Omics-based Chemical Grouping

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Outline

Rationale for case study

Study objectives

Results

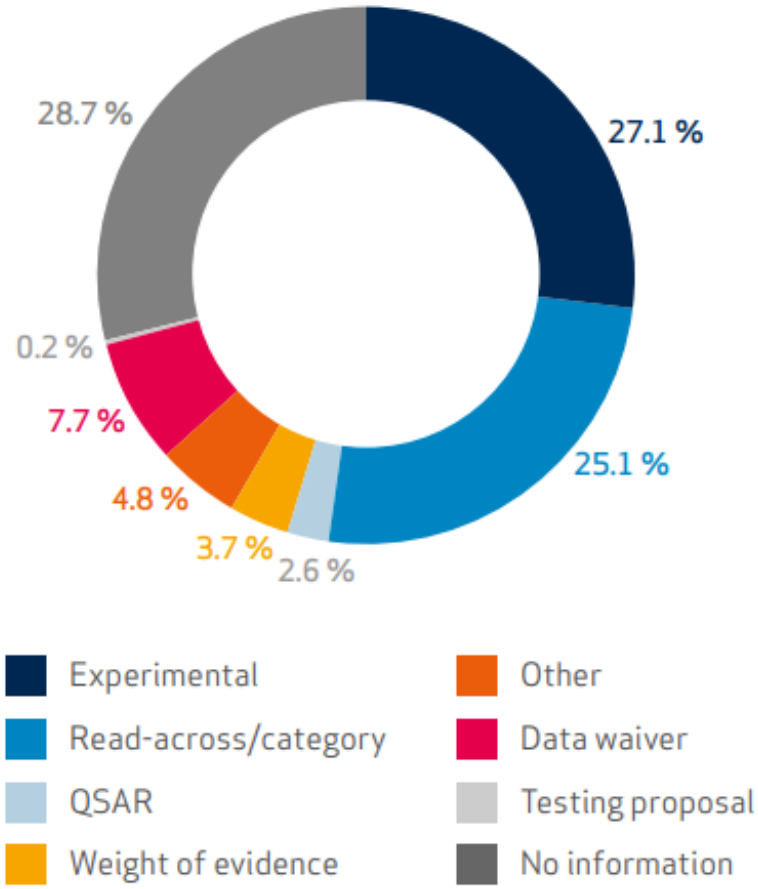
- Conventional vs. omics-based grouping
- Read-across
- Predicting the structural drivers of omics-based grouping

Conclusions from case study

Challenges and where next?

Grouping and read-across

- Most commonly used alternative method - for data-gap filling (https://echa.europa.eu/documents/10162/0/alternatives_test_animals_2020_en.pdf)
- Reduces the need for experimental tests because information on a similar substance (source) is used to predict the properties of another substance (target)
- When Test Guideline studies have been used to generate the data for the source substance, then a properly justified read-across can be used to fulfil REACH information requirements
- While ECHA has advocated using grouping/read-across, it has had to reject the majority of read-across arguments due in part to lack of scientific rigour in defining groups of substances, leading to incompliance



Can we increase the scientific evidence and therefore the acceptance rate of grouping/read-across dossiers by substantiating them with grouping based upon molecular mechanistic data?

View presentation from one of 2 perspectives

1. NAM (omics)-enhanced grouping **to enable read-across**

2. **Omics-based grouping** to support the acceleration of chemical risk assessment, first using 'omics data to screen (e.g. *in vitro*) and then group a large number of substances based on their MoA, prioritising group-representative substances for higher tier testing

   'Group first…' – H2020 PrecisionTox

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Study objectives

1. Select a target substance and series of potential source substances for grouping/read-across (analogue approach)
2. Apply conventional approaches to form a grouping hypothesis
3. Apply omics approaches to substantiate or disprove this grouping hypothesis based on molecular mechanistic data (here using transcriptomics and metabolomics)
4. Conduct read-across to fill the data gap
5. Map ToxPrint chemotypes onto omics-based grouping to predict what structural features are driving that biologically-based grouping

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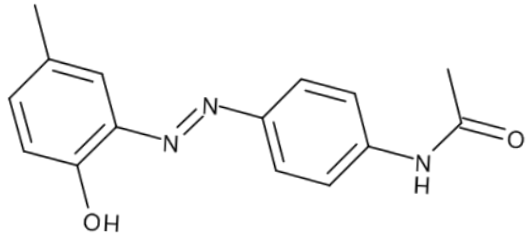
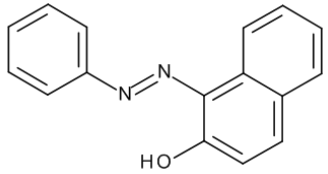
Azo dyes

Target substance:

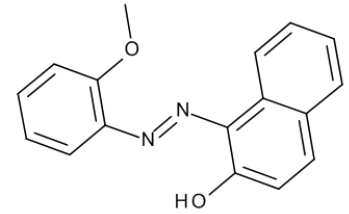


Disperse yellow 3 (DY3)

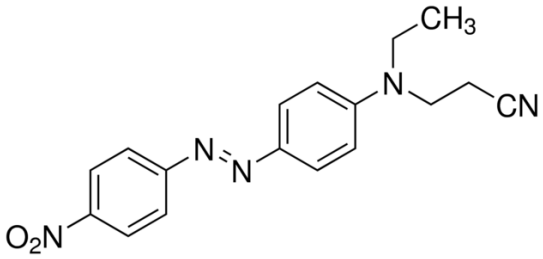
Six potential source substances:



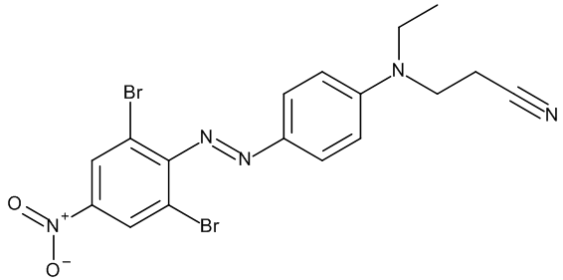
Sudan 1 (S1)



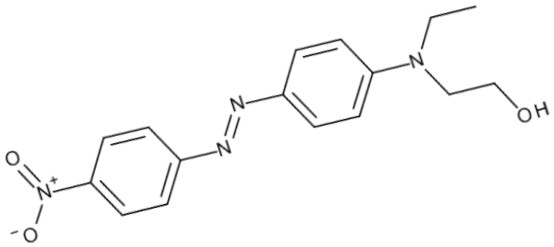
Sudan red G (SRG)



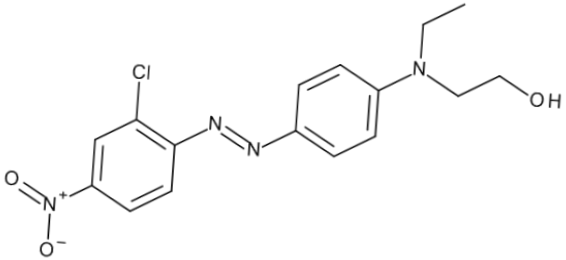
Disperse orange 25 (DO25)



Disperse orange 61 (DO61)



Disperse red 1 (DR1)



Disperse red 13 (DR13)

Need to determine which source substance is most similar to the target

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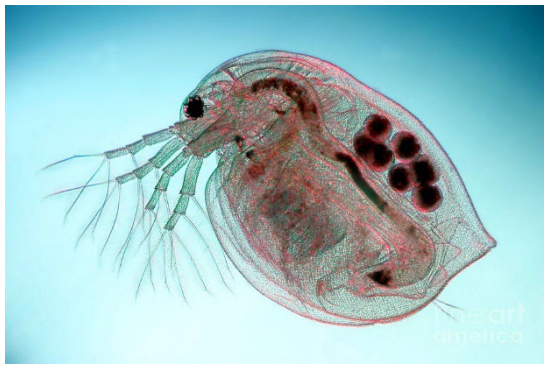
Grouping / read-across scenario

Type: ECHA's Read-Across Assessment Framework, Scenario 2 - analogue approach with single target substance and single source substance

Test system:



Daphnia magna

Expt'al design: low, medium, high doses for each azo dye

Endpoint (to read-across): *Daphnia* chronic reproductive toxicity (OECD TG211)

Principal aim of study was to investigate omics-based grouping, irrespective of the biological test system and test substances

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Conventional approaches to form grouping hypothesis (1)

- OASIS, ECOSAR 2.0, EPA and OECD chemical categories

DY3	Reactive unspecified alert by acute aquatic toxicity MOA (OASIS) Belongs to Phenols, Amides, Phenol amines (ECOSAR 2.0) Belongs to Phenols (EPA New Chemical Categories) Belongs to m,p-Cresols (OECD HPV Chemical Categories)
S1, SRG	Reactive unspecified alert by acute aquatic toxicity MOA (OASIS) Belong to Phenols (ECOSAR 2.0)
DR1, DR13, DO25, DO61	Reactive unspecified alert by acute aquatic toxicity MOA (OASIS) Belong to Neutral organics (ECOSAR 2.0) Only DR13 and DO61 belong to Neutral organics (EPA New Chemical Categories)

- Conclude: DY3 lies in its own group (but note DY3, S1 and SRG are all ‘phenols’)

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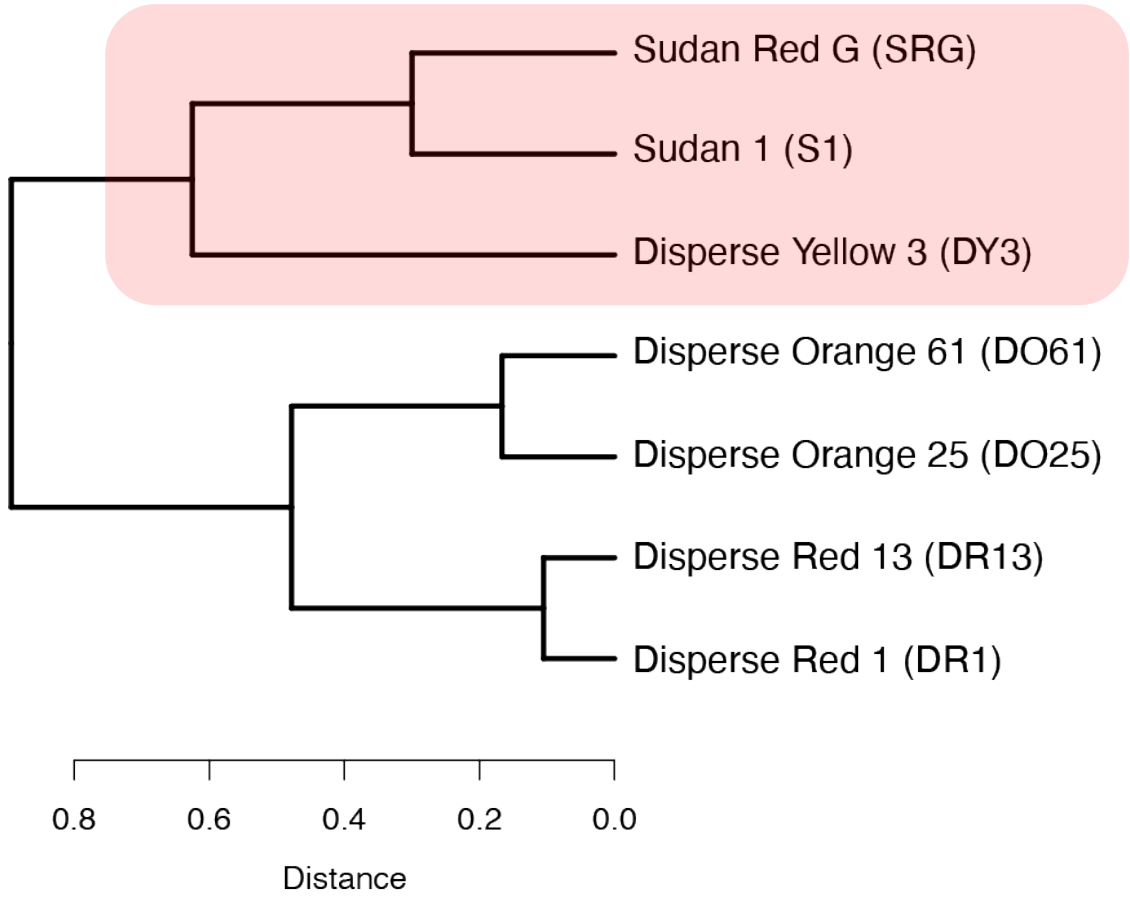
‘Conventional’ approaches to form grouping hypothesis (2)

ToxPrint chemotypes

- Structural fingerprints containing 729 binary descriptors (atoms, bonds, rings, functional groups)
- Tanimoto distance matrix
- Hierarchical cluster analysis

Conclude: consistent with QSAR profiling, DY3 is quantitatively more similar to S1 and SRG than to DR1, DR13, DO25 and DO61



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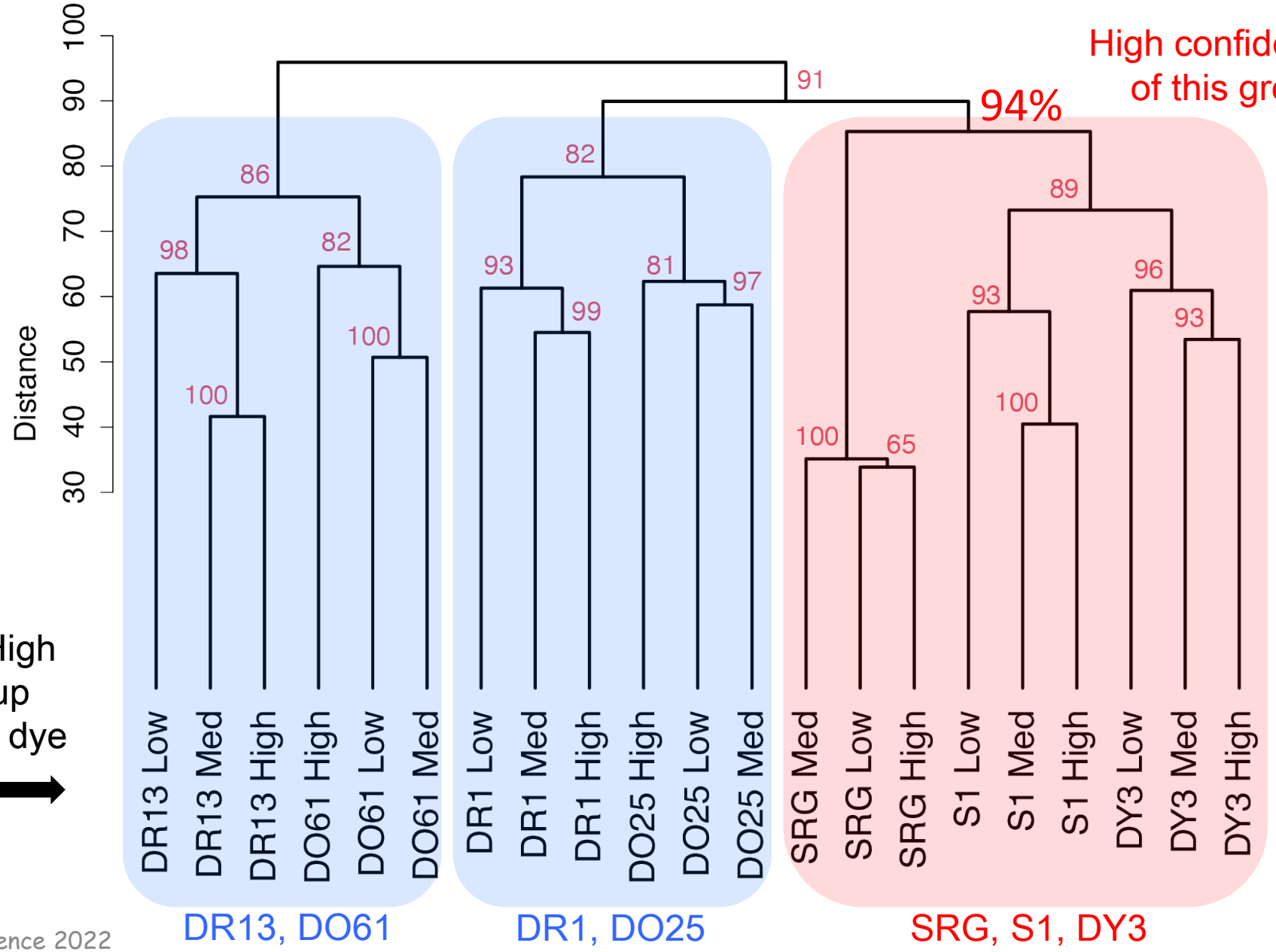
Multi-omics approach to form grouping hypothesis



High confidence in stability of this group (p≈0.06)

Low, Med, High doses group together, per dye

DY3 (target) is most similar to S1 (lead candidate to be source substance)

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Mechanistic anchoring of omics data - transcriptomics

IPA® INGENUITY PATHWAY ANALYSIS

"Cellular stress and injury" pathway group

SRG, S1 and DY3 induce similar pathway perturbations

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Mechanistic anchoring of omics data - metabolomics

OXFORD
SOT | Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 2022, 1–13

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Knowledge-Driven Approaches to Create the MTox700+ Metabolite Panel for Predicting Toxicity

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Grouping hypothesis based on phys-chem and ‘omics data

	Grouping/read-across workflow	Finding
1	Conventional grouping • QSAR profilers • Clustering ToxPrint chemotypes	DY3 might be in its own group, but is most similar to S1 and SRG
2	Omics-based grouping • Clustering multi-omics profiles • Molecular pathway perturbations	DY3 in a group with S1 and SRG, and most similar to S1
3	Final grouping hypothesis	Source = S1 Target = DY3

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Read-across to predict toxicity

Sudan 1 (S1)

Endpoint: Daphnia chronic reproductive toxicity (OECD TG211)

NOEC (measured) ≈ 40 μg/L

LOEC (measured) ≈ 60 μg/L

Disperse yellow 3 (DY3)

Fill data gap in the hazard characterisation of DY3

NOEC (predicted) ≈ 40 μg/L

Experimentally confirmed the prediction:

NOEC (*measured*) ≈ 40 μg/L

LOEC (*measured*) ≈ 75 μg/L

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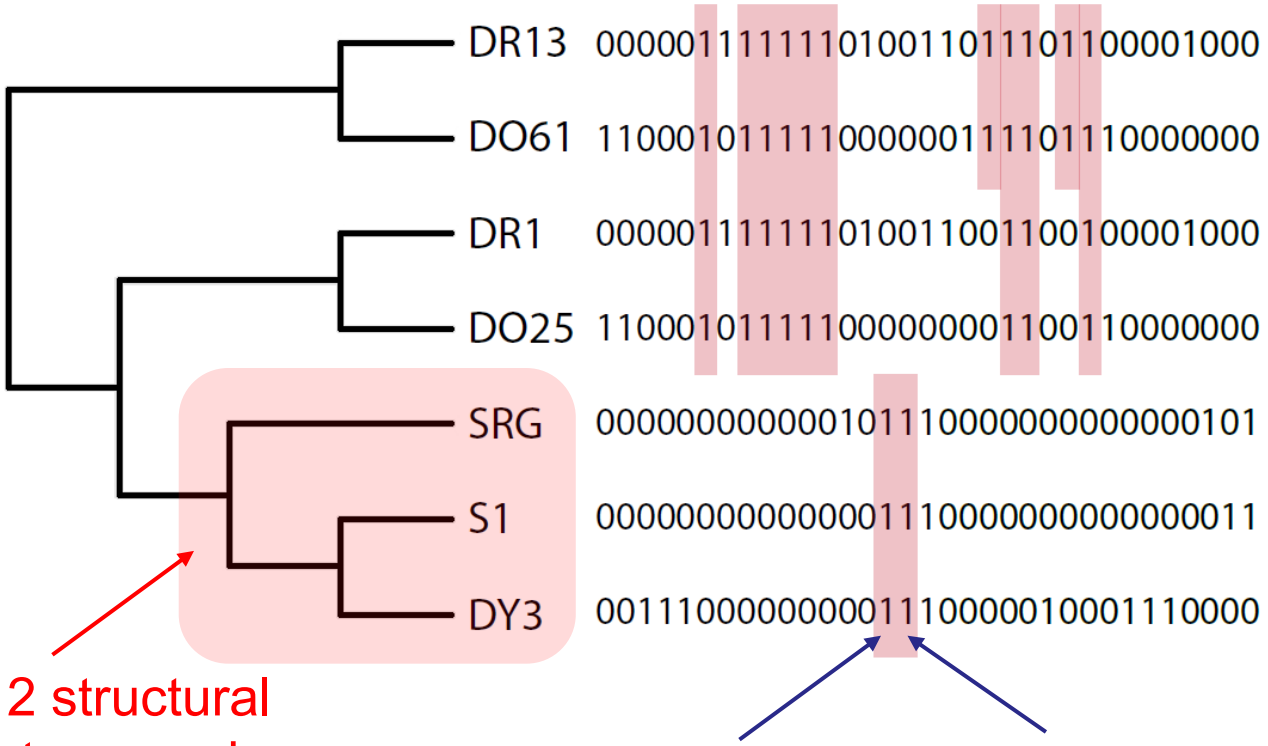
Map ToxPrint chemotypes onto Omics-based grouping

Dendrogram derived from multi-omics grouping

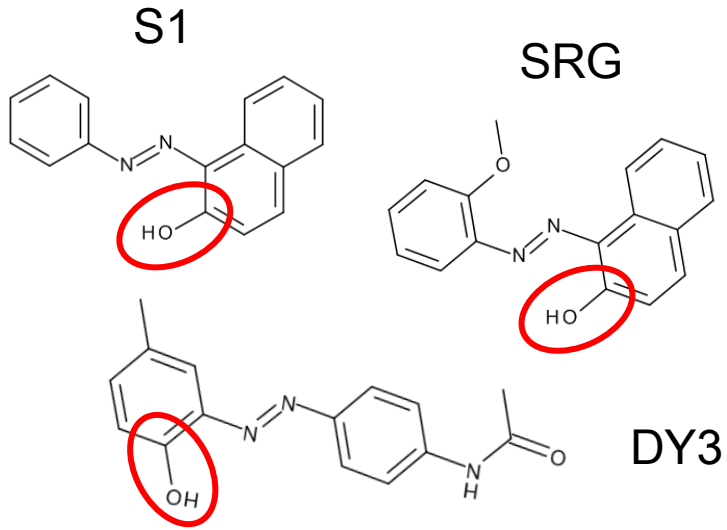
ToxPrint chemotypes – showing only the non-zero structural fragments (33 of 729)



Only 2 structural fragments are unique to this branch

bond: COH_alcohol_aromatic

bond: COH_alcohol_aromatic_phenol



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Conclusions from Case Study

- Established a workflow that enables NAM (‘omics) mechanistic data to be used alongside conventional grouping approaches
- Demonstrated how ‘omics data can provide a quantitative measure of similarity, allowing 7 azo dyes to be reliably grouped, and an optimal source substance identified for read-across
- Experimentally confirmed the read-across prediction
- Using ToxPrint chemotypes, predicted that aromatic phenols are driving this biologically-based grouping
- Paper in preparation

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Where next? – Challenges for omics-based grouping

- Mechanistic anchoring of molecular responses to MoA
- Acceptability ("validation") of 'omics applications
  - Reproducibility / reliability
    - Cefic MATCHING international ring-trial (metabolomics, chemical grouping) - *ongoing*
  - Tiered criteria based on Context of Use (CoU) of metabolomics - *ongoing*
- Reporting of 'omics
  - OECD Omics Reporting Framework (TRF, MRF) - DOI: 10.1016/j.yrtph.2021.105020
  - OECD WPHA proposal *under review* - 'omics-based chemical grouping
- Clear, extensive documentation of omics-based grouping
  - Horizon 2020 PrecisionTox task

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