

Alternatives to Animal Testing for Chemical Risk Assessment

A Defra LINK Project

Project no. LK0984

NON POLAR NARCOSIS QSAR FOR FATHEAD MINNOW

M8 Development of *in silico* models for “non-reactive” toxicity

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This project was sponsored by Defra through the Sustainable Arable Link Programme

September 2009

www.inchemicotox.org

1 Aim of this Document

This document provides supporting information related to the non polar narcosis QSAR for fathead minnow acute toxicity reported in the framework of the Defra LINK LK0984 project. This QSAR is related to Milestones 8 Development of *in silico* models for “non-reactive” toxicity. The QSAR model presented in this document is available on <http://www.inchemicotox.org/>.

The following documentation has been generated using the QSAR Model Reporting Format (QMRF) available at JRC, <http://qsardb.jrc.ec.europa.eu/qmrf/>.

2. QSAR Abstract

A dataset of 66 chemicals previously identified as non polar narcotics to fathead minnow [1, 2] has been used to develop a non polar narcosis QSAR model (Equation 1). The non polar narcosis mechanism of action has often been shown to be related to the lipophilicity of chemicals.

Linear regression analysis was applied to relate the acute toxicity (LC50) to fathead minnow to the logarithm of octanol-water partition coefficient (log P). The following model was obtained:

$$\log (1/\text{LC50})= 0.80 \log P - 4.90 \quad \text{Equation 1}$$

$$n=66; q^2=0.89; r^2=0.90; s=0.39; F=557$$

Where LC50 is the concentration (moles per litre) required to kill 50% of fish within 96h, n is the number of compounds, q^2 is the cross-validated coefficient of determination, r^2 is the square of the correlation coefficient, s is the standard deviation and F is the Fisher statistics.



3. References

- 1 Russom, C. L.; Bradbury, S. P.; Broderius, S. J.; Hammermeister, D. E.; Drummond, R. A. Predicting modes of toxic action from chemical structure: acute toxicity in the fathead minnow (*Pimephales promelas*). *Environmental Toxicology and Chemistry* **1997**, 16, 948–967.
- 2 Raevsky, O. A.; Grigor'ev, V. Y.; Weber, E. E.; Dearden, J. C. Classification and quantification of the toxicity of chemicals to guppy, fathead minnow and rainbow trout: part 1. nonpolar narcosis mode of action. *QSAR Comb. Sci.* **2008**, 27, 274-1281.

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	QMRF identifier (JRC Inventory): To be entered by JRC	
	QMRF Title: Non polar narcosis QSAR for fathead minnow acute toxicity	
	Printing Date: 07-Sep-2009	

1. QSAR identifier

1.1. QSAR identifier (title):

Non polar narcosis QSAR for fathead minnow acute toxicity

1.2. Other related models:

None

1.3. Software coding the model:

2. General information

2.1. Date of QMRF:

07th of September 2009

2.2. QMRF author(s) and contact details:

[1] Fania Bajot Liverpool John Moores University f.bajot@ljmu.ac.uk

[2] Mark Cronin Liverpool John Moores University + 44 151 231 2402
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<http://www.staff.livjm.ac.uk/phamcron/qsar/qsar1.htm>

2.3. Date of QMRF update(s):

2.4. QMRF update(s):

2.5. Model developer(s) and contact details:

[1] Fania Bajot Liverpool John Moores University f.bajot@ljmu.ac.uk

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<http://www.staff.livjm.ac.uk/phamcron/qsar/qsar1.htm>

2.6. Date of model development and/or publication:

07th of September 2009

2.7. Reference(s) to main scientific papers and/or software package:

2.8. Availability of information about the model:

The model is non-proprietary. Information on the algorithm and training set is publicly available.

2.9. Availability of another QMRF for exactly the same model:

None

3. Defining the endpoint - OECD Principle 1

3.1. Species:

Fathead minnow (*Pimephales promelas*)

3.2. Endpoint:

3. Ecotoxic effects 3.3. Acute toxicity to fish (lethality)

3.3. Comment on endpoint:

96 hours

3.4. Endpoint units:

Moles per litre

3.5. Dependent variable:

Fathead minnow LC50 values (moles per litre) were logarithmically transformed (to base 10) and multiplied by minus 1

3.6. Experimental protocol:

Toxicity data were extracted from the US EPA ECOTOX database (<http://cfpub.epa.gov/ecotox/>) and were compiled by Raevsky OA (2008) QSARComb. Sci.27: 1274-1281

3.7. Endpoint data quality and variability:

Data extracted from the US EPA ECOTOX database, therefore likely to be of variable quality

4. Defining the algorithm - OECD Principle 2

4.1. Type of model:

QSAR

4.2. Explicit algorithm:

Linear regression analysis

$$\log 1/LC50 = 0.979 \log P - 4.90$$

4.3. Descriptors in the model:

log P dimensionless logarithm of octanol-water partition coefficient

4.4. Descriptor selection:

One descriptor (log P) chosen empirically from a knowledge of mechanism of action

4.5. Algorithm and descriptor generation:

log P was calculated from SMILES string

4.6. Software name and version for descriptor generation:

KOWWIN v1.67

KOWWIN is part of EPISuite software

Available for download from
<http://www.epa.gov/oppt/exposure/pubs/episuite.htm>
<http://www.epa.gov/oppt/exposure/pubs/episuite.htm>

4.7. Descriptors/Chemicals ratio:

1 descriptor / 66 chemicals

5. Defining the applicability domain - OECD Principle 3

5.1. Description of the applicability domain of the model:

Applicability domain covers a log P range from -0.63 to 4.61. The acute toxicity values (negative logarithm of molar value) ranged from -5.96 to -0.64.

The compounds selected have been identified as non-polar narcotics to fish. i.e. they are non-reactive and cause lethality by accumulation at cellular membranes. They are characterised by being simple organic compounds including alkyl, halogen and ketone substituted mono-aromatic and (fully saturated) alkyl compound.

5.2. Method used to assess the applicability domain:

None

5.3. Software name and version for applicability domain assessment:

5.4. Limits of applicability:

Non-polar narcosis mechanism of acute fish toxicity.

6. Internal validation - OECD Principle 4

6.1. Availability of the training set:

Yes

6.2. Available information for the training set:

CAS RN: Yes

Chemical Name: Yes

Smiles: Yes

Formula: No

INChI: No

MOL file: No

6.3. Data for each descriptor variable for the training set:

All

6.4. Data for the dependent variable for the training set:

All

6.5. Other information about the training set:

66 simple organic compounds including alkyl, halogen and keto

6.6. Pre-processing of data before modelling:

None

6.7. Statistics for goodness-of-fit:

r^2 adjusted for degrees of freedom = 0.895

standard error = 0.386

Fishers statistic = 557

6.8. Robustness - Statistics obtained by leave-one-out cross-validation:

leave-one-out cross validated r^2 = 0.890

6.9. Robustness - Statistics obtained by leave-many-out cross-validation:

6.10. Robustness - Statistics obtained by Y-scrambling:

6.11. Robustness - Statistics obtained by bootstrap:

6.12. Robustness - Statistics obtained by other methods:

7. External validation - OECD Principle 4

7.1. Availability of the external validation set:

No

7.2. Available information for the external validation set:

CAS RN: No

Chemical Name: No

Smiles: No

Formula: No

INChI: No

MOL file: No

7.3.Data for each descriptor variable for the external validation set:

No

7.4.Data for the dependent variable for the external validation set:

No

7.5.Other information about the external validation set:

7.6.Experimental design of test set:

7.7.Predictivity - Statistics obtained by external validation:

7.8.Predictivity - Assessment of the external validation set:

7.9.Comments on the external validation of the model:

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

All compounds are considered to act by non-polar narcosis. This is well established for non-reactive compounds. Acute lethality is brought about by accumulation in cellular membranes causing their disruption

and ultimately death of the organism. The ability of the compound to accumulate in a cellular membrane is thought to be related to its intrinsic hydrophobicity. Hydrophobicity of these compounds is modelled

by log P.

8.2.A priori or a posteriori mechanistic interpretation:

As stated in Section 8.1, hydrophobicity is related to log P and is known to the controlling factor in the acute lethal toxicity of non-polar narcotic compounds. Compounds in this data set were selected a priori

on the basis that they acted as non-polar narcotics.

8.3.Other information about the mechanistic interpretation:

9.Miscellaneous information

9.1.Comments:

This model is related to a large number of models for non-polar narcosis (also termed baseline or minimum toxicity) for acute fish toxicity.

9.2.Bibliography:

9.3.Supporting information:

Training set(s) Test set(s) Supporting information

10.Summary (JRC Inventory)

10.1.QMRF number:

To be entered by JRC

10.2.Publication date:

To be entered by JRC

10.3.Keywords:

To be entered by JRC

10.4.Comments:
To be entered by JRC