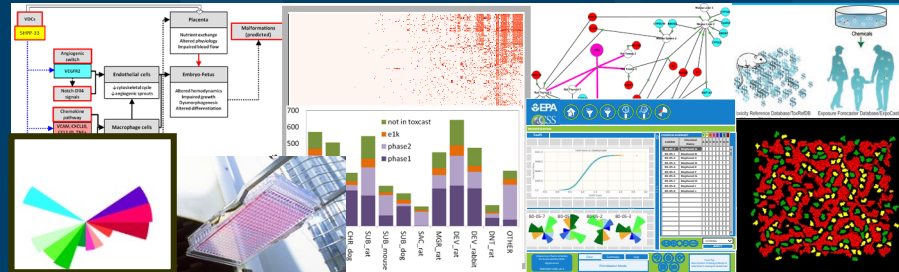


Perspectives on the Development, Evaluation, and Application of *in Silico* Approaches for Predicting Toxicity



Grace Patlewicz
Center for Computational Toxicology and Exposure (CCTE),
US EPA

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

Conflict of Interest Statement

- No conflict of interest declared.
- Disclaimer:
- The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA

Outline

- Regulatory Drivers
- Computational (*in silico*) Toxicology [scope for today's talk]
- Integrated Approaches to Testing and Assessment (IATA) – definitions and Adverse Outcome Pathway (AOP) informed
- Decision contexts and their impact on the approaches applied
- Risk-based prioritisation
- Read-across approaches
 - Generalised Read-across (GenRA)
- Summary remarks
- Acknowledgements

Regulatory and Non-Regulatory drivers

- Societal demands for safer and sustainable chemical products are stimulating changes in toxicity testing and assessment frameworks
- Chemical safety assessments are expected to be conducted faster and with fewer animals, yet the number of chemicals that require assessment is also rising with the number of different regulatory programmes worldwide.
- In the EU, the use of alternatives to animal testing is promoted.
- Animal testing is prohibited in some sectors e.g. EU Cosmetics regulation
- The European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation lays out specific information requirements, based on tonnage level triggers. However, the regulation explicitly expresses the need to use **non-testing approaches** to reduce the extent of experimental testing in animals.

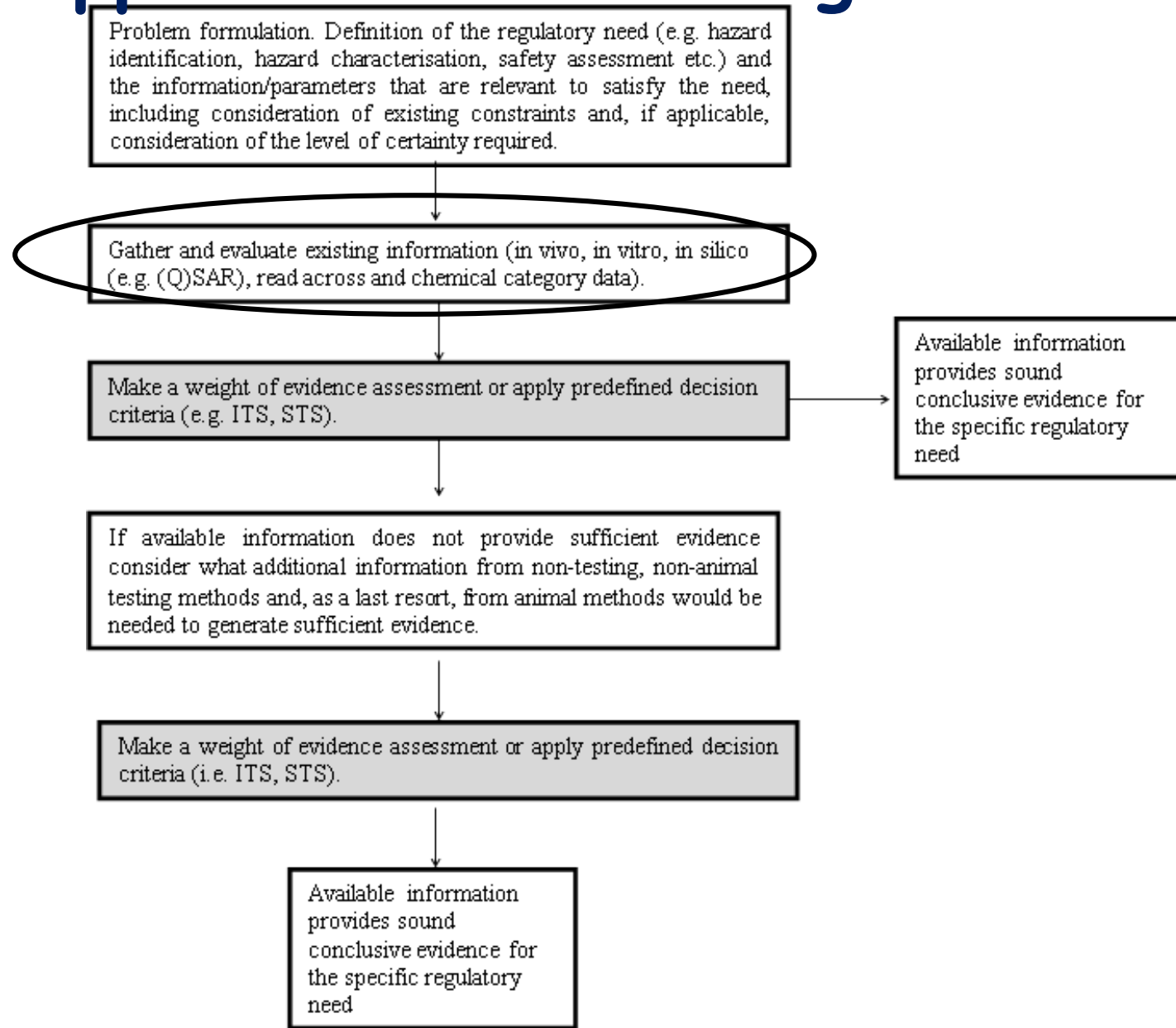
Regulatory and Non-Regulatory drivers

- REACH-like schemes also have been established in China, South Korea, and Turkey.
- In the US, the new Frank Lautenberg Chemical Safety for the 21st Century Act (LCSA) requires that a risk based prioritisation is conducted for all substances in commerce, ~40,000, many of which are lacking sufficient publicly available toxicity information.
- EPA Administrator signed memo 10/9/19 to “direct the agency to aggressively reduce animal testing, including reducing mammal study requests and funding 30% by 2025 and completely eliminating them by 2035”
- Risk based prioritisation is also an important aspect of regulatory frameworks in Canada (the Domestic Substances List), Australia and the EU.
- **Non-testing approaches** offer a means of facilitating the regulatory challenges in chemical safety assessment

Computational (*In Silico*) Toxicology

- 
- Databases/Dashboards of existing information
 - Structure-Activity Relationships (SAR)
 - Quantitative Structure-Activity Relationships (QSAR)
 - Expert Systems
 - Category formation (grouping) read-across
 - Bioinformatics
 - Chemoinformatics
 - Biokinetics (PBPK)

Integrated Approaches to Testing and Assessment (IATA)



Typical Information within an IATA: IATA elements

- Historical information on the chemical of interest
- Non-standard *in vivo* tests
- Information from “similar” chemicals
- Predictions from other ‘non-testing’ approaches such as (Q)SAR
- *In chemico* tests
- *In vitro* tests
- Molecular biology, -omics
- Exposure, (bio-)kinetics

The EPA CompTox Chemicals Dashboard: An Integration Hub for Data Supporting Computational Toxicology

Project Lead: Antony Williams

The CompTox Portal

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

EPA United States Environmental Protection Agency

Environmental Topics Laws & Regulations About EPA Search EPA.gov



**CompTox
Chemicals
Dashboard**



**Aggregated
Publicly Available
Chemical Data
ACToR**



**ToxCast
Dashboard
High-throughput
screening data**



EDSP21 Dashboard
High-throughput screening
and exposure estimates for
evaluating chemicals for
potential endocrine activity



RapidTox
Decision support workflows
to integrate chemistry,
toxicity, and exposure
information



Downloadable Data

- A publicly accessible website delivering access:
 - ~875,000 chemicals with related property data
 - Experimental and predicted physicochemical property data
 - Integration to “biological assay data” for 1000s of chemicals
 - Information regarding consumer products containing chemicals
 - Links to other agency websites and public data resources
 - “Literature” searches for chemicals using public resources
 - “Batch searching” for thousands of chemicals
 - DOWNLOADABLE Open Data for reuse and repurposing

CompTox Chemicals Dashboard



United States
Environmental Protection
Agency

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Share ▼



875 Thousand Chemicals

Chemicals

Product/Use Categories

Assay/Gene

☐ Identifier substring search

See what people are saying, read the dashboard [comments!](#)
Cite the Dashboard Publication [click here](#)

Latest News

[Read more news](#)

New Article regarding the GenRA module

March 9th, 2019 at 1:03:58 PM

A new article regarding "Generalized Read-Across (GenRA): A workflow implemented into the EPA CompTox Chemicals Dashboard" has been published in the ALTEX (Alternatives to Animal Experimentation) journal. Read the article [here](#).

CompTox Chemicals Dashboard

Chemicals

875 Thousand Chemicals



Chemicals

Product/Use Categories

Assay/Gene

Q Bisphenol A



Bisphenol A
DTXSID7020182



Bisphenol A bis(2-hydroxyethyl ether) diacrylate
DTXSID6066991



Bisphenol A bis(2-hydroxyethyl ether) dimethacrylate
DTXSID1066992



Bisphenol A bis(2-hydroxypropyl) ether
DTXSID8051592

Bisphenol A carbonate polymer
DTXSID6027840



Bisphenol A diglycidyl ether
DTXSID6024624



Bisphenol A glycidyl methacrylate
DTXSID7044841



Bisphenol A propoxylate diglycidyl ether
DTXSID10399098

CompTox Chemicals Dashboard Products and Use Categories



875 Thousand Chemicals

[Chemicals](#)[Product/Use Categories](#)[Assay/Gene](#)

CPDat PRODUCT category: personal care hair color
hair colors and dyes characterized as permanent

CPDat PRODUCT category: personal care hair color
hair colors and dyes characterized as for professional use

CPDat PRODUCT category: personal care hair color
hair colors and dyes characterized as temporary

CPDat PRODUCT category: personal care hair color
hair coloring products not otherwise categorized

CPDat PRODUCT category: personal care hair color activator
chemical activators for hair coloring products

CPDat PRODUCT category: personal care hair color developer
chemical developers for hair coloring products

CPDat PRODUCT category: personal care hair color toner
chemical toners for hair coloring products

100 new chemical substances being added, improved support for Toxcast bioassay available. This short video summarizes the advantages of the dashboard of multiple chemical lists and new user interface enhancements across the targeted analysis. [View it here on Youtube.](#)

look forward to your feedback.

CompTox Chemicals Dashboard

Assays and Genes



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875 Thousand Chemicals



Chemicals

Product/Use Categories

Assay/Gene

Q ESR

ASSAY: TOX21_ESRE_BLA_ch1

Data from the assay component TOX21_ESRE_BLA_ch1 was analyzed into 1 a...

ASSAY: TOX21_ESRE_BLA_ch2

Data from the assay component TOX21_ESRE_BLA_ch2 was analyzed into 1 a...

ASSAY: TOX21_ESRE_BLA_ratio

Data from the assay component TOX21_ESRE_BLA_ratio was analyzed into 1...

ASSAY: TOX21_ESRE_BLA_viability

TOX21_ESRE_BLA_viability used a type of growth reporter where loss-of-...

GENE: ESR1

estrogen receptor 1

GENE: esr1.L

estrogen receptor 1 L homeolog

GENE: ESR2

estrogen receptor 2 (ER beta)

GENE: esr2.L

estrogen receptor 2 L homeolog

GENE: esr2a

estrogen receptor 2a

GENE: esr2b

estrogen receptor 2b

GENE: ESR3

Detailed Chemical Pages: Landing page



Bisphenol A

80-05-7 | DTXSID7020182

Searched by DSSTox Substance Id.

DETAILS

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ENV. FATE/TRANSPORT

HAZARD

▶ ADME

▶ EXPOSURE

▶ BIOACTIVITY

SIMILAR COMPOUNDS

GENRA (BETA)

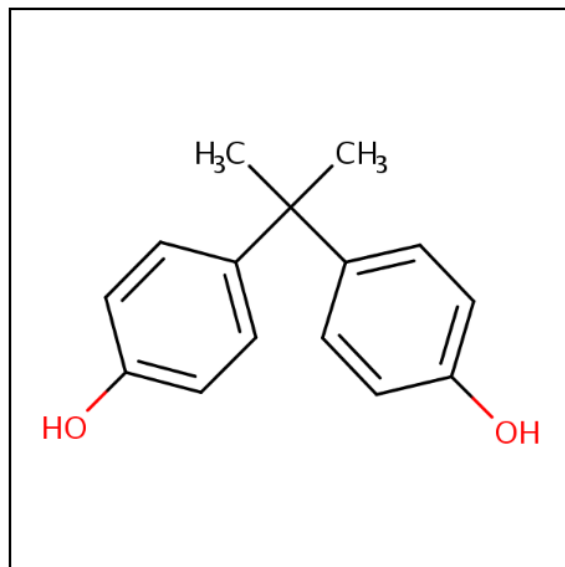
RELATED SUBSTANCES

SYNONYMS

▶ LITERATURE

LINKS

COMMENTS



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 a starting material for the synthesis of plastics, primarily

[Read more](#)

Intrinsic Properties

Structural Identifiers

Linked Substances

Presence in Lists

Record Information

Quality Control Notes

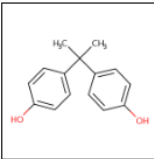
An "Executive Summary"

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TOXCAST: SUMMARY

EDSP21

TOXCAST/TOX21

PUBCHEM

Executive Summary

Quantitative Risk Assessment Values

- ✓ IRIS values available [↗](#)
- ✗ No PPRTV values
- ✓ EPA RSL values available [↗](#)
- ✓ Minimum RfD: **0.050 mg/kg-day** (chronic, IRIS, oral, 8) [↗](#)
- ✗ No RfC calculated
- ✗ IVIVE POD not calculated

Quantitative Hazard Values

- ✓ Minimum oral POD: **3.8 mg/kg-day** (reproductive, HPVIS, oral, 6) [↗](#)
- ✗ No inhalation POD values
- ✓ Lowest Observed Bioactivity Equivalent Level: [CYP1A1](#), [CYP1A2](#), [Tpo](#), [ESR2](#), [ESR1](#), [ESR1](#), [NR1I3](#), [PPARA](#), [NR1I2](#), [Cyp2c11](#), [MMP3](#), [Esr1](#)

Cancer Information

- ✗ No cancer slope factor
- ✗ No inhalation unit risk value
- ✓ Carcinogenicity data available: University of Maryland carcinogenicity warning; [↗](#)
- ✗ No genotoxicity findings reported

Reproductive Toxicology

- ✓ 200 Reproductive toxicity PODs available [↗](#)

REGIONAL SCREENING

Class	THQ	Value
risk-based SSL (mg/kg)	THQ = 0.1	5.8
GIABS (unspecified)	THQ = 1	1
GIABS (unspecified)	THQ = 0.1	1
ABS (unspecified)	THQ = 0.1	0.1
RfDo (mg/kg-day)	THQ = 0.1	0.05
screening level (residential Soil) (mg/kg)	THQ = 0.1	320
screening level (industrial soil) (mg/kg)	THQ = 0.1	4100

An "Executive Summary" Quick Look Tox Info

Executive Summary

Quantitative Risk Assessment Values

- ✓ IRIS values available
- ✗ No PPRTV values
- ✓ EPA RSL values available
- ✓ Minimum RfD: 0.050 mg/kg-day (chronic, IRIS, oral, 8)
- ✗ No RfC calculated
- ✗ IVIVE POD not calculated

Quantitative Hazard Values

- ✓ Minimum oral POD: 3.8 mg/kg-day (reproductive, HPVIS, oral, 6)
- ✗ No inhalation POD values
- ✓ Lowest Observed Bioactivity Equivalent Level: CYP1A1, CYP1A2, Tpo, ESR2, ESR1, ESR1, NR1I3, PPARA, NR1I2, Cyp2c11, MMP3, Esr1

Cancer Information

- ✗ No cancer slope factor
- ✗ No inhalation unit risk value
- ✓ Carcinogenicity data available: University of Maryland carcinogenicity warning
- ✗ No genotoxicity findings reported

Reproductive Toxicology

- ✓ 200 Reproductive toxicity PODs available

Chronic Toxicology

- ✓ 340 Chronic toxicity PODs available

Subchronic Toxicology

- ✓ 12 Subchronic toxicity PODs available

Developmental Toxicology

- ✓ 6 Developmental toxicity PODs available

Acute Toxicology

- ✓ 391 Acute toxicity PODs available

Subacute Toxicology

- ✓ 1 subacute toxicity PODs available

Neurotoxicology

- ✗ No neurotoxicology data available.

Endocrine System

- ✓ Endocrine Disruption Potential. Significant Estrogen and Androgen Receptor activity seen. Chemical was positive in 21 ER assays (out of 35) and was positive in 9 AR assays (tested in 19).

ADME

- ✓ HTTK C_{ss} data are available

Fate and Transport

- ✗ No bioaccumulation concern.
- ✗ No volatility concern.
- ✓ Biodegradation predictions are available
- ✓ BCF predictions are available
- ✓ Vapor Pressure predictions are available

Exposure

- ✓ Exposure estimates are available based on NHANES and SEEM

AOP Information

- ✓ AOP Links: 13, 33, 36, 58, 60, 61, 66, 107, 124, 150, 163, 175, 187, 200

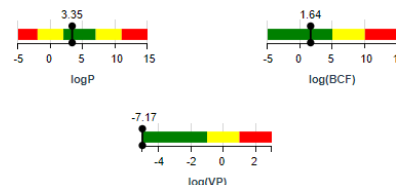
Other Notes

- ✗ No water quality values available.
- ✗ No air quality values available.
- ✓ 14 Occupational exposure values available.

REGIONAL SCREENING

Class	THQ	Value
risk-based SSL (mg/kg)	THQ = 0.1	5.8
GIABS (unspecified)	THQ = 1	1
GIABS (unspecified)	THQ = 0.1	1
ABS (unspecified)	THQ = 0.1	0.1
RfDo (mg/kg-day)	THQ = 0.1	0.05
screening level (residential soil) (mg/kg)	THQ = 0.1	320
screening level (industrial soil) (mg/kg)	THQ = 0.1	4100
screening level (tap water) (ug/L)	THQ = 0.1	77
RfDo (mg/kg-day)	THQ = 1	0.05
screening level (residential soil) (mg/kg)	THQ = 1	3200
screening level (industrial soil) (mg/kg)	THQ = 1	41000
ABS (unspecified)	THQ = 1	0.1
risk-based SSL (mg/kg)	THQ = 1	58
screening level (tap water) (ug/L)	THQ = 1	770

PHYSICHEM PARAMETERS



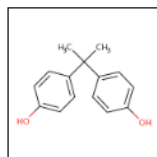
Quantitative Risk Assessment Values

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- ✓ EPA RSL values available
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- ✗ IVIVE POD not calculated

Quantitative Hazard Values

- ✓ Minimum oral POD: 3.8 mg/kg-day (reproductive, HPVIS, oral, 6)
- ✗ No inhalation POD values
- ✓ Lowest Observed Bioactivity Equivalent Level: CYP1A1, CYP1A2, Tpo, ESR2, ESR1, ESR1, NR1I3, PPARA, NR1I2, Cyp2c11, MMP3, Esr1

Physicochemical properties



Bisphenol A

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Searched by Expert Validated Synonym.

Property

[Summary](#)

Summary

[Download](#)

[Columns](#)

[Search query](#)

Property	Experimental average	Predicted average	Experimental median	Predicted median	Experimental range	Predicted range	Unit
LogP: Octanol-Water	3.32 (1)	3.29		3.43	3.32	2.40 to 3.64	
Melting Point	155 (7)	139	156	138	153 to 156	125 to 157	°C
Boiling Point	200 (1)	363		360	200	343 to 401	°C
Water Solubility	5.26e-4 (1)	9.62e-4		1.00e-3	5.26e-4	5.35e-4 to 1.31e-3	mol/L
Vapor Pressure	-	8.37e-7		3.43e-7	-	6.83e-8 to 2.59e-6	mmHg
Flash Point	-	190		190	-	188 to 192	°C
Surface Tension	-	46.0			-	46.0	dyn/cm
Index of Refraction	-	1.60			-	1.60	
Molar Refractivity	-	68.2			-	68.2	cm^3
Polarizability	-	27.0			-	27.0	Å^3
Density	-	1.17		1.17	-	1.14 to 1.20	g/cm^3
Molar Volume	-	200			-	200	cm^3

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TOXCAST: SUMMARY

EDSP21

TOXCAST/TOX21

PUBCHEM

TOXCAST: MODELS

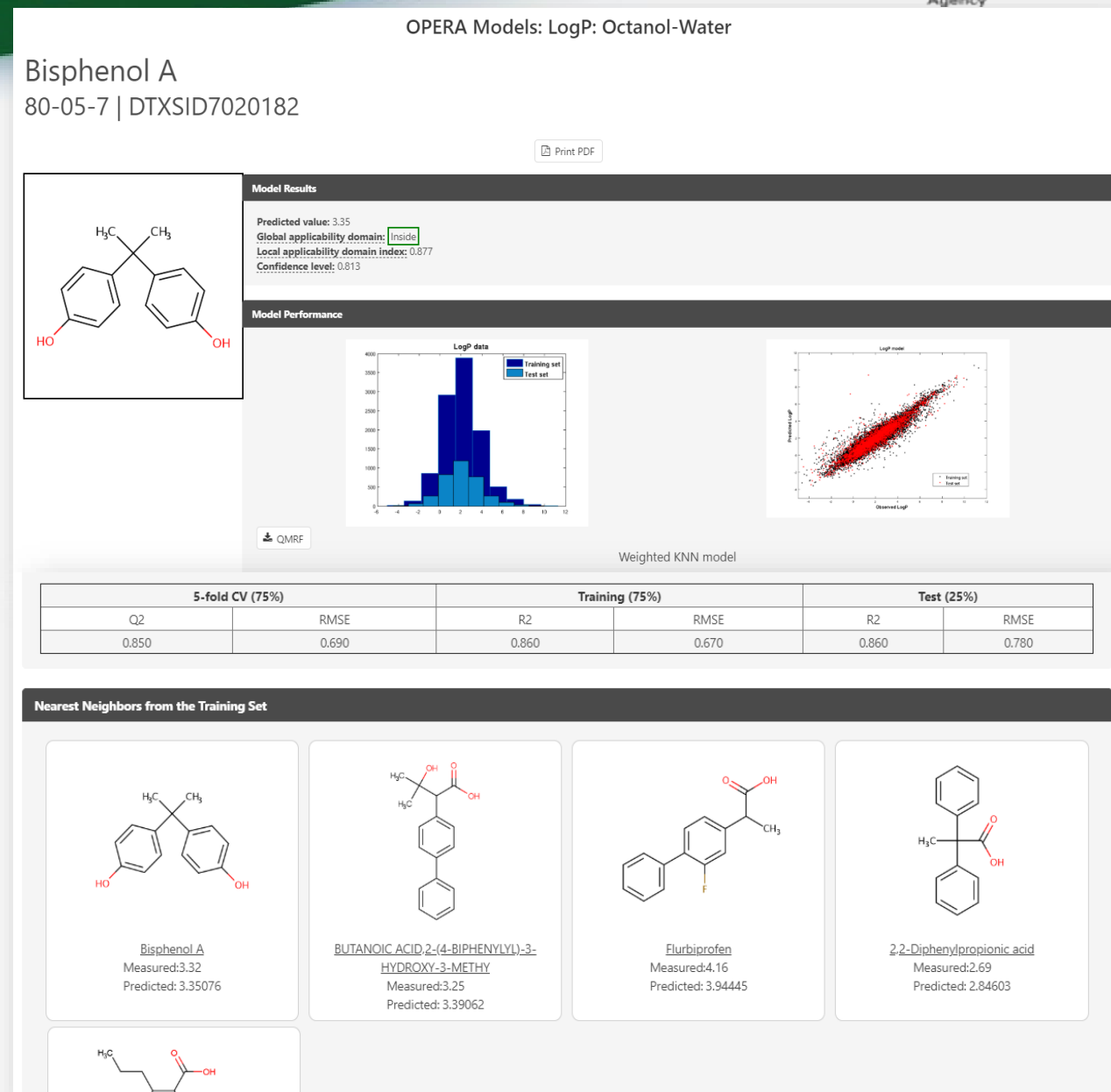
SIMILAR COMPOUNDS

Detailed QSAR Prediction Reports from OPERA

QSAR Prediction Reporting Format (QPRF):
Standardised template to document a prediction
from a given QSAR model

QSAR Model Reporting Format (QMRF)
Template to document a QSAR model itself

**Underpinned by the OECD QSAR Validation
Principles (2004)**



Other Data: Human and Ecological Chemical Hazard Data

 **United States
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SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

SYNONYMS

LITERATURE

LINKS

COMMENTS

Data Type

Point of Departure ▾

Download ▾

Human

Eco

Columns ▾ 10 ▾

Search query

More ▾	Priority ▾	Toxval type ▾	Subtype ▾	Risk assessment class ▾	Value ^	Units ▾	Study type ▾	Exposure route ▾	Species ▾	Subsource ▾	Source ▾
	5	<u>BMDL-10</u>	-	chronic	0.609	mg/kg-day	human	-	mouse	EFSA CEF	EFSA
	5	<u>NOEL</u>	Systemic	repeat dose	3.75	mg/kg-day	repeat dose toxicity : oral	oral	rat	-	ECHA
	6	<u>NOAEL</u>	-	reproductive	3.75	mg/kg-day	reproductive	oral	rat	-	HPVIS
	5	<u>NOEL</u>	Systemic	repeat dose	3.75	mg/kg-day	repeat dose toxicity : oral	oral	rat	-	ECHA
	5	<u>NOEL</u>	Systemic	repeat dose	4.5	mg/kg-day	repeat dose toxicity : oral	oral	mouse	-	ECHA
	5	<u>NOEL</u>	Systemic	repeat dose	4.5	mg/kg-day	repeat dose toxicity : oral	oral	mouse	-	ECHA
	7	<u>LEL</u>	-	subchronic	5	mg/kg-day	subchronic	oral	rat	unpublished_submission	ToxRefDB
	7	<u>nel</u>	-	chronic	5	mg/kg-day	reproductive multigeneration	oral	rat	open_lit	ToxRefDB
	5	<u>NOAEL</u>	-	chronic	5	mg/kg-day	human	-	mouse	EFSA AFC	EFSA
	7	<u>nel</u>	-	subchronic	5	mg/kg-day	subchronic	oral	rat	unpublished_submission	ToxRefDB

1 2 3 4 5 6 7 > >>

- ToxVal Database contains following structured data:
 - ~30,000 chemicals
 - ~750,000 toxicity values
 - ~30 sources of data
 - ~4500 journals cited
 - ~70,000 literature citations

Sources of Exposure to Chemicals

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▼ EXPOSURE

PRODUCT & USE CATEGORIES

CHEMICAL WEIGHT FRACTION

CHEMICAL FUNCTIONAL USE

TOXICS RELEASE INVENTORY

MONITORING DATA

EXPOSURE PREDICTIONS

PRODUCTION VOLUME

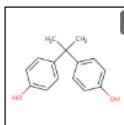
Download ▾

Columns ▾ 10 ▾

Search query

Product or Use Categorization	Categorization type	Number of Unique Products
manufacturing, metals	CPCat Cassette	17
adhesive	CPCat Cassette	17
paint	CPCat Cassette	16
	CPCat Cassette	12
	CPCat Cassette	11
	CPCat Cassette	8
	CPCat Cassette	8
	CPCat Cassette	8
	CPCat Cassette	7
	CPCat Cassette	6

First << < 1 2 3 4 5 6 7 8 9 10 > >> Last



Bisphenol A

80-05-7 | DTXSID7020182

Searched by Expert Validated Synonym.

Download

Columns

Search query

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	19.29	-	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	0.07	-	-	
Volume of Distribution	-	-	6.69	L/kg
Days to Steady State	-	-	8	Days
PK Half Life	-	-	29.83	hours
Human Steady-State Plasma Concentration	-	-	1.98	mg/L

6 records

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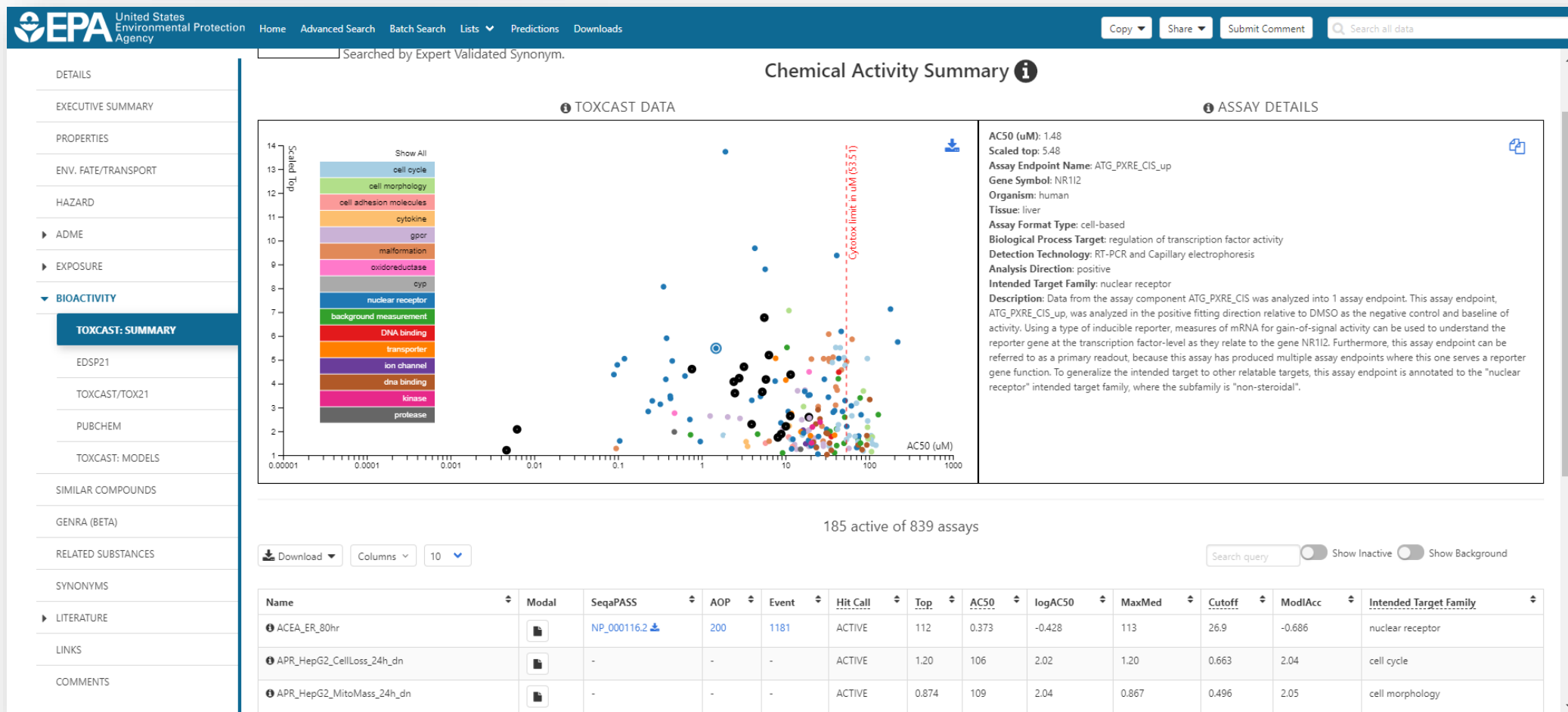
SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

In Vitro Bioassay Screening

ToxCast and Tox21



In Vitro Bioassay Screening

ToxCast and Tox21

EPA United States Environmental Protection Agency

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TOXCAST: SUMMARY

EDSP21

TOXCAST/TOX21

PUBCHEM

TOXCAST: MODELS

SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

SYNONYMS

LITERATURE

Oc1ccc(cc1)C(C)(C)c2ccc(O)cc2

Bisphenol A
80-05-7 | DTXSID7020182
Searched by Expert Validated Synonym.

ToxCast/Tox21

QC Data ID	Grade	Description
Tox21_202992	Pass	Purity>90% and MW confirmed
Tox21_400088	Pass	Purity>90% and MW confirmed

Assay Selection 136 Selected

☒ Active ☐ Inactive ☐ All

Filter assays

- Ceetox/OpAns (2 of 24 selected)
- Odyssey Thera (6 of 17 selected)
- Attagene (4 of 165 selected)
- Tox21/NCGC (44 of 211 selected)
- CellzDirect (3 of 48 selected)
- Bioseek (4 of 174 selected)
- Apredica (8 of 107 selected)
- NHEERL Padilla Lab (1 of 1 selected)
- Novascreen (46 of 167 selected)
- NHEERL's Hunter Lab (0 of 4 selected)
- NCCT's Lab (4 of 4 selected)
- ACEA Biosciences (4 of 6 selected)
- Taniguchi Lab (9 of 19 selected)

A Single Assay Can Have Multiple Charts ☒ Representative Samples Only Bioactivity Summary Number of Charts: 136

CEETOX_H266R_ANDR_dh
HTCCALL ACTIVE
Bisphenol A (80-05-7)
DTXSID7020182
TP0000055008

CEETOX_H266R_TESTO_dh
HTCCALL ACTIVE
Bisphenol A (80-05-7)
DTXSID7020182
TP0000084412

QT_ER_ERWRN_1440
HTCCALL ACTIVE
Bisphenol A (80-05-7)
DTXSID7020182
TP0000190001

25

Exploring ToxCast Data: Downloadable Data

The results after processing through the Pipeline are available on the [ToxCast Dashboard](#), and for most users EPA recommends accessing the data there.

- [ToxCast Chemicals](#)
- [ToxCast Assays](#)

ToxCast Data and Information

- **ToxCast & Tox21 Summary Files.** Data for a single chemical endpoint pair for thousands of chemicals and assay endpoints for 20 variables such as the activity or hit call, activity concentrations, whether the chemical was tested in a specific assay, etc.
 - [Download ToxCast Summary Information](#)
 - [Download ReadMe](#)
- **ToxCast & Tox21 Data Spreadsheet.** A spreadsheet of EPA's analysis of the chemicals screened through ToxCast and the Tox21 collaboration which includes EPA's activity calls from the screening of over 1,800 chemicals.
 - [Download Data](#)
 - [Download ReadMe](#)
- **ToxCast Data Pipeline R Package.** The R computer programming package used to process and model all EPA ToxCast and Tox21 chemical screening data. The files include the R programming package as well as documents that provide overviews of the data analysis pipeline used and the R package. Users will need experience with R to use these files.
 - [Download Package](#)
 - [TCPL Overview](#)

Resources

- [Toxicity Forecaster \(ToxCast\) Fact Sheet](#)
- [ToxCast Publications](#)
- [ToxCast Citation](#)
- [About ToxCast](#)

BUILT-IN "MODULES"



Bisphenol A

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Searched by DSSTox Substance Id.

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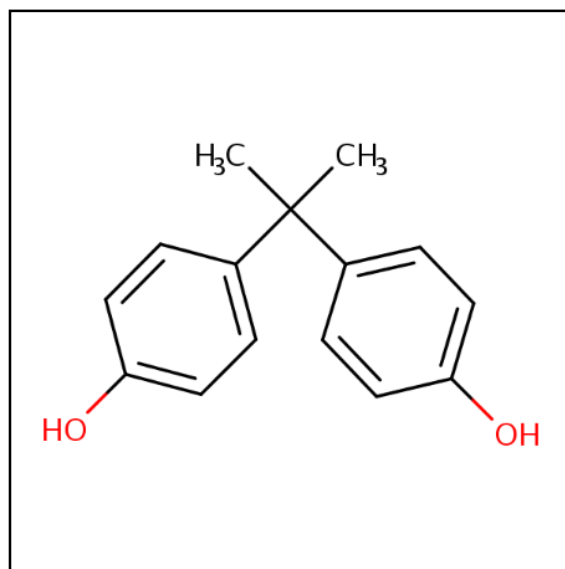
RELATED SUBSTANCES

SYNONYMS

▶ LITERATURE

LINKS

COMMENTS



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 a starting material for the synthesis of plastics, primarily

[Read more](#)

Intrinsic Properties

Structural Identifiers

Linked Substances

Presence in Lists

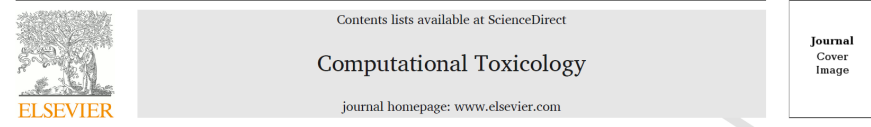
Record Information

Quality Control Notes

Related Publications



Systematically evaluating read-across prediction and performance using a local validity approach characterized by chemical structure and bioactivity information



Navigating through the minefield of read-across frameworks: A commentary perspective

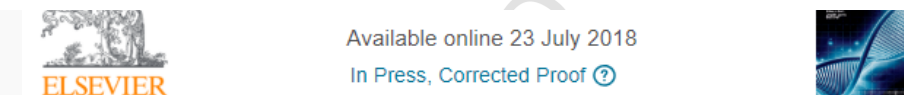
Grace Patlewicz^{a,*}, Mark T.D. Cronin^b, George Helman^{a,c}, Jason C. Lambert^d, Lucina E. Lizarraga^d, Imran Shah^a

^a National Center for Computational Toxicology (NCCT), Office of Research and Development, US Environmental Protection Agency (US EPA), 109 TW Alexander Dr, Research Triangle Park (RTP), NC 27711, USA

^b School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK

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^d National Center for Evaluation Assessment (NCEA), US Environmental Protection Agency (US EPA), 26 West Martin Luther King Dr, Cincinnati, OH 45268, USA



Extending the Generalised Read-Across approach (GenRA): A systematic analysis of the impact of physicochemical property information on read-across performance

George Helman^{a,b}, Imran Shah^b, Grace Patlewicz^b✉

Short Communication

Generalized Read-Across (GenRA): A Workflow Implemented into the EPA CompTox Chemicals Dashboard

George Helman^{1,2}, Imran Shah², Antony J. Williams², Jeff Edwards², Jeremy Dunne² and Grace Patlewicz²

¹Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN, USA; ²National Center for Computational Toxicology (NCCT), Office of Research and Development, US Environmental Protection Agency (US EPA), Research Triangle Park, NC, USA



Transitioning the generalised read-across approach (GenRA) to quantitative predictions: A case study using acute oral toxicity data

George Helman^{a,b}, Imran Shah^b, Grace Patlewicz^{b,*}

^a Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN, USA
^b National Center for Computational Toxicology (NCCT), Office of Research and Development, US Environmental Protection Agency (US EPA), Research Triangle Park, NC, USA

ARTICLE INFO

Keywords:
Generalized read-across (GenRA)
Acute oral toxicity
Quantitative predictions

ABSTRACT:
Read-sentences in dose-toxicity discovery GenRA chem the ei cross range lar ch



Quantitative prediction of repeat dose toxicity values using GenRA

G. Helman^{a,b}, G. Patlewicz^b, I. Shah^{b,*}

^a Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN, USA

^b National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, USA

Point of contact:
Grace Patlewicz & Imran Shah

have recently gained popularity in the field of read-across to automatically fill data. Previously, we developed the generalized read-across (GenRA) tool, which utilizes conjunction with chemical descriptor information to derive local validity domains to *in vivo* toxicity studies. Here, we modified GenRA to quantitatively predict point of obtained from US EPA's Toxicity Reference Database (ToxRefDB) version 2.0. To evaluate GenRA predictions, we first aggregated oral Lowest Observed Adverse Effect Levels (LOAEL) for 1,014 chemicals by systemic, developmental, reproductive, and cholinesterase effects. The mean LOAEL values for each chemical were converted to log molar equivalents. Applying GenRA to all chemicals with a minimum

Generalised Read-Across (GenRA)

DETAILS

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BIOACTIVITY

TOXCAST. SUMMARY

PUBCHEM

TOXCAST. DATA

TOXCAST. MODELS

SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

SYNONYMS

LITERATURE

LINKS

COMMENTS

Bisphenol A

80-05-7 | DTXSID7020182

Searched by Expert Validated Synonym.

Neighbors by: Chem: Morgan Fgprts Filter by: In vivo data

4-(2-Methylbutan-2-yl)phenol

4-(1,1,3,3-Tetrahydro-2H-isobenzofuran-2-yl)phenol

Diethylstilbestrol

Methylparaben

4-(4-Hydroxyphenyl)butan-2-one

Phenol

4-Nitrophenol

Acetaminophen

tert-Butylhydroquinone

Bisphenol A

Ethylparaben

4-(2-Methylbutan-2-yl)phenol

4-(1,1,3,3-Tetrahydro-2H-isobenzofuran-2-yl)phenol

Diethylstilbestrol

Methylparaben

4-(4-Hydroxyphenyl)butan-2-one

Phenol

4-Nitrophenol

Acetaminophen

tert-Butylhydroquinone

Bisphenol A

Ethylparaben

of Analogs 10

Next

Run Read-Across

GenRA

Min: 0

Min: 0

Filter:

Similarity Weight: 0.25

Download: Filetype

1.00

0.48

0.45

0.29

0.28

0.28

0.26

0.26

0.26

0.25

Bisphenol A

4-(2-Methylbutan-2-yl)phenol

4-(1,1,3,3-Tetrahydro-2H-isobenzofuran-2-yl)phenol

Diethylstilbestrol

Methylparaben

tert-Butylhydroquinone

Acetaminophen

4-Nitrophenol

Phenol

4-(4-Hydroxyphenyl)butan-2-one

Ethylparaben

CHR:Abdominal Cavity

CHR:Adrenal Gland

CHR:Artery (General)

CHR:Auditory Staircase Re...

CHR:Bile duct

CHR:Blood

CHR:Blood vessel

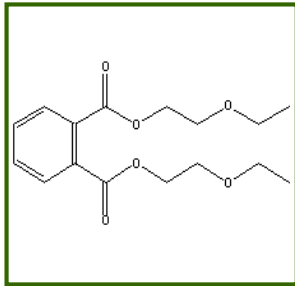
CHR:Body Weight

CHR:Bone

30

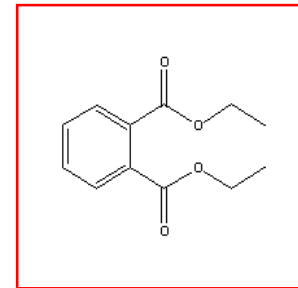
Read-across

- Read-across describes the method of filling a data gap whereby a chemical with existing data values is used to make a prediction for a 'similar' chemical.
- A target chemical is a chemical which has a data gap that needs to be filled i.e. the subject of the read-across.
- A source analogue is a chemical that has been identified as an appropriate chemical for use in a read-across based on similarity to the target chemical and existence of relevant data.



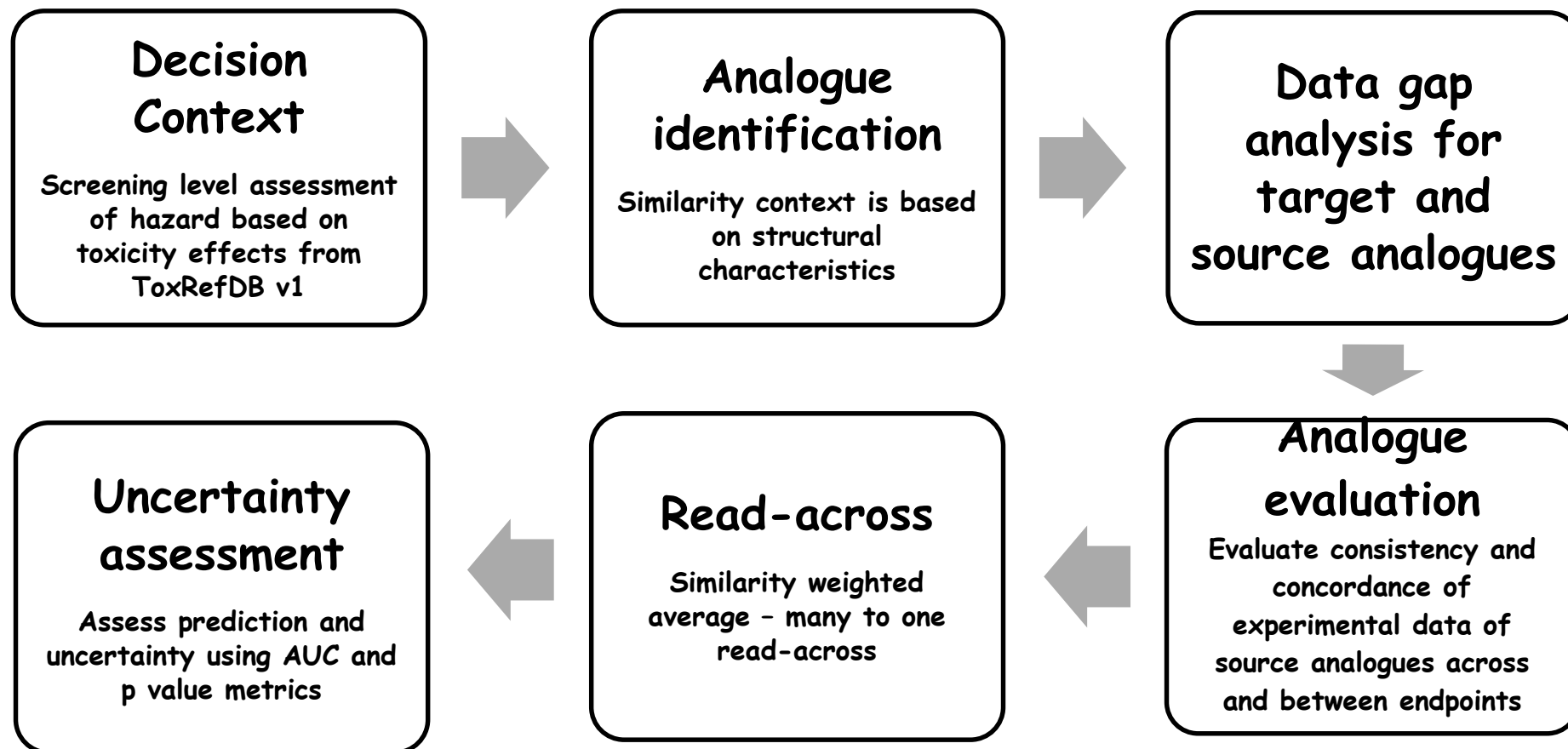
Known to be harmful

Acute toxicity?



Predicted to be harmful

Read-across workflow in GenRA v1.0



GenRA tool in practice

- Structured as a workflow

Fluconazole
86386-73-4 | DTXSID3020627
Searched by DSSTox Substance Id.

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BIOACTIVITY
SIMILAR COMPOUNDS
GENRA
RELATED SUBSTANCES
SYNONYMS
LITERATURE
LINKS
COMMENTS

Step One: Analog Identification and Evaluation

Neighbors by: Chem: Morgan Fgrpts Filter by: invivo data

Similarity context

Fluconazole

Bromuconazole
Flusilazole
Cyproconazole
Ipoconazole
Pyrasulfotole m...
Metconazole
Myclobutanil
Tetraconazole
Fenbuconazole

of Analogs 10

Next

GenRA tool in practice

GenRA

Step Two: Data Gap Analysis & Generate Data Matrix

Neighbors by: Chem: Morgan Fgrpts Filter by: invivo data

Summary Data Gap Analysis Group: ToxRef By: Tox Fingerprint **Generate Data Matrix** Read-Across

Chemical Structure Diagram: A central molecule, Acrolein diethyl acetal, is connected to several other molecules: Ethylene glycol, Ethion, Myrcene, Chloroethoxyfos, 2-Ethoxyethyl alcohol, bis(2-Chloro-1-hydroxyethyl) ether, Methyleugenol, Fosamine ammonium, Ethoprop, and Butanal oxime.

Data Gap Analysis Table:

	bio h21	bio h21	chem_ct	tox brf
Fluconazole	3	714	15	0
Hexaconazole	43	819	18	345
Flusilazole	28	819	9	345
Cyproconazole	14	819	16	408
Pyrasulfotole metabolite ...	0	0	18	234
Myclobutanil	15	818	15	345
Fenbuconazole	34	819	17	345
Tetraconazole	35	819	20	345
Metconazole	35	215	15	82
Iponazole	46	232	16	180
Bromuconazole	24	277	13	345

Read-Across Matrix:

	Fluconazole	Hexaconazole	Flusilazole	Cyproconazole	Pyrasulfotole metab...	Myclobutanil	Fenbuconazole	Tetraconazole	Metconazole	Iponazole	Bromuconazole	Butanal oxime
CHR:Abdominal Cavity												
CHR:Adrenal Gland												
CHR:Artery (General)												
CHR:Auditory Startle Re...												
CHR:Bile duct												
CHR:Blood												
CHR:Blood vessel												
CHR:Body Weight												
CHR:Bone												
CHR:Bone Marrow												
CHR:Brain												
CHR:Liver												
CHR:Lung												

of Analogs: 10 **Next**

Data gap analysis

45

Run GenRA

Names and CASRNs to Support Searches

 **EPA** United States
Environmental Protection
Agency

Home Advanced Search Batch Search Lists ▼ Predictions Downloads

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Bisphenol A

80-05-7 | DTXSID7020182

Searched by DSSTox Substance Id.

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▶ ADME

▶ EXPOSURE

▶ BIOACTIVITY

SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

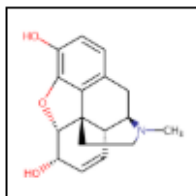
SYNONYMS

▶ LITERATURE

LINKS

COMMENTS

25 ▼



Morphine

57-27-2 | DTXSID9023336

Searched by Approved Name.

Abstract Sifter

1) Select PubMed starting point query then 2) click on Retrieve. 

Select a Query Term

Select a Query Term

Hazard

Fate and Transport

Metabolism/PK/PD

Chemical Properties

Exposure

Mixtures

Male Reproduction

Androgen Disruption

Female Reproduction

GeneTox

Cancer

Clinical Trials

Embryo and embryonic development

Child (infant through adolescent)

Dust and Exposure

Food and Exposure

Water and Exposure

Algae

Disaster / Emergency

Retrieve Articles

Optionally, edit the query before retrieving.

"57-27-2" OR "Morphine"

Child (infant through adolescent)

Dust and Exposure

Food and Exposure

Water and Exposure

Algae

Disaster / Emergency



^{ws} Optionally, edit the query before retrieving.

("57-27-2" OR "Morphine") AND ((water OR groundwater OR drinking water) AND Environmental Exposure)

Literature Searching

37 of 37 articles loaded...

To find articles quickly, enter terms to sift abstracts.

☐	wastewater	Spectrometry ↓	EPA	Total	PMID	Year	Title	Authors	Journal	Rev
☐	4	2	0	6	29274731	2017	Simultaneous analysis of opioid analgesics and thei...	Krizman-Matasic; Kostanjevecki; Ahel; Terzic	Journal of chromatography. A	
☐	0	1	0	1	25768972	2015	Evaluating external contamination of polybrominate...	Poon; Aleksa; Carnevale; Kapur; Goodyer; Koren	Therapeutic drug monitoring	
☐	0	1	0	1	22544551	2012	Spatial distribution of illicit drugs in surface waters o...	Vazquez-Roig; Andreu; Blasco; Morillas; Picó	Environmental science and pollution research inter...	
☐	1	1	0	2	20801487	2010	Analysis of illicit and illicit drugs in waste, surface an...	Berset; Brenneisen; Mathieu	Chemosphere	
☐	1	1	0	2	17935751	2007	Illicit drugs, a novel group of environmental contami...	Zuccato; Castiglioni; Bagnati; Chiabrando; Grassi; ...	Water research	
☐	2	1	1	4	17607391	2007	Using environmental analytical data to estimate lev...	Bones; Thomas; Paull	Journal of environmental monitoring : JEM	
☐	3	1	2	6	17180984	2006	Simultaneous determination of psychoactive drugs ...	Hummel; Löffler; Fink; Ternes	Environmental science & technology	
☐	6	0	0	6	30583189	2018	Assessment of drugs of abuse in a wastewater trea...	Kumar; Tschärke; O'Brien; Mueller; Wilkins; Padhye	The Science of the total environment	
☐	0	0	3	3	30488421	2018	Effect of enriched environment during adolescence ...	Mohammadian; Najafi; Miladi-Gorji	Developmental psychobiology	
☐	3	0	0	3	29574368	2018	Estimation of the consumption of illicit drugs during ...	Foppe; Hammond-Weinberger; Subedi	The Science of the total environment	
☐	1	0	0	1	28787791	2017	Evaluation of in-sewer transformation of selected illi...	Gao; Banks; Li; Jiang; Lai; Mueller; Thai	The Science of the total environment	
☐	9	0	0	9	28472697	2017	Occurrence and fate of illicit drugs and pharmaceuti...	Causanilles; Ruepert; Ibáñez; Emke; Hernández; d...	The Science of the total environment	
☐	0	0	0	0	28010888	2016	Dose-dependent effects of morphine on lipopolysac...	Mottaz; Schönenberger; Fischer; Eggen; Schirmer; ...	Environmental pollution (Barking, Essex : 1987)	
☐	0	0	0	0	27746311	2016	Effects of voluntary exercise on the viability, prolifer...	Haydari; Safari; Zarbakhsh; Bandegi; Miladi-Gorji	Neuroscience letters	
☐	0	0	0	0	27261879	2016	Genotoxic effects induced by the exposure to an en...	Parolini; Magni; Castiglioni; Binelli	Ecotoxicology and environmental safety	
☐	3	0	0	3	27179320	2016	Temporal trends in drug use in Adelaide, South Aus...	Tschärke; Chen; Gerber; White	The Science of the total environment	

External Links to ~80 websites

 United States
Environmental Protection
Agency

Home Advanced Search Batch Search Lists Predictions Downloads

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Bisphenol A

80-05-7 | DTXSID7020182
Searched by Approved Name.

DETAILS

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SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

SYNONYMS

LITERATURE

LINKS

COMMENTS

General

- EPA Substance Registry Service
- Household Products Database
- Chemical Entities of Biological Interest (ChEBI)
- PubChem
- Chempidier
- CPCat
- DrugBank
- HMDB
- Wikipedia
- MSDS Lookup
- ChEMBL
- Chemical Vendors
- CalEPA Office of Environmental Health Hazard Assessment
- NIOSH Chemical Safety Cards
- ToxPlanet
- ACS Reagent Chemicals
- Wikidata
- ChemHat: Hazards and Alternatives Toolbox
- Wolfram Alpha
- ScrubChem
- ECHA Brief Profile
- ECHA Infocard
- ChemAgora

Toxicology

- ACToR
- OH₂ DrugPortal
- CCRIS
- ChemView
- CTD
- eChemPortal
- Gene-Tox
- HSDB

Analytical

- FOR-IDENT
- NEMI: National Environmental Methods Index
- RSC Analytical Abstracts
- Tox21 Analytical Data
- MONA: MassBank North America
- mzCloud
- NIST IR Spectrum
- NIST MS Spectrum

Prediction

- 2D NMR HSQC/HMBC Prediction
- Carbon-13 NMR Prediction
- Proton NMR Prediction
- ChemRTP Predictor
- LSERD

CHEMICAL LISTS AND CATEGORIES

An Example List

Hepatic metabolic clearance and plasma protein binding data PHASE 1

Search WETMORE2012 Chemicals

☐ Identifier substring search

List Details

Description: Data from the Wetmore *et al.* paper [Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment](#). Hepatic metabolic clearance and plasma protein binding data were experimentally measured for ca. 240 ToxCast Phase I chemicals. The experimental data were used in a population-based *in vitro*-to-*in vivo* (IVIVE) extrapolation model to estimate the daily human oral dose, called the oral equivalent dose, necessary to produce steady-state *in vivo* blood concentrations equivalent to *in vitro* AC(50) (concentration at 50% of maximum activity) or lowest effective concentration values across more than 500 *in vitro* assays. The work was split into two phases. This is phase 1 (2012) and the second phase is [available here \(2015\)](#).

Number of Chemicals: 238

238 chemicals

Select all

Download ▼

Send to Batch Search

Default ▼



CASRN ✕

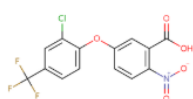
DTXSID ✕

Mass ✕



Hide chemicals that are: ▼

Filter by Name or CASRN

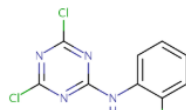


Acifluorfen

CASRN: 50594-66-6

DTXSID: DTXSID0020022

Mass: 360.996485

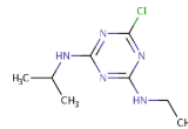


Anilazine

CASRN: 101-05-3

DTXSID: DTXSID9020089

Mass: 273.957979

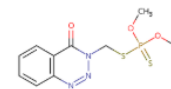


Atrazine

CASRN: 1912-24-9

DTXSID: DTXSID9020112

Mass: 215.093773



Azinphos-methyl

CASRN: 86-50-0

DTXSID: DTXSID3020122

Mass: 317.005771

BATCH SEARCHING

- Singleton searches are useful but what if you need data on LOTS of chemicals at the same time...
- Typical questions
 - What is the list of chemicals for the formula $C_xH_yO_z$
 - Can I get chemical lists in Excel files? In SDF files?
 - Can I include properties in the download file?

REAL-TIME PREDICTIONS

Real-Time Predictions

EPA United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Share Search all data

Atrazine

100%

Select properties to predict

H T.E.S.T.

C

N

O

S

P

F

Cl

Br

I

PT

- ☒ Toxicological properties
 - ☒ 96 hour fathead minnow LC50
 - ☒ 48 hour D. magna LC50
 - ☒ 48 hour T. pyriformis IGC50
 - ☒ Oral rat LD50
 - ☒ Bioaccumulation factor
 - ☒ Developmental toxicity
 - ☒ Ames mutagenicity
 - ☒ Estrogen Receptor RBA
 - ☒ Estrogen Receptor Binding
- ☒ Physical properties
 - ☒ Normal boiling point
 - ☒ Melting point
 - ☒ Flash point
 - ☒ Vapor pressure
 - ☒ Density
 - ☒ Surface tension
 - ☒ Thermal conductivity
 - ☒ Viscosity
 - ☒ Water solubility

Calculate

Chemical structure of Atrazine: CC1=NC2=C(N1)N=CN=C2C(=N1)N(C)CC(C)Cl

Chiral

- Computational toxicology encompasses many types of data streams that are integrated together to address different decision contexts both regulatory and non regulatory
- The EPA CompTox Chemicals Dashboard provides access to data for ~875,000 chemicals that addresses many of these data streams

Acknowledgements



Credit: the Research Triangle Foundation

EPA-RTP

- *An enormous team of contributors from CCTE, especially the IT software development team*
- *Our curation team for their care and focus on data quality*
- *Multiple centers and laboratories across the EPA*
- *Many public domain databases and open data contributors*

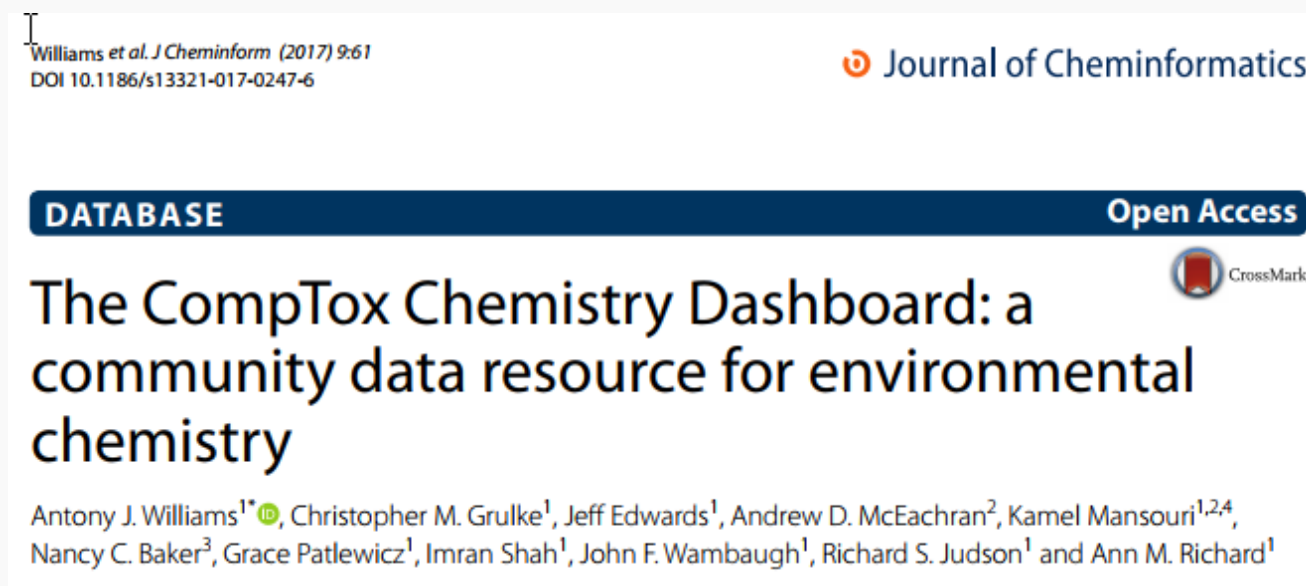
Contact for the CompTox Chemicals Dashboard

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Williams.Antony@epa.gov

ORCID: <https://orcid.org/0000-0002-2668-4821>



<https://doi.org/10.1186/s13321-017-0247-6>