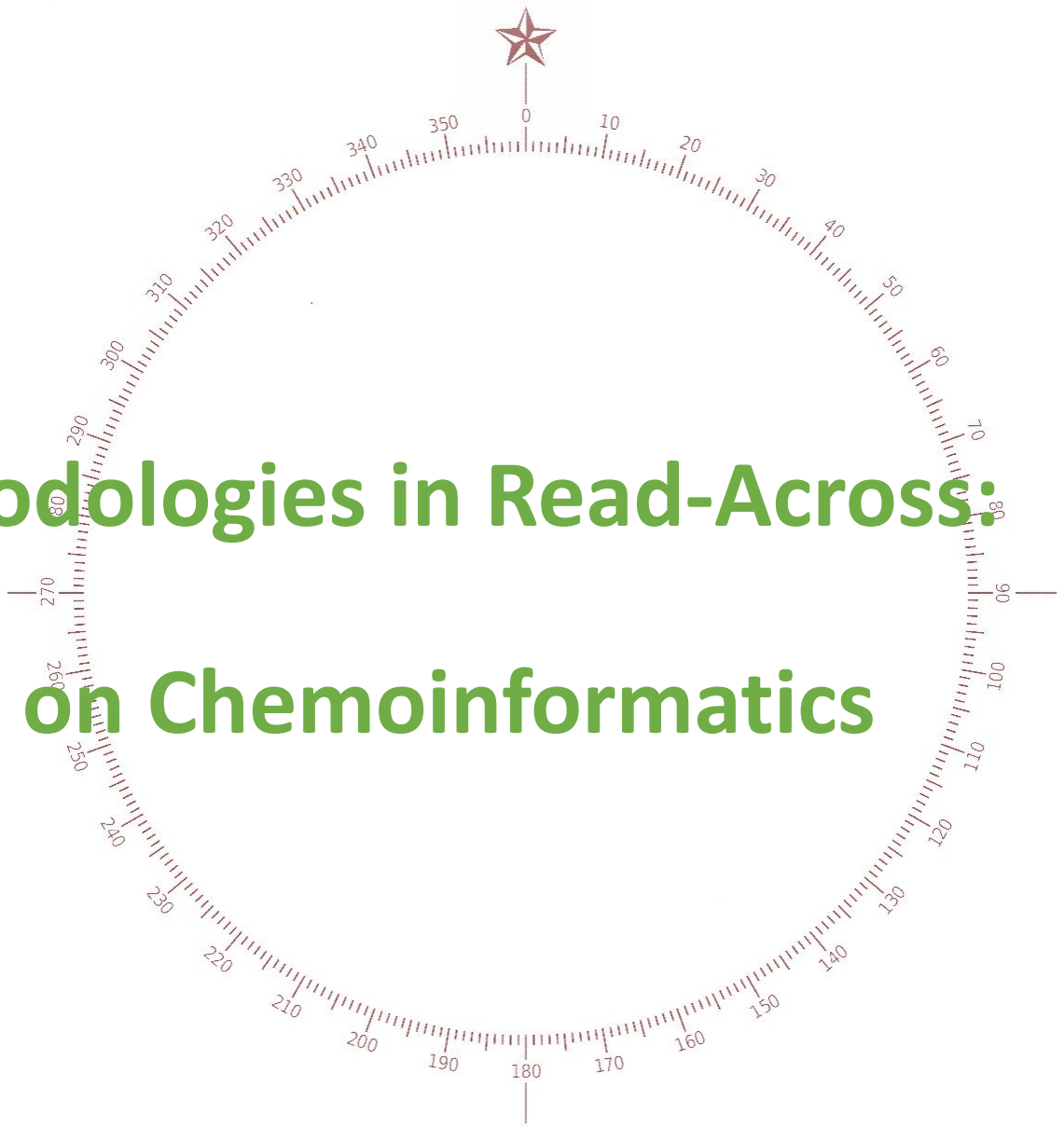
TOX NAVIGATION



# New Approach Methodologies in Read-Across: a Workflow Based on Chemoinformatics

Elena Fioravanzo

Director - ToxNavigation

# Outline

- Read-across workflow

- Case studies

  - Genotoxicity
    - ✓ vanillin, a food related substance
    - ✓ heptanamide, a drug impuritiy

  - Skin sensitization
    - ✓ 4-nitrobenzoyl chloride
    - ✓ 1,3-Propanediamine, N-(3-aminopropyl)

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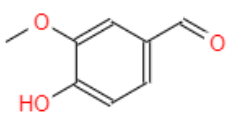
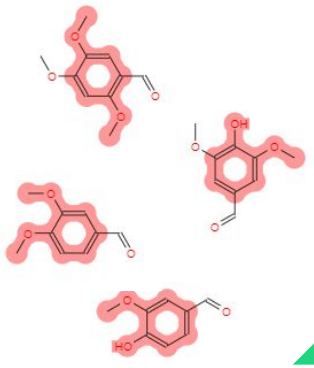
# Read-Across workflow

1 2 3 4 5

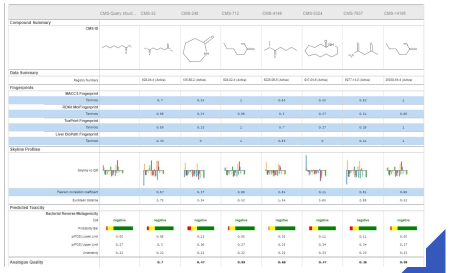



## Target



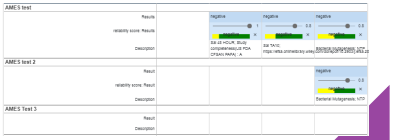

## Find analogues

- Biological similarity
- Chemical similarity
- Reactivity similarity



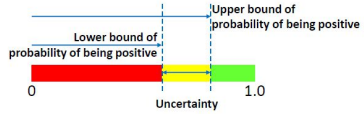
## Rate analogues

- Chemical similarity
- Reactivity similarity
- **Analogue quality**




## Find data and rate

- Study reliability




## Combine & read-across

- Weight of Evidence
- **Assessment Table**

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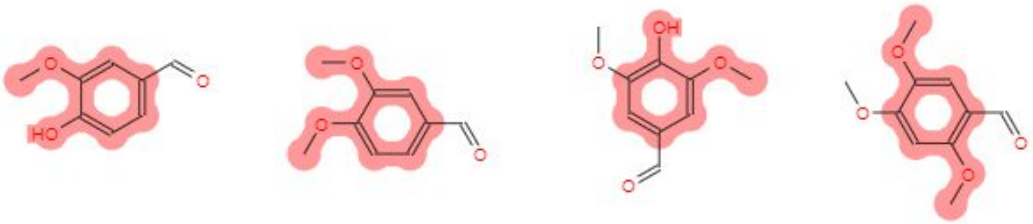
2 Find analogues

## BIOLOGICAL SIMILARITY

***MOA Group*** DNA binding
***Chemical group*** Hydroquinone



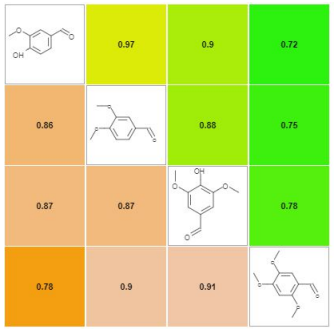
## CHEMICAL SIMILARITY

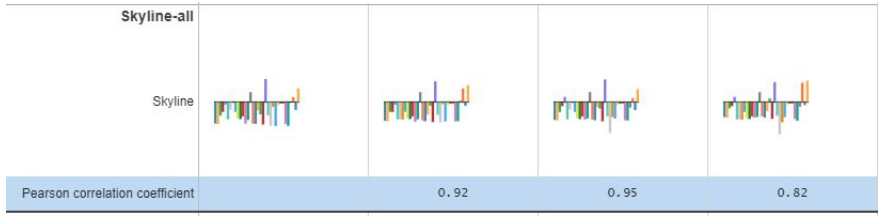
***Structure-based***

- Different Fingerprints (MACCS, RDKIT, ToxPrint)
- Similarity measure is Tanimoto coefficient

***Properties***

- Calculated with CORINA Symphony (MN-AM)
- Holistic description (includes phys-chem)
- Similarity measure is Pearson coefficient



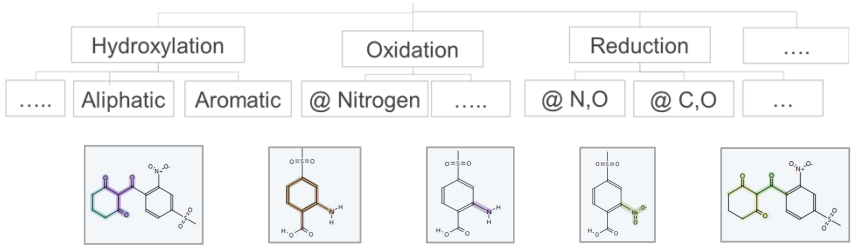




## REACTIVITY SIMILARITY

***Metabolic reactivity rules***

- Liver BioPath Rules

**Reaction types**




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

*M*: metabolic reaction sites common to parent and metabolite

*P*: total number of metabolic reaction sites in parent

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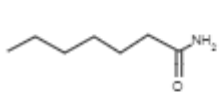
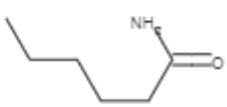
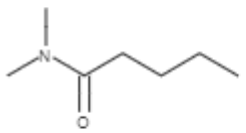
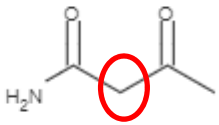
3 Rate analogues

## ANALOGUE QUALITY

- Geometric mean of the three types of similarity defined
- Analogues contain the chemical group features (if any) of the MOA

| | Target | CMS-712 | CMS-4149 | CMS-7937 |
|---|---|---|---|---|
| **Compound Summary** | | | | |
| CMS ID |  |  |  |  |
| Structure-based (MAACS) | | 1 | 0.63 | 0.62 |
| Structure-based (RDKit) | | 0.96 | 0.50 | 0.51 |
| Structure-based (ToxPrint) | | 1 | 0.70 | **0.29** |
| Reactivity similarity | | 1 | 0.63 | **0.11** |
| **Analogue Quality** | | **0.99** | **0.61** | **0.32** |

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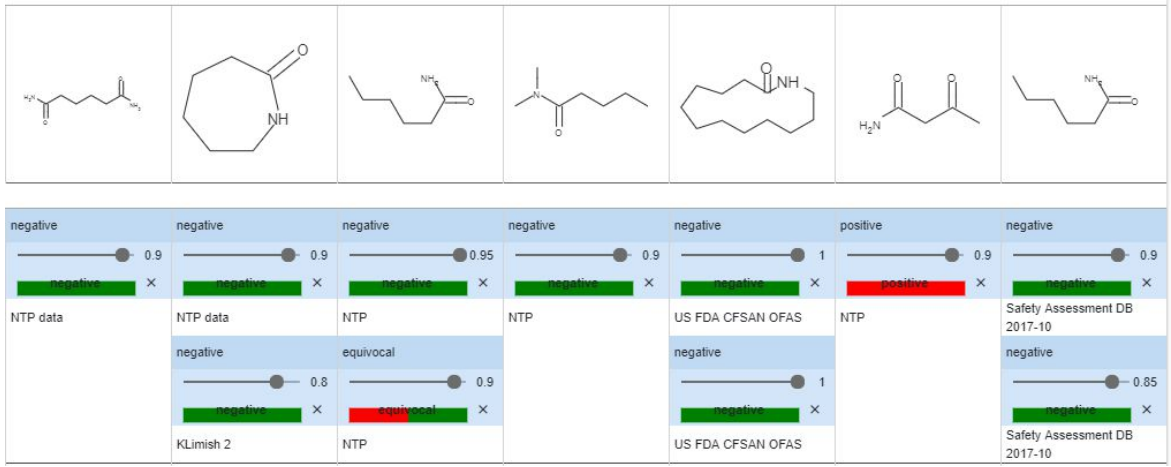
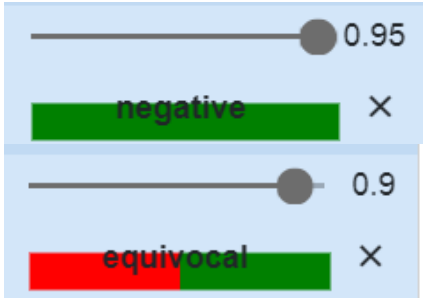
4 Find data and rate

## STUDY RELIABILITY

| | Study reliability criteria |
|---|---|
| 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 |
| 0.5 | Studies either missing records or not conducted and at least two deficiencies in the five aspects (no replicates, no info on control) |



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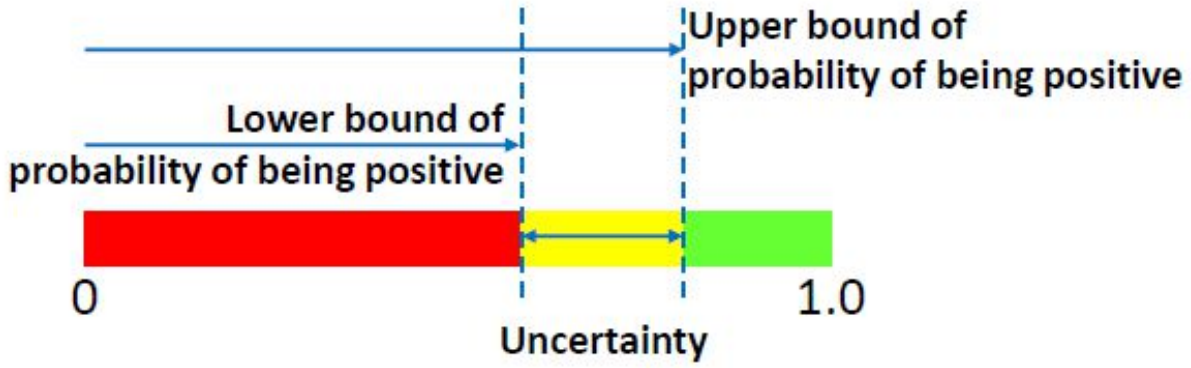
5 Combine & read-across

## WEIGHT OF EVIDENCE*

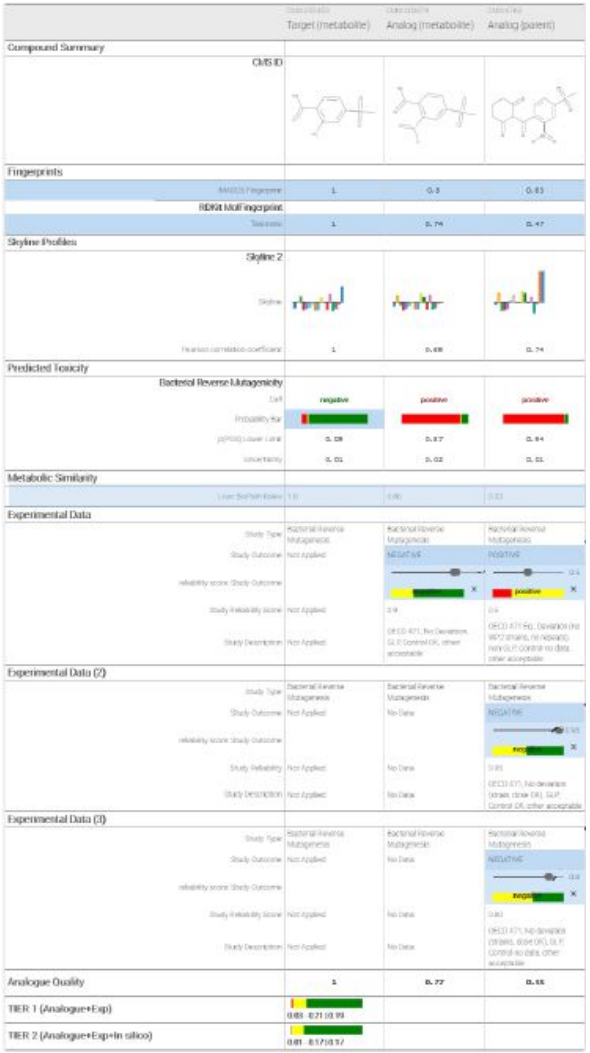
- Combine two or three sources of evidence according to Dempster-Shafer Theory (DST)
  - Analogue quality
  - Experimental data with reliability score
  - QSAR
- Belief function (weighing step)

Belief (probability) = analogue quality * study reliability




* Rathman JF, Yang C, Zhou H. "Dempster-Shafer theory for combining in silico evidence and estimating uncertainty in chemical risk assessment." Computational Toxicology. 2018;6:16-31.

## ASSESSMENT TABLE

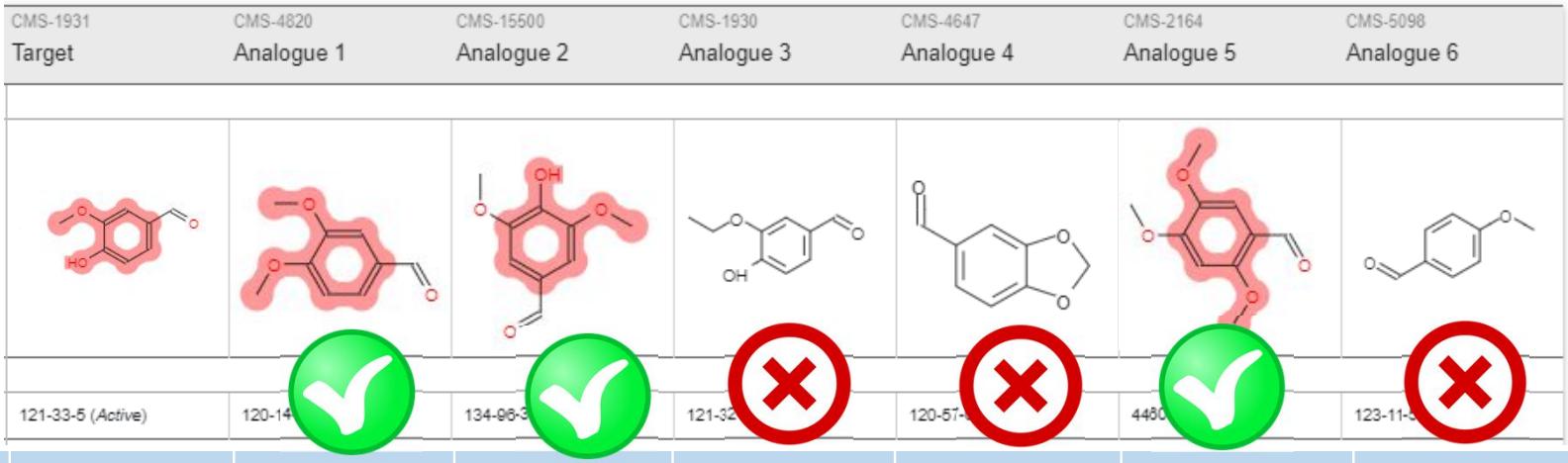


# Genotoxicity of vanillin

**BIOLOGICAL SIMILARITY**

***MOA Group*** DNA binding
***Chemical group*** Hydroquinone

**CHEMICAL SIMILARITY**
***Structure-based***
***Properties***
**REACTIVITY SIMILARITY**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Structure-based (MAACS) | | 0.86 | 0.87 | 0.87 | 0.54 | 0.78 | 0.85 |
| Structure-based (RDKit) | | 0.97 | 0.90 | 0.89 | 0.85 | 0.72 | 0.66 |
| Structure-based (ToxPrint) | | 0.70 | 1.00 | 0.91 | 0.50 | 0.70 | 0.70 |
| Reactivity similarity | | 0.67 | 0.78 | 0.80 | 0.45 | 0.44 | 0.40 |
| Properties similarity | | 0.92 | 0.95 | 0.97 | 0.83 | 0.82 | 0.67 |
| **Analogue Quality** | | **0.82** | **0.90** | | | **0.69** | |

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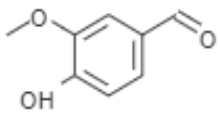
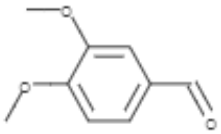
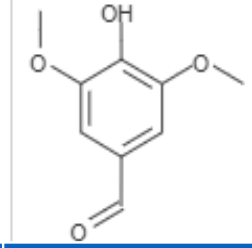
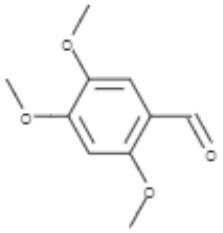
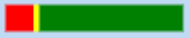
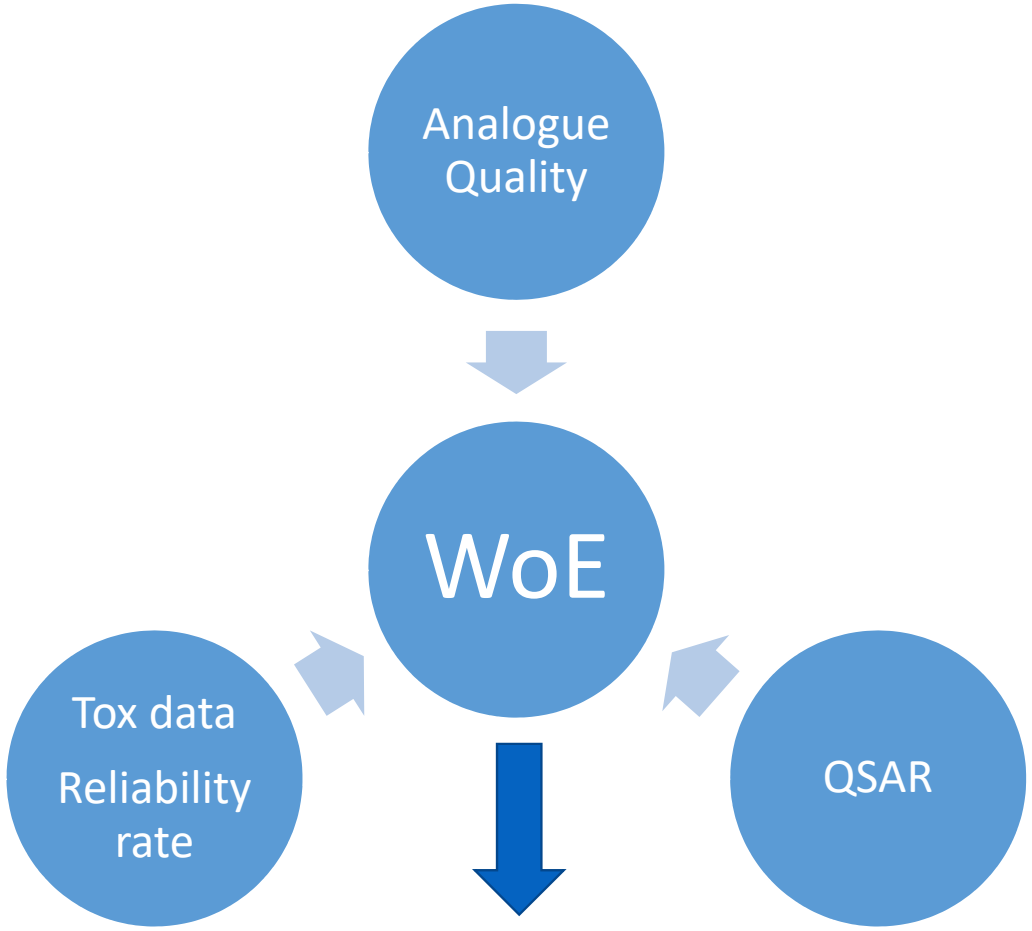
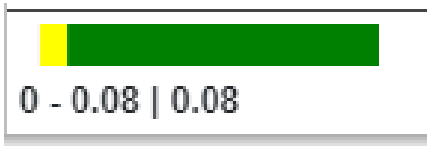
# Genotoxicity of vanillin

| CMS-1931 Target | CMS-4820 Analogue 1 | CMS-15500 Analogue 2 | CMS-2164 Analogue 5 |
|---|---|---|---|
|  |  |  |  |
| | **0.82** | **0.90** | **0.69** |
| 121-33-5 (*Active*) | 120-14-9 (*Active*) | 134-96-3 (*Active*) | 4460-86-0 (*Active*) |
| | 1 negative × | 0.9 negative × | 0.9 negative × |
| | | | 0.9 negative × |
|  | | | |



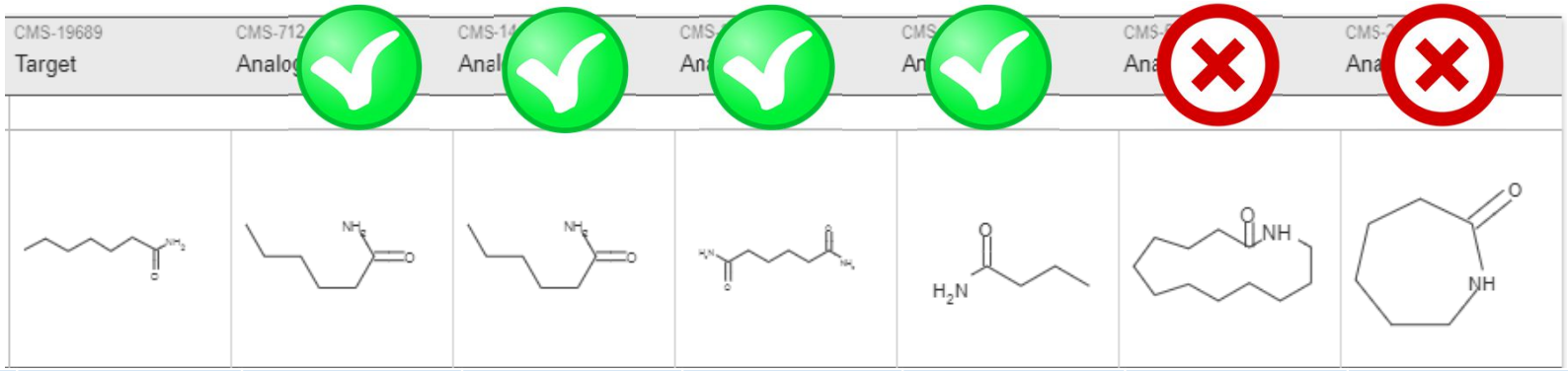

Predicted negative with an uncertainty < 0.1



# Genotoxicity of heptanamide

**BIOLOGICAL SIMILARITY**
***MOA Group*** none
***Chemical group*** Amide

**CHEMICAL SIMILARITY**
***Structure-based***
***Properties***
**REACTIVITY SIMILARITY**

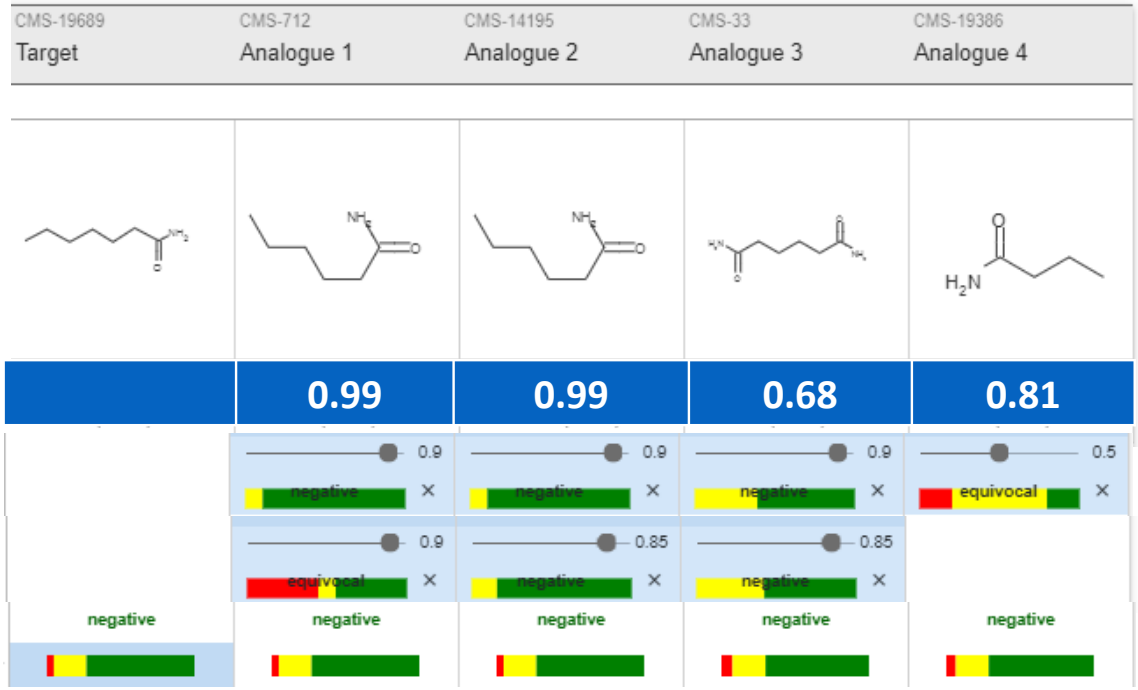


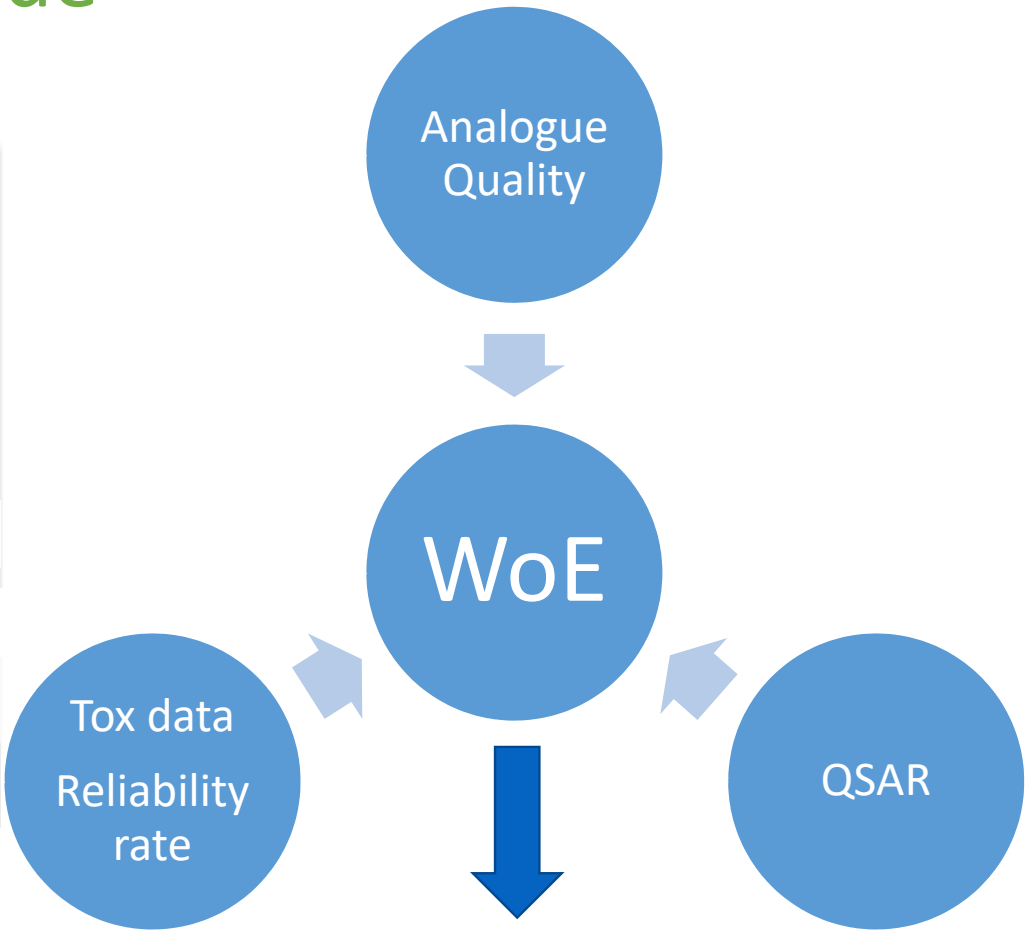

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Structure-based (MAACS) | | 1 | 1 | 0.7 | 0.86 | 0.55 | 0.55 |
| Structure-based (RDKit) | | 0.96 | 0.96 | 0.96 | 0.65 | 0.57 | 0.54 |
| Structure-based (ToxPrint) | | 1 | 1 | 0.89 | 0.89 | 0.27 | 0.23 |
| Reactivity similarity | | 1 | 1 | 0.33 | 1 | 0 | 0 |
| Properties similarity | | 0.98 | 0.98 | 0.44 | 0.44 | 0.07 | -0.25 |
| **Analogue Quality** | | **0.99** | **0.99** | **0.68** | **0.81** | 0.46 | 0.40 |

Details

- Properties similarity: very different lipofilicity and solubility profile

# Genotoxicity of heptanamide




Predicted negative with an uncertainty ~ 0.3

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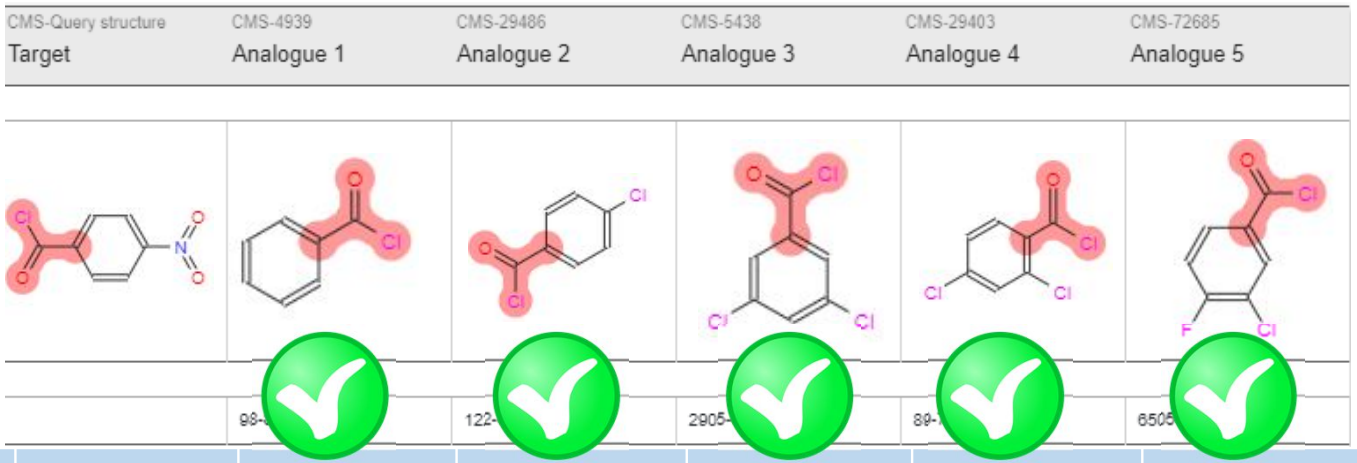
# Skin sensitization potential of 4-nitrobenzoyl chloride

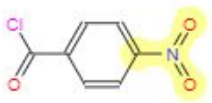
**BIOLOGICAL SIMILARITY**

***MOA Group*** Acylation
***Chemical group*** Acyl Alides

**CHEMICAL SIMILARITY**
***Structure-based***
***Properties***
**REACTIVITY SIMILARITY**



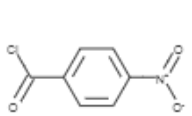
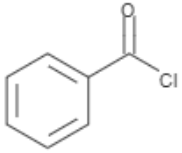
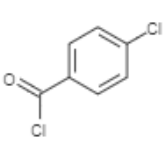
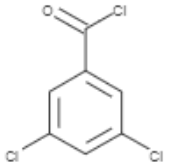
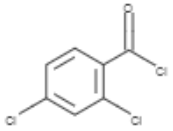

| | | | | | | |
|---|---|---|---|---|---|---|
| Structure-based (MAACS) | | 0.37 | 0.36 | 0.36 | 0.36 | 0.35 |
| Structure-based (RDKit) | | 0.52 | 0.47 | 0.42 | 0.38 | 0.38 |
| Structure-based (ToxPrint) | | 0.63 | 0.63 | 0.56 | 0.56 | 0.5 |
| **Reactivity similarity** | | **0.17** | **0.33** | **0** | **0.33** | **0** |
| Properties similarity | | 0.71 | 0.75 | 0.73 | 0.72 | 0.73 |
| **Analogue Quality** | | **0.70** | **0.67** | **0.58** | **0.59** | **0.58** |

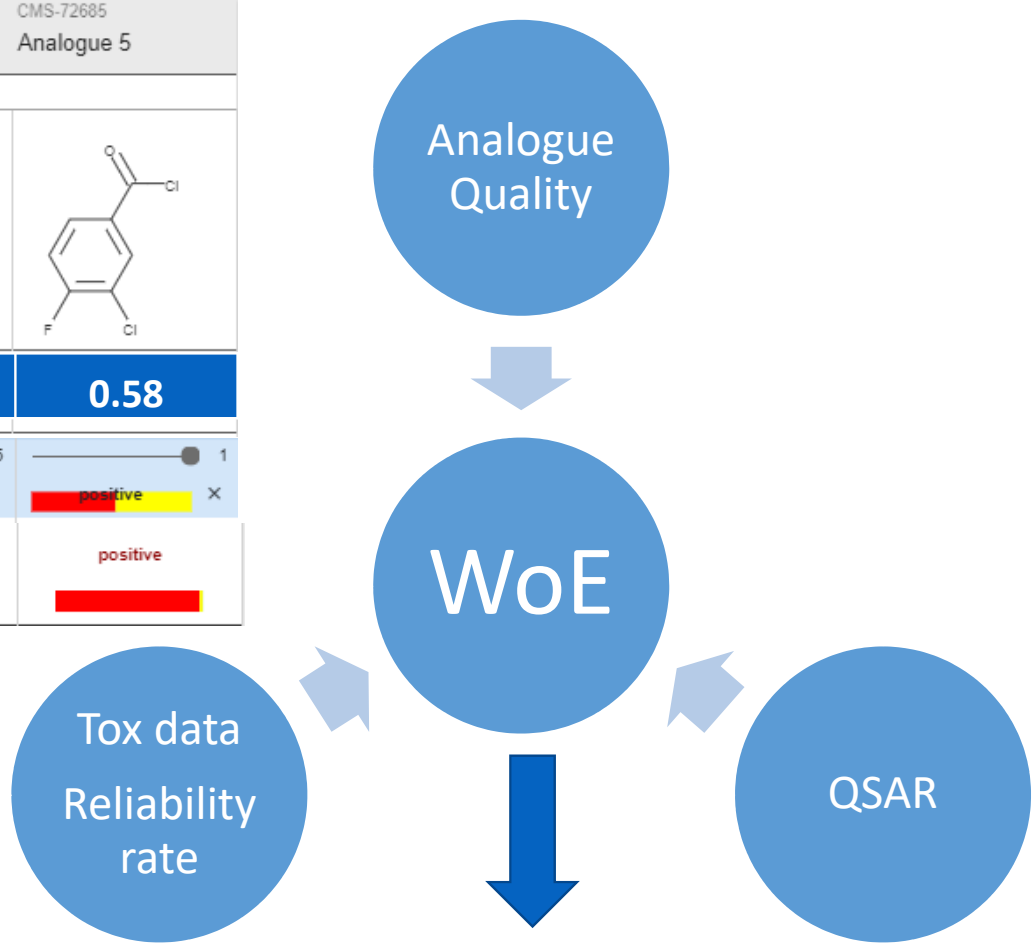


- ☐ aromatic hydroxylation (o-position to C-substituent) 7 atoms
- ☐ aromatic hydroxylation (o-position to N-substituent) 7 atoms
- ☑ nitro reduction (NO2 aromatic) 4 atoms

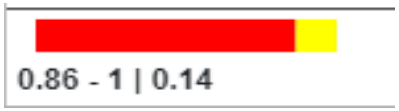
- ☑ aromatic hydroxylation (o-position to two substituents) 7 atoms

# Skin sensitization potential of 4-nitrobenzoyl chloride

| CMS-Query structure<br>Target | CMS-4939<br>Analogue 1 | CMS-29486<br>Analogue 2 | CMS-5438<br>Analogue 3 | CMS-29403<br>Analogue 4 | CMS-72685<br>Analogue 5 |
|---|---|---|---|---|---|
|  |  |  |  |  |  |
| | **0.70** | **0.67** | **0.58** | **0.59** | **0.58** |
| | 1 positive | 0.8 positive | 1 positive | 0.5 negative | 1 positive |
| positive | positive | positive | positive | positive | positive |




Predicted positive with an uncertainty ~ 0.14



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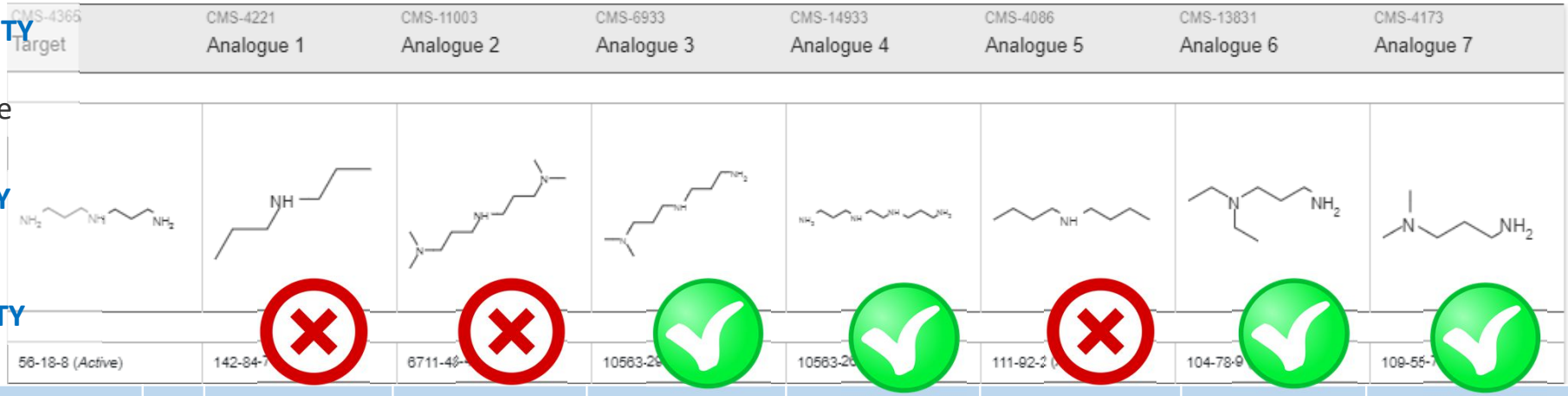
# Skin sensitization potential of CAS# 56-18-8

**BIOLOGICAL SIMILARITY**
***MOA Group*** none
***Chemical group*** Amine

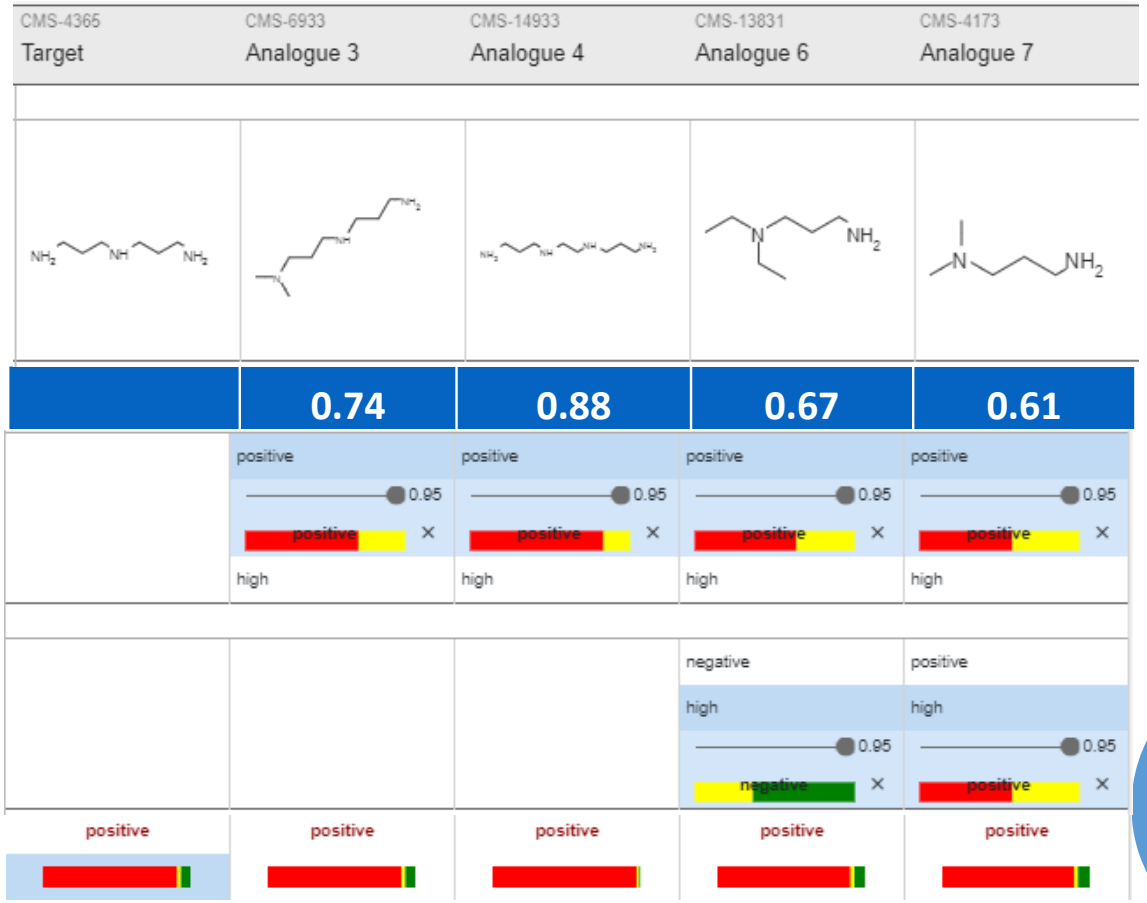
**CHEMICAL SIMILARITY**
***Structure-based***
***Properties***
**REACTIVITY SIMILARITY**

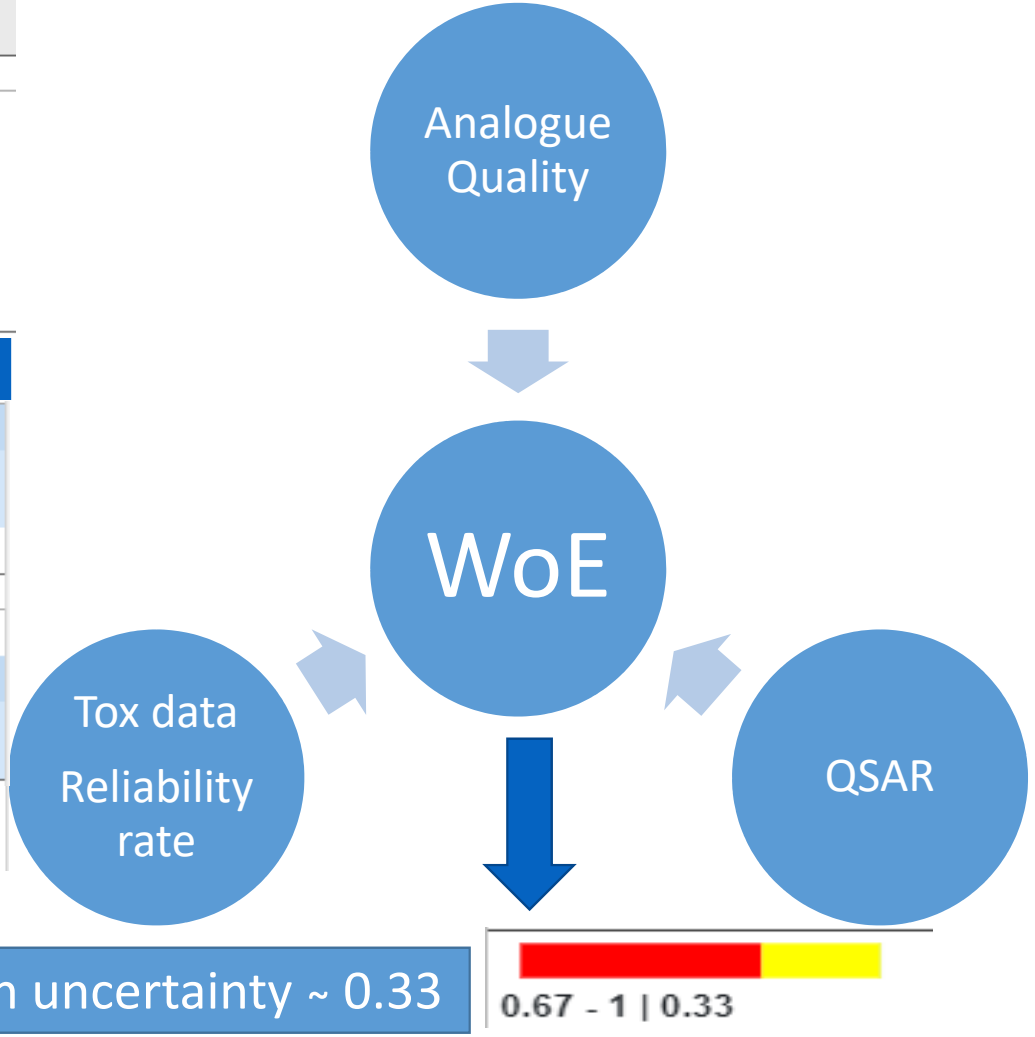



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Structure-based (MAACS) | | 0.68 | 0.66 | 0.76 | 0.90 | 0.66 | 0.75 | 0.71 |
| Structure-based (RDKit) | | 0.79 | 0.76 | 0.76 | 0.68 | 0.65 | 0.62 | 0.56 |
| Structure-based (ToxPrint) | | 0.56 | 0.60 | 0.80 | 0.89 | 0.50 | 0.60 | 0.60 |
| **Reactivity similarity** | | **0.14** | **0.13** | **0.50** | **1** | **0.13** | **0.50** | **0.38** |
| Properties similarity | | 0.87 | 0.68 | 0.97 | 0.92 | 0.84 | 0.93 | 0.94 |
| **Analogue Quality** | | **0.52** | **0.51** | **0.74** | **0.88** | **0.48** | **0.67** | **0.61** |

Rational: primary vs secondary or tertiary amine. There is a difference in the QSAR predictions and experimental data => use the primary amine

# Skin sensitization potential of CAS# 56-18-8




Predicted positive with an uncertainty ~ 0.33

# Summary and Future Plans

- Chemoinformatics to support selection of analogues for the read-across
- WoE to address and estimate uncertainties
- Consistent methodology, customizable, but standardized and reproducible

- Metabolites analysis
- Workflow for RDT
- Workflow for mixtures and UVCB substances

MN-AM

TOX NAVIGATION

# Thank You

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