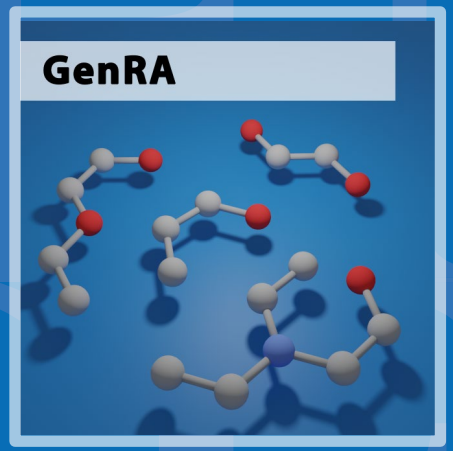
EPA United States Environmental Protection Agency

EPA Center for Computational Toxicology and Exposure (CCTE)

Generalized Read-Across (GenRA) Virtual Training



Grace Patlewicz, U.S. EPA CCTE

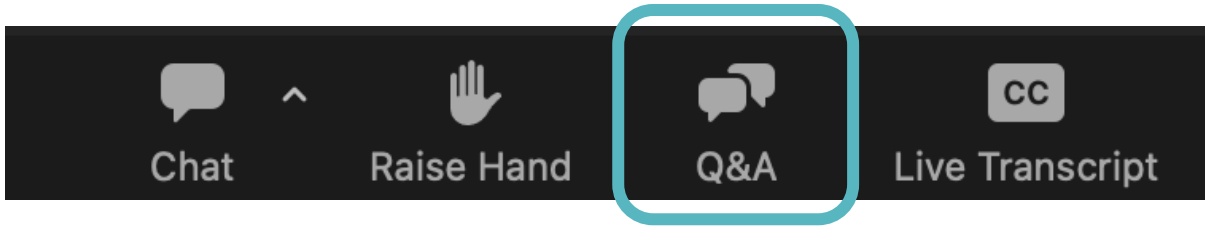
Meeting Logistics

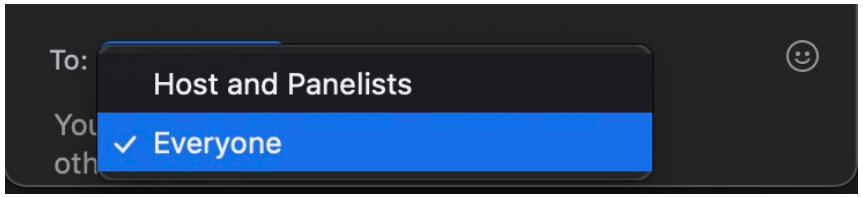
If you have a question for the presenters, use the Zoom Q&A feature.

If you prefer to call in by phone, please refer to the Meeting Invite to obtain the phone number and passcode.

Please update your Zoom name to your first and last name.

This webinar will be recorded and posted to the CCTE NAMs Training website.





EPA NAMs Pilot Training Program

- New Approach Methodologies (NAMs) Training Program is a deliverable in the Agency's Work Plan, first released in 2019 and updated in 2021.
  - Previous trainings include ECOTOX, CompTox Chemicals Dashboard
- Goal: Develop, implement and maintain an engaging training program.
  - Interactive case studies to encourage active learning
  - Train the trainer
  - Obtain feedback
- More trainings are being planned
- The EPA NAMs training website includes existing training resources, including recordings and guidance documents.

EPA NAMs Training: www.epa.gov/chemical-research/new-approach-methods-nams-training

AGENDA

- Welcome and Introductions
- Background of GenRA
- Functionalities and Features of GenRA
- A Walk Through Example
- Summary
- Breakout Session
  - A walk through with a data poor chemical
  - Practical applications of GenRA
  - Read-across predictions and interpretations
- Debrief Session

Conflict of Interest Statement

- No conflicts of interest to declare.

- Disclaimer:

The views expressed herein are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

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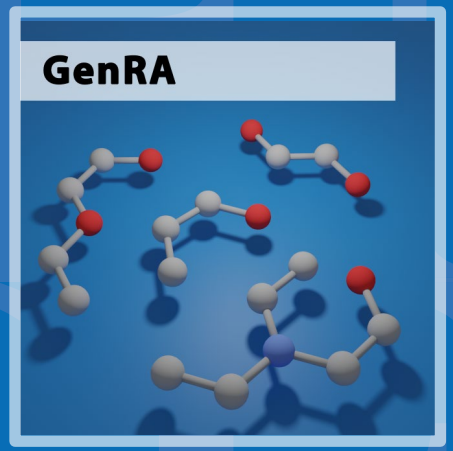

Grace Patlewicz, U.S. EPA CCTE

GenRA Project Team

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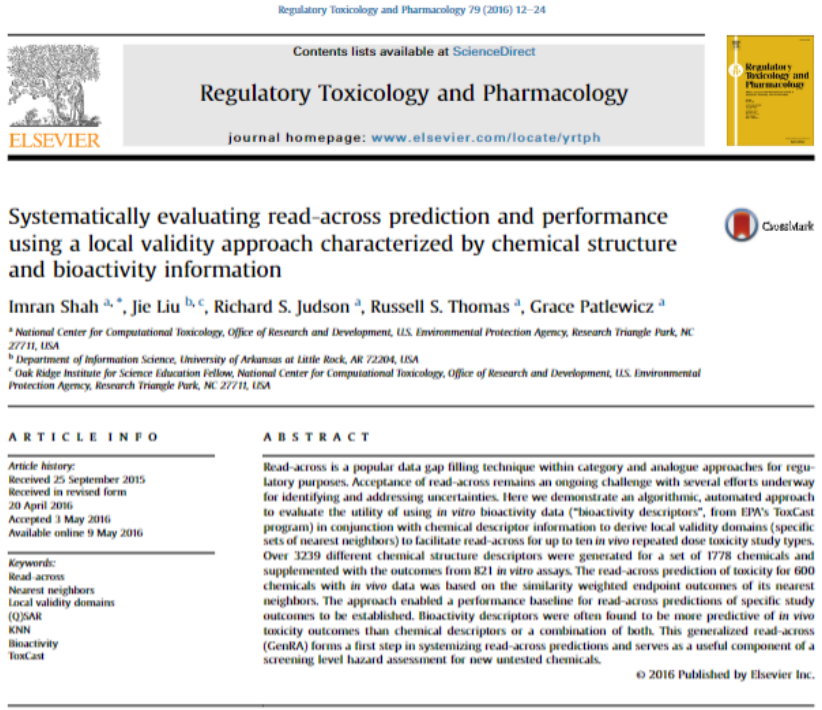
Generalized Read-Across (GenRA)

- Predicting toxicity as a similarity-weighted activity of nearest neighbors based on chemistry and bioactivity descriptors (Shah et al, 2016)
- **Goal:** To establish an objective performance baseline for read-across and quantify the uncertainty in the predictions made



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

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

Imran Shah [a, *], Jie Liu [b, c], Richard S. Judson [a], Russell S. Thomas [a], Grace Patlewicz [a]

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ABSTRACT

Read-across is a popular data gap filling technique within category and analogue approaches for regulatory purposes. Acceptance of read-across remains an ongoing challenge with several efforts underway for identifying and addressing uncertainties. Here we demonstrate an algorithmic, automated approach to evaluate the utility of using *in vitro* bioactivity data ("bioactivity descriptors", from EPA's ToxCast program) in conjunction with chemical descriptor information to derive local validity domains (specific sets of nearest neighbors) to facilitate read-across for up to ten *in vivo* repeated dose toxicity study types. Over 3239 different chemical structure descriptors were generated for a set of 1778 chemicals and supplemented with the outcomes from 821 *in vitro* assays. The read-across prediction of toxicity for 600 chemicals with *in vivo* data was based on the similarity weighted endpoint outcomes of its nearest neighbors. The approach enabled a performance baseline for read-across predictions of specific study outcomes to be established. Bioactivity descriptors were often found to be more predictive of *in vivo* toxicity outcomes than chemical descriptors or a combination of both. This generalized read-across (GenRA) forms a first step in systemizing read-across predictions and serves as a useful component of a screening level hazard assessment for new untested chemicals.

$$y_i^{\beta,\alpha} = \frac{\sum_j^k s_{ij}^{\alpha} x_j^{\beta}}{\sum_j^k s_{ij}^{\alpha}}$$

Jaccard similarity:

$$s_{ij} = \frac{\sum_l (x_{il} \wedge x_{jl})}{\sum_l (x_{il} \vee x_{jl})}$$

$\alpha \equiv \{chm, bio, bc\}$

$\beta \equiv \{bio, tox\}$

y_i = *predicted activity of chemical* (c_i)

x_j^{β} = *activity of* c_j in β

s_{ij}^{α} = *Jacccard similarity between* $\boldsymbol{x}_i^{\alpha}, \boldsymbol{x}_j^{\alpha}$

k = *up to* k *nearest neighbours*

Read-Across Tools

Computational Toxicology 3 (2017) 1–18

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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]

(Patlewicz et al., 2017)

Table 1
Summary of key features of selected publicly available read-across tools.

	AIM	ToxMatch	Ambit	OECD Toolbox	CBRA	ToxRead	CIIPro
Development timeline	Java based version is dated 2012. Initial development of web version was 2005.	First public version released in Dec 2006	Original AMBIT tool was developed in 2004–2005	Proof of concept released in 2008	Implementation of the Low et al. [27]	Implementation of Gini et al. [22]	Implementation described in Russo et al. [45]
Type of Tool	Standalone	Standalone	Web-based and standalone	Standalone or Client/Server	Standalone	Standalone	Web-based
Latest Version	1.01 (Nov 2013) Static	1.07 (Jan 2009) Static	3.0.3 Ongoing Enhanced in 2013–2015	3.4 (July 2016) Version 4 released April 2017 Ongoing	0.75 First release	0.11 BETA Ongoing	First release
Developed by	SRC Inc	Ideaconsult Ltd	Ideaconsult Ltd	LMC, Bourgas	Fourches Lab at North Carolina State University	Istituto di Ricerche Farmacologiche Mario Negri	Zhu Research Group at Rutgers University
Available from	https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool	https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/toxmatch	http://cefic-lri.org/lri_toolbox/ambit/	www.qsartoolbox.org	http://www.fourches-laboratory.com/software	http://www.toxread.eu/	http://ciipro.rutgers.edu/
Accepted Chemical Input	CAS, Name, SMILES, structure drawing/import	CAS, Name, SMILES, InChI	Name, identifiers, SMILES, InChI	CAS, Name, SMILES, structure drawing, MOL, sdf	Mol file, descriptors as txt	SMILES	PubChem CID, CAS, IUPAC, SMILES, InChI
Endpoint Coverage	N/A	Any based on user input	IUCLID[a] 5-supported endpoints (43 total)	Any as per the regulatory endpoints	Any based on user input	Mutagenicity and Bioconcentration Factor (BCF)	Any based on user input
Analogue Identification Approach	Fragment matching	Distance and correlation based similarity indices based on descriptors or fingerprints	Substructure or similarity searching using structure, name, SMILES, InChI	Category definition followed by subcategorisations	Tanimoto distance using chemical and biological descriptors	VEGA similarity algorithm	Weighted Estimated Biological Similarity
Neighbour Selection	Automatic	Automatic	Manual	Automatic + Manual Filter	Automatic	Automatic	Automatic + Manual Filter
Data Source	Tool provides inventory index	User provided or tool provided	User and tool provided	User provided or tool provided	User provided	Tool provided as a result of the EU ANTARES project	User provided but tool provides PubChem *in vitro* data
Quantitative vs Qualitative	N/A	Both	User determined - Qualitative	Both	Qualitative	Qualitative for mutagenicity, quantitative for BCF	Qualitative
Visualisation	None	Standard 2D plots, histograms and similarity matrix	None	Standard 2D Plots	Radial plot of neighbours	Interactive Neighbour plot	Activity Plot
Output/Export	Output reports in the form of HTML, pdf or Excel	sdf or txt files of data, image files of plots	Assessment report as docx or xlsx, data matrix as xlsx	IUCLID format, pdf and rtf files of prediction report, text files of data, image files of plots etc	NA	Image file of plot	Tabulation of predictions and image of similarity plot

[a] IUCLID stands for International Uniform Chemical Information Database. IUCLID is a software program for the administration of data on chemical substances first developed to fulfill EU information requirements under REACH.

GenRA – Overall goal

Quantify the contribution that different similarity contexts play in toxicity prediction and how that differs depending on the toxicity endpoint of interest, the chemical of interest and whether it mirrors expert driven read-across

Quantify level of confidence for prediction made

=> objective, reproducible read-across assessments

GenRA Summary

- **Read-across** is a commonly used technique to fill data gaps.
- **Read-across** is an expert-driven approach which is challenging from a reproducibility and scalability perspective.
- **GenRA** is an algorithmic approach to permit objective and reproducible read-across predictions.
  - Presents opportunities for how NAM data can be incorporated.
- **GenRA v1.0 (2018)** established a baseline in performance.
  - The approach relied on chemical descriptors to predict binary toxicity values. Our ongoing research programme aims to characterize other contexts of similarity (e.g., mechanistic, reactivity, and metabolism) and quantify their contribution in predicting toxicity outcomes.
- Subsequent versions through to the current Version 3.2 have added a number of significant new features whilst addressing bug fixes.

GenRA Milestones

Released September 2018
- Integrated into the EPA CompTox Chemicals Dashboard (CCD)

Released March 2021
- A python package (genra-py) to facilitate batch processing using user specific datasets.

Released December 2021
- A standalone web app linked to the CCD

Released February 2022
- UI rebuilt using AG Grid
- Custom fingerprints
- Ketcher drawing palette

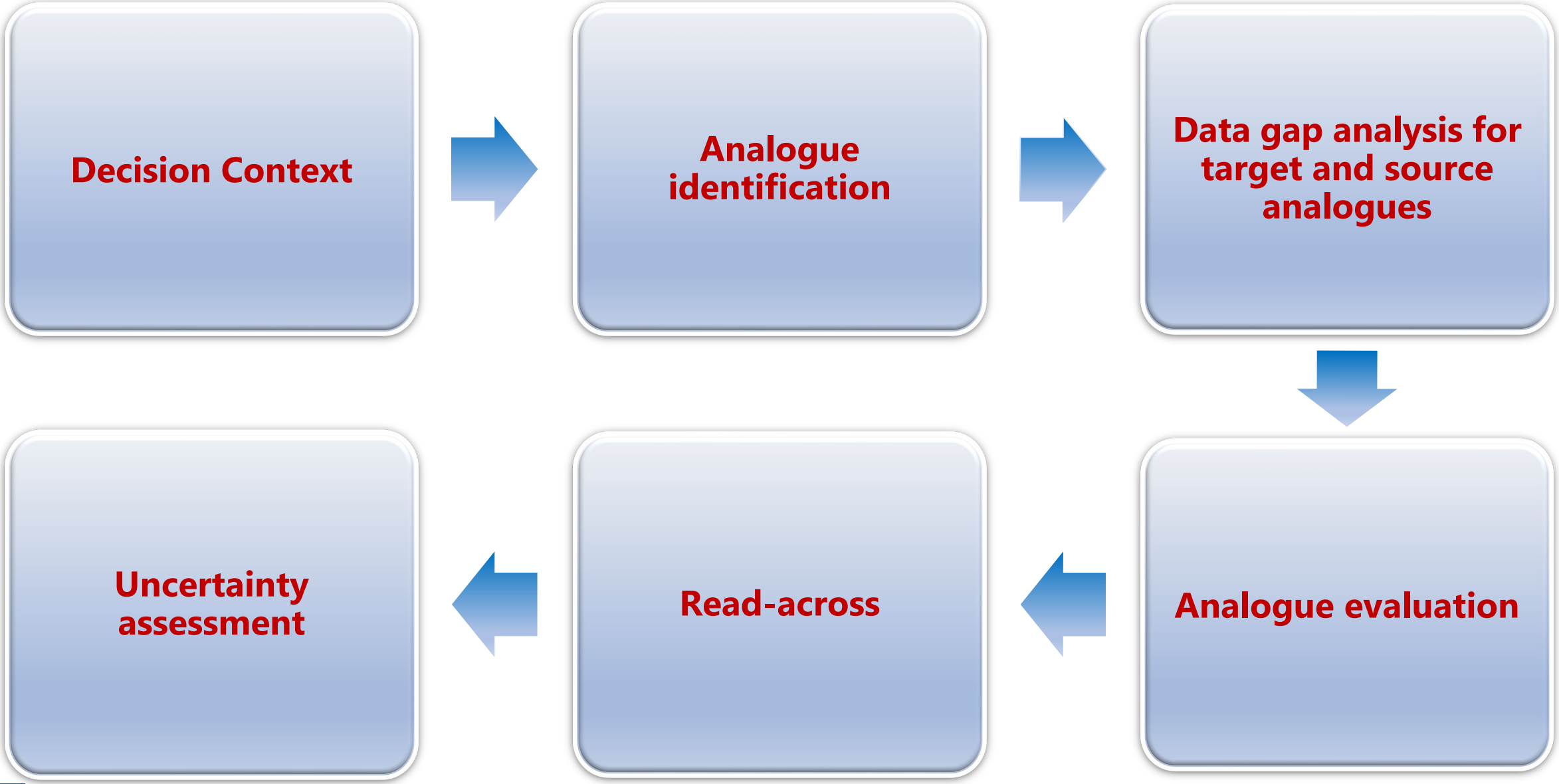
Released September 2022
- New visualization tool: Neighborhood explorer graph
- Physical property and e-fate visualization tool
- Potency prediction using ToxRefDB data
- Hit call outcome prediction of ToxCast assays

Released March 2023
- Major speed up
- New download and sorting options
- New AIM chemical fingerprints

GenRA Functionalities

- **Search** for candidate source analogues based on different identifiers e.g. SMILES, CAS, Name etc. or introduce a chemical structure/SMILES using the Ketcher drawing pad;
- **Identify** candidate source analogues on the basis of chemical, bioactivity fingerprints or a combination of both using the custom hybrid option;
- **Download** the top 100 candidate source analogues, their pairwise similarities and their chemical/bioactivity fingerprint matrices;
- **View** chemical neighborhoods via a neighborhood explorer graph visualization tool and filter on the basis of ToxCast or ToxRefDB data;
- **Compare** the distribution of relevant physicochemical properties across candidate source analogues;
- **Make binary *in vitro* predictions** of ToxCast assay outcomes or binary *in vivo* toxicity predictions on the basis of study type-toxicity effect using ToxRefDB data;
- **Make potency-based predictions** of study type-toxicity effects using ToxRefDB data;
- **Sort predictions** based on number of positive/negative toxicity effects or on the basis of the prediction confidence. Download the predictions in a spreadsheet format for subsequent review and assessment.

Conceptual read-across workflow in GenRA



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Accessing GenRA

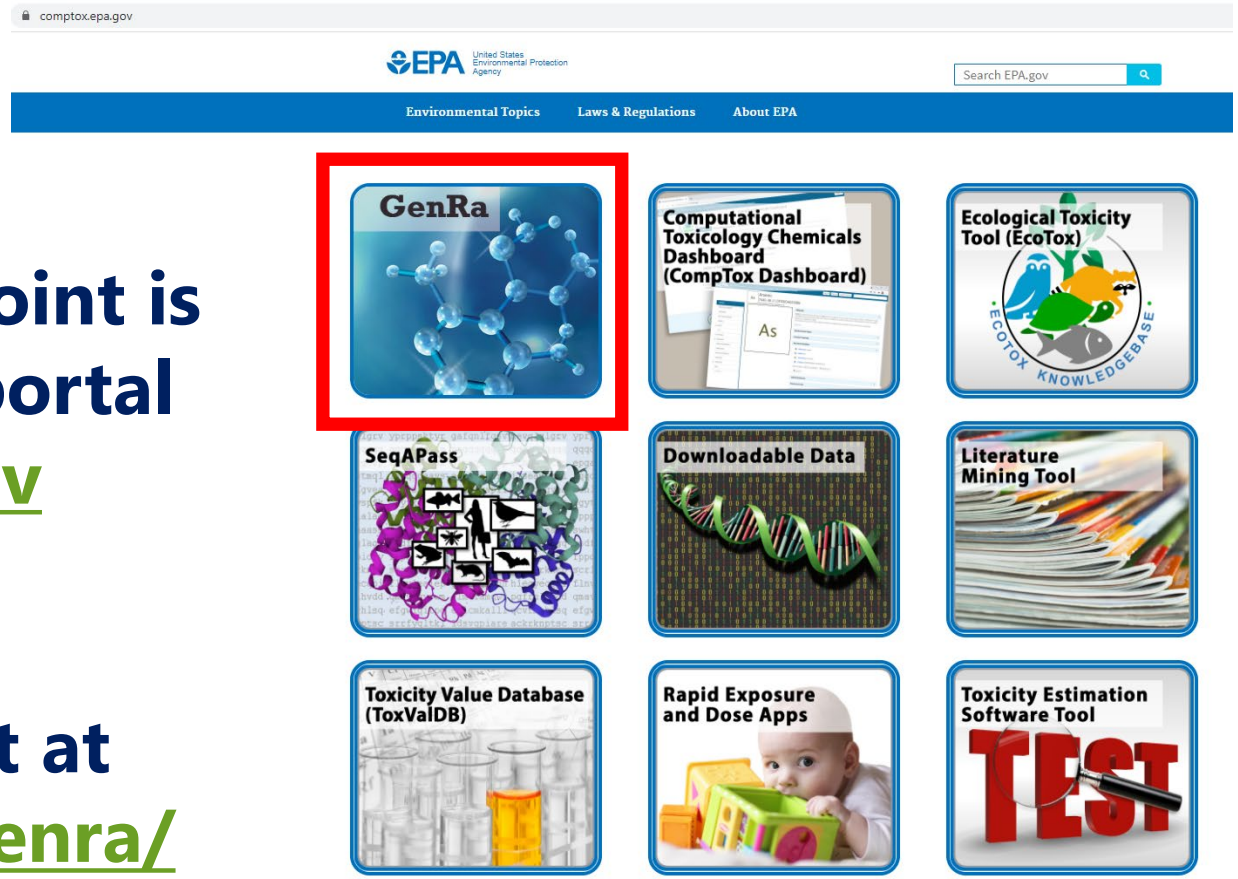
Main Entry Point

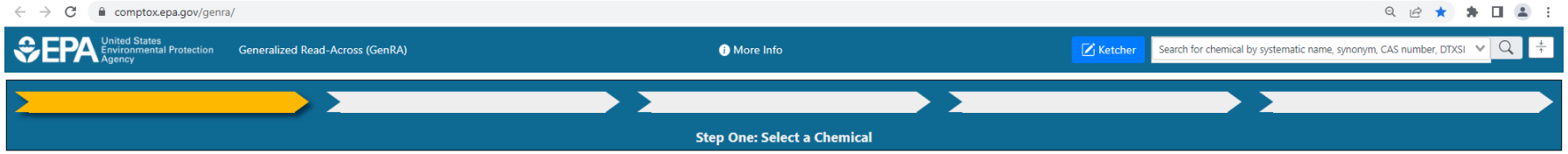
GenRA main entry point is from the comptox portal

comptox.epa.gov

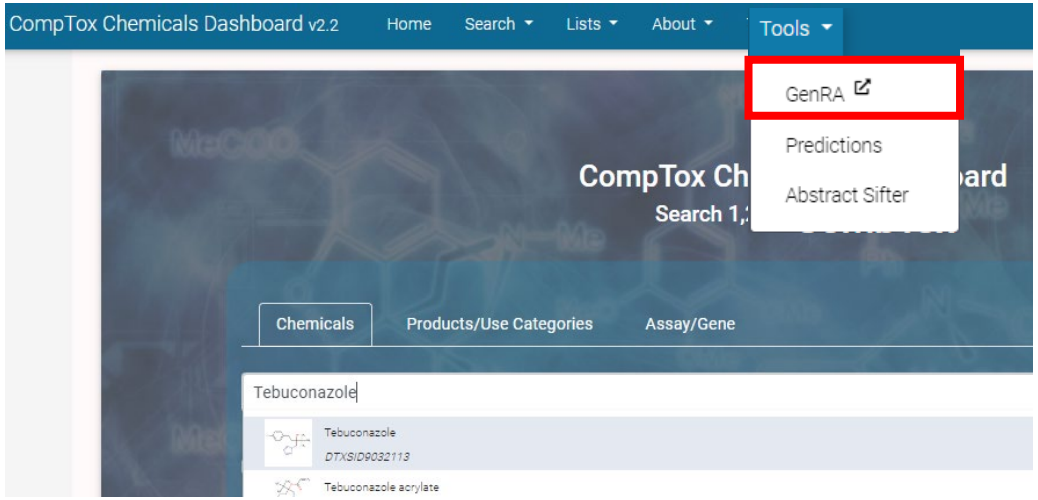
GenRA entry point at

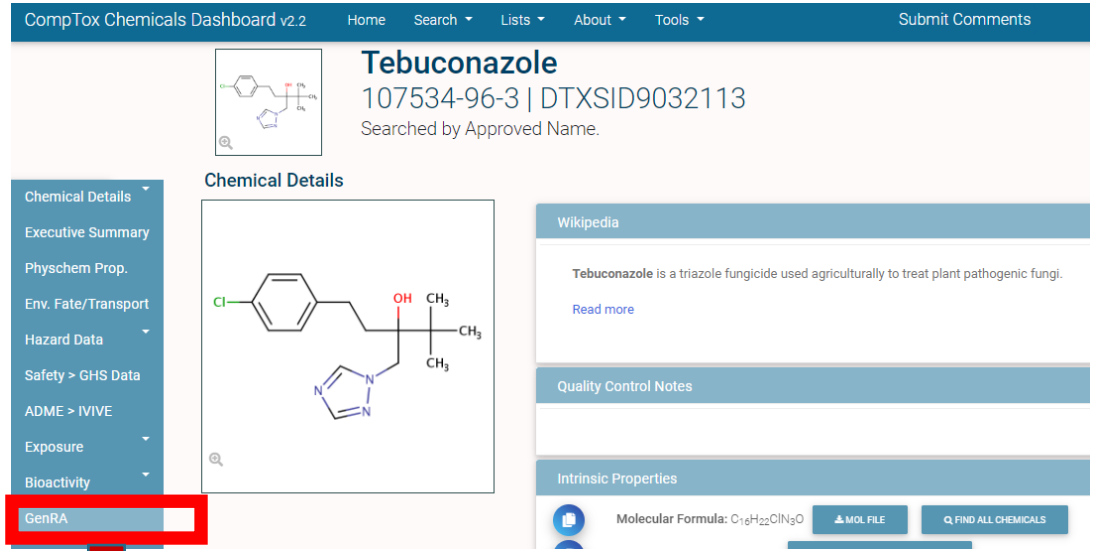
comptox.epa.gov/genra/

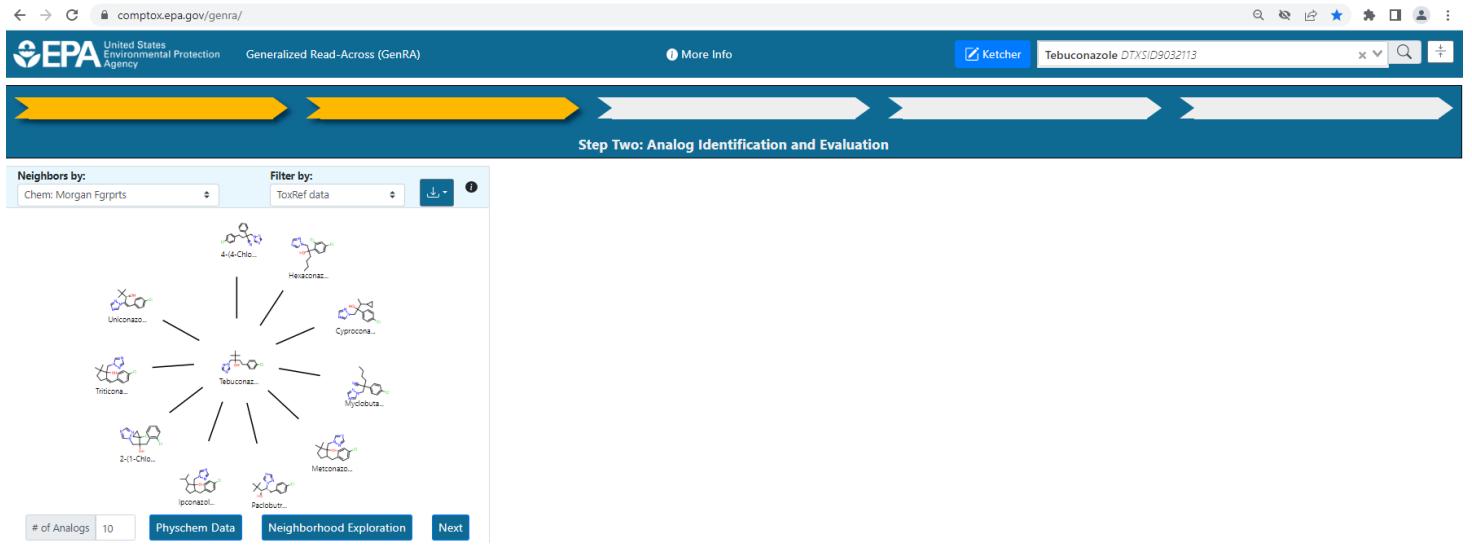




Alternative Entry Points







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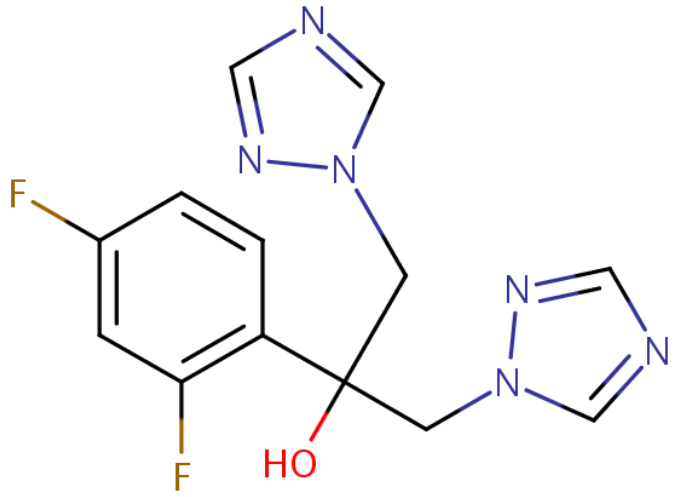
Demonstration of GenRA (Part 1)

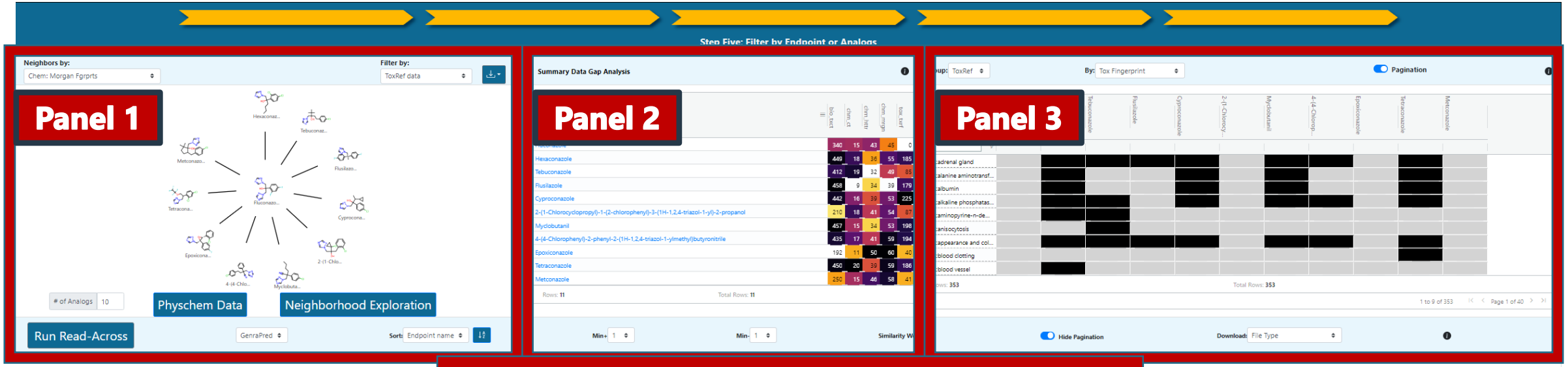
Example Walkthrough

Fluconazole (A Data Rich Chemical)



- **IUPAC Name:** 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol
- **CAS RN:** 86386-73-4
- **DSSTox substance identifier (DTXSID):** DTXSID3020627
- **Molecular Formula:** $C_{13}H_{12}F_2N_6O$
- **SMILES:** OC(CN1C=NC=N1)(CN1C=NC=N1)C1=C(F)C=C(F)C=C1
- **InChIKey:** RFHAOTPXVQNOHP-UHFFFAOYSA-N

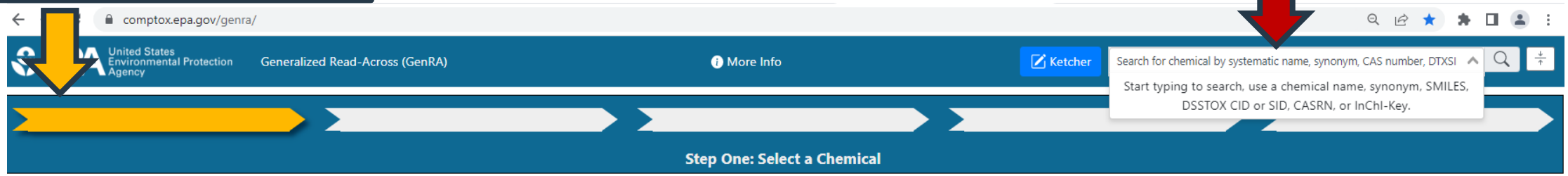
GenRA Workflow Overview



Basic Search

Step 1: Select a Chemical

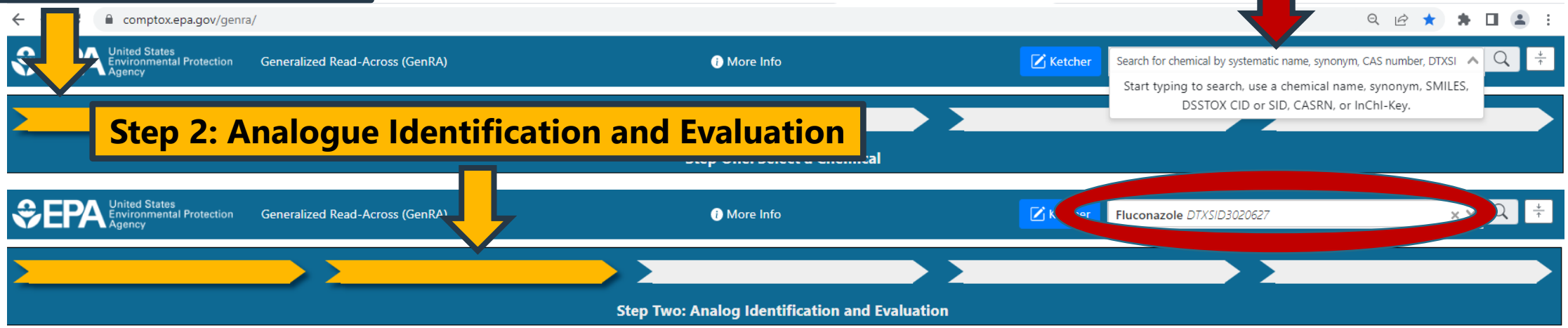
Search for a chemical of interest (target) using the search box

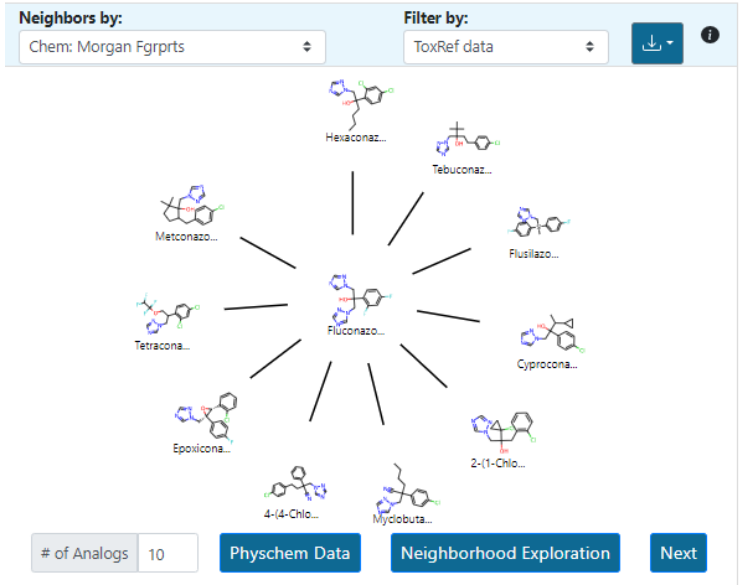


Basic Search

Search for a chemical of interest (target) using the search box

Step 1: Select a Chemical

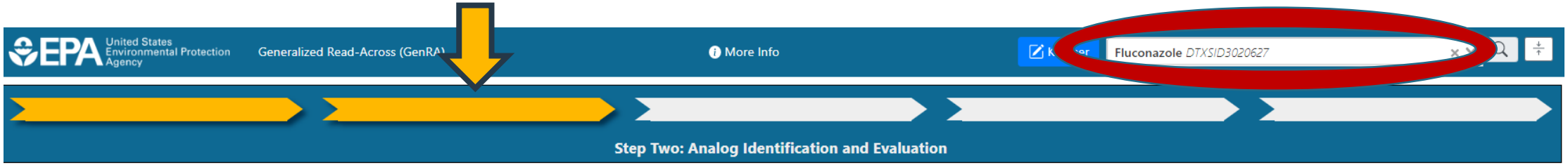


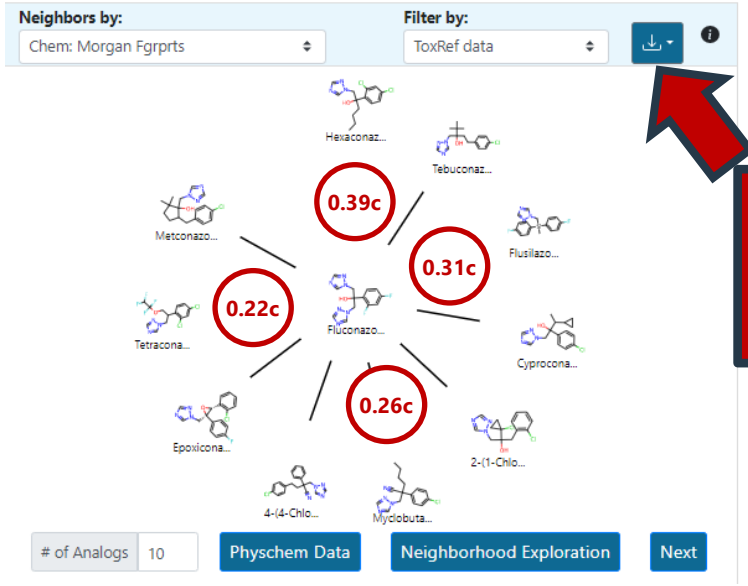


- Radial plot with target in the center and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)

Analogue Identification and Evaluation

Step 2: Analogue Identification and Evaluation





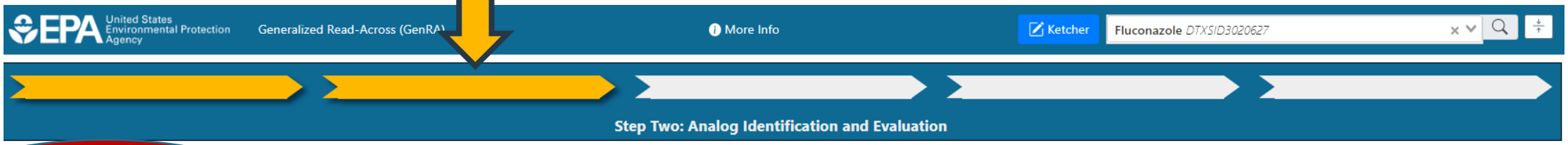
- Radial plot with target in the center and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)

Downloads
Top ~100 nearest neighbors (CSV)
Radial Plot Image (png)

NEW

Analogue Identification and Evaluation

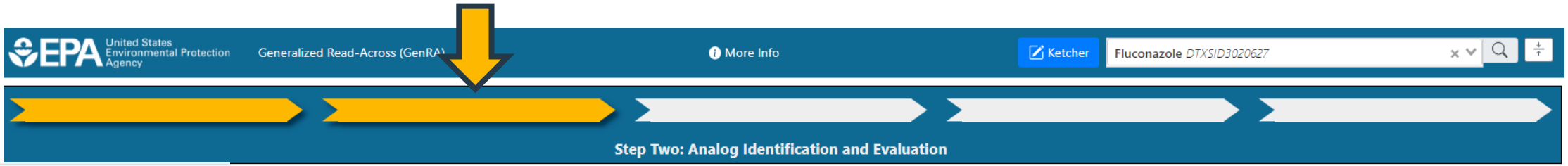
Step 2: Analogue Identification and Evaluation

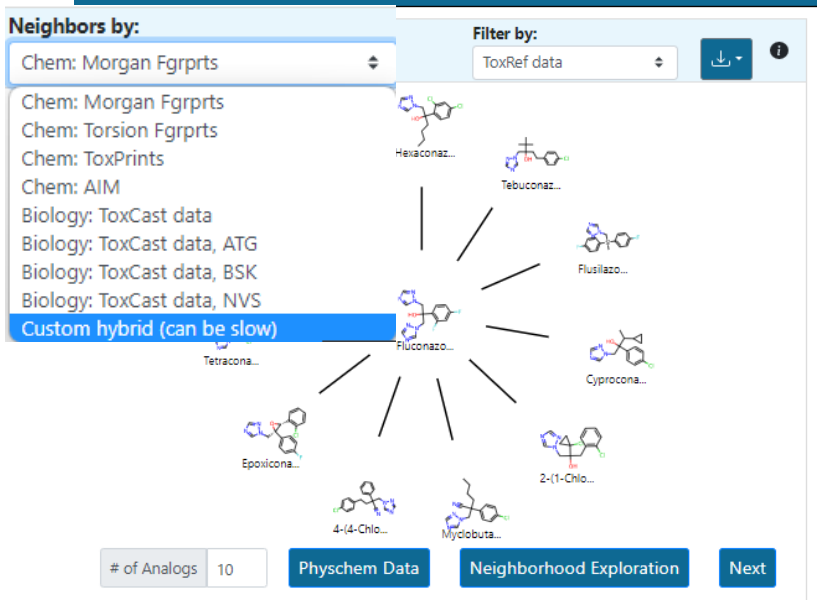


- Radial plot with target in the center and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)
- Default 10 analogues based on Morgan chemical fingerprints and prefiltered based on ToxRefDB data

Analogue Identification and Evaluation

Step 2: Analogue Identification and Evaluation

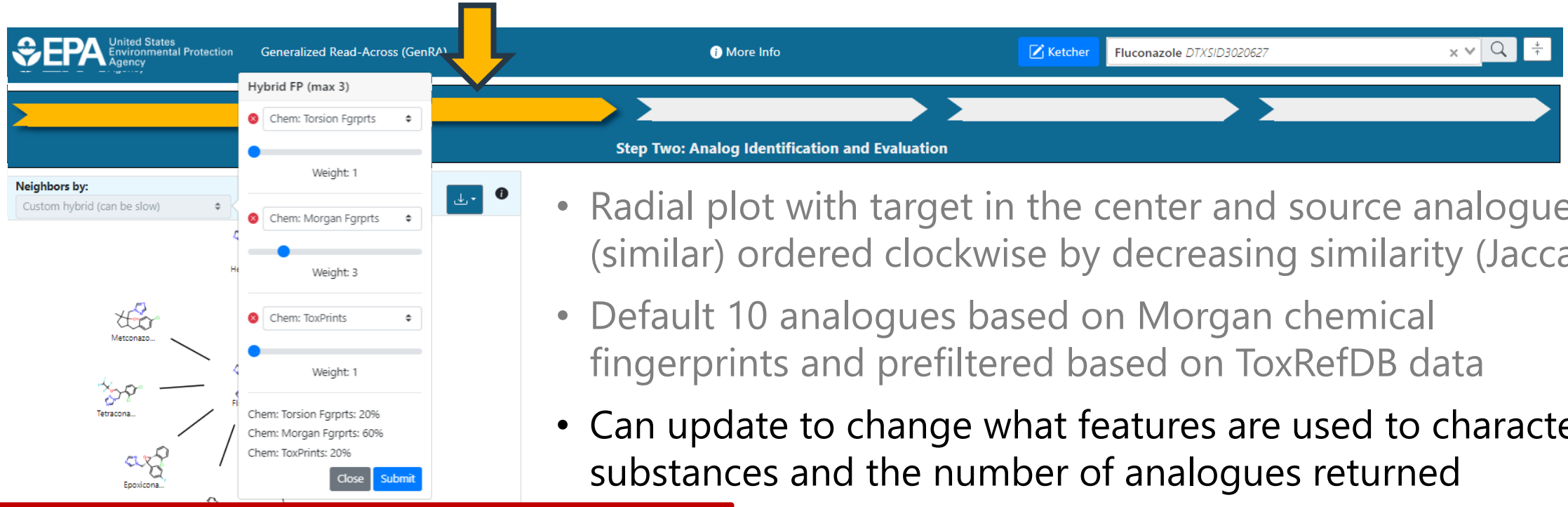




- Radial plot with target in the center and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)
- Default 10 analogues based on Morgan chemical fingerprints and prefiltered based on ToxRefDB data
- Can update to change what features are used to characterize substances and the number of analogues returned

Analogue Identification and Evaluation

Step 2: Analogue Identification and Evaluation



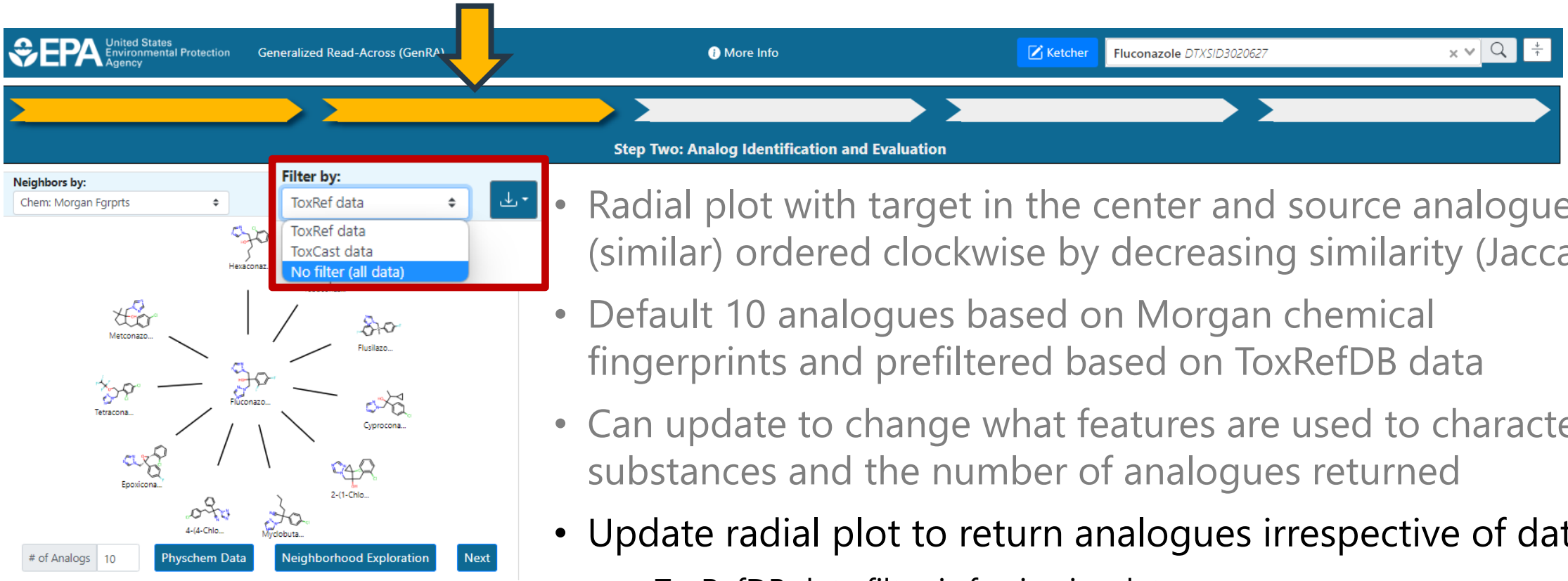
- Radial plot with target in the center and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)
- Default 10 analogues based on Morgan chemical fingerprints and prefiltered based on ToxRefDB data
- Can update to change what features are used to characterize substances and the number of analogues returned

Custom Hybrid

Choose up to 3 fingerprints
e.g. 20% Torsion Fingerprints, 60% Morgan Fingerprints, and 20% ToxPrints

Analogue Identification and Evaluation

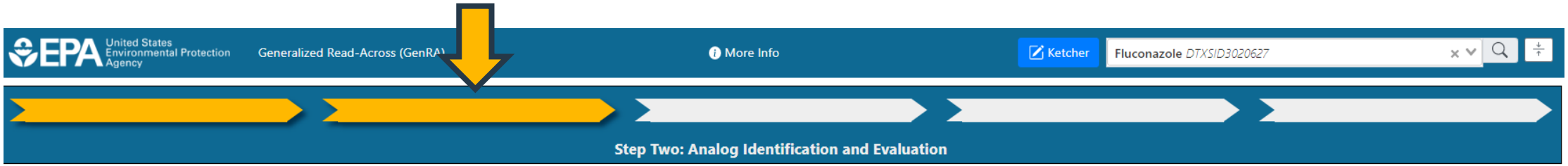
Step 2: Analogue Identification and Evaluation

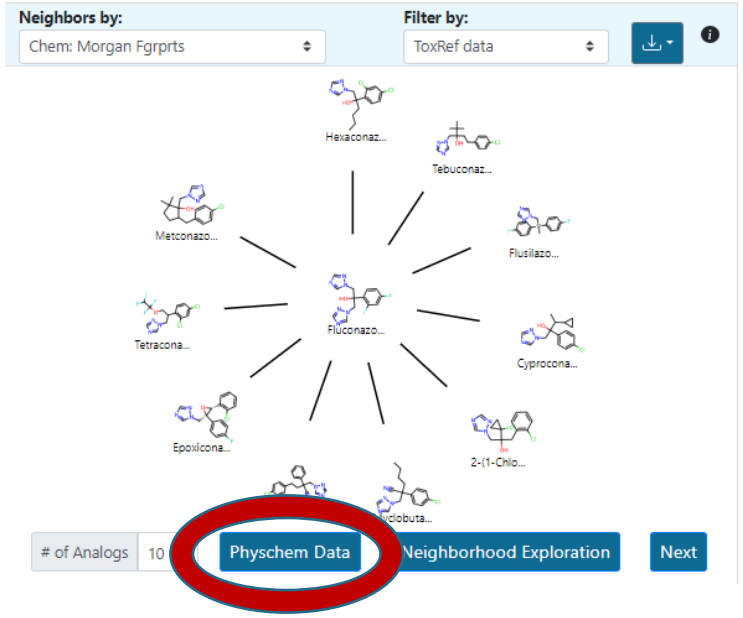


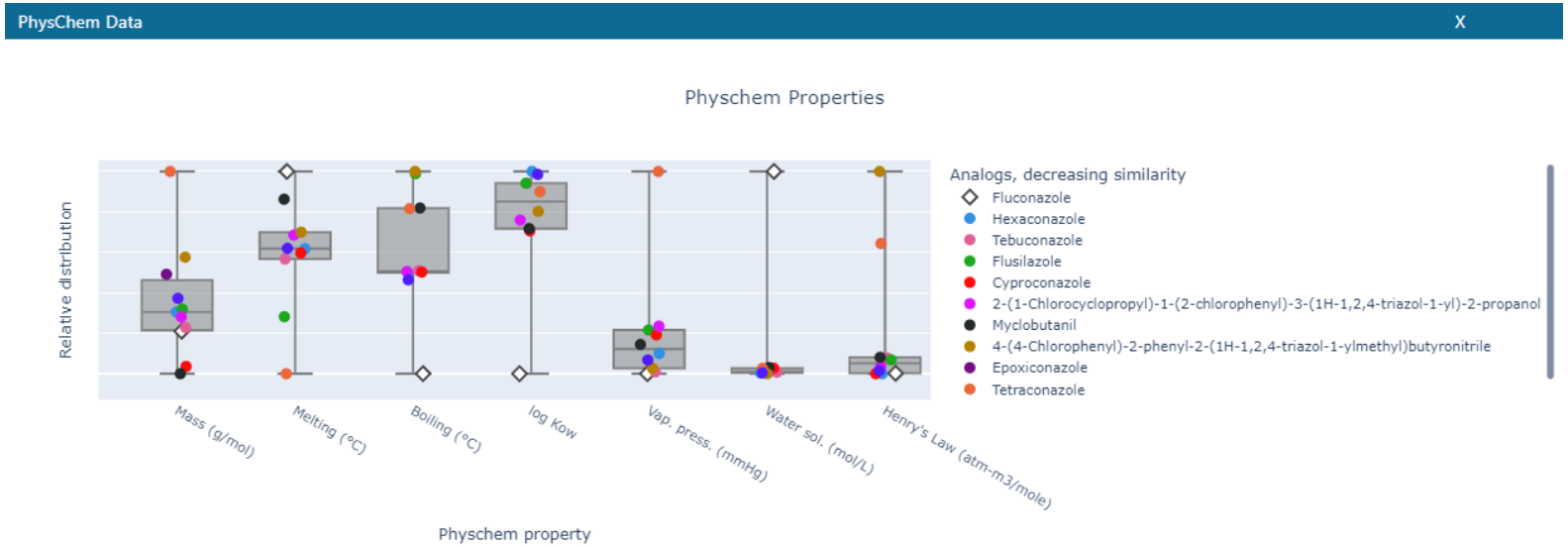
- Radial plot with target in the center and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)
- Default 10 analogues based on Morgan chemical fingerprints and prefiltered based on ToxRefDB data
- Can update to change what features are used to characterize substances and the number of analogues returned
- Update radial plot to return analogues irrespective of data
  - ToxRefDB data filter is for *in vivo* data
  - ToxCast data filter is for *in vitro* data
  - No filter – returns the most similar analogues irrespective of data

Analogue Identification and Evaluation

Step 2: Analogue Identification and Evaluation

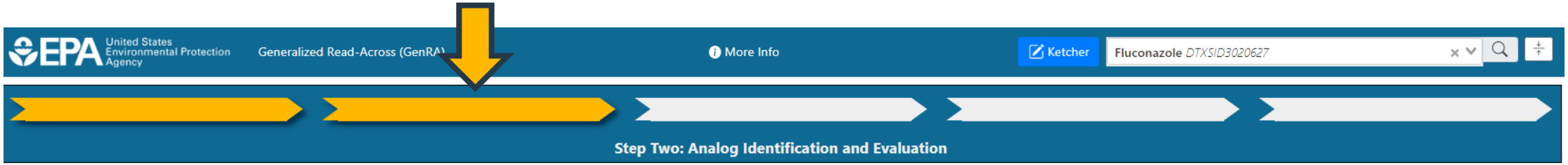


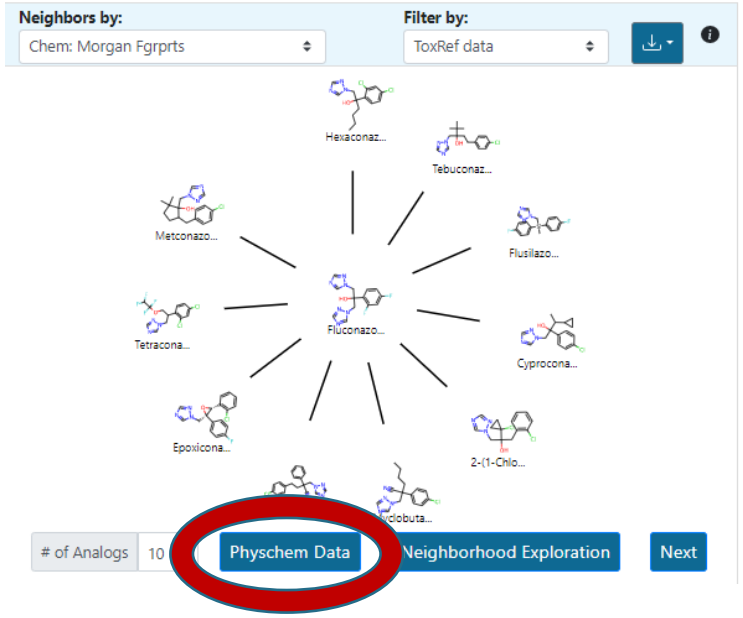




Analogue Identification and Evaluation

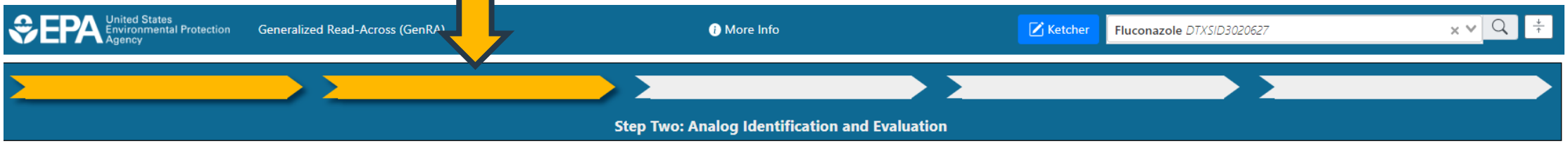
Step 2: Analogue Identification and Evaluation

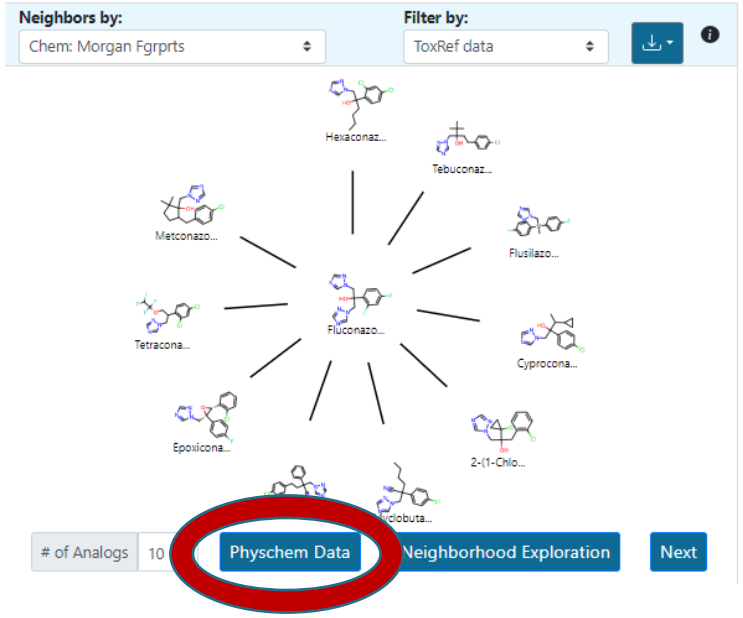




Analogue Identification and Evaluation

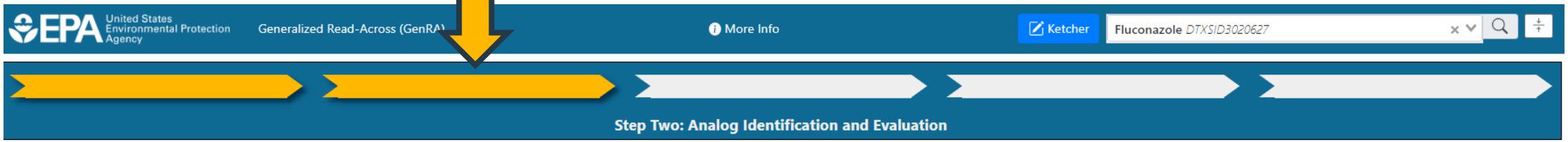
Step 2: Analogue Identification and Evaluation

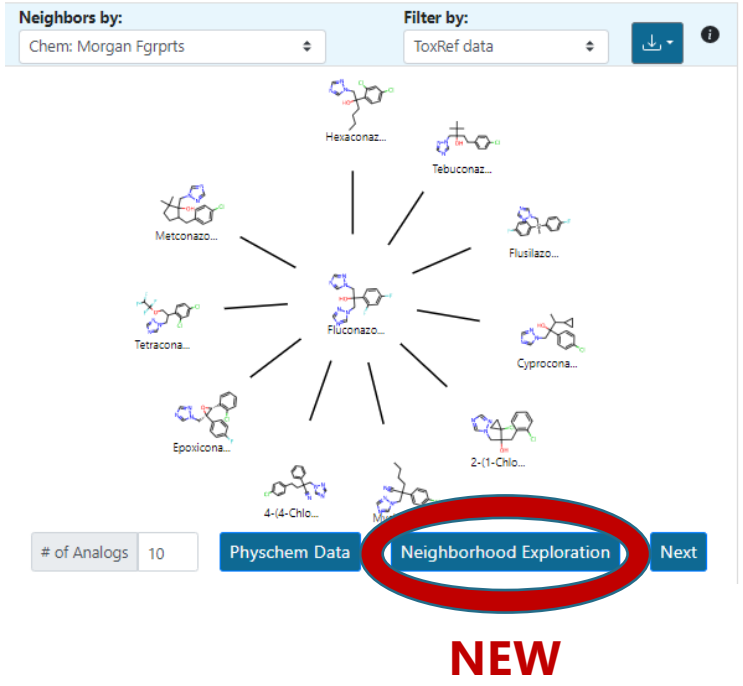




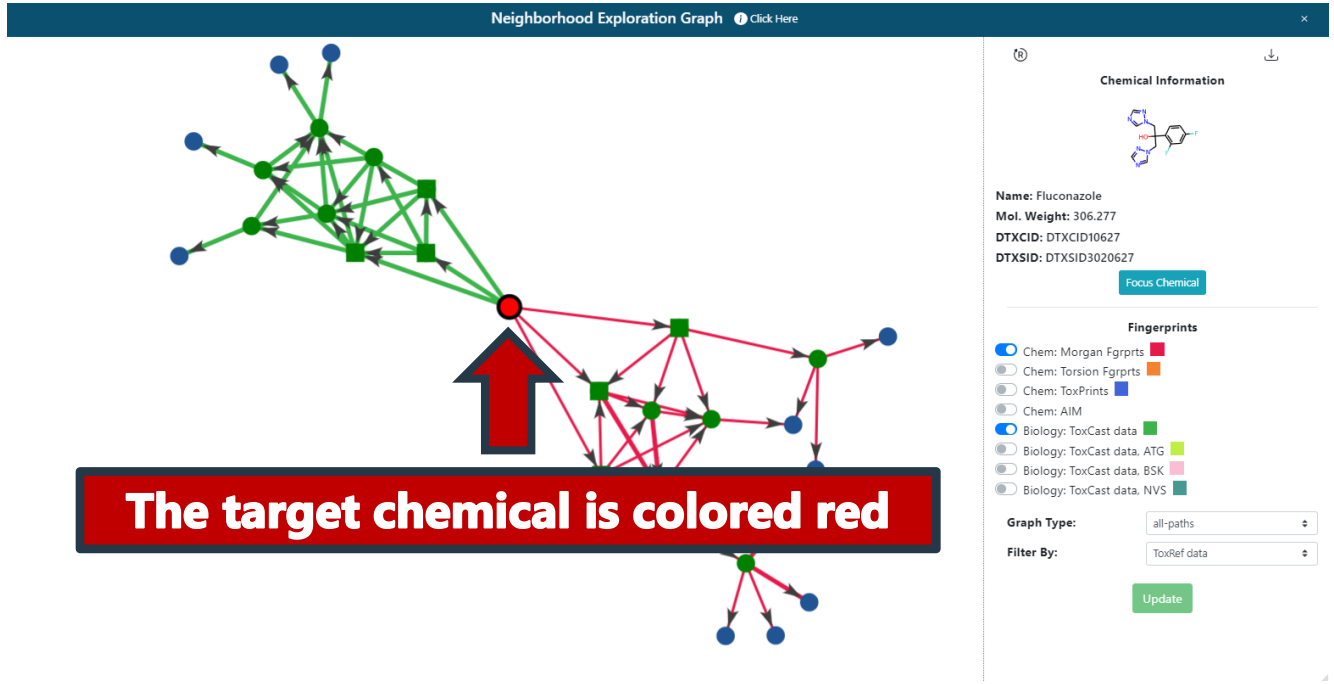
Analogue Identification and Evaluation

Step 2: Analogue Identification and Evaluation





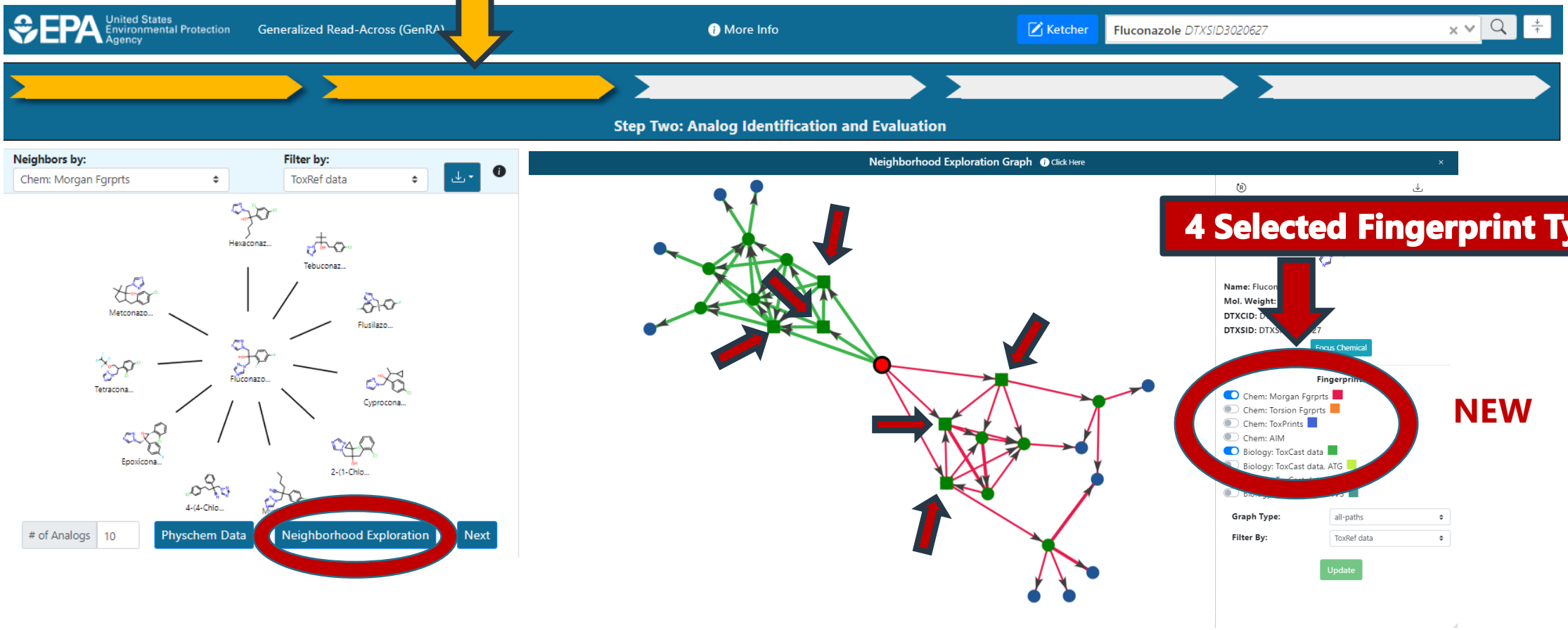
NEW



The target chemical is colored red

Analogue Identification and Evaluation

Step 2: Analogue Identification and Evaluation



- Line thickness proportional to similarity between analogues (thicker=more similar)
- Squares are top 3 highest similarity analogues to your target for the chosen fingerprint type

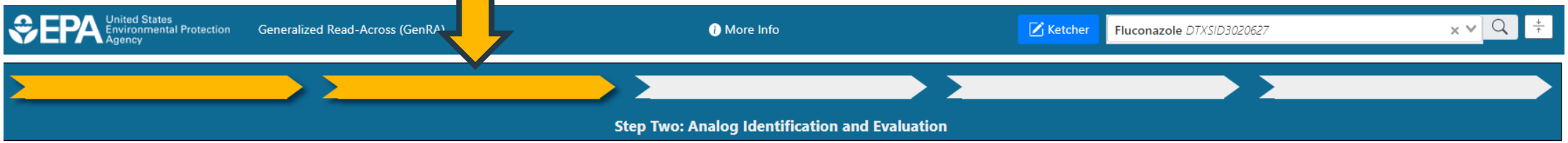
Analogue Identification and Evaluation

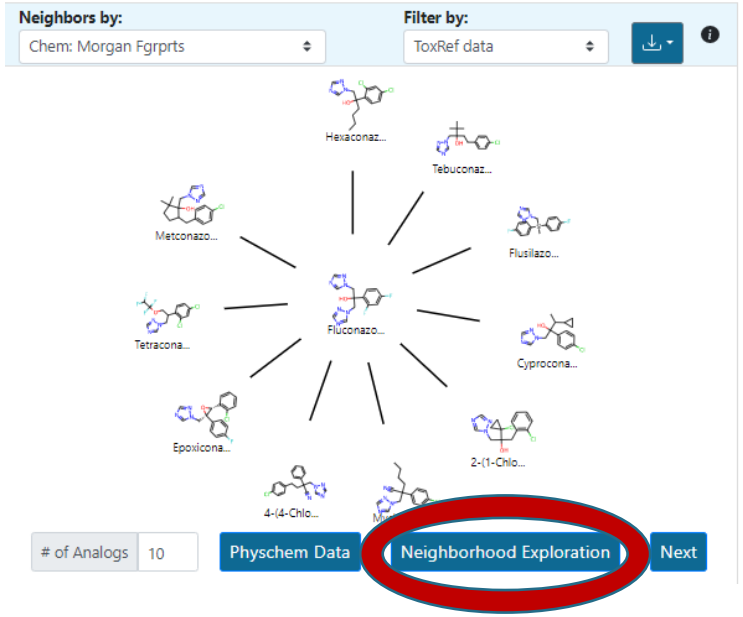
Step 2: Analogue Identification and Evaluation

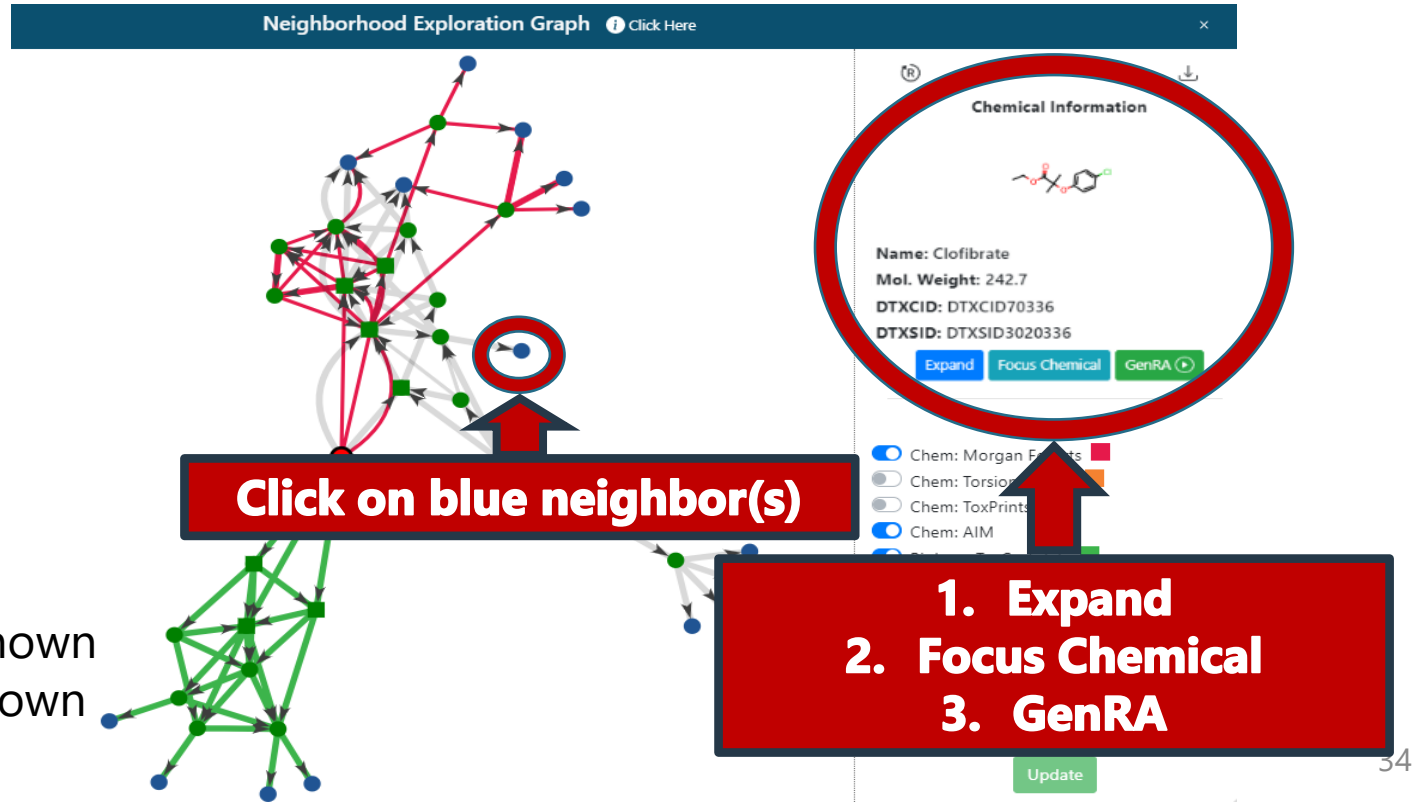
NEW Chemical Fingerprint AIM

Analogue Identification and Evaluation

Step 2: Analogue Identification and Evaluation



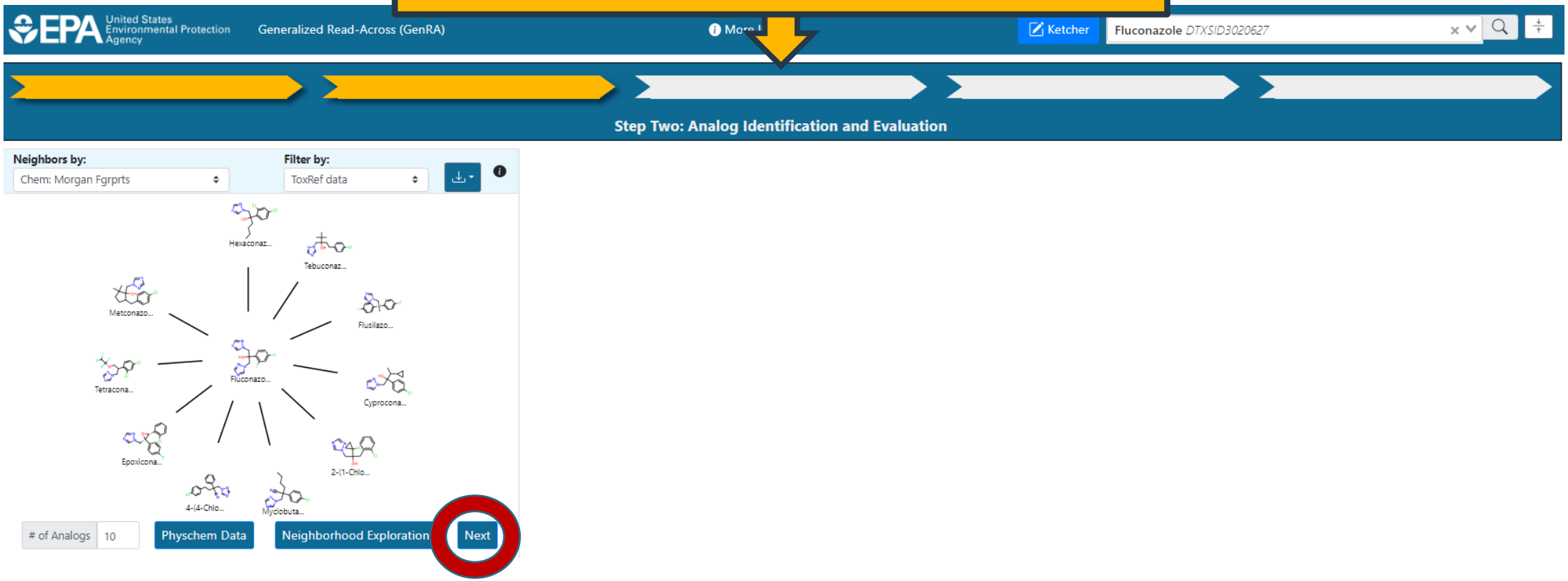




- Green markers indicate all neighbors shown
- Blue markers indicate neighbors not shown

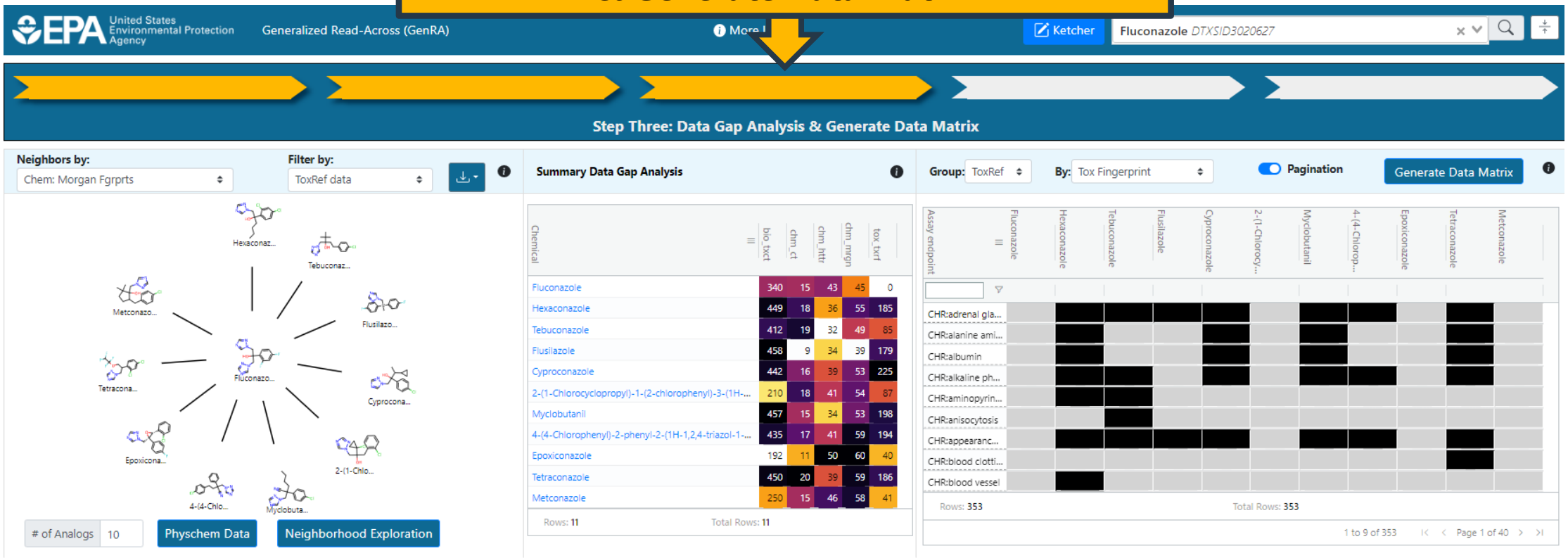
Data Gap Analysis

Step 3: Data Gap Analysis & Generate Data Matrix



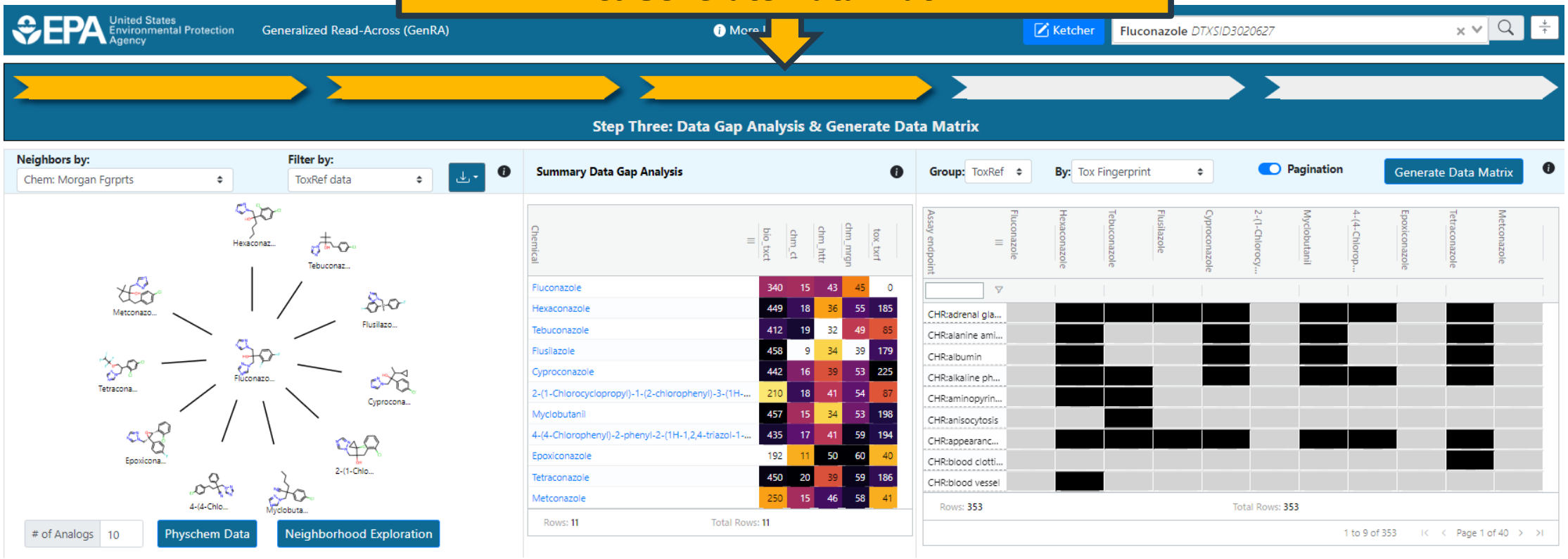
Data Gap Analysis

Step 3: Data Gap Analysis & Generate Data Matrix



Data Gap Analysis

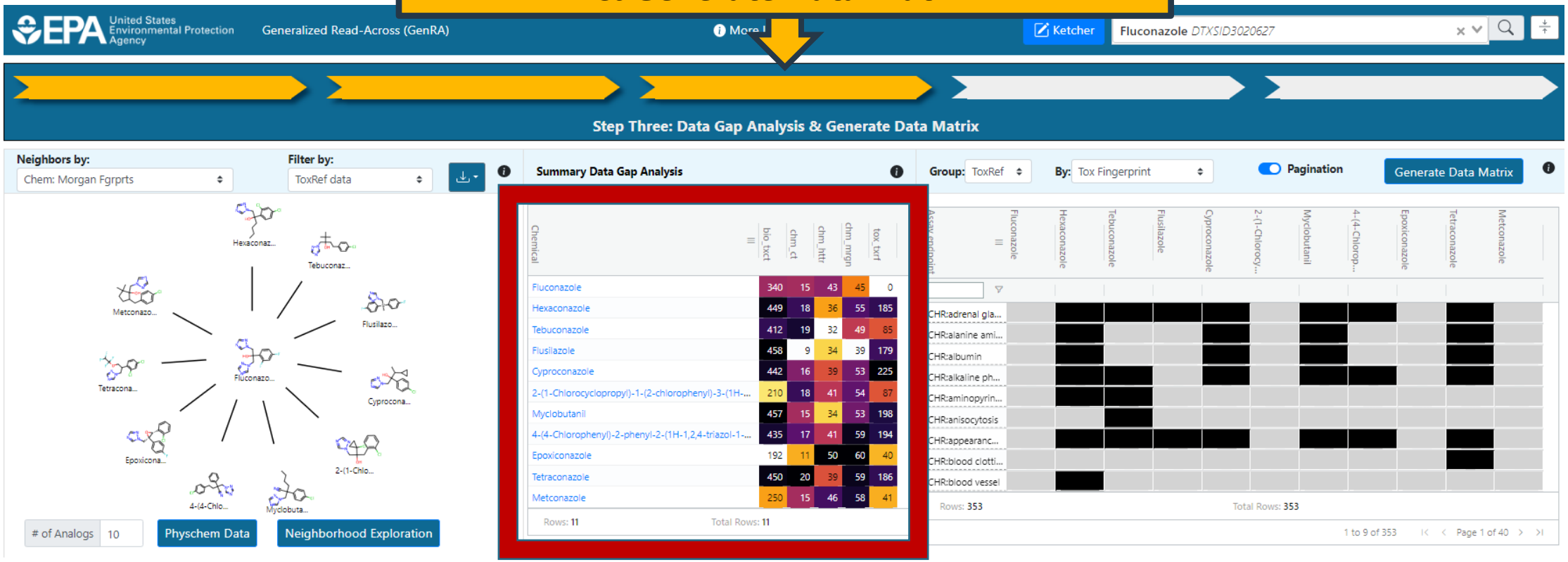
Step 3: Data Gap Analysis & Generate Data Matrix



- How data poor is my target and what data exists for the source analogues identified?
- Do the data for the source analogues address the data gaps of interest for the target chemical?

Data Gap Analysis

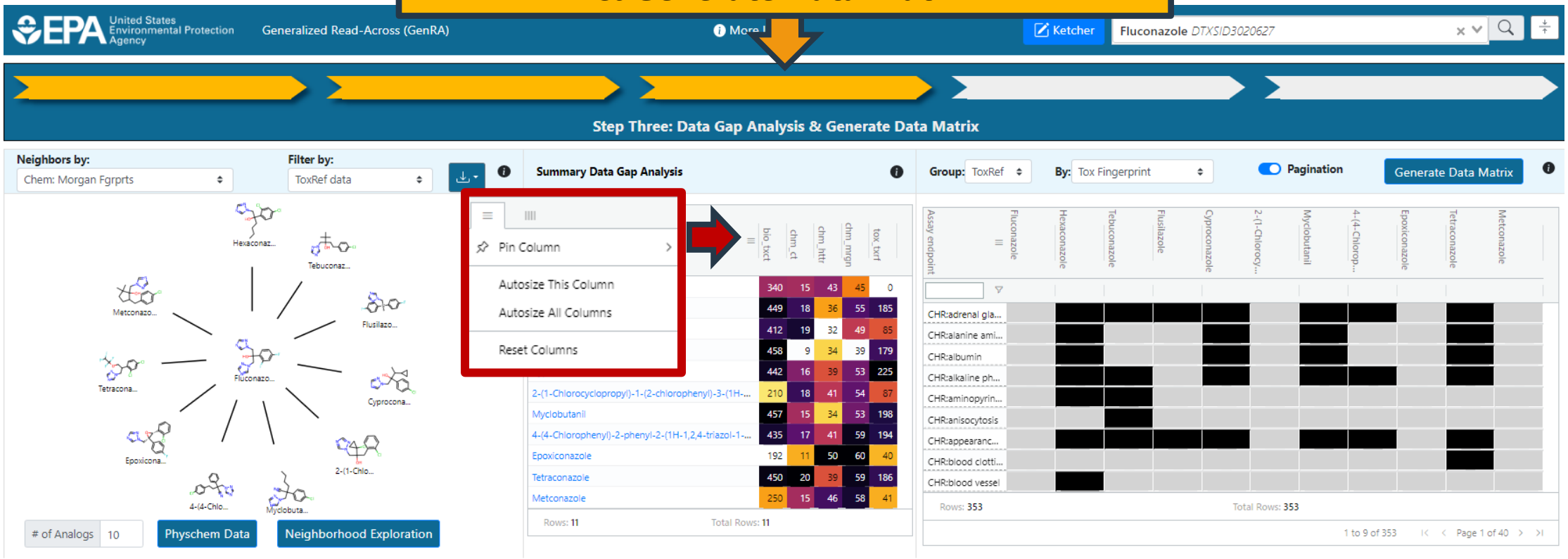
Step 3: Data Gap Analysis & Generate Data Matrix



- Summary of the data availability associated with the target chemical and its identified source analogues.
- The quantity of data associated with a given chemical is indicated by the number of records and the darkness of the associated box.

Data Gap Analysis

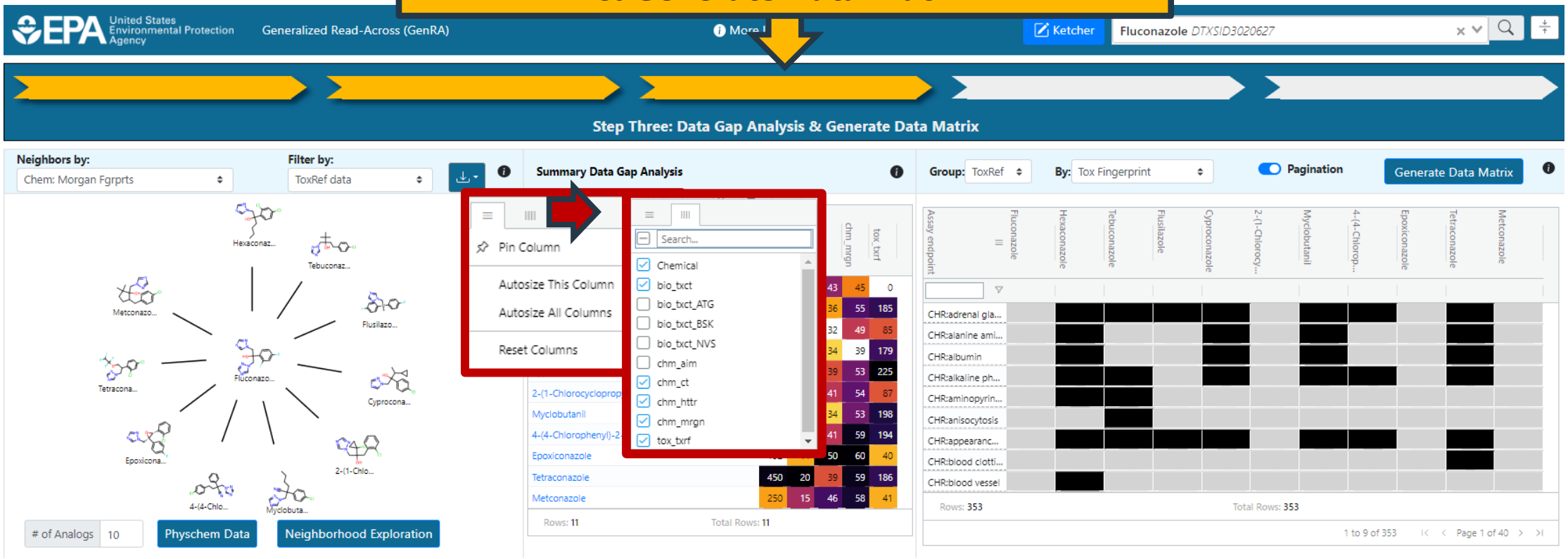
Step 3: Data Gap Analysis & Generate Data Matrix



- To see more data streams click the ☰ icon at the top of the Chemicals column, then the |||I icon.

Data Gap Analysis

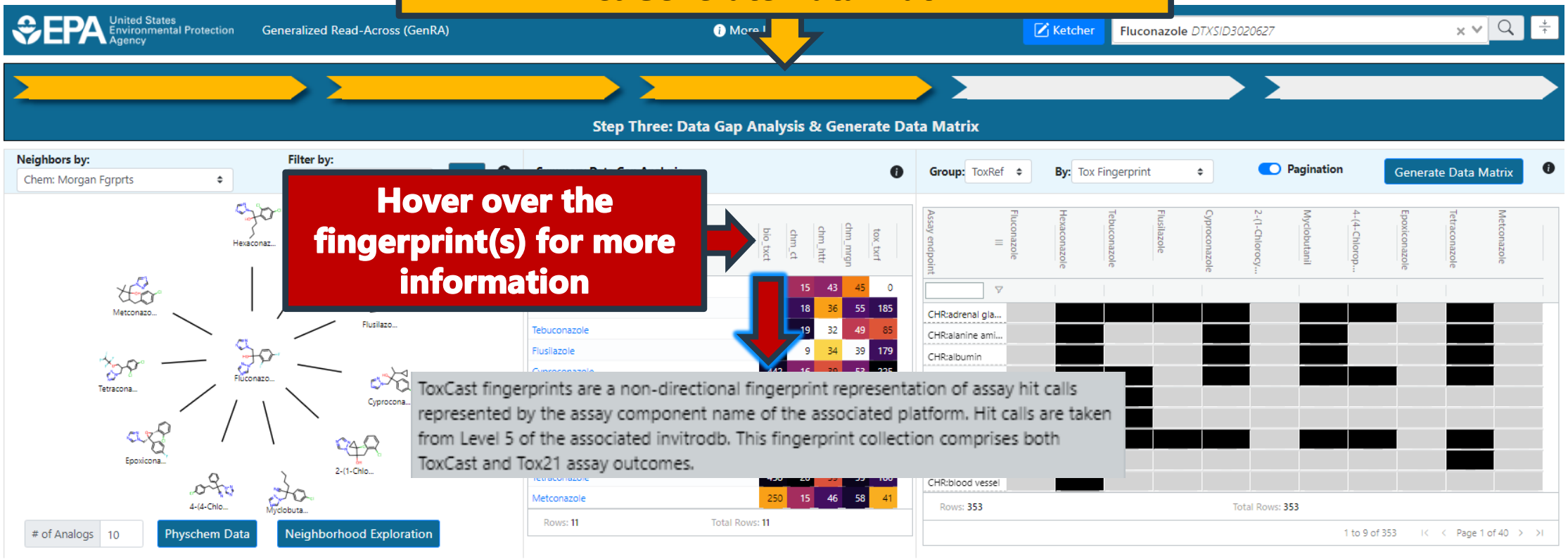
Step 3: Data Gap Analysis & Generate Data Matrix



- To see more data streams click the ☰ icon at the top of the Chemicals column, then the ||| icon.
- This panel starts to provide a perspective to inform data gaps.

Data Gap Analysis

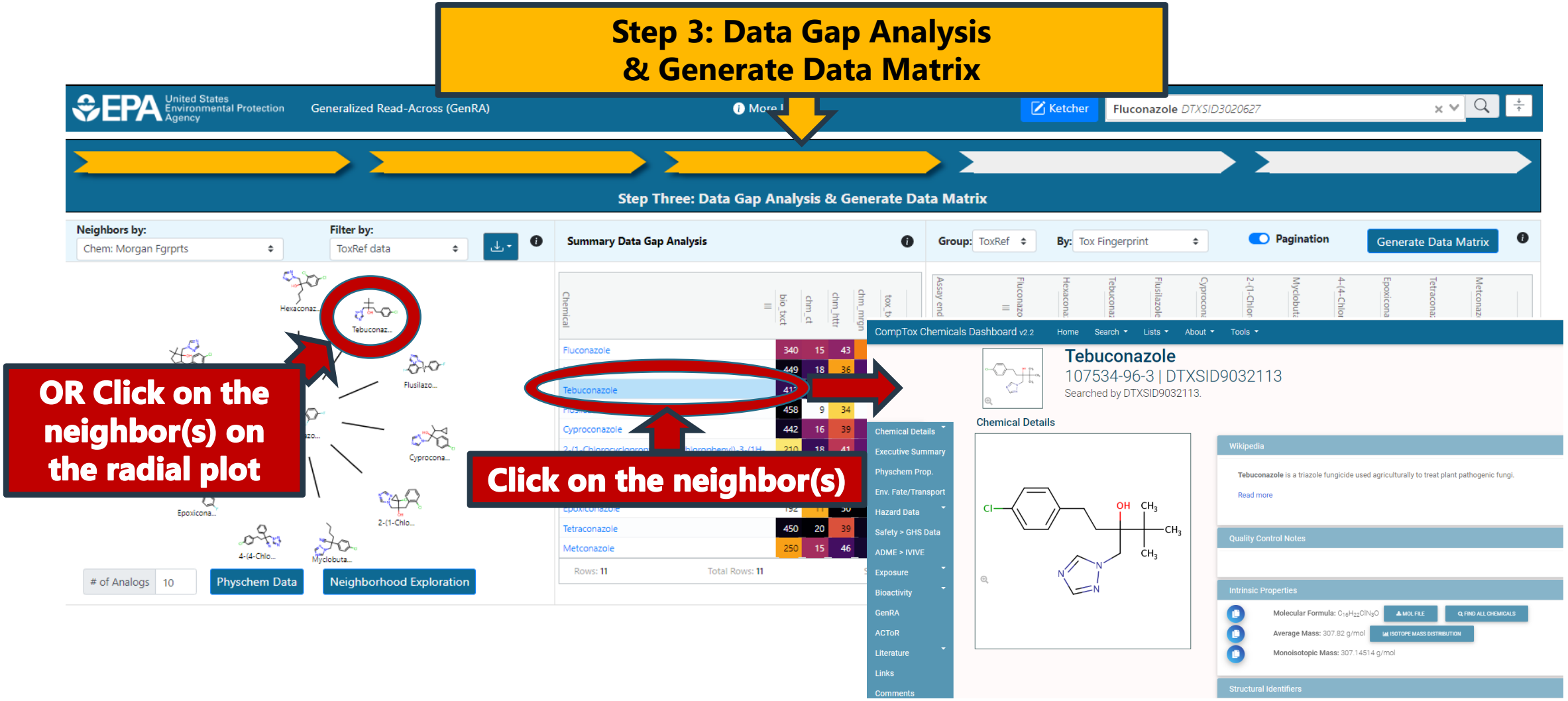
Step 3: Data Gap Analysis & Generate Data Matrix



- To see more data streams click the ☰ icon at the top of the Chemicals column, then the ||| icon.
- This panel starts to provide a perspective to inform data gaps.

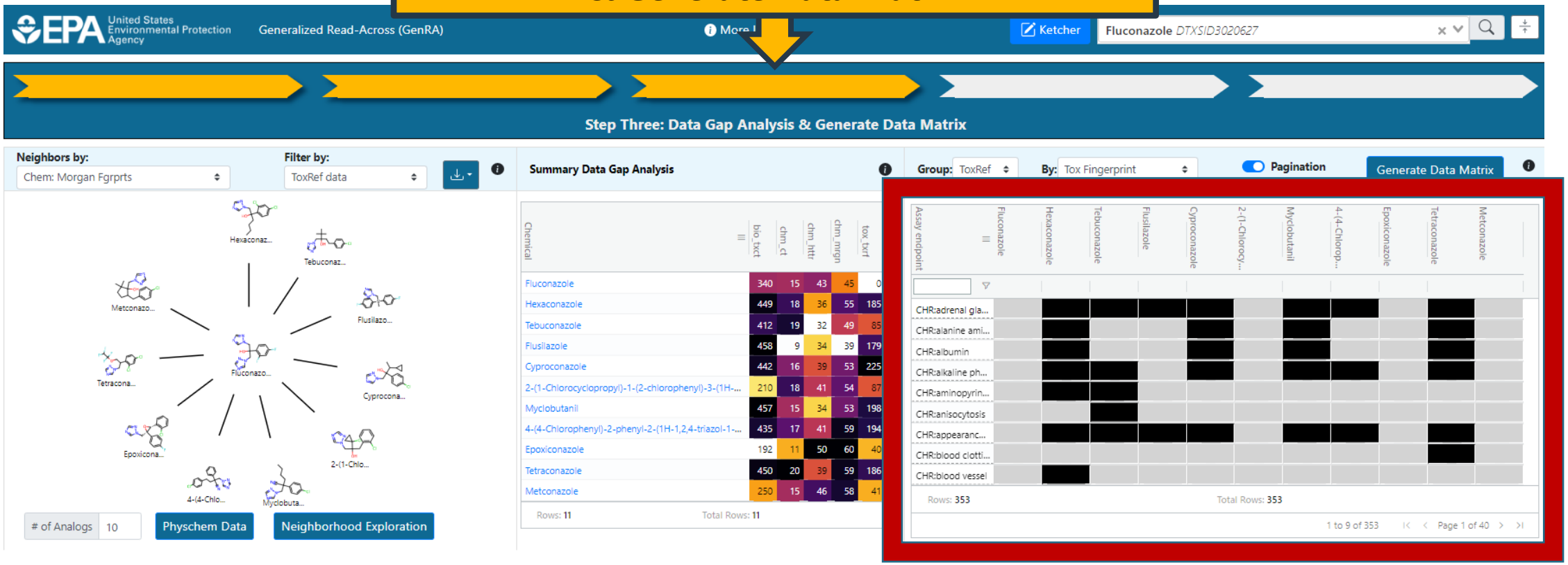
Data Gap Analysis

Step 3: Data Gap Analysis & Generate Data Matrix



Data Gap Analysis

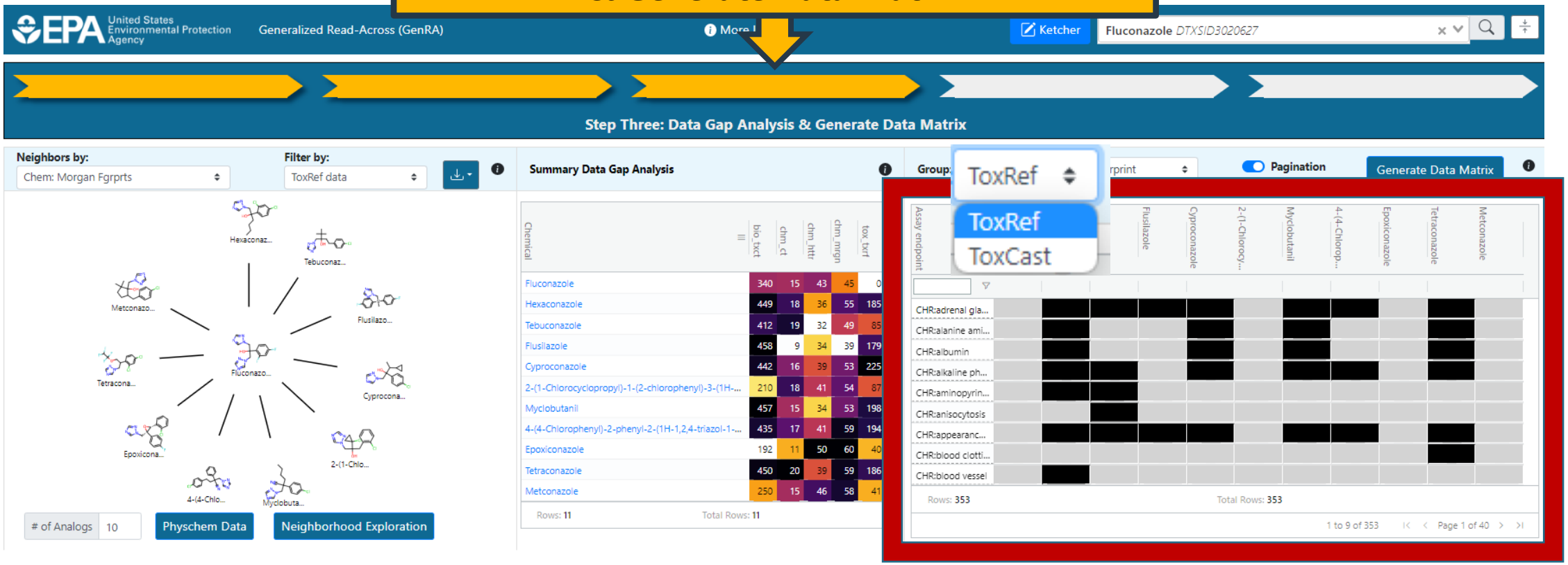
Step 3: Data Gap Analysis & Generate Data Matrix



- The toxicity information by default is an expanded grid view of which types of toxicity effect information are available across the analogues.

Data Gap Analysis

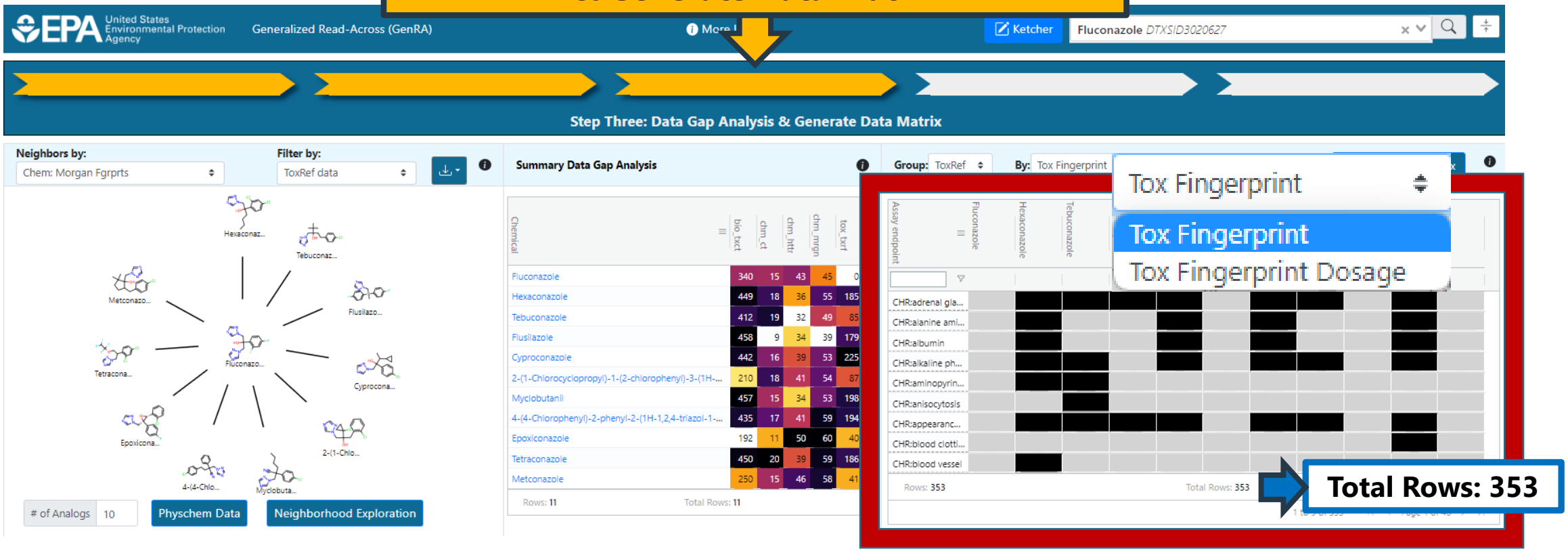
Step 3: Data Gap Analysis & Generate Data Matrix



- Default binary representations of toxicity data arising from ToxRefDB
- Consistent with the filter by option in the Panel 1

Data Gap Analysis

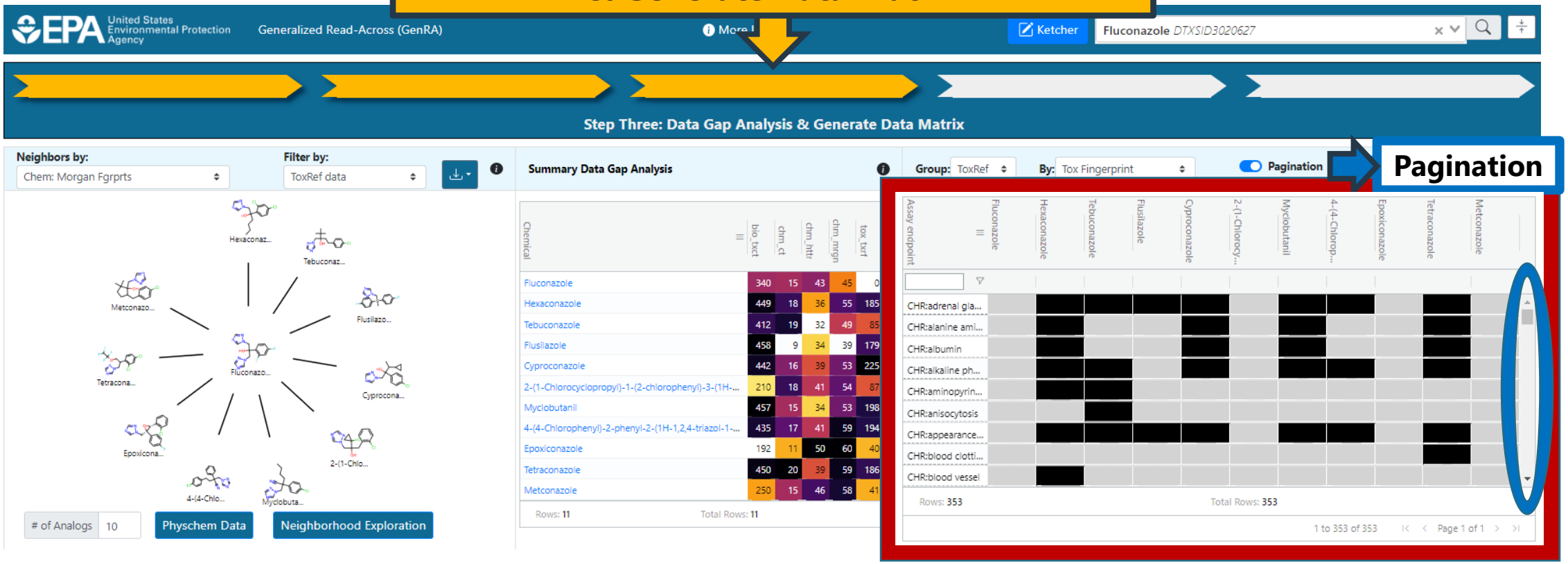
Step 3: Data Gap Analysis & Generate Data Matrix



- Tox fingerprint reflects the toxicity effects within each study type.
- Over 300 different study type-toxicity combinations

Data Gap Analysis

Step 3: Data Gap Analysis & Generate Data Matrix



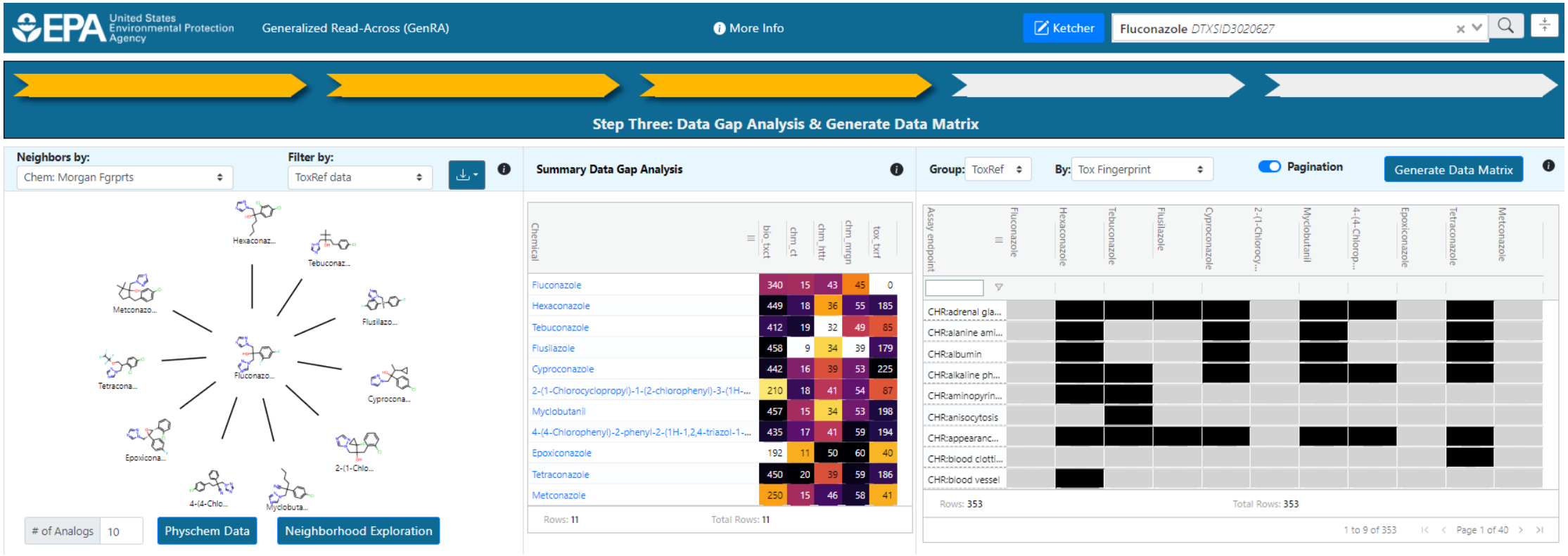
- Tox fingerprint reflects the toxicity effects within each study type.
- Over 300 different study type-toxicity combinations
- Pagination option to scroll through the toxicity effects

Data Gap Analysis

Step 3: Data Gap Analysis & Generate Data Matrix

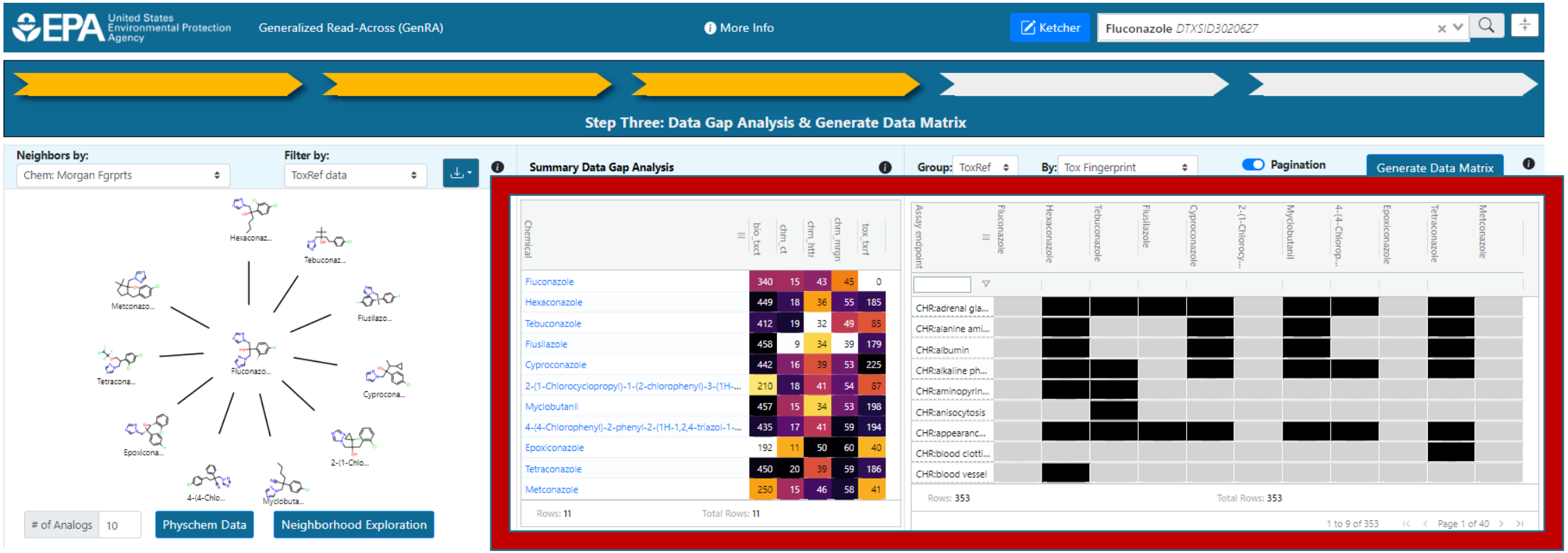
- Represents presence or absence of toxicity endpoint data
- Informs the data gap analysis step of the workflow

Analogue Evaluation



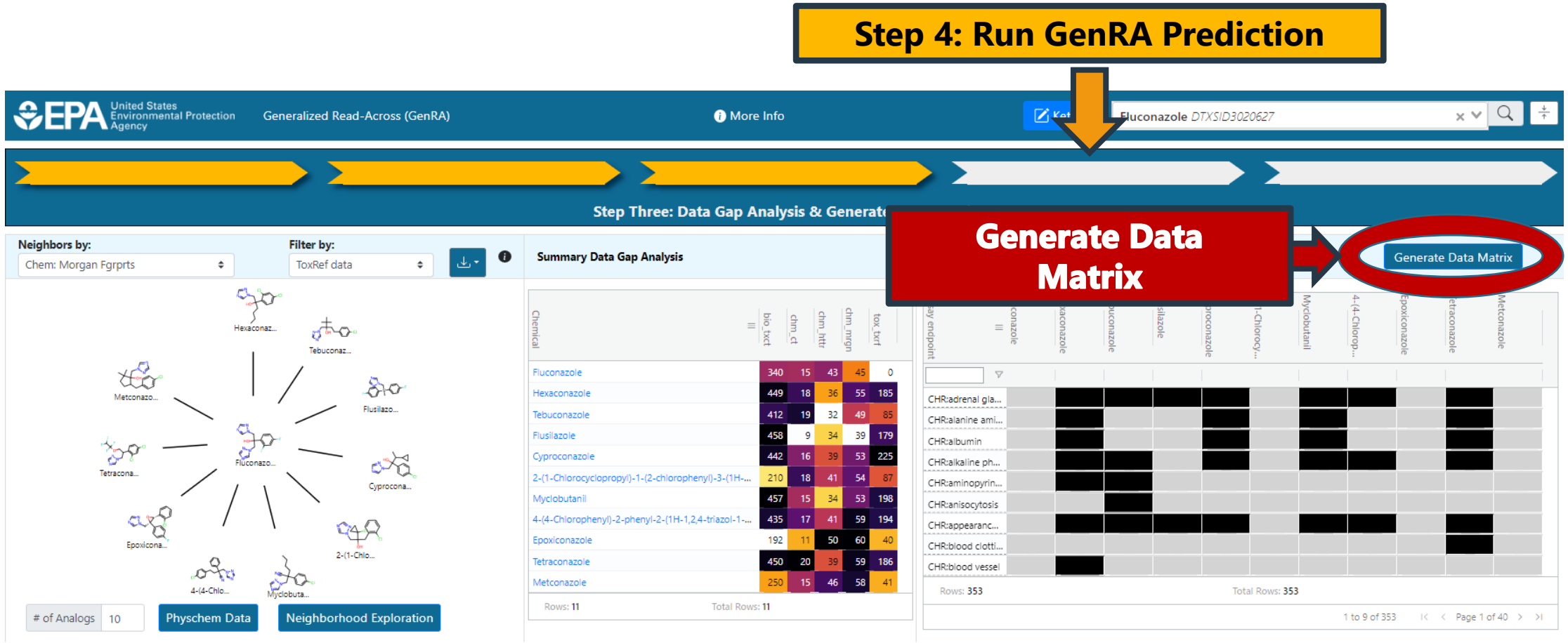
- Evaluating the suitability and relevance of the source analogues identified
- Data gap analysis across the source analogues and the target
- Little data for the source analogues or they fail to address the data gaps of interest
  - Change the number of neighbors or select a different similarity context.

Analogue Evaluation



- Both Panels 2 and 3 provide a context of available data for the source analogues
  - the quantity of data and its type (Panel 2)
  - across study type on the basis of the toxicity effects (Panel 3)

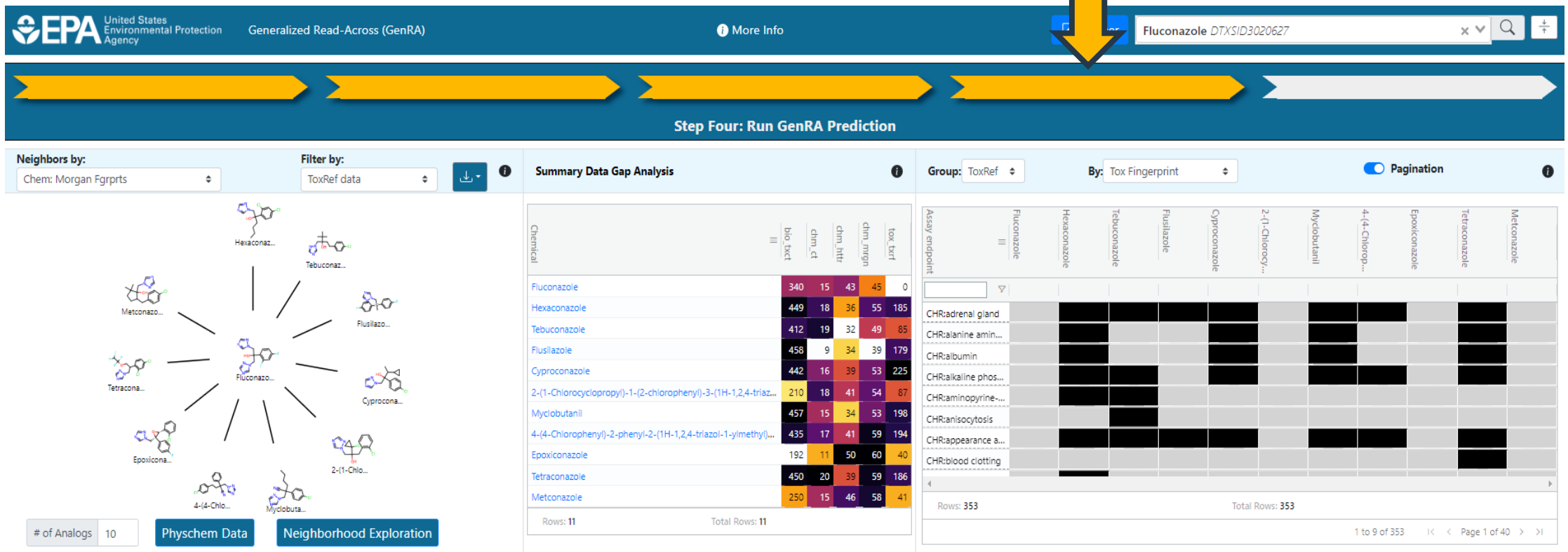
Analogue Evaluation



- More detailed evaluation of the source analogues
  - Click the Generate Data Matrix button
  - Evaluate source analogues' concordance and consistency within and across the study types

Data Gap Analysis/Data Matrix View

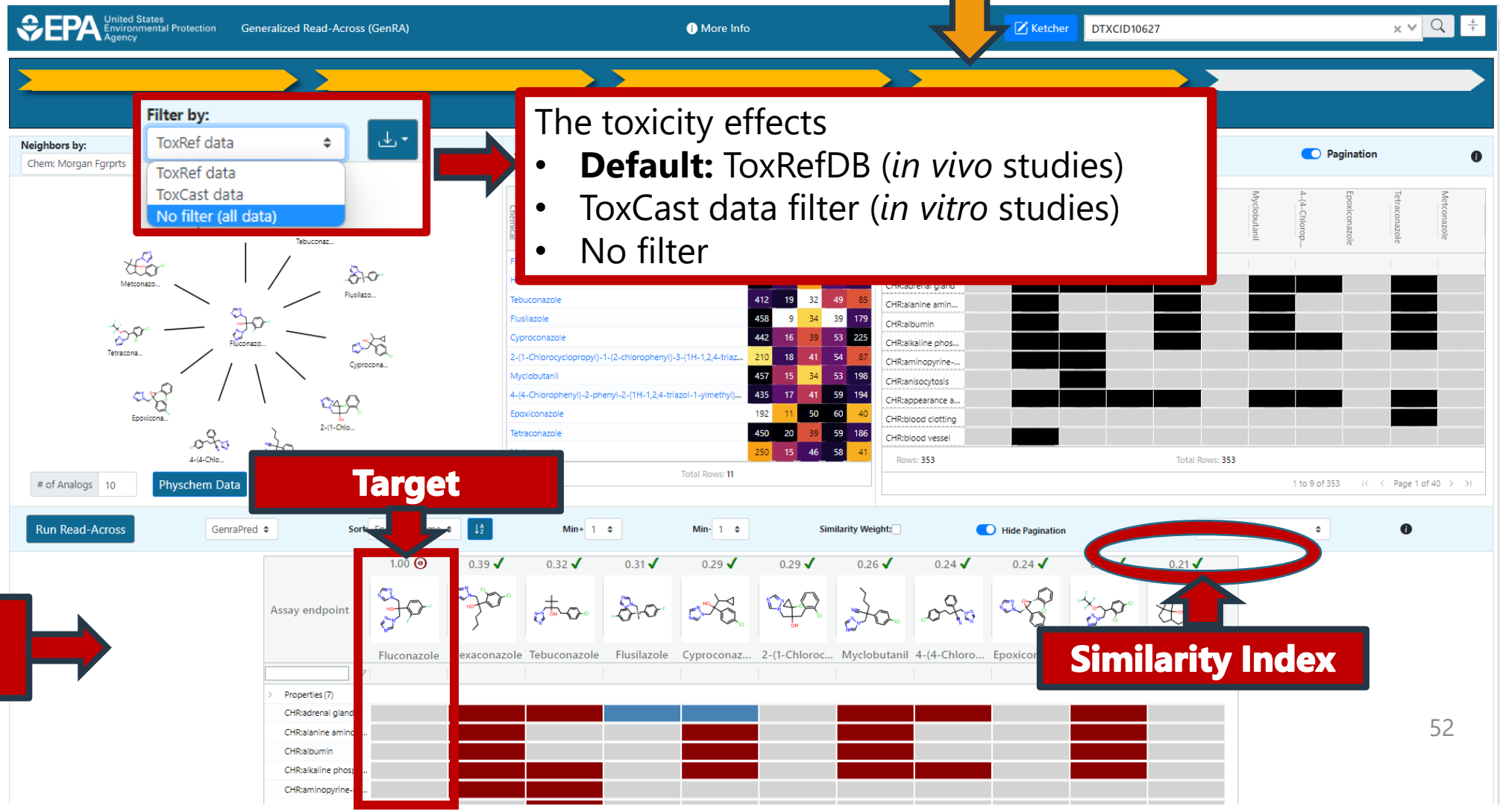
Step 4: Run GenRA Prediction



- This creates a DATA MATRIX VIEW in Panel 4

Data Gap Analysis/Data Matrix View

Step 4: Run GenRA Prediction

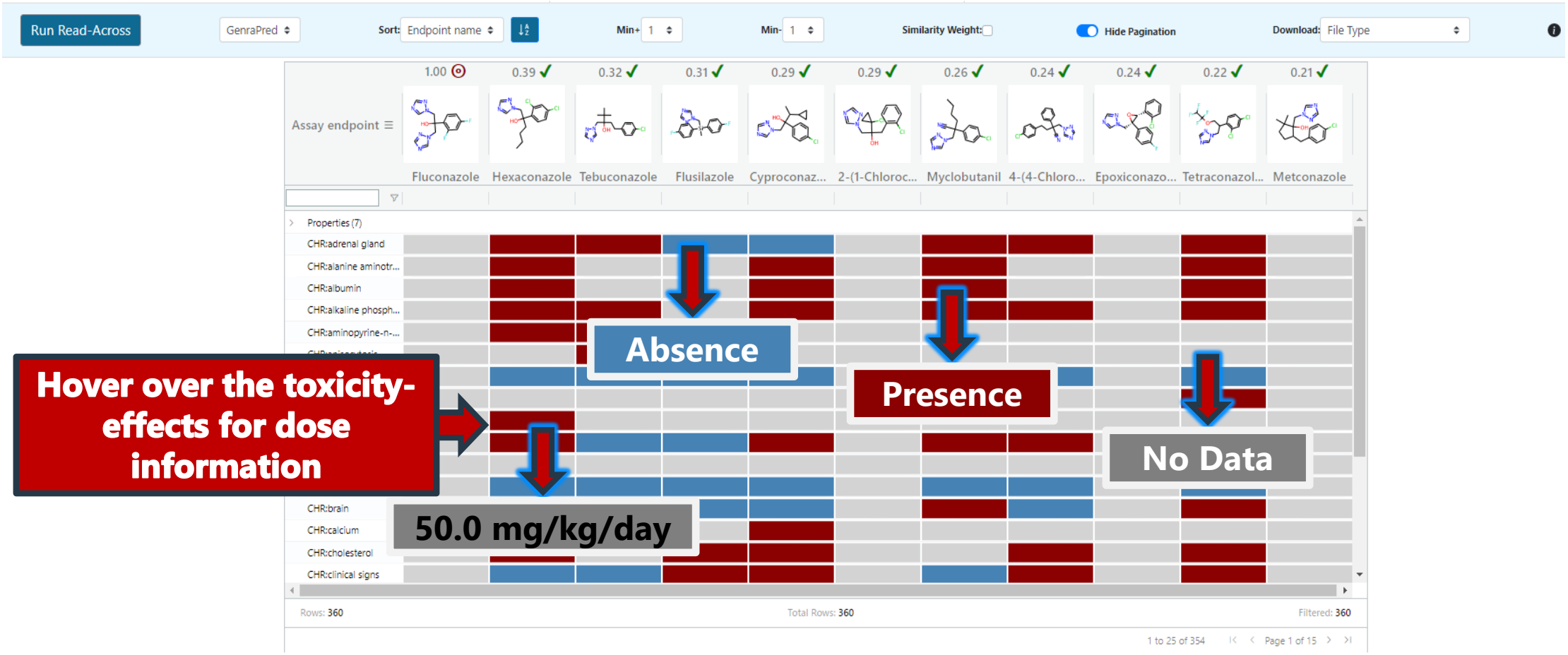


Data Gap Analysis/Data Matrix View

Toxicity Effects

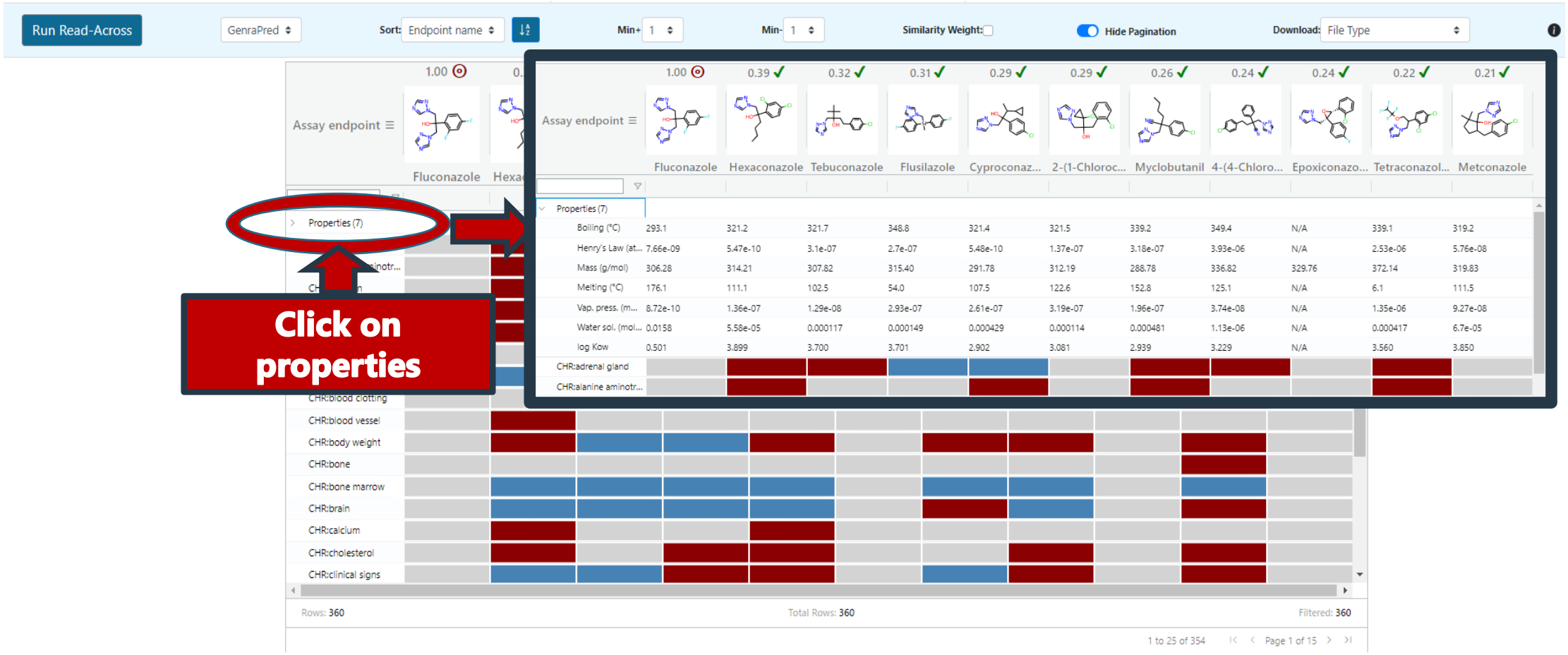
- The source analogues are ordered by their pairwise similarity relative to the target chemical
- The toxicity effects *(in vivo* studies from ToxRefDB) are populated across the analogues
- ToxCast data filter is for *in vitro* data and no filter is without considering any data
- Binary data / predictions and Potency data / predictions

Data Gap Analysis/Data Matrix View



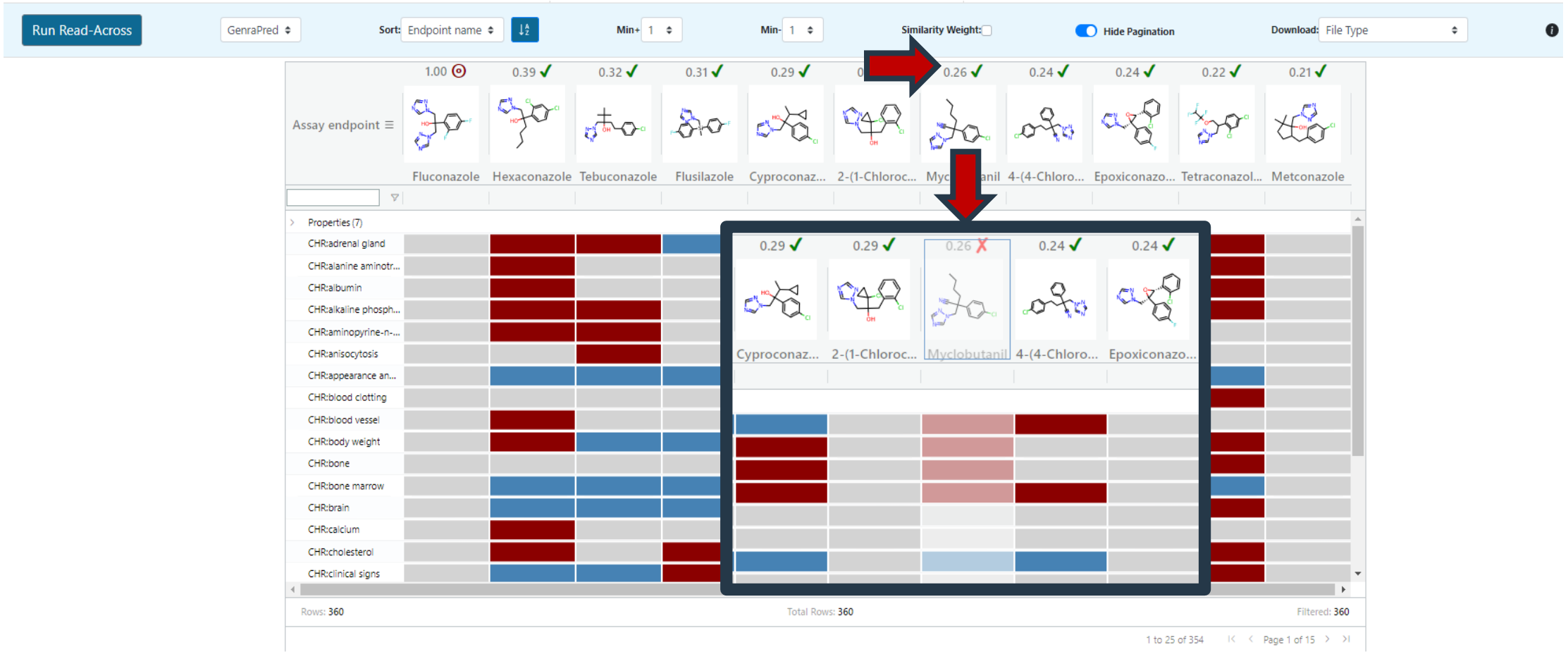
- Blue indicates 'Absence' of toxicity effects
- Red indicates 'Presence' of toxicity effects
- Grey represents 'No Data'
- Endpoints are measured in mg/kg/day=minimum dose for observed effects

Data Gap Analysis/Data Matrix View



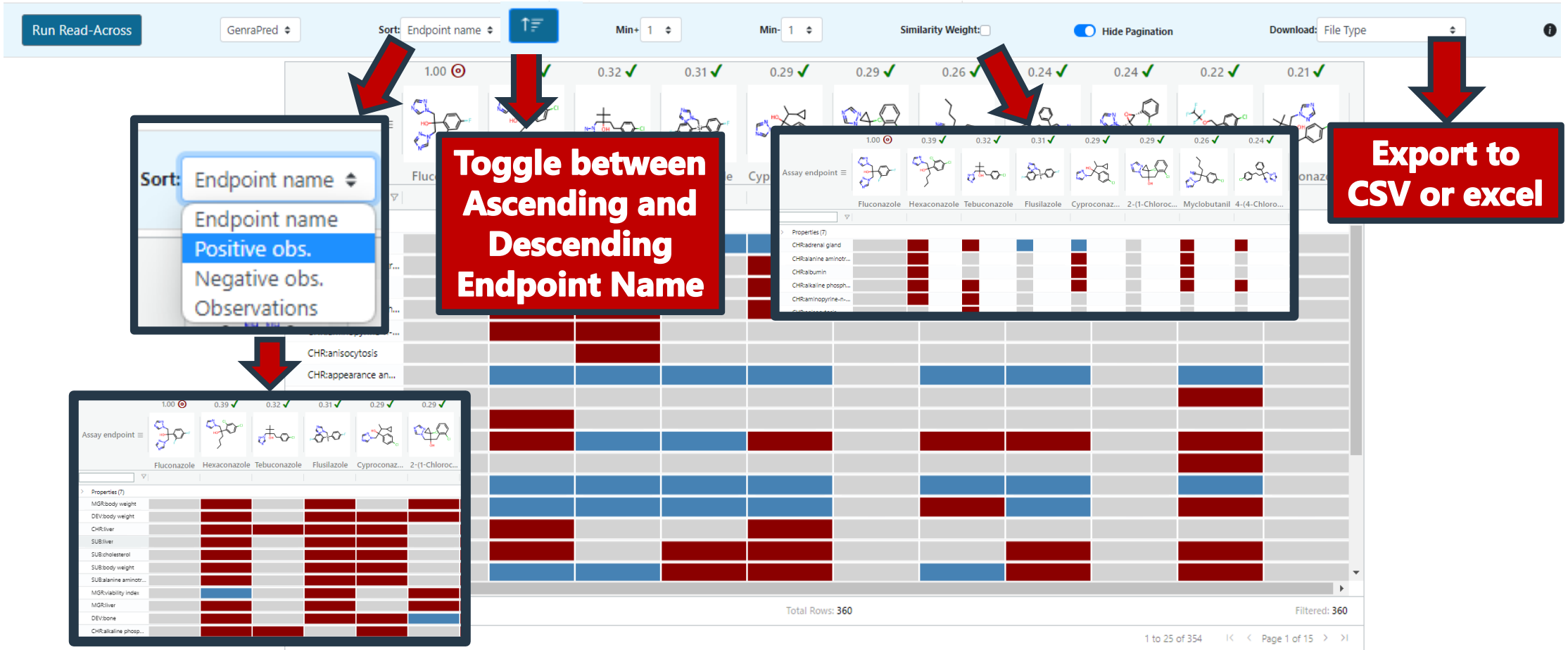
- Click on the 'Properties' arrow to evaluate (OPERA predicted) physical property and e-fate information across analogues

Data Gap Analysis/Data Matrix View



- Removing Analogues within the Data Matrix:
- De-select directly from analogue bar

Data Gap Analysis/Data Matrix View



- Toggle between ascending and descending endpoint name
- The data displayed can be filtered by specific effects (Sort by Observations)
- Similarity Weight checkbox modifies the size of the box to reflect the pairwise similarity metric.

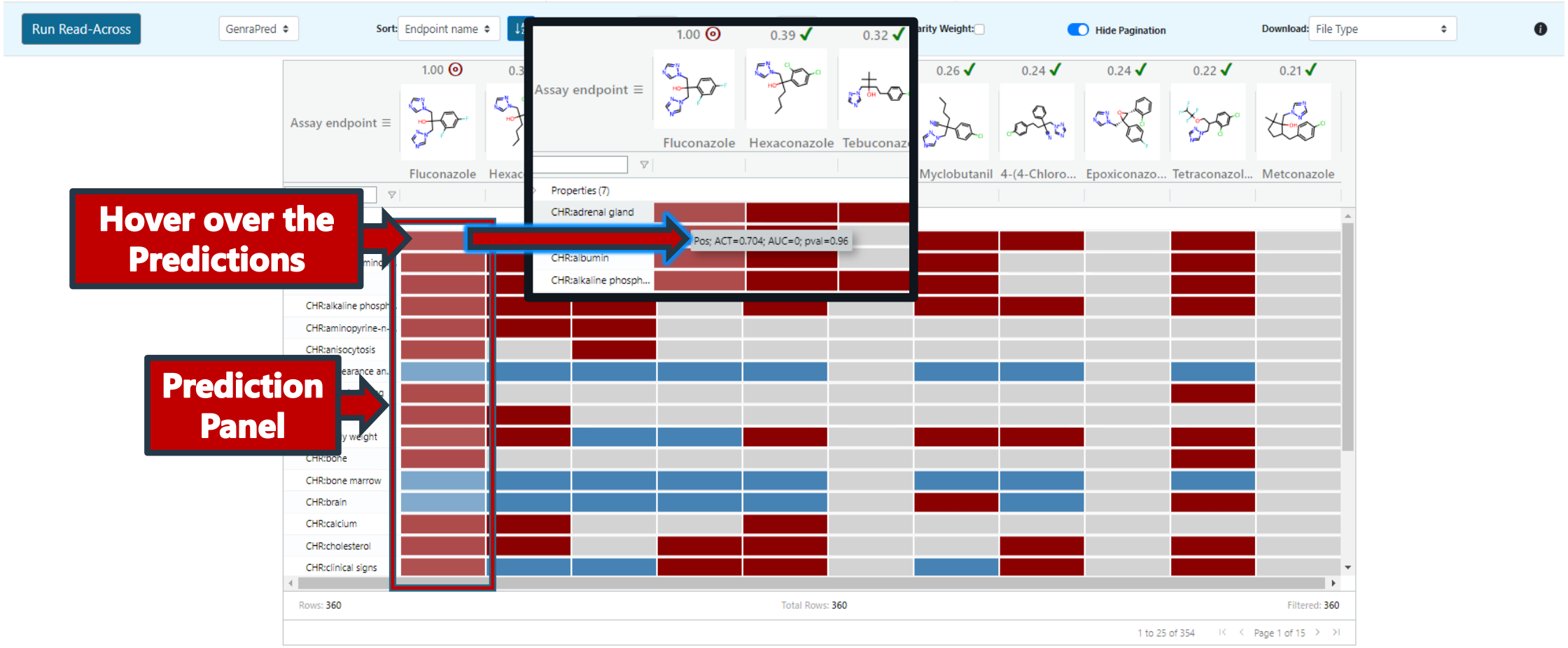
Data Gap Filling

- This step generates GenRA predictions.
  - GenraPred: Legacy prediction engine, binary only, reports confidence
  - GenraPy: Binary and continuous prediction, no confidence reporting (Yet!)

Data Gap Filling Predictions

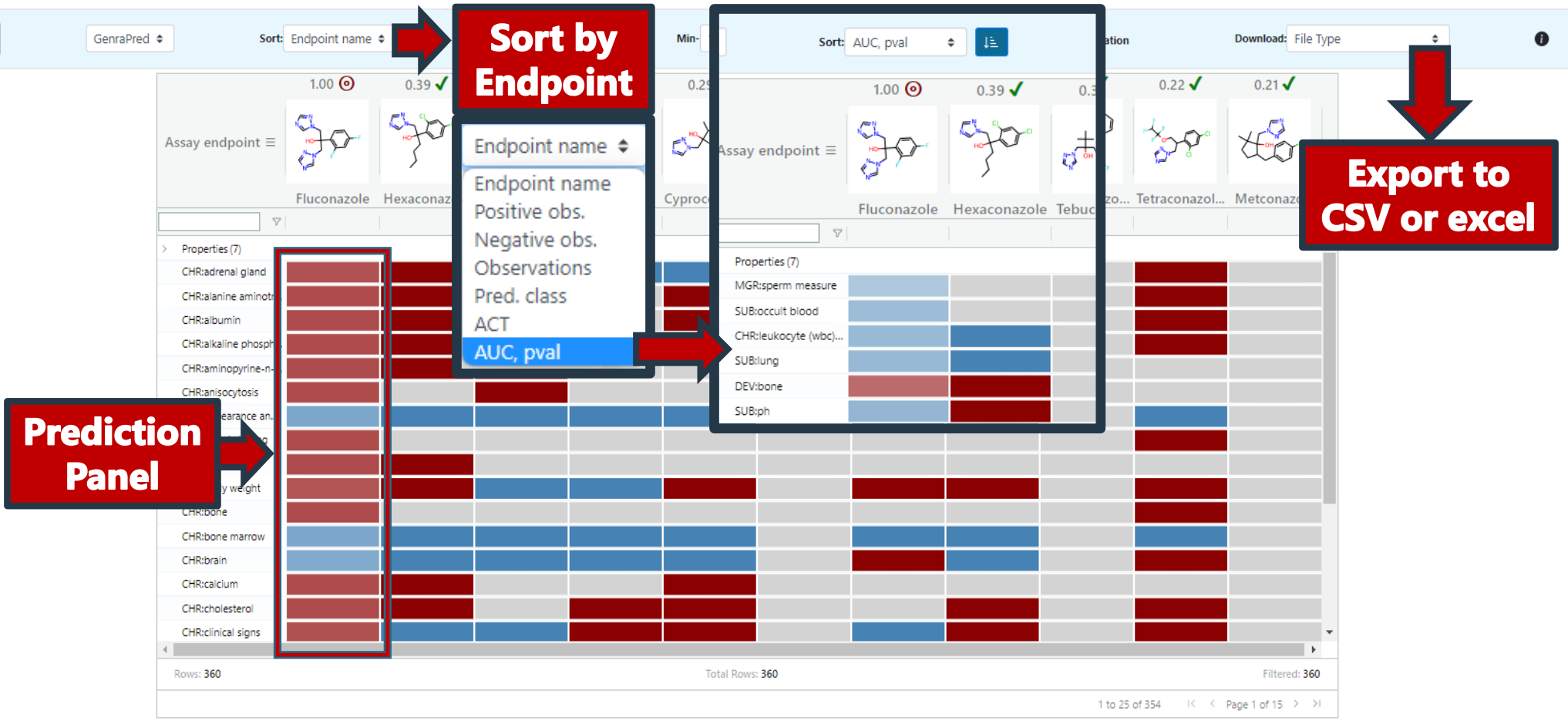
Step 5: Filter by Endpoint or Analogue

Data Gap Filling Predictions



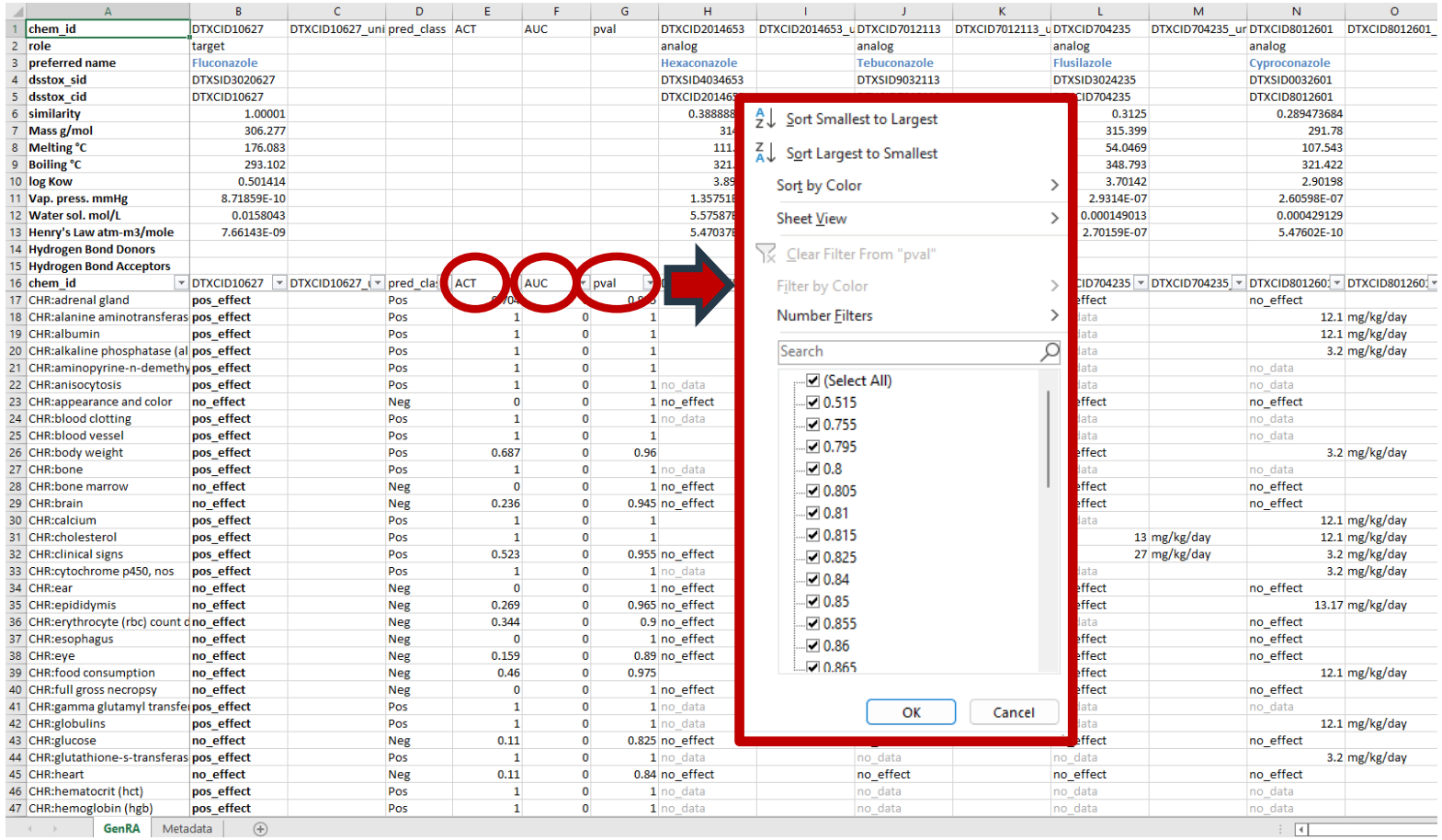
- The opacity of the predictions reflects the confidence in the prediction
- A faint colored prediction will denote lower confidence in the prediction.

Data Gap Filling Predictions



- Endpoints can be sorted
- Predictions can be exported by clicking on the 'Download' button

Exporting Results



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	chem_id	DTXCID10627	DTXCID10627_uni	pred_class	ACT	AUC	pval	DTXCID2014653	DTXCID2014653_u	DTXCID7012113	DTXCID7012113_u	DTXCID704235	DTXCID704235_ur	DTXCID8012601	DTXCID8012601_
2	role	target						analog		analog		analog		analog	
3	preferred name	Fluconazole						Hexaconazole		Tebuconazole		Flusilazole		Cyproconazole	
4	dsstox_sid	DTXSID3020627						DTXSID4034653		DTXSID9032113		DTXSID3024235		DTXSID0032601	
5	dsstox_cid	DTXCID10627						DTXCID201463				CID704235		DTXCID8012601	
6	similarity	1.00001						0.388888				0.3125		0.289473684	
7	Mass g/mol	306.277						314				315.399		291.78	
8	Melting °C	176.083						111				54.0469		107.543	
9	Boiling °C	293.102						321				348.793		321.422	
10	log Kow	0.501414						3.89				3.70142		2.90198	
11	Vap. press. mmHg	8.71859E-10						1.35751				2.9314E-07		2.60598E-07	
12	Water sol. mol/L	0.0158043						5.57587				0.000149013		0.000429129	
13	Henry's Law atm-m3/mole	7.66143E-09						5.47037				2.70159E-07		5.47602E-10	
14	Hydrogen Bond Donors														
15	Hydrogen Bond Acceptors														
16	chem_id	DTXCID10627	DTXCID10627_(	pred_clas	ACT	AUC	pval	D				CID704235	DTXCID704235	DTXCID801260	DTXCID801260
17	CHR:adrenal gland	pos_effect		Pos			0.9					effect		no_effect	
18	CHR:alanine aminotransferas	pos_effect		Pos	1	0	1					data		12.1	mg/kg/day
19	CHR:albumin	pos_effect		Pos	1	0	1					data		12.1	mg/kg/day
20	CHR:alkaline phosphatase (al	pos_effect		Pos	1	0	1					data		3.2	mg/kg/day
21	CHR:aminopyrine-n-demethy	pos_effect		Pos	1	0	1					data		no_data	
22	CHR:anisocytosis	pos_effect		Pos	1	0	1	no_data				data		no_data	
23	CHR:appearance and color	no_effect		Neg	0	0	1	no_effect				effect		no_effect	
24	CHR:blood clotting	pos_effect		Pos	1	0	1	no_data				data		no_data	
25	CHR:blood vessel	pos_effect		Pos	1	0	1					data		no_data	
26	CHR:body weight	pos_effect		Pos	0.687	0	0.96					effect		3.2	mg/kg/day
27	CHR:bone	pos_effect		Pos	1	0	1	no_data				data		no_data	
28	CHR:bone marrow	no_effect		Neg	0	0	1	no_effect				effect		no_effect	
29	CHR:brain	no_effect		Neg	0.236	0	0.945	no_effect				effect		no_effect	
30	CHR:calcium	pos_effect		Pos	1	0	1					data		12.1	mg/kg/day
31	CHR:cholesterol	pos_effect		Pos	1	0	1						13 mg/kg/day	12.1	mg/kg/day
32	CHR:clinical signs	pos_effect		Pos	0.523	0	0.955	no_effect					27 mg/kg/day	3.2	mg/kg/day
33	CHR:cytochrome p450, nos	pos_effect		Pos	1	0	1	no_data				data		3.2	mg/kg/day
34	CHR:ear	no_effect		Neg	0	0	1	no_effect				effect		no_effect	
35	CHR:epididymis	no_effect		Neg	0.269	0	0.965	no_effect				effect		13.17	mg/kg/day
36	CHR:erythrocyte (rbc) count d	no_effect		Neg	0.344	0	0.9	no_effect				data		no_effect	
37	CHR:esophagus	no_effect		Neg	0	0	1	no_effect				effect		no_effect	
38	CHR:eye	no_effect		Neg	0.159	0	0.89	no_effect				effect		no_effect	
39	CHR:food consumption	no_effect		Neg	0.46	0	0.975					effect		12.1	mg/kg/day
40	CHR:full gross necropsy	no_effect		Neg	0	0	1	no_effect				effect		no_effect	
41	CHR:gamma glutamyl transfer	pos_effect		Pos	1	0	1	no_data				data		no_data	
42	CHR:globulins	pos_effect		Pos	1	0	1	no_data				data		12.1	mg/kg/day
43	CHR:glucose	no_effect		Neg	0.11	0	0.825	no_effect				effect		no_effect	
44	CHR:glutathione-s-transferas	pos_effect		Pos	1	0	1	no_data		no_data		no_data		3.2	mg/kg/day
45	CHR:heart	no_effect		Neg	0.11	0	0.84	no_effect		no_effect		no_effect		no_effect	
46	CHR:hematocrit (hct)	pos_effect		Pos	1	0	1	no_data		no_data		no_data		no_data	
47	CHR:hemoglobin (hgb)	pos_effect		Pos	1	0	1	no_data		no_data		no_data		no_data	

- Snapshot of a sample prediction output produced in the Excel (xlsx) export file
- The **AUC** performance measure and the **p-value** that is associated with the prediction are provided
- P values can be sorted. (**High p-values = non-significant confidence in the predictions**)
- The actual experimental data for the source analogues is also reflected.

GenRA Summary

- GenRA is an attempt to move towards an objective read-across approach where uncertainties and performance can be quantified.
- Provides opportunities for different NAM data to be incorporated.
- GenRA v1.0 established a baseline in performance. Research has continued to evaluate performance using other contexts of similarity e.g. physicochemical similarity, targeted transcriptomic similarity, metabolic similarity.
- New features coming include defined categories and/or user specific neighbourhoods, other similarity contexts and other *in vivo* toxicity data streams.

More information…

epa.gov/chemical-research/generalized-read-across-genra

Related Topics: Safer Chemicals Research

CONTACT US

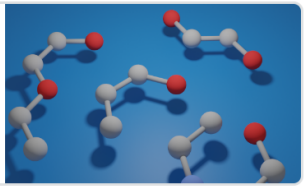
Generalized Read-Across (GenRA)

Access GenRA

GenRA | Web Application

About

GenRA | About



User Manual

Learn to navigate and utilize GenRA.

GenRA | Manual

Release Notes

Access information on the latest and previous versions of GenRA.

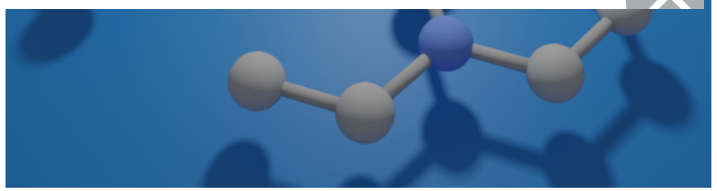
GenRA | Release Notes

Training

Explore training materials for GenRA and other tools through the New Approach Methods (NAMs) Training Site.

NAMs Training

perspective. GenRA is an algorithmic approach to permit objective and reproducible read-across predictions of *in vivo* toxicity and *in vitro* bioactivity.



More Resources

- GenRA: Resource Hub
- Access GenRA
- GenRA: About
- GenRA: User Manual
- GenRA: Release Notes
- New Approach Methods Training

United States Environmental Protection Agency

Q&A

Thank You!

Contact us if you have

- GenRA questions: genra.support@epa.gov
- Future NAMs training questions: NAM@EPA.gov

Save the date for our next training!

HTTK

November 8th, 2023