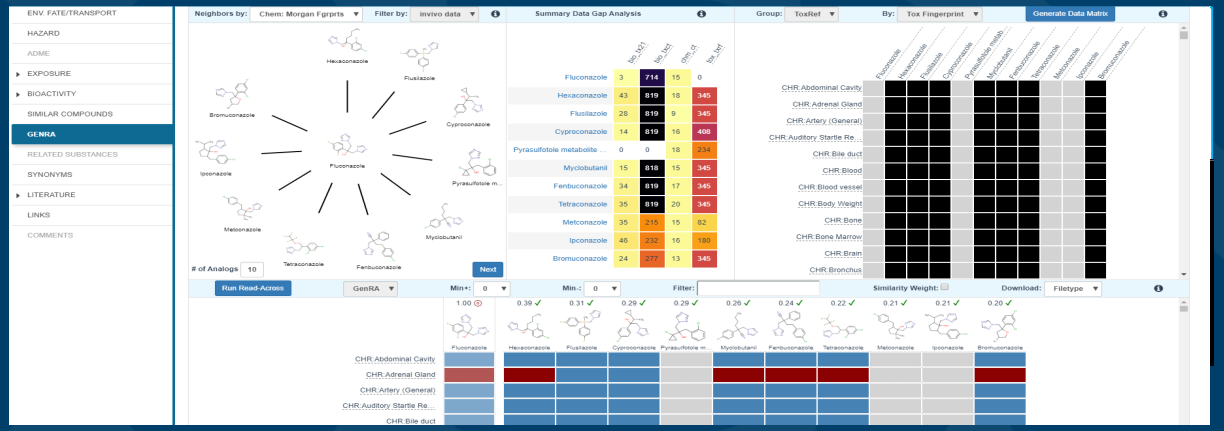
Generalised Read-Across GenRA, research, implementation and practical application



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Outline

- Definitions
- Landscape of read-across guidance & tools
- Re-thinking the read-across problem
- Summary remarks
- Acknowledgements

Definitions: Chemical grouping approaches

A chemical category is a group of chemicals whose physico-chemical and human health and/or environmental toxicological and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristics).

- Read-across describes one of the techniques for filling data gaps in either the analogue or category approaches i.e. not to be confused with the "analogue approach"
- "Analogue approach" refers to grouping based on a very limited number of chemicals (e.g. target substance + source substance)
- "Category approach" is used when grouping is based on a more extensive range of analogues (e.g. 3 or more members)

Landscape of read-across – 'Guidance'

- Intended to address:
- 1) the development of read-across
  - i.e. the process of deriving an analogue/category approach to facilitate a read-across prediction
  - technical regulatory guidance (OECD grouping document (2014), ECHA (Chapter R6, (2008)) and many publications in the scientific literature (Wu et al., 2010; ECETOC, 2012; Wang et al., 2012, Patlewicz et al., 2013)
- 2) the assessment (evaluation) of the read-across justification
  - technical regulatory guidance (ECHA RAAF, 2015,2017; OECD IATA templates) and publications in the scientific literature (Blackburn and Stuard, 2014; Patlewicz et al., 2015; Schultz et al., 2015)

Issues surrounding the consistency and concordance of the different guidance available

Landscape of read-across tools

- A number of different tools exist both in the public domain and commercially
- Examples include EPA's AIM, OECD Toolbox, JRC Toxmatch, Leadscope, MN-AM's ToxGPS, ToxRead, CBRA..

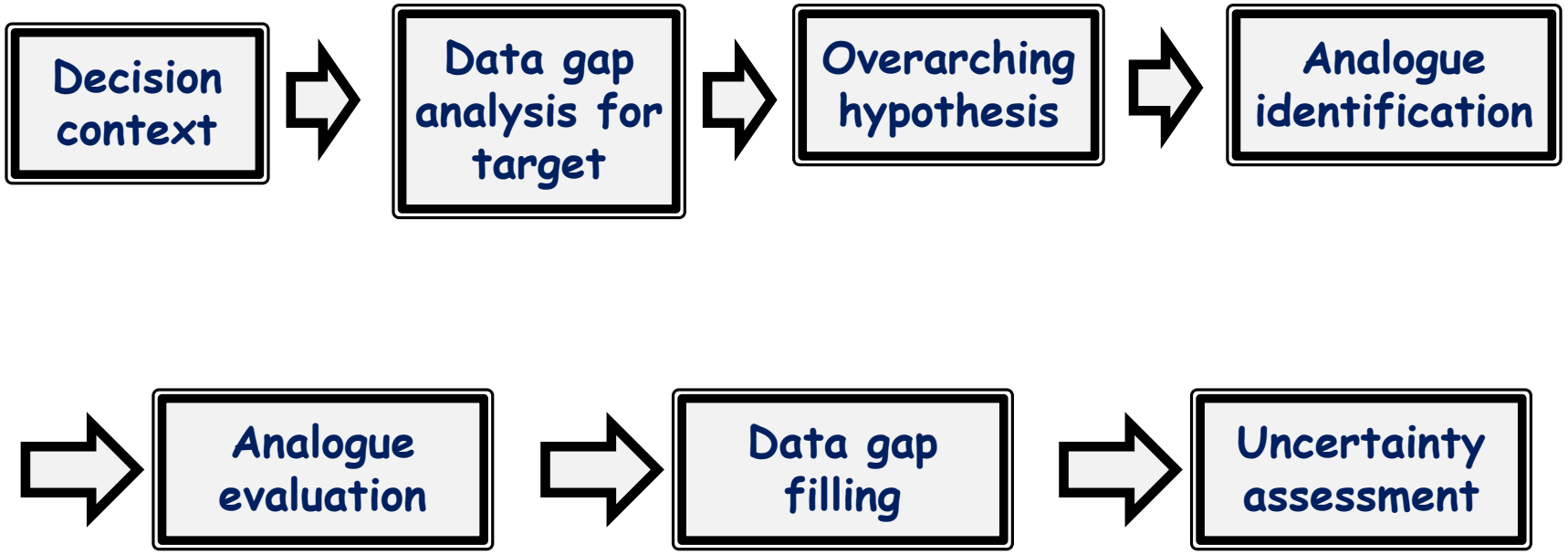
Difficult to compare and contrast these tools in terms of their utility

Need a consistent framework/workflow to understand their scope and utility and for what decision context(s) they might be useful for

Re-thinking the read-across problem

- Objective 1. Define the category (read-across) workflow
- Objective 2. Understand the scope and capability of existing read-across tools
- Objective 3. Identify an objective means of quantifying the performance of read-across and quantifying the uncertainties – Generalised Read-across (GenRA)
- Objective 4: Propose a harmonised hybrid read-across workflow
- Objective 5. Extend the approach to fold in expert driven considerations but in an objective manner

Objective 1: Defining the category (read-across) workflow



Patlewicz et al., 2013; ECETOC, 2012

Objective 2: Scope and capability of read-across tools

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

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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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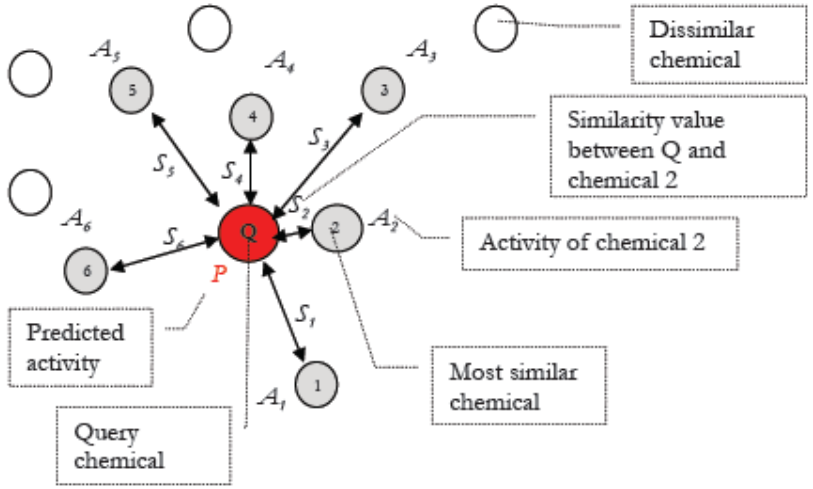
Objective 3: GenRA (Generalised Read-Across)

- Predicting toxicity as a similarity-weighted activity of nearest neighbours based on chemistry and/or bioactivity descriptors
- Goal: to systematically evaluate read-across performance and uncertainty using available data
- The approach enabled a performance baseline for read-across predictions of toxicity effects within specific study outcomes to be established



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

Jaccard similarity:

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

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

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

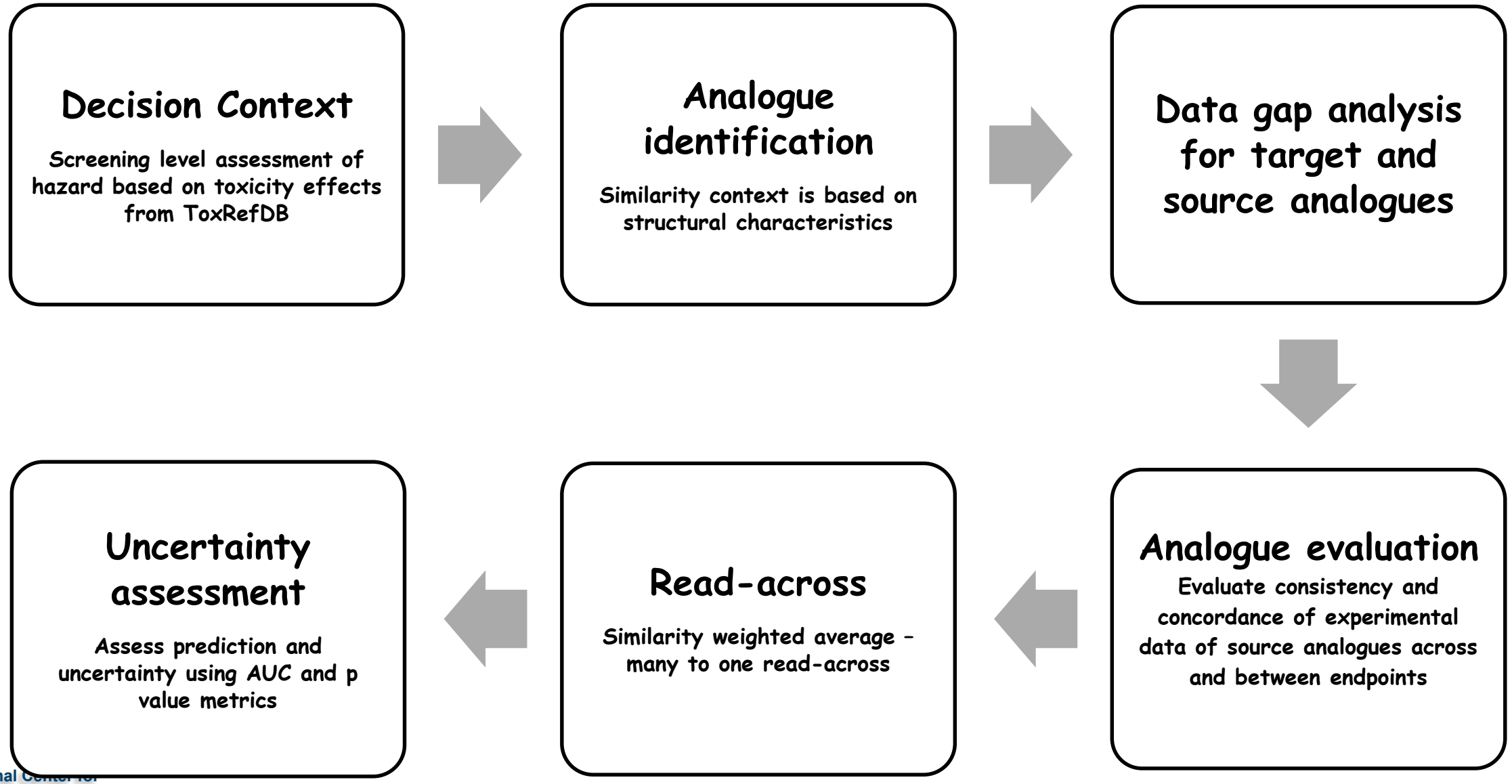
y_i = predicted activity of chemical (c_i)

x_j^{β} = activity of c_j in β

s_{ij}^{α} = Jacccard similarity between $x_i^{\alpha}, x_j^{\alpha}$

k = up to k nearest neighbours

Objective 3: Read-across workflow in GenRA



Objective 3: GenRA tool in reality

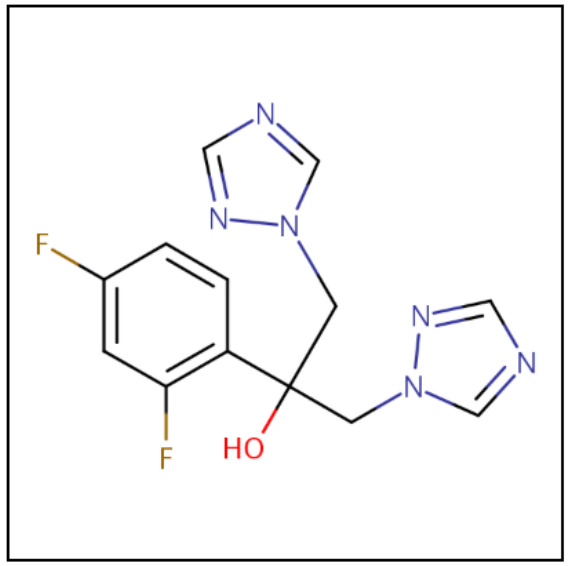
- Integrated into the EPA CompTox Chemicals dashboard as a new addition

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, coccidiodomycosis, 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: $C_{13}H_{12}F_2N_8O$ Mol File

Find All Chemicals

Average Mass: 306.277 g/mol Isotope Mass Distribution

Monoisotopic Mass: 306.104065 g/mol

Structural Identifiers

Linked Substances

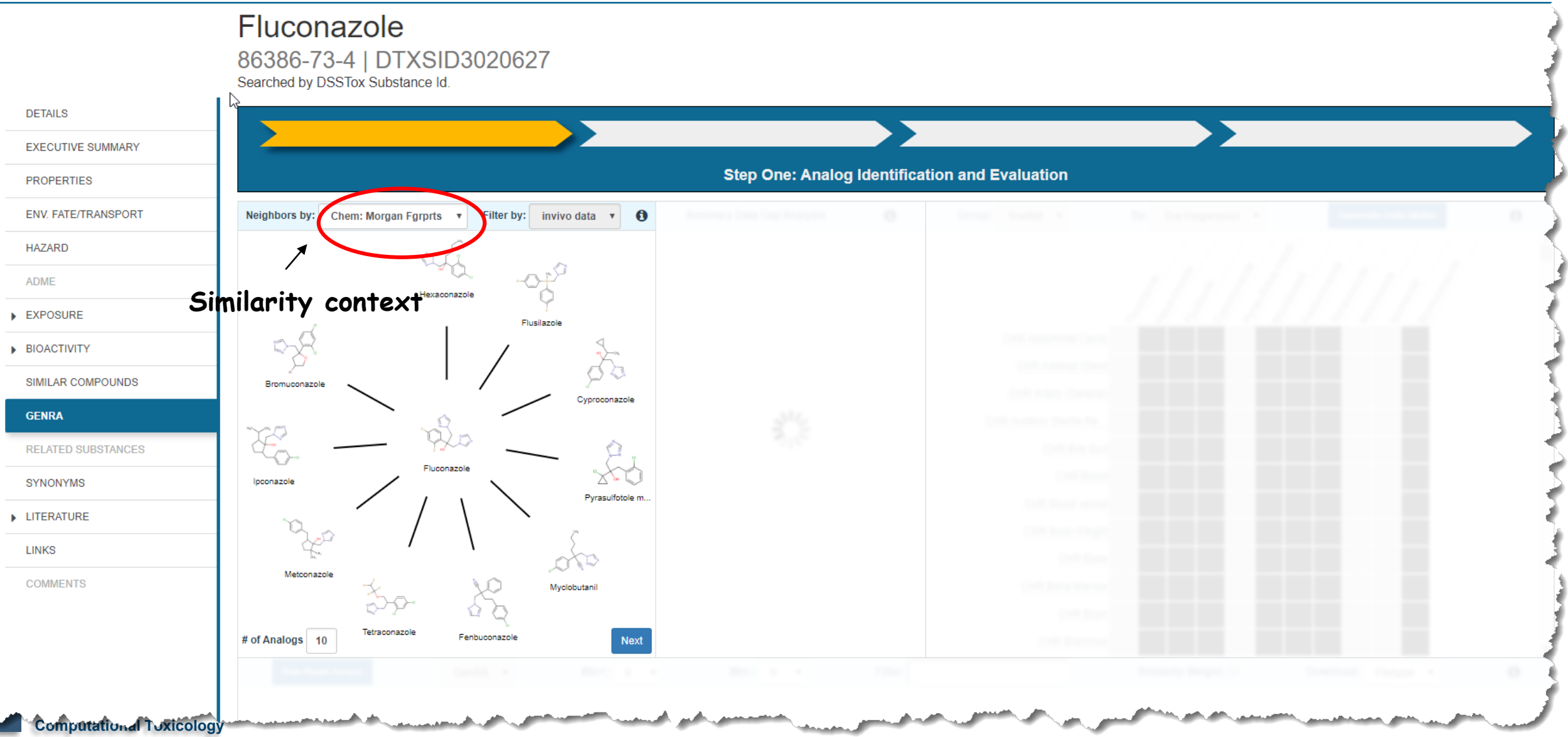
Presence in Lists

Record Information

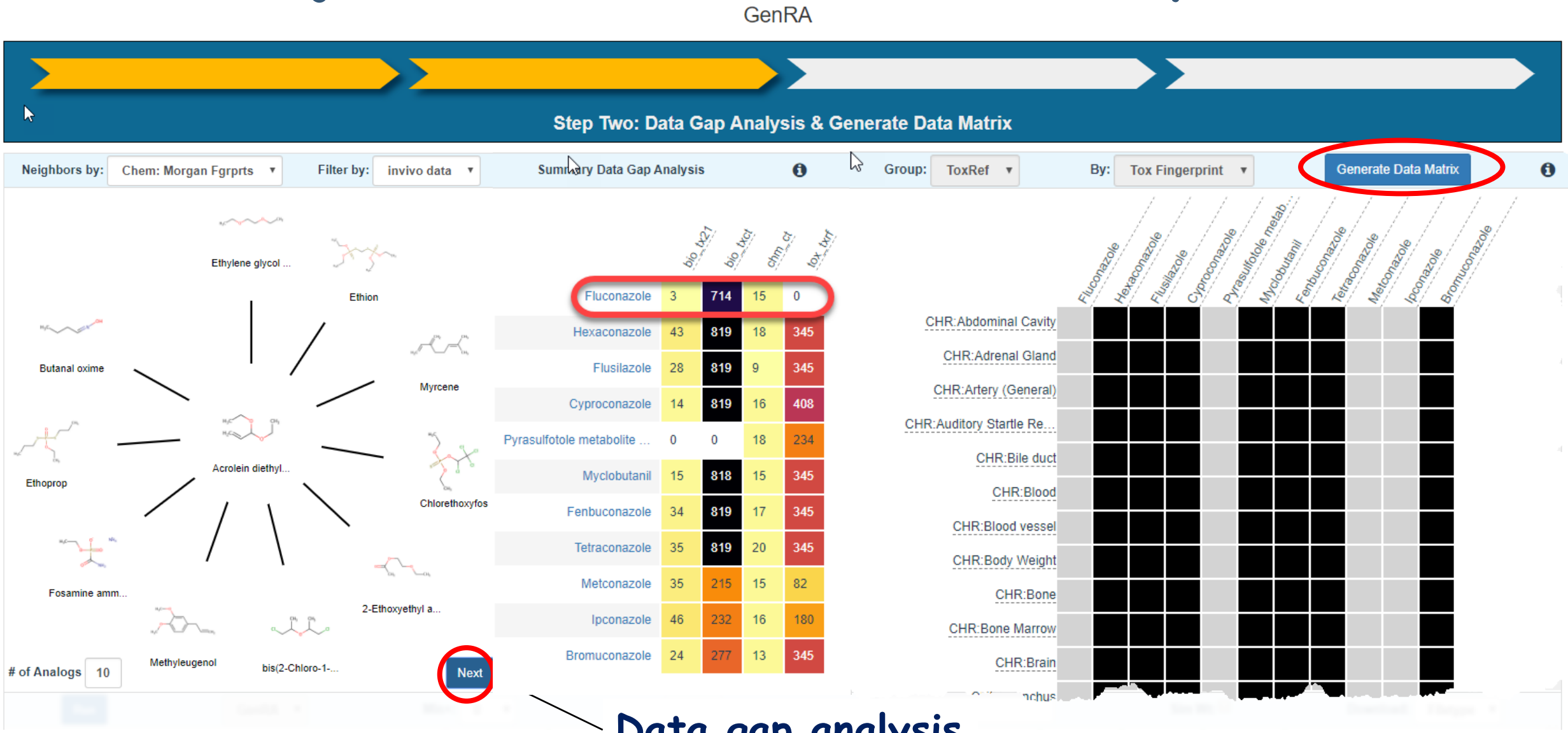
Quality Control Notes

Objective 3: GenRA tool in reality

- Structured as a workflow

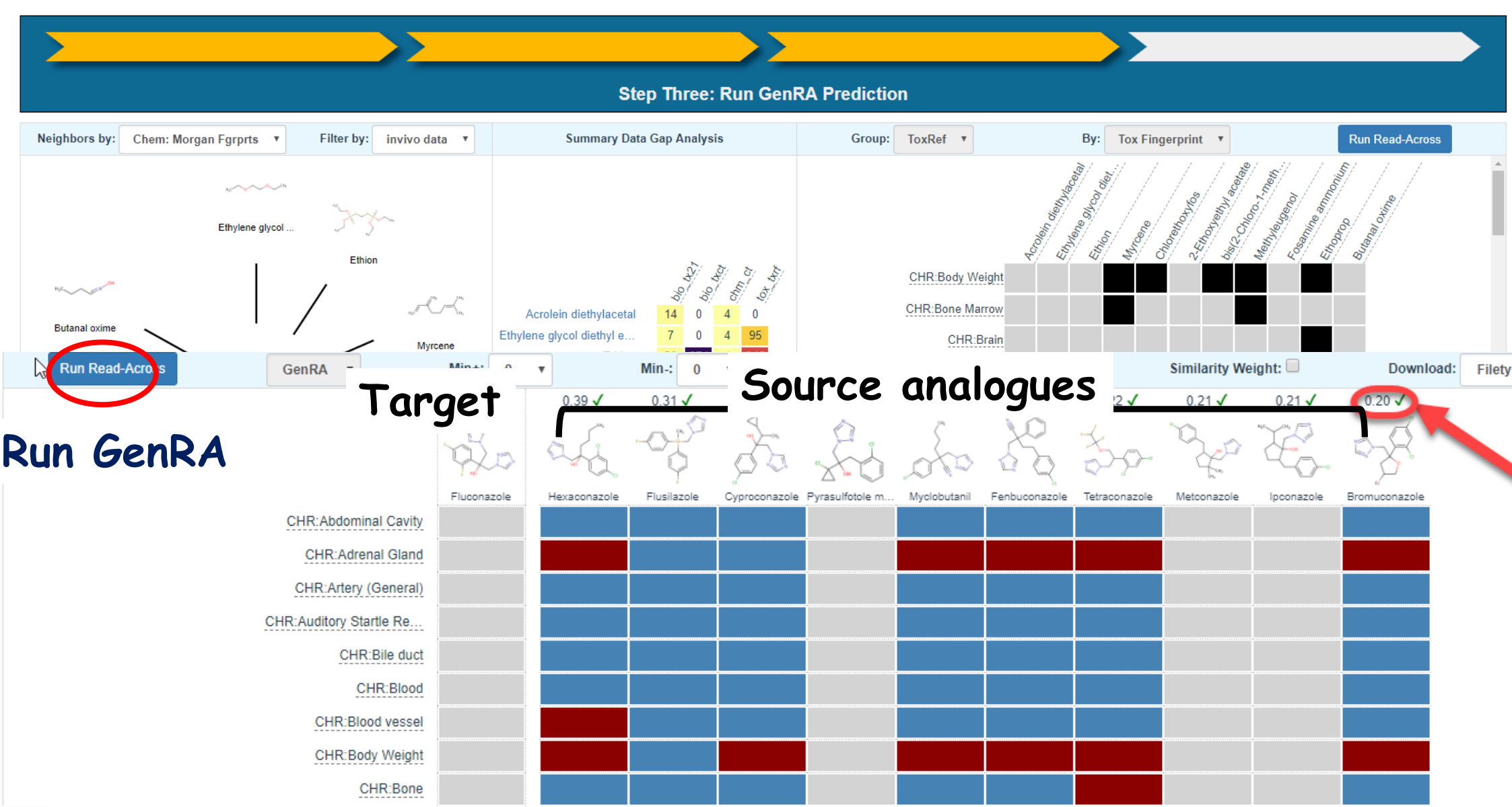


Objective 3: GenRA tool in reality



Data gap analysis

Objective 3: GenRA tool in reality



Objective 2: Extending the suite of read-across tools but addressing an unmet need

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 available	X	X	X For Ames & BCF	NA
Data gap analysis	NA	X	X Data matrix can be exported	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	Just released August 2018

Objective 4: A harmonised hybrid read-across workflow

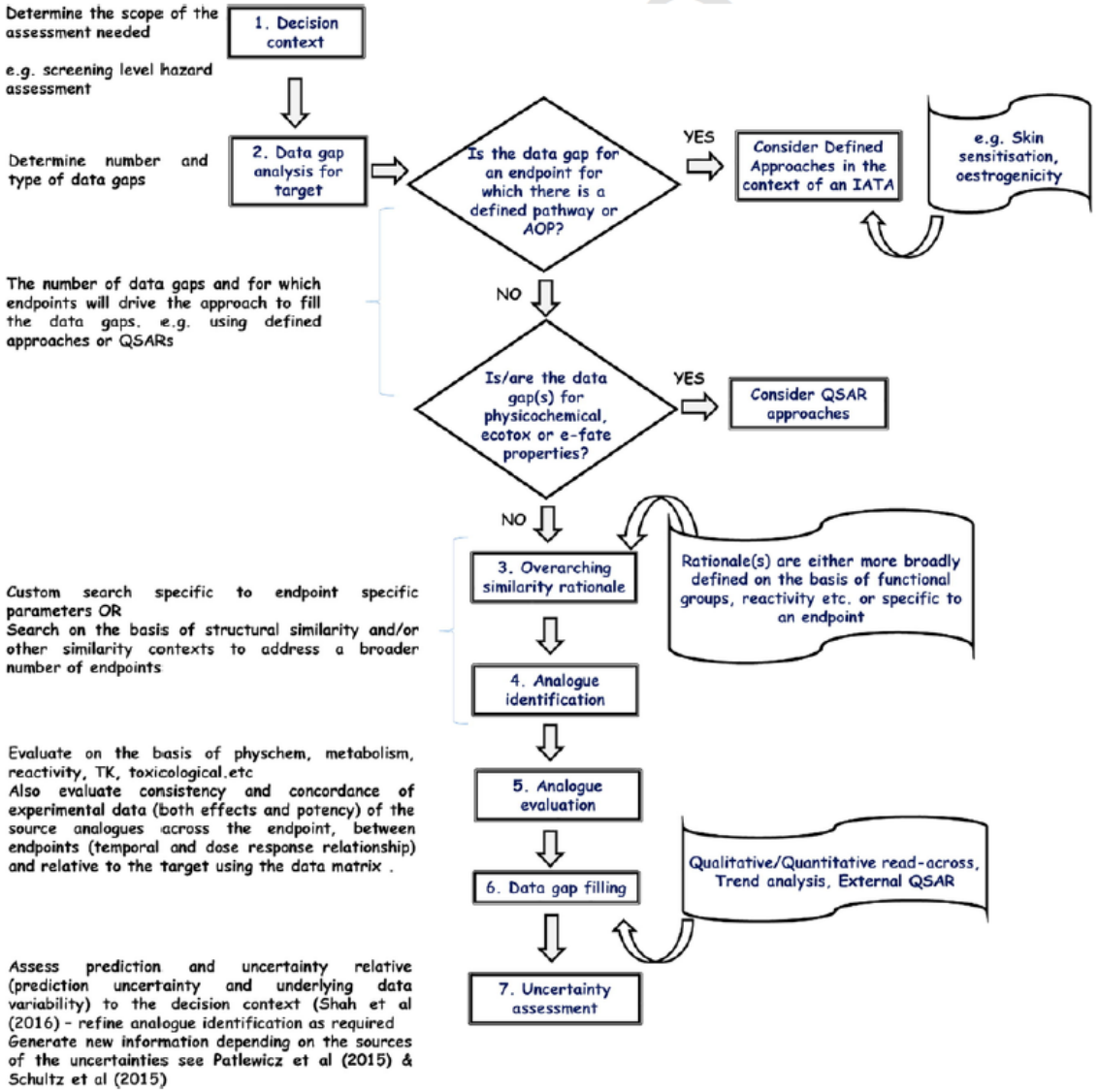


Fig. 9. A harmonised hybrid development and assessment framework.

Folding in the learnings in GenRA to inform and update a harmonised workflow

Patlewicz et al., 2018

Objective 4: A harmonised hybrid read-across workflow

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Journal Cover Image

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

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Objective 5: GenRA – Next Steps

- Ongoing research:
- Summarising and aggregating the toxicity effect predictions to guide end users – what are the effects to be concerned about and which effect predictions are we most confident about
- 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
- 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
  - Starting with quantitative data – e.g. acute rat oral toxicity, ToxRefDB v2

Physchem Similarity Context

- Important context of similarity in read-across
- Models "bioavailability"
- Properties selected: Lipinski Rule of 5 (LogP, MW, # HB donors/acceptors)
- Two approaches investigated as a means to identify source analogs and evaluate their predictive performance relative to GenRA:

Approach 1: "Filter"

Subcategorise from a set of analogues identified based on structural similarity

'Common' approach

Approach 2: "Search Expansion"

"Frontload" both structure and physchem into analogue identification

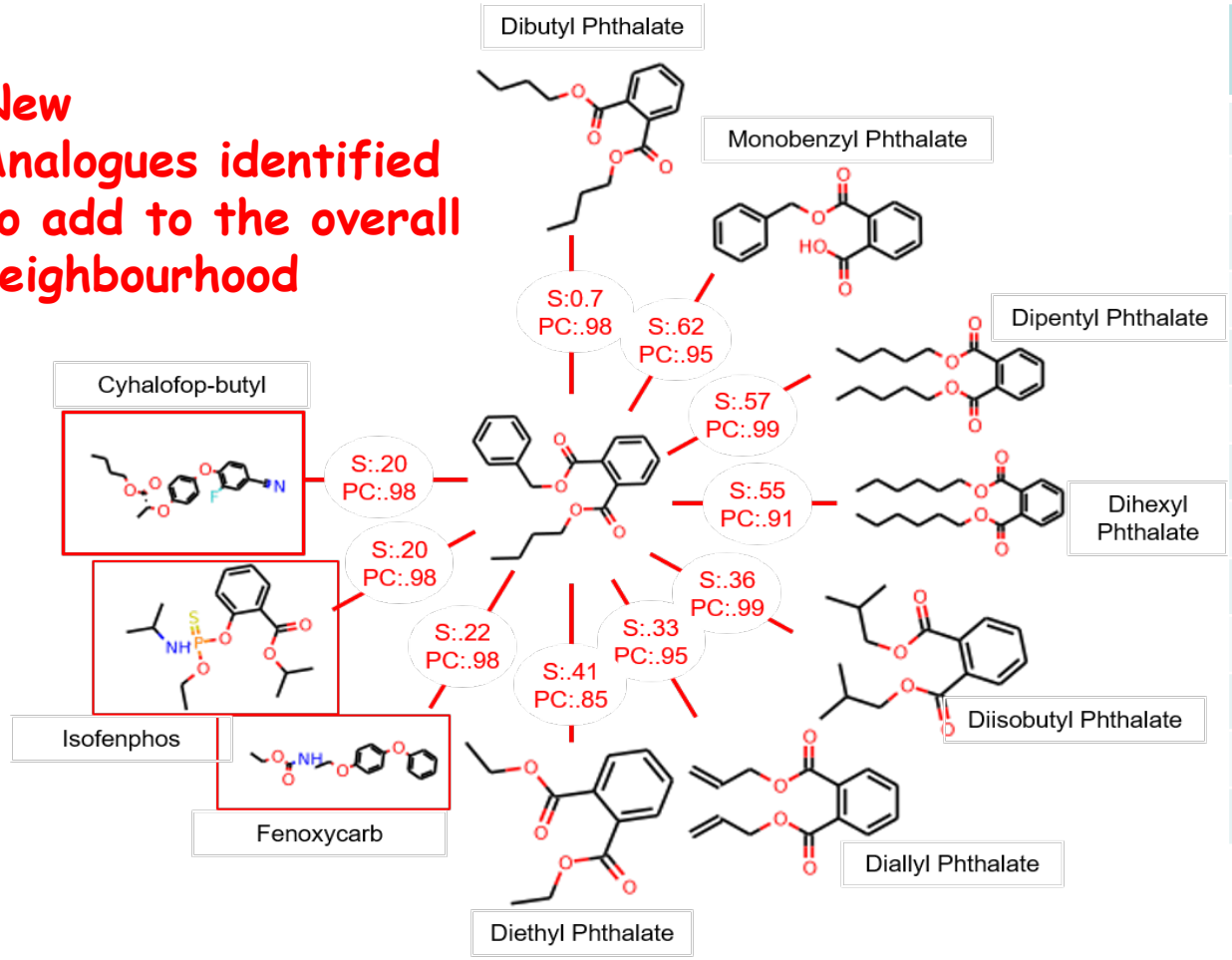
'Novel' approach

Helman et al., 2018

Case Study: Butyl Benzyl Phthalate

Approach 2: Search Expansion

New Analogues identified to add to the overall neighbourhood



Endpoint	Baseline Prediction	Structure + Pchem Prediction
Body Weight	.78	.79
Clinical Chemistry	.27	.60
Food Consumption		
Hematology		
Kidney		
Liver		
Mortality		
Pancreas		
Prostate		
Skin		
Spleen		
Tissue NOS		
Urinary Bladder	0	0

- Adding phys-chem to similarity search overturns incorrect predictions for 2 endpoints
- Improves many others

EPA United States Protection

"S

Flucona
86386-73-
Searched by DSS

DETAILS
EXECUTIVE SUMMARY
PROPERTIES
ENV. FATE/TRANSPORT
HAZARD
ADME
EXPOSURE
BIOACTIVITY
SIMILAR COMPOUNDS
GENRA
RELATED SUBSTANCES
SYNONYMS
LITERATURE
LINKS
COMMENTS

Phys
Stru

Neigh

Bromuconazole

Ipconazole

Metconazole

# of Analogs 10

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

George Helman [a, b], Imran Shah [b], Grace Patlewicz [b]

Show more

https://doi.org/10.1016/j.comtox.2018.07.001

Highlights

- GenRA approach is summarised in the context of the category workflow.
- The impact of physicochemical information on read-across performance was assessed in 2 ways: filtering and search expansion.
- Search expansion resulted in an up to 9% improvement in read-across performance for 10 of the 50 data rich target organs.
- Results are summarised on a neighbourhood (chemical category) basis.
- A case study substance is used to compare and contrast the read-across performance using the 2 approaches.

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Summary remarks

- Provided a perspective of the state of the science
- Outlined our research direction of read-across and how this fits within the context of the overall landscape of read-across
- Demonstrated the latest addition to the EPA CompTox dashboard – GenRA
- Presented highlights of on-going analysis

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