A Mechanistically-Based QSAR Approach to Predict Aquatic Toxicity of Reactive Compounds

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INTRODUCTION: MechoA classification scheme (Bauer *et al.*, 2018)

3 kinds of reactivity for 3 Molecular Initiating Events

- Hard electrophiles → Adducts to amino residues
- Soft electrophiles → Adducts to thiol residues
- Radical-generating compounds → Reactive Oxygen Species (ROS)

MechoA 3.1 (hard electrophiles)	MechoA 3.2 (soft electrophiles)	MechoA 3.3 (radical-generating)
• *aldehydes* • *benzaldehydes* • *epoxides* • *aziridines* • *etc.*	• *α,β-unsaturated carbonyl (e.g. acrylates)* • *α,β-unsaturated nitriles* • *quinones* • *etc.*	• *peroxides* • *disulfides* • *etc.*

GOAL: MODEL DEVELOPMENT TO PREDICT AQUATIC TOXICITY FOR **MECHOA 3.1 (HARD ELECTROPHILES)**

❑ Definition of the endpoint (*i.e.* predicted toxicity parameter):

Table 1: endpoint definition for each model

	Algae	Crustacea (acute)	Crustacea (chronic)	Fish (acute)	Fish (chronic)
Species	*Pseudokirchneriella s.* *Desmodesmus s.*	*Daphnia magna*	*Daphnia magna*	*multiple*	*multiple*
Time	72h (+/- 24h)	48h	21d	96h	32d
Measure(s)	EC50	EC50	EC10 (MATC)	LC50	EC10 (MATC)
Effect(s)	growth rate	mobility	reproduction	mortality	growth

❑ Mathematical model: Simple Linear Regression between Toxicity and Water Solubility (Mackay *et al*. 2009, Thomas *et al*., 2015)

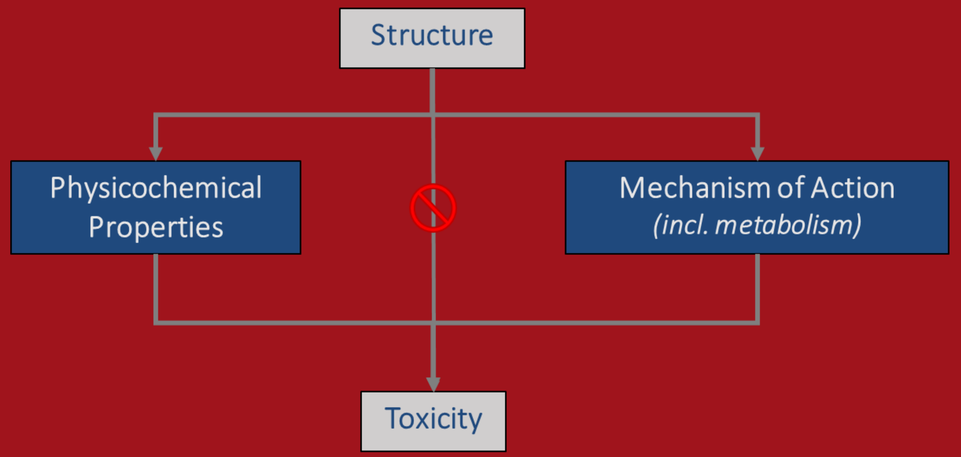
❑ Data source: ECOTOX database and REACH dossiers

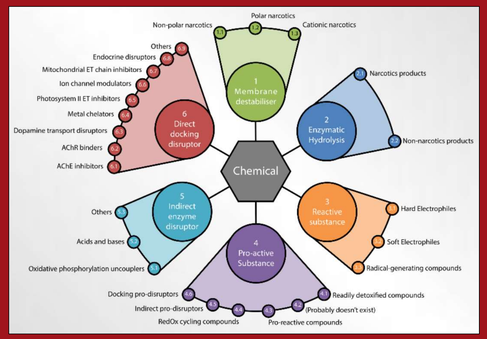
❑ Data treatment: reassessment of study reliability (case per case)

Table 2: statistical measurements for each model

	Algae	Crustacea (acute)	Crustacea (chronic)	Fish (acute)	Fish (chronic)
$N_{(training\ set)}$	27	47	9	27	5
R^2	0.82	0.89	0.90	0.82	0.66
RMSE	0.27	0.27	0.27	0.22	0.36
$N_{(validation\ set)}$	13	16	-	16	-
Q^2	0.87	0.79	-	0.61	-
RMSEP	0.23	0.36	-	0.22	-

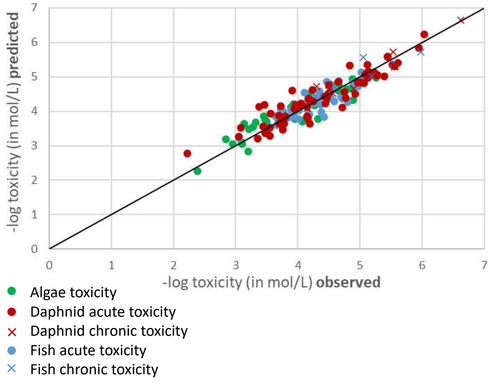
Structural similarity alone does not fully explain toxicity of reactive compounds. A mechanistic approach is necessary for accurate predictions.





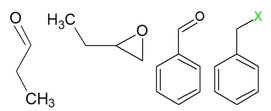
VALIDATION:

Figure 1: Global concordance for the 5 models to predict aquatic toxicity of reactive hard electrophiles (MechoA 3.1 compounds)

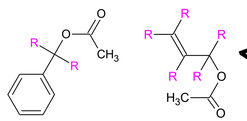


Concordance Correlation Coefficient (CCC) = 0.9319

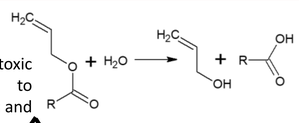
SUMMARY:



Simple **(benz)aldehydes, epoxides and benzyl halides** follow the same trend: MechoA 3.1-based model is relevant!



Benzyl/allyl alkanoates follow toxicity of MechoA 3.1 ONLY IF R = H. If not, the toxicity is comparable with esters narcosis (MechoA 2.1).



Allyl alkanoates have toxic behaviour conforming to MechoA 3.1 for daphnids and algae.

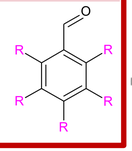
MechoA 3.1 (hard electrophiles)

MechoA 2.1 (enzymatic hydrolised)
Hypothesis: Esters are only moderately good leaving groups. thus steric hindrance can easily prevent nucleophilic substitution.

Allyl alkanoates are even more toxic than MechoA 3.1 for fish.
Hypothesis: esters can be hydrolysed thus producing allyl alcohol, a powerful toxic agent.

Benzaldehydes with o-hydroxy OR o-carbonyl group are more toxic than other reactive compounds for all species.

Aromatic substituents of benzaldehydes can increase or decrease the toxicity.



Vanillin derivatives can be detoxified by fish.

Scan QR code to download the poster

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