	QMRF identifier (JRC Inventory): **Q17-416-0041**
	QMRF Title: **BIOVIA toxicity prediction model – prenatal developmental toxicity**
	Printing Date: **Dec 11, 2019**

1.QSAR identifier

1.1.QSAR identifier (title):

BIOVIA toxicity prediction model – prenatal developmental toxicity

1.2.Other related models:

None

1.3.Software coding the model:

BIOVIA Discovery Studio v4.5

Optimize your drug discovery process with a flexible application that delivers predictive science to its required depth.

Dassault Systèmes, BIOVIA Corp., 5005 Wateridge Vista Drive, San Diego, CA92121, USA http://www.3dsbiovia.com

2.General information

2.1.Date of QMRF:

7/5/2015

2.2.QMRF author(s) and contact details:

Deqiang Zhang Dassault Systemes, BIOVIA Corp. 5005 Wateridge Vista Drive, San Diego, CA 92121, USA Deqiang.Zhang@3ds.com http://www.3dsbiovia.com

2.3.Date of QMRF update(s):

N/A

2.4.QMRF update(s):

N/A

2.5.Model developer(s) and contact details:

Deqiang Zhang Dassault Systemes, BIOVIA Corp. 5005 Wateridge Vista Drive, San Diego, CA 92121, USA Deqiang.Zhang@3ds.com http://www.3dsbiovia.com

2.6.Date of model development and/or publication:

2015

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

BIOVIA Discovery Studio v4.5 http://www.3dsbiovia.com/products/discovery-studio/

2.8.Availability of information about the model:

The model is proprietary (available as a commericcial product), but the algorithm is publically available. The training set is also proprietary, however, it is embedded with the model and can be retrieved with similarity search when a prediction is conducted. No external test is conducted except cross-validation.

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

None

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Rat

3.2.Endpoint:

4.Human Health Effects 4.16.In vivo pre-natal-developmental toxicity

3.3.Comment on endpoint:

The Developmental Toxicity Potential (DTP) model was developed from 374 open-literature references. The model includes only rat oral data. Two types of studies were removed from the database prior to further evaluation: single-dose studies in which developmental as well as maternal toxicity were observed at that dose, and studies in which neither developmental nor maternal toxicity was observed at the highest dose.

For the remaining studies, the following scoring scheme was adopted:

Score 1: No developmental toxicity (DT) even at maternotoxic (MT) doses;

Score 2: Strict concordance between DT and MT, i.e. no DT nor MT at one dose, and both DT and MT at a higher dose;

Score 3: DT at the dose preceding MT;

Score 4: DT at least 2 doses below that which produced MT.

Scores 2,3 and 4 were combined into one group, so that the resultant model distinguishes between no evidence of DTP vs. any evidence of DTP.

3.4.Endpoint units:

Dimensionless - Yes/No Binary Classification

3.5.Dependent variable:

Classification as toxic or non-toxic

3.6.Experimental protocol:

The test protocol is outlined in Health Effects Test Guidelines: OPPTS 870.3550 Reproduction/Developmental Toxicity Screening Test [EPA 712–C–00–367], available online at

3.7.Endpoint data quality and variability:

All the data were collected from open literature with the original reference identified with each compound.

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

QSAR model derived from Bayesian binary classification

4.2.Explicit algorithm:

Bayesian Classification

A modified Bayesian learning method is used. The algorithm is described in Xia X, Maliski EG, Gallant P & Rogers D(2004). Journal of Medicinal Chemistry. 47(18) 4463- 4470

Pcorr(Active|F) = (A + P(Active)*K)/(B + K).

(For K = 1/P(Active), this is the Laplacian correction.)

4.3.Descriptors in the model:

[1]ALogP unitless The calculated partition-coefficient of a compound between 1-octanol and water

[2]Molecular_Weight gram/mole The calculated molecular weight by summing the average atomic weight of all the atoms in the molecule.

[3]Num_H_Donors unitless Number of hydrogen bond donors.

[4]Num_H_Acceptors unitless Number of hydrogen bond acceptors in the molecule.

[5]Num_RotatableBonds unitless Number of rotatable bonds in the molecule.

[6]Molecular_FractionalPolarSurfaceArea unitless The fraction of polar surface area over the total molecular surface area.

[7]SCFP_6 unitless Extended-connectivity SYBYL atom type fingerprint with a maximum length of 6 bonds

4.4.Descriptor selection:

A pool of most commonly used descriptors (ALogP, Molecule_Weight, Num_H_Donors, Num_H_Acceptors, Molecular_FractionPolarSurfaceArea, ECFP_2, ECFP_4, ECFP_6, ECFP_8, ECFP_10, ECFP_12, FCFP_2, FCFP_4, FCFP_6, FCFP_8, FCFP_10, FCFP_12, SCFP_2, SCFP_4, SCFP_6, SCFP_8, SCFP_10, SCFP_12) were selected randomly to build models. The model with the best leave-one-out cross-validated ROC score is selected to build the final model. In addition, Bayesian model has a built-in mechanism to select the most statitstically-significant descriptors.

4.5.Algorithm and descriptor generation:

(1) The ALogP is the Ghose/Crippen group-contribution estimate for LogP, where P is the relative solubility of a compound in octanol versus water. See Ghose, A.K., Viswanadhan, V.N., and Wendoloski, J.J., "Prediction of Hydrophobic (Lipophilic) Properties of Small Organic Molecules Using
Fragment Methods: An Analysis of AlogP and CLogP Methods." J. Phys. Chem. A, 1998, 102, 3762-3772.

(2) Molecular weight is calculated using the atomic weights of the individual atoms in the molecule.

(3) Hydrogen bond acceptors are defined as heteroatoms (O, N, S, or P) with one or more lone pairs, excluding atoms with positive formal charges, amide and pyrrole-type nitrogens, and aromatic oxygen and sulfur atoms in heterocyclic rings.

(4) Hydrogen bond donors are defined as heteroatoms (O, N, S, or P) with one or more attached hydrogen atoms.

(5) Molecular_FractionPolarSurfaceArea is calculated from the polar surface area and total surface area using a 2D approximation to each molecule.

(6) The fingerprint generation method is based on one of the original algorithms in computational organic chemistry called the Morgan algorithm. The goal of the Morgan algorithm is to assign a unique identity to each atom in a molecule so that a molecule can be described in a way that is invariant to the original numbering of atoms. The algorithm has two parts: the assignment of an initial code to each atom, and an iterative part in which each atom code is updated to reflect the codes of each atom's neighbors.

SCFP_8 is calculated by first assigning atom types (SCFP_0) using SYBYL atom types, and an n iterative process is used to generate features that represent each atom in progressively larger structural neighborhoods. After each iteration, the new feature codes for the atoms are added to

the set of features from all previous steps. The process completes when the desired size is reached and the set of all features is returned as the fingerprint.

4.6.Software name and version for descriptor generation:

Dassult Systemes BIOVIA Pipeline Pilot Server

Built on the BIOVIA Foundation, Pipeline Pilot enables scientists to rapidly create, test and publish scientific services that automate the process of accessing, analyzing and reporting scientific data, either for the scientist's personal use or for sharing across the scientific community. Using Pipeline Pilot, scientist, researchers, engineers, and analysts with little or no software development experience can create scientific protocols that can be executed through a variety of interfaces including Accelrys Web Port, other Accelrys solutions such as Accelrys Electronic Lab Notebook, Isentris, Chemical Registration and third-party applications such as Microsoft SharePoint or customer-developed applications. These protocols aggregate and provide immediate access to volumes of disparate research data locked in silos. They automate the scientific analysis of the data and enable researchers to rapidly explore, visualize and report results

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4.7.Chemicals/Descriptors ratio:

Number of chemicals = 270

Number of descriptors = 7

Chemicals/Descriptors = 38.8

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

The applicability domain of the model is defined by the range of descriptors of training set chemicals. The applicability domain is only a qualititive measure on how reliable the prediction is. There is no quantative measure on how reliable the prediction is.

5.2.Method used to assess the applicability domain:

If a continuous descriptor is out of range of the training set, a warning is issued for the input compound. For the fingerprint descriptors, if a new feature not seen in the training set is found, a warning message is issued for that feature.

5.3.Software name and version for applicability domain assessment:

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Built on the BIOVIA Foundation, Pipeline Pilot enables scientists to rapidly create, test and publish scientific services that automate the process of accessing, analyzing and reporting scientific data, either for the scientist's personal use or for sharing across the scientific community. Using Pipeline Pilot, scientist, researchers, engineers, and analysts with little or no software development experience can create scientific protocols that can be executed through a variety of interfaces including Accelrys Web Port, other Accelrys solutions such as Accelrys Electronic Lab Notebook, Isentris, Chemical Registration and third-party applications such as Microsoft SharePoint or

customer-developed applications. These protocols aggregate and provide immediate access to volumes of disparate research data locked in silos. They automate the scientific analysis of the data and enable researchers to rapidly explore, visualize and report results.
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5.4.Limits of applicability:

Property Min Max Mean Std. Dev.
ALogP -7.685 8.435 2.1067 2.23
Molecular_Weight 32.042 973.67 288.22 156.83
Num_H_Donors 0 9 1.4481 1.5856
Num_H_Acceptors 0 16 3.9037 3.0753
Num_RotatableBonds 0 19 3.9704 3.5118
Molecular_FractionalPolarSurfaceArea 0 0.894 0.2458 0.15375

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: Yes

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:

The data used to train the model consisted of 270 samples. 142 of them are in the positive category. The training set is proprietary, however, it is emmbedded with the model and can be retrieved with similarity search when a prediction is conducted.

6.6.Pre-processing of data before modelling:

None

6.7.Statistics for goodness-of-fit:

N/A

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

ROC score=0.750 (LOO)
True Positive = 95
False Negative = 47
False Positive = 33

True Negative = 95

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

ROC score = 0.607 (Leave 10% out)

Sensitivity = 0.866

Specificity = 0.906

Concordance = 0.885

6.10.Robustness - Statistics obtained by Y-scrambling:

N/A

6.11.Robustness - Statistics obtained by bootstrap:

N/A

6.12.Robustness - Statistics obtained by other methods:

N/A

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:

Due to the small size of the available data, no data were reserved for external validation purpose.

7.6.Experimental design of test set:

N/A

7.7.Predictivity - Statistics obtained by external validation:

N/A

7.8.Predictivity - Assessment of the external validation set:

N/A

7.9.Comments on the external validation of the model:

N/A

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

Features contributing the most from SCFP_6 are included in attachment.

8.2.A priori or a posteriori mechanistic interpretation:

posteriori: these features are selected purely based on their Bayesian score

8.3.Other information about the mechanistic interpretation:

N/A

9.Miscellaneous information

9.1.Comments:

The model is extensible, i.e., it can be extended by feeding new
training data to create an improved model.

9.2.Bibliography:

Xia X, Maliski EG, Gallant P & Rogers D(2004). Journal of Medicinal Chemistry. 47(18) 4463- 4470
http://pubs.acs.org/doi/full/10.1021/jm0303195

9.3.Supporting information:

qmrf508_qmrf450_dtp 270.sdf	http://qsardb.jrc.ec.europa.eu/qmrf/protocol/Q17-416-0041/attachment/A1101
qmrf508_qmrf450_DTP-features.png	http://qsardb.jrc.ec.europa.eu/qmrf/protocol/Q17-416-0041/attachment/A1102

Test set(s)Supporting information

10.Summary (JRC QSAR Model Database)

10.1.QMRF number:

Q17-416-0041

10.2.Publication date:

2017-09-27

10.3.Keywords:

rat;prenatal;developmental toxicity;BIOVIA Discovery Studio;

10.4.Comments:

old# Q50-54-55-508