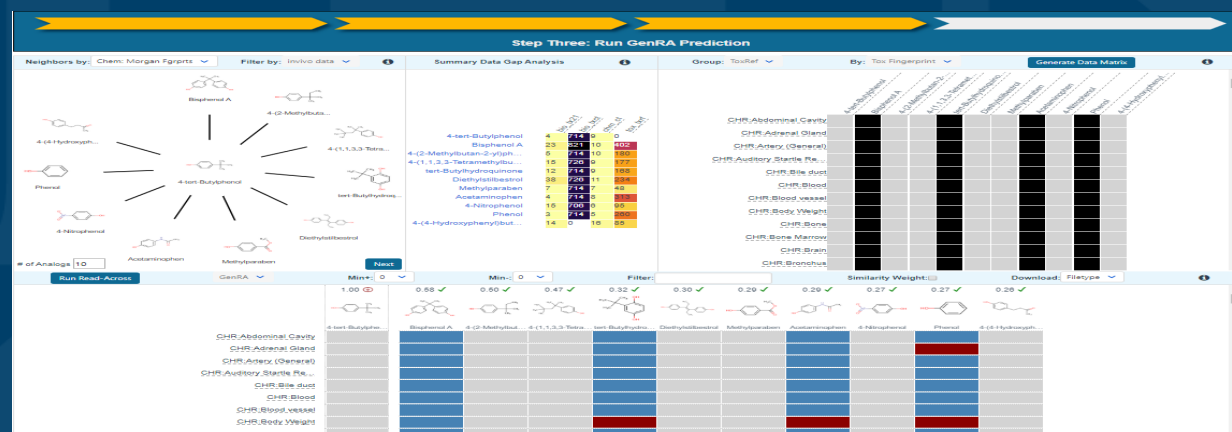



The EPA CompTox Chemicals Dashboard and Generalised read across (GenRA) for chemicals prioritisation and assessment



Grace Patlewicz
National Center for Computational Toxicology (NCCT), US EPA

- Introduction to the EPA CompTox Chemicals Dashboard
- Read-across - existing resources
- Generalised Read-across (GenRA) approach
- GenRA implementation
- Practical application
- Ongoing research to enhance GenRA
- Acknowledgements

The screenshot displays the iCASS Dashboard interface. On the left, the 'Chemicals - 1' panel shows a table with columns for 'Chemical Name', 'CASRN', and 'Chemical Name'. The entry for 'Bisphenol A' (CASRN 80-05-7) is highlighted. Below this, the 'Filters - 0' panel shows a table with columns for 'List', 'Field', and 'Value'. The main 'Assays - 1001' panel shows a table with columns for 'Assay Endpoint Name', 'Assay Component Endpoint Name', and 'Gene Symbol'. The table lists various endpoints for 'ACEA_T40_30hr_Negative' and 'ACEA_T40_30hr_Positive', including 'APR_HepG2_CellCycleArrest_th_dn', 'APR_HepG2_CellCycleArrest_th_up', 'APR_HepG2_CellLoss_th_dn', 'APR_HepG2_CellLoss_th_up', 'APR_HepG2_MitochondriaCSK_th_dn', 'APR_HepG2_MitochondriaCSK_th_up', 'APR_HepG2_MitoLoss_th_dn', 'APR_HepG2_MitoLoss_th_up', 'APR_HepG2_MitoArrest_th_dn', 'APR_HepG2_MitoArrest_th_up', 'APR_HepG2_MitoArrestPaf_th_up', 'APR_HepG2_MitoArrestPaf_th_dn', and 'APR_HepG2_MitoArrestPaf_th_up'. The right panel shows a scatter plot titled 'Chemical Activity Summary' for 'Active endpoints for 80-05-7'. The x-axis is 'AC50 (uM)' on a log scale from 0.001 to 100. The y-axis is 'Scaled Top of the Curve' from 0.0 to 9.7. The plot shows data points for various endpoints, color-coded by biological process: background measurement (green), cell adhesion molecule (blue), cell cycle (orange), cell morphology (yellow), cytokine (red), cell binding (purple), esterase (brown), gpcr (pink), growth factor (light blue), hydrolase (light green), ion channel (dark blue), kinase (dark red), and lysase (dark purple). A legend on the right lists these categories. Below the plot, a note states: 'Scaled response is calculated by dividing the response values by the activity cutoff enabling response comparisons across assay endpoints.'



United States
Environmental Protection
Agency

EDSP21 Dashboard

Endocrine Disruption Screening Program for the 21st Century

[Chemical Summary](#) |
 [Public Information](#) |
 [Bioactivity Summary](#) |
 [Bioactivity](#) |
 [High-Throughput Exposure](#) |
 [Assay Definitions](#) |
 [Discovery](#)

EDSP Dashboard Overview

EDSP Dashboard Overview

Congress requires EPA to ["Develop Disruptor Screening Program"](#) to evaluate chemicals for potential endocrine disruption, and there are thousands of chemicals of interest to the program. EPA researchers developed the Endocrine Disruption Screening Program for the 21st Century Dashboard (EDSP21 Dashboard) to provide access to new chemical data on over 1,800 chemicals of interest.

The purpose of the EDSP21 Dashboard is to help the Endocrine Disruptor Screening Program evaluate chemicals for endocrine-related activity.

The data for this version of the Dashboard comes from various sources -


- Rapid, automated (or in vitro high-throughput) chemical screening data generated by the EPA's Toxicity Forecaster (ToxCast) project and the federal Toxicity Testing in the 21st century (Tox21) collaboration.
- Chemical exposure data and prediction models (EpoCastDB).
- High quality chemical structures and annotations (ChEMBL).
- Physchem Properties Database (PhysChemDB).

ToxCast Data Use Considerations

- The activity of a chemical in a specific assay does not necessarily mean that it will cause toxicity or an adverse health outcome. There are many factors that determine whether a chemical will cause a specific adverse health outcome.
- Careful review is required to determine the use of the data in a particular decision context.
- Interpretation of ToxCast data is expected to change over time as both the science and analytical methods improve.

EPA will continuously add functionality and improve overall usability and performance.

To get the best possible experience using the EDSP Dashboard application we recommend using Mozilla Firefox or Google Chrome.



The CompTox Portal

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

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

EPA CompTox Chemicals Dashboard

- 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: Landing Page



United States
Environmental Protection
Agency

Home Advanced Search Batch Search Lists ▼ Predictions Downloads

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](#)

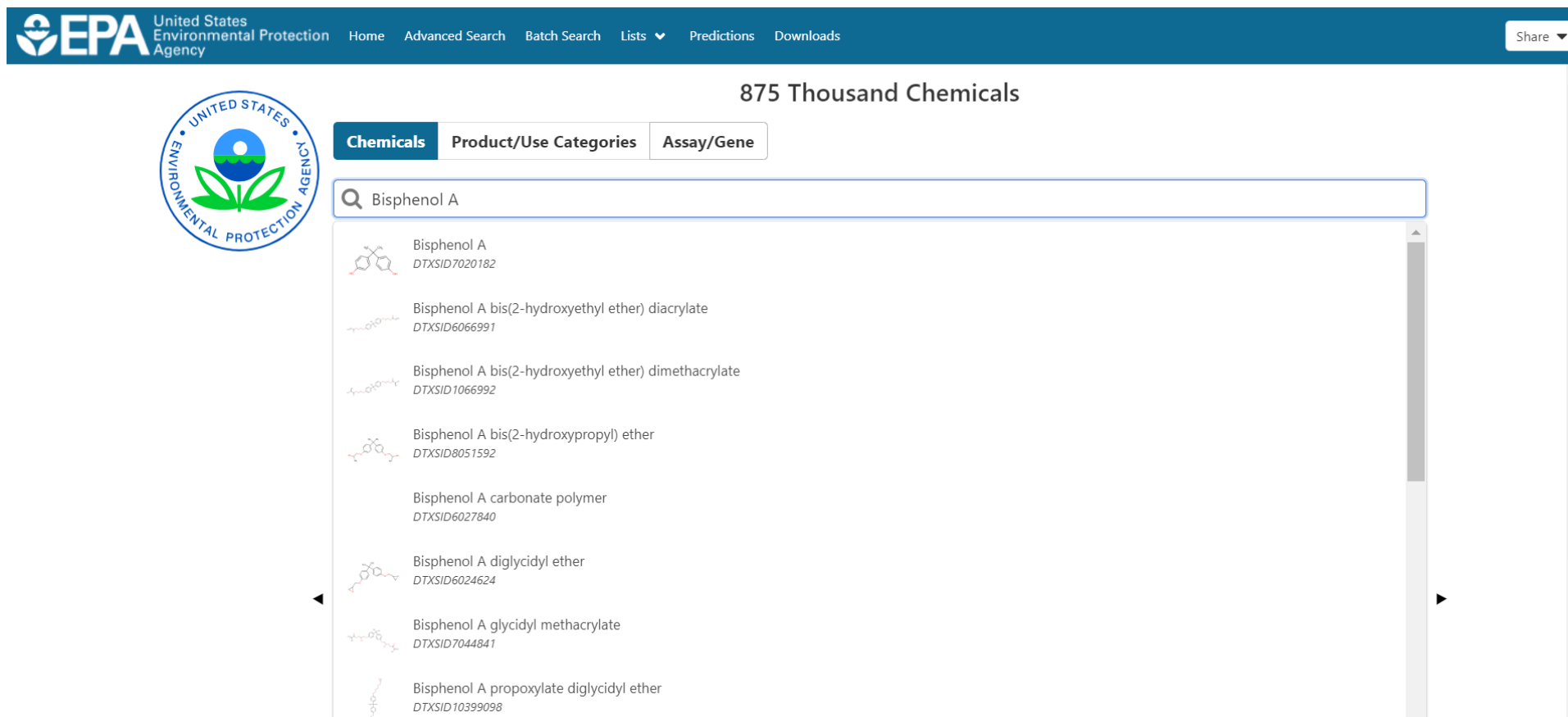
New Article regarding the GenRA module

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: Landing Page


- Different entry points depending on domain of interest



The screenshot shows the EPA CompTox Chemicals Dashboard landing page. The top navigation bar is blue with the EPA logo and text: "United States Environmental Protection Agency", "Home", "Advanced Search", "Batch Search", "Lists", "Predictions", "Downloads", and a "Share" button. Below the navigation bar, the text "875 Thousand Chemicals" is displayed. To the left is the EPA seal. In the center, there are three tabs: "Chemicals" (selected), "Product/Use Categories", and "Assay/Gene". Below the tabs is a search bar containing "Bisphenol A". The search results list several chemical entries, each with a chemical structure icon, the name, and a DTXSID number:

Chemical Name	DTXSID
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: Landing Page for a specific chemical


United States
Environmental Protection
Agency

Home
Advanced Search
Batch Search
Lists
Predictions
Downloads

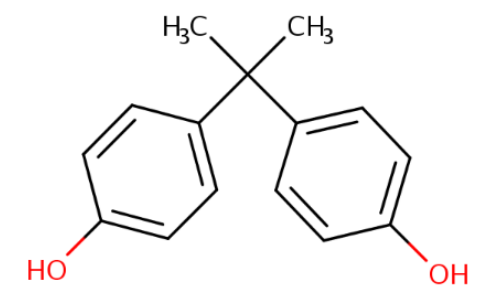
Copy
Share
Submit Comment
Search all data

Bisphenol A

80-05-7 | DTXSID7020182

Searched by DSSTox Substance Id.

DETAILS
EXECUTIVE SUMMARY
PROPERTIES
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

CompTox Chemicals Dashboard: Executive Summary

 United States
Environmental Protection
Agency

HomeAdvanced SearchBatch SearchLists▼PredictionsDownloads

Copy▼Share▼Submit Comment

 Search all data

DETAILS

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

HAZARD

▶ ADME

▶ EXPOSURE

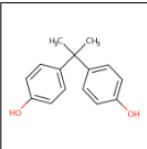
▼ BIOACTIVITY

TOXCAST: SUMMARY

EDSP21

TOXCAST/TOX21

PUBCHEM



Bisphenol A

80-05-7 | DTXSID7020182

Searched by Expert Validated Synonym.

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 [↗](#)

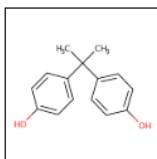
Executive Summary

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

National Center for
Computational Toxicology

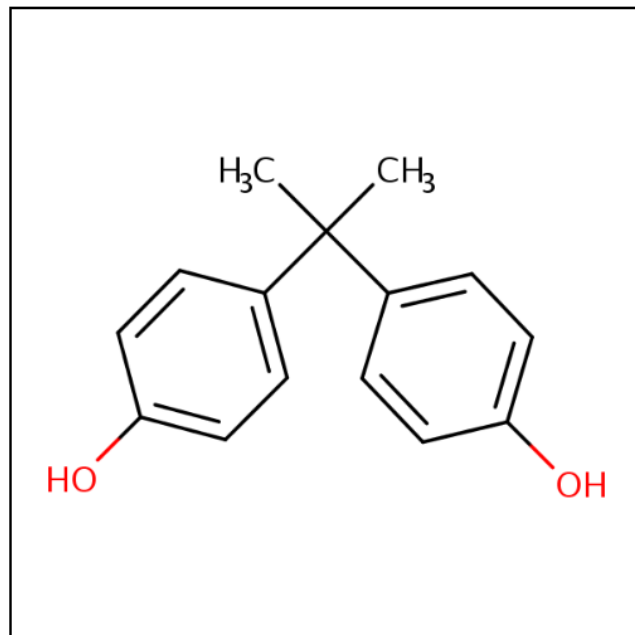
Generalised Read-Across (GenRA) as a workflow module



Bisphenol A

80-05-7 | DTXSID7020182

Searched by DSSTox Substance Id.



DETAILS

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

HAZARD

▶ ADME

▶ EXPOSURE

▶ BIOACTIVITY

SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

SYNONYMS

▶ LITERATURE




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 (0.344 wt % at 83 °C).


BPA is a starting material for the synthesis of plastics, primarily certain polycarbonates

...
[Read more](#)

Intrinsic Properties

 **Molecular Formula:** $\text{C}_{15}\text{H}_{16}\text{O}_2$  Mol File  Find All Chemicals

 **Average Mass:** 228.291 g/mol  Isotope Mass Distribution

 **Monoisotopic Mass:** 228.11503 g/mol



Structural Identifiers

Linked Substances

Presence in Lists

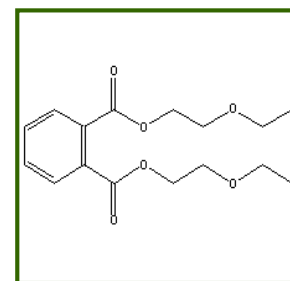
Definitions: Read-across

- 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.

	Source chemical	Target chemical
Property		

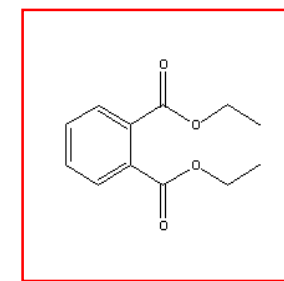
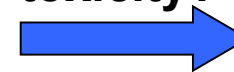
● Reliable data

○ Missing data



**Known to be
harmful**

**Acute
toxicity?**

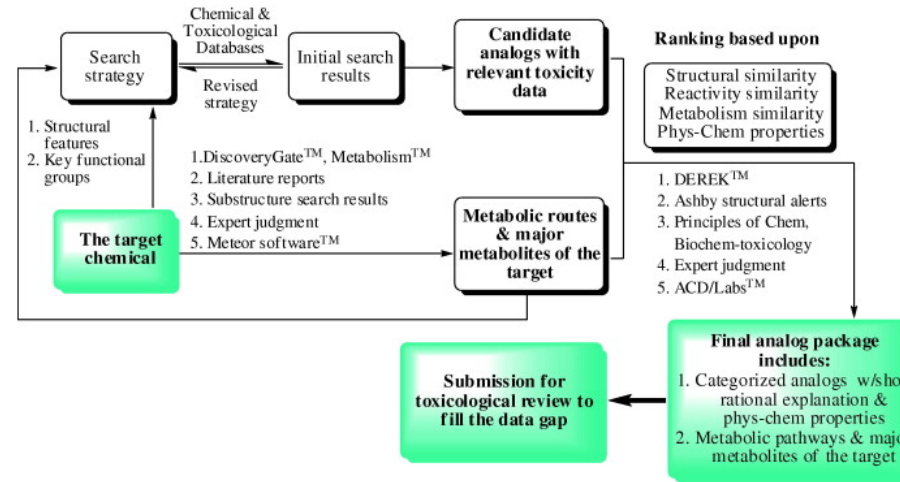
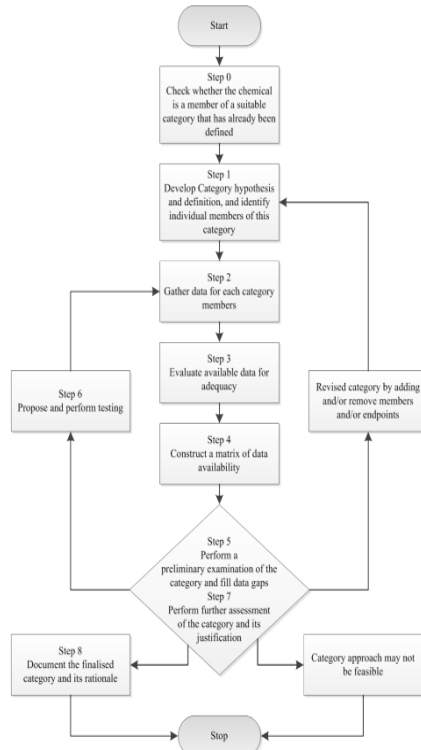


**Predicted to be
harmful**

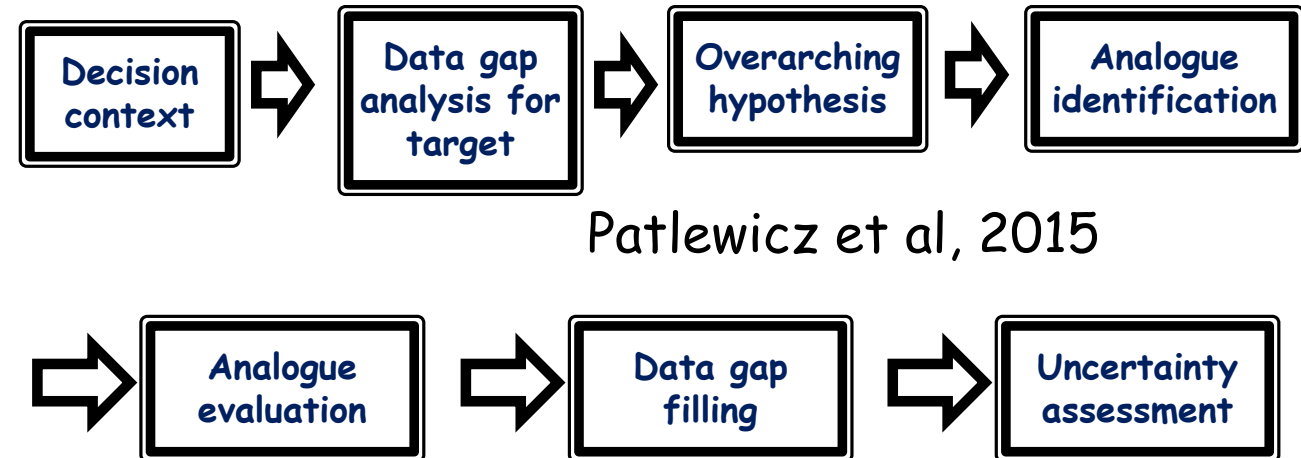
Frameworks for developing category/analogue approaches

OECD (2014)

Figure 3 - Stepwise approach to category development



Wu et al, 2010



Patlewicz et al, 2015

Frameworks for the assessment of read-across

READ ACROSS UNCERTAINTY EVALUATION QUESTIONNAIRE FOR:

Target chemical (SOI) = (list CAS#)

INSTRUCTIONS

Complete the Questionnaire. Answer the questions for each endpoint where SAR was conducted, and follow instructions listed in each section below. (In general, NO responses indicate potential areas of uncertainty in the proposed read across.)

Questions	Responses by Endpoint	
	Repeat Dose Toxicity	Reproductive Toxicity
<u>Section I. Chemical similarity between source (analogue) and target (SOI)</u>		
1. For each endpoint, list the CAS#s of the source (analogues) contributing the critical study for the read across for		
2. What is the 'suitability rating' of the analogue?	CAS#	Suitability of Analog contributing data Are all features of SOI covered or differences in conservative direction
	<input type="checkbox"/> Suit <input type="checkbox"/> Suit (skip to se <input type="checkbox"/> Suit (continue of the inte	
3. Are any differences in functional groups and associ: be more reactive than the target)?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> UNKNOWN <input type="checkbox"/> No Differences	
	<input type="checkbox"/> NO <input type="checkbox"/> UNKNOWN <input type="checkbox"/> No Differences NOTES, if any:	

Blackburn and Stuard (2014)

Table 2

Scientific confidence considerations in Read-across evaluation.

Data issues	Similarity rationale
Analogue/category approach	Similarity rationale/hypothesis that underpins the analogue/category approach <ul style="list-style-type: none"> - Metabolic transformation - Structural similarity
Completeness of data matrix – No of data gaps e.g. source analogue(s) have many data points to address, target substance has a handful of data gaps.	Analogue validity <ul style="list-style-type: none"> - Analogue similarity with respect to general and endpoint specific considerations - Rationalization of why structural differences do not impact the toxicity
Quality of data for source analogues – e.g. Klimisch scores of 1 or 2	Concordance of effects and potency (if relevant) per endpoint <ul style="list-style-type: none"> • Presence or absence of adverse effects • Type of read-across (Qualitative, Quantitative, Trend Analysis) Concordance of effects and potency (if relevant) across endpoints

Patlewicz et al (2015)

Read-across resources: Selected read-across tools

Computational Toxicology 3 (2017) 1–18



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Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox



Navigating through the minefield of read-across tools: A review of in silico tools for grouping



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

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

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

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Read-across

(Q)SAR

Trend analysis

Nearest neighbor

ABSTRACT

Read-across is a popular data gap filling technique used within analogue and category approaches for regulatory purposes. In recent years there have been many efforts focused on the challenges involved in read-across development, its scientific justification and documentation. Tools have also been developed to facilitate read-across development and application. Here, we describe a number of publicly available read-across tools in the context of the category/analogue workflow and review their respective capabilities, strengths and weaknesses. No single tool addresses all aspects of the workflow. We highlight how the different tools complement each other and some of the opportunities for their further development to address the continued evolution of read-across.

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Read-across resources: Selected read-across frameworks



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journal homepage: www.elsevier.com

Journal
Cover
Image

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

^c Oak Ridge Institute for Science and Education (ORISE), 1299 Bethel Valley Road, Oak Ridge, TN 37830, USA

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

Read-across resources:

Selected read-across examples/decision contexts

Regulatory Toxicology and Pharmacology 106 (2019) 197–209



ELSEVIER

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



Exploring current read-across applications and needs among selected U.S. Federal Agencies

Grace Patlewicz^{a,*}, Lucina E. Lizarraga^b, Diego Rua^c, David G. Allen^d, Amber B. Daniel^d, Suzanne C. Fitzpatrick^e, Natàlia Garcia-Reyero^f, John Gordon^g, Pertti Hakkinen^h, Angela S. Howard^d, Agnes Karmaus^d, Joanna Matheson^g, Moiz Mumtazⁱ, Andrea-Nicole Richarz^j, Patricia Ruiz^l, Louis Scarano^k, Takashi Yamada^l, Nicole Kleinstreuer^m

^aNational Center for Computational Toxicology, U.S. Environmental Protection Agency, 109 TW Alexander Dr, Research Triangle Park, NC, 27709, USA

^bNational Center for Environmental Assessment, U.S. Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH, 45268, USA

^cCenter for Devices and Radiological Health, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD, 20993, USA

^dILS, P.O. Box 13501, Research Triangle Park, NC, 27709, USA

^eCenter for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD, 20740, USA

^fEnvironmental Laboratory, U.S. Army Engineer Research and Development Center, 3909 Halls Ferry Rd., Vicksburg, MS, 39180, USA

^gU.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD, 20850, USA

^hNational Library of Medicine, 6707 Democracy Blvd., Bethesda, MD, 20892, USA

ⁱAgency for Toxic Substances and Disease Registry, 1600 Clifton Rd., Chamblee, GA, 30341, USA

^jEuropean Commission, Joint Research Centre (JRC), Ispra, Italy

^kOffice of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC, 20460, USA

^lDivision of Risk Assessment, Biological Safety Research Center, National Institute of Health Sciences, 3-25-26, Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa, 210-9501, Japan

^mNational Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709, USA

More than just a 'REACH' regulatory context ICCVAM Read-Across Workgroup



Regulatory Toxicology and Pharmacology 106 (2019) 278–291



ELSEVIER

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



Predicting estrogen receptor activation by a group of substituted phenols: An integrated approach to testing and assessment case study

Francina Webster^{*}, Matthew Gagné, Grace Patlewicz, Prachi Pradeep, Nicholas Trefiak, Richard S. Judson, Tara S. Barton-Maclaren



ARTICLE INFO

Keywords:

New approach methodology (NAM)
Integrated approach for testing and assessment (IATA)
Read-across
4-Tert-butylphenol
2,4-Di-tert-butylphenol
Octabenzene
Endocrine disruption
Estrogen
Administered equivalent dose (AED)
Bioactivity exposure ratio (BER)

ABSTRACT

Traditional approaches for chemical risk assessment cannot keep pace with the number of substances requiring assessment. Thus, in a global effort to expedite and modernize chemical risk assessment, New Approach Methodologies (NAMs) are being explored and developed. Included in this effort is the OECD Integrated Approaches for Testing and Assessment (IATA) program, which provides a forum for OECD member countries to develop and present case studies illustrating the application of NAM in various risk assessment contexts. Here, we present an IATA case study for the prediction of estrogenic potential of three target phenols: 4-tert-butylphenol, 2,4-di-tert-butylphenol and octabenzene. Key features of this IATA include the use of two computational approaches for analogue selection for read-across, data collected from traditional and NAM sources, and a workflow to generate predictions regarding the targets' ability to bind the estrogen receptor (ER). Endocrine disruption can occur when a chemical substance mimics the activity of natural estrogen by binding to the ER and, if potency and exposure are sufficient, alters the function of the endocrine system to cause adverse effects. The data indicated that of the three target substances that were considered herein, 4-tert-butylphenol is a potential endocrine disruptor. Further, this IATA illustrates that the NAM approach explored is health protective when compared to *in vivo* endpoints traditionally used for human health risk assessment.

A harmonised hybrid read-across workflow

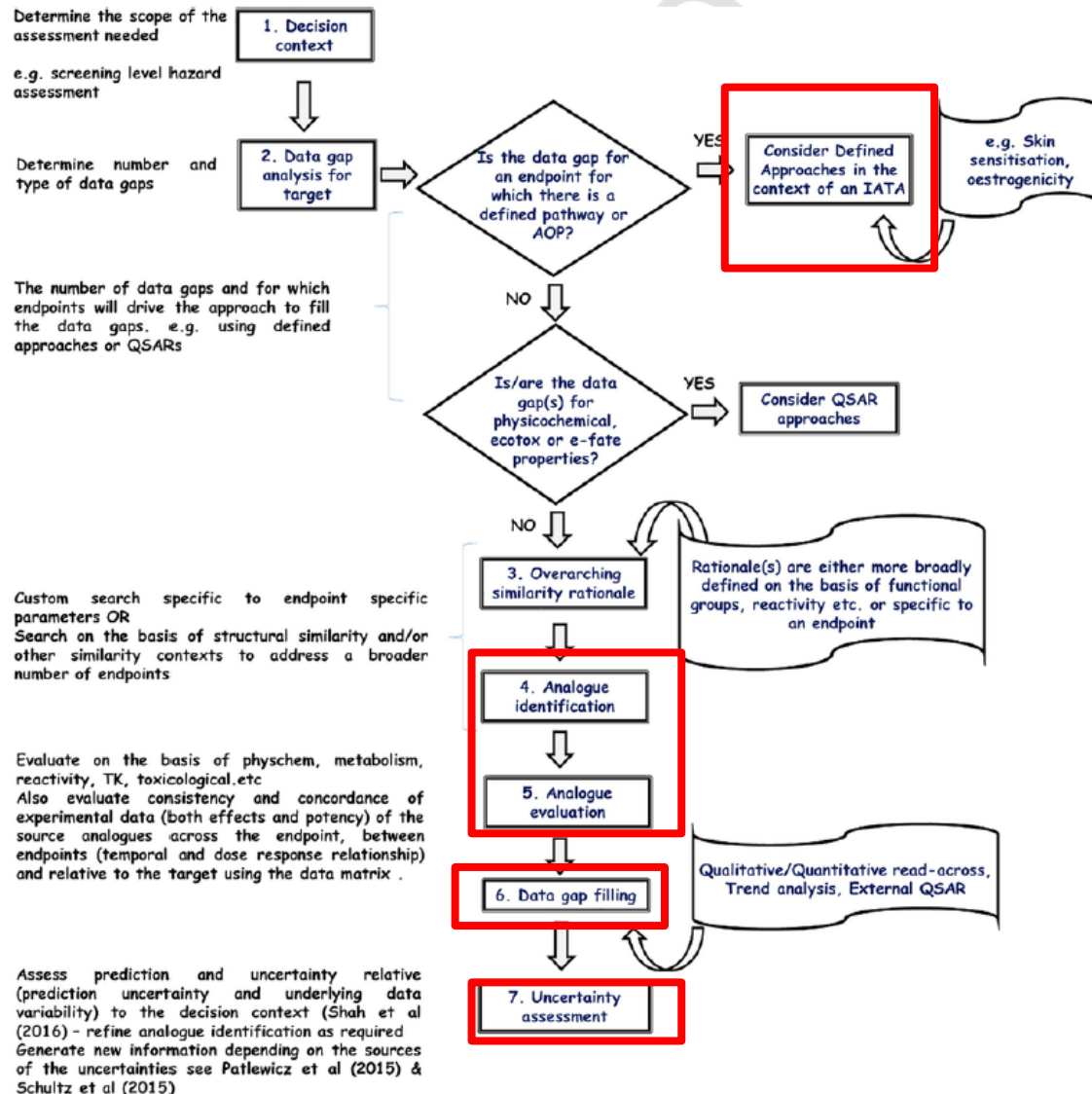


Fig. 9. A harmonised hybrid development and assessment framework.

- Where do other NAM fit?
- How should we transition to data-driven approaches? Limit subjectivity
- What about characterising the uncertainty of the predictions made?
- Generalisability/Scalability of read-across - coverage of read-across for inventories of chemicals?

Patlewicz et al., 2018

Selected read-across tools

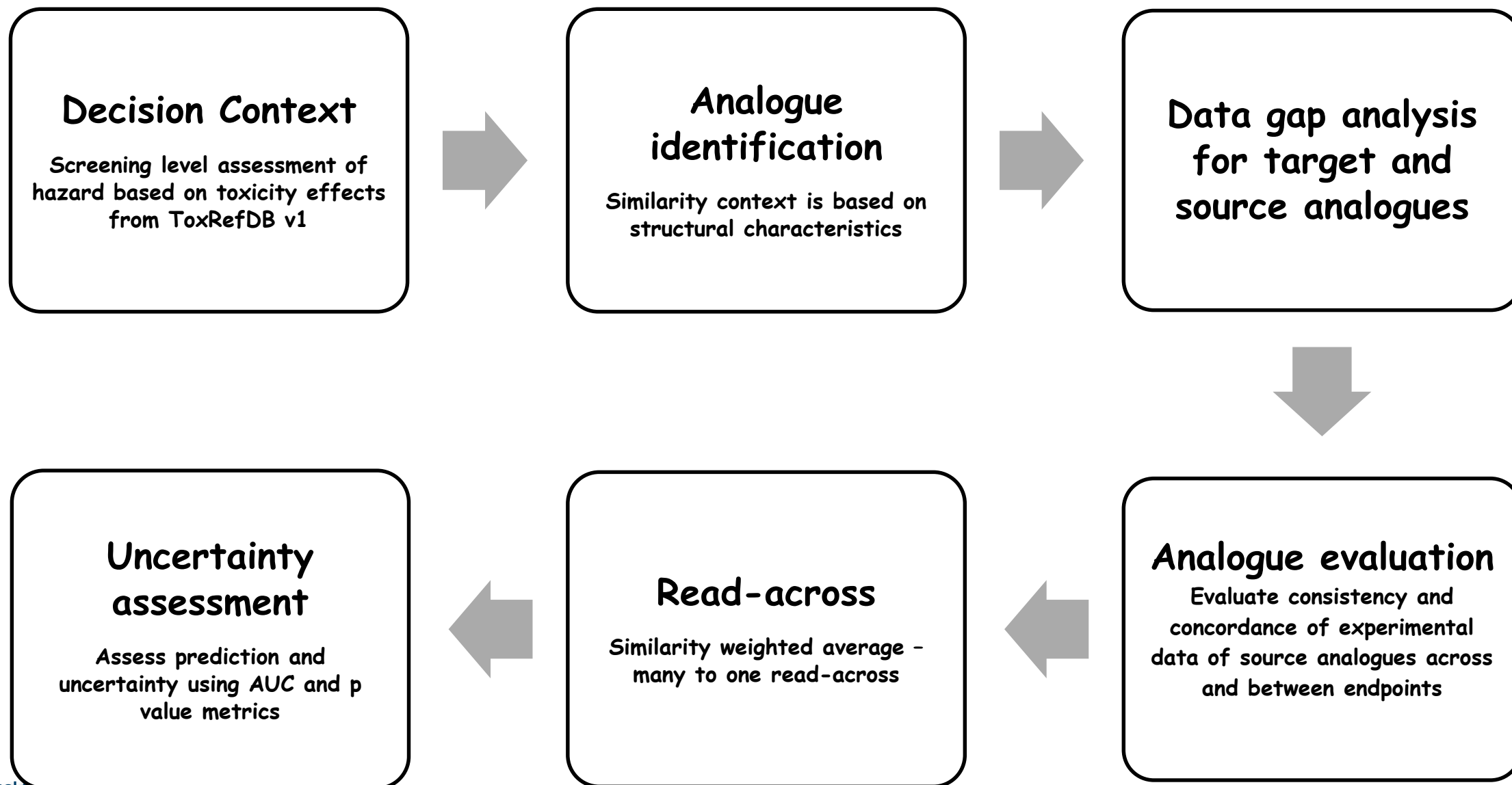
Tool	AIM	ToxMatch	AMBIT	OECD Toolbox	CBRA	ToxRead	GenRA
Analogue identification	X	X	X	X	X	X	X
Analogue Evaluation	NA	X	X by other tools availabl e	X	X	X For Ames & BCF	NA
Data gap analysis	NA	X	X Data matrix can be exporte d	X Data matrix viewable	NA	NA	X Data matrix can be exported
Data gap filling	NA	X	User driven	X	X	X	X
Uncertainty assessment	NA	NA	NA	X	NA	NA	X
Availability	Free	Free	Free	Free	Free	Free	Free

GenRA

- **GenRA (Generalised Read-Across)**
- Predicting toxicity as a similarity-weighted activity of nearest neighbours based on chemistry and bioactivity descriptors
- Systematically evaluates read-across performance and uncertainty using available data

Jaccard similarity:

Read-across workflow in GenRA



GenRA tool in practice

Fluconazole

86386-73-4 | DTXSID3020627

Searched by DSSTox Substance Id.

DETAILS

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

HAZARD

ADME

► EXPOSURE

► BIOACTIVITY

SIMILAR COMPOUNDS

GENRA

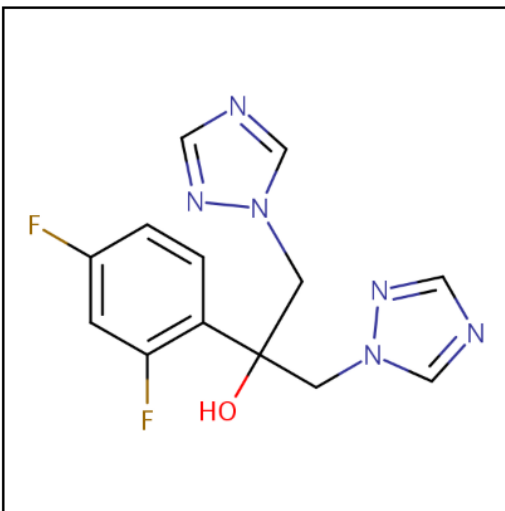
RELATED SUBSTANCES

SYNONYMS

► LITERATURE

LINKS

COMMENTS



Wikipedia

Fluconazole is an antifungal medication used for a number of fungal infections. This includes candidiasis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, dermatophytosis, and pityriasis versicolor. It is also used to prevent candidiasis in those who are at high risk such as following organ transplantation, low birth weight babies, and those with low blood neutrophil counts. It is given either by mouth or by injection into a vein.

Common side effects include vomiting

...
[Read more](#)

Intrinsic Properties

Molecular Formula: C₁₃H₁₂F₂N₆O Mol File

Average Mass: 306.277 g/mol Isotope Mass Distribution

Monoisotopic Mass: 306.104065 g/mol

Find All Chemicals

Structural Identifiers

Linked Substances

Presence in Lists

Record Information

Quality Control Notes

GenRA tool in practice

DETAILS

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

HAZARD

ADME

EXPOSURE

BIOACTIVITY

SIMILAR COMPOUNDS

GENRA

RELATED SUBSTANCES

SYNONYMS

LITERATURE

LINKS

COMMENTS

Fluconazole

86386-73-4 | DTXSID3020627

Searched by DSSTox Substance Id.

Neighbors by: Chem: Morgan Fgrprts

Filter by: invivo data

Similarity context

of Analogs 10

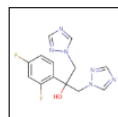
Next

Step One: Analog Identification and Evaluation

Summary Data Table

Chemical	Similarity	Weight	Score
Fluconazole	1.0	1.0	1.0
Bromuconazole	0.9	0.9	0.9
Flusilazole	0.8	0.8	0.8
Cyproconazole	0.7	0.7	0.7
Pyrasulfotole m...	0.6	0.6	0.6
Myclobutanil	0.5	0.5	0.5
Fenbuconazole	0.4	0.4	0.4
Tetraconazole	0.3	0.3	0.3
Metconazole	0.2	0.2	0.2
Ipoconazole	0.1	0.1	0.1

GenRA tool in practice



Fluconazole

86386-73-4 | DTXSID3020627

Searched by DSSTox Substance Id.

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GENRA (BETA)

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SYNONYMS

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COMMENTS

Generalized Read-Across (GenRA)

Step Two: Data Gap Analysis & Generate Data Matrix

Neighbors by: Chem: Morgan Fgprts

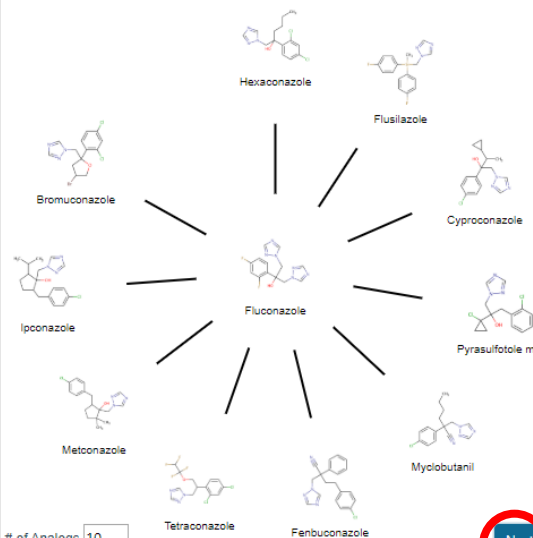
Filter by: invivo data

Summary Data Gap Analysis

Group: ToxRef

By: Tox Fingerprint

Generate Data Matrix



	bio h21	bio h22	ctm ct	tox ref
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
Ipcanazole	46	232	16	180
Bromuconazole	24	277	13	345

	Fluconazole	Hexaconazole	Flusilazole	Cyproconazole	Pyrasulfotole metabolite	Myclobutanil	Fenbuconazole	Tetraconazole	Metconazole	Ipcanazole	Bromuconazole
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:Bronchus											

Next

Data gap analysis

GenRA tool in practice

EPA United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Copy Share Submit Comment Search all data

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

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Generalized Read-Across (GenRA)

Step Two: Data Gap Analysis & Generate Data Matrix

Neighbors by: Chem: Morgan Fgprpts Filter by: In vivo data Summary Data Gap Analysis Group: ToxRef By: Tox Fingerprint Generate Data Matrix

of Analogs: 10

Fluconazole

Hexaconazole
Flusilazole
Cyproconazole
Pyrausufotile m...
Myclobutani
Fenbuconazole
Tetraconazole
Metconazole
Iaconazole
Bromuconazole

	bio_1act1	bio_1act2	bio_1act3	bio_1act4	bio_1act5
Fluconazole	3	714	15	0	
Hexaconazole	43	819	18	345	
Flusilazole	28	819	9	345	
Cyproconazole	14	819	18	408	
Pyrausufotile metabolite...	0	0	18	234	
Myclobutani	15	818	15	345	
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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:Bronchus

Source Analogues

Run Read-Across GenRA Min+: 0 Similarity Weight: Download: Filetype

1.00 0.39 0.31 0.29 0.29 0.26 0.24 0.22 0.21 0.21 0.20

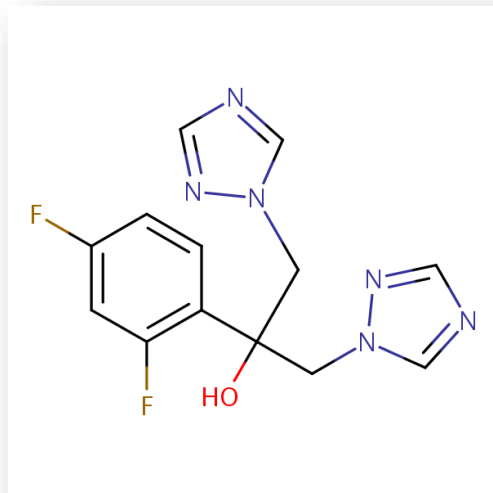
Target

Fluconazole Hexaconazole Flusilazole Cyproconazole Pyrausufotile m... Myclobutani Fenbuconazole Tetraconazole Metconazole Iaconazole Bromuconazole

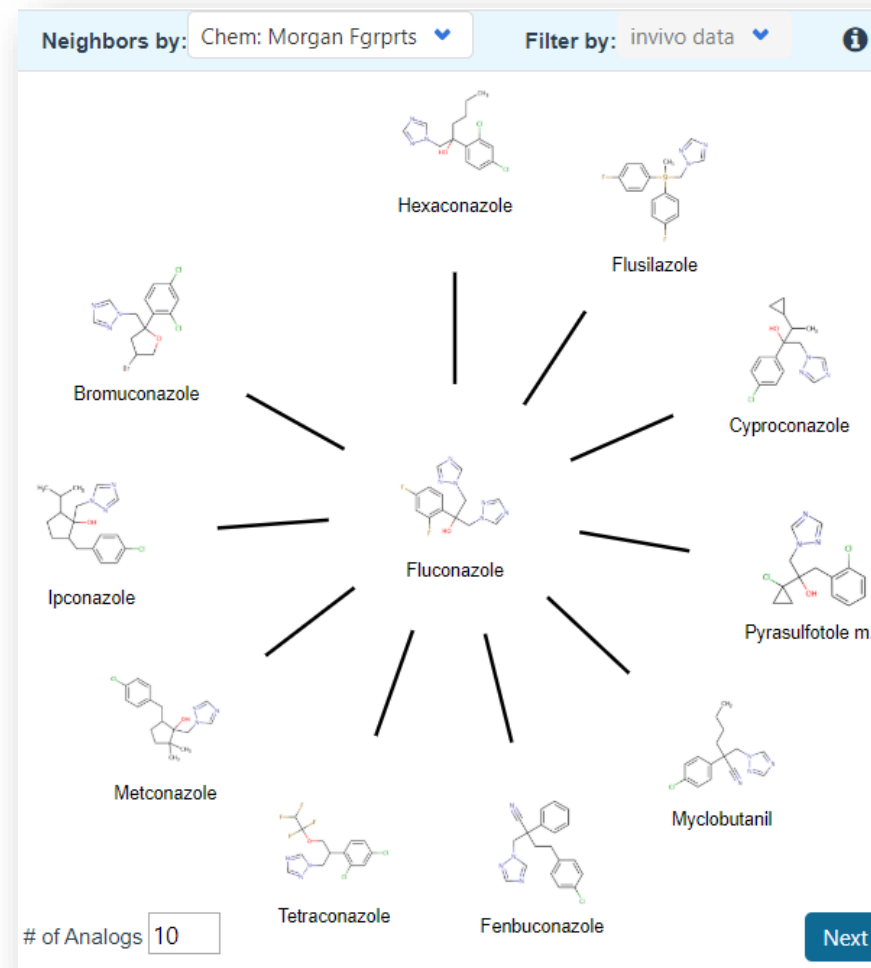
CHR:Abdominal Cavity
CHR:Adrenal Gland
CHR:Artery (General)
CHR:Auditory Startle Re...
CHR:Bile duct
CHR:Blood
CHR:Blood vessel
CHR:Body Weight
CHR:Bone

Run GenRA

GenRA in practice - step by step

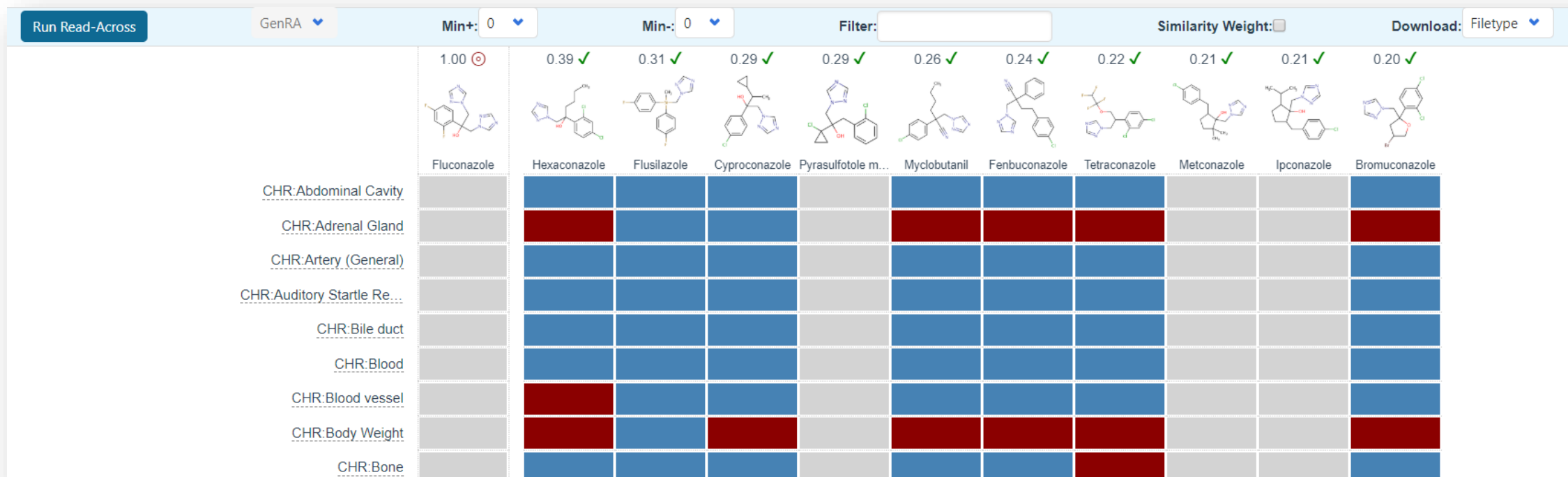


- Analogue identification:
- Similarity based on Morgan chemical fingerprints and selecting a default of 10 source analogues



GenRA in practice - step by step

- Data matrix view of source analogues relative to target chemical



GenRA in practice - step by step

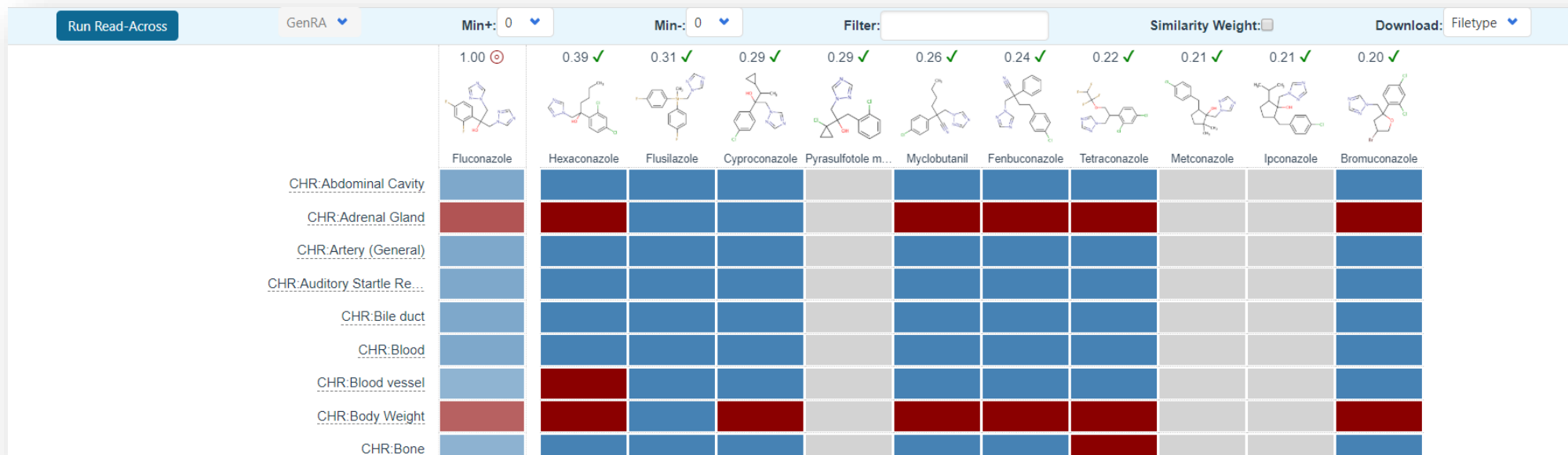


Look for
commonality in
profile across
target effects

What are the
most common
effects across
analogues

GenRA in practice - step by step

- Updated Data matrix view with GenRA predictions for target chemical



- Predictions are binary (yes/no) for toxicity effects within ToxRefDB v1 studies.
- Predictions summarised on a study level basis. Red: "positive" and Blue: "negative".

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 Patlewicz^{2}*

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, Research Triangle Park (RTP), NC, USA

Abstract

Generalized Read-Across (GenRA) is a data driven approach which makes read-across predictions on the basis of a similarity weighted activity of source analogues (nearest neighbors). GenRA has been described in more detail in the literature (Shah et al., 2016; Helman et al., 2018). Here we present its implementation within the EPA's CompTox Chemicals Dashboard to provide public access to a GenRA module structured as a read-across workflow. GenRA assists researchers in identifying source analogues, evaluating their validity and making predictions of *in vivo* toxicity effects for a target substance. Predictions are presented as binary outcomes reflecting presence or absence of toxicity together with quantitative measures of uncertainty. The approach allows users to identify analogues in different ways, quickly assess the availability of relevant *in vivo* data for those analogues and visualize these in a data matrix to evaluate the consistency and concordance of the available experimental data for those analogues before making a GenRA prediction. Predictions can be exported into a tab-separated value (TSV) or Excel file for additional review and analysis (e.g., doses of analogues associated with production of toxic effects). GenRA offers a new capability of making reproducible read-across predictions in an easy-to-use-interface.

GenRA – Ongoing research

- Summarising and aggregating the toxicity effect predictions to guide end users
- Consideration of other information to define and refine the analogue selection – e.g. physicochemical similarity, metabolic similarity, reactivity similarity...
- EPA New Chemical Categories
- Quantifying the impact of physicochemical similarity on read-across performance
- Quantifying the impact of reactivity similarity on read-across performance

GenRA - Ongoing research

- Dose response information to refine scope of prediction beyond binary outcomes
- Transitioning from qualitative to quantitative predictions - how to apply and interpret GenRA in screening level hazard assessment (e.g. effect level or point-departure [NOAEL, LOAEL, etc.] predictions)
- Using quantitative data from acute rat oral toxicity, ToxRefDB v2 [1 manuscript submitted, 1 in internal clearance]

Take home messages

- Harmonised framework for read-across provides opportunities for expanded integration of NAM data
- GenRA developed is aligned with this framework
- Initial GenRA (baseline) considers structural similarity but current work has evaluated the quantitative impact of physicochemical similarity (as it relates to bioavailability) and transitioned to quantitative predictions of effect levels or PODs
- Illustrated how GenRA baseline can be applied in practice

Acknowledgements

- Many but in particular..

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- Jason Lambert

- NCEA

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