Development and improvement of mechanistic (High Accuracy)-QSAR model platform to predict acute and chronic aquatic toxicity

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INTRODUCTION

Quantitative Structure Activity Relationship (QSAR) models are relevant alternative methods in response to the need to reduce testing on vertebrates, time to market and cost compared to standard methods. Compared to experiments, they provide meaningful information to increase our mechanistic understanding of chemical impact on organisms, whether they are used alone or in mixtures. When developed following the 5 OECD principles and using reliable experimental data, they constitute important stand alone or complementary approaches to other alternative methods and can be used for regulatory purposes (e.g., REACH) if accompanied by the appropriate statistical formats[1]. This poster presents the philosophy and scientific pillars of iSafeRat® QSARs developed by KREATiS[2], the diversity of endpoints and mechanisms of action (MechoA) covered and the main holistic approach in which they are integrated.

5 OECD principles:

- ✓ A defined endpoint
- ✓ An unambiguous algorithm
- ✓ A defined domain of applicability
- ✓ Robustness and predictivity check
- ✓ A mechanistic interpretation, if possible

METHODS

ECHA EUROPEAN CHEMICALS AGENCY

Regulatory dossier

Physicochemical and ecotoxicological study collection and expertise

Example of elements of data quality and OECD guideline compliance check

	Algae (OCDE 201)	Crustacea (OCDE 202&211)		Fish (OCDE 203&210)	
Exposure	Acute and "chronic"	Acute	Chronic	Acute	Chronic
Species	Multiple	Daphnia magna		Multiple	
Time	72h	48h	21d	96h	35-90d
Endpoint	EC10 (MATC) and EC50	EC50	EC10 (MATC)	LC50	EC10 (MATC)
Effect	Growth	Mobility	Reproduction	Mortality	Growth, survival
Curated data	431	343	113	343	53
Reliable data	**72**	**79**	**20**	**50**	**11**

Regression building and mechanistic understanding investigation

Statistical analyses for internal and external validation

Fig. 1

RESULTS

Based on this workflow (see figure 1), 26 acute and 10 chronic ecotoxicological models were developed corresponding to circled MechoA sub-classes (see Fig. 2 below). Chronic toxicity models were more complicated than acute to develop, data availability being the limiting factor especially for certain endpoints (chronic data on fish and *Daphnia*) as 1/ under REACH, these tests are only required for substances manufactured or imported at >100 TPA (Annex IX) and 2/ certain substances can be tricky to test (e.g., volatility, hydrolysis, adsorption). These models allow comparison in terms of the relative reactivity of the different mechanisms of action and variability of acute to chronic ratios as well as the potential to quantitatively predict acute and chronic endpoints for risk assessment purposes without systematic recourse to experimental studies. The trends obtained from quality data, spanning a wide range of water solubilities, increase faith in the predicted outcomes compared to a single empirical study on the same substance (see examples of acute and chronic regressions in figures 3, 4, 5).

Chemical SMILES

Log Kow model

Experimental log Kow value — Predicted log Kow value

Water Solubility model

Experimental water solubility value — Predicted water solubility value

Ecotoxicological model

Choice of model [3]

Predicted ecotoxicological endpoints
(i.e., EC50, LC50, EC10 and IC95%)

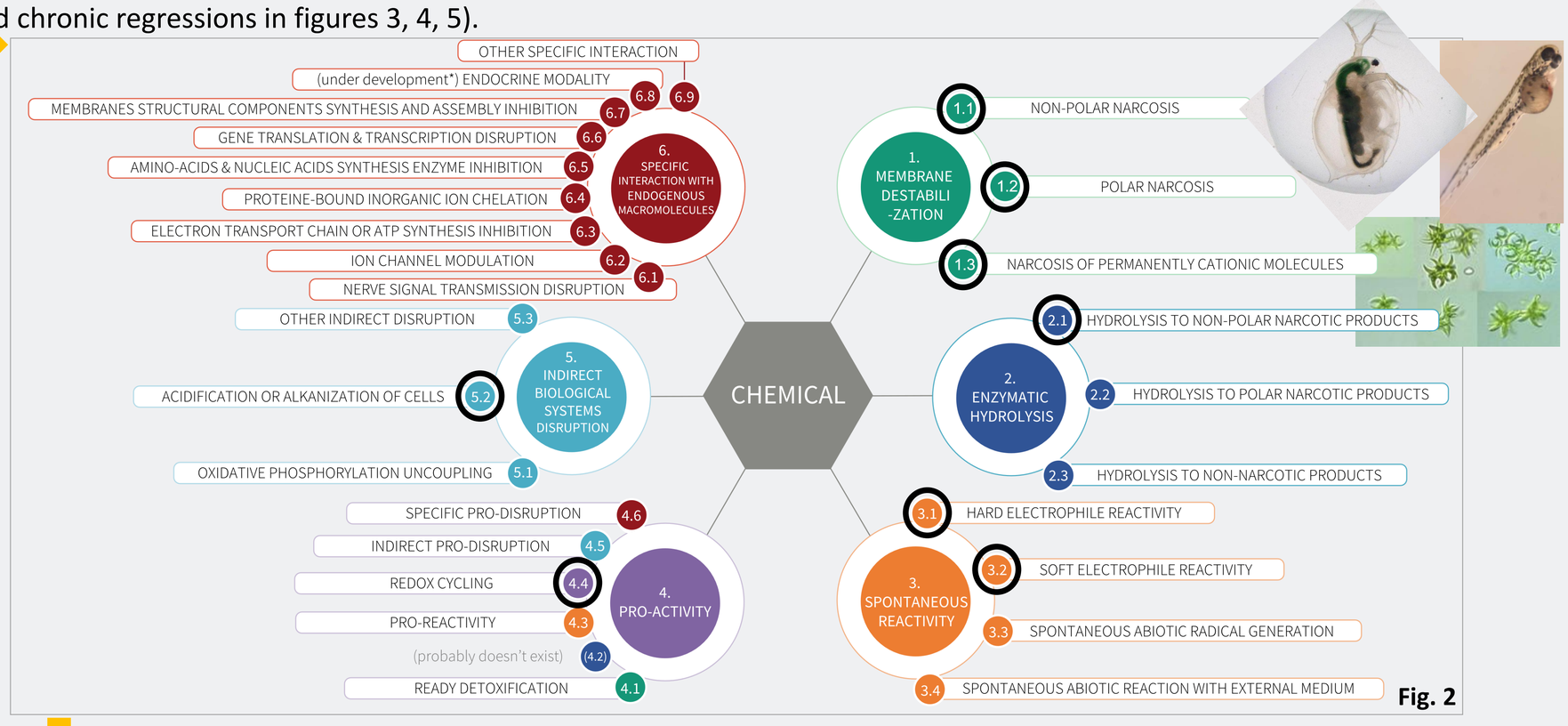

Fig. 2

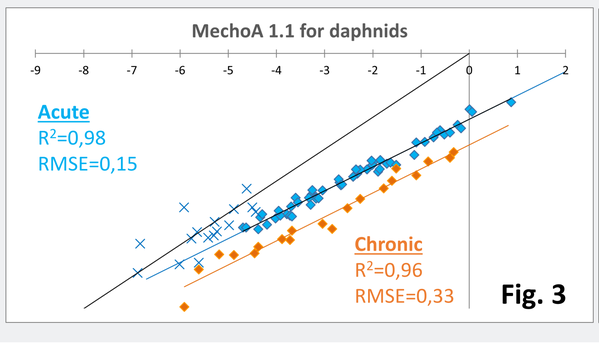

Fig. 3

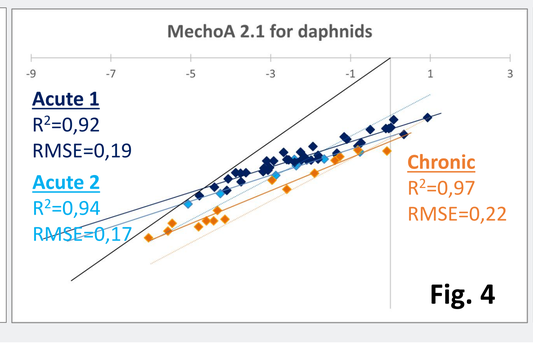

Fig. 4

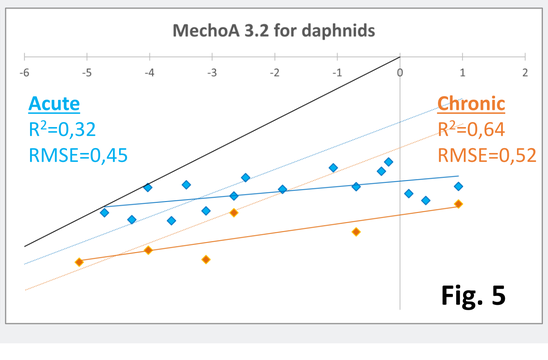

Fig. 5

CONCLUSION

Relative reactivities of different MechoAs can be compared i.e., in figures 3, 4, and 5 comparing three MechoAs on daphnia studies (acute and chronic). MechoA 1.1 can be seen to be less reactive than 2.1 which appears less reactive than 3.1 (flattened regression). Acute to chronic ratios are not always parallel, which allows us to project mechanistic hypotheses as to, for example the capacity of the organisms to metabolise the substance adequately. Also, criteria such as R^2 are not always good indicators of model validity (see MechoA 3.2) as the R^2 is the relationship between the descriptor and the predicted endpoint. Therefore, the more reactive the chemical moiety the less dependent toxicity will be on hydrophobicity. But this does not mean the prediction will be less reliable. Further models are still under development.

REFERENCES

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