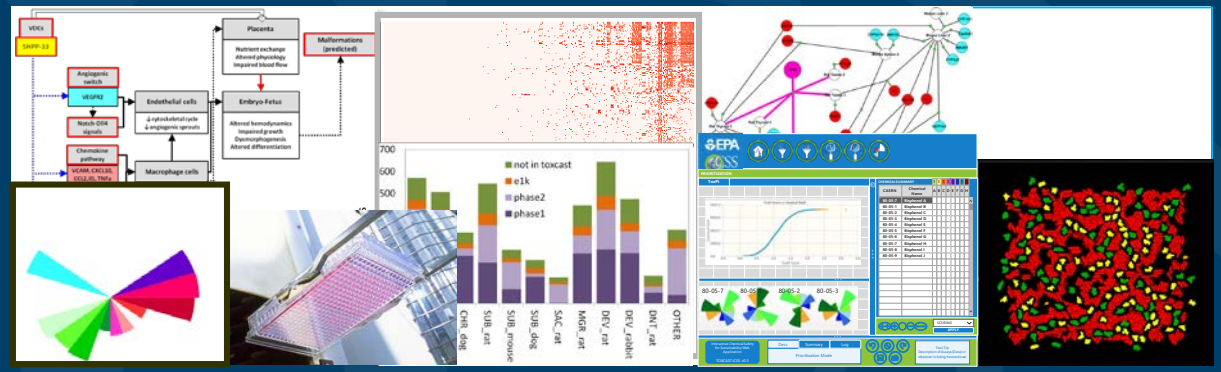
Navigating Through the Minefield of Read-Across: From Research to Practical Tools



Grace Patlewicz, George Helman*, Imran Shah

National Center for Computational Toxicology
***ORISE Fellow**

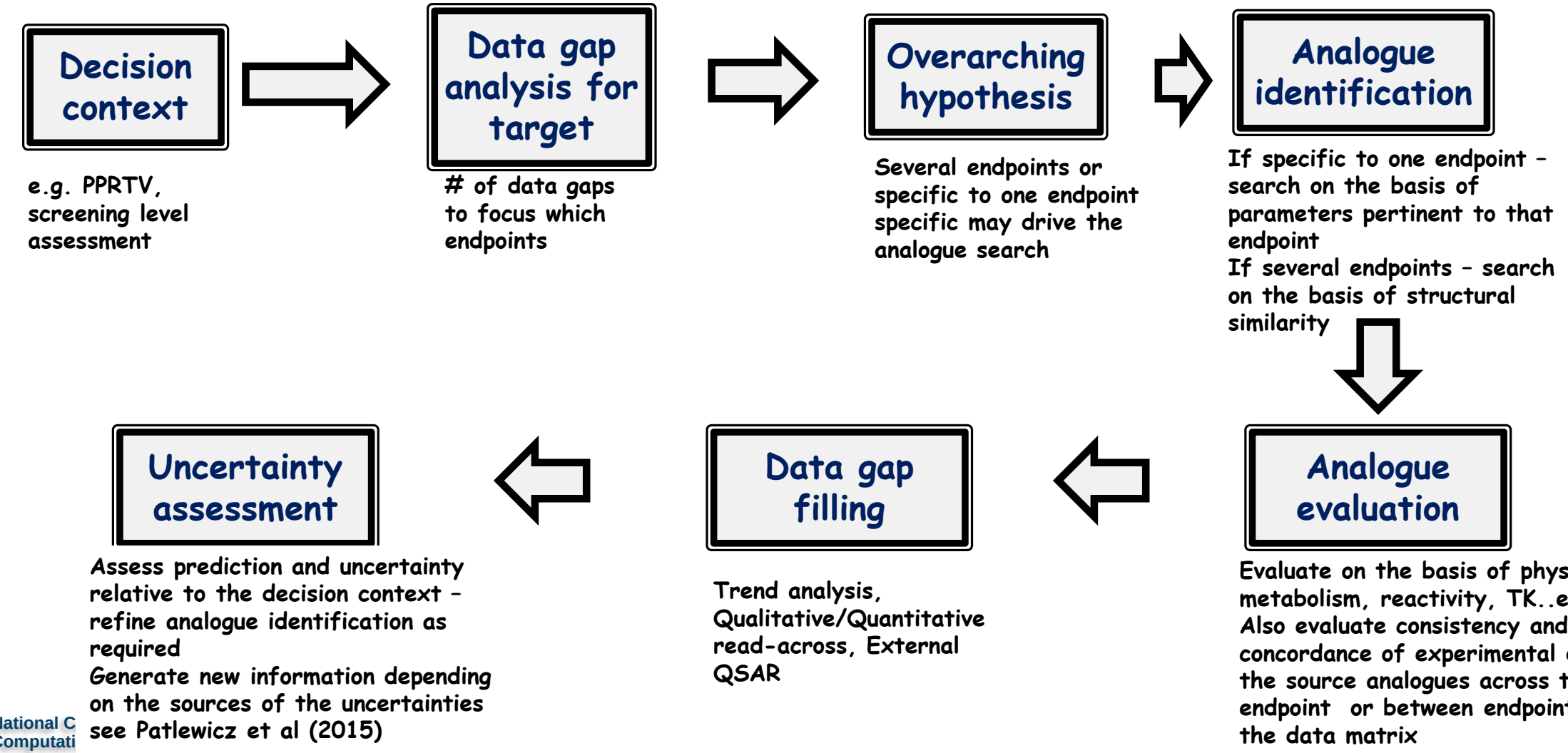
Outline

- Background, Concepts and Definitions
- Category workflow and selected tools for read-across
- Uncertainty assessment in read-across
- Quantifying Uncertainty & Assessing Performance of Read-Across
- From Research to Implementation
- Summary

Background & definitions

- Read-across describes one of the data gap filling techniques used within analogue and category approaches
- "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)

Category Workflow



Selected Read-Across Tools

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

Selected Read-Across Tools – Review

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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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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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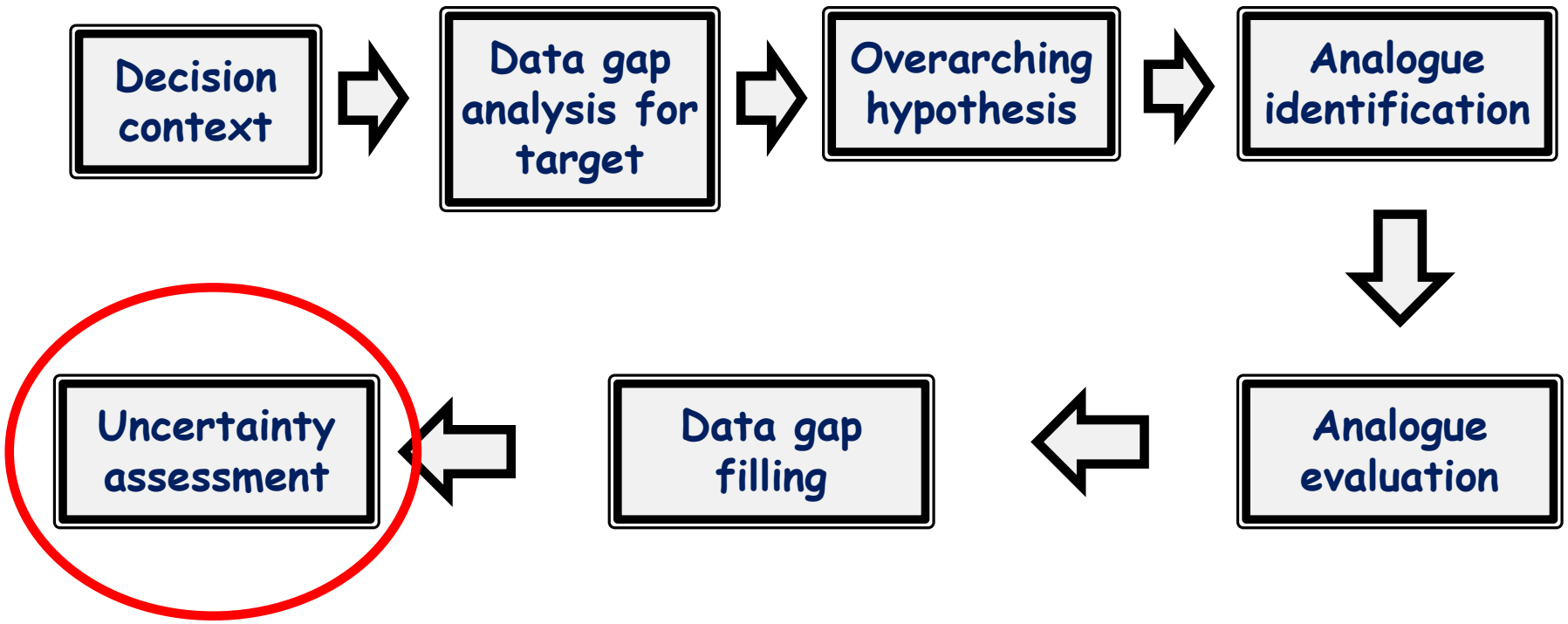
The Category Workflow



Sources of Uncertainty

- Analogue or category approach? (# analogues)
- Completeness of the data matrix – no. of data gaps
- Data quality for the underlying analogues for the target and source analogues
- Consistency of data across the data matrix – concordance of effects and potency across analogues

Sources of Uncertainty (cont'd)

- Overarching hypothesis/similarity rationale – how to identify similar analogues and justify their similarity for the endpoint of interest
- Address the dissimilarities and whether these are significant from a toxicological standpoint
- Presence vs. absence of toxicity
- Toxicokinetics

Uncertainty assessment

- There are several frameworks which aim to identify, document and address the uncertainties associated with read-across inferences/predictions
  - Blackburn & Stuard (2014)
  - Patlewicz et al (2015)
  - Schultz et al (2015)
  - ECHA RAAF (2015)

- However read-across acceptance relies on a subjective expert assessment

- There is no objective measure of read-across performance

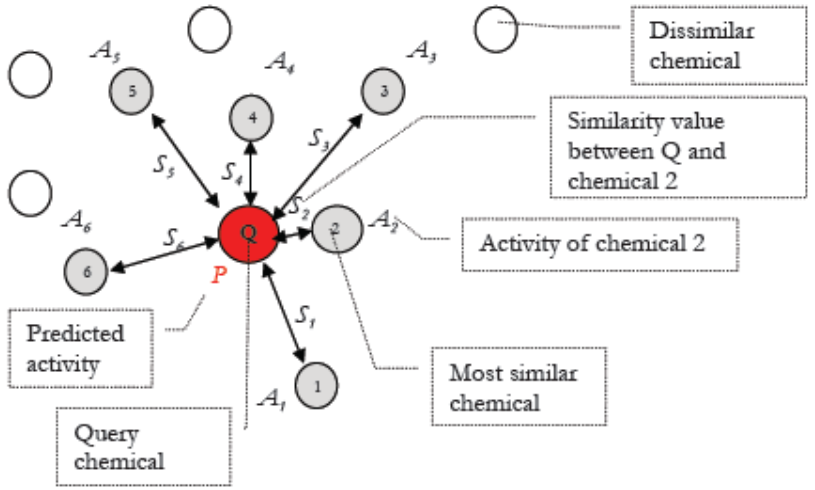
Quantifying Uncertainty & Assessing Performance of Read-Across

- GenRA (Generalised Read-Across) is a "local validity" approach
- Predicting toxicity as a similarity-weighted activity of nearest neighbors based on chemistry and bioactivity descriptors
- Generalised version of Chemical-Biological Read-Across (CBRA) developed by Low et al (2013)
- Systematically evaluates read-across performance and uncertainty using available data

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

Jaccard similarity:

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



GenRA - Approach

I. Data

1,778 Chemicals
3,239 Structure descriptors (chm)
820 Bioactivity assays (bio)
ToxCast
574 Apical outcomes (tox)
ToxRefDB

II. Define Local neighborhoods

Use K-means analysis to group chemicals by similarity
Use cluster stability analysis
~ 100 local neighborhoods

III. GenRA

Use GenRA to predict apical outcomes in local neighbor hoods
Evaluate impact descriptors (chm, bio, bc) on prediction
Quantify uncertainty

GenRA – Performance in Each Cluster

- No preselection of descriptors was performed
- Tested and compared
  - Chemical descriptors
  - Bioactivity descriptors
  - Hybrid of chemical and bioactivity descriptors
- Use GenRA to predict the similarity weighted toxicity scores for each
  - Toxicity type (β)
  - Descriptor ={chm,bio,bc} (α)
  - No. of nearest neighbors (k)
  - Similarity score threshold (s_{ij}^{α})
- Calculate performance by comparing predicted y^{tox} and true x^{tox} for all chemicals using area under ROC curve (AUC)
- Bioactivity descriptors were often found to be more predictive of in vivo toxicity outcomes

GenRA – Insights and Next Steps

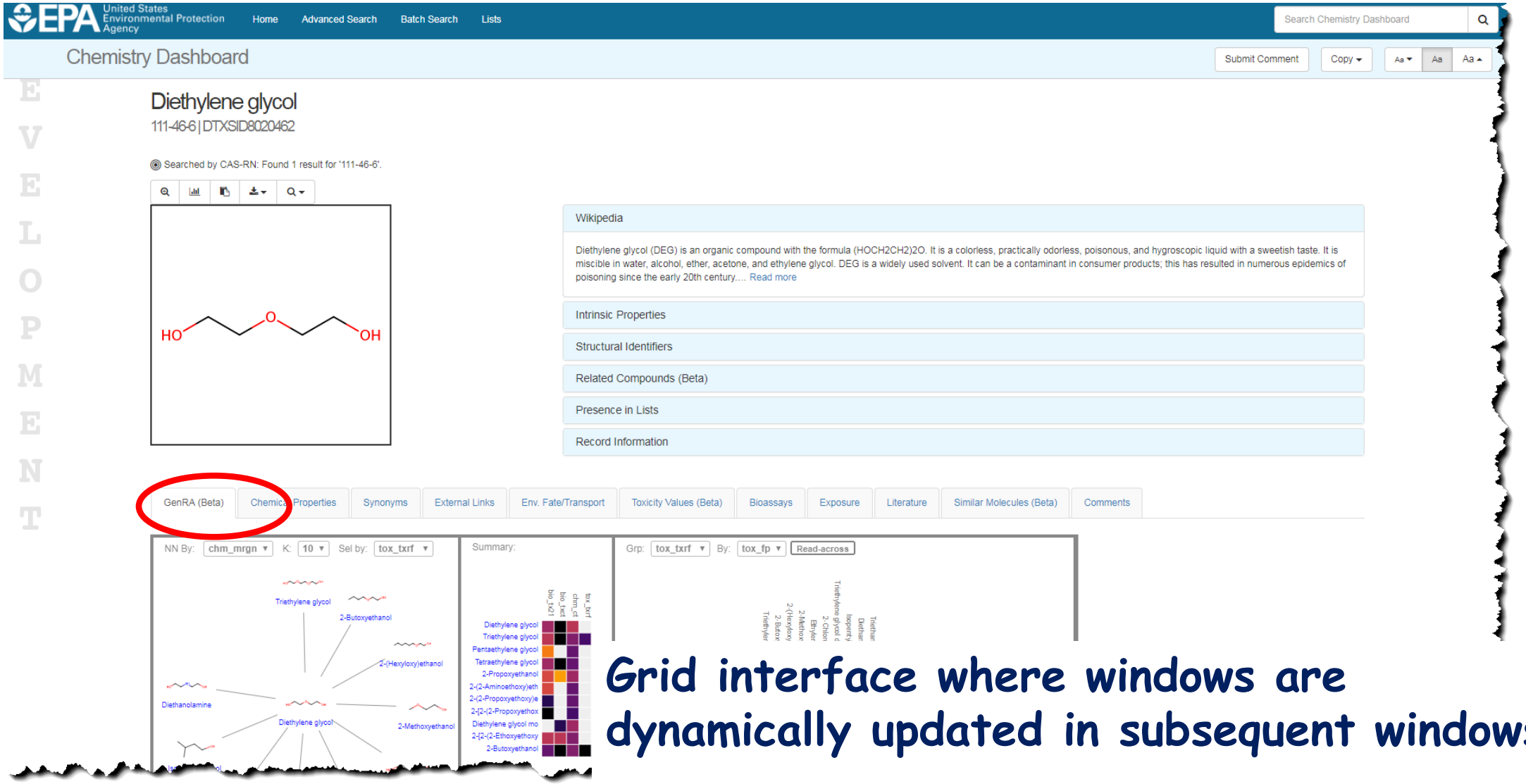
- The approach enabled a performance baseline for read-across predictions of specific study outcomes to be established but was still context dependent on the endpoint and the chemical

- Ongoing analysis:
- Consideration of other information to refine the analogue selection – e.g. physicochemical similarity, TK similarity, metabolic similarity, reactivity similarity…

From research to implementation: GenRA prototype

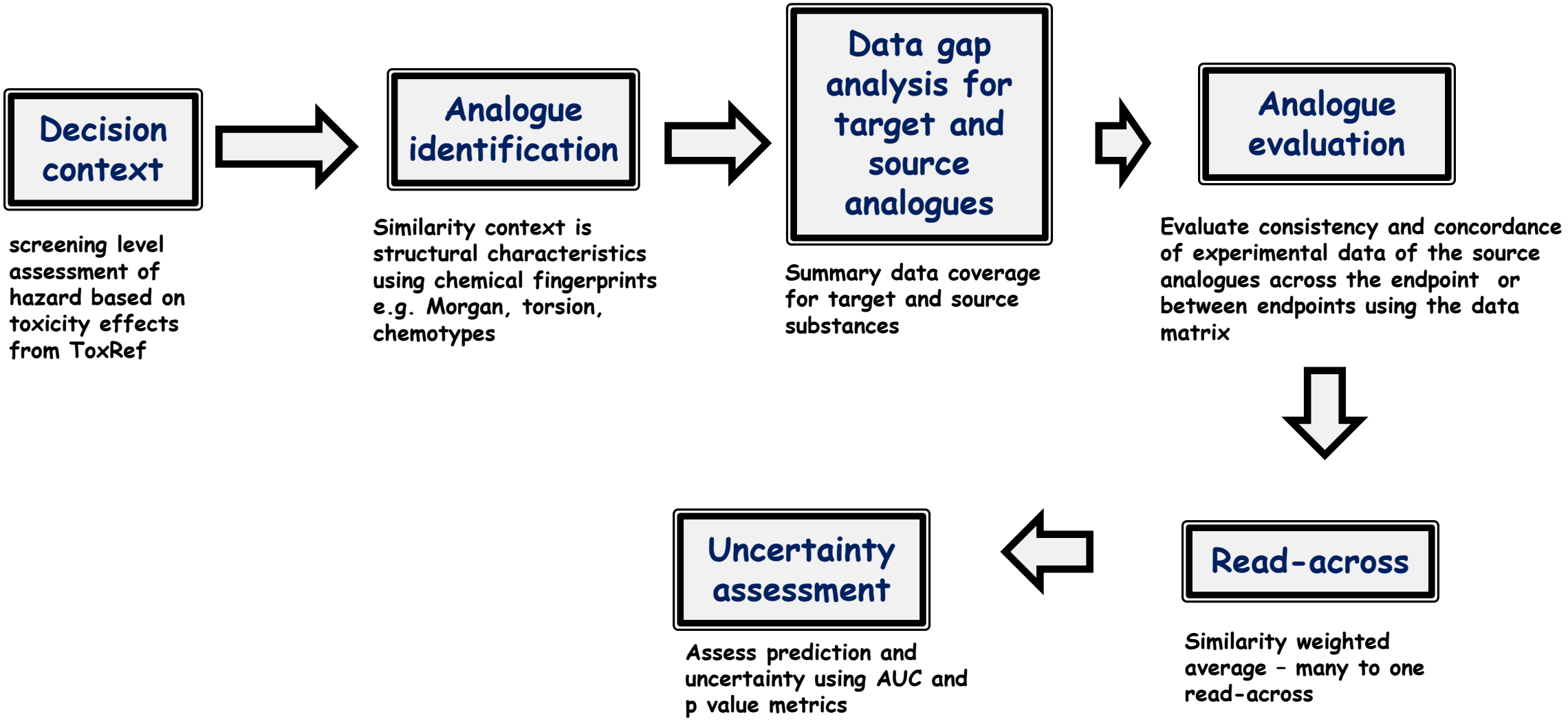
- Intent is to integrate objective read-across functionality as part of ongoing dashboard efforts see https://comptox.epa.gov/dashboard
- A limited release of GenRA is currently available on EPA's development server

Integration via a GenRA tab



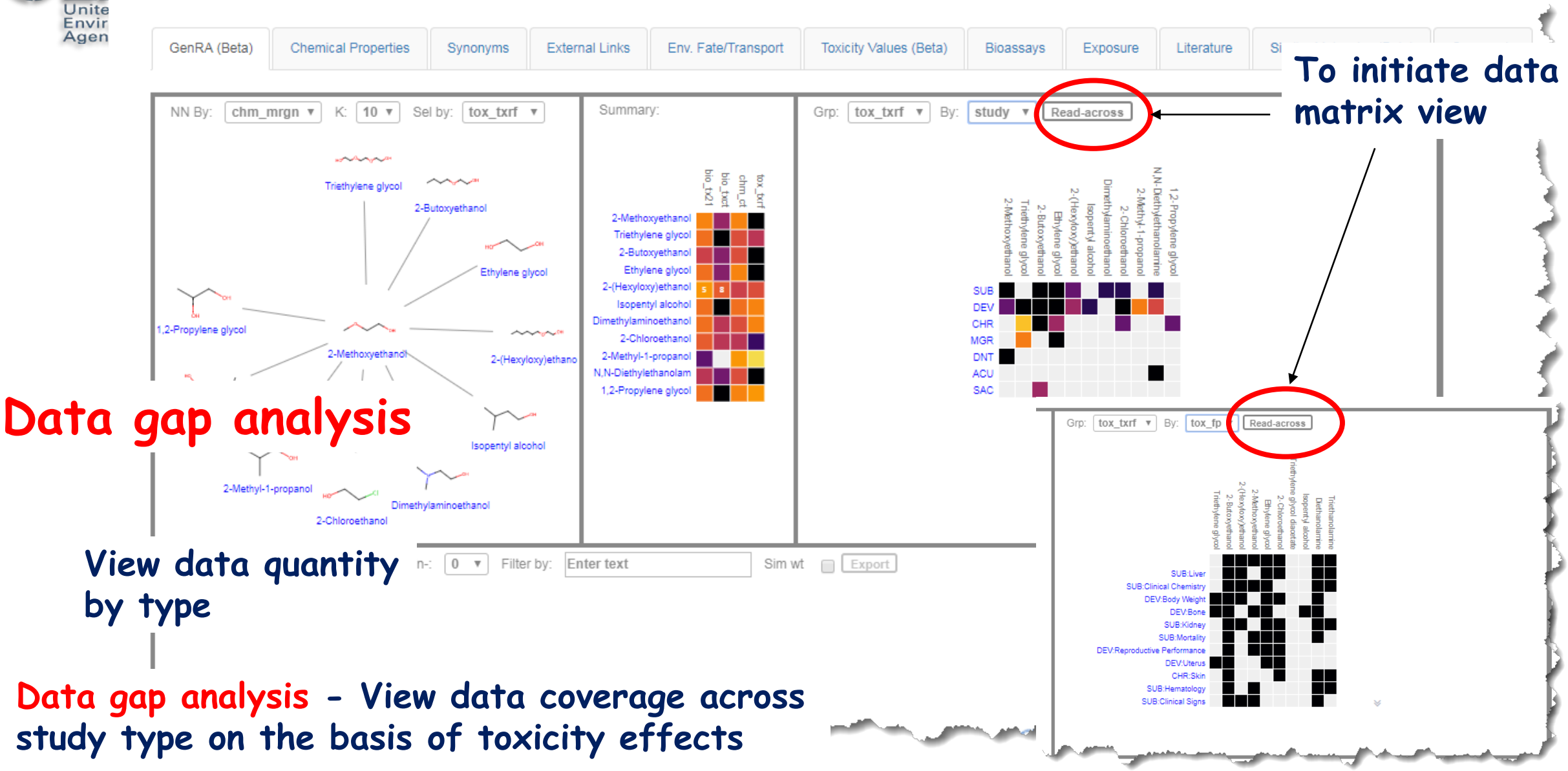
Grid interface where windows are dynamically updated in subsequent windows

Current Category Workflow in GenRA



Similarity context

Analogue identification: Search for source analogues on the basis of chemical fingerprints, filtered by availability of in vivo data

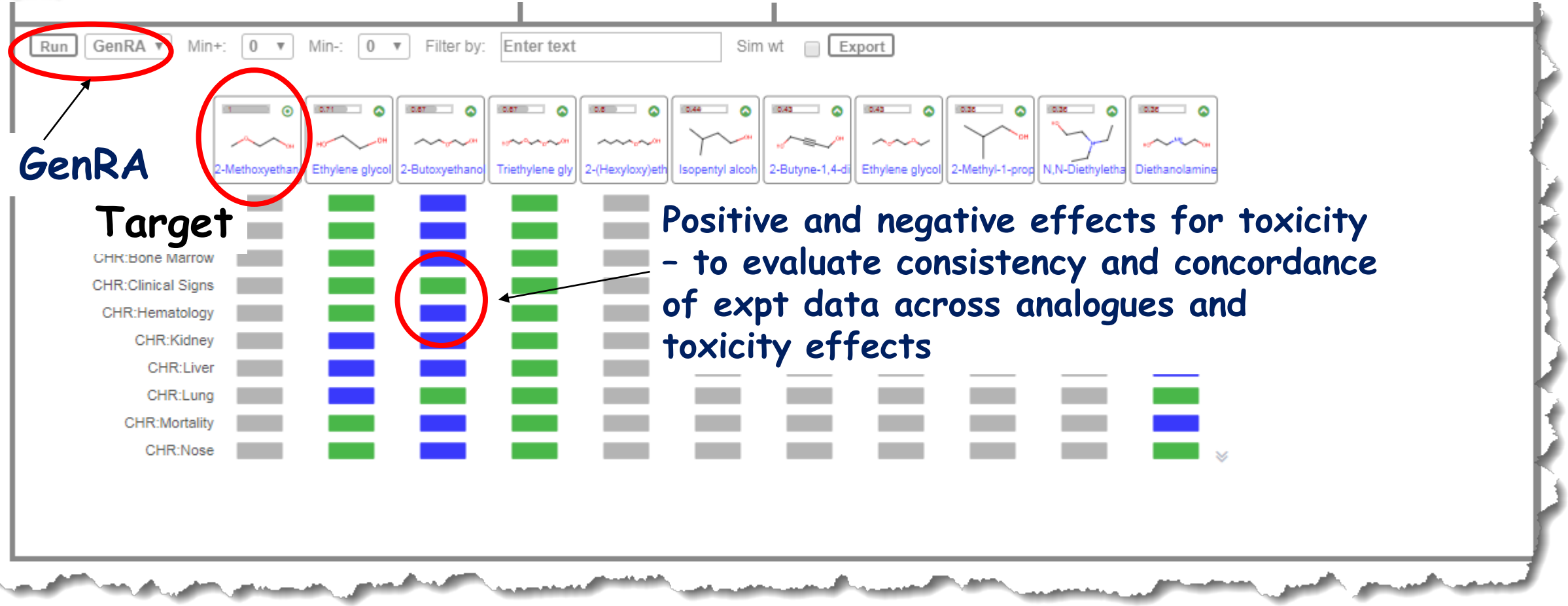


Data gap analysis

View data quantity by type

Data gap analysis - View data coverage across study type on the basis of toxicity effects

Analogue evaluation using data matrix view



Run GenRA

Target

Positive and negative effects for toxicity – to evaluate consistency and concordance of expt data across analogues and toxicity effects

Data gap filling using GenRA within data matrix

Export to a csv file

A	B	C	D	E	F	G	H	I	J	K
cls	target	analog	analog	analog	analog	analog	analog	analog	analog	
label	2-Methoxyethanol	Ethylene glycol	2-Butoxyethanol	Triethyler	2-(Hexylo	Isopentyl	2-Butyne-	Ethylene g	2-Methyl-1-propanol	
dsstox_cid	DTXCID804182	DTXCID40597	DTXCID904097	DTXCID60	DTXCID60	DTXCID70	DTXCID90	DTXCID30	DTXCID601759	
casrn	109-86-4	107-21-1	111-76-2	112-27-6	112-25-4	123-51-3	110-65-6	629-14-1	78-83-1	
jaccard	1	0.714285714	0.666666667	0.666667	0.6	0.444444	0.428571	0.428571	0.375	
CHR:Bone Marrow	GenRA Neg Act=0 (0.326) AUC=0 p=0.685	no_effect	125.000 ppm	no_effect	no_data	no_data	no_data	no_data	no_data	
DEV:Bone	GenRA TP Act=1 (1) AUC=0 p=1(50.000 ppm)	750.000 mg/kg/day	100.000 ppm	5630.000	no_effect	0.500 pp	no_effect	100.000 r	no_effect	
MGR:Bone	GenRA Pos Act=1 (0.517) AUC=0 p=0.51	1333.330 mg/kg/day	no_data	no_effect	no_data	no_data	no_data	no_data	no_data	
SUB:Bone	GenRA FN Act=0 (0.483) AUC=0 p=0.66(546.000 mg/kg/day)	no_effect	500.000 ppm	no_data	no_effect	no_data	no_data	no_data	no_data	
SUB:Bone Marrow	GenRA FN Act=0 (0.483) AUC=0 p=0.65(297.000 mg/kg/day)	no_effect	62.500 ppm	no_data	no_effect	no_data	no_data	no_data	no_data	

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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	Beta for Internal testing

Summary

- Still many challenges remain in read-across
- Quantifying the uncertainty of read-across prediction is a critical issue
- Have illustrated the research directions being taken within NCCT and work to implement these into practical tools

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