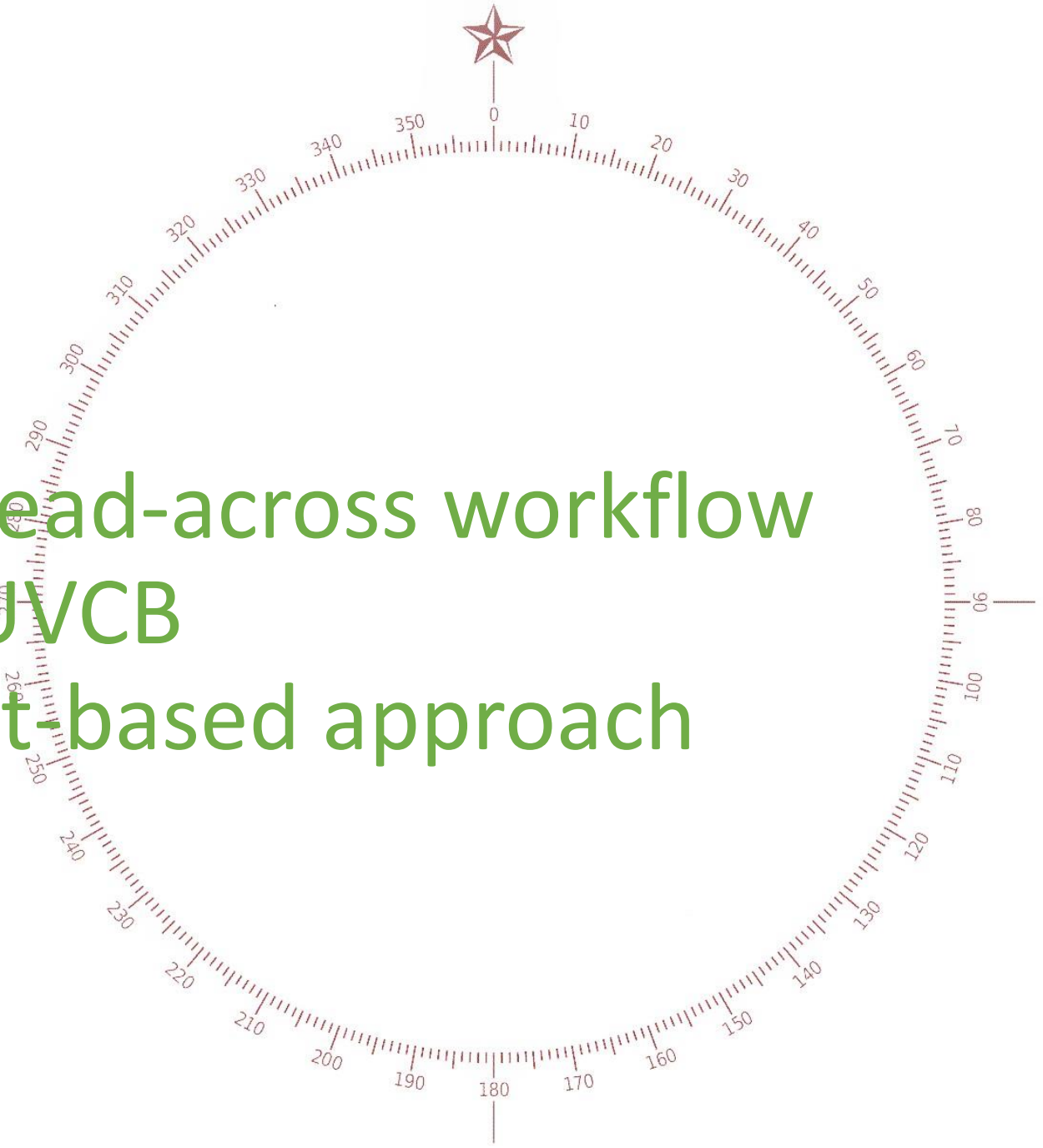
TOX NAVIGATION



A cheminformatics read-across workflow for UVCB with a constituent-based approach

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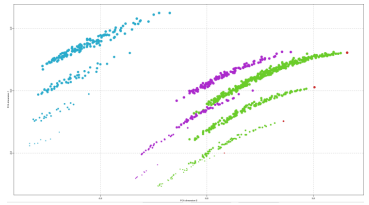
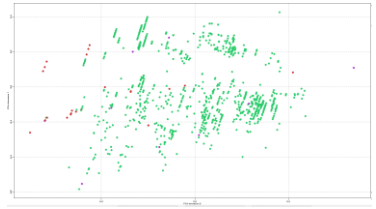
Constituents approach

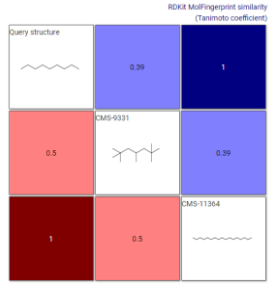
1. Group the constituents in blocks based on structural similarity/mode of action
   - Enumerate all the isomers of the UVCB
   - Describe all the isomers with Steric, Hydrophobic, ADME, Electronic
   - Principal Component Analysis (PCA) and Hierarchical cluster analysis



2. Identify representative structures for each block
   - Inspection of the clusters
   - Selection of the centroids of each cluster as rep structures
   - Comparison of the whole UVCB and the rep structures



3. Obtain reliable hazard information on these constituents
   - Search for existing data and Data gap analysis
   - Consider QSAR and Read-across for data gaps



4. Integrate the information
   - Weight of Evidence
   - Combine the sources of evidence and estimate the uncertainty

5. Derive conclusions on hazardous properties of UVCB substance

Case study

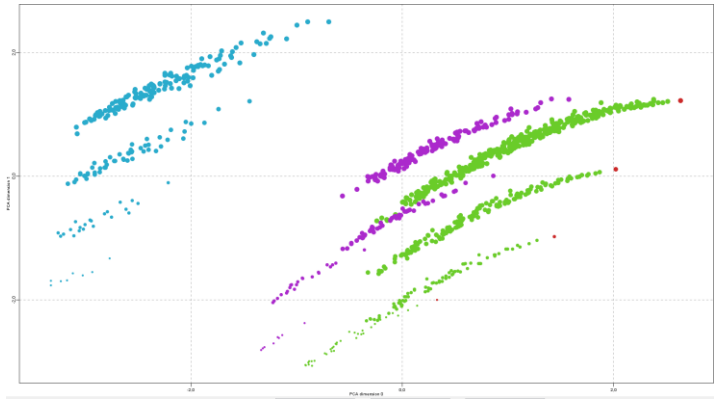
CAS 64742-82-1, Hydrocarbons, C9-C12, n-alkanes, branched alkanes, cycloalkanes, aromatics (2 – 25 %), EC 919-446-0.

- Variables
  - Number of carbon atoms: from 9 to 12
  - Functional groups: n-alkanes, branched, cyclo, aromatics
  - Position of the functional groups

21 Representative structures

- 11 centroids of the clusters
- 9 with toxicity data
- 1 to cover high lipophilic / low solubility chemical space after the analysis of the phys-chem properties

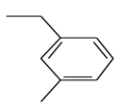
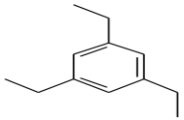
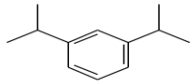
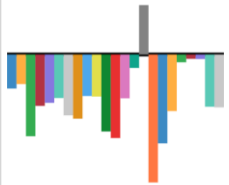
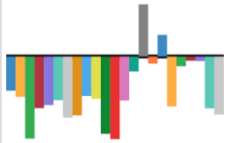
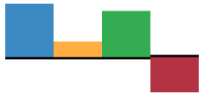
Molecular Formula	n isomers	type
C9H20	35	linear and branched
C10H22	75	linear and branched
C11H24	159	linear and branched
C12H26	355	linear and branched
C9H12	8	aromatic
C10H14	22	aromatic
C11H16	51	aromatic
C12H18	136	aromatic
C9H18	8	cyclo
C10H20	22	cyclo
C11H22	51	cyclo
C12H24	136	cyclo
Total isomers	**1058**	



Cluster #	N	Description
1	1	C11, aromatic, long R
2	1	C12, aromatic, long R
3	8	C9, aromatic
4	50	C11, aromatic
5	491	C12, branched, cyclo
6	210	C11, linear, branched, cyclo
7	135	C12, aromatic
8	75	C10, branched, linear
9	22	C10, cyclo
10	22	C10, aromatic
11	43	C9 linear, branched

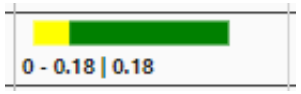
Case study

ID	Exp In Vitro Chromosome Aberration	Exp Skin Sensitization
1		
2		
3		
4	negative	negative
5		
6		negative
7		
8		
9	negative	
10	negative	negative
11		
12	negative	negative
13		
14		
15	negative	negative
16		
17		
18		
19		
20		
21	negative	negative

	Target	Analogue 1	Analogue 2
			
Registry Numbers		25340-18-5 (Active)	99-62-7 (Active)
Structural similarity			
MACCS Fingerprint		0.83	0.60
RDKit MolFingerprint		0.97	0.80
ToxPrint Fingerprint		1.00	0.56
Metabolic reactivity similarity			
Liver BioPath Fingerprint		0.50	0.27
Physicochemical similarity			
Skyline			
Pearson similarity		0.80	0.94
Reactivity similarity			
Skyline			
Pearson similarity		0.99	1.00
ADME profile			
Caco-2	Highly permeable	Highly permeable	Highly permeable
PPB	Moderately bound	Strongly bound	Strongly bound
CNS	Penetrant	Penetrant	Penetrant
HIA	Highly absorbed	Highly absorbed	Highly absorbed
LogP	Optimal	Lipophilic	Lipophilic
Solubility	Insoluble	Insoluble	Highly insoluble

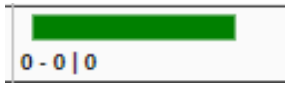
54 analogues

In *vitro* chromosome aberration



30 analogues

Skin sensitization



Agreement with experimental data?

Thank You

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