	QMRF identifier (JRC Inventory): **To be entered by JRC**
	QMRF Title: **Insubria QSAR PaDEL-Descriptor model for prediction of (Benzo-)Triazoles toxicity in** *Oncorhynchus mykiss*
	Keywords: PaDEL-Descriptor; GA-OLS; *Oncorhynchus mykiss L* **C50; (Benzo-)Triazoles; QSARINS; INSUBRIA**
	Printing Date: **9-mar-2015**

1. QSAR identifier

1.1. QSAR identifier (title):

Insubria QSAR PaDEL-Descriptor model for prediction of (Benzo-)Triazoles

toxicity in *Oncorhynchus mykiss*

Keywords: PaDEL-Descriptor; GA-OLS; *Oncorhynchus mykiss L* C50;

(Benzo-)Triazoles; QSARINS; INSUBRIA

1.2. Other related models:

S.Cassani, S. Kovarich, E.Papa, P.P. Roy, L.v.d.Wal, P. Gramatica.

Daphnia and fish toxicity of (benzo)triazoles: Validated QSAR models,and

interspecies quantitative activity–activity modelling, J.Haz. Mater.

2013, 258-259, 50-60. [1]

1.3. Software coding the model:

PaDEL-Descriptor

A software to calculate molecular descriptors and fingerprints, version 2.18 [2]

Yap Chun Wei, phayapc@nus.edu.sg

http://padel.nus.edu.sg/software/padeldescriptor/index.html

QSARINS

Software for the development, analysis and validation of QSAR MLR models, version 1.2 (also

verified with version 2.2, 2015)

Prof. Paola Gramatica, paola.gramatica@uninsubria.it

http://www.qsar.it/

2. General information

2.1. Date of QMRF:

04/02/2015

2.2. QMRF author(s) and contact details:

[1]Stefano Cassani Insubria University, Department of Theoretical and Applied Sciences (DiSTA),

via J.H. Dunant 3, 21100 Varese (Italy) +390332421439 stefano.cassani@uninsubria.it

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http://www.qsar.it/

2.3. Date of QMRF update(s):

2.4. QMRF update(s):

2.5. Model developer(s) and contact details:

[1]Stefano Cassani Insubria University, Department of Theoretical and Applied Sciences (DiSTA),

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[3]Alessandro Sangion Insubria University, Department of Theoretical and Applied Sciences (DiSTA), via J.H. Dunant 3, 21100 Varese (Italy) +390332421439 a.sangion@hotmail.it http://www.qsar.it/

2.6.Date of model development and/or publication:

Developed in 2013, Published in 2014 [4]

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

[1]Cassani, S. et al. Daphnia and fish toxicity of (benzo)triazoles: Validated QSAR models,and interspecies quantitative activity–activity modelling, J.Haz. Mater. 2013, 258-259, 50-60. DOI: 10.1016/j.jhazmat.2013.04.025

[2]Yap, C.W. PaDEL-descriptor: an open source software to calculate molecular descriptors and fingerprints. 2011, J.Comput.Chem. 32, 1466-1474 DOI: 10.1002/jcc.21707

[3]Gramatica P., et al. QSARINS: A new software for the development, analysis and validation of QSAR MLR models, J. Comput. Chem. (Software News and Updates), 2013, 34 (24), 2121-2132. DOI: 10.1002/jcc.23361

[4]Gramatica P., et al. QSARINS-chem: Insubria datasets and new QSAR/QSPR models for environmental pollutants in QSARINS, J. Comput. Chem. (Software News and Updates), 2014, 35 (13), 1036-1044. DOI: 10.1002/jcc.23576

2.8.Availability of information about the model:

Non-proprietary. Defined algorithm, available in QSARINS [3,4]. Training and prediction sets are available in the attached sdf files of this QMRF (section 9) and in the QSARINS-Chem database [4].

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

No other information available

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Oncorhynchus mykiss

3.2.Endpoint:

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

3.3.Comment on endpoint:

A selected set of experimental LC_{50}(96h) data was taken from FOOTPRINT PPDB (Pesticide Properties DataBase) online database [5].

3.4.Endpoint units:

The median lethal concentrations are reported as the logarithm of the inverse molar concentration: log(1/LC50)

3.5.Dependent variable:

log (1/LC50) or pLC50

3.6.Experimental protocol:

OECD 203 test protocol

3.7.Endpoint data quality and variability:

The data classified as "verified data", "verified data used for regulatory purposes" and "unverified data from known source" were included in model development. The classification of "verified data",

"verified data used for regulatory purposes" and "unverified data from known source" was given directly by the FOOTPRINT PPDB database [5].

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:
QSAR - Multiple linear regression model (OLS - Ordinary Least Square)

4.2.Explicit algorithm:
Log 1/LC50 O.mykiss SOM Split model

OLS-MLR method. Model developed on a training set of 52 compounds

Log 1/LC50 O.mykiss Ordered response split model

OLS-MLR method. Model developed on a training set of 52 compounds

Log 1/LC50 O.mykiss FULL model

OLS-MLR method. Model developed on a training set of 75 compounds

SOM Split model equation: $pLC50 = 3.49 + 0.32\ VP\text{-}1 - 0.18\ nHBAcc - 1.23\ minHBd$

Ordered Response Split model equation: $pLC50: 3.48 + 0.32\ VP\text{-}1 - 0.18\ nHBAcc - 1.11\ minHBd$

Full model equation: $pLC50 = 3.62 + 0.30\ VP\text{-}1 - 0.17\ nHBAcc - 1.20\ minHBd$

The modeling descriptors, calculated in PaDEL-Descriptor 2.18, are:
VP-1, nHBAcc, minHBd. See section 4.3 for a more detailed description of the three descriptors.

4.3.Descriptors in the model:
[1]VP-1 dimensionless Valence path, order 1. It is related to molecular dimension and branching, and increasing values of this variable are related to an increase in the observed toxicity values. Additionally, being slightly correlated with LogP in the studied dataset, VP-1 also encodes for hydrophobic properties of molecules

[2]nHBAcc dimensionless Number of hydrogen bond acceptors (using CDK HBondAcceptorCountDescriptor algorithm)

[3]minHBd dimensionless Minimum E-States for (strong) Hydrogen Bond donors

4.4.Descriptor selection:
A total of 729 molecular descriptors of differing types (0D, 1D, 2D) were calculated in PaDEL-Descriptor 2.18 [2]. Constant and semi-constant values and descriptors found to be correlated pairwise were excluded in a pre-reduction step (one of any two descriptors with a correlation greater than 0.98 was removed to reduce redundant information), and a final set of 227 molecular descriptors were used as input variables for variable subset selection. The models were initially developed by the all-subset-procedure, and then GA was applied to obtain the final population of models (three variables). The optimized parameter used was Q2LOO (leave-one-out). The GA-VSS, by Ordinary Least Squares regression (OLS), included in QSARINS [3,4], was applied to select only the best

combination of descriptors from input pool: 3 modeling descriptors
selected from 227.

4.5. Algorithm and descriptor generation:

Multiple linear regression (Ordinary Least Square method) was applied to
generate the model.

Molecular descriptors were generated by PaDEL-Descriptor software [2].
The input files for descriptor calculation contain information on atom
and bond types, connectivity, partial charges and atomic spatial
coordinates, relative to the minimum energy conformation of the
molecule, and were firstly obtained by the semi empirical AM1 method
using the package HYPERCHEM 7.03. Then, these files were converted by
OpenBabel 2.3.2 into MDL-MOL format and used as input for the
calculation of descriptors in PaDEL-Descriptor. Any user can re-derives
the model calculating the molecular descriptors by PaDEL-Descriptor 2.18
software (recently included in QSARINS 2.2) and applying the given
equation (automatically done by QSARINS 2.2).

4.6. Software name and version for descriptor generation:

PaDEL-Descriptor

A software to calculate molecular descriptors and fingerprints, version 2.18
Yap Chun Wei, Department of Pharmacy, National University of Singapore.
http://padel.nus.edu.sg/software/padeldescriptor/index.html

HYPERCHEM

Software for molecular drawing and conformational energy optimization, version 7.03 (2002)
Phone: (352)371-7744
http://www.hyper.com/

OpenBabel

Open Babel: The Open Source Chemistry Toolbox. Used for conversion between HYPERCHEM
files (hin) and MDL-MOL files, version 2.3.2 (2012)
Contact not available
http://openbabel.org/wiki/Main_Page

4.7. Chemicals/Descriptors ratio:

Split by SOM model: 52 chemicals / 3 descriptors = 17.33
Split by Ordered response model: 52 chemicals / 3 descriptors= 17.33
Full model: 75 chemicals / 3 descriptors = 25

5. Defining the applicability domain - OECD Principle 3

5.1. Description of the applicability domain of the model:

The applicability domain of the model was verified by the leverage
approach and fixed thresholds has been used to define both structural
and response outliers (see section 5.4). The plot of leverages (hat
diagonals) versus standardised residuals, i.e. the Williams plot,
verified the presence of response outliers (i.e.compounds with

cross-validated standardized residuals greater than 2.5 standard deviation units) and chemicals very structurally influential in determining model parameters parameters (i.e. compounds with a leverage value (h) greater than 3p'/n (h*), where p' is the number of model variables plus one, and n is the number of the objects used to calculate the model).

For new compounds without experimental data, leverage can be used as a quantitative measure for evaluating the degree of extrapolation: for compounds with a high leverage value (h > h*), that are structural outliers, predictions should be considered less reliable. In QSARINS the Insubria graph allows to identify for which chemicals the predictions are inter- or extrapolated by the model.

Response and descriptor space:

Range of experimental pLC50 *O.mykiss* values: 1.92 / 6.7

Range of descriptor values: VP-1: 1.51 / 10; nHBAcc: 1 / 13; minHBd: 0 / 0.80.

5.2. Method used to assess the applicability domain:

As it has been stated in section 5.1, the structural applicability domain of the model was assessed by the leverage approach, providing a cut-off hat value (h*=0.160). HAT values are calculated as the diagonal elements of the HAT matrix:

$$H = X(X^T X)^{-1} X^T$$

The response applicability domain can be verified by the standardized residuals in cross-validation greater than 2.5 standard deviation units

5.3. Software name and version for applicability domain assessment:

QSARINS

Software for the development, analysis and validation of QSAR MLR models, version 1.2 (verified also with 2.2, 2015)

Prof. Paola Gramatica; paola.gramatica@uninsubria.it

http://www.qsar.it/

5.4. Limits of applicability:

SOM Split model domain: outliers for structure, hat>0.231 (h*): azimsulfuron (120162-55-2). Outliers for response, standardised residuals > 2.5 standard deviation units: fenchlorazole-ethyl (103112-35-2), fluroxypyr methylheptyl ester (81406-77-3). **Ordered Response Split model domain**: outliers for structure, hat>0.231 (h*): azimsulfuron (120162-55-2). Outliers for response, standardised residuals > 2.5 standard deviation units: fenchlorazole-ethyl (103112-35-2), fluroxypyr methylheptyl ester (81406-77-3), mepanipyrim (110235-47-7). **FULL model domain**: outliers for structure, hat>0.160 (h*): no. Outliers for response, standardised residuals > 2.5 standard deviation units: fenchlorazole-ethyl (103112-35-2), fluroxypyr methylheptyl ester (81406-77-3), mepanipyrim (110235-47-7).

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: Yes

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:

To verify the predictive capability of the proposed models, the whole dataset (n=75) was split, before model development, into training sets used for model development and prediction sets used later for external validation. Two different splitting techniques were applied: by structural similarity (Self Organizing Maps, SOM, n training= 52) and by ordered response (n training=52). In the SOM splitting, training and prediction set are structurally balanced, being the splitting based on the structural similarity analysis (performed with Kohonen artificial neural network, K-ANN or SOM method included in KOALA software [11]). In the Ordered response splitting chemicals have been ordered according to their increasing toxicity and one out of every three chemicals has been assigned to the prediction set (always including the most and the least persistent compound in the training set, i.e. the lowest and the highest pLC50). This splitting guarantees that the training set covers the entire range of the modeled response.

6.6.Pre-processing of data before modelling:

Transformation of LC50 (mg/L) into Log1/LC50 (mol/L)

6.7.Statistics for goodness-of-fit:

SOM Split model:

R^2= 0.76; CCCtr [6,7]=0.86; RMSE= 0.54

Ordered response split model:

R^2= 0.76; CCCtr=0.87; RMSE= 0.52

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

SOM Split model:

Q^2_{LOO}= 0.71; CCCcv=0.84; RMSEcv= 0.59

Ordered response Split model:

Q^2_{LOO}= 0.72; CCCcv=0.84; RMSEcv= 0.56

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

SOM Split model:

$Q^2_{LMO_{30\%}}$= 0.73.

Ordered response split model:

$Q^2LMO_{30\%}= 0.73$.

Values of Q^2LMO (average value for 2000 iterations, with 30% of chemicals put out at every iteration) that are high and close to the original Q^2LOO, mean that the model is robust and stable.

6.10. Robustness - Statistics obtained by Y-scrambling:

SOM Split model:

$R^2y\text{-sc}= 0.06$

Ordered response split model:

$R^2y\text{-sc}= 0.06$.

Low value of scrambled R^2 (average value for 2000 iterations, in where the Y-responses are randomly scrambled), means that the model is not given by chance-correlation.

6.11. Robustness - Statistics obtained by bootstrap:

No information available (since we have calculated Q^2LMO)

6.12. Robustness - Statistics obtained by other methods:

No information available

7. External validation - OECD Principle 4

7.1. Availability of the external validation set:

Yes

7.2. Available information for the external validation set:

CAS RN: Yes

Chemical Name: Yes

Smiles: Yes

Formula: Yes

INChI: No

MOL file: No

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

All

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

All

7.5. Other information about the external validation set:

To verify the predictive capability of the proposed models, the dataset (n=75) was split, before model development, into a training set used for model development and a prediction set used later for external validation. Two different splitting techniques were applied: by structural similarity (SOM) and by sorted response (n external validation set =23 in both cases); the range of pLC50 are: 2.85 / 5.99 for SOM prediction set, 2.85 / 6.26 for Ordered Response prediction set.

7.6. Experimental design of test set:

In the case of split by sorted response model, chemicals were ordered according to their increasing activity, and one out of every three chemicals was put in the prediction set (always including the most and the least active compounds in the training set). The splitting based on structural similarity (SOM) takes advantages of the clustering

capabilities of Kohonen Artifical Neural Network, allowing the selection
of a structurally meaningful training set and an equally representative
prediction set.Through its clustering capabilities, SOM ensures that both sets are
homogeneously distributed within the entire area of the descriptor space;
in this case the chemicals in both sets, selected to maximize the coverage
of the descriptor space (i.e. representativity), represent the structural
variety of the studied data set in a balanced way. The selected training
chemicals are those with the minimal distance from the centroid of each
cell in the top map. In this case, the representative points of the
prediction set are close (in the same cell of the top map) to
representative points of the training set in the multidimensional
structural descriptor

7.7.Predictivity - Statistics obtained by external validation:

SOM Split model:

Q^2extF1 [8]= 0.76; Q^2extF2 [9]= 0.75; Q^2extF3
[10]= 0.83; CCCex=0.88; RMSE= 0.46

Ordered response split model:

Q^2extF1= 0.74; Q^2extF2= 0.74; Q^2extF3=
0.77; CCCex=0.86; RMSE= 0.51

The high values of external $Q^2$and concordance correlation
coefficient-CCC (threshold for accepting the external Q^2F1-F2-F3 is 0.70, threshold for CCC is 0.85,
[7]), show that the
proposed model is predictive, when applied to chemicals never seen
during the model development (prediction sets).

7.8.Predictivity - Assessment of the external validation set:

The splitting methodology based on similarity analysis and by Ordered
response allowed for the selection of meaningful training sets and
representative prediction sets.
Training and prediction sets are balanced according to both structure
and response. In particular, for response the range of pLC50 values are
[1.92 / 6.7][2.85 / 5.99] and [1.92 / 5.99][2.85 / 6.7] respectively for
SOM and Ordered Response training and prediction sets.
As much as concern structural representativity, the range of descriptors
values is:
VP-1: SOM Split training set (1.51 / 10), prediction set (2.74 / 9.61);
Ordered response split training set (1.51 / 10), prediction set (2.74 /
9.61)
nHBAcc: SOM Split training set (3 / 12), prediction set (1 / 13);
Ordered response split training set (2 / 13), prediction set (1 / 10)
minHBd: SOM Split training set (0 / 0.78), prediction set (0 / 0.80);
Ordered response split training set (0 / 0.80), prediction set (0 / 0.78)

The applicability domain of the model on the prediction set has
been verified by the Williams plot: in SOM splitting, only one compound
of the prediction set is recognised as outlier for structure (no
outliers for response); in the ordered by response splitting, only 1

chemicals of the prediction set is outlier for response (no outliers for structure). These results are a proof of the good applicability domain of the proposed model.

7.9. Comments on the external validation of the model:

The full (N Training set=75) model was then applied to a further Evaluation Set (for an additional external validation) composed of 18 (B)TAZs, became available in the literature. The following parameters are related to this further external validation:

RMSEex= 0.51; CCCex= 0.86; Q^2extF1=0.78; Q^2extF2=0.78; Q^2extF3=0.77.

Given the good results, the proposed model is actual predictive also for the new 18 chemicals available in the further Evaluation Set.

8. Providing a mechanistic interpretation - OECD Principle 5

8.1. Mechanistic basis of the model:

The model was developed by statistical approach. No mechanistic basis for this physico-chemical property was set a priori, but a mechanistic interpretation of molecular descriptors was provided a posteriori (see 8.2).

8.2. A priori or a posteriori mechanistic interpretation:

A posteriori mechanistic interpreation:

The PaDEL-descriptor full model equation, included in QSARINS [3,4] is:**pLC50**= 3.62 + 0.30 VP-1 – 0.17 nHBAcc – 1.20 minHBd

VP-1 is Valence path order 1, which it is related to molecular dimension and branching, and increasing values of this variable are related to an increase in the observed toxicity values. Additionally, being slightly correlated with LogP in the studied dataset, VP-1 also encodes for hydrophobic properties of molecules; generally high values of this descriptor are connected to high/medium toxicity (correlation with pLC50 0.64). nHBAcc is Number of hydrogen bond acceptors (using CDK HBondAcceptorCountDescriptor algorithm), a constitutional descriptor that describes capability of chemicals in participating in H-bonding, and minHBd is Minimum E-States for (strong) Hydrogen Bond donors; the last two descriptors are negatively correlated with the toxicity in fish.

8.3. Other information about the mechanistic interpretation:

no other information available

9. Miscellaneous information

9.1. Comments:

Given the good results of the external validation, this model has a good applicability domain and therefore unsuccessful applications are probably very reduced. Anyhow, the check of outliers by the Williams plot and the Insubria graph for chemicals without experimental data (see

section 5.1) will allow to verify the model applicability.

To predict pLC50 for new (Benzo-)Triazoles without experimental data, it is suggested to apply the equation of the **Full Model**, developed on all the available chemicals (N Training=75).

The full model was then applied to a further Evaluation Set (for an additional external validation) composed of 18 (B)TAZs, became available in the literature. The equation (reported also in section 4.2) and the statistical parameters of the full model, also when applied to the EV, are the following:

pLC50= 3.62 + 0.30 VP-1 - 0.17 nHBAcc - 1.20 minHBd

N Training set= 75 (*full model applied to the Evaluation Set-EV, N=18);
R^2= 0.76; Q^2LOO = 0.73; Q^2LMO$_{30\%}$= 0.73; CCC = 0.86; CCCcv = 0.85; RMSE= 0.51; RMSEcv = 0.54; RMSEex*=
0.51; CCCex*= 0.86; Q^2extF1*=0.78; Q^2extF2*=0.78; Q^2extF3*=0.77.

Given the good results (see parameters above), the proposed model is actual predictive also for the new 18 chemicals available in the further Evaluation Set.

9.2.Bibliography:

[1]S.Cassani, S. Kovarich, E.Papa, P.P. Roy, L.v.d.Wal, P. Gramatica. Daphnia and fish toxicity of (benzo)triazoles: Validated QSAR models,and interspecies quantitative activity–activity modelling, J.Haz. Mater. 2013, 258-259, 50-60. DOI: 10.1016/j.jhazmat.2013.04.025

[2]Yap, C.W. PaDEL-descriptor: an open source software to calculate molecular descriptors and fingerprints. J.Comput.Chem. 2011, 32, 1466-1474. DOI: 10.1002/jcc.21707

[3]Gramatica P., et al. QSARINS: A new software for the development, analysis and validation of QSAR MLR models, J. Comput. Chem. (Software News and Updates), 2013, 34 (24), 2121-2132. DOI: 10.1002/jcc.23361

[4]Gramatica P., et al. QSARINS-chem: Insubria datasets and new QSAR/QSPR models for environmental pollutants in QSARINS, J. Comput. Chem. (Software News and Updates), 2014, 35 (13), 1036-1044. DOI: 10.1002/jcc.23576

[5]FOOTPRINT PPDB (Pesticide Properties DataBase), 2009 http://sitem.herts.ac.uk/aeru/ppdb/en/ (accessed 30, Jan 2015)

[6]Chirico N. and Gramatica P., Real external predictivity of QSAR models: how to evaluate it? Comparison of different validation criteria and proposal of using the concordance correlation coefficient, J. Chem. Inf. Model. 2011, 51, 2320-2335. DOI: 10.1021/ci200211n

[7]Chirico N. and Gramatica P., Real External Predictivity of QSAR Models. Part 2. New Intercomparable Thresholds for Different Validation Criteria and the Need for Scatter Plot Inspection, J. Chem. Inf. Model. 2012, 52, 2044–2058 DOI: 10.1021/ci300084j

[8]Shi L.M. et al. QSAR Models Using a Large Diverse Set of Estrogens, J. Chem. Inf. Comput. Sci. 41 (2001) 186–195. DOI: 10.1021/ci000066d

[9]Schuurman G. et al. External Validation and Prediction Employing the Predictive Squared Correlation Coefficient - Test Set Activity Mean vs Training Set Activity Mean, J. Chem. Inf. Model. 48 (2008) 2140-2145. DOI: 10.1021/ci800253u

[10]Consonni V. et al. Comments on the Definition of the Q2 Parameter for QSAR Validation, J. Chem. Inf. Model. 49 (2009) 1669-1678 DOI: 10.1021/ci900115y

[11]KOALA Rel. 1.0 for Windows, 2001. R.Todeschini, V. Consonni, A. Mauri, Milan, Italy url not available

9.3.Supporting information:

Training set(s)

BTAZ O. mykiss tox_ord resp_train.sdf	file:///C:\Documents and Settings\lab-qsar\Desktop\PaDEL QMRF da mandare 2015\BTAZ tox\FIsh\BTAZ O. mykiss tox_ord resp_train.sdf
BTAZ O. mykiss tox_SOM_train.sdf	file:///C:\Documents and Settings\lab-qsar\Desktop\PaDEL QMRF da mandare 2015\BTAZ tox\FIsh\BTAZ O. mykiss tox_SOM_train.sdf

Test set(s)

BTAZ O. mykiss tox_ord resp_pred.sdf	file:///C:\Documents and Settings\lab-qsar\Desktop\PaDEL QMRF da mandare 2015\BTAZ tox\FIsh\BTAZ O. mykiss tox_ord resp_pred.sdf
BTAZ O. mykiss tox_SOM_pred.sdf	file:///C:\Documents and Settings\lab-qsar\Desktop\PaDEL QMRF da mandare 2015\BTAZ tox\FIsh\BTAZ O. mykiss tox_SOM_pred.sdf

Supporting information

BTAZ O. mykiss tox_FULL.sdf	file:///C:\Documents and Settings\lab-qsar\Desktop\PaDEL QMRF da mandare 2015\BTAZ tox\FIsh\BTAZ O. mykiss tox_FULL.sdf

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