http://www.orcid.org/0000-0002-2668-4821

Delivering The Benefits of Chemical-Biological Integration in Computational Toxicology at the EPA

Antony Williams[†], *Kamel Mansouri, Chris Grulke, Keith Houck, Ann Richard, Jeff Edwards, Matt Martin, John Wambaugh, Grace Patlewicz, Imran Shah, Richard Judson, Kevin Crofton and Russell Thomas*

National Center for Computational Toxicology
U.S. Environmental Protection Agency, RTP, NC

August 21-25, 2016
ACS Fall Meeting, Philadelphia, PA

Who is NCCT?

- National Center for Computational Toxicology – part of EPA's Office of Research and Development

- Research driven by EPA's *Chemical Safety for Sustainability Research Program*
  - Develop new approaches to **evaluate** the **safety** of chemicals
  - Integrate advances in biology, biotechnology, chemistry, exposure science and computer science

- Goal - To identify **chemical exposures** that may disrupt biological processes and cause adverse outcomes.

Scientific leadership

https://www.epa.gov/chemical-research/toxicity-forecasting

EPA United States Environmental Protection Agency

EPA US Environmental Protection Agency

Español | 中文: 繁體版 | 中文: 简体版 | Tiếng Việt | 한국어

Learn the Issues | Science & Technology | Laws & Regulations | About EPA

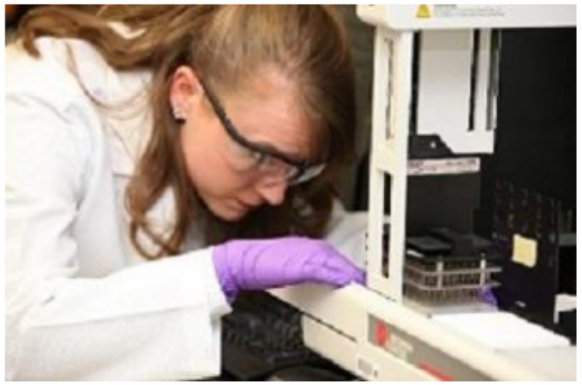
Search EPA.gov

Related Topics: Safer Chemicals Research

Contact Us Share

Toxicity Forecasting

Advancing the Next Generation of Chemical Evaluation



EPA needs rapid and efficient methods to prioritize, screen and evaluate thousands of chemicals. EPA's Toxicity Forecaster (ToxCast) generates data and predictive models on thousands of chemicals of interest to the EPA. ToxCast uses high-throughput screening methods and computational toxicology approaches to rank and prioritize chemicals. In fact, EPA's Endocrine Disruption Screening Program (EDSP) is working to use ToxCast to rank and prioritize chemicals.

Computational Toxicology Research Updates

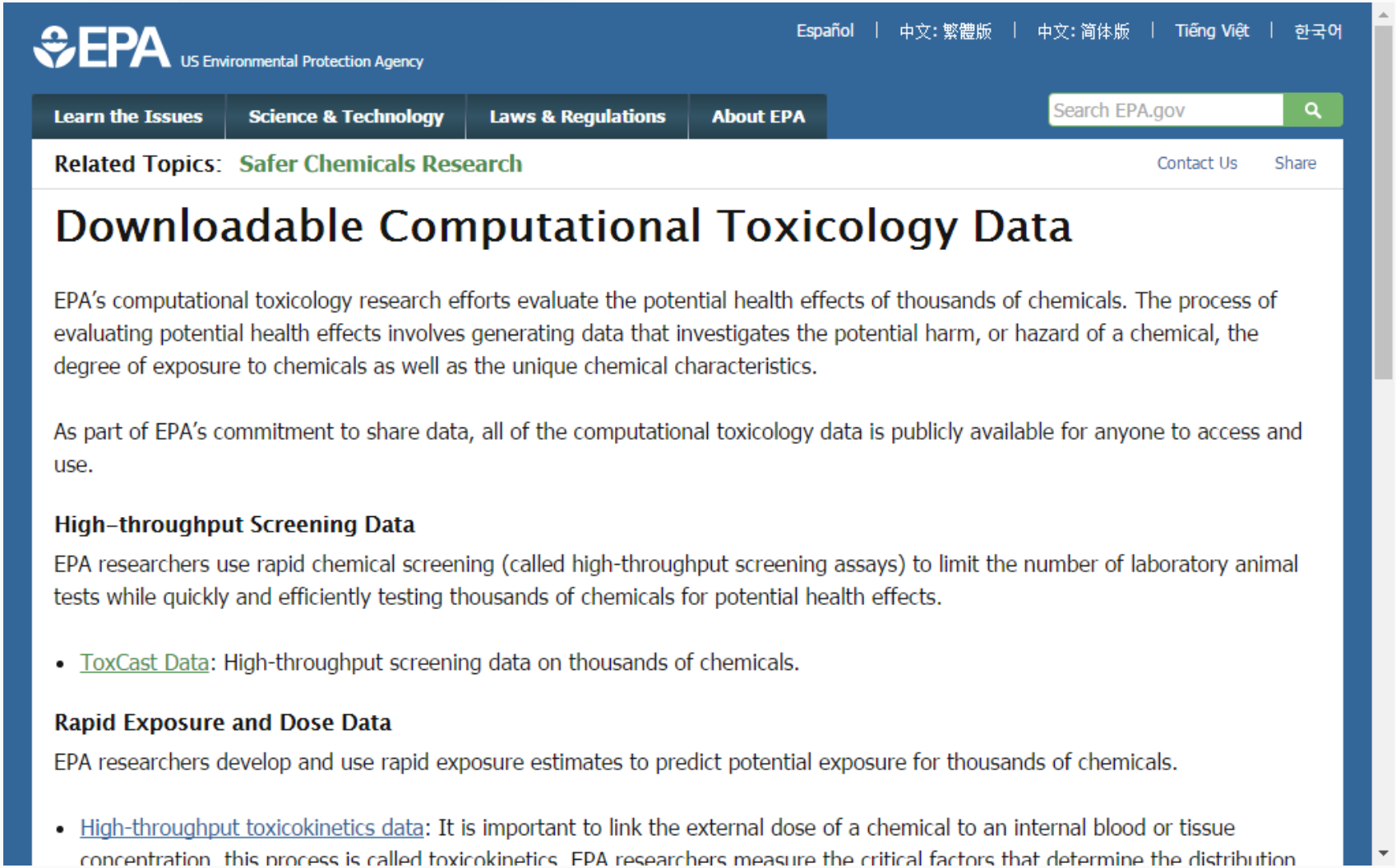
Get ToxCast Updates

sign up

- ToxCast has data on over 1,800 chemicals from a broad range of sources including industrial and consumer products, food additives, and potentially "green" chemicals that could be safer alternatives to existing chemicals.
- ToxCast screens chemicals in over 700 high-throughput assays that cover a range of high-

Our Bioassay Data

https://www.epa.gov/chemical-research/downloadable-computational-toxicology-data



EPA US Environmental Protection Agency

Español | 中文: 繁體版 | 中文: 简体版 | Tiếng Việt | 한국어

Learn the Issues | Science & Technology | Laws & Regulations | About EPA

Search EPA.gov

Related Topics: Safer Chemicals Research

Contact Us Share

Downloadable Computational Toxicology Data

EPA's computational toxicology research efforts evaluate the potential health effects of thousands of chemicals. The process of evaluating potential health effects involves generating data that investigates the potential harm, or hazard of a chemical, the degree of exposure to chemicals as well as the unique chemical characteristics.

As part of EPA's commitment to share data, all of the computational toxicology data is publicly available for anyone to access and use.

High-throughput Screening Data

EPA researchers use rapid chemical screening (called high-throughput screening assays) to limit the number of laboratory animal tests while quickly and efficiently testing thousands of chemicals for potential health effects.

- ToxCast Data: High-throughput screening data on thousands of chemicals.

Rapid Exposure and Dose Data

EPA researchers develop and use rapid exposure estimates to predict potential exposure for thousands of chemicals.

- High-throughput toxicokinetics data: It is important to link the external dose of a chemical to an internal blood or tissue concentration, this process is called toxicokinetics. EPA researchers measure the critical factors that determine the distribution

Our Exposure Predictions

EPA United States Environmental Protection Agency

EPA US Environmental Protection Agency

Español | 中文: 繁體版 | 中文: 简体版 | Tiếng Việt | 한국어

Learn the Issues | Science & Technology | Laws & Regulations | About EPA

Search EPA.gov

Related Topics: Safer Chemicals Research

Contact Us Share

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.

Pictured Above: Farfield Exposure Examples

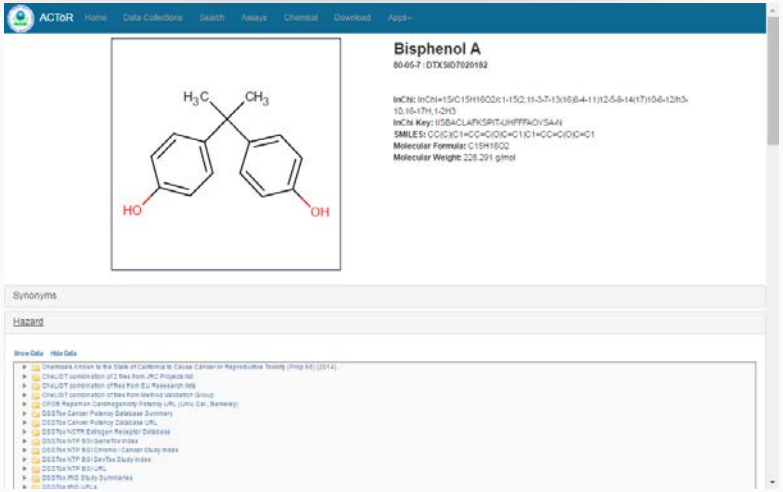
› Farfield Exposure Models

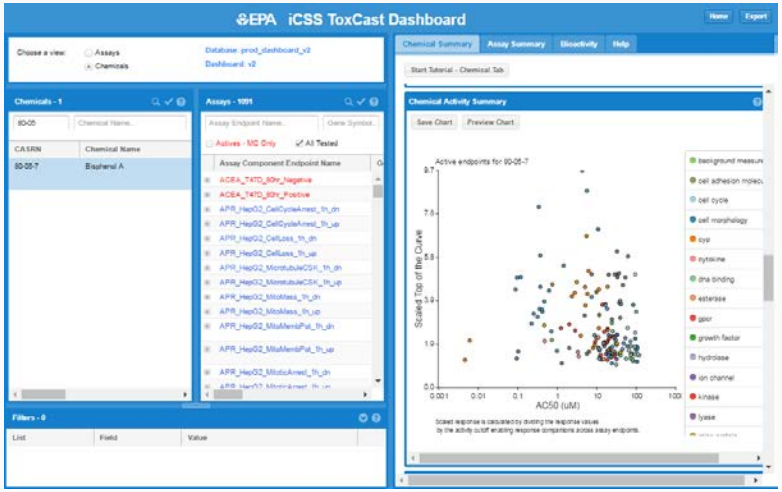
› Nearfield Exposure Models

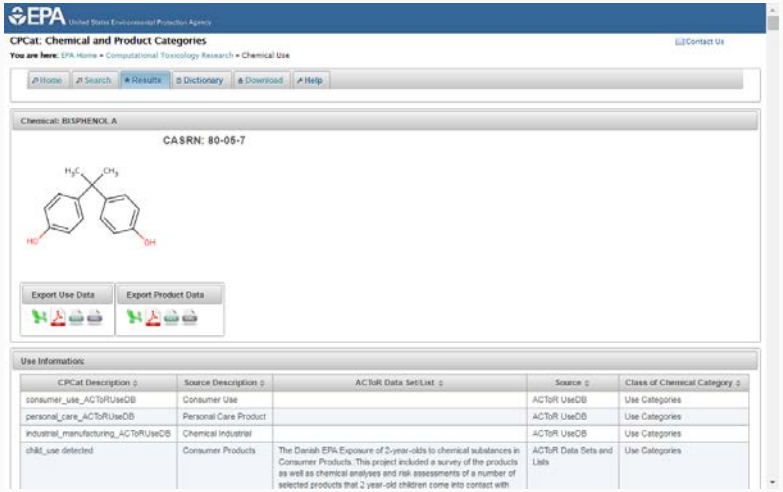
Evaluating High-throughput Exposure Predictions

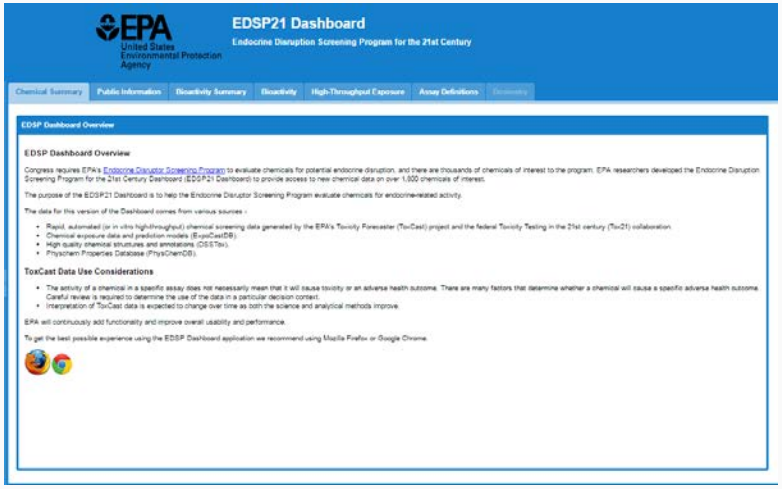
EPA is currently evaluating the effectiveness of high-throughput exposure models

Our Dashboard Applications





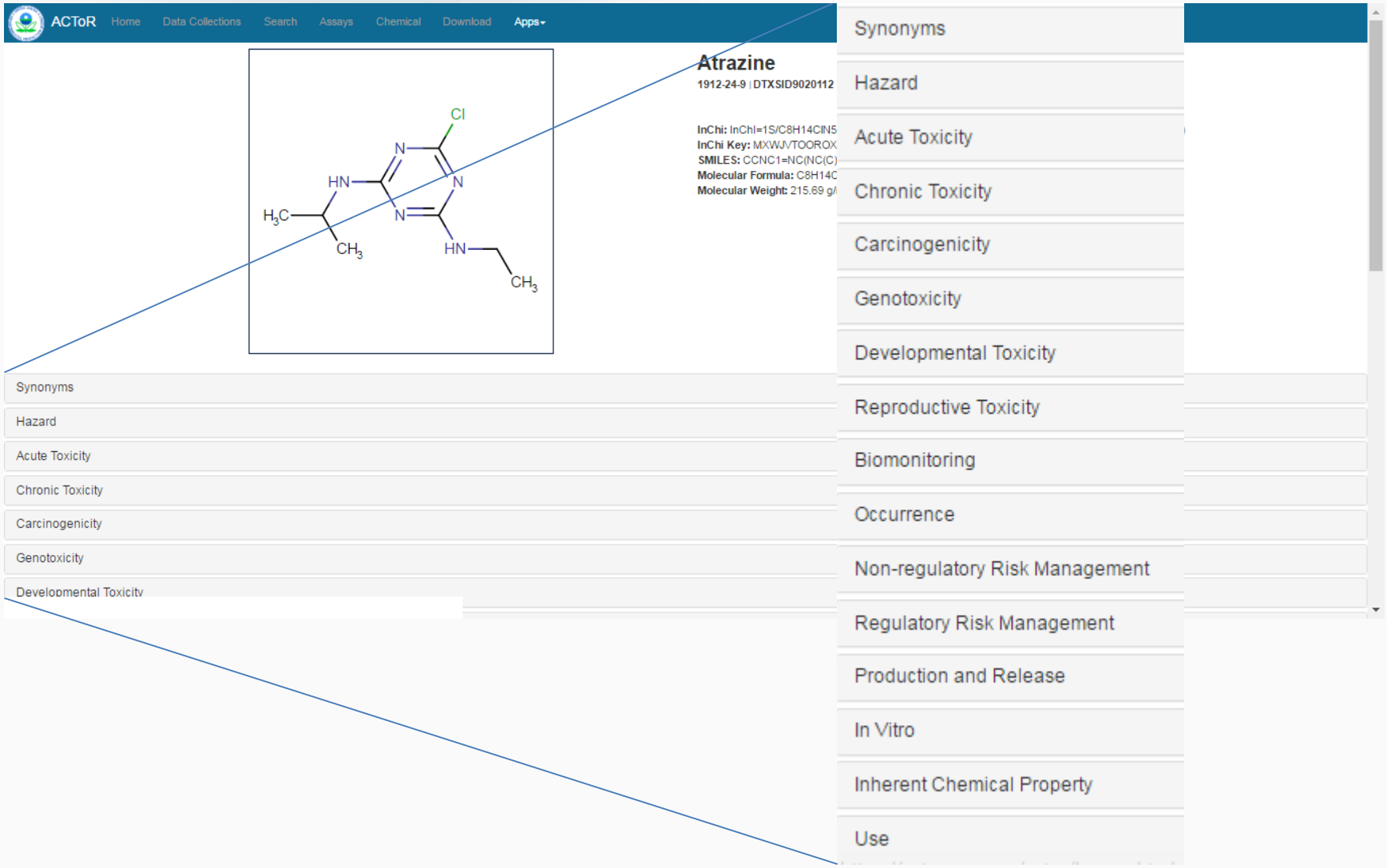




ACToR
https://actor.epa.gov/actor/

- Aggregated Computational Toxicology Resource
- A warehouse of publicly available chemical toxicity data
- Aggregates data from >1000 public sources on >500,000 chemicals

ACToR
https://actor.epa.gov/actor/



ACToR
https://actor.epa.gov/actor/

Genotoxicity

Show Data Hide Data

- CheLIST combination of files from Method Validation Group
- DSSTox NTP BSI GeneTox Index
- DSSTox NTP BSI URL
- Genotoxicity Data In Vitro from EPA HPVIS
- NLM TOXNET CCRIS Data MSTU - MUTAGENICITY STUDIES

Genotoxicity Data In Vitro from EPA HPVIS

Result Group:

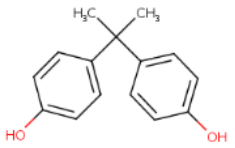
Component Name	Value
Conclusion	Negative
Conclusion (GeneTox)	This study was judged to have given a negative result since the observed increase in the first experiment was not reproducible.
Dose Remarks	30 - 50 g/mL with activation20 - 40 g/mL without activation
Genotoxic Effect	Negative
GLP	No Data
Metabolic Activation	With and Without
Method/Guideline Followed	No Data
Program Flag	HPVIS
Reliability	2
Results Remarks	With metabolic activation: 50 g/mLWithout metabolic activation: None reported In the first test with metabolic activation an increase in the percentage of metaphases with chromosome aberrations from bisphenol A treated cultures was observed only at the top dose in the presence of cytotoxicity; 14% at 50 g/mL compared to 3% in controls. In these high-dose cultures it was stated that cell confluence was reduced by approximately 70%. In the second test no significant increases were observed in with metabolic activation; only 3% of cells at the highest dose had aberrations. No significant increases in aberrations were observed without metabolic activation with bisphenol A evidently being tested up to "toxic levels." The positive controls produced clear increases in chromosome aberrations.
Species	Mammalian Cell Line
Sponsor Name	General Electric Company - Plastics
Sponsored Chemical Result Type	72162-28-8
Strain	Chinese Hamster Ovary (CHO)

Ivett, J.L., Brown, B.M., Rodgers, C., Anderson, B.E., Ressnick, M.A. and Zeiger, E. 1989. Chromosomal aberrations and sister chromatid exchange tests in Chinese hamster ovary . Environ. Mol. Mutagen. 14:165-187. As cited in the EU Risk Assessment. Data entered into the HPVIS extracted from the robust

CPCat
https://actor.epa.gov/actor/

Chemical: BISPHENOL A

CASRN: 80-05-7



Export Use Data | Export Product Data

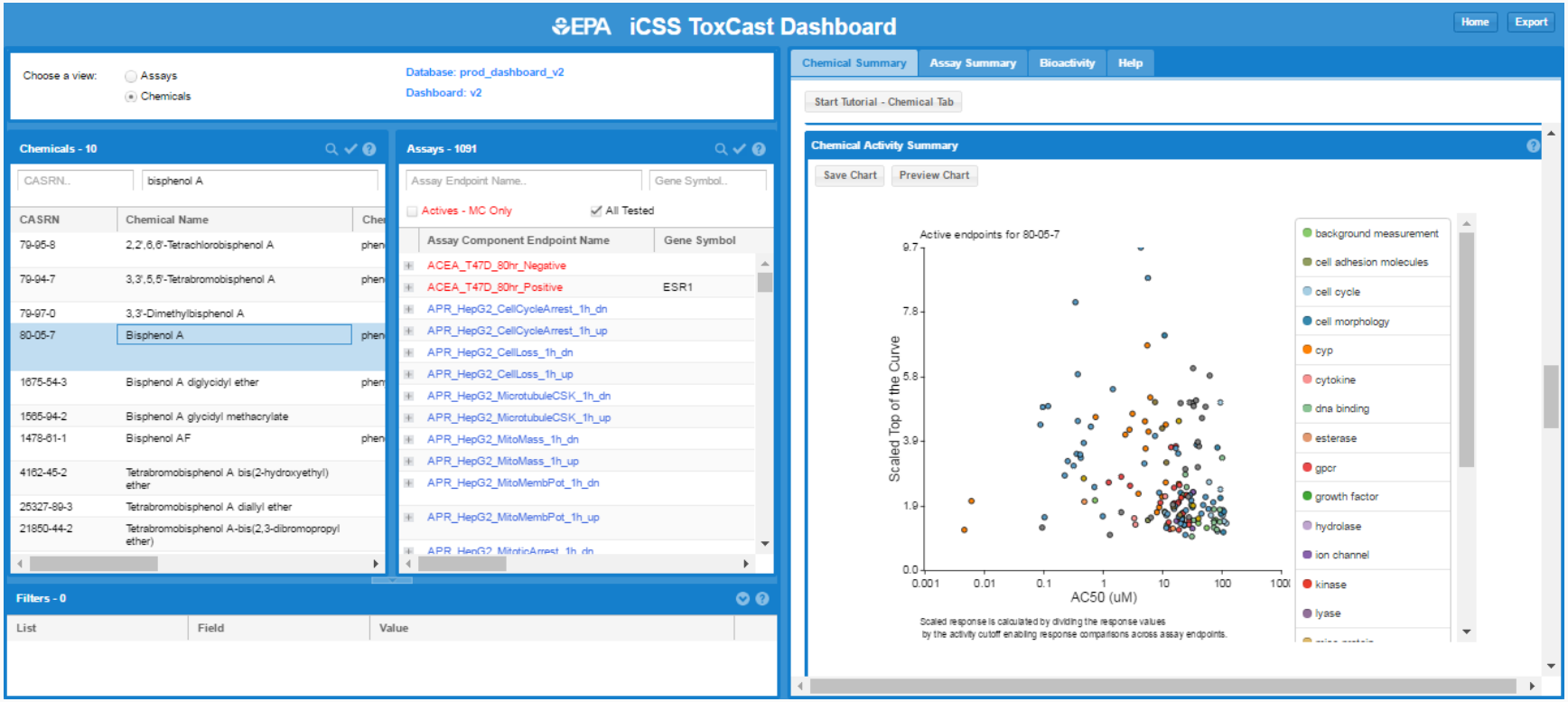
Chemical and Product Categories is a database containing information mapping >43,000 chemicals to a set of terms categorizing their usage or function.

Use Information:

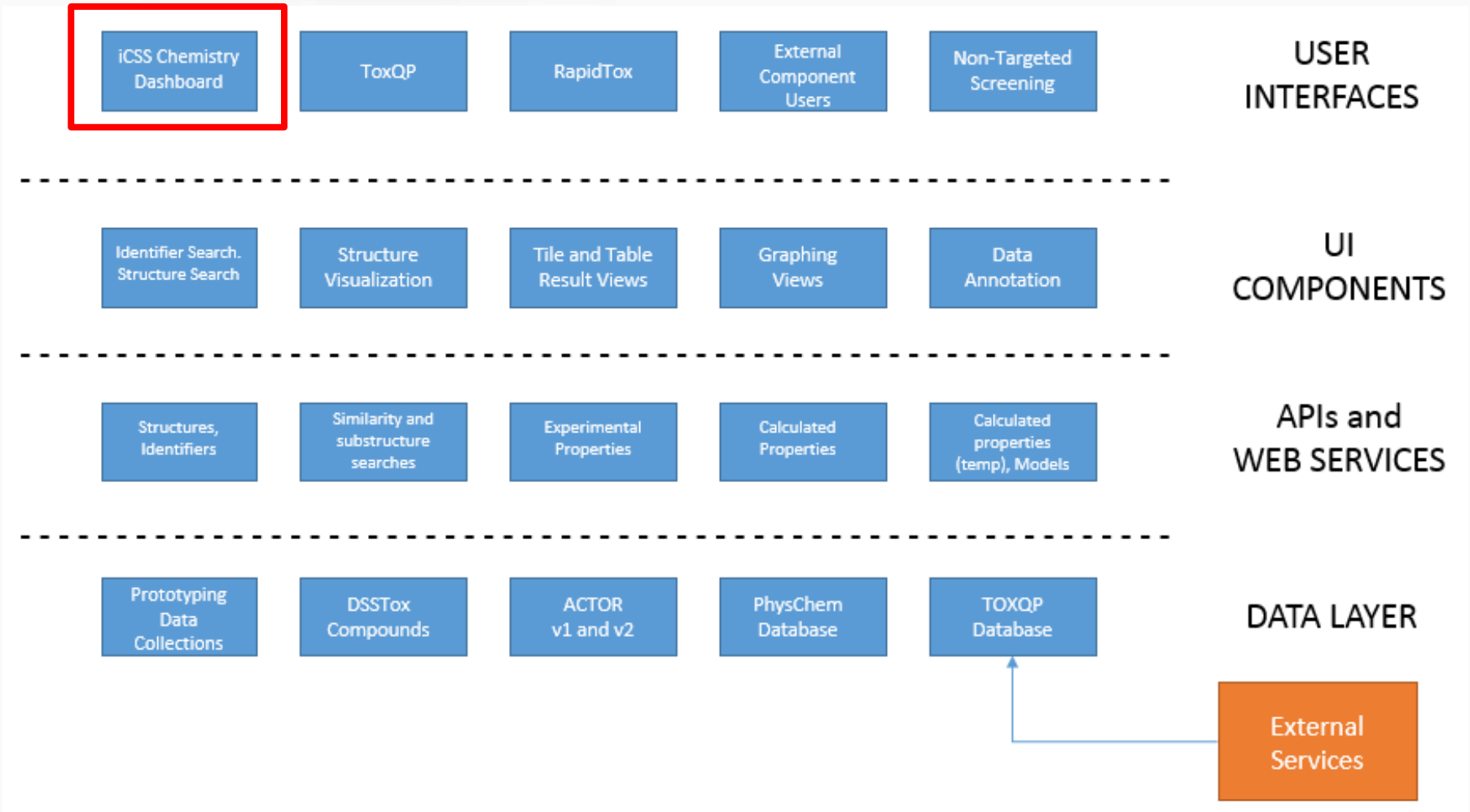
CPCat Description	Source Description	ACToR Data Set/List	Source	Class of Chemical Category
consumer_use_ACToRUseDB	Consumer Use		ACToR UseDB	Use Categories
personal_care_ACToRUseDB	Personal Care Product		ACToR UseDB	Use Categories
industrial_manufacturing_ACToRUseDB	Chemical Industrial		ACToR UseDB	Use Categories
child_use detected	Consumer Products	The Danish EPA:Exposure of 2-year-olds to chemical substances in Consumer Products.:This project included a survey of the products as well as chemical analyses and risk assessments of a number of selected products that 2 year-old children come into contact with throughout the course of a day. A total of 12 product groups were included in the survey phase. Selected products from 10 of these product groups were subsequently included in a screening phase and several problematic substances were subjected to quantitative analysis. A risk assessment was also performed for a number of problematic substances.	ACToR Data Sets and Lists	Use Categories
consumer_use detected	Consumer Products	TNO Nederlands Organisation for Applied Scientific Research:Hazardous Chemicals in Consumer Products:In this study 33 consumer products, including body care products, toys, textiles, deodorizers and cleaners, have been tested for the presence of bisphenol-A, alkylphenols and ethoxylates, phthalates, musks and organotin compounds.	ACToR Data Sets and Lists	Use Categories
child_use	Consumer Products:	(state of) Washington:Washington Childrens Safe Product Act (CSPA) Reporting Rule. List of chemical of high concern to children (CHCC)	ACToR Data Sets and	Use Categories

Toxcast Dashboard
https://actor.epa.gov/dashboard/

- To interrogate chemical screening data from ToxCast and the Tox21 collaboration



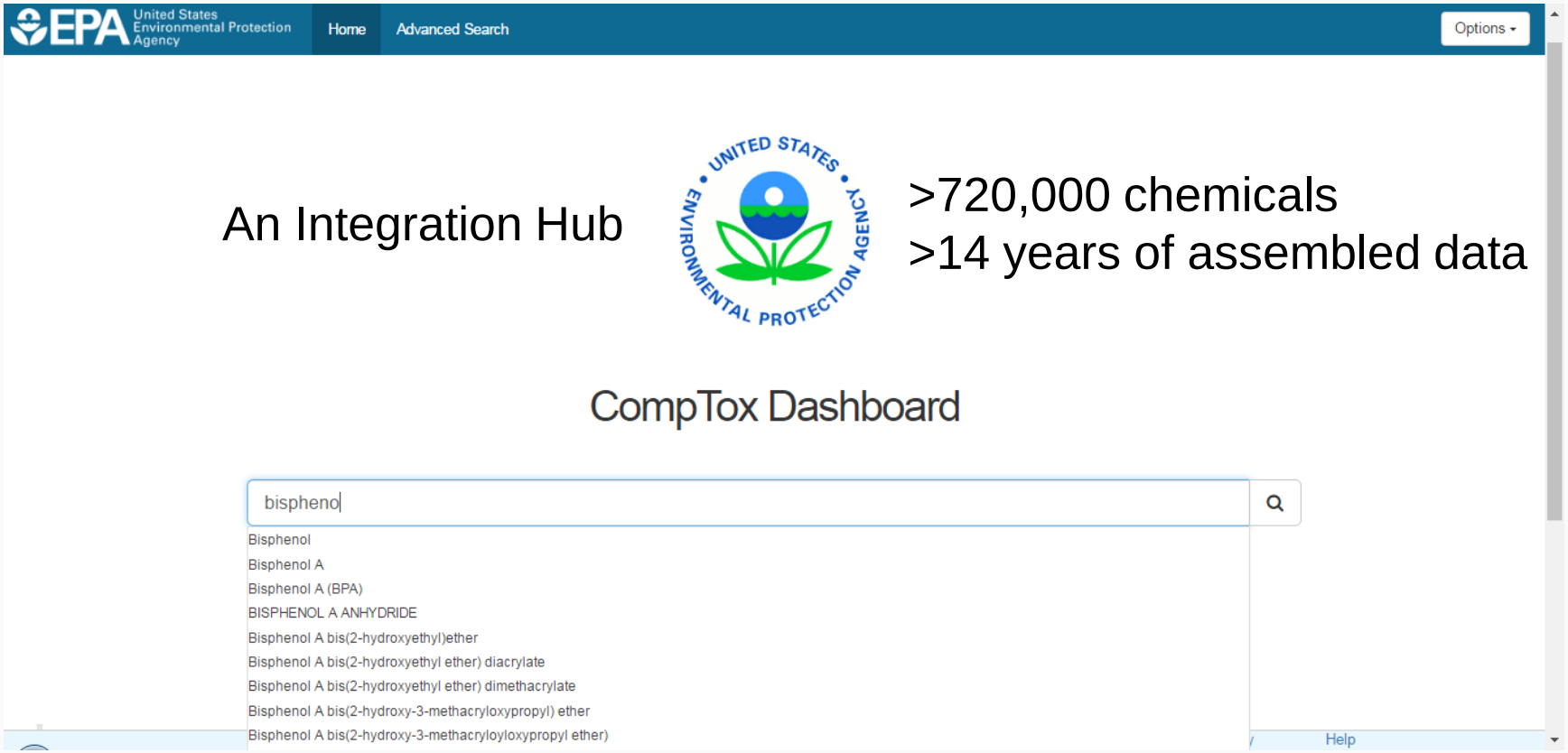
Our Developing Architecture



Our **Latest** Dashboard https://comptox.epa.gov

- Providing access to our “curated chemistry”
- Database of chemicals, mapped to identifiers, and tens of thousands of experimental physchem properties
- Predictive models and calculation details
- An integration hub for NCCT applications
- A link farm across 10s of EPA and Public websites

Our **Latest** Dashboard
https://comptox.epa.gov



15 years of Curated Data

ELSEVIER

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

Volume 499, Issue 1, 29 January 2002, Pages 27–52

Mutation Research Frontiers

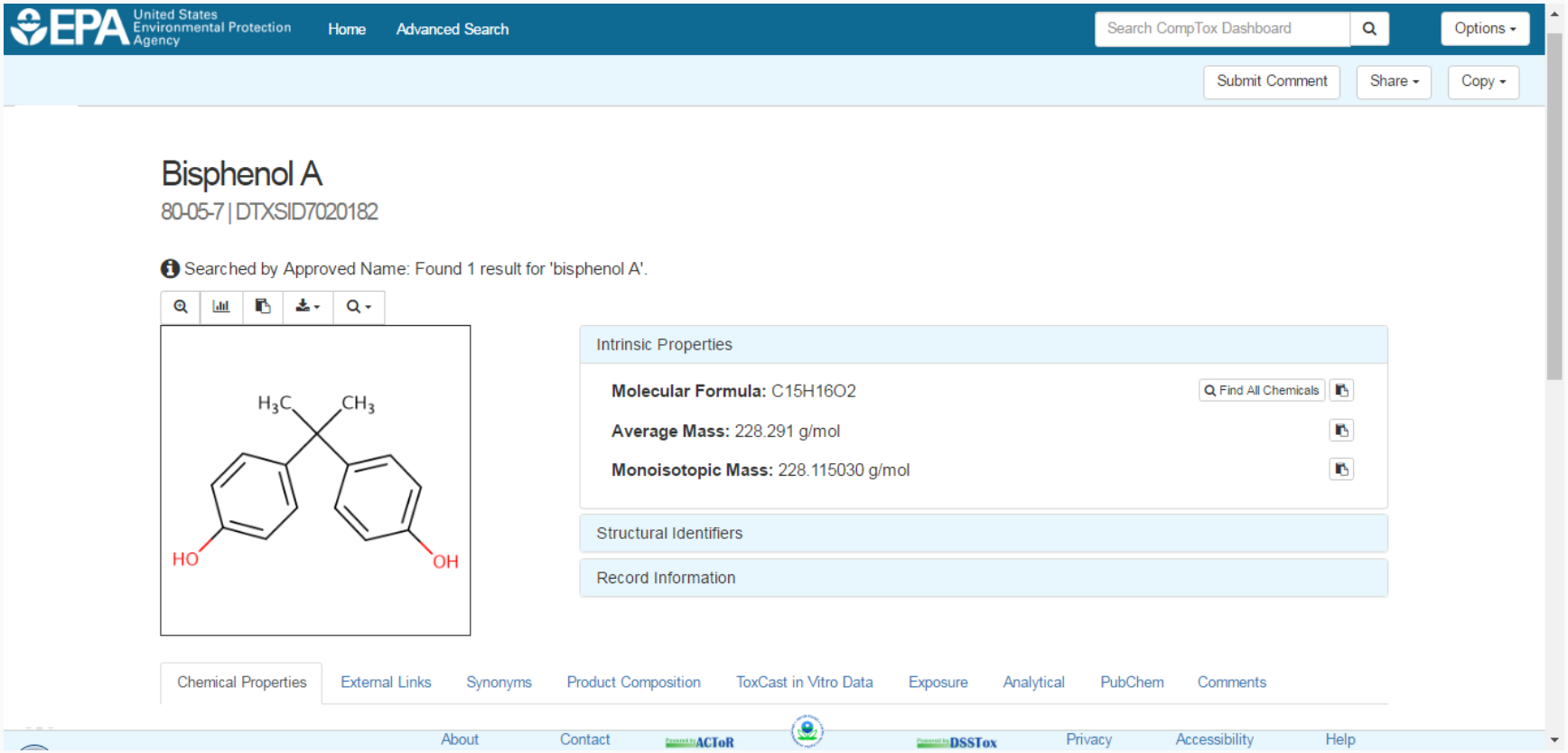
Distributed structure-searchable toxicity (DSSTox) public database network: a proposal

Ann M. Richard[a], , , ClarLynda R. Williams[a, b]

Show more

http://dx.doi.org/10.1016/S0027-5107(01)00289-5

Bisphenol A (Accessing DSSTox Data)



Chemical Properties External Links Synonyms Product Composition ToxCast in Vitro Data Exposure PubChem Comments

Physicochemical Properties

EPA United States Environmental Protection Agency

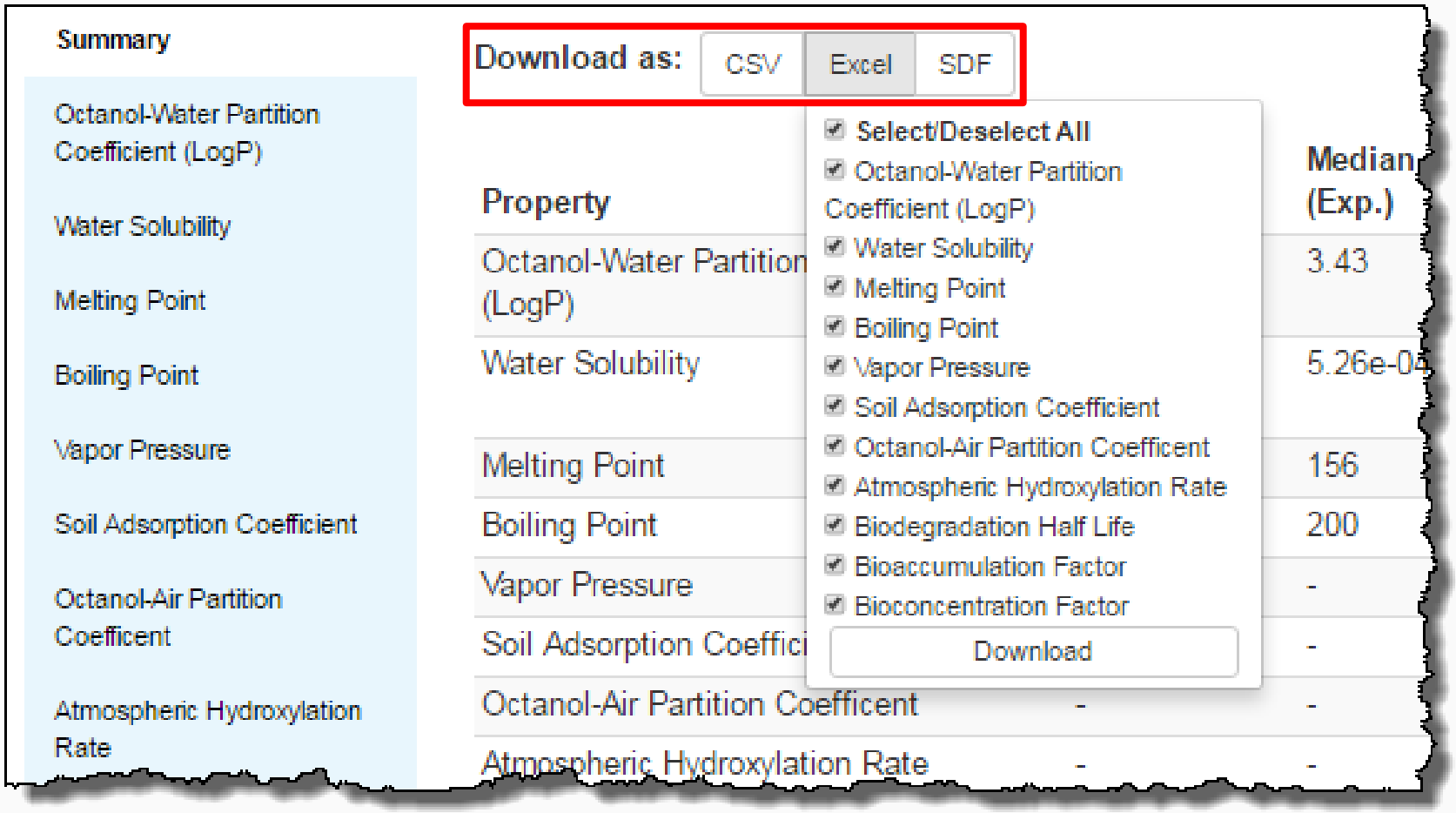
Summary

- Octanol-Water Partition Coefficient (LogP)
- Water Solubility
- Melting Point
- Boiling Point
- Vapor Pressure
- Soil Adsorption Coefficient
- Octanol-Air Partition Coefficent
- Atmospheric Hydroxylation Rate
- Biodegradation Half Life
- Bioaccumulation

Download as: CSV | Excel | SDF

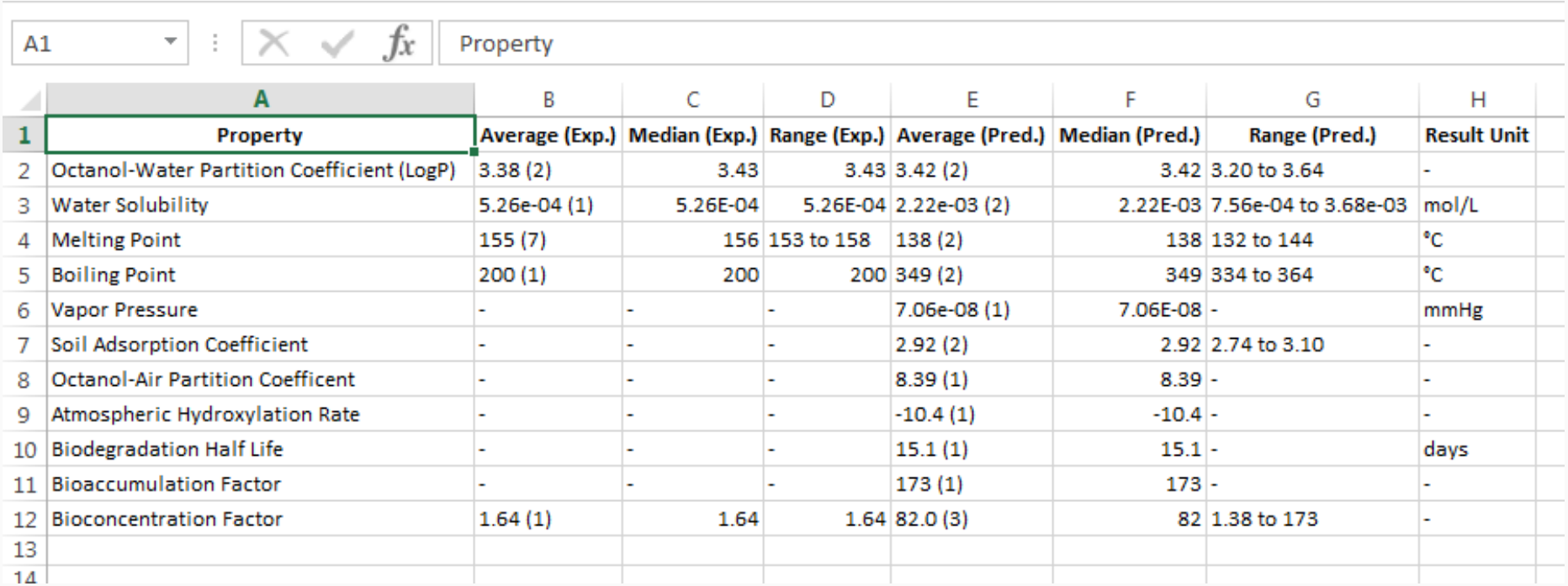
Property	Average (Exp.)	Median (Exp.)	Range (Exp.)	Average (Pred.)	Median (Pred.)	Range (Pred.)	Result Unit
Octanol-Water Partition Coefficient (LogP)	3.38 (2)	3.43	3.43	3.42 (2)	3.42	3.20 to 3.64	-
Water Solubility	5.26e-04 (1)	5.26e-04	5.26e-04	2.22e-03 (2)	2.22e-03	7.56e-04 to 3.68e-03	mol/L
Melting Point	155 (7)	156	153 to 158	138 (2)	138	132 to 144	°C
Boiling Point	200 (1)	200	200	349 (2)	349	334 to 364	°C
Vapor Pressure	-	-	-	7.06e-08 (1)	7.06e-08	-	mmHg
Soil Adsorption Coefficient	-	-	-	2.92 (2)	2.92	2.74 to 3.10	-
Octanol-Air Partition Coefficent	-	-	-	8.39 (1)	8.39	-	-
Atmospheric Hydroxylation Rate	-	-	-	-10.4 (1)	-10.4	-	-
Biodegradation Half Life	-	-	-	15.1 (1)	15.1	-	days
Bioaccumulation Factor	-	-	-	173 (1)	173	-	-
Bioconcentration Factor	1.64 (1)	1.64	1.64	82.0 (3)	82.0	1.38 to 173	-

Data Downloads



Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

Data Download: Excel



A1 | Property

	A	B	C	D	E	F	G	H
1	**Property**	**Average (Exp.)**	**Median (Exp.)**	**Range (Exp.)**	**Average (Pred.)**	**Median (Pred.)**	**Range (Pred.)**	**Result Unit**
2	Octanol-Water Partition Coefficient (LogP)	3.38 (2)	3.43	3.43	3.42 (2)	3.42	3.20 to 3.64	-
3	Water Solubility	5.26e-04 (1)	5.26E-04	5.26E-04	2.22e-03 (2)	2.22E-03	7.56e-04 to 3.68e-03	mol/L
4	Melting Point	155 (7)	156	153 to 158	138 (2)	138	132 to 144	°C
5	Boiling Point	200 (1)	200	200	349 (2)	349	334 to 364	°C
6	Vapor Pressure	-	-	-	7.06e-08 (1)	7.06E-08	-	mmHg
7	Soil Adsorption Coefficient	-	-	-	2.92 (2)	2.92	2.74 to 3.10	-
8	Octanol-Air Partition Coefficent	-	-	-	8.39 (1)	8.39	-	-
9	Atmospheric Hydroxylation Rate	-	-	-	-10.4 (1)	-10.4	-	-
10	Biodegradation Half Life	-	-	-	15.1 (1)	15.1	-	days
11	Bioaccumulation Factor	-	-	-	173 (1)	173	-	-
12	Bioconcentration Factor	1.64 (1)	1.64	1.64	82.0 (3)	82	1.38 to 173	-
13								
14								

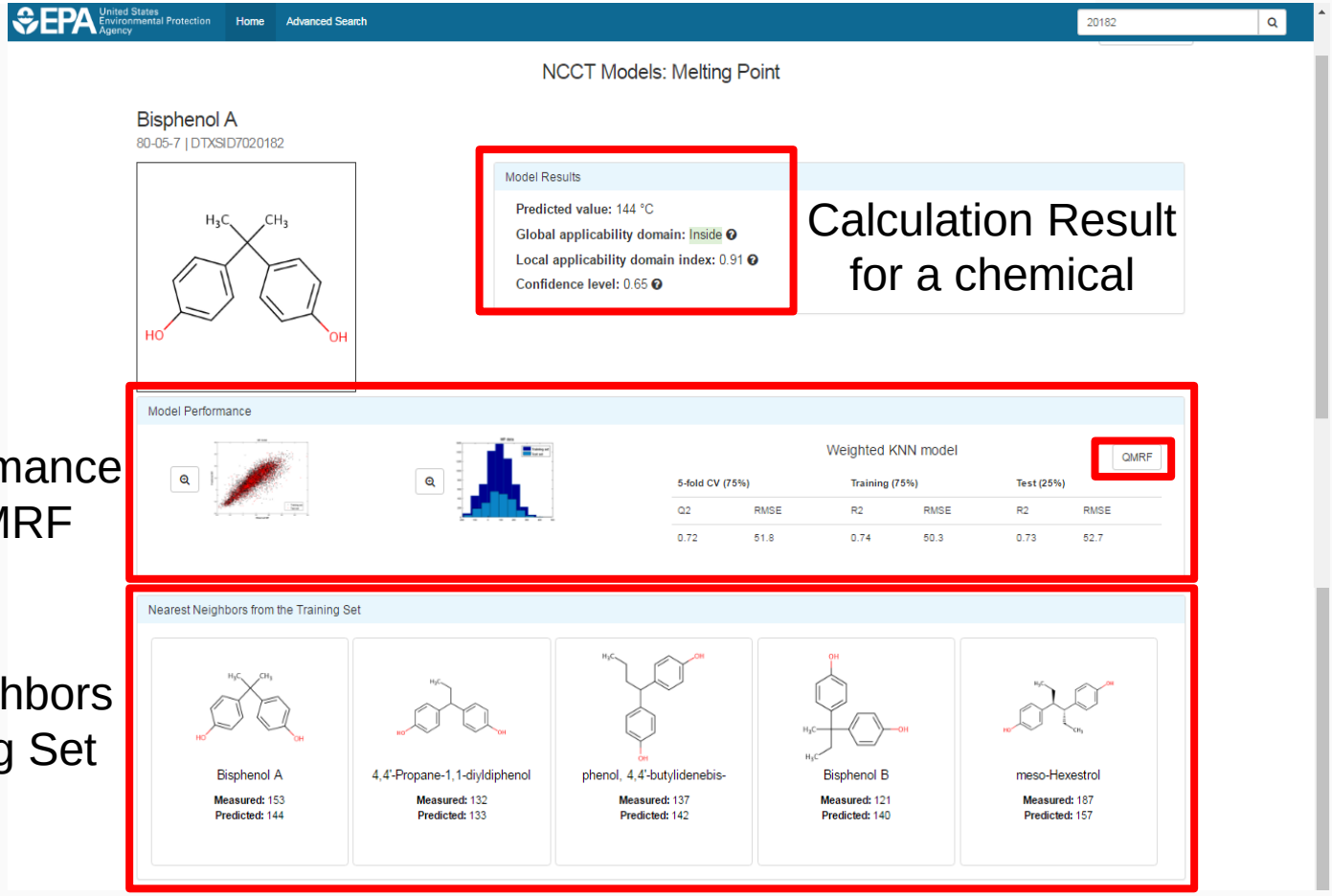
Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

Predictions for >720,000 Chemicals

- NCCT_Model predictions built on curated data
- All chemicals in CompTox Dashboard pushed through all predictive models
- Predicted data made available, with detailed **MODEL REPORTS**

Predicted Data

Predicted		
Source	**Result**	**Calculation Details**
EPISUITE	132 °C	Not Available
NCCT	144 °C	NCCT Model Report



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

QMRF_NCCT_MP_08212016 - Adobe Acrobat Pro

File Edit View Window Help

Create Customize

1 / 10 143% Tools Fill & Sign Comment

QMRF	*QMRF identifier (JRC Inventory):* **To be entered by JRC**
	QMRF Title: **MP:** Melting point prediction **from the** NCCT Models Suite.
	Printing Date: **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

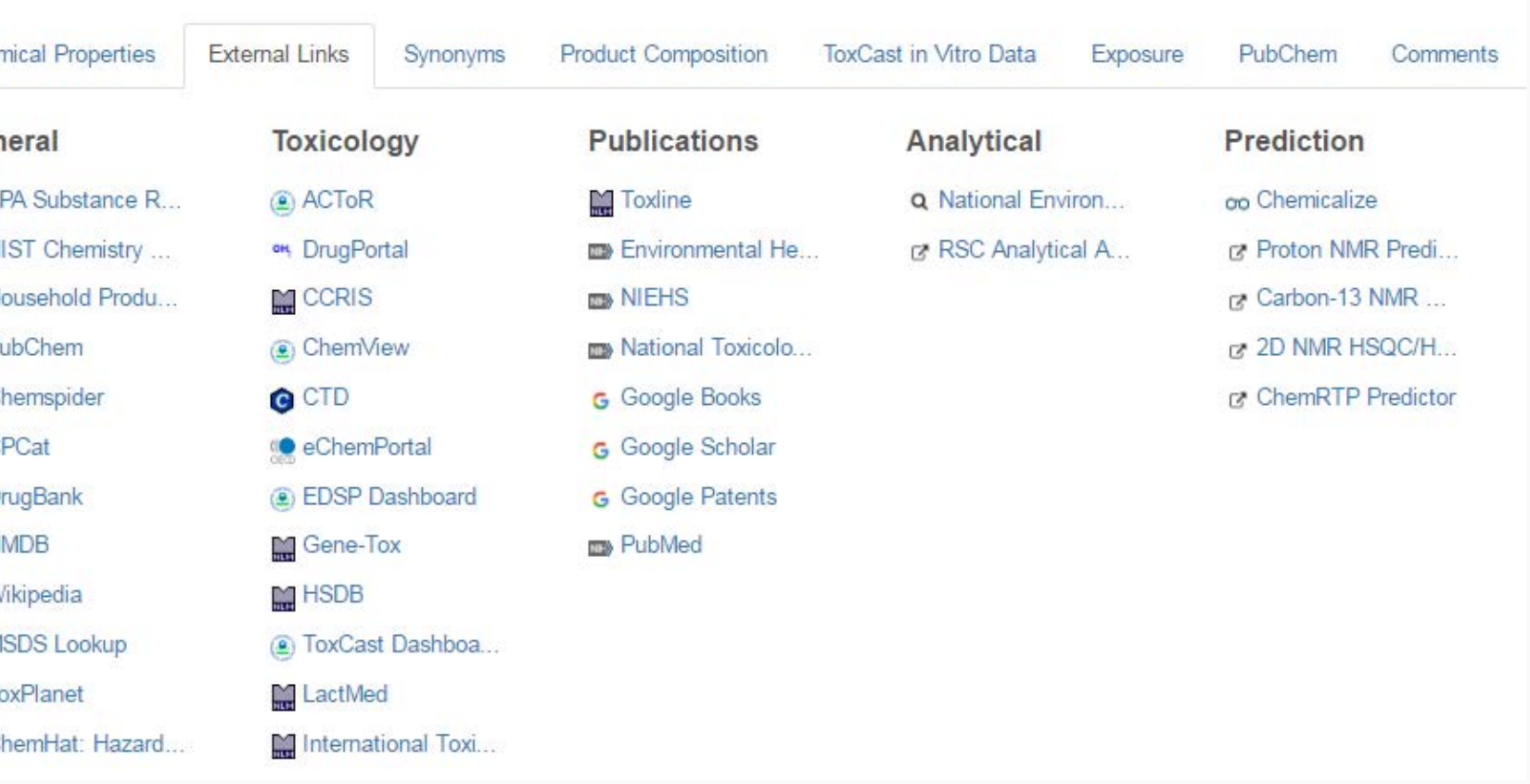
1.3.Software coding the model:

NCCT_models V1.02

Suite of QSAR models to predict physicochemical properties and environmental fate of organic chemicals

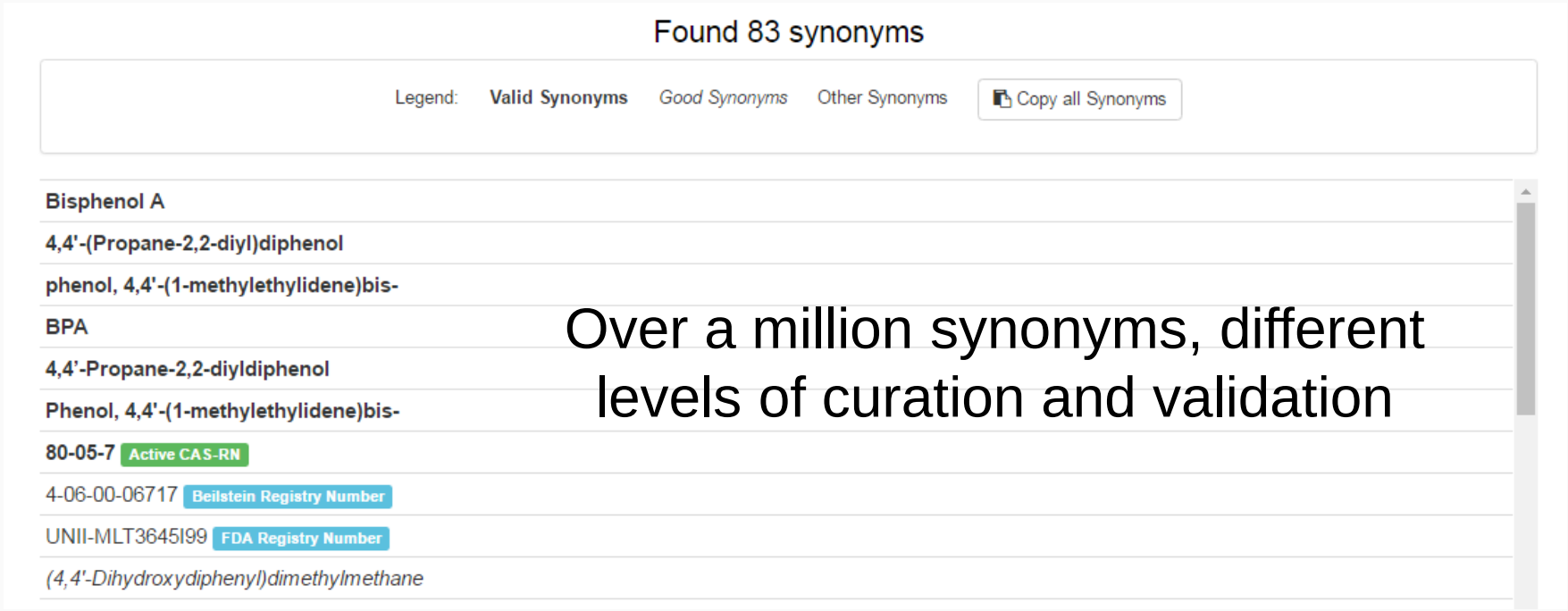
Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

External Links



Chemical Properties External Links Synonyms Product Composition ToxCast in Vitro Data Exposure PubChem Comments

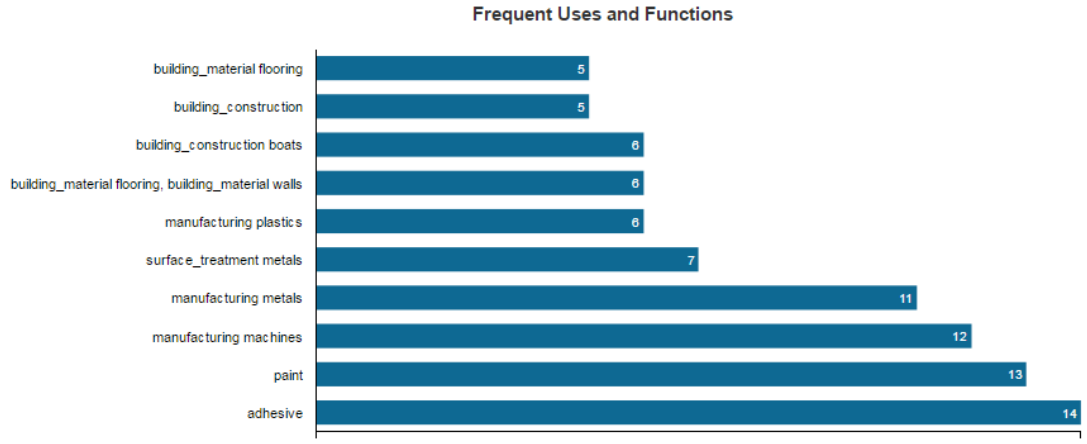
Synonyms



Over a million synonyms, different levels of curation and validation

Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

Functional Use and Composition (Integrating CPCat Data)



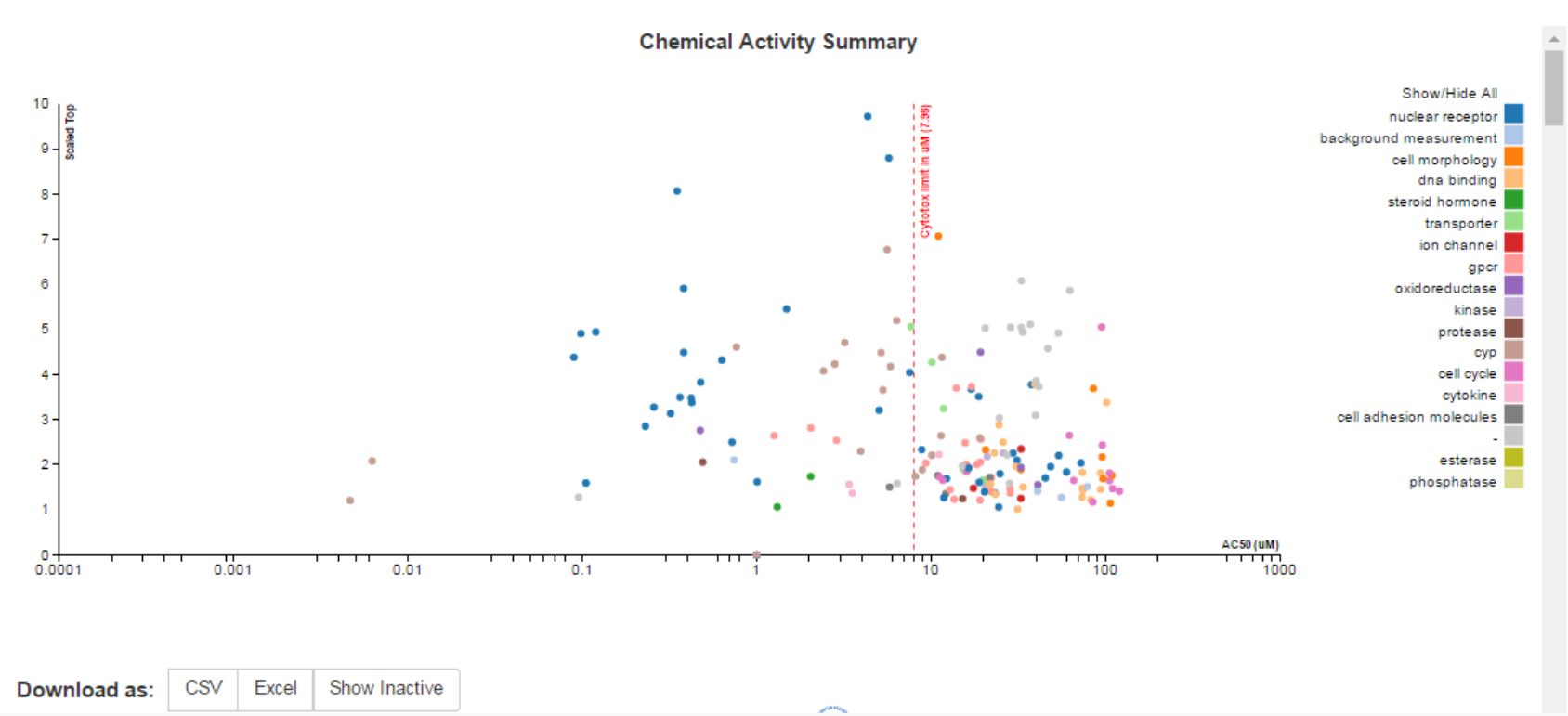
Download as: CSV Excel

Product Composition

Product	Percent Composition ↓	Manufacturer
BISPHENOL-A (BPA)	100%	GENERAL ELECTRIC COMPANY
EPOXY PASTE PIGMENTS, 3402-3408	<100%PPM	SYSTEM THREE RESINS
ISOPROPYLIDENEDIPHENOL, 99+%, 23965-8	99%+	ALDRICH CHEMICAL CO
BISPHENOL A (RESIN GRADE) (43106)	97.8%	SHELL OIL COMPANY
4,4-ISOPROPYLIDENEDIPHENOL, 97%, 13302-7	97%	ALDRICH CHEMICAL CO
ICO-PATCH EPOXY RESIN HARDENER, PART B	80%	INTERNATIONAL COATINGS CO
ADHESIVE-SCOTCH-WELD (R) 2216 B GRAY	72%	3M COMPANY
EPOCAST HARDENER 946, FPC 5000	45%	CIBA-GEIGY CORP
EPOLITE 1350 HANDENER	35-50	HEXCEL CORP, RESINS GROUP
EL CHEM NO 200 PRIMER PART B	22.5%	ELECTRO CHEMICAL ENGINEERING &

Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

Bioassay Screening Data (Integrating ToxCast Data)



Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

Bioassay Screening Data (Integrating ToxCast Data)

Assay Name	Hit Call	Top	Scaled Top	AC50 ↓	log AC50	Intended Target Family
APR_Hepat_CellLoss_48hr_dn						
APR_HepG2_OxidativeStress_24h_up						
APR_HepG2_MitoMass_24h_dn						
APR_Hepat_DNADamage_48hr_up						
APR_HepG2_CellLoss_24h_dn						
APR_HepG2_OxidativeStress_72h_up						
ATG_HSE_CIS_up						
APR_Hepat_DNADamage_24hr_up						
APR_Hepat_CellLoss_24hr_dn						
APR_Hepat_Steatosis_24hr_up						
APR_HepG2_CellLoss_72h_dn						

APR_HepG2_OxidativeStress_72h_up

Assay Name: APR_HepG2_OxidativeStress_72h_up

Gene Symbol: null

Organism: human

Tissue: liver

Assay Format Type: cell-based

Biological Process Target: oxidative phosphorylation

Detection Technology: Fluorescence

Analysis Direction: positive

Intended Target Family: cell cycle

Description: Data from the assay component APR_HepG2_OxidativeStress_72hr was analyzed into 2 assay endpoints. This assay endpoint, APR_HepG2_OxidativeStress_72h_up, was analyzed in the positive fitting direction relative to DMSO as the negative control and baseline of activity. Using a type of viability reporter, measures of protein for gain-of-signal activity can be used to understand the signaling at the pathway-level as they relate to the gene . Furthermore, this assay endpoint can be referred to as a primary readout, because this assay has produced multiple assay endpoints where this one serves a signaling function. To generalize the intended target to other relatable targets, this assay endpoint is annotated to the "cell cycle" intended target family, where the subfamily is "stress response".

Exposure Data – NHANES and ExpoCast Predictions

EPA United States Environmental Protection Agency

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

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

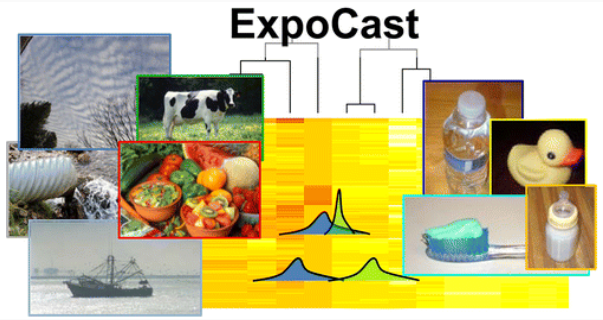
Exposure Predictions (mg/kg-bw/day)

	Ages 6-11	Ages 12-19	Ages 20-65	Ages 65+	BMI > 30	BMI < 30	Repro. Age Females	Females	Males	Total
Median	6.30e-05	2.68e-05	2.05e-05	1.61e-05	1.69e-05	2.67e-05	1.11e-05	1.11e-05	3.89e-05	2.11e-05
95th Percentile	5.82e-03	2.00e-03	1.61e-03	2.18e-03	1.45e-03	2.26e-03	1.57e-03	9.09e-04	3.34e-03	2.00e-03

National Health and Nutrition Examination Survey

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

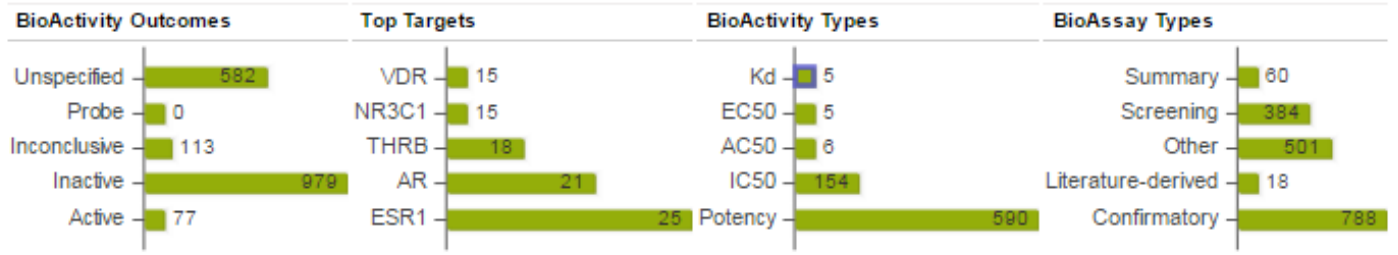
Environ. Sci. Technol., **2013**, *47* (15), pp 8479–8488



Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

PubChem integration

Biological Activities

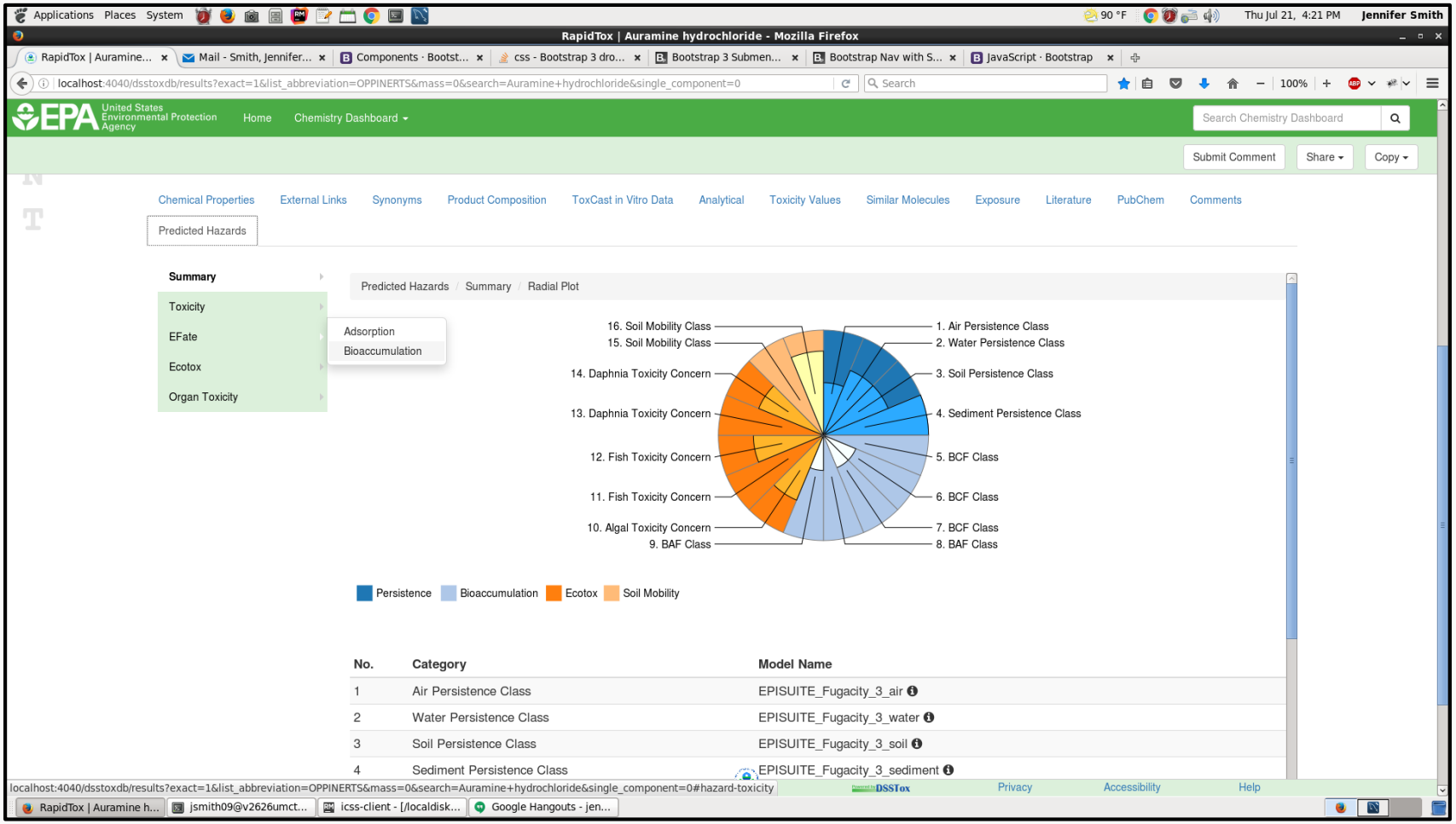


Structure	Substance SID	Activity			Compound Name	Bioassay Name
		Outcome	Type	Value [µM]		
	312534041	Inactive			Bisphenol A	Screen for inhibitors of RMI FANCM (MM2) intereaction [AID:1159607, Type: Other, PubMed ID:26962873]
	144214049	Inconclu...	Potency	62.1889	Bisphenol A	qHTS assay for small molecule agonists of the p53 signaling pathway [AID:651631, Type: Confirmatory]
	144214049	Inactive	Potency		Bisphenol A	qHTS assay for small molecules that induce genotoxicity in human embryonic kidney cells expressing luciferase-tagged ATAD5 [AID:651632, Type: Confirmatory]
	144214049	Inconclu...	Potency	55.4259	Bisphenol A	qHTS assay for small molecule agonists of the p53 signaling pathway - cell viability [AID:651633, Type: Confirmatory]
	144214049	Inactive	Potency		Bisphenol A	qHTS assay for small molecules that induce genotoxicity in human

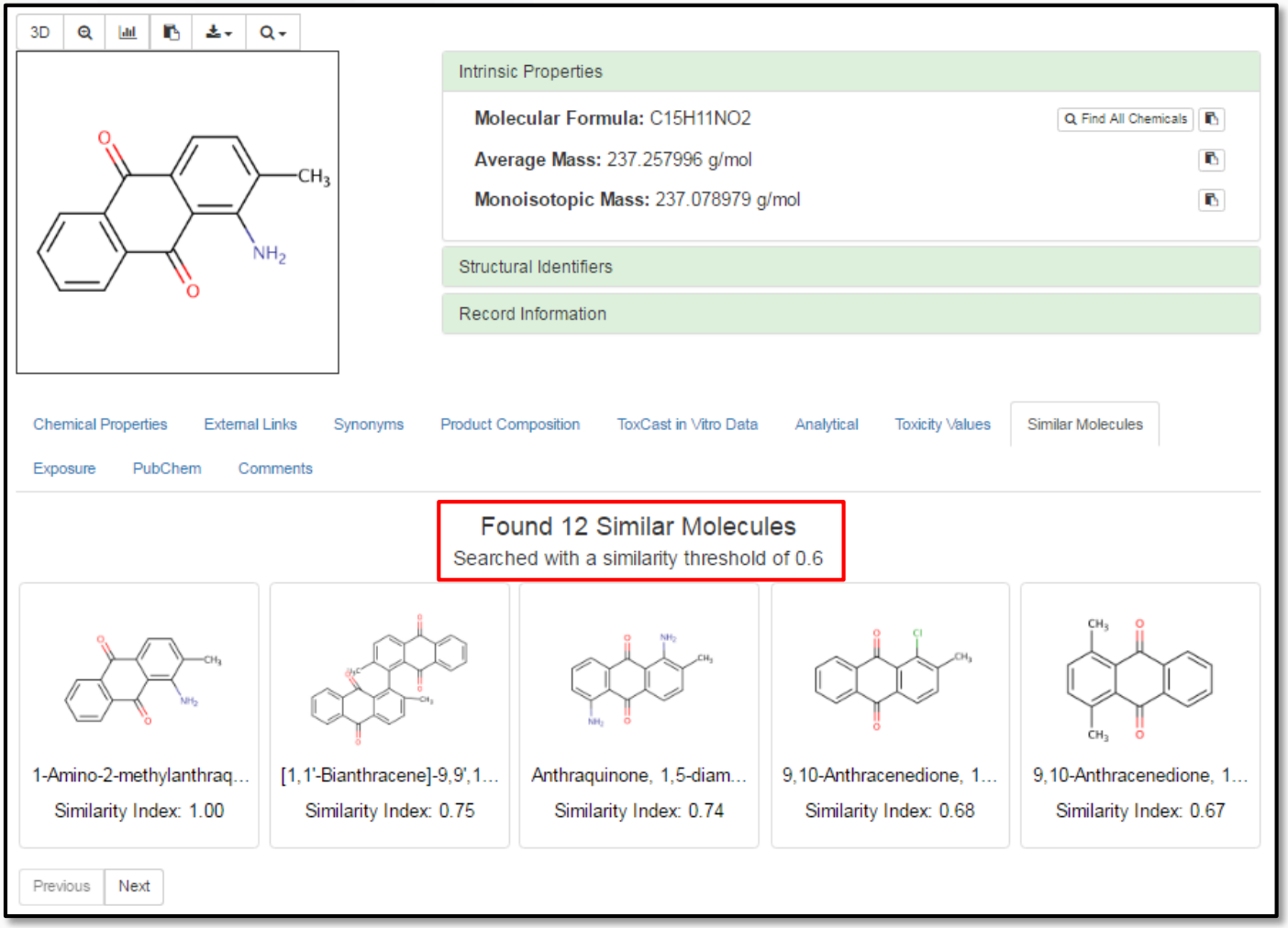
Page 1 of 176 | Displaying 1 - 10 of 1751

Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure | PubChem | Comments

Work in Progress: Environmental Fate, Transport and Toxicity



Work in Progress: Analog Identification and Similarity Search



Conclusions

- NCCT has been delivering data, algorithms, models and software tools for a decade
- A new flexible architecture to support multiple both internal and external apps
- First iteration of CompTox dashboard supports chemistry based searches
- Future concept…

Future Search Possibilities

Acknowledgements

Kamel Mansouri
Chris Grulke
Keith Houck
Ann Richard
Jeff Edwards
Matt Martin
John Wambaugh
Grace Patlewicz
Imran Shah
Richard Judson
Kevin Crofton
Russell Thomas