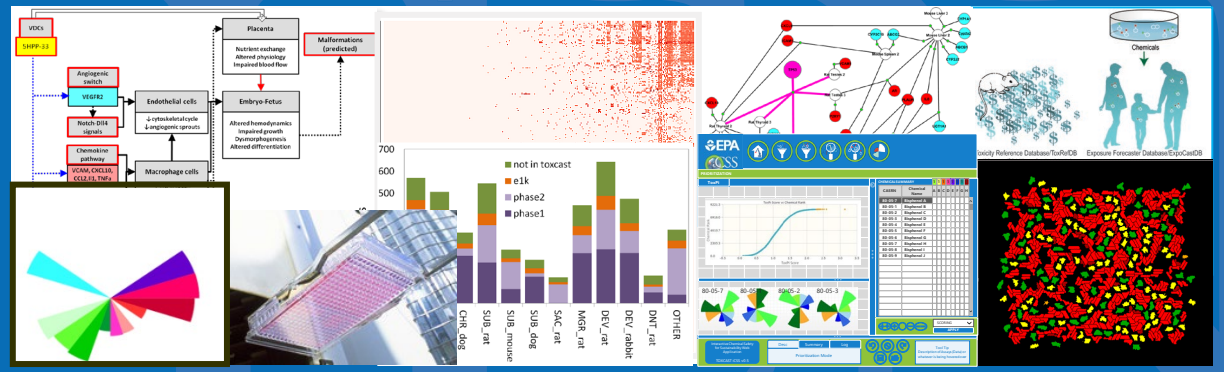
Primer on New Versions of CompTox Chemicals Dashboard and Generalised Read-Across: GenRA Version 3...



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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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EPA United States Environmental Protection Agency

Outline

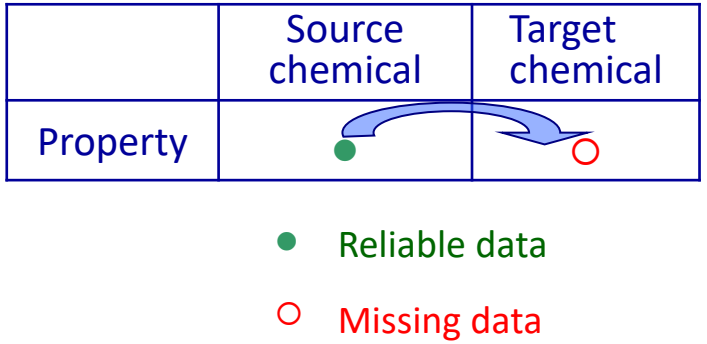
- Wait was there a Version 2 of GenRA…?
- Recap of Generalised Read-Across (GenRA)
- Current research focus
- GenRA Version 3 – new features and functionality
- Walk through on how to use Version 3
- Summary remarks

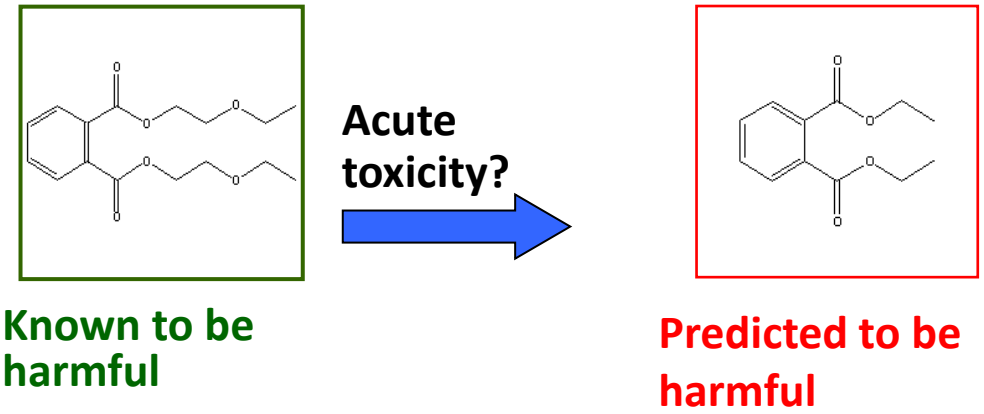
Wait was there a Version 2?

- Yes! But you probably missed it….
- There was a public release in December 2021..but Version 3 saw significant refinements hence this COP is intended to showcase everything that was developed for Version 2 and all that is new in Version 3 at the same time.

Background: 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.
- Used within analogue and category approaches.
- 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.





Ongoing issues with read-across

- Although there is much guidance for developing read-across assessment, acceptance remains an issue, not helped since read-across still remains a subjective, expert driven assessment.
- One issue thwarting acceptance relates to the "uncertainty of the read-across prediction".
- As such there have been many efforts to identify the sources of uncertainty in read-across, characterise them in a consistent manner and identify practical strategies to address and reduce those uncertainties.
- Notable in these efforts have been the development of frameworks for the assessment of read-across, evaluating the utility of New Approach Methods (NAMs).
- Quantifying uncertainty and performance of read-across is still a need as are ways to better characterise different similarity contexts (metabolism, reactivity etc.)

7

Other Read-Across Tools

Computational Toxicology 3 (2017) 1–18

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

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Nearest neighbours

ABSTRACT

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

Published by

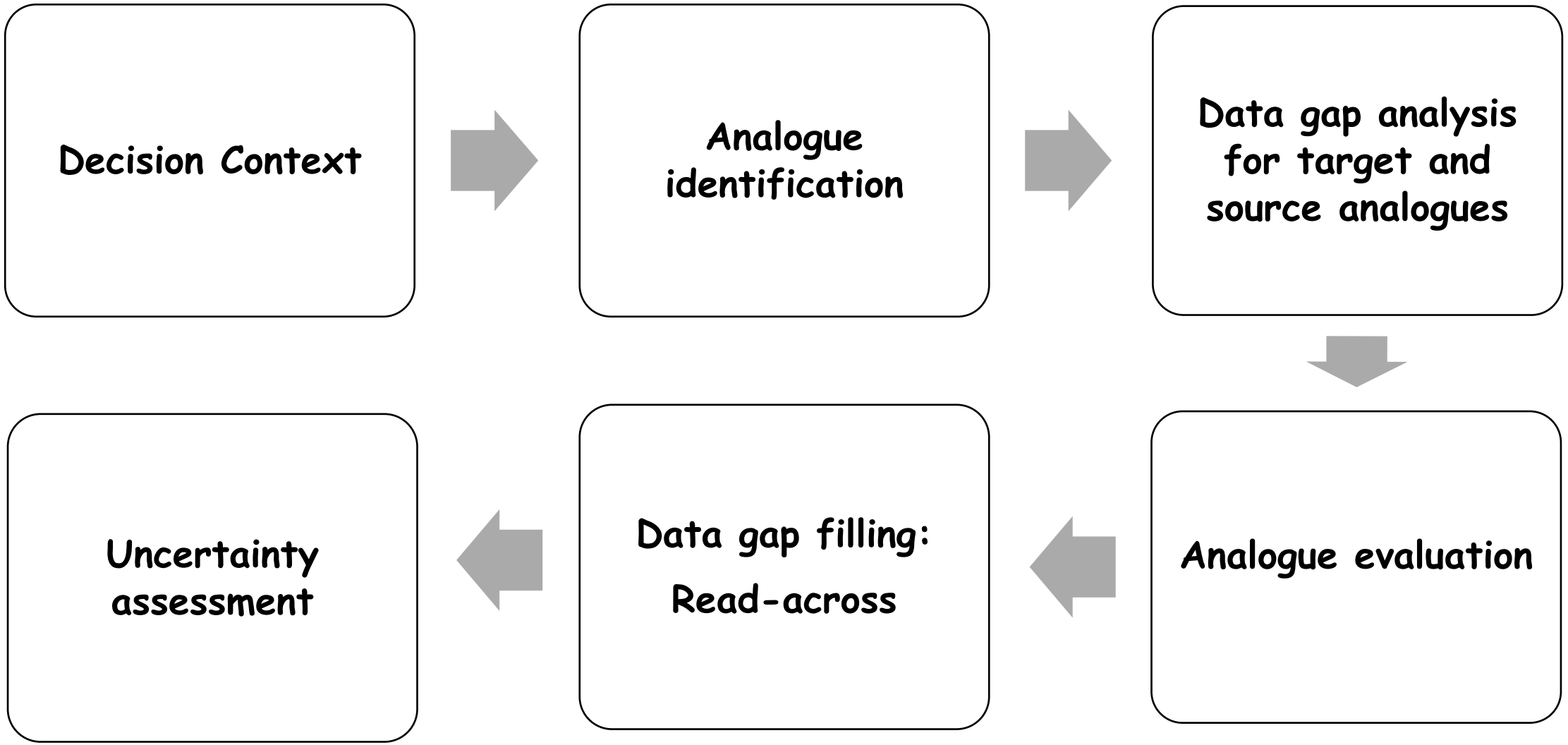
(Patlewicz et al., 2017)

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.

Read-across workflow



A harmonised hybrid read-across workflow

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com

Journal Cover Image

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

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- Where do NAM data fit?
- How should we transition to data-driven approaches?
- Quantifying the uncertainty in the read-across predictions made?

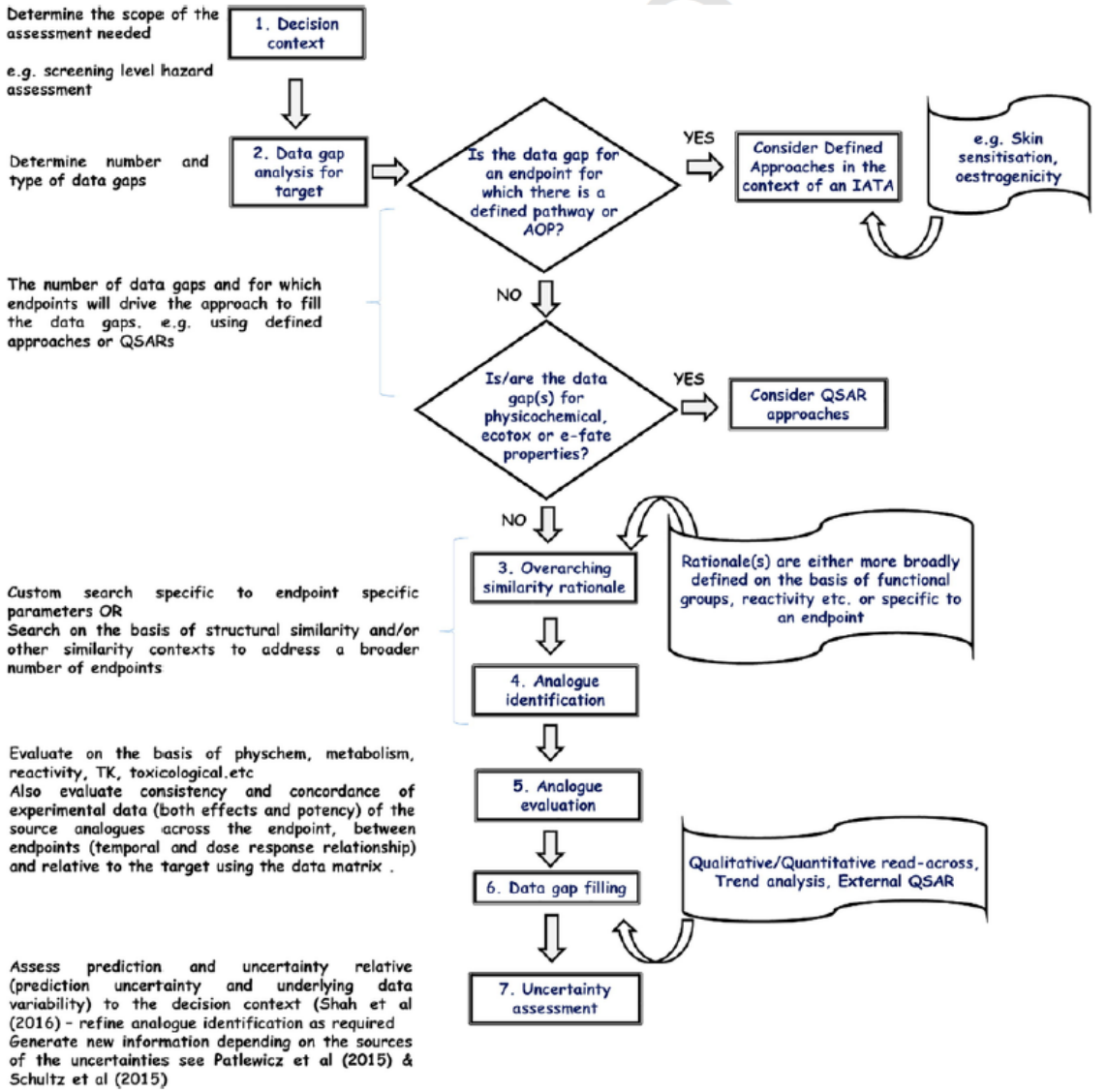


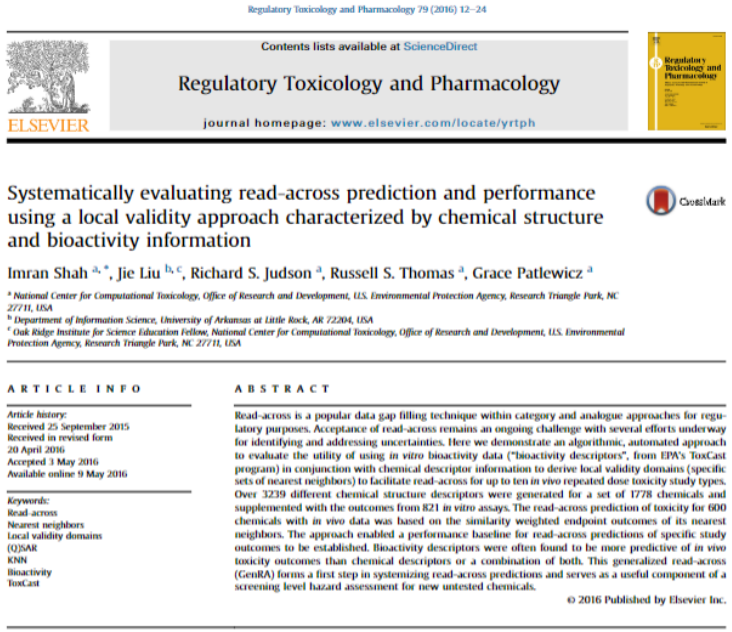
Fig. 9. A harmonised hybrid development and assessment framework.

Patlewicz et al., 2018

United States Environmental Protection Agency

GenRA (Generalised Read-Across)

- Predicting toxicity as a similarity-weighted activity of nearest neighbours 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



Regulatory Toxicology and Pharmacology 79 (2016) 12–24

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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

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KNN
Bioactivity
ToxCast

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:

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

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

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

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 workflow in GenRA v1.0

Decision Context

Screening level assessment of hazard based on toxicity effects from ToxRefDB v1

Analogue identification

Similarity context is based on structural characteristics

Data gap analysis for target and source analogues

Analogue evaluation

Evaluate consistency and concordance of experimental data of source analogues across and between endpoints

Read-across

Similarity weighted average – many to one read-across

Uncertainty assessment

Assess prediction and uncertainty using AUC and p value metrics

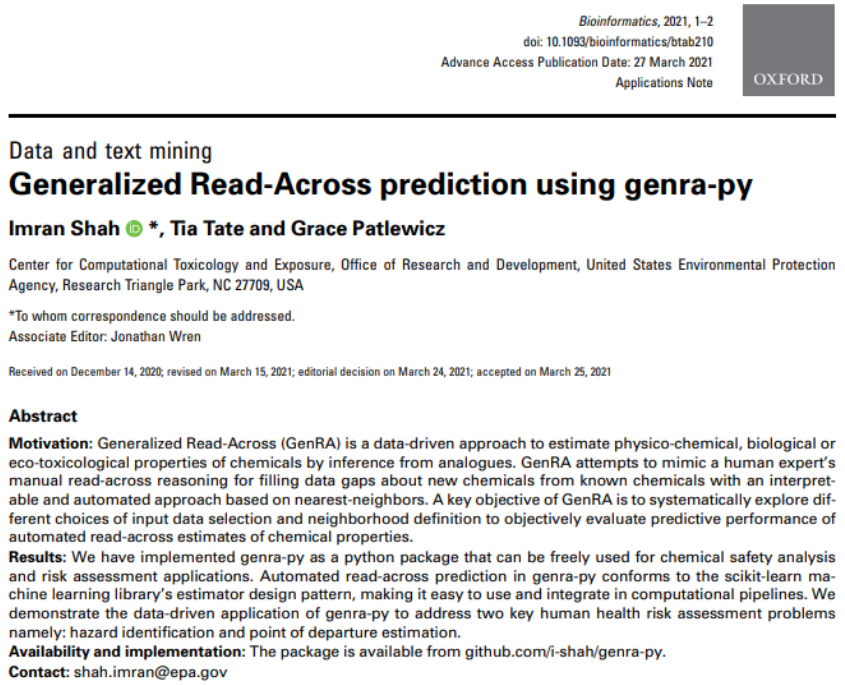
GenRA tool in reality

- GenRA v1.0 Integrated into the EPA CompTox Chemicals Dashboard

Related GenRA tools

- An alternative and programmatic batch means of using GenRA is available through genra-py, a standalone python library to enable user specific datasets to be analysed – see https://github.com/i-shah/genra-py (Shah et al, 2021)

- See https://github.com/patlewig/UNC_Rax for example to test out the tool with a specific acute toxicity example. (Relies on Binder – underpinned by Docker)



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Applications Note

OXFORD

Data and text mining

Generalized Read-Across prediction using genra-py

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Abstract

Motivation: Generalized Read-Across (GenRA) is a data-driven approach to estimate physico-chemical, biological or eco-toxicological properties of chemicals by inference from analogues. GenRA attempts to mimic a human expert's manual read-across reasoning for filling data gaps about new chemicals from known chemicals with an interpretable and automated approach based on nearest-neighbors. A key objective of GenRA is to systematically explore different choices of input data selection and neighborhood definition to objectively evaluate predictive performance of automated read-across estimates of chemical properties.

Results: We have implemented genra-py as a python package that can be freely used for chemical safety analysis and risk assessment applications. Automated read-across prediction in genra-py conforms to the scikit-learn machine learning library's estimator design pattern, making it easy to use and integrate in computational pipelines. We demonstrate the data-driven application of genra-py to address two key human health risk assessment problems namely: hazard identification and point of departure estimation.

Availability and implementation: The package is available from github.com/i-shah/genra-py.

Contact: shah.imran@epa.gov

GenRA – Current research

- Consideration of other information to define and refine the analogue selection & evaluation
  - physicochemical similarity (Helman et al 2018)
  - metabolic similarity (Boyce et al, 2022; Groff et al, *in prep*)
  - reactivity similarity (Nelms et al 2018)
  - transcriptomics similarity (Tate et al, 2021)
- Transitioning to quantitative predictions of toxicity
  - Using GenRA to predict Lowest Observed Adverse Effect Level (LOAEL), acute oral (median lethal dose) LD50 (Helman et al 2019a,b)
- Developing a compendium of expert driven read-across examples to investigate how data driven read-across with NAM data can mirror expert assessments (*in prep*)

GenRA Version 2 Highlights

- Version 2:
- Maintains existing read-across workflow
- Complete rebuild of GenRA Version 1.0
- ToxRefDB updated from Version 1 to Version 2
- ToxCast data updated to latest public release
- Chemical fingerprints recomputed to factor in additional substances in the DSSTox database that had been registered since initial release
- Ability to search for analogues without prefiltering on the basis of ToxRefDB data
- GenRA decoupled from the Dashboard i.e. an independent application but one which is still linked to the Dashboard

EPA United States Environmental Protection Agency

GenRA Version 3 Highlights

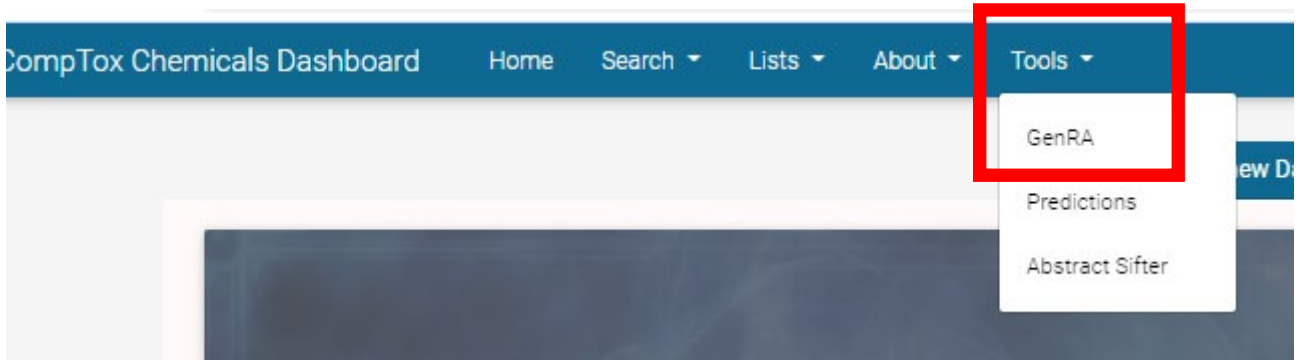
- Version 3
- UI rebuilt using AG Grid to provide more out of the box interactivity
- Custom fingerprints (users can specify fingerprint combinations based on existing fingerprints provided)
- Ketcher drawing palette to allow SMILES/MOL to be introduced and predictions to be made for substances not already within the Dashboard
- Contact email added to track bugs/refinements

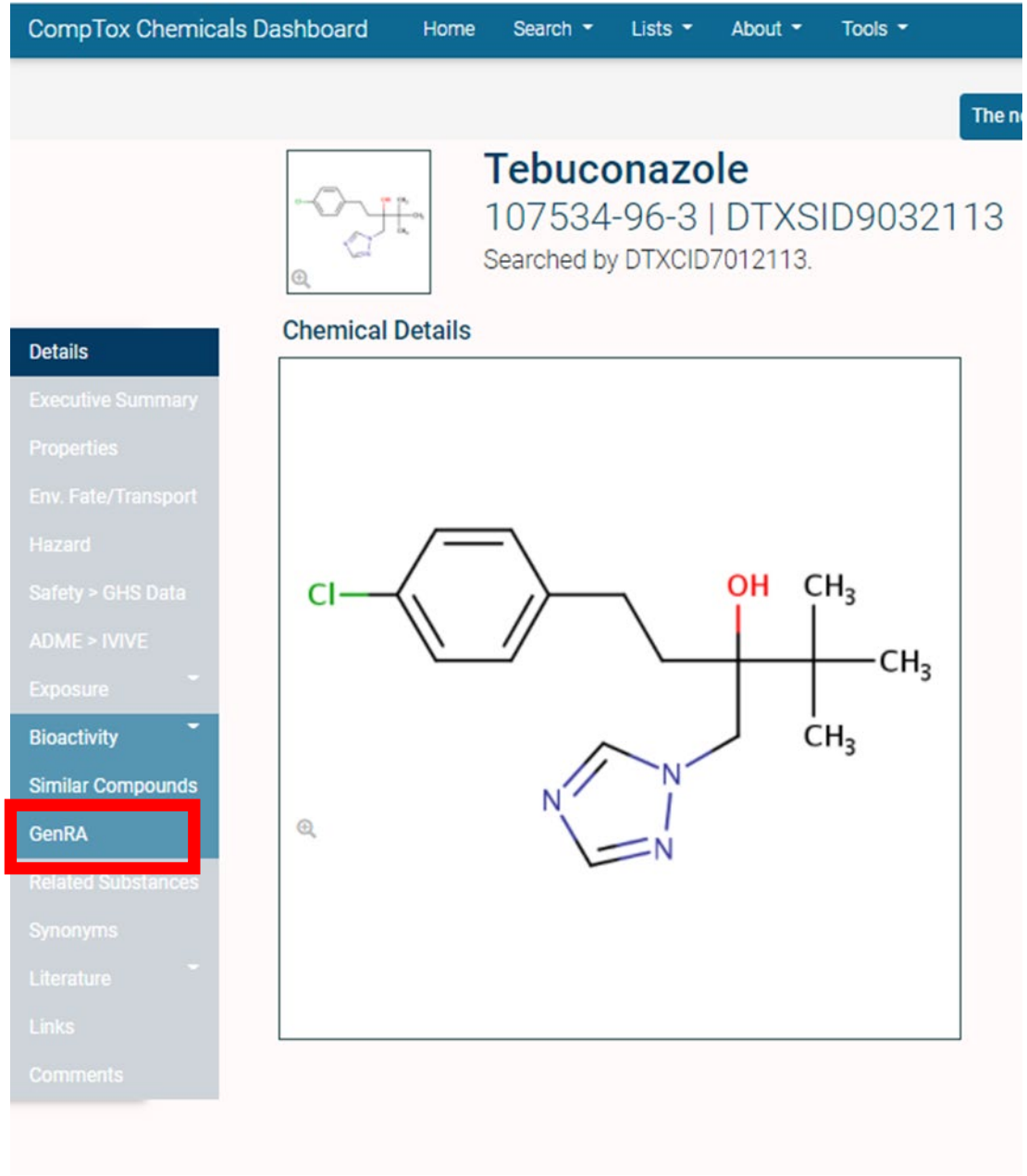
GenRA Version 3

Main entry point is from the portal comptox.epa.gov

However, can be accessed from the landing page within the Dashboard for a specific chemical or from the Tools menu within the Dashboard

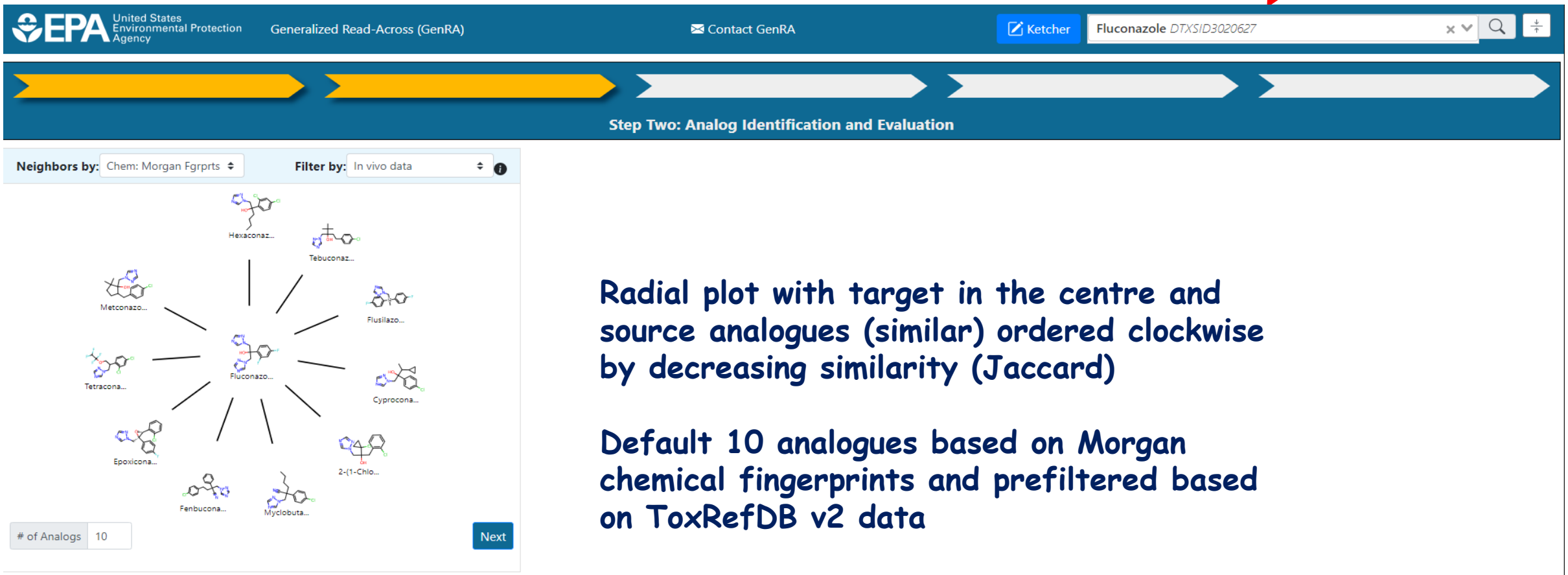
Alternative entry points





GenRA v3 in practice

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

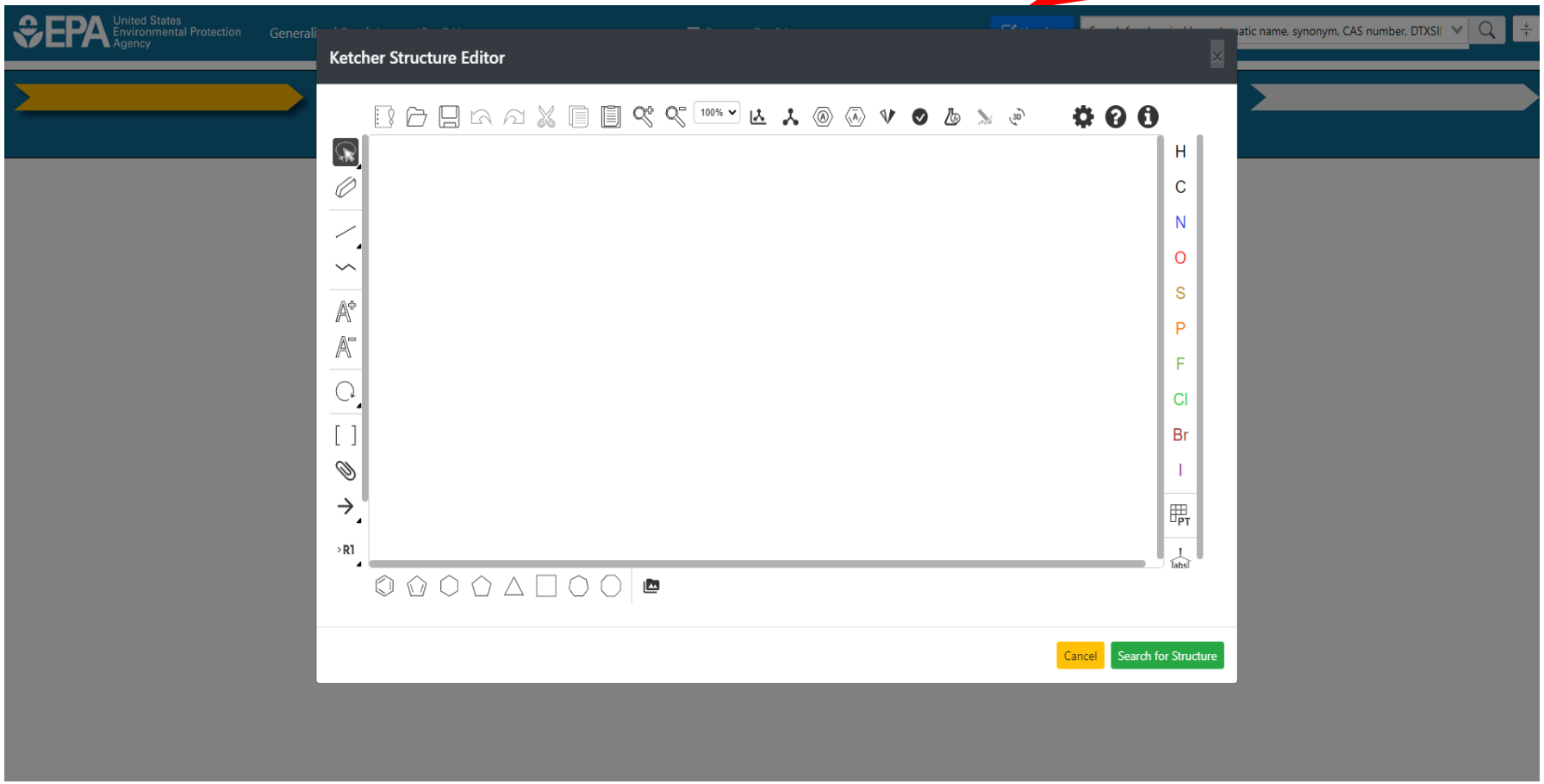


Radial plot with target in the centre and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)

Default 10 analogues based on Morgan chemical fingerprints and prefiltered based on ToxRefDB v2 data

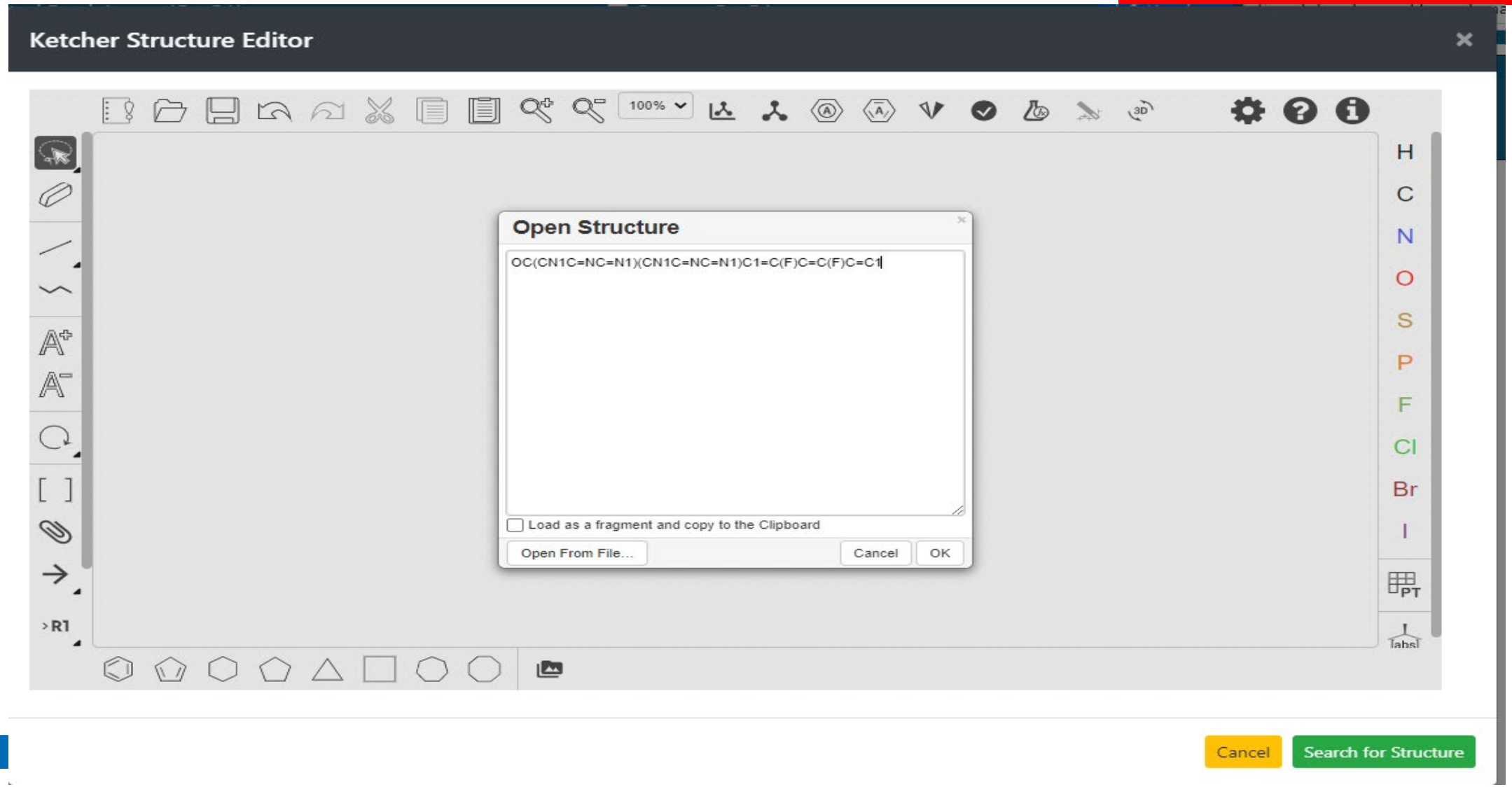
GenRA v3 in practice

Search for a chemical of interest (target) using the Ketcher

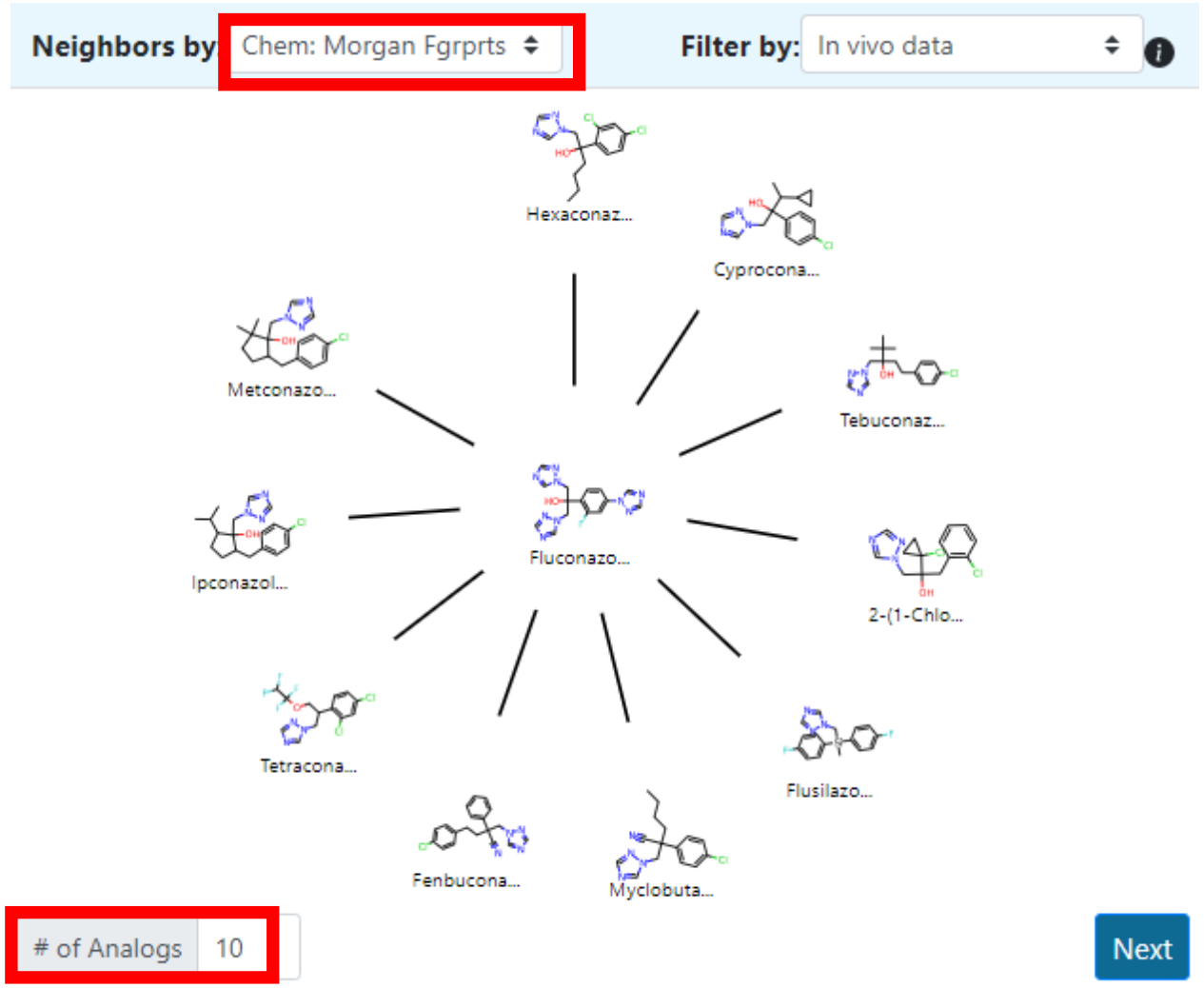


GenRA v3 in practice

Search for a chemical of interest (target) using the Ketcher



GenRA v3 in practice

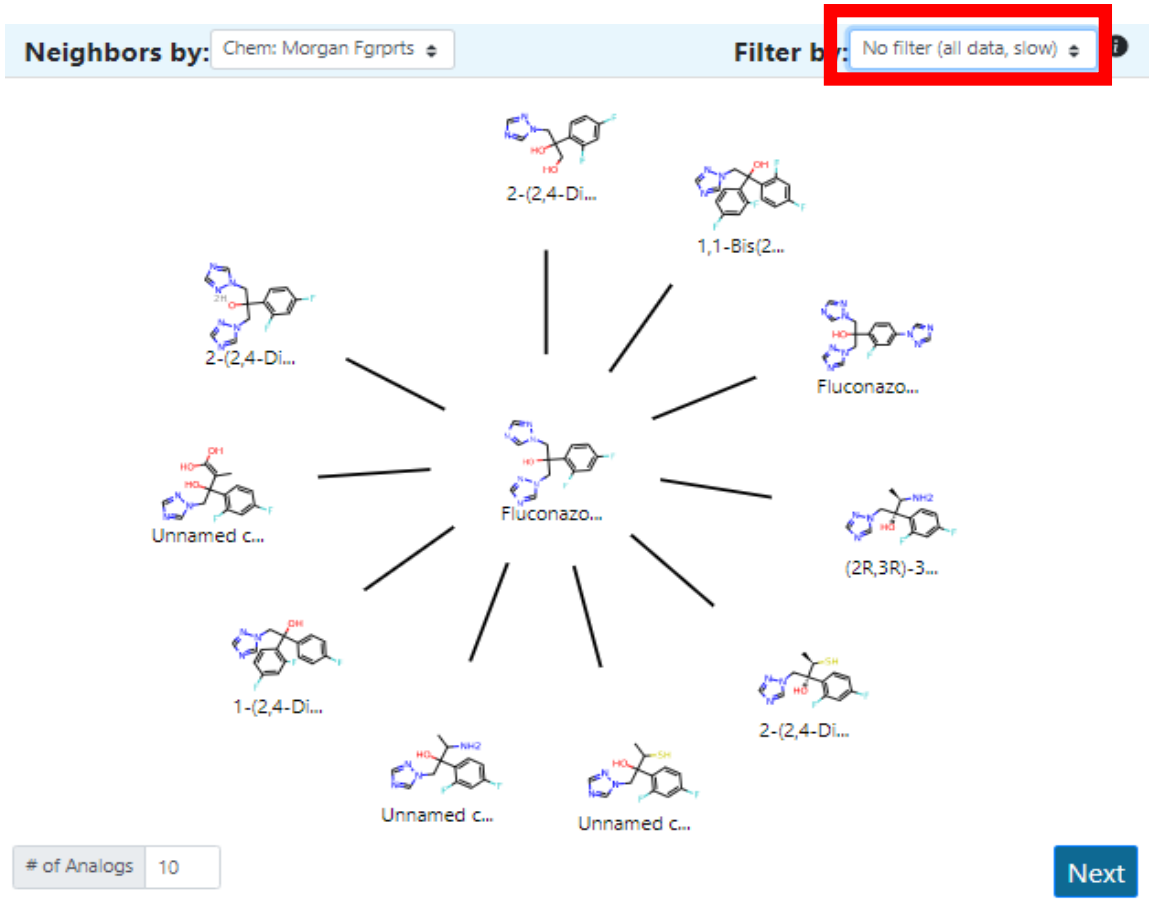


Radial plot with target in the centre and source analogues (similar) ordered clockwise by decreasing similarity (Jaccard)

Default 10 analogues based on Morgan chemical fingerprints and prefiltered based on ToxRefDB v2 data

Can update to change what features are used to characterise substances and the number of analogues returned

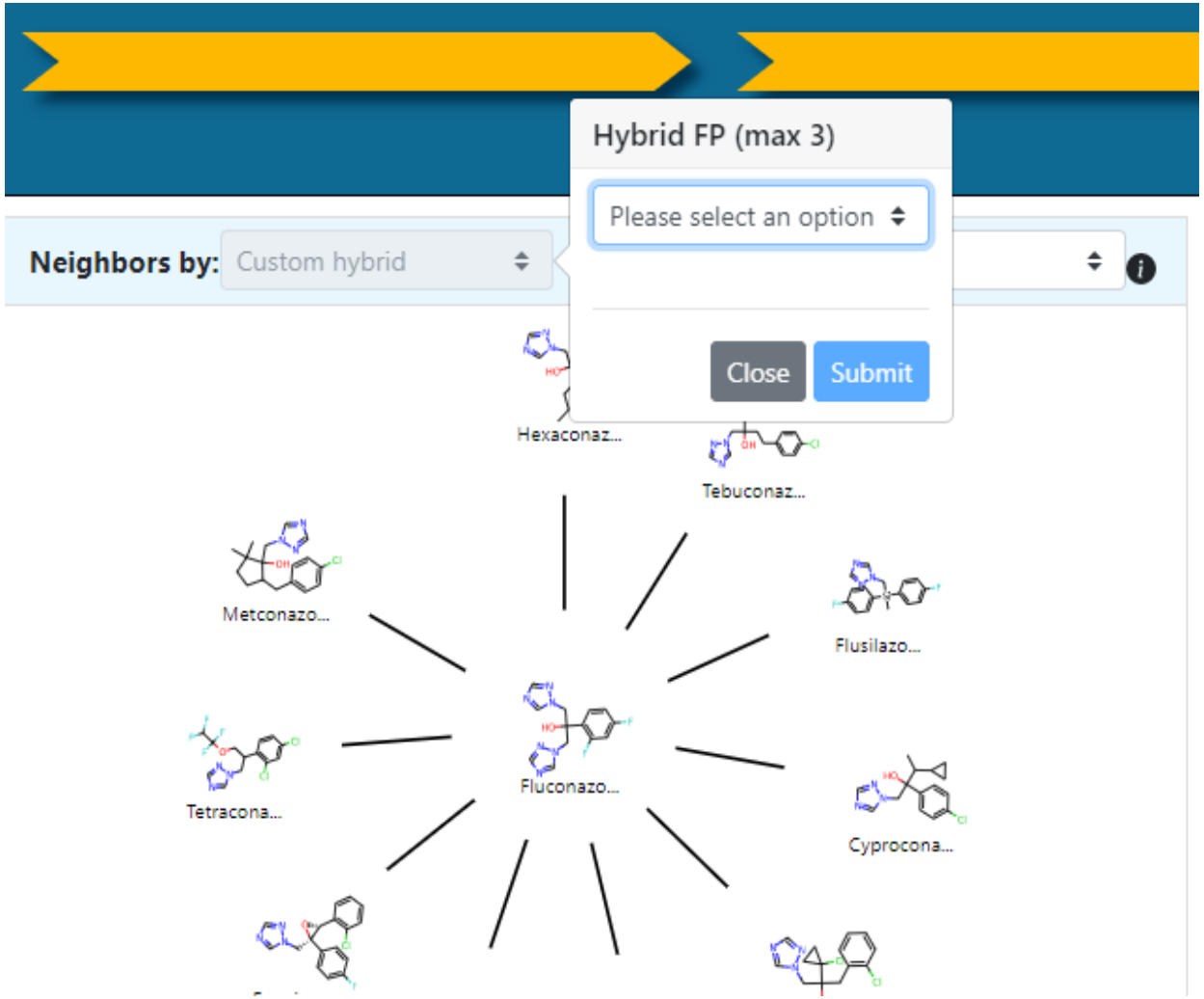
GenRA v3 in practice



Update radial plot to return analogues irrespective of ToxRefDB v2 data

Caution! This can be quite slow

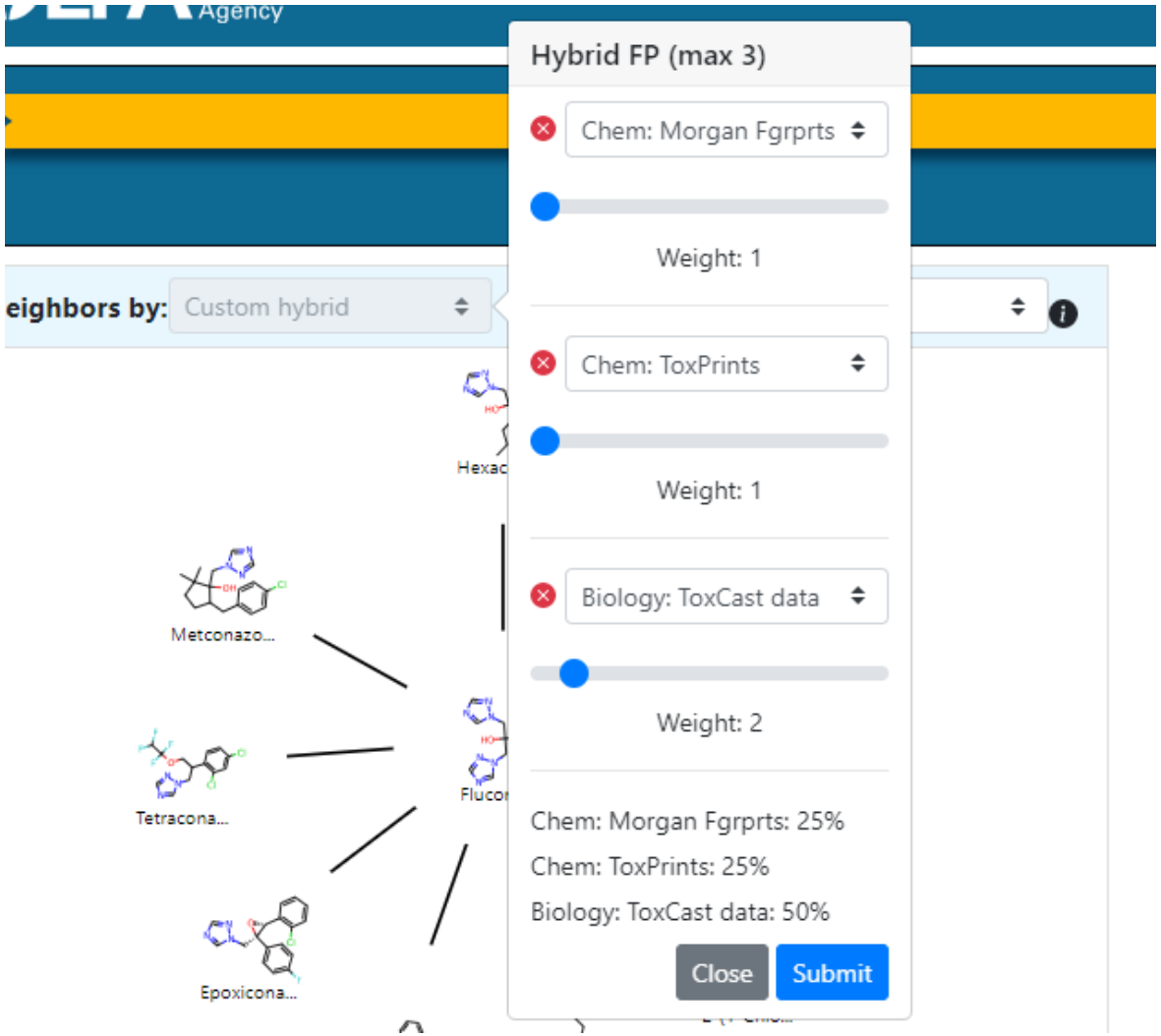
GenRA v3 in practice



Custom Fingerprints

Choose up to 3 fingerprints e.g. 50% ToxCast vs 50% Chemical Morgan Fingerprints & 25% ToxPrints

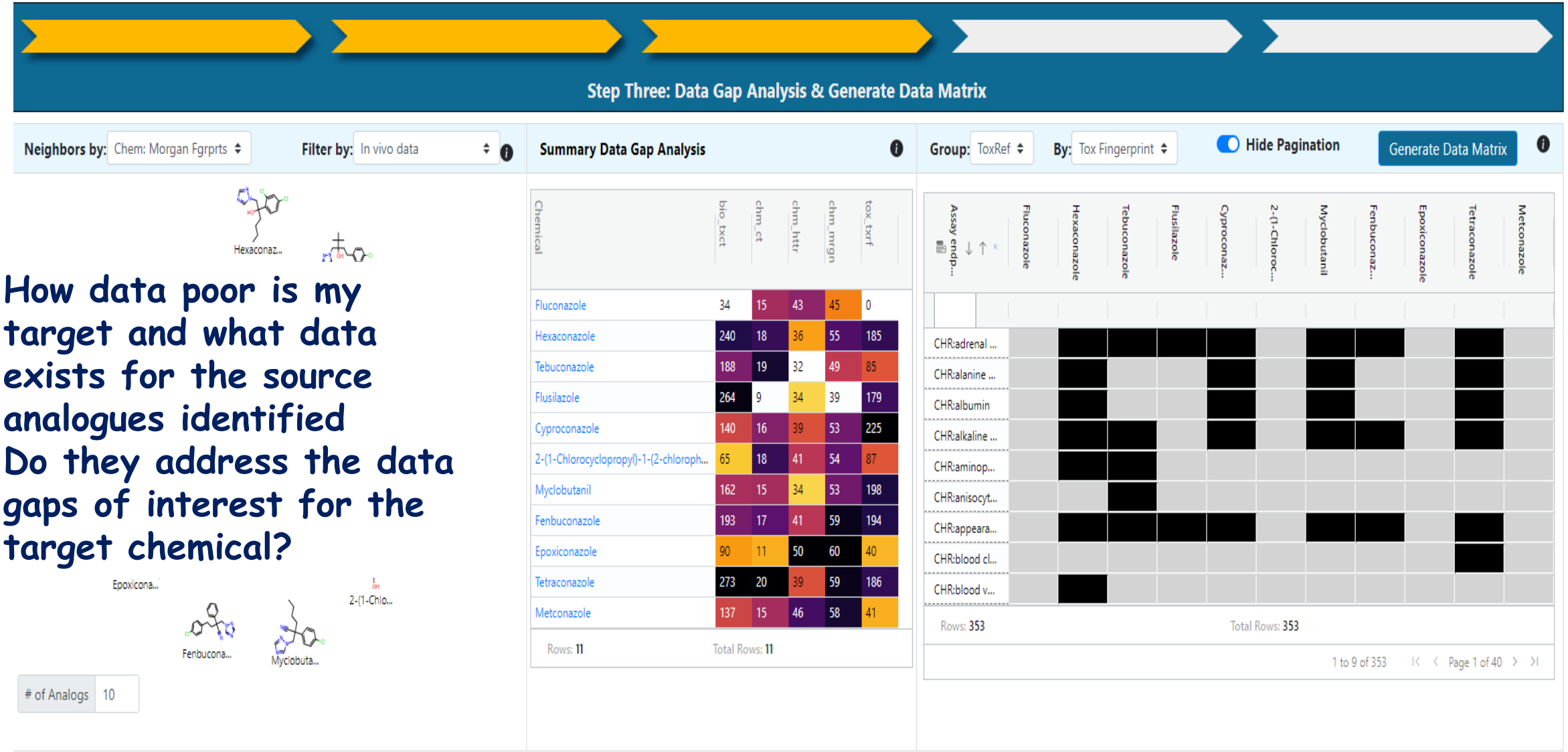
GenRA v3 in practice



Custom Fingerprints

Choose up to 3 fingerprints
e.g. 50% ToxCast vs 25% Chemical Morgan Fingerprints & 25% ToxPrints

GenRA v3 in practice

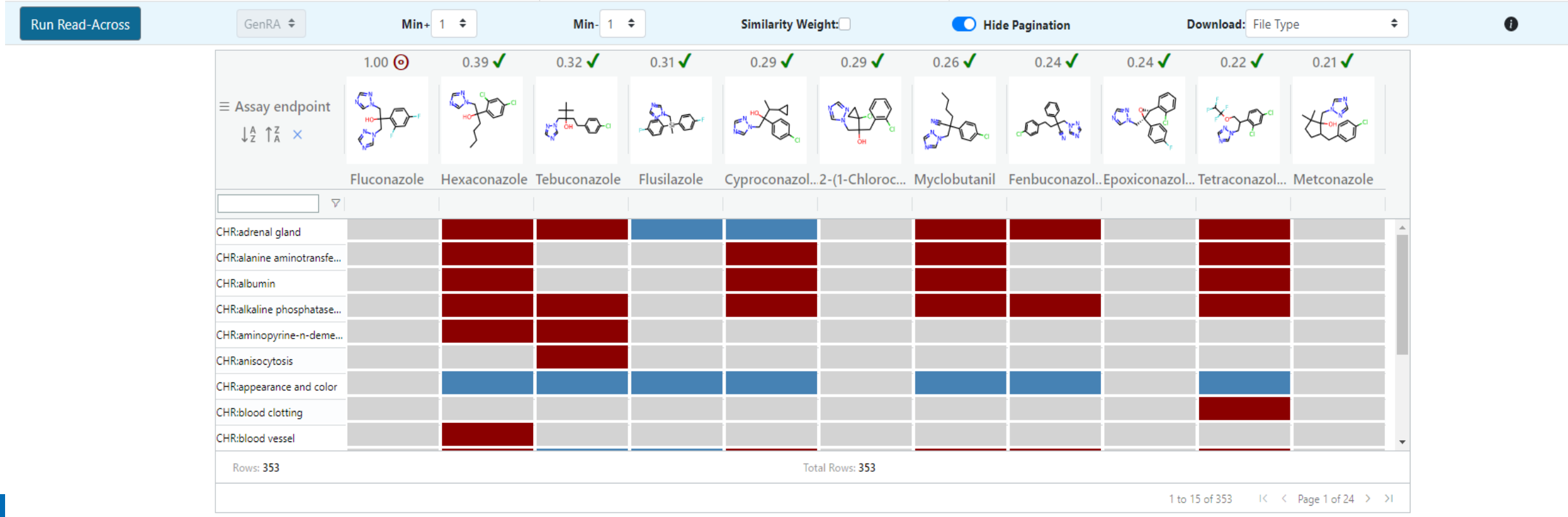


- How data poor is my target and what data exists for the source analogues identified
- Do they address the data gaps of interest for the target chemical?

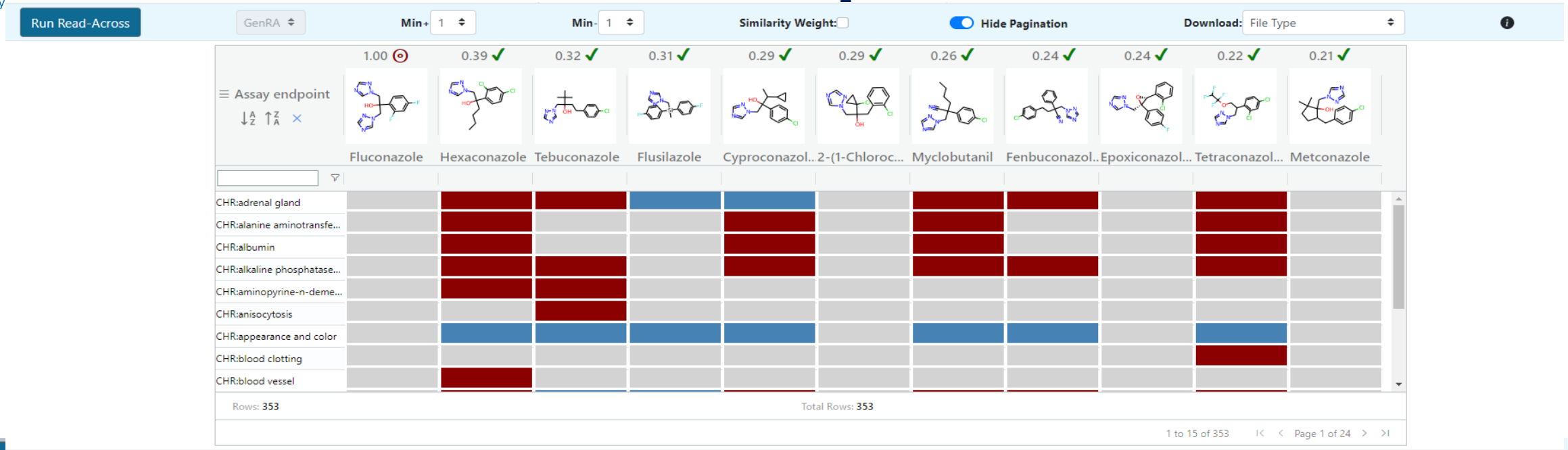
GenRA v3 tool in practice

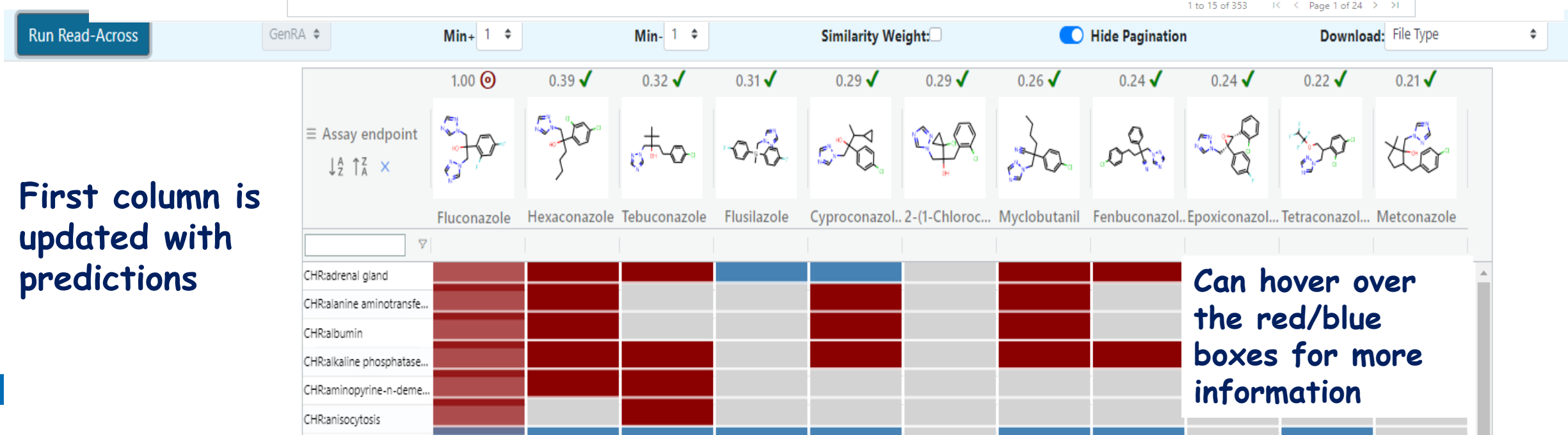
What is the consistency and concordance across my source analogues?
Should I deselect analogues from consideration from the entire set of predictions?
Should I consider subcategorising the analogues selected?

Toxicity data represented as binary outcomes – red (positive), blue (negative), grey (no data)



GenRA v3 in practice





First column is updated with predictions

Can hover over the red/blue boxes for more information

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GenRA v3 in practice

- Database underpinning GenRA v3.0: ToxRefDB v2
  - Different study types and effects within them are predicted e.g. chronic_liver is annotated as CHR_liver
  - Negative effects are inferred from guideline profiles which define the required tests for each study type. The assumption is that the study required an evaluation but no effects were reported.
  - Positive results – min dose at which toxicity effects are observed in a study
- Prediction: Similarity weighted activity
- Performance is categorised by the Area under the Curve (AUC) of the Receiving Operating Characteristic (ROC)
  - The significance was empirically estimated by constructing a null distribution by permuting the toxicity values 100 times and calculating the fraction of times the AUC was more extreme than what would be observed by chance (this is reported as the p-value).

GenRA v3 in practice

- Ability to export the predictions as an excel file
- Output can be analysed in different ways

chem_id	DTXCID10627	DTXCID10627_uni	DTXCID2014653	DTXCID2014653_u	DTXCID7012113	DTXCID7012113_u	DTXCID704235	DTXCID704235_ur	DTXCID8012601	DTXCID8012601_u	DTXCID1024338	DTXCID1024338_u	DTXCID304315	DTXCID304315_ur	D
role	target		analog		analog		analog		analog		analog		analog		a
preferred name	Fluconazole		Hexaconazole		Tebuconazole		Flusilazole		Cyproconazole		2-(1-Chlorocyclopropyl)-1-(2-chlorc		Myclobutanil		F
dsstox_sid	DTXSID3020627		DTXSID4034653		DTXSID9032113		DTXSID3024235		DTXSID0032601		DTXSID3044338		DTXSID8024315		D
dsstox_cid	DTXCID10627		DTXCID2014653		DTXCID7012113		DTXCID704235		DTXCID8012601		DTXCID1024338		DTXCID304315		D
molecular weight	306.277		314.21		307.82		315.399		291.78		312.19		288.78		
similarity	1		0.389		0.324		0.312		0.289		0.286		0.256		
CHR:adrenal gland	GenRA Pos; ACT=None; AUC=0.0; pval=0.945		4.7	mg/kg/day	4.39	mg/kg/day	no_effect		no_effect		no_data		393.5	mg/kg/day	
CHR:alanine aminotransferas	GenRA Pos; ACT=None; AUC=0; pval=1		50	mg/kg/day	no_data		no_data		12.1	mg/kg/day	no_data		40	mg/kg/day	r
CHR:albumin	GenRA Pos; ACT=None; AUC=0; pval=1		50	mg/kg/day	no_data		no_data		12.1	mg/kg/day	no_data		40	mg/kg/day	r
CHR:alkaline phosphatase (al	GenRA Pos; ACT=None; AUC=0; pval=1		10	mg/kg/day	482.9	mg/kg/day	no_data		3.2	mg/kg/day	no_data		15.68	mg/kg/day	
CHR:aminopyrine-n-demethy	GenRA Pos; ACT=None; AUC=0; pval=1		4.7	mg/kg/day	482.9	mg/kg/day	no_data		no_data		no_data		no_data		r
CHR:anisocytosis	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		77.3	mg/kg/day	no_data		no_data		no_data		no_data		r
CHR:appearance and color	GenRA Neg; ACT=None; AUC=0; pval=1		no_effect		no_effect		no_effect		no_effect		no_data		no_effect		r
CHR:blood clotting	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		no_data		no_data		no_data		no_data		no_data		r
CHR:blood vessel	GenRA Pos; ACT=None; AUC=0; pval=1		50	mg/kg/day	no_data		no_data		no_data		no_data		no_data		r
CHR:body weight	GenRA Pos; ACT=None; AUC=0.0; pval=0.94		6.1	mg/kg/day	no_effect		no_effect		3.2	mg/kg/day	no_data		39.21	mg/kg/day	
CHR:bone	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		no_data		no_data		no_data		no_data		no_data		r
CHR:bone marrow	GenRA Neg; ACT=None; AUC=0; pval=1		no_effect		no_effect		no_effect		no_effect		no_data		no_effect		r
CHR:brain	GenRA Neg; ACT=None; AUC=0.0; pval=0.93		no_effect		no_effect		no_effect		no_effect		no_data		393.5	mg/kg/day	r
CHR:calcium	GenRA Pos; ACT=None; AUC=0; pval=1		50	mg/kg/day	no_data		no_data		12.1	mg/kg/day	no_data		no_data		r
CHR:cholesterol	GenRA Pos; ACT=None; AUC=0; pval=1		50	mg/kg/day	no_data		13	mg/kg/day	12.1	mg/kg/day	no_data		no_data		
CHR:clinical signs	GenRA Pos; ACT=None; AUC=0.0; pval=0.965		no_effect		no_effect		27	mg/kg/day	3.2	mg/kg/day	no_data		no_effect		
CHR:cytochrome p450, nos	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		no_data		no_data		3.2	mg/kg/day	no_data		no_data		r
CHR:ear	GenRA Neg; ACT=None; AUC=0; pval=1		no_effect		no_effect		no_effect		no_effect		no_data		no_effect		r
CHR:epididymis	GenRA Neg; ACT=None; AUC=0.0; pval=0.93		no_effect		no_effect		no_effect		13.17	mg/kg/day	no_data		125	mg/kg/day	r
CHR:erythrocyte (rbc) count d	GenRA Neg; ACT=None; AUC=0.0; pval=0.84		no_effect		no_data		no_data		no_effect		no_data		40	mg/kg/day	r
CHR:esophagus	GenRA Neg; ACT=None; AUC=0; pval=1		no_effect		no_effect		no_effect		no_effect		no_data		no_effect		r
CHR:eye	GenRA Neg; ACT=None; AUC=0.0; pval=0.86		no_effect		77.3	mg/kg/day	no_effect		no_effect		no_data		no_effect		r
CHR:food consumption	GenRA Neg; ACT=None; AUC=0.0; pval=0.99		267	mg/kg/day	no_effect		no_effect		12.1	mg/kg/day	no_data		40	mg/kg/day	r
CHR:full gross necropsy	GenRA Neg; ACT=None; AUC=0; pval=1		no_effect		no_effect		no_effect		no_effect		no_data		no_effect		r
CHR:gamma glutamyl transfe	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		no_data		no_data		no_data		no_data		40	mg/kg/day	r
CHR:globulins	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		no_data		no_data		12.1	mg/kg/day	no_data		no_data		r
CHR:glucose	GenRA Neg; ACT=None; AUC=0.0; pval=0.875		no_effect		no_effect		no_effect		no_effect		no_data		no_effect		r
CHR:glutathione-s-transferas	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		no_data		no_data		3.2	mg/kg/day	no_data		no_data		r
CHR:heart	GenRA Neg; ACT=None; AUC=0.0; pval=0.85		no_effect		no_effect		no_effect		no_effect		no_data		no_effect		r
CHR:hematocrit (hct)	GenRA Pos; ACT=None; AUC=0; pval=1		no_data		no_data		no_data		no_data		no_data		no_data		

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GenRA v3 in practice

- Rank order positive results based on AUC and p values
- Look at the distribution of positive vs negatives predictions
- Explore what effects are being identified for the source analogues – consider identifying the underlying data for source analogues (elsewhere on the Dashboard) – is there a critical effect that is driving the toxicity that should be compared with the target chemical predictions?
- ……
- Depends on the decision context and the level of uncertainty that can be tolerated.

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

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GenRA Summary

- GenRA is an attempt to move towards an objective read-across approach where uncertainties and performance can be quantified. Provides opportunities for NAM data to be incorporated.
- GenRA v1.0 established a baseline in performance. The approach relied on chemical descriptors to predict binary toxicity values but work continues to characterise other contexts of similarity (e.g. mechanistic, reactivity, metabolism) and quantify their contribution in predicting *in vivo* toxicity outcomes.
- GenRA v3.0 now released is a standalone web app linked to the Dashboard. A python package (genra-py) was released (March 2021) to facilitate batch processing using user specific datasets.

GenRA Research Team

- Imran Shah (co-lead)
- Past and present* students
- Mark Nelms
- George Helman
- Willysha Jenkins
- Tia Tate
- Matthew Boyce
- Louis Groff*
- Matthew Adams*

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Questions ?

Submit via the GenRA application
genra.support@epa.gov