	CPCat Cassette	17
paint	CPCat Cassette	16
manufacturing machines	CPCat Cassette	12
manufacturing plastics	CPCat Cassette	11
building_material flooring	CPCat Cassette	8
construction	CPCat Cassette	8

- Chemical Properties
- Env. Fate/Transport
- Synonyms
- External Links
- Toxicity Values (Beta)
- Exposure
- Bioassays
- Similar Molecules (Beta)
- Literature
- Comments

- Data gathered from multiple online data sources – text mining and data downloads



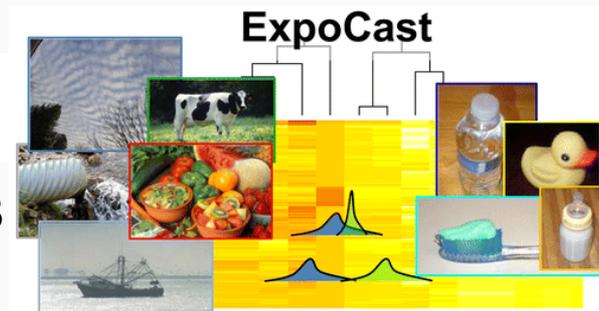
- CASRN and name mappings to produce curated structure set with functional uses
- Produce Functional Use (FuseDB) and build predicted functional use models



## National Health and Nutrition Examination Survey

High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project

*Environ. Sci. Technol.*, **2013**, 47 (15), pp 8479–8488



Product & Use Categori...  
 Chemical Weight Fraction  
 Chemical Functional Use  
**Monitoring Data**  
 Exposure Predictions

Download as:

**National Health and Nutrition Examination Survey (NHANES) Inferences** (mg/kg-bw/day)

	Lower 95th Limit	Upper 95th Limit	Median
Ages 6-11	3.80e-05	4.92e-05	4.33e-05
Ages 12-19	2.55e-05	3.38e-05	2.93e-05
Ages 20-65	2.79e-05	3.27e-05	3.02e-05
Ages 65+	1.91e-05	2.31e-05	2.10e-05
BMI > 30	2.38e-05	2.74e-05	2.55e-05
BMI < 30	3.02e-05	3.30e-05	3.16e-05
Repro. Age Females	2.83e-05	3.31e-05	3.06e-05
Females	2.58e-05	3.03e-05	2.80e-05
Males	2.94e-05	3.37e-05	3.15e-05
Total	2.86e-05	3.08e-05	2.97e-05

Chemical Properties

Env. Fate/Transport

Synonyms

External Links

Toxicity Values (Beta)

**Exposure**

Bioassays

Similar Molecules (Beta)

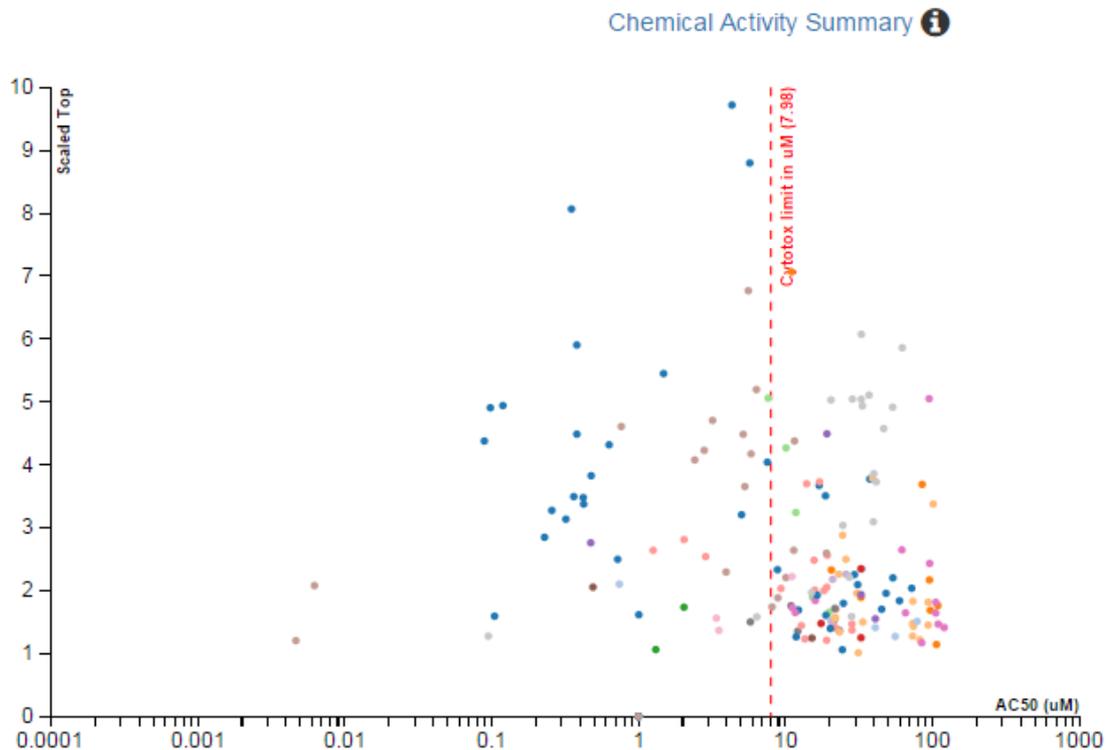
Literature

Comments

# ToxCast and Tox21 Bioassays

**ToxCast**

- PubChem
- ScrubChem (Beta)



- Show/Hide All
- nuclear receptor
  - background measurement
  - cell morphology
  - dna binding
  - steroid hormone
  - transporter
  - ion channel
  - gpcr
  - oxidoreductase
  - kinase
  - protease
  - cyp
  - cell cycle
  - cytokine
  - cell adhesion molecules
  -

Chemical Properties

Env. Fate/Transport

Synonyms

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# ToxCast and Tox21 Bioassays

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Background

Assay Name	Hit Call	Top	Scaled Top	AC50	log AC50 ↓	Intended Target Family
APR_Hepat_CellLoss_48hr_dn	ACTIVE	1.41	1.41	120	2.08	cell cycle
APR_HepG2_MitoMass_24h_dn	ACTIVE	0.874	1.76	109	2.04	cell morphology
APR_HepG2_OxidativeStress_24h_up	ACTIVE	1.20	1.47	110	2.04	cell cycle
APR_Hepat_DNADamage_48hr_up	ACTIVE	1.84	1.14	107	2.03	cell morphology
APR_HepG2_CellLoss_24h_dn	ACTIVE	1.20	1.81	106	2.02	cell cycle
APR_HepG2_OxidativeStress_72h_up	ACTIVE	1.80	1.65	106	2.02	cell cycle
ATG_HSE_CIS_up	ACTIVE	1.59	3.38	102	2.01	dna binding

Chemical Properties

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# PubChem Bioassay Data Integration

ToxCast

**PubChem**

ScrubChem (Beta)

## PubChem Biological Activities

PUBCHEM > COMPOUND > BISPHENOL A > BIOLOGICAL TEST RESULTS > BIOASSAY RESULTS >

### BioAssay Results

Refine/Analyze

Download

All (1,852) **Active(92)** Inconclusive(135) Inactive(1,038) Unspecified(587)

1 to 10 of 92 **1** 2 3 ... 10

Activity

Activity	Activity Value [µM]	Substance SID	BioAssay AID	BioAssay Name	Target
Active		81140	155	NCI Yeast Anticancer Drug Screen. Data for the rad50 strain	
Active		81140	157	NCI Yeast Anticancer Drug Screen. Data for the mec2-1 strain	
Active		68531	161	NCI Yeast Anticancer Drug Screen. Data for the sgs1 mgt1 strain	
Active		81140	165	NCI Yeast Anticancer Drug Screen. Data for the cln2 rad14 strain	
Active		81140	167	NCI Yeast Anticancer Drug Screen. Data for the bub3 strain	

Chemical Properties

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Select Term: Hazard

Retrieve Articles 108 Articles (out of 108)

Add additional query terms to filter abstracts:  
estrogen rodent exposure

Edit the Query Before Retrieving Articles  
("80-05-7" OR "Bisphenol A" OR "bisphenol A") AND (NOAEL OR NOEL OR LOEL OR Rfd OR "reference dose" OR "reference concentration" OR "adverse effect level"[tiab] OR "cancer slope factor"[tiab])

Search and Count

estro...	rodent	expo...	Total	PMID	PubYr	Title
9	0	0	9	16235731	2005	Reproductive stimulation by low doses of xenoestrogens contrasts with the view of hormesis as an adaptive response.
7	0	0	7	11351429	2001	Estrogenic potency of chemicals detected in sewage treatment plant effluents as determined by in vivo assays with Japanese medaka...
6	2	2	10	23582095	2013	The estrogenic content of rodent diets, bedding, cages, and water bottles and its effect on bisphenol A studies.
5	0	0	5	11993873	2002	Something from "nothing"—eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effe...
4	0	5	9	27571134	2016	Impact of Low Dose Oral Exposure to Bisphenol A (BPA) on the Neonatal Rat Hypothalamic and Hippocampal Transcriptome: A CLAR...

Record: 3 of 108

Title: The estrogenic content of rodent diets, bedding, cages, and water bottles and its effect on bisphenol A studies.

Abstract: The lowest observed adverse effect level for bisphenol A (BPA) in mice and rats is currently poorly defined due to inconsistent study designs and results in published studies. The objectives of the current study were to (1) compare the estrogenic content of rodent diets, bedding, cages, and water bottles used in animal studies. Our literature review indicated that low-dose BPA animal studies have inconsistent results and that factors contributing to this inconsistency are the uses of high-phytoestrogen diets and the different routes of exposure. In 44% (76 of 172) of all reports, rodents were exposed to BPA via the subcutaneous route. Our literature review further indicated that the type of diet, bedding, caging, and water bottles used in BPA studies were not always reported. Only 37% (84 of 172) of the reports described the diet used. In light of these findings, we recommend the use of a diet containing low levels of phytoestrogen (less than 20 µg/g diet) and metabolizable energy (approximately 3.1 kcal/g diet) and estrogen-free bedding, cages, and water bottles for studies evaluating the estrogenic activity of endocrine-disrupting compounds such as BPA. The oral route of BPA exposure should be used when results are to be extrapolated to humans.

Chemical Properties

Env. Fate/Transport

Synonyms

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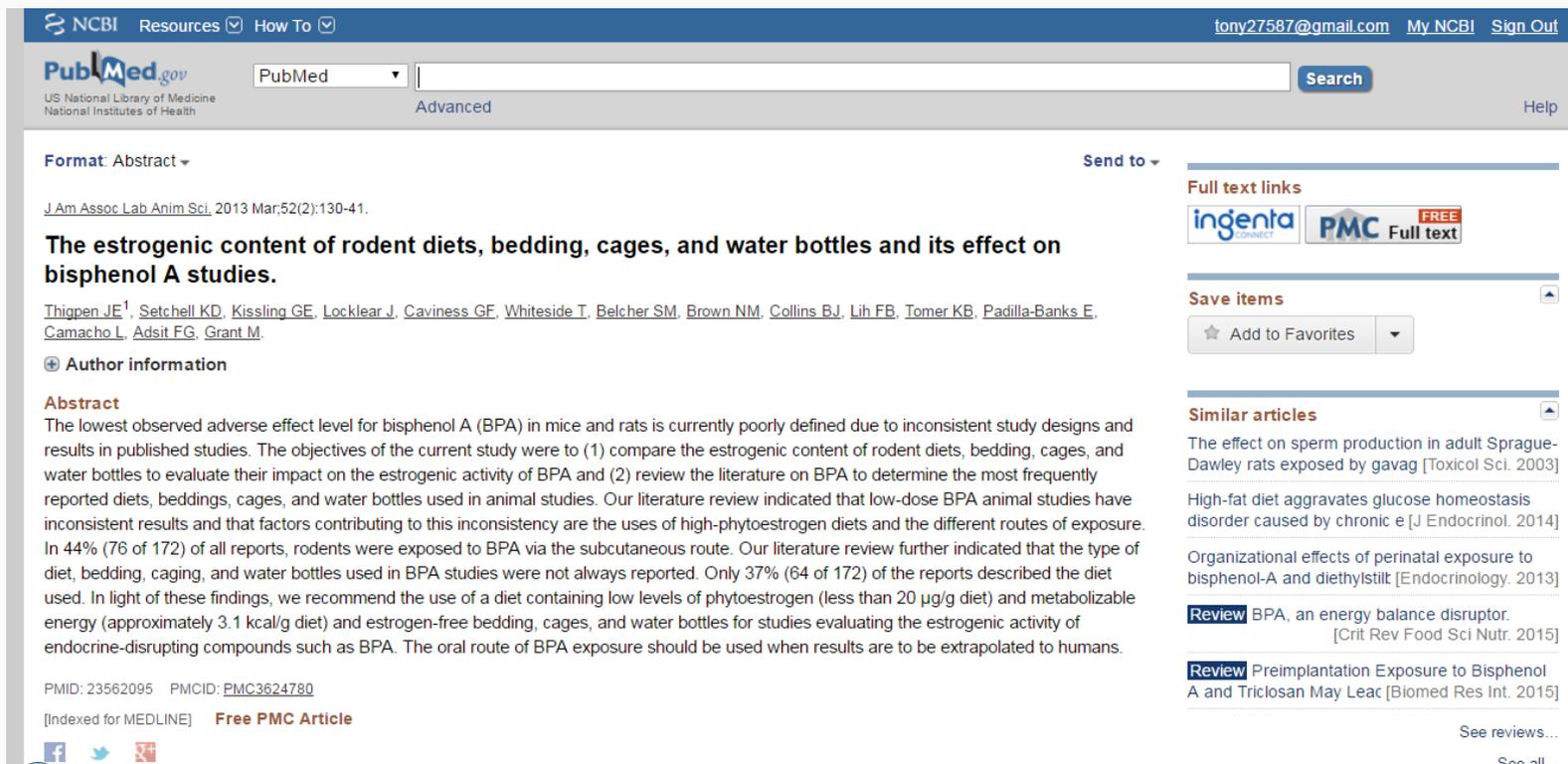
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*J Am Assoc Lab Anim Sci*, 2013 Mar;52(2):130-41.

### The estrogenic content of rodent diets, bedding, cages, and water bottles and its effect on bisphenol A studies.

Thigpen JE<sup>1</sup>, Setchell KD, Kissling GE, Locklear J, Caviness GF, Whiteside T, Belcher SM, Brown NM, Collins BJ, Lih FB, Tomer KB, Padilla-Banks E, Camacho L, Adsit FG, Grant M.

Author information

**Abstract**  
The lowest observed adverse effect level for bisphenol A (BPA) in mice and rats is currently poorly defined due to inconsistent study designs and results in published studies. The objectives of the current study were to (1) compare the estrogenic content of rodent diets, bedding, cages, and water bottles to evaluate their impact on the estrogenic activity of BPA and (2) review the literature on BPA to determine the most frequently reported diets, beddings, cages, and water bottles used in animal studies. Our literature review indicated that low-dose BPA animal studies have inconsistent results and that factors contributing to this inconsistency are the uses of high-phytoestrogen diets and the different routes of exposure. In 44% (76 of 172) of all reports, rodents were exposed to BPA via the subcutaneous route. Our literature review further indicated that the type of diet, bedding, caging, and water bottles used in BPA studies were not always reported. Only 37% (64 of 172) of the reports described the diet used. In light of these findings, we recommend the use of a diet containing low levels of phytoestrogen (less than 20 µg/g diet) and metabolizable energy (approximately 3.1 kcal/g diet) and estrogen-free bedding, cages, and water bottles for studies evaluating the estrogenic activity of endocrine-disrupting compounds such as BPA. The oral route of BPA exposure should be used when results are to be extrapolated to humans.

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Review BPA, an energy balance disruptor. [Crit Rev Food Sci Nutr. 2015]  
Review Preimplantation Exposure to Bisphenol A and Triclosan May Leac [Biomed Res Int. 2015]

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AND

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RW Tyl - Environmental health perspectives, 2009 - search.proquest.com

Abstract Myers et al.[Environ Health Perspect 117: 309-315 (2009)] argued that Good Laboratory Practices (GLPs) cannot be used as a criterion for selecting data for risk assessment, using **bisphenol A** (BPA) as a case study. They did not discuss the role (s) of Cited by 53 Related articles All 13 versions Web of Science: 34 Cite Save

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M Wright-Walters, C Volz, E Talbott, [D Davis](#) - Science of the Total ..., 2011 - Elsevier

An aquatic **hazard** assessment establishes a derived predicted no effect concentration (PNEC) below which it is assumed that aquatic organisms will not suffer adverse effects from exposure to a chemical. An aquatic **hazard** assessment of the endocrine disruptor **Bisphenol** Cited by 50 Related articles All 7 versions Web of Science: 34 Cite Save

**Bisphenol A: acute aquatic toxicity**

HC Alexander, DC Dill, LW Smith... - Environmental ..., 1988 - Wiley Online Library

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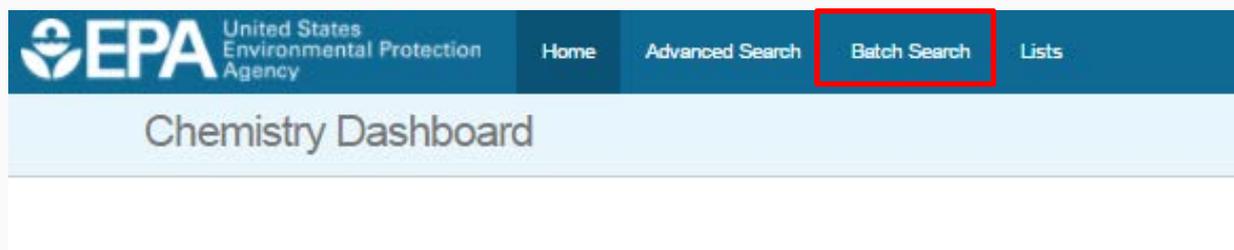
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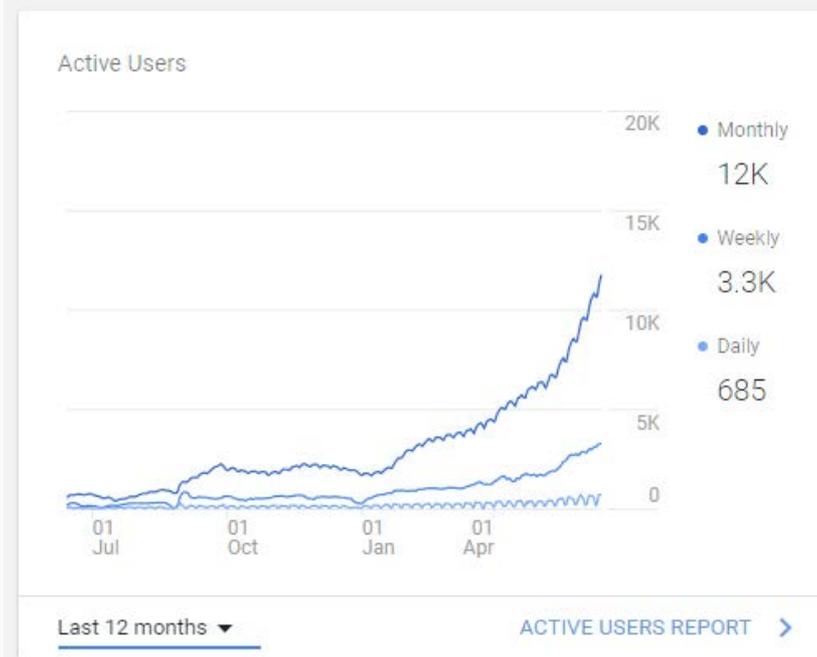
- I have a 5000 CAS Numbers (or Names) – is there data available?
  - Has any Toxcast data been run?
  - Are there Toxicity Data values available?
  - Are there predicted exposure data?
  - Can I get predicted physchem data for my model?



# We get lots of user feedback..

- Online since April 2016
- Feedback welcomed!

How are your active users trending over time?



- Semi-automated **decision support tool** for high-throughput risk assessments
- Use Dashboard “architecture”, existing data streams and add new data – e.g. Global Hazard Summary and ECHA data
- Combine data streams into **quantitative toxicity values** with uncertainty estimates

# Risk Assessments Generally Contain a Standard Set of Components

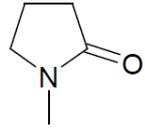


**EPA** United States Environmental Protection Agency  
 EPA Document# 740-R1-5002  
 March 2015  
 Office of Chemical Safety and Pollution Prevention

**TSCA Work Plan Chemical Risk Assessment**

**N-Methylpyrrolidone:  
 Paint Stripper Use**

**CASRN: 872-50-4**



March 2015

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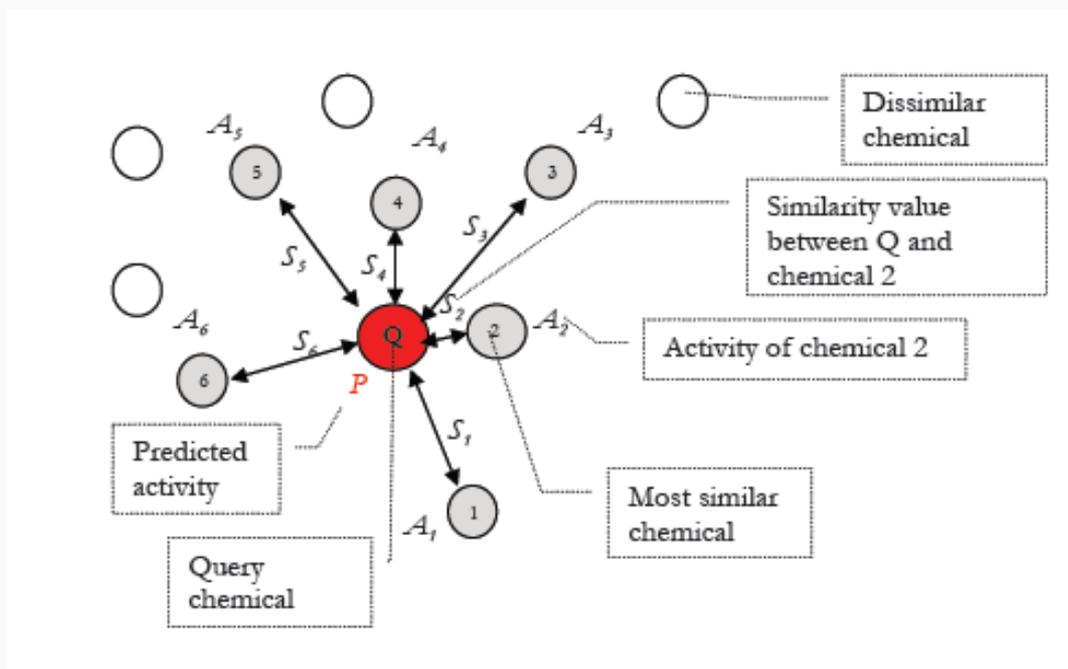
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We are assembling these components to deliver RapidTox

# Quantifying Uncertainty & Assessing Performance of Read-Across - GenRA

- **“Chemical-Biological Read-Across”** - predict toxicity as a similarity-weighted activity of nearest neighbors
- Evaluates read-across performance and uncertainty using available data



# Work-in-progress

NN By: chm\_mrgn K: 10 Sel by: tox\_txf

Summary:

	tox_txf	ohm_cl	bio_tact	bio_1a21
Fluconazole	Yellow	Orange	Orange	Orange
Fosfluconazole	Yellow	Orange	Orange	Orange
Voriconazole	Yellow	Orange	Orange	Orange
Flutriafol	Yellow	Orange	Orange	Orange
Hexaconazole	Orange	Orange	Orange	Orange
Tebuconazole	Orange	Orange	Orange	Orange
Flusilazole	Orange	Orange	Orange	Orange
Cyproconazole	Orange	Orange	Orange	Orange
Pyrasulfotole metabo	Orange	Orange	Orange	Orange
1,2,4-Triazole-1-ace	Orange	Orange	Orange	Orange
Myclobutanil	Orange	Orange	Orange	Orange

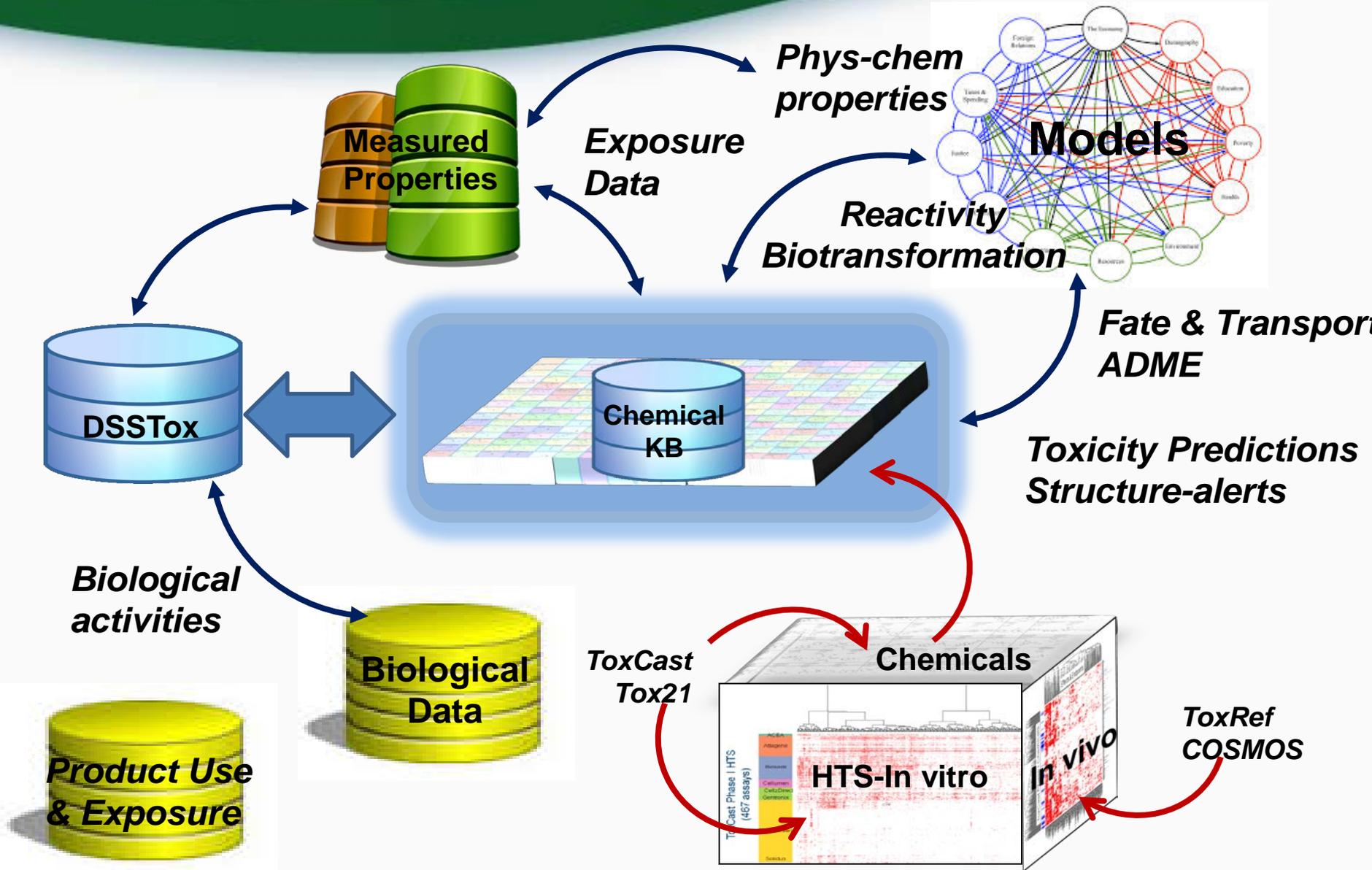
Grp: tox\_txf By: tox\_fp Read-across

	Hexaconazole	Flusilazole	Cyproconazole	Myclobutanil	Fenbuconazole	Tetraconazole	Metconazole	Ipconazole	Bromuconazole	Triticonazole
SUB:Body Weight	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
DEV:Body Weight	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
SUB:Clinical Chemistry	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
DEV:Bone	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
CHR:Liver	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
CHR:Clinical Chemistry	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
MGR:Liver	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
MGR:Body Weight	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
DEV:Clinical Signs	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
SUB:Adrenal Gland	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black
SUB:Hematology	Black	Black	Black	Black	Black	Black	Black	Black	Black	Black

Run GenRA Min+: 0 Min-: 0 Filter by: Enter text Sim wt  Export

	Fluconazole	Hexaconazole	Flusilazole	Cyproconazole	Myclobutanil	Fenbuconazole	Tetraconazole	Metconazole	Ipconazole	Bromuconazole	Triticonazole
CHR:Adrenal Gland	Grey	Blue	Green	Green	Blue	Blue	Blue	Grey	Grey	Blue	Blue
CHR:Blood vessel	Grey	Blue	Green	Green	Blue	Blue	Blue	Grey	Grey	Green	Green
CHR:Body Weight	Grey	Blue	Green	Green	Blue	Blue	Blue	Grey	Grey	Blue	Blue
CHR:Bone	Grey	Green	Green	Green	Green	Green	Blue	Grey	Grey	Green	Green
CHR:Brain	Grey	Green	Green	Green	Blue	Green	Blue	Grey	Grey	Blue	Blue
CHR:Clinical Signs	Grey	Green	Blue	Blue	Blue	Blue	Green	Grey	Grey	Blue	Green
CHR:Epididymis	Grey	Green	Green	Green	Blue	Green	Green	Grey	Grey	Blue	Green
CHR:Eye	Grey	Green	Green	Green	Green	Green	Green	Grey	Grey	Green	Blue
CHR:Food Consumption	Grey	Blue	Green	Blue	Blue	Green	Green	Grey	Grey	Green	Blue
CHR:Heart	Grey	Green	Green	Green	Green	Green	Blue	Grey	Grey	Blue	Blue

We're not done yet...



# Acknowledgements



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and...

*Many other contributors  
from across EPA-ORD*

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