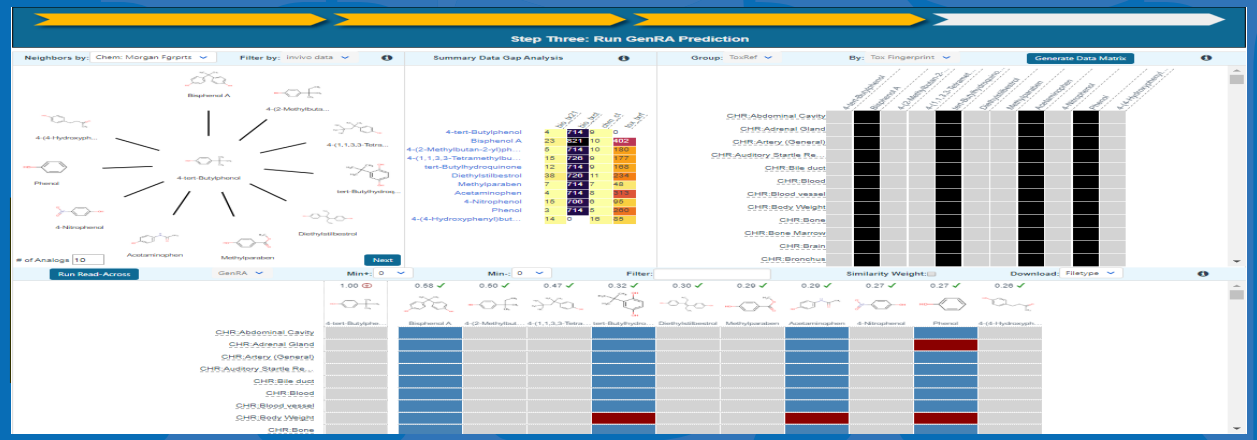
Transitioning Generalised Read-across (GenRA) towards quantitative predictions



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Conflict of Interest Statement

No conflict of interest declared.

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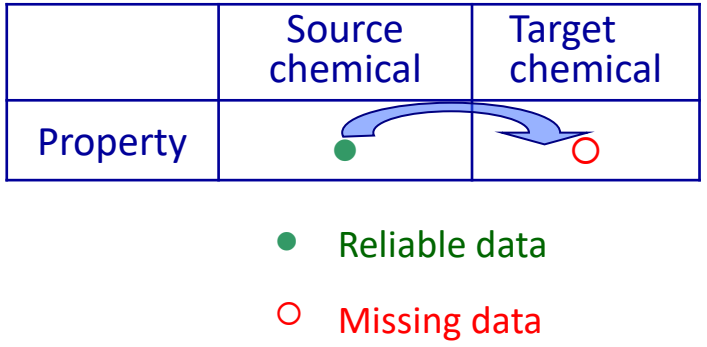
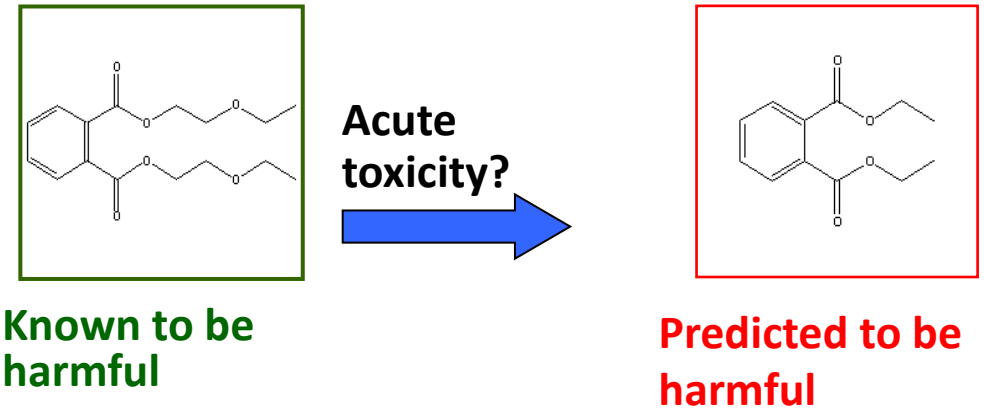
Outline

- Putting Read-across in context – a hybrid harmonised read-across workflow
- Overview of the Generalised Read-across (GenRA) approach
- Transitioning from 'qualitative' to 'quantitative' predictions
  - LD50 values from acute oral rodent toxicity studies
  - LOAEL values from repeated dose toxicity studies
  - Evaluation of predictions
- Summary Remarks
- Acknowledgements

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.





A harmonised hybrid read-across workflow

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

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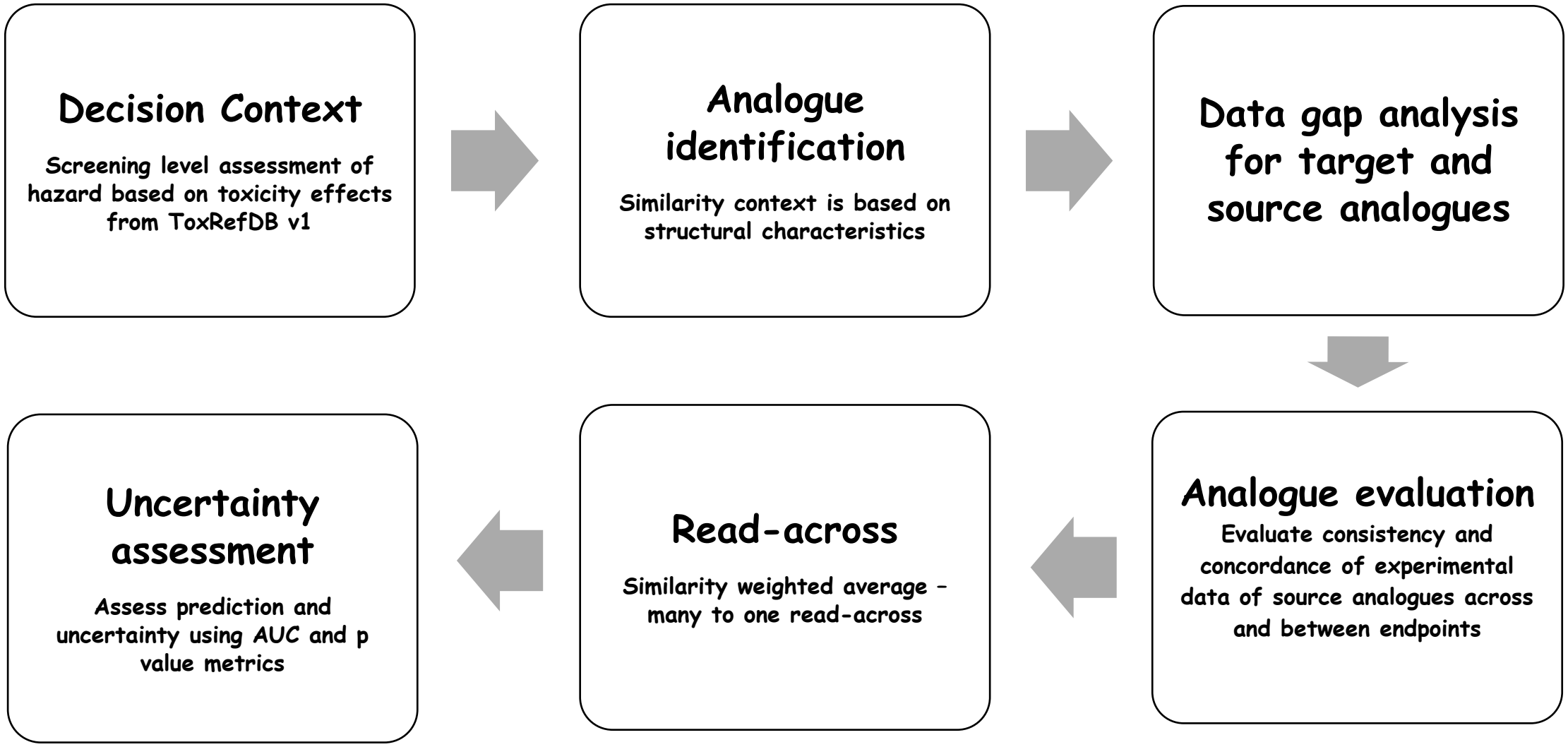
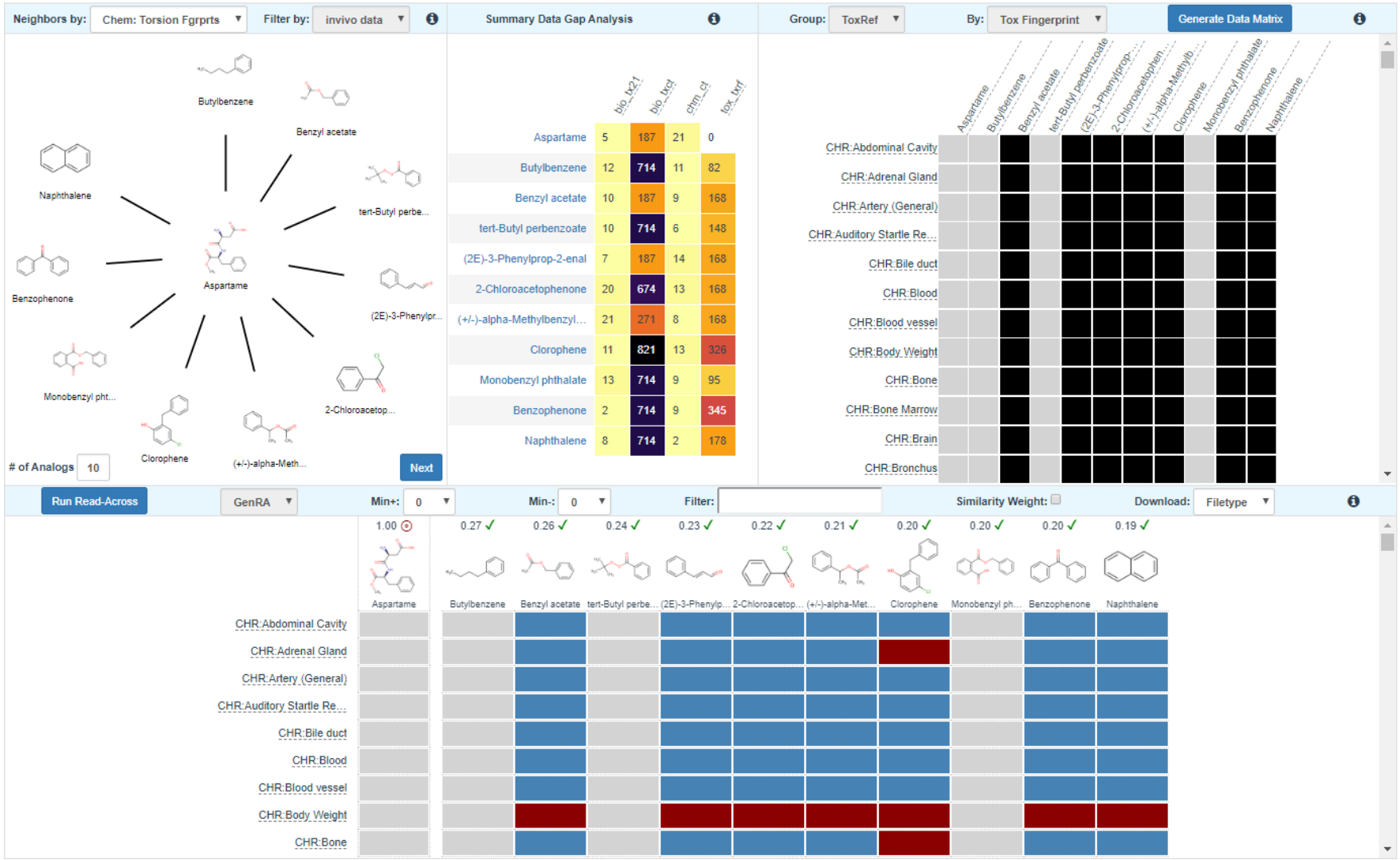
Read-across workflow in GenRA v1.0



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

GenRA tool in reality

- Integrated into the EPA CompTox Chemicals dashboard



GenRA – Next Steps

- 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

Case study: Acute toxicity

- Transitioning GenRA to make quantitative predictions
- Investigated extending GenRA using the acute oral rat systemic toxicity data collected as part of the ICCVAM Acute toxicity workgroup
- NICEATM-NCCT effort to collate a large dataset of acute oral toxicity to evaluate the performance of existing predictive models and investigate the feasibility of developing new models

Acute toxicity: Dataset creation

Database Resource	Rows of Data (number of LD50 values)	Unique CAS
ECHA (ChemProp)	5533	2136
JRC AcutoxBase	637	138
NLM HSDB	4082	2238
OECD (eChemPortal)	10206	2314
PAI (NICEATM)	364	293
TEST (NLM ChemIDplus)	13689	13545

Rat oral LD50s:
16,297 chemicals total
34,508 LD50 values

Require unique LD50 values with mg/kg units

15,688 chemicals total
21,200 LD50 values

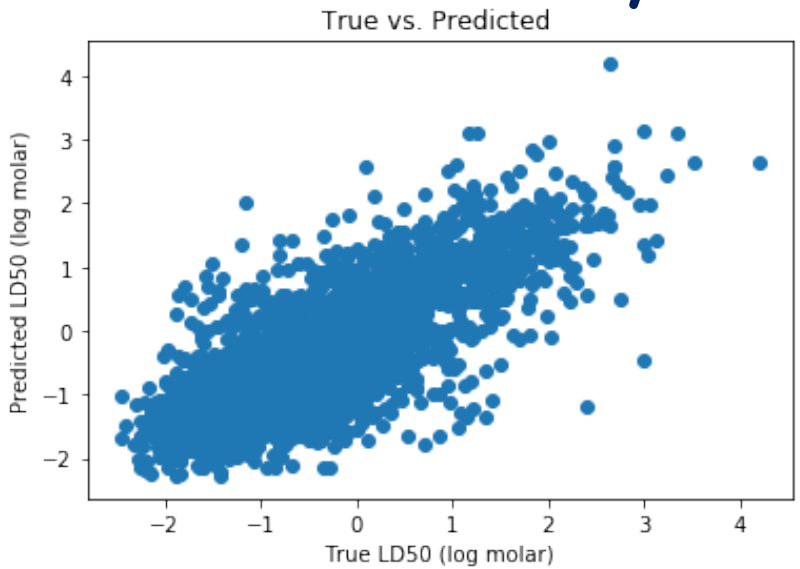
Preprocessing for modelling

11,992 chemicals
16,173 LD50 values

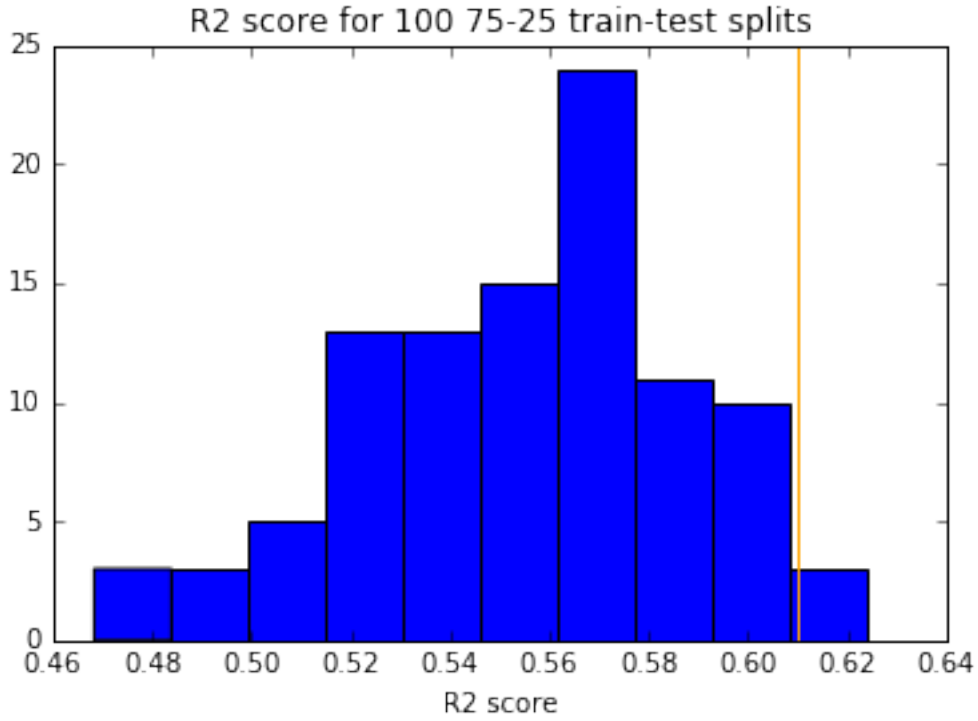
Karmaus et al, 2018; Kleinstreuer et al., 2018

GenRA approach : Overall 'global' performance

- Search for a maximum of 10 nearest neighbours on entire dataset
- Use a min similarity threshold of 0.5



- Linear regression used to fit predicted and observed LD50 values
- R^2 = 0.61
- RMSE = 0.58



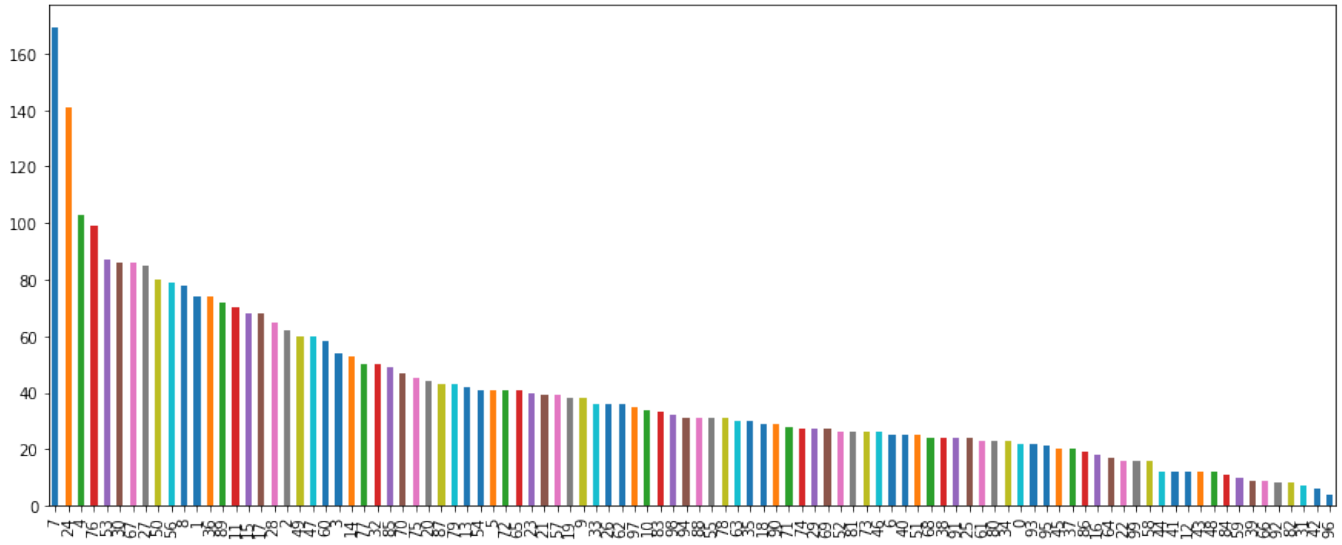
- Monte Carlo CV
- Estimate confidence in R2
- 75-25 train-test splits
- R^2 values range from 0.46 to 0.62

Evaluating 'local' performance

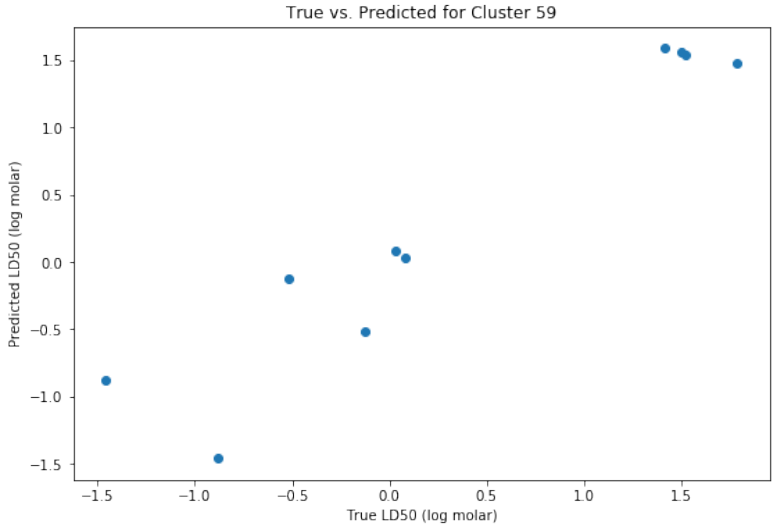
Clustered chemicals into 100 groups on the basis of ToxPrint fingerprints

Explored performance on the basis of individual clusters to gauge what sorts of chemicals resulted in significantly improved performance (R2) relative to the overall 'global' performance reported using 10 nearest neighbours and a similarity of 0.5

Average R2 values improved (R2>0.61) for 19 out of the 100 clusters, some up to 0.91



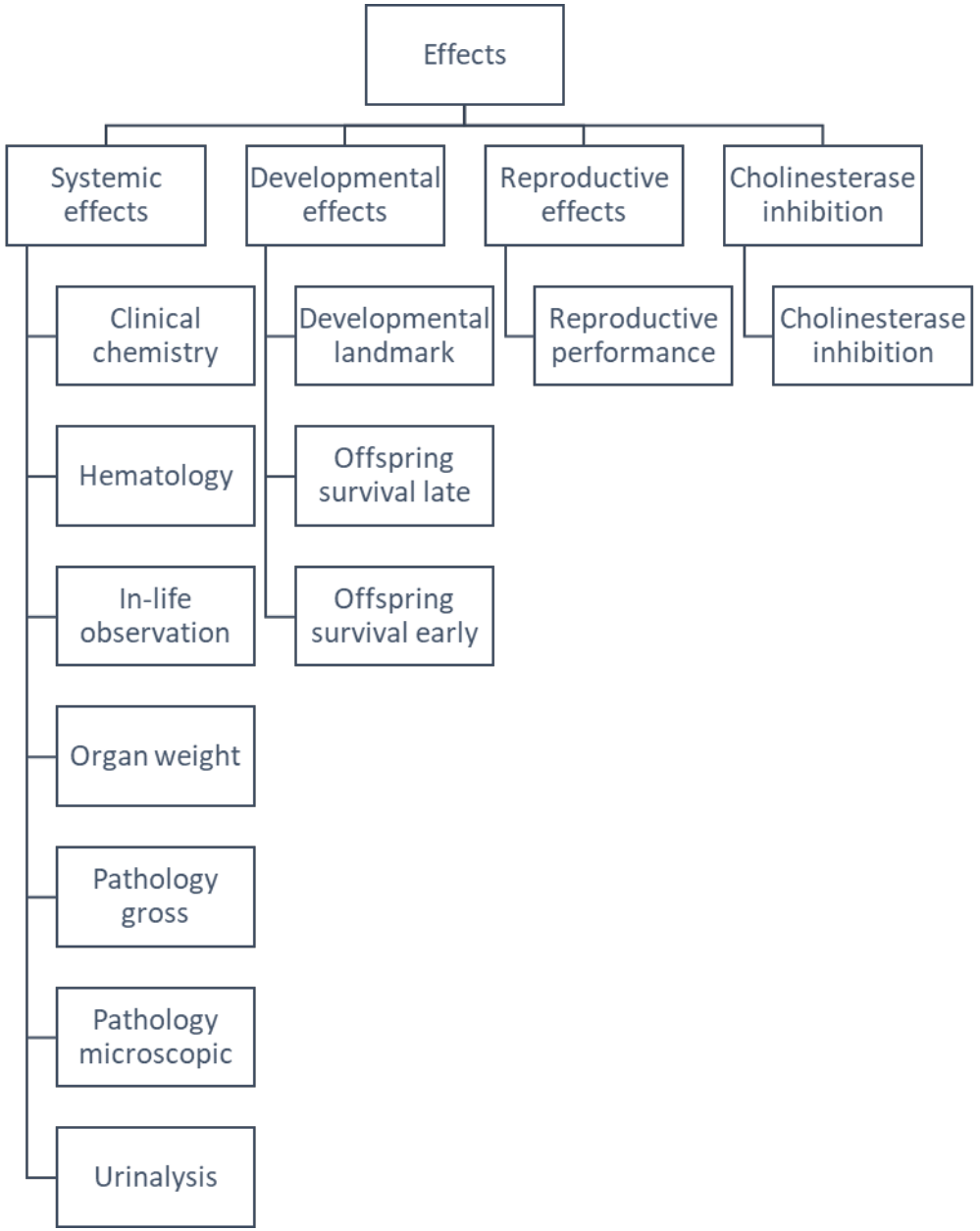
Carbamate containing substances



Case study – Repeated Dose toxicity

- How does GenRA perform using POD values from ToxRefDB 2.0.
- POD: Point of departure, or points on a dose-response curve corresponding to an observed effect level or no effect level
- POD types: LOAEL (lowest observed adverse effect level), NOAEL (no observed adverse effect level), LEL (lowest effect level), NEL (no effect level)
- 4 Broad endpoint categories: cholinesterase, developmental, reproductive, systemic effects
- 27,564 chemical level LOAEL values across 1049 substances

Overview of ToxRefDB v2.0 POD types



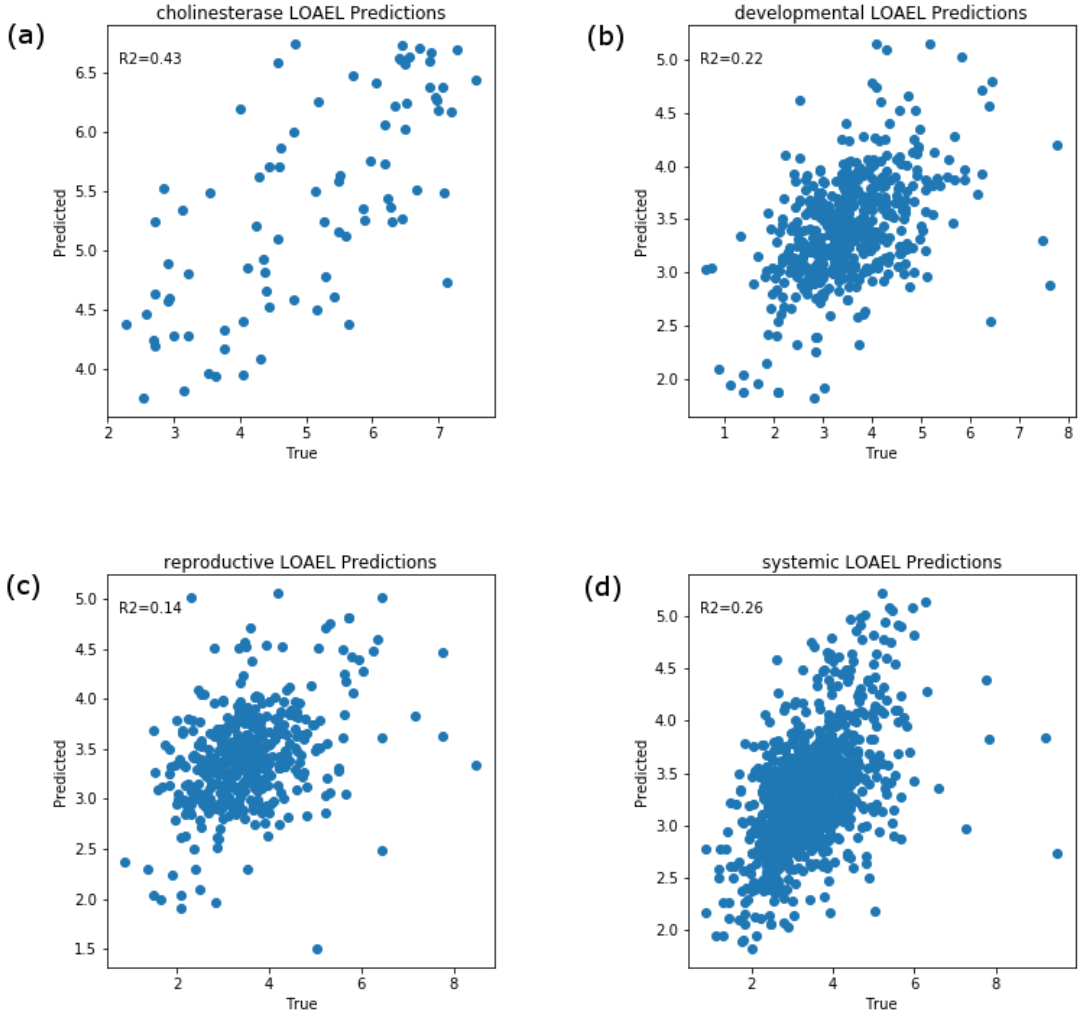
4 Endpoint Categories

14 endpoint types

GenRA analysis approach

- For chemicals that contain multiple LOAEL values, aggregate them by taking the mean or the min and converting that to the log molar equivalents
- Use GenRA to predict LOAEL values using Morgan chemical fingerprints
- Search for a maximum of 10 nearest neighbours (k) with a min similarity (s) threshold of 0.05. Default values aimed at maximising the ability to predict LOAELs for as many chemicals as possible.
- Conduct a grid search over k (number of nearest neighbors) and s (similarity threshold) to find optimal values for R2
- Cluster analysis was performed to find local neighborhoods of chemicals where approach performs particularly well.

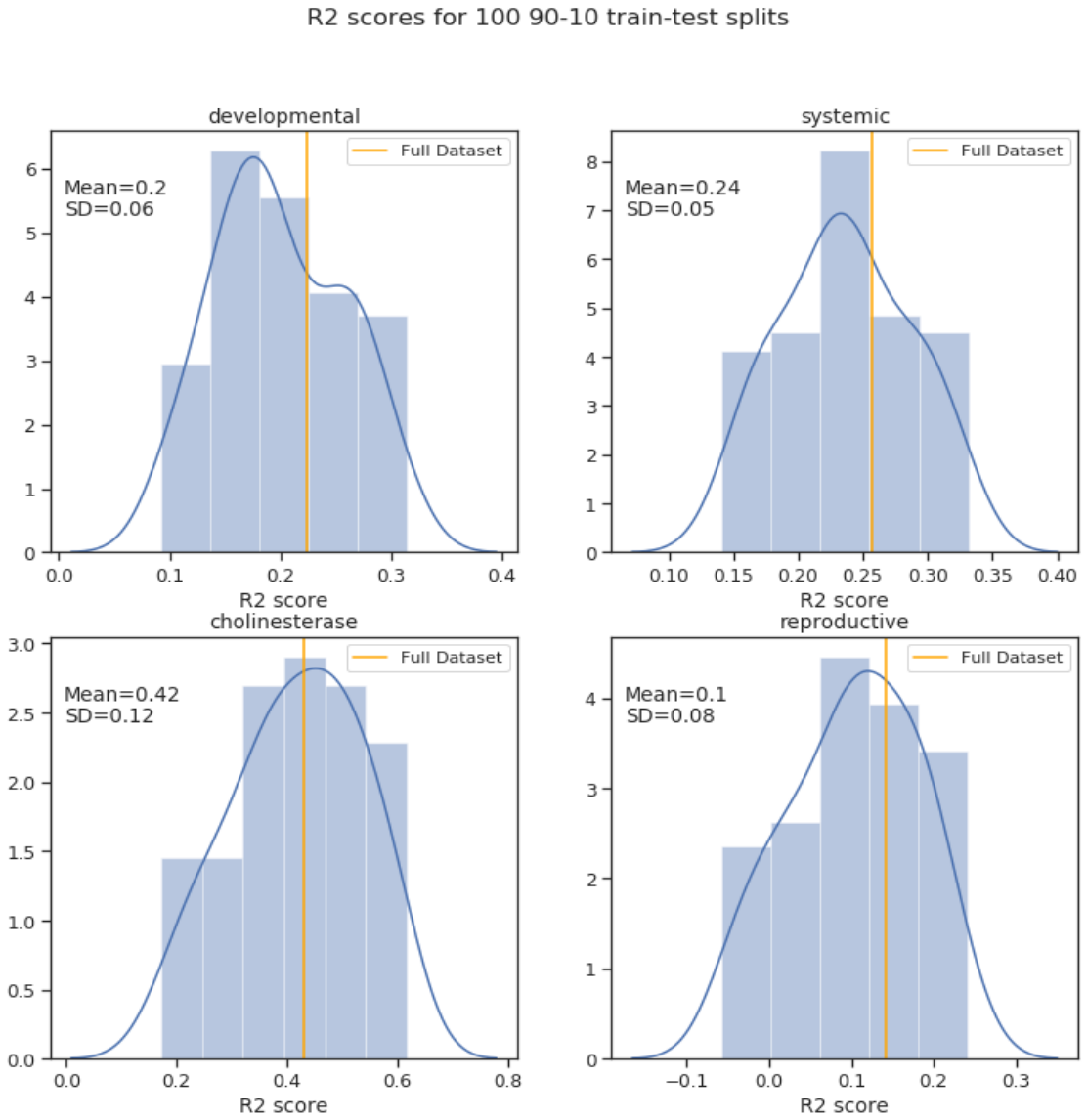
GenRA approach : Overall 'global' performance



GenRA Predictions using Morgan fingerprints with k=10 and s=0.05 (mean aggregated LOAELs)
Linear regression used to fit predicted and observed LOAEL values

Endpoint Category	R2
Cholinesterase	0.43
Developmental	0.22
Reproductive	0.14
Systemic	0.26

Monte Carlo Cross Validation

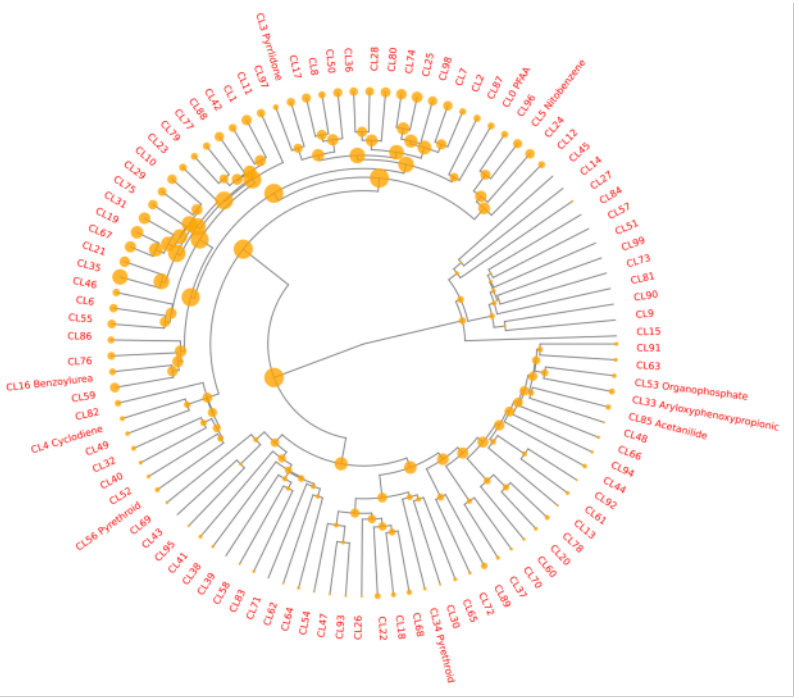


- Cross-validation testing
- 90-10 train-test splits

Endpoint	mean R2 & std
systemic toxicity	0.24±0.05
developmental toxicity	0.2±0.06
reproductive toxicity	0.1±0.08
cholinesterase inhibition	0.42±0.12

Evaluating 'local' performance

Clustered chemicals into 100 groups on the basis of Morgan fingerprints (re-used the clusters derived from GenRA v1.0)



Local GenRA predictions performed better than the global prediction by endpoint categories in 36 out of the 100 clusters.
Represent 22% (222/1014) of all chemicals

The average R2 values for systemic, developmental, reproductive effects and cholinesterase inhibition for these 36 clusters were 0.73, 0.66, 0.60 and 0.79, respectively.

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
  - transitioning to quantitative predictions of 'PODs' with 2 case studies – acute toxicity LD50 values and LOAELs from repeated dose toxicity studies

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