A Solution Guiding Read-Across Workflow based on Chemoinformatics and Safety Assessment

C Yang[1,2,3*], J Rathman[2,3], J Marusczyk[1], A Tarkhov[1], T Kleinöder[1], B Bienfait[1], O Sacher[1], A Mostrag[2], C Schwab[1] , T Magdziarz[1], J Park[2], E Fioravanzo[4], M Cronin[5]

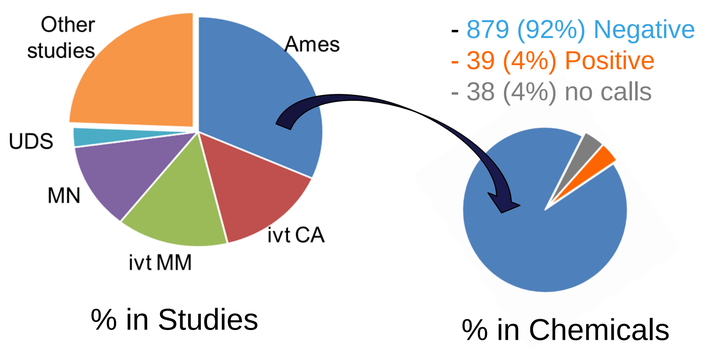
*chihae.yang@mn-am.com

[1]Molecular Networks GmbH, Nürnberg, Germany; [2]Altamira LLC, Columbus OH, USA; [3]The Ohio State University, Columbus, OH, USA; [4]ToxNavigation, East Molesey, UK; [5]Liverpool John Moores University, UK

OBJECTIVES

- Establish a clear path for Read-Across based on genetic toxicity assessment of pesticidal metabolites and impurities
- Compliant with EFSA guideline for weight of evidence (WOE)[1]
  - Assemble, weight, integrate
  - Relevance, reliability, consistency
- To demonstrate a reproducible WOE process implemented in a software solution
  - Combine evidence by Decision Theory to give outcome and uncertainty
  - Capture complex workflow
  - Save, export, report, and share the results set

EFSA PESITICIDE DATABASE – GENETIC TOXICITY



% in Studies

% in Chemicals

- EFSA **Public** Database: genetic toxicity of pesticides and their metabolites (released in July 2017)[2]
- 956 chemical species comprised of parents and related components (350 actives; 560 metabolites, etc.)
- Genetic toxicity data from 17,927 tests for 23 endpoints
- Fewer than 5% of the chemical species were missing 3 or more essential regulatory endpoints
- Data available for actives, but not always for metabolites or impurities

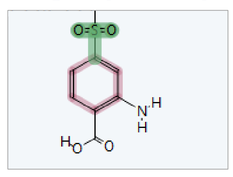
Target → Find Analogues (1) → Rate Analogues (2) → Find Data and Rate (3) → Combine & Read-Across (4)

BIOLOGICAL SIMILARITY (1) → CHEMICAL SIMILARITY (1,2) → REACTIVITY SIMILARITY (1,2)

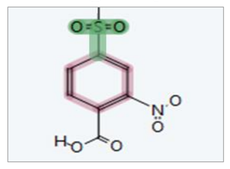
MOA Group: Hydroxyphenylpyruvate Dioxygenase (HPPD) inhibition

Chemical Group: Triketones

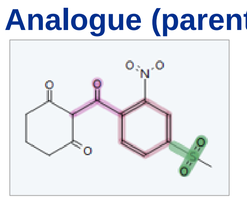
Target (AMBA)



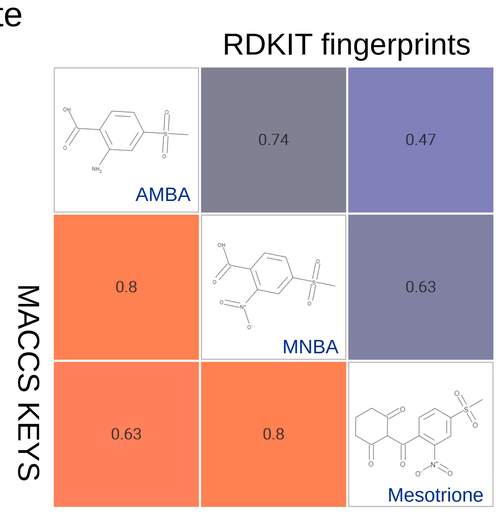
Analogue (MNBA)



Analogue (parent)

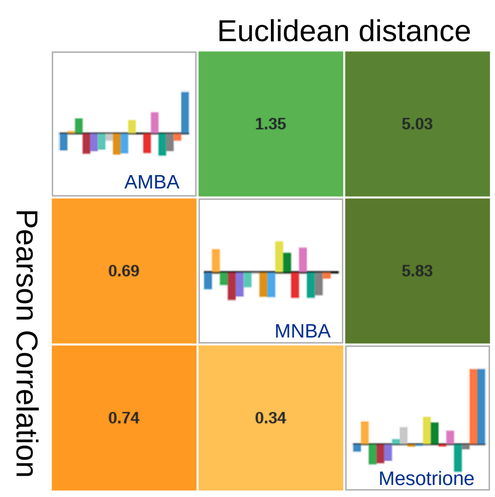


Structure-based



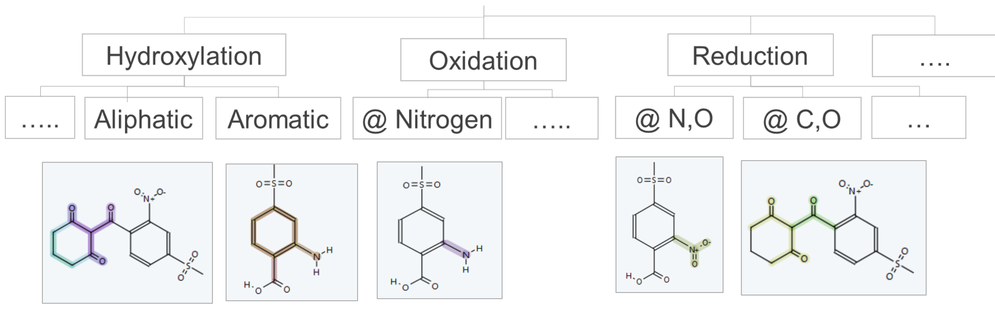
- Similarity measure is Tanimoto coefficient (= 1 - Jaccard distance)
- Need to compare similarity scores for multiple fingerprints
- ToxPrints (pre-defined features) and circular fingerprints are good options

Properties



- Molecular properties included (from left to right)[3]: Rotatable bonds, HBD, HBA, Lipinski rule violations, Stereo centers, Molecular weight, Complexity, ASA, McGowan volume, TPSA, Dipole moment, Polarizability, logS, XlogP, Diameter, Heats of formation, HOMO/LUMO gap
- Calculated properties are standardized against entire database

Reaction Types



$$\text{Metabolic Reactivity Similarity} = \frac{M}{P}$$

M: metabolic reaction sites common to parent and metabolite
P: total number of metabolic reaction sites in parent

- The metabolic reactivity rules are available in ChemTunes (Liver BioPath Rules)
- Public SyGMa rules are available https://github.com/3D-e-Chem/sygma

ANALOGUE QUALITY (2)

- Geometric mean of the three types of similarity defined above
- Analogues contain the triketone group features

STUDY RELIABILITY (3)

1) OECD guideline and deviation
2) GLP compliance
3) Study design with respect to species, strains, cell lines, metabolic activation
4) Study design with respect to concentration, dose levels and ranges, number of duplicates, repeats
5) Control information

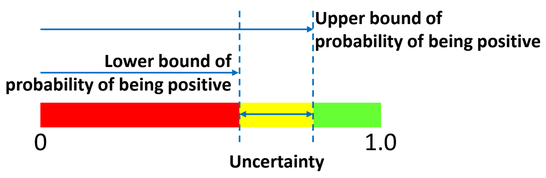
Reliability Score	Description
1.0	Meets all five criteria. Also the number of revertant counts at a given conc. level are available along with the precipitation and cytotoxicity information.
0.95	Meets all five criteria, but no conc. level detailed reading.
0.85	Studies either missing records or not conducted and at least one deficiency in the five aspects.
0.70	Studies either missing records or not conducted and at least two deficiencies in the five aspects.
0.50	Studies either missing records or not conducted and at least two deficiencies in the five aspects (no replicates, no info on control)

WEIGHT OF EVIDENCE (4)

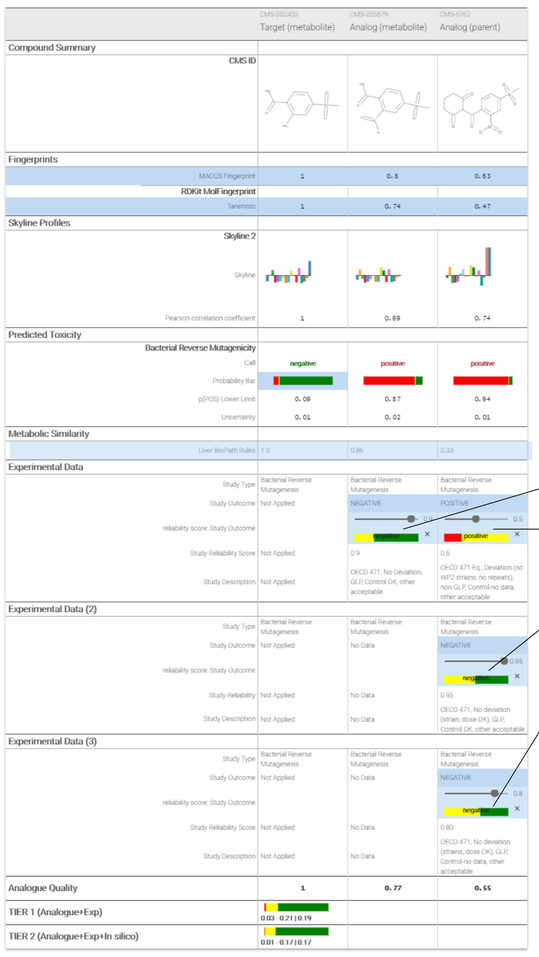
- Combine two sources of evidence according to Dempster-Shafer Theory (DST)[5]
  - Analogue quality
  - Experimental data with reliability score
- Belief function (weighing step)

$$\text{belief(probability)} = \text{analogue quality} \cdot \text{study reliability}$$

- Extend to all sources of evidence
  - Analogue (MNBA) with 1 experiment
  - Analogue (Parent) with 3 experiments
  - Consider all data when the reliability can be scored



ASSESSMENT TABLE (4)



READ-ACROSS CONCLUSION

Combined results from the two analogues can be used for read-across and the outcome was negative (probability of being positive = 0.03) in Ames test with uncertainty of 0.19. The read-across predicted the correct outcome.

SUMMARY AND FUTURE

- Lining up evidences and weight of evidence integration based on DST have been applied to the cases of EFSA genetic toxicity for metabolites
- Metabolic reactivity similarity was applied to measure the metabolic potential of targets and analogues
- Consistent and detailed criteria were established to rate the study reliability
- The workflow has been captured in the ToxGPS software solution[4]
- Quantitative numeric endpoint read-across is being designed

REFERENCES

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