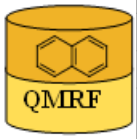	*QMRF identifier (ECB Inventory):*Q2-10-1-43 *QMRF Title:* QSAR Model for Eye irritation (Draize test) *Printing Date:*Sep 8, 2009	

1.QSAR identifier

1.1.QSAR identifier (title):

QSAR Model for Eye irritation (Draize test)

1.2.Other related models:

Published in TOXICOLOGICAL SCIENCES 76, 384-391 (2003)

1.3.Software coding the model:

QSARModel 3.3.8 Turu 2, Tartu, 51014, Estonia http://www.molcode.com

2.General information

2.1.Date of QMRF:

30.01.2009

2.2.QMRF author(s) and contact details:

Molcode model development team Molcode Ltd Turu 2, Tartu, 51014, Estonia models@molcode.com http://www.molcode.com

2.3.Date of QMRF update(s):

-

2.4.QMRF update(s):

-

2.5.Model developer(s) and contact details:

Molcode model development team Molcode Ltd Molcode Ltd Turu 2, Tartu, 51014, Estonia models@molcode.com http://www.molcode.com

2.6.Date of model development and/or publication:

30.01.2009

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

[1]Correlation of blood-brain penetration and human serum albumin binding with theoretical descriptors, M. Karelson, D. Dobchev, T. Tamm, I. Tulp, J. Jänes, K. Tämm, A. Lomaka, D. Savchenko, G. Karelson, ARKIVOC 16, 38-60 (2008)

[2]QSAR study of pharmacological permeabilities Mati Karelson, Gunnar Karelson, Tarmo Tamm, Indrek Tulp, Jaak Jänes, Kaido Tämm, Andre Lomaka, Deniss Savchenko, and Dimitar Dobchev, 2,2009, pp. 218 - 238

2.8.Availability of information about the model:

All information in full detail is available.

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

No other QMRF available for the same model.

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Rabbit

3.2.Endpoint:

4.Human health effects 4.9.Eye irritation/corrosion

3.3.Comment on endpoint:

Draize rabbit eye test scores, as modified maximum average score (MMAS), for 68 pure bulk liquids were adjusted by the liquid-saturated vapor pressure P°. These 68 adjusted scores, as log (MMAS/P°), were shown to be completely equivalent to eye irritation thresholds (EIT), expressed as log (1/EIT), for 23 compounds in humans.

Weighted tissue damage after 21 days exposure.

3.4.Endpoint units:

Modified maximum average score (MMAS) divided by the molarity of the pure liquid -

3.5.Dependent variable:

log (MMAS/P°) and log (1/EIT) instead of MMAS/P° and EIT

3.6.Experimental protocol:

Draize rabbit eye test. The in vivo rabbit eye irritation/corrosion data have been generated since 1981 in studies carried out according to OECD Test Guideline 405 (EU B.5) and following the principles of Good Laboratory Practice. By Draize in vivo rabbit-eye test (Draize et al., 1944), a 0.1-ml (or weight equivalent) sample of test substance is placed into the eye. Eye irritation is defined as production of changes in the eye, which are fully reversible within 21 days of application, whereas eye corrosion is defined as production of tissue damage in the eye, or serious physical decay of vision, which is not fully reversible within 21 days of application. The tissue grades are combined into a weighted score; the highest average score across test animals is termed the maximum average score (MAS). The modified Draize scores were defined as modified maximum average score (MMAS) divided by the molarity of the pure liquid; the latter is given by 1000 times the density of the pure liquid divided by the liquid molecular weight. The MMAS refer to the effect of pure bulk liquids, whereas the EIT (in ppm) are established from the effect of the vapor of liquids at some particular partial pressure. The MMAS data were selected from European Center for Ecotoxicology and Toxicology of Chemicals databank (ECETOC, 1998).

References:

ECETOC manual No. 48(2) (1998). Eye Irritation Reference Chemicals Data Bank, 2nd ed. ECETOC, Brussels.

The EIT data were selected from the article "Quantification of Chemical Vapors in Chemosensory Research" published by J. Enrique Cometto-Muñiz, William S. Cain and Michael H. Abraham in the journal "Chemical senses" 28: 467–477, 2003.

3.7.Endpoint data quality and variability:

Experimental data from different sources has been validated as consistent (ref. TOXICOLOGICAL SCIENCES 76, 384-391 (2003))

Statistics:

-the experimental results have been obtained using Draize test scores for 68 compounds (several sources but highly standardized procedure) and EIT (Eye Irritation Threshold) for 23 compounds.

The Draize test scores and EIT can be compared as

(log(MMAS/P0)=log(1/EIT) +m'').
max value: 2.37
min value: -5.24
standard deviation: 1.538
skewness: 0.886

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

2D and 3D regression-based QSAR Multilinear regression model based on 3-D quantum chemical descriptors.

4.2.Explicit algorithm:

multilinear regression QSAR
log(MMAS/P0) = 0.005 * Gravitation index (all bonds) (AM1) + 6.816 * HASA-1/TMSA (AM1) - 3.586 * Lowest e-e repulsion (1-center) (AM1) - 30.864* Max nucleophilic reactivity index (AM1) for C atoms + 2.822

4.3.Descriptors in the model:

[1][1] Gravitation index (all bonds)(AM1) amu2/Å2 sum over masses of all bonded atoms divided by squared bond lengths, based on AM1 calculation
[2][2]HASA-1/TMSA (AM1) relative solvent-accessible surface area of H-bonding acceptor atoms (from AM1 calculation)
[3]Lowest e-e repulsion (1-center) (AM1) eV from AM1 calculation
[4]Max nucleophilic reactivity index (AM1) for C atoms 1/eV sum of squares of highest occupied molecular orbital coefficients for a carbon atom, from AM1 calculation

4.4.Descriptor selection:

Initial pool of ~1000 descriptors. Descriptor selection based on a set of statistical selection rules, including Fisher criterion, variance check,
intercorrelation check, signifficance check for 1- and 2-parameter correlations (in terms of
correlation coefficient and t-test)

4.5.Algorithm and descriptor generation:

1D, 2D, and 3D theoretical calculations quantum chemical descriptors derived from MMFFs(vacuum) AM1 calculation. Model developed by using multilinear regression.

4.6.Software name and version for descriptor generation:

QSARModel 3.3.8
http://www.molcode.com

4.7.Descriptors/Chemicals ratio:

0.055

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

Applicability domain based on training set:
By chemical identity: Organic liquids (diverse set of aromatic, cyclic and aliphatic alcohols, esters, halogeno compounds, ketones).
By descriptor value range: The model is suitable for compounds that have the descriptors
in the following range: Gravitation index(all bonds)(AM1) (min: 213.606, max:

2497.675),
HASA- 1/TMSA(AM1)(min: 0, max: 0.318), Lowest e-e repulsion (1-center) (AM1)(min:
1.296, max: 3.543), Max nucleophilic reactivity index (AM1) for C atoms (0.002, 0.052).

5.2.Method used to assess the applicability domain:

presence of functional groups in structures
Range of descriptor values in training set with ±30% confidence
Descriptor values must fall between maximal and minimal descriptor values of training set ±30%.

5.3.Software name and version for applicability domain assessment:

QSARModel 3.3.8
http://www.molcode.com

5.4.Limits of applicability:

-

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:No
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:

data points: 72, negative: 69, positive values: 3

6.6.Pre-processing of data before modelling:

-

6.7.Statistics for goodness-of-fit:

R2= 0.893 (Correlation coefficient);
S2= 0.267 (Standard error of the estimate);
F= 140.539 (Fisher statistics)

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

R2cv= 0.877 LOO

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

R2cv= 0.874 LMO

6.10.Robustness - Statistics obtained by Y-scrambling:

-

6.11.Robustness - Statistics obtained by bootstrap:

-

6.12.Robustness - Statistics obtained by other methods:

ABC analysis (2:1 training : prediction) on sorted data divided into 3 subsets (A;B;C). Training set formed with 2/3 of the compounds (set A+B, A+C, B+C) and validation set consisted of 1/3 of the compounds (C,B,A) average R2 (fitting) = 0.899, average R2 (prediction) = 0.860

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:No
Formula:No
INChI:No
MOL file:Yes

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:

data points: 8, negative: 7, positive values: 1

7.6.Experimental design of test set:

the full experimental dataset was sorted according to increasing values of SP and each tenth compound was assigned to the test set.

7.7.Predictivity - Statistics obtained by external validation:

R2 = 0.802

7.8.Predictivity - Assessment of the external validation set:

The descriptors of the test set are in the limit of applicability

7.9.Comments on the external validation of the model:

The validation R2 for the test set is very good.

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

According to the model equation, eye irritation depends on the hydrogen bond donor and acceptor capabilities of a liquid as well as on the the overall shape and bulkiness. The key issue is the transport from eye surface into the biophase, binding to the phospholipid membrane and possible binding to the receptor.See section 8.3

8.2.A priori or a posteriori mechanistic interpretation:

a posteriori mechanistic interpretation, consistent with published scientific interpretations of experiments.

8.3.Other information about the mechanistic interpretation:

The descriptor HASA-1/TMSA (AM1) reflects transfer of the compounds to a phase characterized by hydrogen bonding and descriptors Lowest e-e repulsion (1-center) (AM1) for C atoms reflect the transfer of the compounds to a phase that is quite polar and

hydrophobic.

Ref.TOXICOLOGICAL SCIENCES 76, 384-391 (2003)

9.Miscellaneous information

9.1.Comments:

Draize rabbit eye test scores, as modified maximum average score (MMAS), for 68 pure bulk liquids were adjusted by the liquid-saturated vapor pressure P°. These 68 adjusted scores, as log (MMAS/P°), were shown to be completely equivalent to eye irritation thresholds (EIT), expressed as log (1/EIT), for 23 compounds in humans.

9.2.Bibliography:

[1]Correlation of blood-brain penetration and human serum albumin binding with theoretical descriptors, ARKIVOC 16, 38-60 (2008). http://www.arkat-usa.org/get-file/26925

[2]QSAR study of pharmacological permeabilities 2,2009, pp. 218 - 238. http://www.arkat-usa.org/get-file/28078

[3]Draize Rabbit Eye Test Compatibility with Eye Irritation Thresholds in Humans: A Quantitative Structure-Activity Relationship Analysis, Toxicological science 76, 384-391 (2003) http://toxsci.oxfordjournals.org/cgi/reprint/76/2/384

9.3.Supporting information:

Training set(s)

Eye irritation training.sdf	http://qsardb.jrc.it:80/qmrf/download_attachment.jsp?name=qmrf43_Eye irritation training.sdf

Test set(s)

Eye_irritation_testset.sdf	http://qsardb.jrc.it:80/qmrf/download_attachment.jsp?name=qmrf43_Eye_irritation_testset.sdf

10.Summary (JRC QSAR Model Database)

10.1.QMRF number:

Q2-10-1-43

10.2.Publication date:

2009/07/28

10.3.Keywords:

eye irritation, MMAS

10.4.Comments:

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