

# The ToxRead tool for read-across

EU LIFE CONCERT REACH final workshop  
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# THE TOOLS



112 (Q)SAR freely available models for regulatory purposes.

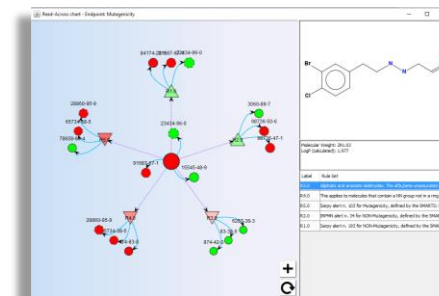
Different areas:

- Human toxicity
- Eco-toxicity
- Environmental
- Physico-chemical
- Toxicokinetics



Reproducible read-across evaluation for 23 endpoints showing similar compounds and SAs in common between chemicals.

**TOXREAD**



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## ToxRead

toxRead assists user in making reproducible read across evaluations.

ToxRead shows the similar chemicals and also the structural alerts and relevant features in common between chemicals.

The software shows the most similar compounds (up to six), and the features associated with the target compound. For each structural alert it also indicates the most similar compounds which contain that structural alert.

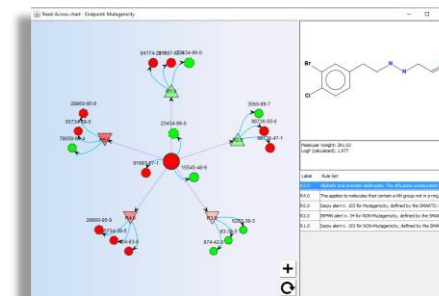
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Reproducible read-across evaluation for 23 endpoints showing similar compounds and **SAs** in common between chemicals.

**TOXREAD**



# Read-Across: critical points

Read-Across requires experts in chemistry, biology, environmental sciences, ...

## EXPERT'S MANY FACES

- Expert reasoning is **rare** and **expensive**
- Expert reasoning is **subjective**
- Experts may give **different weights** to a feature
- Experts may be aware of and use **different sets of rules**
- Experts may over-rely on past experience and **miss new evidence**
- Expert reasoning is **irreproducible**

# Read-Across: critical points

Read-Across requires experts in chemistry, biology, environmental sciences, ...

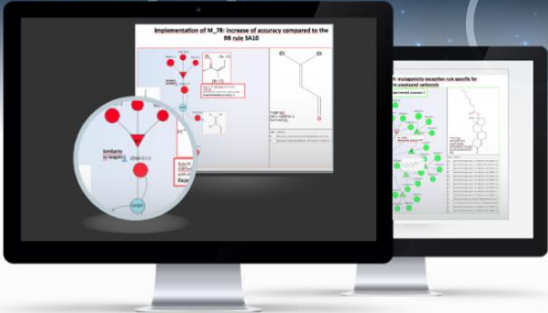
## TOXREAD

- Is freely **available** and **downloadable**
- Is **objective**
- **Accuracy** and **p-value** calculated for each SAs
- **Several rulesets** are available for different endpoints
- Is always **updating**
- Is **reproducible**

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ToxRead 0.25

Insert SMILES:  
c1cc(Cl)c(Br)cc1CCNNCC=O

Number of similar molecules: 3

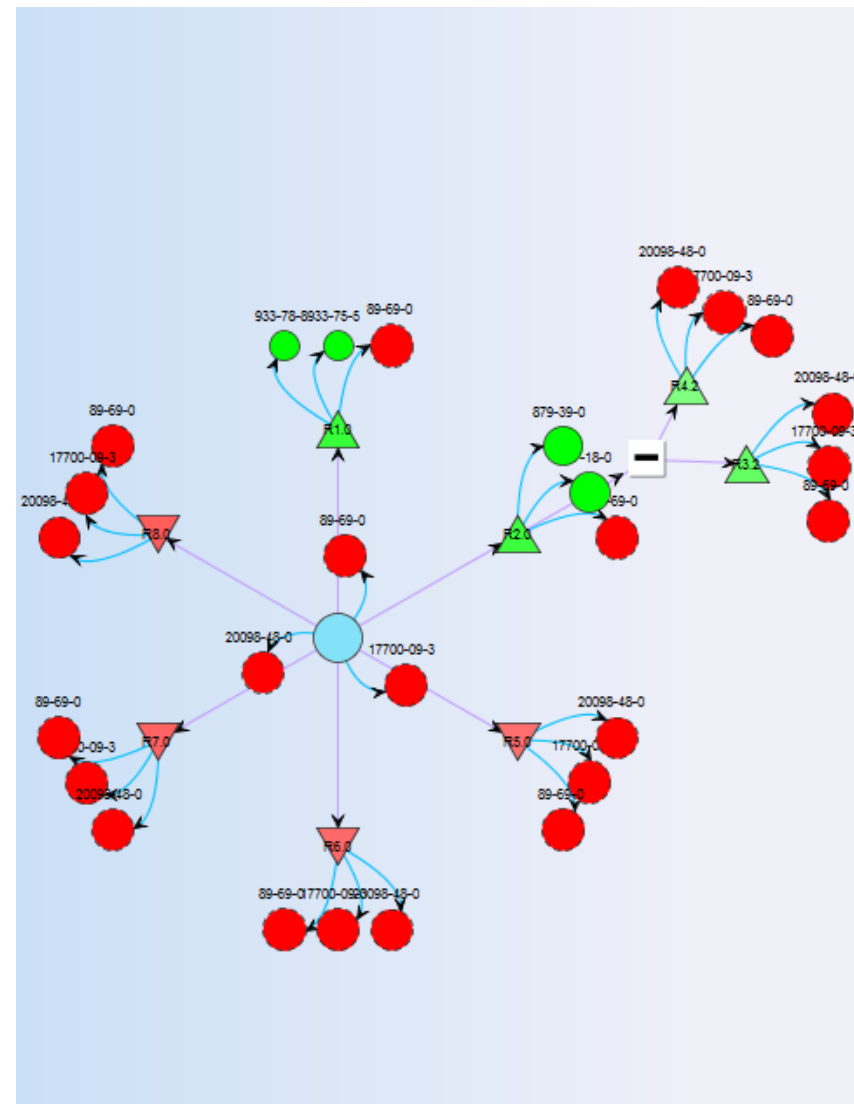
Endpoint: Mutagenicity

- In vitro Micronucleus assay
- In vivo Micronucleus assay
- Androgen Receptor-mediated effect
- Skin Irritation
- Aromatase activity
- Eye Irritation
- Rat LD50 toxicity
- Reproductive toxicity (CONCERT)
- Persistence (soil): 568
- Persistence (water): 351
- Ready Biodegradability: 728
- Reproductive Toxicity: 1974
- LogP: 9959
- BCF: 857

Run

## THE OUTPUT

- ❖ **Target** molecule in the center of the visualization panel
- ❖ Target compound directly connected to **most similar molecules** (in the inner circle)
- ❖ **Structural alerts** in the triangles
- ❖ **Paths** connect molecules sharing the same structural alert
- ❖ **Shape:** circles are molecules, triangles are structural alerts
- ❖ **Circle dimension:** related to similarity
- ❖ **Color:** red or green with different saturation indicates active or non-active at different levels
- ❖ Clicking on **nodes** shows structure, explanation, etc.



## 23 ENDPOINTS AVAILABLE, 27 RULESETS

Endpoint	DB size	Rule sets	Multiple rulesets
Algae toxicity (biocides)	361	1	
Algae chronic toxicity	407	1	
Androgen Receptor-mediated effect	1664	1	
Aromatase Activity	326	1	
BCF	857	1	
Carcinogenicity (CGX)	1197	2	CGX model, Benigni-Bossa ruleset
Eye Irritation	1137	1	
Hepatotoxicity	1051	1	
In vitro Micronucleus assay	414	1	
In vivo Micronucleus assay	1228	1	
Microbes toxicity (biocides)	35	1	
Mutagenicity	6060	4	Benigni-Bossa, IRFMN, SARpy , CRS4
Nephrototoxicity	200	1	
Persistence (sediment)	297	1	
Persistence (soil)	568	1	
Persistence (water)	351	1	
Rat LD50 toxicity	8476	1	
Ready Biodegradability	728	1	
Reproductive Toxicity	1974	1	
Reproductive Toxicity (CONCERT)	1320	1	
Respiratory sensitization in human	80	1	
Skin Irritation	303	1	
Skin Sensitization	679	1	





## CONCERT REACH – 10 new ENDPOINTS/RULESETS AVAILABLE

Endpoint	DB size	Rule sets	Multiple rulesets
Algae toxicity (biocides)	361	1	
Algae chronic toxicity	407	1	
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# NEW MODULES: SOME EXAMPLES

## EYE IRRITATION

Read-Across chart - Endpoint: Eye Irritation

Details of molecule 93-70-9

Details of molecule 93-70-9

Name: (no name)  
 CAS: 93-70-9  
 SMILES: CC(=O)CC(=O)NC1=C(Cl)C=CC=C1  
 Similarity to target: 0.772

Experimental activity: Not Irritant

Molecular Weight: 211.68

Details of molecule 176972-62-6

Details of molecule 176972-62-6

Name: (no name)  
 CAS: 176972-62-6  
 SMILES: COC(=O)NC(CC1=CC=CC=C1)C(O)CC1  
 Similarity to target: 0.766

Experimental activity: Irritant

Molecular Weight: 257.76

# NEW MODULES: SOME EXAMPLES

## EYE IRRITATION

Read-Across chart - Endpoint: Eye Irritation

Details of rule Eye Irritation alert no. 35

H3C—CH3

Name: Eye Irritation alert no. 35  
Description: Structural alert for eye Irritant compounds, defined by the SMARTS: CC

List of molecules where the rule applies (max 100)

Export molecules	CAS	SMILES	Similarity	Experimental value
	93-70-9	<chem>CC(=O)CC(=O)NC1=C(C)C=CC=C1</chem>	0.772	Not Irritant
	176972-62-6	<chem>COC(=O)NC(C1=CC=CC=C1)C(O)CCl</chem>	0.766	Irritant

Details of rule Eye Irritation alert no. 89

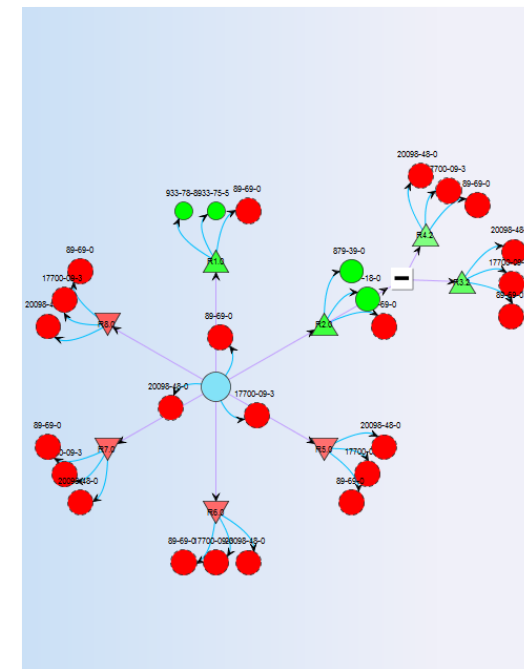
Name: Eye Irritation alert no. 89  
Description: Structural alert for eye NOT Irritant compounds, defined by the SMARTS: CCc1ccccc1

List of molecules where the rule applies (max 100)

Export molecules	CAS	SMILES	Similarity	Experimental value
	176972-62-6	<chem>COC(=O)NC(C1=CC=CC=C1)C(O)CCl</chem>	0.766	Irritant
	123989-31-1	<chem>CC(C=C)C(O)C1=CC=C(C)C=C1</chem>	0.757	Not Irritant

## CONCLUSIONS

- A **cooperative approach**, where the pieces of evidence are conceptually ordered and shown
- The expert gets a picture
  - Centered in the target molecule
  - With levels of details
  - Making use of the available knowledge
- Easily **integrated** with results of **SAR-QSAR** methods
- Thanks to the CONCERT REACH, **additional modules**
- It's a first step...



# THANKS

Does anyone have any questions?  
<https://www.life-concertreach.eu/>





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# ToxRead similarity computation




Similarity is calculated with an index resulting from the weighted combination of

- a fingerprint
- three structural keys based on molecular descriptors
  - built with constitutional descriptors (number of atoms, number of certain bonds, etc), descriptors focused on hetero-atoms, and descriptors for specific functional groups (such as nitro groups, sulfonic groups etc).
- They can account the number of some features or functional groups and not only their presence/absence.



# Read-Across

	Substance 1	Substance 2
Property		



	Substance 1	Substance 2	Substance 3
Property			



 Reliable source data  
 Missing data