High-Accuracy QSARs for reliable regulatory endpoint predictions and Environmental Risk Assessment

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Replacing Experimentation

HA-QSARs vs classical QSARs

- HA-QSARs are High-Accuracy QSARs which differ from classical QSARs as these only provide approximations of experimental values often limiting their use to PBT screening purposes.
- HA-QSAR models generate predictions that are reliable enough to replace experimental studies for regulatory use.
- Each HA-QSAR prediction may be accompanied (if required) by documents justifying the validity of the models and reliability of predictions following the five OECD principles.

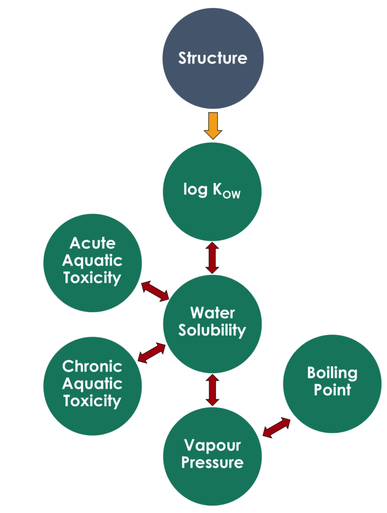

Fig. 1: HA-QSAR holistic approach

HA-QSARs in Environmental Risk Assessment

- The reliability in the outcome of an Environmental Risk Assessment (ERA) mainly depends on the data quality and sufficiency. Thus, the higher the quality of the data, the higher the confidence in the outcome of the ERA.
- HA-QSARs can be used to generate reliable predictions to carry out hazard assessments for ERA.
- However, this poster focusses on how the HA-QSAR holistic modelling approach (see Fig. 1) can be used to further advance the concepts of ecotoxicology within risk assessment.

1. Holistic approach for experimental study validation

KREATiS models follow a "holistic approach" (see Fig. 1) where predicted properties are related to each other by the laws of phase-equilibrium thermodynamics[1,2]. Log Kow is linked to water solubility but further physicochemical or even biological properties can also be interlinked. An example of how this approach can be used for study validation is as follows:

A 48h-EC50 for algae at 25 mg/L (assessed as a Klimisch 2 valid result[3]) was reported for mesitylene based on biomass. HA-QSAR predictions for the 72h-ErC50 algae are: 3.5 mg/L (using structure as input) and a mean value of 3.6 mg/L (using valid exp. data on other endpoints as inputs). Thus, the experimental value of 25 mg/L is not suitable for use in risk assessment.

Table 1: HA-QSAR predictions of algae growth rate inhibition for mesitylene (CAS# 108-67-8) from properties using holistic approach[4].

Input properties	72h-ErC50 (mg/L) to algae*
log K_{OW}	4.3
Water Solubility	2.6
Acute Toxicity to daphnid	5.5
Chronic Toxicity to daphnid	4.3
Vapour Pressure	2.2
Boiling Point	2.6
	3.6 (mean derived value)

**derived from exp. values of several properties*

Conclusion: The holistic approach is a powerful tool to validate exp. results and QSAR predictions alike.

2. Influence of metabolism on chronic toxicity

A recurrent question in ecotoxicology is whether the rapidity of parent substance metabolism influences the chronic toxicity result for baseline toxic chemicals. The study was performed by dividing a MOA 1 test set in to readily biodegradable and non-biodegradable groups.

The hypothesis was made that readily biodegradable substances would also likely be readily metabolised while non-biodegradable substances would be expected to be less rapidly metabolised.

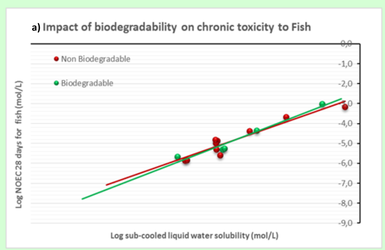

Fig. 2. Relationship between chronic toxicity to a) fish and b) daphnids for substances expected to metabolise rapidly or slowly (based on biodegradation)[5]

In the case of the substances reviewed, no difference in chronic endpoint values were observed for daphnids or for fish between supposed 'readily metabolisable' or 'less metabolisable' substances (see Fig. 2).

Conclusion for MOA 1 substances: the chronic toxicity to daphnids and fish is a priori not influenced by metabolic breakdown

3. Existence of Acute to Chronic Ratios for fish and daphnids

The fish and daphnid acute and chronic regressions were compared in order to determine if an acute to chronic ratio (ACR) can be obtained for MOA 1. substances. Based on the available valid data a significant regression with a high R^2 value was determined for both fish and daphnids.

From Fig. 3, the difference between acute and chronic values was observed to be approximately 1 order of magnitude (i.e. a factor of 10) for fish and just less than this value for daphnids.

There was no observable difference in slope between the regression lines for acute and chronic studies.

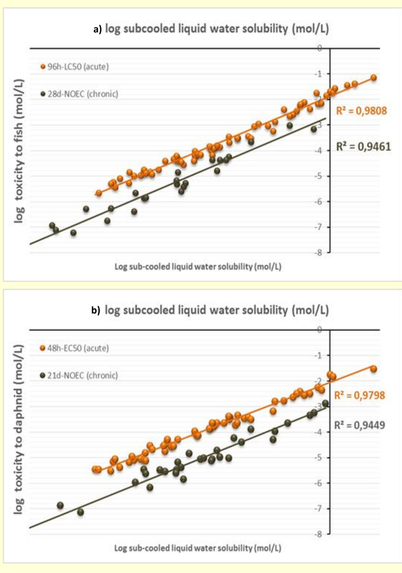

Fig. 3. Relationship between acute and chronic toxicity values versus subcooled liquid solubility for a) fish and b) daphnids[5]

Conclusion: This study supports the use of a factor of 10 as an acceptable ACR for fish and daphnids for MOA 1 substances. The results from these studies are part of a publication which is currently under preparation.

Summary

HA-QSARs have already justified their value in regulatory ecotoxicology to replace experimentation.

In this poster, the above case studies have been used to further demonstrate their role to provide alternative solutions to current challenges within ecological risk assessment.

References

[1] Thomas P., Dawick J., Lampi M., Lemaire P., Presow S., van Egmond R., Burgos M.G. (2013) Activity based relationships for aquatic ecotoxicology data: use of the activity approach to strengthen MOA predictions. ECETOC Technical Report no. 120.

[2] Thomas P, Dawick J, Lampi M, Lemaire P, Presow S, Van Egmond R, Arnot J, Mackay D, Mayer P, Galay Burgos M (2015). Application of the activity framework for assessing aquatic ecotoxicology data for organic chemicals. Environ. Sci. Technol. (In press).

[3] Klimisch H.J., Andreae M., Tillmann U. (1997) A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul Toxicol Pharmacol. 25(1), 1-5.

[4] Bicherel P, Bauer F, Sahigara F, Thomas P. Use of a holistic approach in validation: QSAR models versus experimental data. Poster presented at SETAC Europe 25th annual meeting 2015, Barcelona, Spain.

[5] Thomas P, Bicherel P, Sahigara F. High Accuracy QSARs for the prediction of acute and chronic aquatic toxicity. Poster presented at SETAC Europe 25th annual meeting 2015, Barcelona, Spain.

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