

Alternatives to Animal Testing for Chemical Risk Assessment

A Defra LINK Project

Project no. LK0984

POLAR NARCOSIS QSAR FOR GUPPY

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

Prepared by:

Fania Bajot
School of Pharmacy and Chemistry,
Liverpool John Moores University,
Byrom Street, Liverpool, L3 3AF, England
F.Bajot@ljmu.ac.uk

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www.inchemicotox.org

1 Aim of this Document

This document provides supporting information related to the polar narcosis QSAR for guppy 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 98 chemicals previously identified as polar narcotics to guppy [1, 2] has been used to develop a polar narcosis QSAR model (Equation 1). The 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 guppy to the logarithm of octanol-water partition coefficient (log P). The following model was obtained:

$$\log (1/\text{LC50})= 0.73 \log P - 3.743 \quad \text{Equation 1}$$

$$n=98; q^2=0.79; r^2=0.80; s=0.42; F=388$$

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 Katritzky, A. R.; Tatham, D. B.; Maran, U. Theoretical descriptors for the correlation of aquatic toxicity of environmental pollutants by quantitative structure-toxicity relationships. *Journal of Chemical Information and Computer Sciences* **2001**, 41, 1162-1176.
- 2 Raevsky, O. A.; Grigor'ev, Veniamin Y.; Dearden, J. C.; Weber, Eric E. Classification and quantification of the toxicity of chemicals to guppy, fathead minnow, and rainbow trout. Part 2. Polar narcosis mode of action. *QSAR Comb. Sci.* **2009**, 28, 163-174.

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	QMRF identifier (JRC Inventory): To be entered by ECB	
	QMRF Title: Polar narcosis QSAR for guppy acute toxicity	
	Printing Date: 09-Sep-2009	

1. QSAR identifier

1.1. QSAR identifier (title):

Polar narcosis QSAR for guppy 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
M . T . C r o n i n @ l j m u . a c . u k
<http://www.staff.livjm.ac.uk/phamcron/qsar/qsar1.htm>

2.3. Date of QMRF update(s):

None

2.4. QMRF update(s):

None

2.5. Model developer(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
M . T . C r o n i n @ l j m u . a c . u k
<http://www.staff.livjm.ac.uk/phamcron/qsar/qsar1.htm>

2.6. Date of model development and/or publication:

11th 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:

Guppy (*Poecilia reticulata*)

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:

Guppy 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 (2009)
QSAR

*Comb. Sci.*28: 163–174

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

$$\log 1/LC50 = 0.730 \log P - 3.743$$

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 the 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 / 98 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 -1.31 to 6.21. The acute toxicity values (negative logarithm of molar value) ranged from -4.54 to 0.58.

The compounds selected have been identified as 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 phenol derivatives and aniline derivatives compounds.

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:

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:

98 simple organic compounds including phenol derivatives and aniline derivatives compounds.

6.6.Pre-processing of data before modelling:

None

6.7.Statistics for goodness-of-fit:

r2 adjusted for degrees of freedom = 0.800

standard error = 0.418

Fishers statistic = 388

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

leave-one-out cross validated r2 = 0.793

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 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 be the controlling factor in the acute lethal toxicity of 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 polar narcosis for acute fish toxicity.

9.2.Bibliography:

9.3.Supporting information:

Training set(s)

Rainbow trout non polar narcosis.txt	file:///M:\LINK Project\QMRF\Rainbow trout non polar narcosis.txt
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Test set(s)Supporting information

10.Summary (ECB Inventory)

10.1.QMRF number:

To be entered by ECB

10.2.Publication date:

To be entered by ECB

10.3.Keywords:

To be entered by ECB

10.4.Comments:

To be entered by ECB