High Accuracy QSARs for the prediction of acute and chronic aquatic toxicity

Paul THOMAS, Pascal BICHEREL, Faizan SAHIGARA

KREATiS, Knowledge & Research in Environment And Toxicology in Silico

KREATiS SAS, 23 rue du Creuzat, ZAC St Hubert, 38080 L'ISLE D'ABEAU, FRANCE

www.kreatis.eu

Replacing Experimentation

Introduction

The thermodynamic relationship between the chemical activity and the toxicity of narcotic chemicals to aquatic organisms has recently been hypothesised (Mackay *et al,* 2009[1]; Mayer & Reichenberg, 2006[2]). In 2013, an ECETOC task force completed an extensive project on a large existing dataset to validate this hypothesis. The task force tentatively proposed the relationship between water solubility and acute and chronic effects for MOA 1 substances and this was recently made available as ECETOC Technical Report 120[3]. Using these data as a starting point, KREATiS extensively reworked these tentative algorithms and created the first High Accuracy QSARs (HA-QSARs)[4] with $R^2 > 0.95$ for acute ecotoxicity to fish, daphnia and algae.

Once the acute toxicity QSAR results had been demonstrated to be at least as accurate as experimental data for MOA 1 substances[5], the work was then extended to the chronic toxicity endpoints for MoA1 substances (where metabolism and analytical issues may potentially influence the experimental results and therefore accuracy in predictions). The chronic QSAR work was undertaken as part of the DAMIER project described in another poster (WE027).

The aims of this work were to consider the pertinence of accounting for metabolism in QSARs for chronic studies and the relevance of the Acute to Chronic Ratio (ACR) concept.

Methods

iSafeRat® Holistic approach to predict physicochemical and ecotoxicological endpoints:

The iSafeRat® Toolbox uses a holistic calculation method where a series of models interrelated by the laws of phase-equilibrium thermodynamics can be predicted in a cascade approach. By default, the log K_{OW} of the target chemical structure is predicted using a fragment-based approach from a structure given as a user input but these can be replaced by experimental data. The derived log K_{OW} is then used as an input to generate the prediction for solubility and from that, ecotoxicity (Fig. 1) by means of a linear regression model for acute and chronic toxicity at three trophic levels (fish, algae and invertebrates).

Once the chronic dataset had been validated the regressions were used for two specific sub-studies:

1) The fish and daphnid chronic data were divided into two groups: chronic endpoints for substances which were considered to be readily biodegradable according to the literature and those which were found to fail ready biodegradation studies. Ready biodegradation tests were used in the absence of available data on metabolic rates for the test substances.
2) 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.

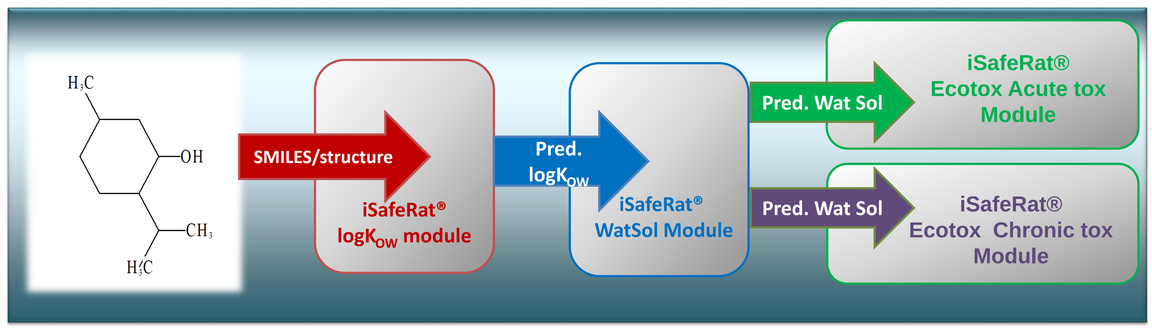

Figure 1: A schematic overview of iSafeRat® approach for acute and chronic aquatic toxicity predictions

Results and Conclusions

Influence of readily and non-readily metabolised substances on fish chronic toxicity results.

A recurrent question in ecotoxicity QSAR circles 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. It is recognised that metabolic rates and routes may differ between prokaryote and eukaryote organisms and that biodegradation results depend upon mineralisation of the substance while metabolisation may be only a primary degradation step but still sufficient to reduce toxicity lower than that of the parent substance. 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.

Existence of Acute to Chronic Ratios for fish and daphnids

Based on the available valid data a significant regression with a high R^2 value was determined for both fish and daphnids. The difference between acute and chronic values was approximately 1 order of magnitude (i.e. a factor of 10) for fish and just less than this value for daphnids. In Fig. 3 no significant difference in slope is observed between the regression lines for acute and chronic studies regardless of their water solubility (very approximately inversely proportional to log K_{OW}).

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.

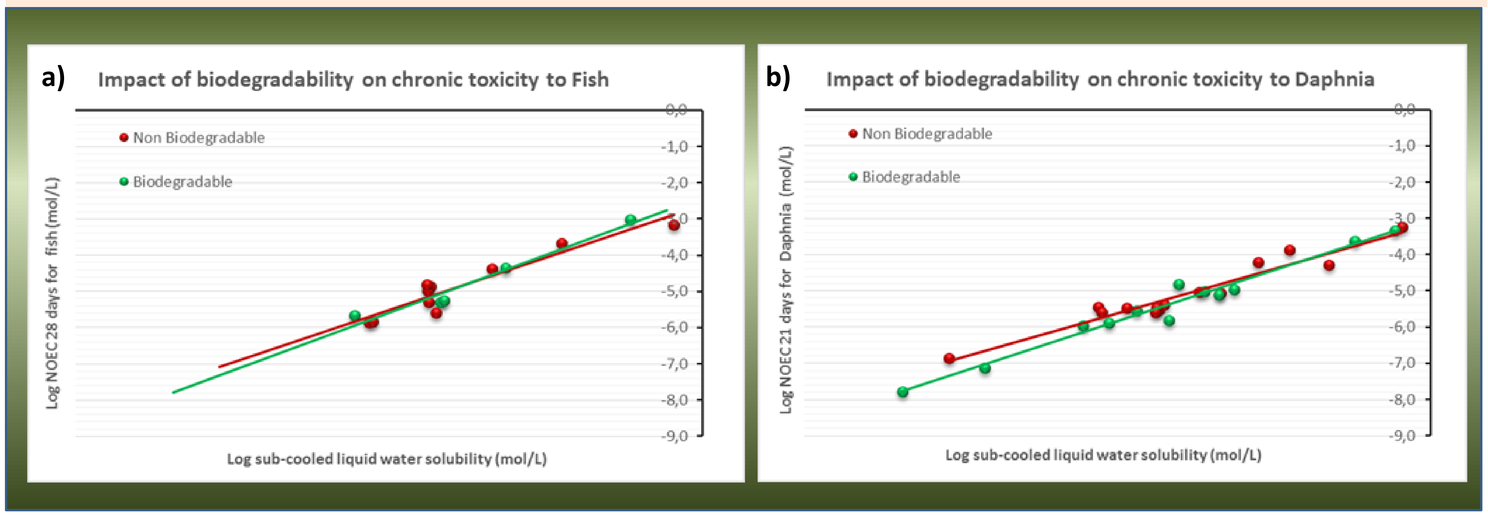

Figure 2. Relationship between chronic toxicity to a) fish and b) daphnids for substances expected to metabolise rapidly or slowly (based on biodegradation)

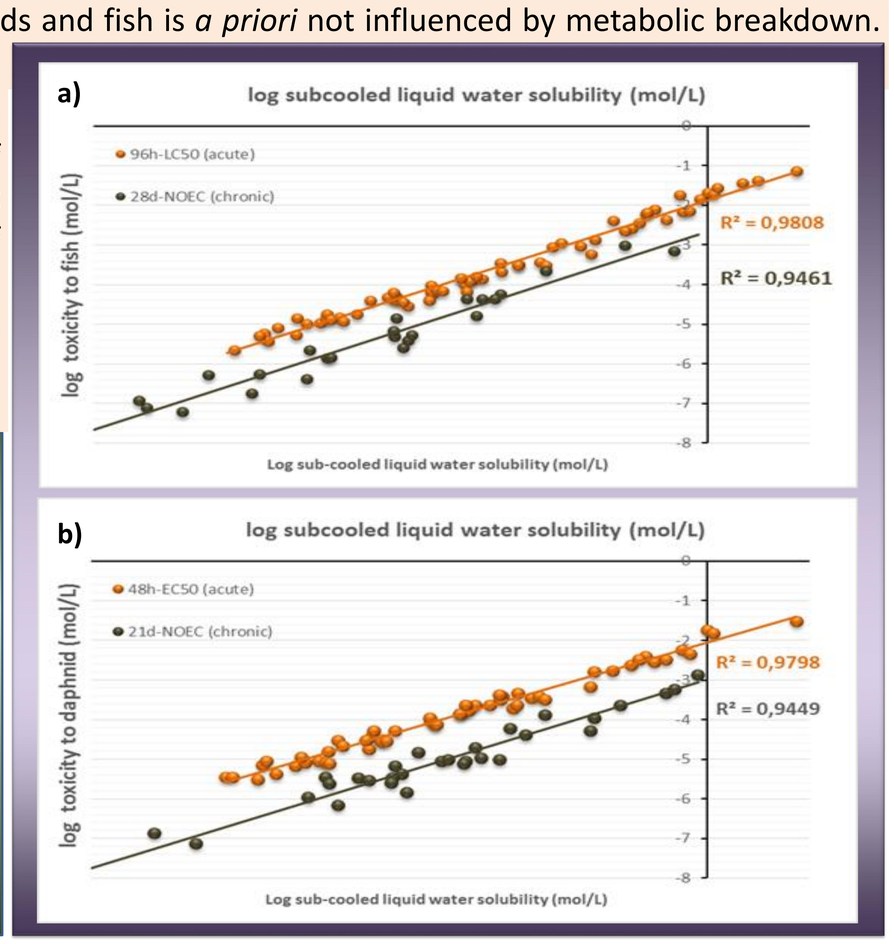

Figure 3. Relationship between acute and chronic toxicity values versus subcooled liquid solubility for a) fish and b) daphnids

References

1 MacKay D, Arnot J, Petkova E, Wallace K, Call D, Brooke L, Veith G (2009). The physicochemical basis of QSARs for baseline toxicity. *SAR and QSAR in Environmental Research* 20:3, 393-414.
2 Mayer, P.; Reichenberg, F. (2006). Can highly hydrophobic organic substances cause aquatic baseline toxicity and can they contribute to mixture toxicity? *Environ. Toxicol. Chem. 25,* 2639–2644.
3 ECETOC Technical Report No. 120, 2013. Activity-Based Relationships for Aquatic Ecotoxicology Data: Use of the Activity Approach to Strengthen MoA Predictions.
4 iSafeRat® – in Silico Algorithms For Environmental Risk And Toxicity version 1.3
5 Sahigara F, Bicherel P, Thomas P (2014). iSafeRat HA-QSARs vs. commonly used predictive models: A statistical comparison. Poster no. WE232. SETAC 24th annual meeting, Basel, Switzerland

Poster No. WE017

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