Building a compendium of expert driven read-across (EDRA) cases to investigate the utility of New Approach Methodology (NAM) data in Generalized Read-Across (GenRA)

#P231

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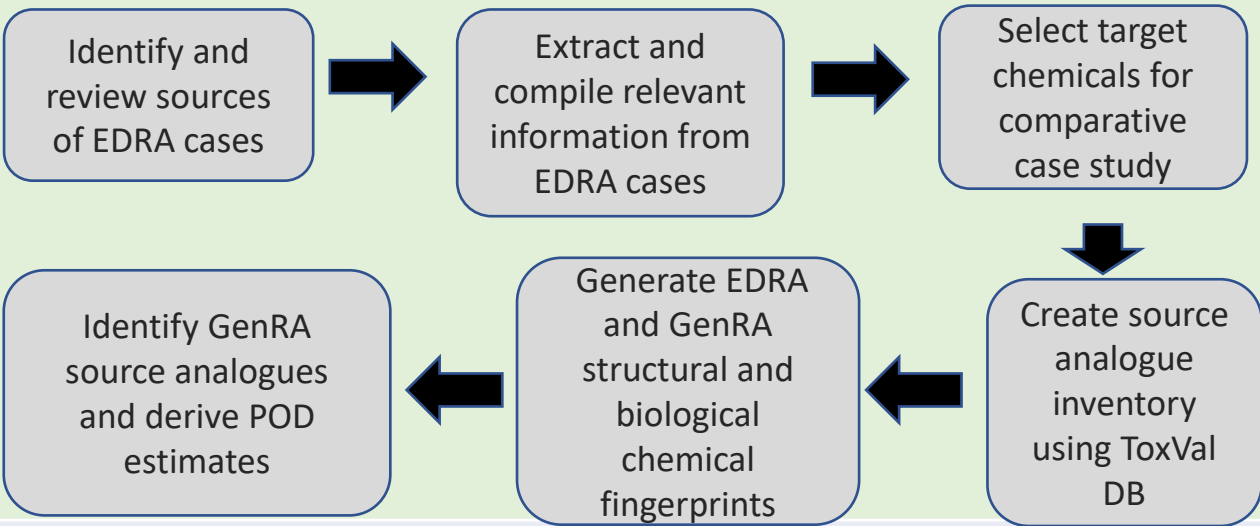
OBJECTIVES

- Create a compendium of established and accepted expert driven read-across (EDRA) examples that have been published in the literature.
- Extract the data and justification supporting the EDRA examples e.g., identity of source analogues, toxicity data
- Compare and contrast case studies of EDRA with those derived objectively with NAM data using GenRA
- As a proof of concept, identify structural and biologically based source analogues for 2 substances that were assessed as part of the Provisional Peer Review Toxicity Values (PPRTVs) and estimate their points of departure (PODs) using GenRA

APPROACH

Identify and review sources of EDRA cases → Extract and compile relevant information from EDRA cases → Select target chemicals for comparative case study → Create source analogue inventory using ToxVal DB → Generate EDRA and GenRA structural and biological chemical fingerprints → Identify GenRA source analogues and derive POD estimates

MAIN RESULTS

GenRA POD estimates for sec-Butylbenzene based on Chemical and Bioactivity based analogues

EDRA POD Estimate (mg/kg-day)	GenRA Estimate Chemical Fingerprints (mg/kg-day)	GenRA Estimate Biological Fingerprints (mg/kg-day)
110	76.14	188.08

FUTURE DIRECTIONS

- Expand dataset to include all EDRA cases presented in published PPRTVs and modify inclusion criteria.
- Repeat structural and biological fingerprint comparison using pairwise and Nearest Neighbor analyses.
- Evaluate similarity and dissimilarity in analogue selection for new dataset.
- Use GenRA to compute PODs and compare them to published PODs for all PPRTV chemicals.
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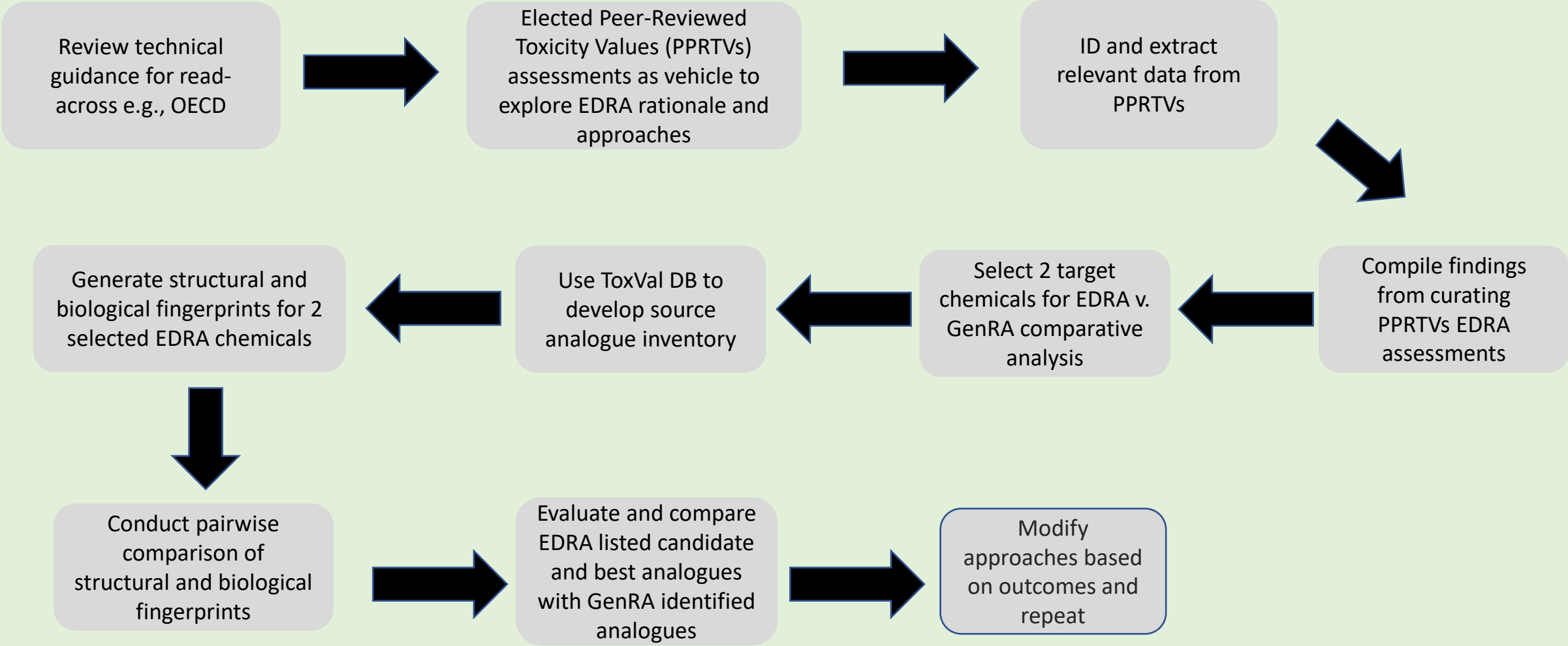
OBJECTIVES

- Create a compendium of expert driven read-across (EDRA) cases.
- Categorize the examples based on source e.g., Provisional Peer Review Toxicity Values (PPRTVs) , OECD IATA Case studies etc.
- Identify what types of information are reported. Extract relevant information – identity of the target and source analogues, structural information, supporting information to justify the similarities as well as the toxicity data underlying the read-across prediction being made.
- Evaluate how EDRA derived POD values compare to those derived objectively on the basis of NAM data such as the High Throughput Screening (HTS) data generated as part of the ToxCast program using GenRA.
- As a proof of concept, identify structural and biologically based source analogues for 2 substances that were assessed as part of the PPRTVs and estimate their points of departure (PODs) using GenRA.
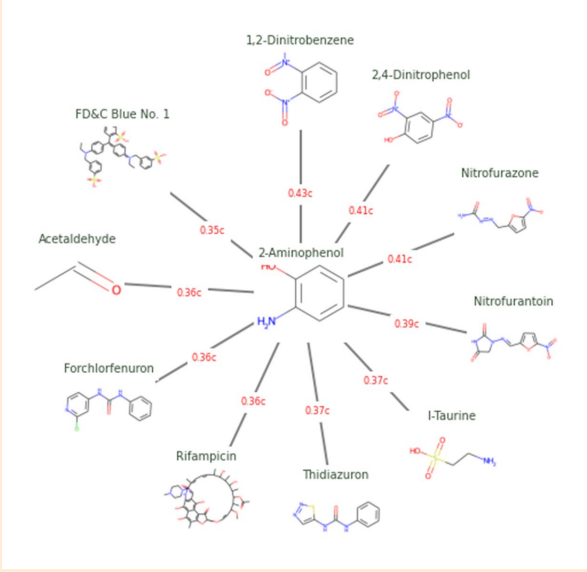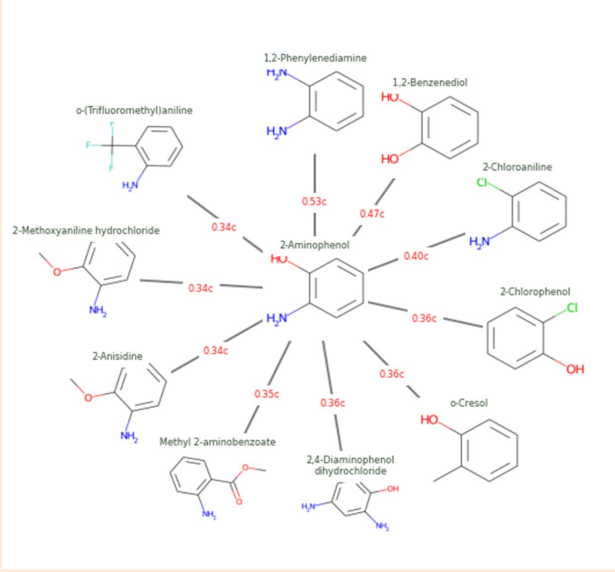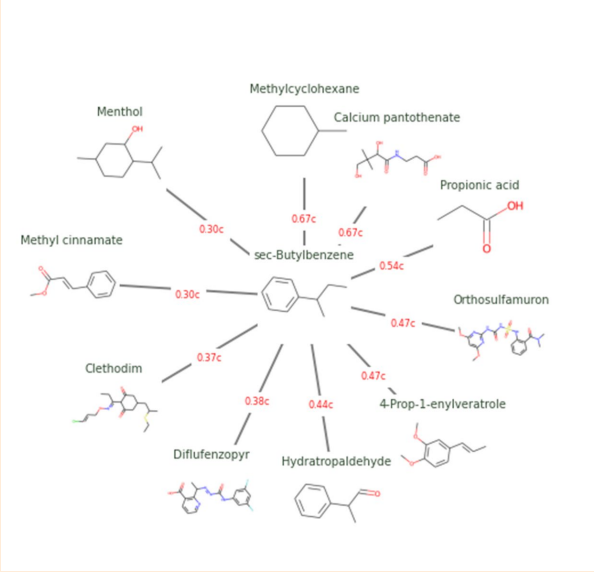
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APPROACH

Review technical guidance for read-across e.g., OECD

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Elected Peer-Reviewed Toxicity Values (PPRTVs) assessments as vehicle to explore EDRA rationale and approaches

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ID and extract relevant data from PPRTVs

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Generate structural and biological fingerprints for 2 selected EDRA chemicals

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Use ToxVal DB to develop source analogue inventory

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Select 2 target chemicals for EDRA v. GenRA comparative analysis

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Compile findings from curating PPRTVs EDRA assessments

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Conduct pairwise comparison of structural and biological fingerprints

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Evaluate and compare EDRA listed candidate and best analogues with GenRA identified analogues
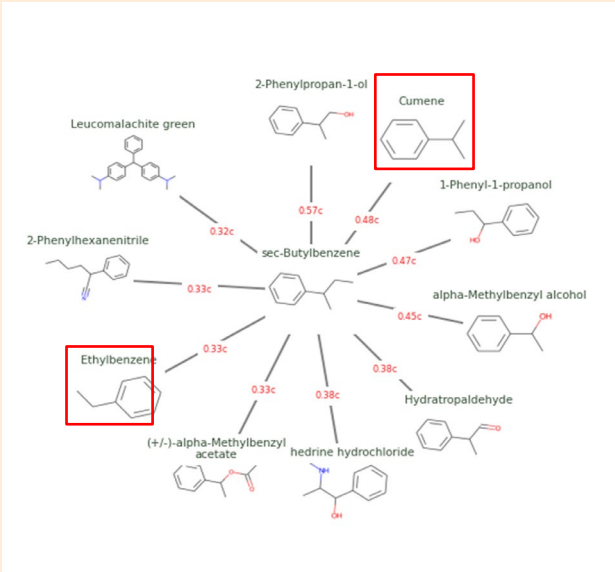
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Modify approaches based on outcomes and repeat

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MAIN RESULTS

DDRA identified chemical structural (left) and biological (right) analogues for sec-Butylbenzene

DDRA identified chemical structural (left) and biological (right) analogues for o-Aminophenol

Evaluation of GenRA and EDRA derived POD values for sec-Butylbenzene

EDRA POD Estimate (mg/kg-day)	GenRA Estimate Chemical Fingerprints (mg/kg-day)	GenRA Estimate Biological Fingerprints (mg/kg-day)
110	76.14	188.08

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SUMMARY AND IMPACT

In this study, we generated a compendium of 30 EDRA assessments using data extracted from published PPRTVs. We used these sn current methodologies and rationale around expert driven candidate analogue selection. With the information gathered, we condu case study that compared GenRA candidate analogue selections with the published EDRA recommendations for two target chemica using NAM data, we were able to identify the same or similar candidate structural analogues for sec-Butylbenzene as found in the assessment. PODs derived for this target chemical using chemical and biological fingerprints methods were comparable with the pu
Steps in progress:

- ❖ Expand dataset to include all EDRA cases presented in published PPRTVs and modify inclusion criteria.
- ❖ Repeat structural and biological fingerprint comparison using pairwise and Nearest Neighbor analyses.
- ❖ Consider additional bioactivity data-streams including transcriptomics and cell painting.
- ❖ Evaluate similarity and dissimilarity in analogue selection for new dataset.
- ❖ Use GenRA to compute the PODs and compare them to the published PODs for all PPRTV chemicals.
- ❖ Collaborate with chemical assessment practitioners to discuss the development/utility of hybridized approaches to read-across