Activity based relationships for aquatic ecotoxicology data: use of the activity approach to strengthen MoA predictions

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Background

The relationship between Chemical Activities (as defined by phase equilibrium thermodynamics) and toxicity of narcotic chemicals was originally hypothesised at the end of the 1930s but has only recently been reanimated (Mayer & Reichenberg (2006); Mackay *et al*. (2009)).

When considering the potential for toxicity of non-polar narcotic substances, the property of interest is the hydrophobicity of the substance. The fundamental determinant of hydrophobicity is the solute's activity coefficient (γ_i) in water. This property can be viewed as the ratio of the activity (or fugacity) of the solute to the activity (or fugacity) that the solute would have if it were in a solution consisting entirely of pure solute. The activity coefficient can also be regarded as the inverse expression of solubility, where a solute that is only sparingly soluble in a solvent (e.g. water), will have a high activity coefficient. When expressed as a mode fraction, the activity coefficient is the reciprocal of the solubility (Mackay, 2001). Substances with an activity coefficient that is less than 20 can be considered highly soluble in water, or even miscible. In comparison, a poorly water soluble substance, like DDT (water solubility of 5.5 mg/L; 10^{-7} Mol/L) has an activity coefficient (γ_i) of over 500,000.

According to these authors, chemical activities can be used to determine toxicity for narcotics for any species (mammals, fish, invertebrates…) regardless of the exposure medium (air, water…) as the toxic effect is hypothesized to occur at a specific activity in the organisms (estimated by the Mackay *et al*. at around 0.01). Thus, at least for narcotics toxicity can be substituted for another form of activity such as a physico-chemical parameter (e.g. solubility) and the regression slope of this parameter versus toxicity is expected to be 1. Nevertheless, the authors found that in practice the slope for this relationship is actually closer to 0.8.

This study focussed on the approach used by these authors taking data from an existing, presumed valid database (ECHA disseminated database of the REACH Phase I dossiers), to explore the approach and verify the results from the MacKay *et al*. model.

Issues/Methods

The original dataset from MacKay *et al*. (2009) included polar as well as non-polar narcotic substances on a mixture of species (including rodents!) and some scatter was observed in the graph.

The authors decided that, based on a validated dataset (ECHA) and by separating the Modes of action, it should be possible to improve the model outcome.

Furthermore Trophic levels were separated out into fish, invertebrates and algae and into short and long term endpoints to compare slopes and intersects between species and acute and chronic endpoints.

Once compiled, it became clear that the dataset needed further refinement and a series of rules were introduced to remove unacceptable data (for example, endpoints based on too short study duration were removed to avoid including datapoints which were not at steady state). Of the original 900 ecotoxicity data classed as valid from the ECHA disseminated database only 450 remained.

Solubility and melting point data were also procured from the same source. Data were only used when reliable experimental studies for both physico-chemical and toxicity data were available.

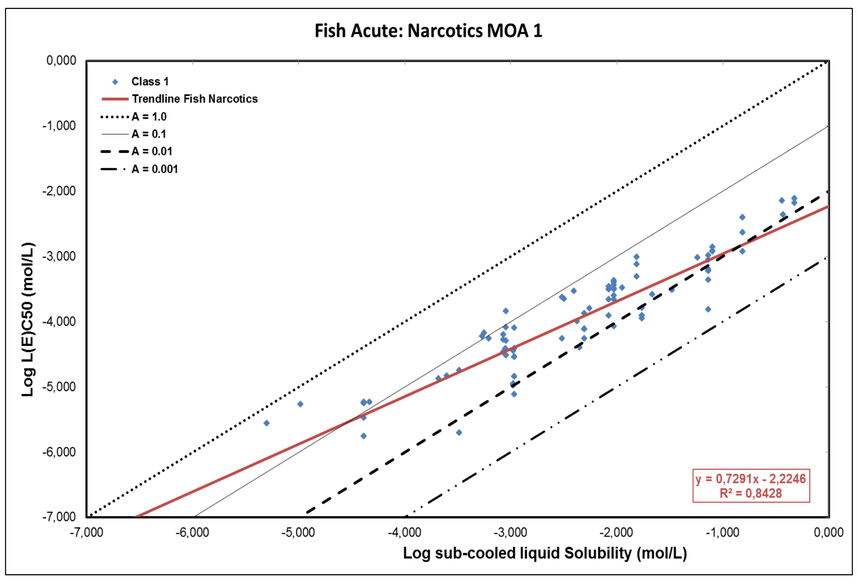
Sub-cooled liquid solubility was calculated using the fugacity ratios to correct for solid solubility values.

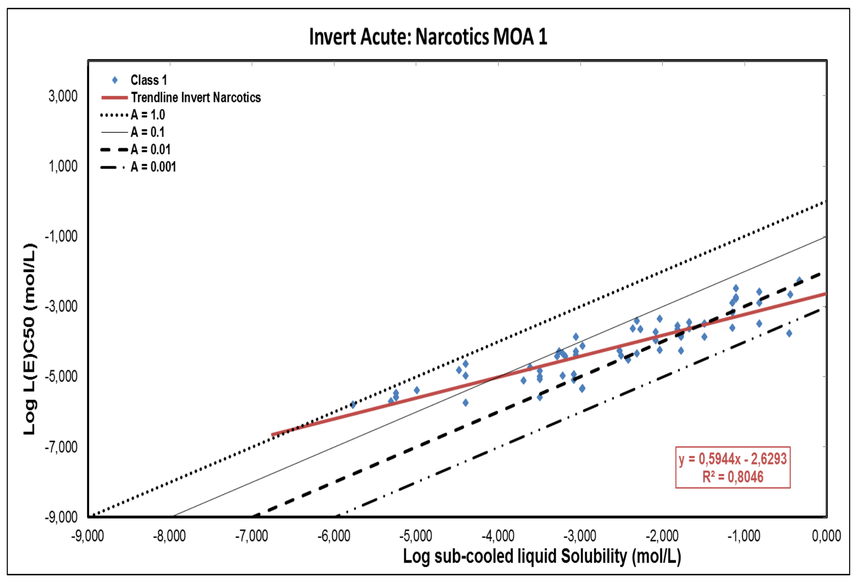
Toxicity data was plotted per trophic level and per duration (acute or chronic) versus sub-cooled liquid solubility.

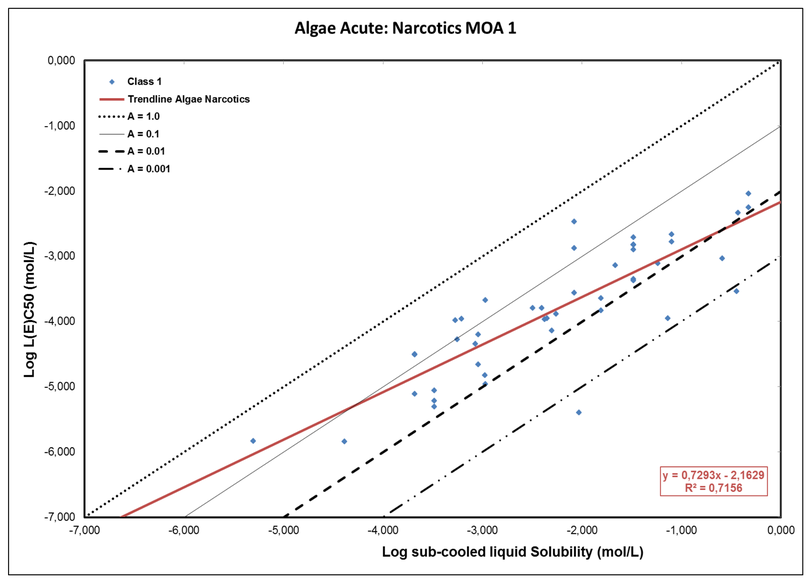
Results are plotted below:

Acute and chronic models for MOA 1

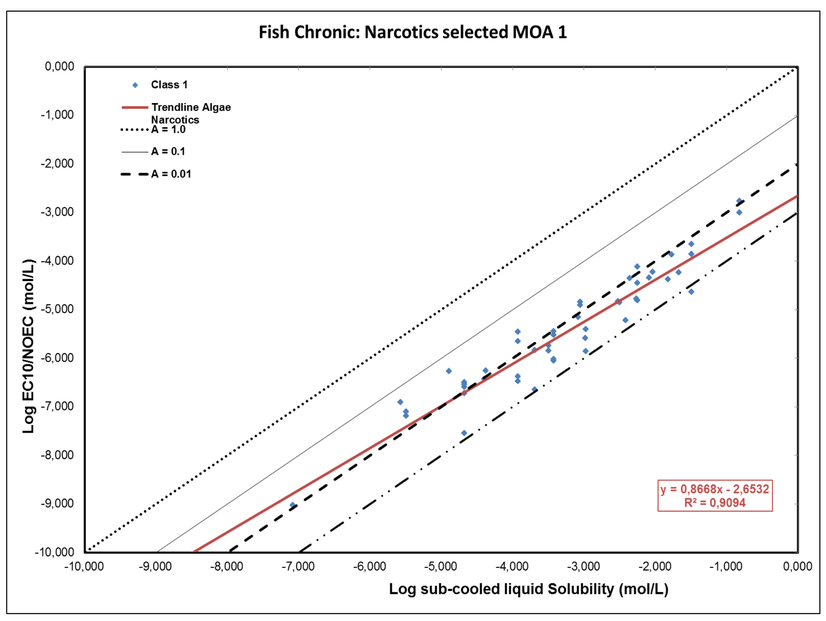
Acute regression slopes for the three trophic levels

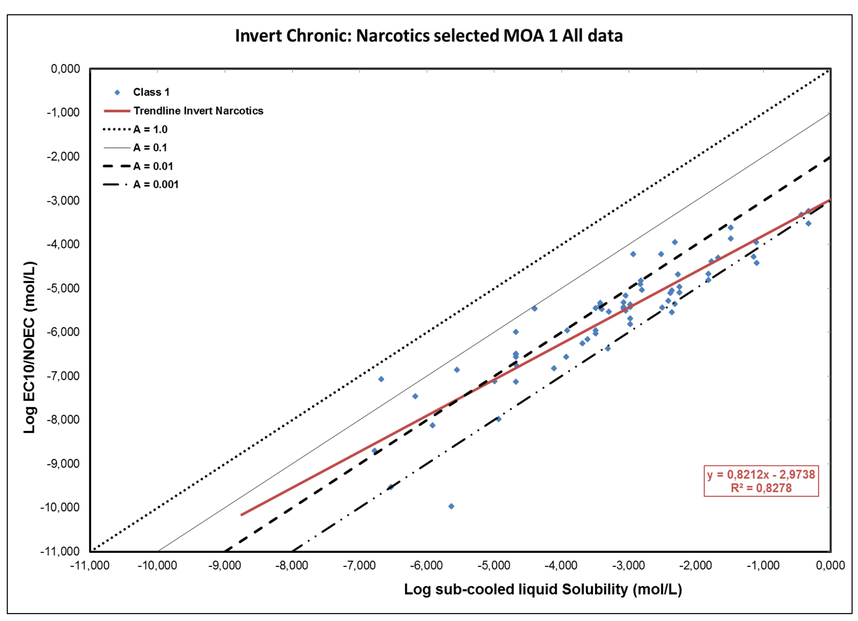


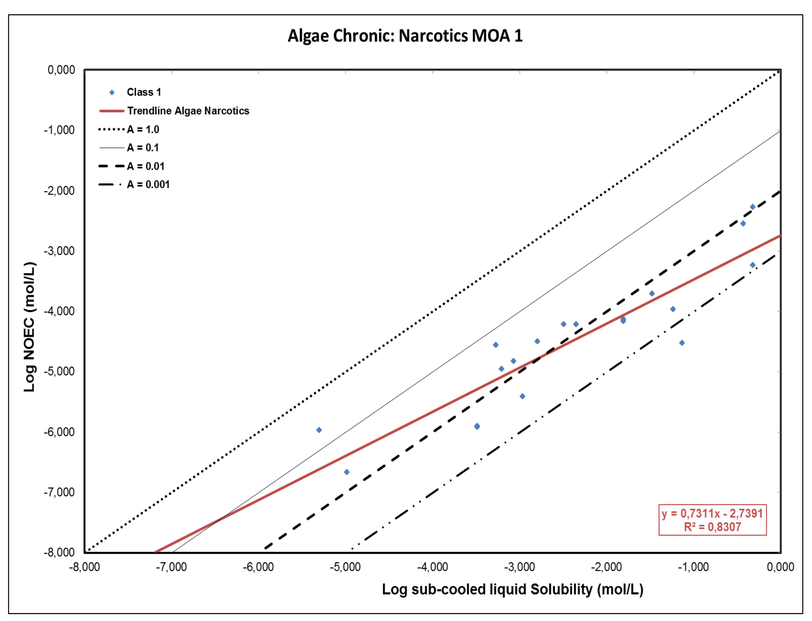




Chronic regression slopes for the three trophic levels







Results and Conclusion:

The following conclusions can be made based on this exercise:

- ❑ The results, based on an entirely different dataset are in line with those from Mackay *et al*'s work;
- ❑ For MoA 1 substances the task force found strong similarities in slopes for both acute and chronic data between the trophic levels examined suggesting that for baseline narcosis, specific species issues (behaviour and biology) may play a minor role in determining toxicity at equilibrium;
- ❑ For MoA 1 substances, the intercepts for chronic activities were systematically lower (approximately half a log unit) than for acute activities;
- ❑ For MoA 1 substances, equilibrium of high log K_{OW} substances does not always appear to be reached within the timeframe of the standard acute toxicity test (from approximately log K_{OW} 4-5).
- ❑ The authors recommend that a specific (gold standard) database should be prepared based on appropriate technical protocols and incorporating techniques such as passive dosing which would improve the predictions and understanding of activity relationships within and between MoAs;
- ❑ The activity concept has not yet been applied in risk assessment. The authors are of the opinion that this work demonstrates proof of concept for application in the development of QSARS to predict acute and chronic toxicity. Ultimately these QSARs could reduce both acute and chronic experimental studies in a regulatory context.

References

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Mackay D. 2001. Multimedia environmental models, The fugacity approach 2nd edition, Taylor and Francis.

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