

	QMRF identifier (JRC Inventory): Q17-471-0057
	QMRF Title: Lazar model for Salmonella typhimurium mutagenicity
	Printing Date: Dec 11, 2019

1. QSAR identifier

1.1. QSAR identifier (title):

Lazar model for Salmonella typhimurium mutagenicity

1.2. Other related models:

1.3. Software coding the model:

lazar

lazar Lazy Structure- Activity Relationships. See

<https://github.com/opentox/lazar/tree/b2b9cc5d14d10a62025486c5b3abbbbeb06bf0ec6>

info@in-silico.ch

<https://lazar.in-silico.ch>

2. General information

2.1. Date of QMRF:

21 September 2017

2.2. QMRF author(s) and contact details:

Christoph Helma in silico toxicology gmbh Rastatterstr. 41, CH-4057 Basel info@in-silico.ch www.in-silico.ch

2.3. Date of QMRF update(s):

2.4. QMRF update(s):

2.5. Model developer(s) and contact details:

Christoph Helma in silico toxicology gmbh Rastatterstr. 41, CH-4057 Basel info@in-silico.ch www.in-silico.ch

2.6. Date of model development and/or publication:

2017

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

[1] Maunz A, Gütlein M, Rautenberg M, Vorgrimmler D, Gebele D and Helma C (2013) lazarus: a modular predictive toxicology framework. Front. Pharmacol. 4:38

<http://dx.doi.org/10.3389/fphar.2013.00038>

[2] Helma C, Gebele D, Rautenberg M (2017) Lazar, software available at <https://lazar.in-silico.ch>, source code available at

<https://github.com/opentox/lazar/tree/b2b9cc5d14d10a62025486c5b3abbbbeb06bf0ec6>

<https://doi.org/10.5281/zenodo.215483>

2.8. Availability of information about the model:

Prediction interface and validation results available at <https://lazar.in-silico.ch>

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

3. Defining the endpoint - OECD Principle 1

3.1. Species:

Salmonella typhimurium

3.2. Endpoint:

3.3. Comment on endpoint:

3.4. Endpoint units:

3.5. Dependent variable:

Mutagenicity

3.6. Experimental protocol:

3.7. Endpoint data quality and variability:

4. Defining the algorithm - OECD Principle 2

4.1. Type of model:

Classification

4.2. Explicit algorithm:

modified k-nearest neighbour classification (weighted majority vote), see
<https://github.com/opentox/lazar/tree/b2b9cc5d14d10a62025486c5b3abbbbeb06bf0ec6>

4.3. Descriptors in the model:

MP2D fingerprints (Bender et al. 2004)

4.4. Descriptor selection:

none

4.5. Algorithm and descriptor generation:

lazar

4.6. Software name and version for descriptor generation:

lazar, submitted version:
<https://github.com/opentox/lazar/tree/b2b9cc5d14d10a62025486c5b3abbbbeb06bf0ec6>

4.7. Chemicals/Descriptors ratio:

not applicable (classification based on activities of neighbours,
descriptors are used for similarity calculation)

5. Defining the applicability domain - OECD Principle 3

5.1. Description of the applicability domain of the model:

No predictions are made for query compounds without similar structures in the training data. Similarity is determined as the Tanimoto coefficient of Molprint 2D fingerprints with a threshold of 0.1. Predictions based on a low number and/or very dissimilar neighbours or on neighbours with conflicting experimental measurements should be treated with caution.

5.2. Method used to assess the applicability domain:

Number and similarity of training set compounds (part of the main lazarus algorithm): At least 2 compounds with similarity > 0.1 are required for a prediction.

5.3. Software name and version for applicability domain assessment:

lazar, submitted version:
<https://github.com/opentox/lazar/tree/b2b9cc5d14d10a62025486c5b3abbbbeb06bf0ec6>

5.4. Limits of applicability:

Compounds without similar substances in the training dataset

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: Yes

MOL file: Yes

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

No

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

Yes

6.5.Other information about the training set:

Original data from: <http://cheminformatics.org/datasets/>

6.6.Pre-processing of data before modelling:

none

6.7.Statistics for goodness-of-fit:

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

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

3 independent 10-fold crossvalidations:

Num folds: 10

Num instances: 4069

Num unpredicted: 49

Accuracy: 0.761

Weighted accuracy: 0.809

True positive rate: 0.742

True negative rate: 0.801

Positive predictive value: 0.886

Negative predictive value: 0.6

Num folds: 10

Num instances: 4069

Num unpredicted: 50

Accuracy: 0.758

Weighted accuracy: 0.807True positive rate: 0.74True negative rate: 0.796

Positive predictive value: 0.883

Negative predictive value: 0.596

Num folds: 10Num instances: 4069

Num unpredicted: 47

Accuracy: 0.758Weighted accuracy: 0.808

True positive rate: 0.739True negative rate: 0.798

Positive predictive value: 0.884Negative predictive value: 0.594

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:

Chemical Name:

Smiles:

Formula:

INChI:

MOL file:

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

Unknown

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

Unknown

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:

Compounds with similar structures (neighbours) are assumed to have similar activities as the query compound.

8.2. A priori or a posteriori mechanistic interpretation:

A posteriori for individual predictions

8.3. Other information about the mechanistic interpretation:

Hypothesis about biochemical mechanisms can be derived from individual predictions by inspecting neighbours and relevant descriptors.

Neighbors are compounds that are similar in respect to a certain endpoint and it is likely that compounds with high similarity act by similar mechanisms as the query compound. Links at the webinterface prove an easy access to additional experimental data and literature citations for the neighbours and the query structure.

Please note that lazar predictions are based on neighbours. Descriptors are only used for the calculation of similarities.

9. Miscellaneous information

9.1. Comments:

Public model interface: <https://lazar.in-silico.ch>

Source code: <https://github.com/opentox/lazar/tree/b2b9cc5d14d10a62025486c5b3abbbbeb06bf0ec6>

Docker image: <https://hub.docker.com/r/insilicotox/lazar/>

9.2. Bibliography:

- [1]Helma C, Gebele D, Rautenberg M (2017) Lazar, software available at <https://lazar.in-silico.ch>,source code available at <https://github.com/opentox/lazar/tree/b2b9cc5d14d10a62025486c5b3abbbbeb06bf0ec6>
<https://doi.org/10.5281/zenodo.215483>
- [2]Helma C, Rautenberg M and Gebele D (2017) Nano-Lazar: Read across Predictions for Nanoparticle Toxicities with Calculated and Measured Properties. *Front. Pharmacol.* 8:377
<https://dx.doi.org/10.3389%2Ffphar.2017.00377>
- [3]Lo Piparo et al (2014), Automated and reproducible read-across like models for predicting carcinogenic potency. *Regulatory Toxicology and Pharmacology*.70 (1) 370-378
<https://doi.org/10.1016/j.yrtph.2014.07.010>
- [4]Maunz A and Helma C (2008). Prediction of chemical toxicity with local support vector regression and activity-specific kernels. *SAR and QSAR in Environmental Research* 19 (5-6) 413-431
<http://dx.doi.org/10.1080/10629360802358430>
- [5]Helma C (2006) Lazy structure-activity relationships (lazar) for the prediction of rodent carcinogenicity and Salmonella mutagenicity. *Molecular Diversity* 10 (2), 147–158
<http://dx.doi.org/10.1007/s11030-005-9001-5>
- [6]Bender et al (2004) Molecular similarity searching using atom environments, information-based feature selection, and a nave bayesian classifier. *J. Chem. Inf. Comput. Sci.* 44 (1) 170–178
<https://doi.org/10.1021/ci034207y>

9.3.Supporting information:

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

10.Summary (JRC QSAR Model Database)

10.1.QMRF number:

Q17-471-0057

10.2.Publication date:

2017-10-10

10.3.Keywords:

Salmonella typhimurium;Ames;reverse mutation;mutagenicity;Lazar;

10.4.Comments:

To be entered by JRC