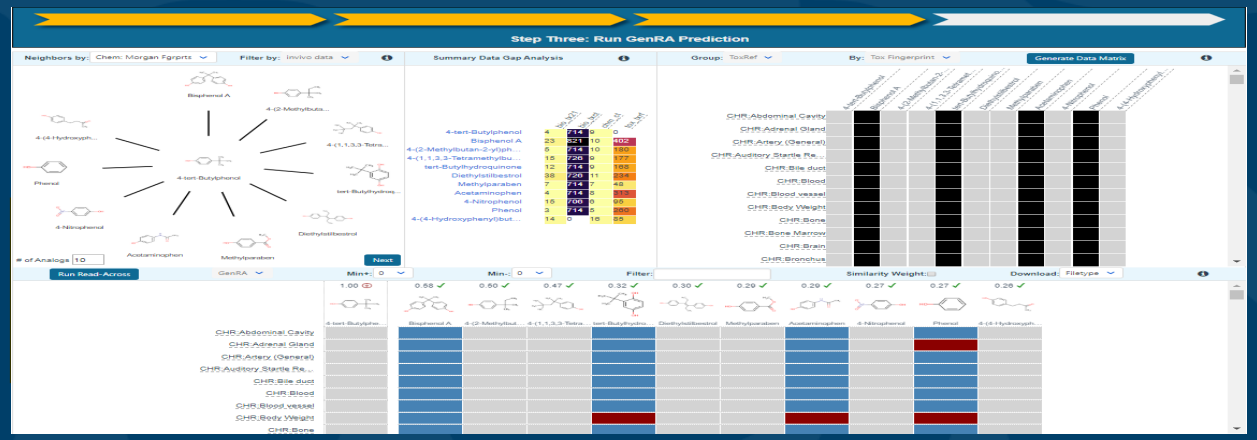
Transitioning towards objective read-across approaches: Generalised Read-across (GenRA)



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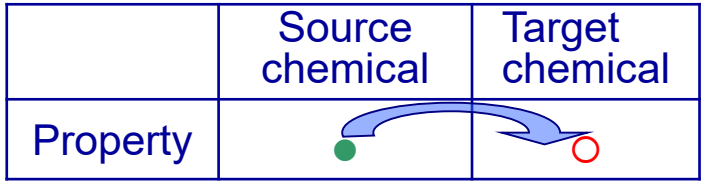
Outline

- Putting Read-across in context
- Overview of the Generalised Read-across (GenRA) approach
- Implementation of GenRA in the CompTox Chemicals Dashboard
- Refinement of the GenRA approach: work in progress & current applications
- Summary Remarks
- Acknowledgements
- References

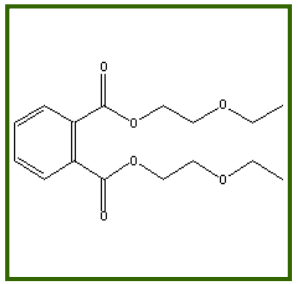
Definitions: Read-across

- Read-across describes the method of filling a data gap whereby a chemical with existing data values is used to make a prediction for a 'similar' chemical.
- A target chemical is a chemical which has a data gap that needs to be filled i.e. the subject of the read-across.
- A source analogue is a chemical that has been identified as an appropriate chemical for use in a read-across based on similarity to the target chemical and existence of relevant data.



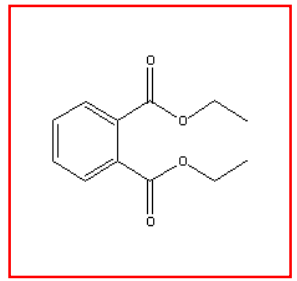
● Reliable data

○ Missing data



Known to be harmful

Acute toxicity?



Predicted to be harmful

A harmonised hybrid read-across workflow

- Many frameworks/workflows for the development and evaluation of read-across e.g. OECD grouping guidance, ECHA R6, RAAF etc.
- Can be challenging to orient what the similarities and differences are between these workflows?
- Where new approach methods fit?
- How to scale up read-across approach for large numbers of substances in a systemic and reproducible manner?

Determine the scope of the 1. Decision

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

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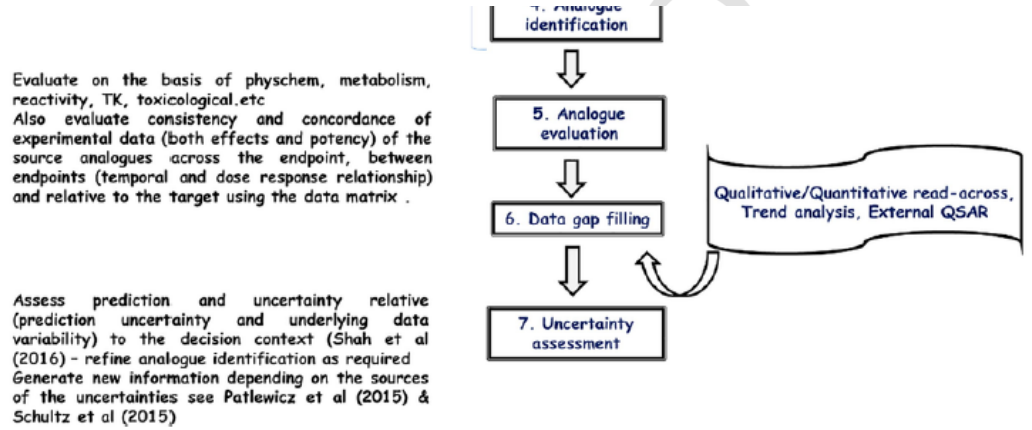

Fig. 9. A harmonised hybrid development and assessment framework.

Selected read-across tools

- Several 'read-across' tools exist
- How do they compare and contrast?
- Which tool or combination of tools can be used for a specific decision context?

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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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Selected read-across tools

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

GenRA (Generalised Read-Across)

- Predicting toxicity as a similarity-weighted activity of nearest neighbours based on chemistry and bioactivity descriptors (Shah et al, 2016)
- Generalised version of the Chemical-Biological Read-Across (CBRA) developed by Low et al (2013)
- Goal: To establish an objective performance baseline for read-across and quantify the uncertainty in the predictions made

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

Jaccard similarity:

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

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

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

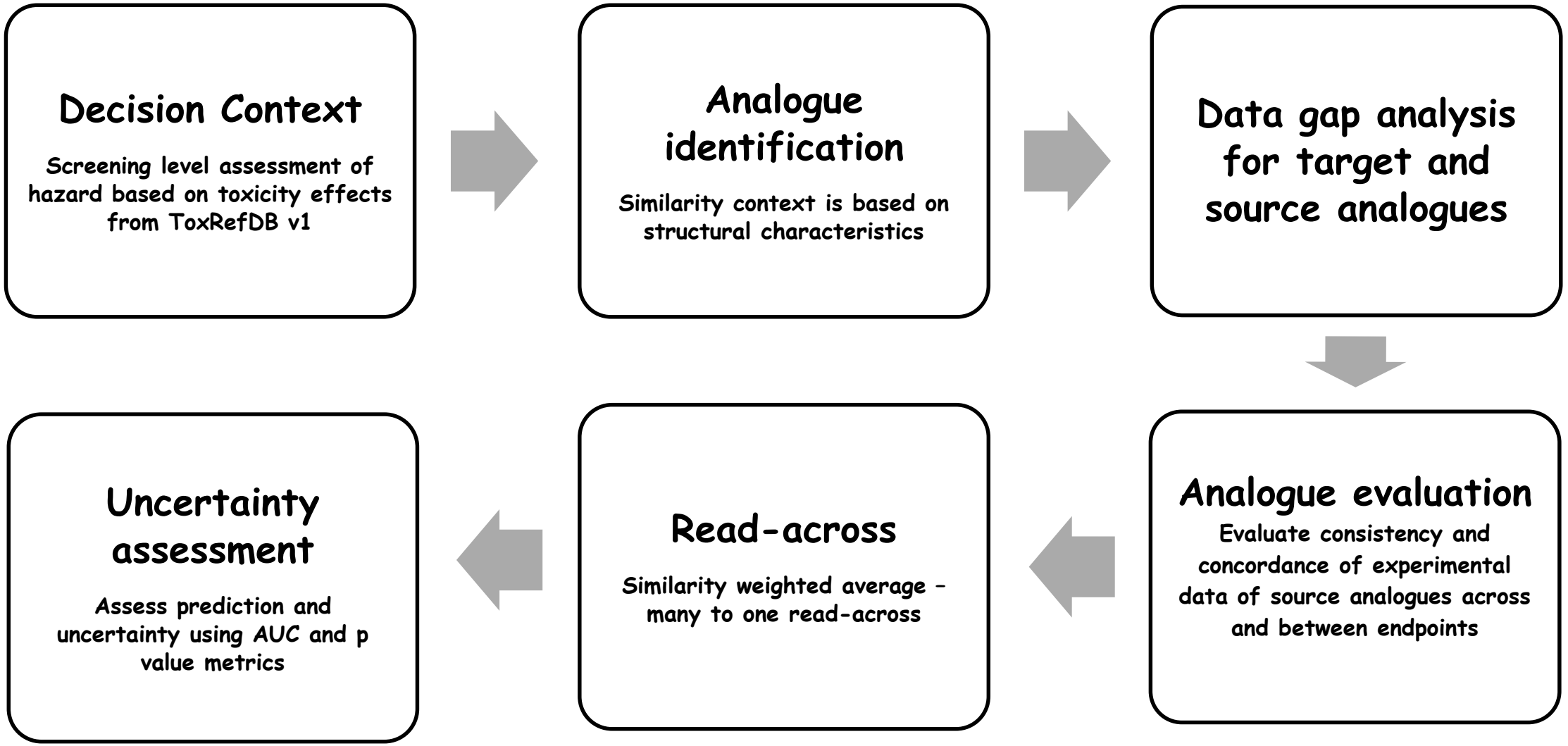
y_i = predicted activity of chemical (c_i)

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



Activity was translated into a binary score (1,0)

GenRA tool in reality

- Integrat

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Short Communication

Generalized Read-Across (GenRA): A workflow implemented into the EPA CompTox Chemicals Dashboard

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Abstract

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

GenRA – Next Steps

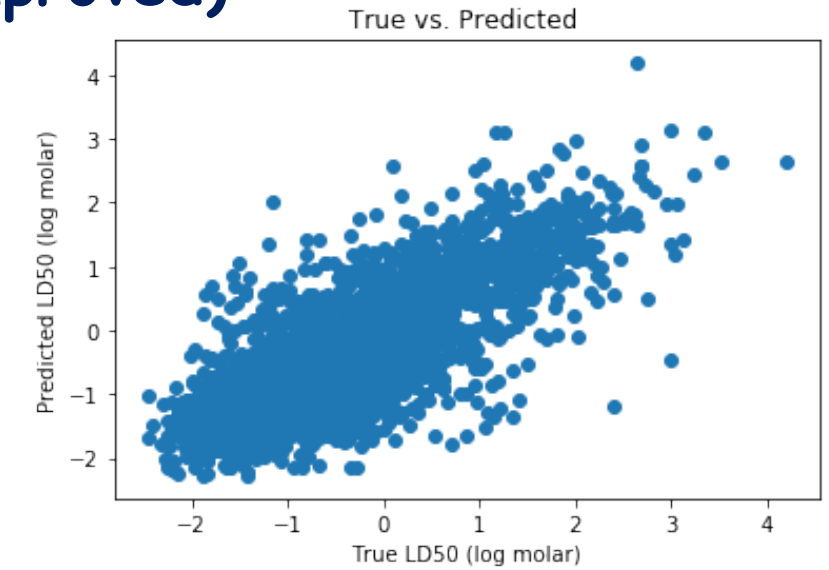
- Ongoing research:

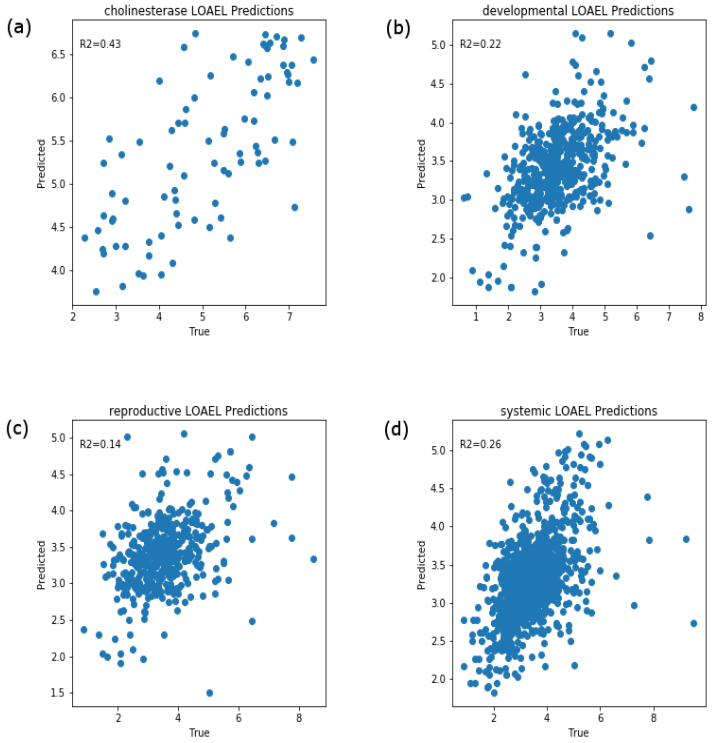
- Summarising and aggregating the toxicity effect predictions to guide end users – what effect predictions are we most confident about (digesting & interpreting the predictions more efficiently)

- Consideration of other information to define and refine the analogue selection & evaluation – e.g. physicochemical similarity, metabolic similarity, reactivity similarity, bioactivity similarity (transcriptomics similarity)…
  - Quantifying the impact of physicochemical similarity on read-across performance (Helman et al., 2018)

GenRA – Next Steps

- Dose response information to refine scope of prediction beyond binary outcomes
  - Analyses with quantitative data – acute rat oral toxicity (LD50 values), ToxRefDB v (LOAEL values)
  - Overall 'global' performance was reasonable – categories of chemicals could be readily identified where perfor improved)





GenRA – Applications

- Opportunities to refine how read-across is conducted within Provisional Peer review toxicity values (PPRTVs) assessments
- Exploring how GenRA can be used to inform read-across of PFAS within defined structural categories

Summary

- Harmonised framework for read-across provides opportunities for NAM data
- GenRA developed is aligned with this framework
- Illustrated how GenRA baseline can been applied in practice
- Highlight ongoing research in extending the approach & current applications

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