SAMPLE: QSAR Prediction Reporting Format (QPRF)

Skin Sensitization (OECD 406): Guinea Pig Maximization Test Index

Substance: Pigment Yellow, 2-((4-nitrophenyl)diazenyl)-3-oxo-N-phenylbutanamide

OECD guideline: *The adequacy of a prediction depends on the following conditions: a)* ***the (Q)SAR model is scientifically valid****: the scientific validity is established according to the OECD principles for (Q)SAR validation; b)* ***the (Q)SAR model is applicable to the query chemical****: a (Q)SAR is applicable if the query chemical falls within the defined applicability domain of the model; c)* ***the (Q)SAR result is reliable****: a valid (Q)SAR that is applied to a chemical falling within its applicability domain provides a reliable result; d)* ***the (Q)SAR model is relevant for the regulatory purpose****: the predicted endpoint can be used directly or following an extrapolation, possibly in combination with other information, for a particular regulatory purpose.*

1. Substance

1.1 CAS number:

1657-16-5

1.2 EC number:

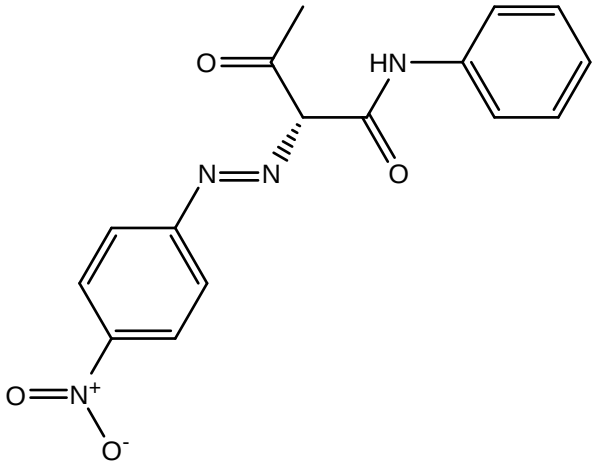
216-754-0

1.3 Chemical name:

pigment yellow, 2-((4-nitrophenyl)diazenyl)-3-oxo-N-phenylbutanamide

1.4 Structural formula:

$C_{16}H_{14}N_4O_4$



1.5 Structure codes:

a. SMILES:

O=C(C)[C@@H](/N=N/C1=CC=C([N+]([O-])=O)C=C1)C(NC2=CC=CC=C2)=O, not used for prediction

b. InChI:

InChI=1S/C16H14N4O4/c1-11(21)15(16(22)17-12-5-3-2-4-6-12)19-18-13-7-9-14(10-8-13)20(23)24/h2-10,15H,1H3,(H,17,22)/b19-18+/t15-/m1/s1, not used for prediction

c. Other structural representation:

3D Mol file used for prediction

d. Stereochemical features:

R,E isomer considered

2. General information

2.1 Date of QPRF:

10.02.2012

2.2 QPRF author and contact details:

Kaido Tämm, Ph.D; Tarmo Tamm, Ph.D
University of Tartu // Department of Chemistry
Ravila 14a, Tartu 50411, Estonia
Email: karu@ut.ee // Phone: +3725213075

3. Prediction

3.1 Endpoint (OECD Principle 1)

a. Endpoint:

Human health effects, skin sensitization (OECD 406) QSAR 4.6. Guinea pig maximization test index.

b. Dependent variable:

ss

3.2 Algorithm (OECD Principle 2)

a. Model or submodel name:

Skin sensitation: Guinea pig maximisation test (ANN)

b. Model version:

10.10.2010

c. Reference to QMRF:

The QMRF "Nonlinear ANN QSAR Model for Skin sensitization (GPMT)" has been recently composed and has not yet been published by JRC, still being in the reviewing stage.

d. Predicted value (model result):

ss = 0.92, class: very strong sensitizer

e. Predicted value (comments):

Very strong sensitizer, according to five scale classification: (non-sensitizers, weak sensitizers, moderate sensitizers, strong sensitizers, very-strong sensitizers).

Following EU CLP criteria (Xi R43), if measured experimentally, the predicted value would correspond to "**Category 1**" in the CLP classification system of:

Category 1	No Category

f. Input for prediction:

3D Mol file, as indicated in 1.5

g. Descriptor values:

HOMO - LUMO energy gap (AM1)	7.33
Lowest resonance energy (AM1) for C - H bonds	-11.12
Highest n-n repulsion (AM1) for C - H bonds	40.16
Number of rings	2
Lowest exchange energy (AM1) for C - C bonds	-7.92
Highest coulombic interaction (AM1) for C - H bonds	3.85
Max nucleophilic reactivity index (AM1) for O atoms	5.4E-3

3.3 Applicability domain (OECD principle 3)

a. Domains:

i. *descriptor domain*

All descriptor values for pigment yellow fall in the applicability domain (training set value ±30%).

ii. *structural fragment domain*

pigment yellow is structurally rather similar to the training set compounds, the training set contains aromatic azo-compounds, carbonyl-, nitro- and amide functionalities. The training set contains compounds of similar size to the studied compound.

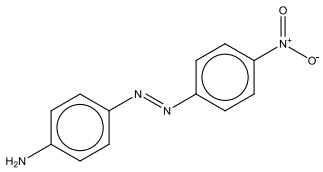
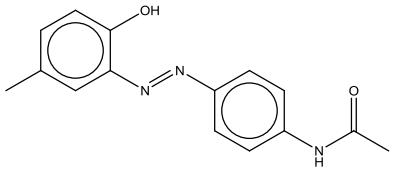
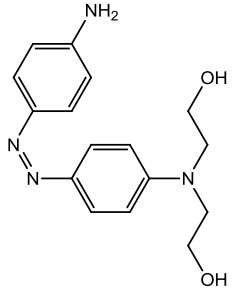
iii. *mechanism domain*

pigment yellow is considered to be in the same mechanistic domain(s) as the molecules in the training set.

iv. *metabolic domain, if relevant*

n/a

b. Structural analogues:

CAS	Structure	Smiles	Source	Value	
				Exp	Pred
730-40-5		c1cc(ccc1N)/N=N/c1ccc([N](O)=O)cc1	training	0.83	0.95
2832-40-8		c1(/N=N/c2ccc(cc2)NC(C)=O)c(ccc(c1)C)O	validation	0.83	1.0
20721-50-0		OCCN(c1ccc(/N=N/c2ccc(N)cc2)cc1)CCO	training	1.0	0.90

c. Considerations on structural analogues:

The structural analogues are rather similar to the studied compound. The structural analogues are evaluated correctly. Due to the many possible mechanisms, direct structural read-across is complicated, however, (pro)electrophilic centers that are one important indicator of skin sensitizing potential are present in all structures.

3.4 The uncertainty of the prediction (OECD principle 4)

The training set is not from one lab but a collection from several. However, previous and present successful modelling support its consistency. The statistical quality of the model supports reliable predictions. Skin sensitization is a difficult endpoint due to the multitude of possible mechanisms and the individual response of test animals. The studied compound is similar to the training set compounds, adding to prediction reliability. All structural analogues were evaluated correctly within the present model.

Considering the dataset, model statistical quality and prediction reliability, a reliability score (Klimisch score) "2" could be assigned to the present prediction.

The prediction reliability is estimated as 88 %.

3.5 The chemical and biological mechanisms according to the model underpinning the predicted result (OECD principle 5).

Skin sensitization is believed to be underpinned by mechanisms based on chemical reactivity (with the chemical behaving as an electrophile), in most cases binding covalently to a skin protein leading it to becoming antigenic. It has been agreed that the key to predicting likely sensitization potential is being able to predict electrophilic reactivity and pro-electrophilicity. The present model includes a number of chemical reactivity descriptors accounting for these effects. One of the most important descriptors is the HOMO–LUMO energy gap which accounts for the stability and reactivity of the molecule. The importance of this molecular feature was confirmed also by other authors (related to the mechanism of action). Other carbon, oxygen and hydrogen reactivity descriptors contribute to the frontier orbital energy gap descriptor.

4. Adequacy

4.1 Regulatory purpose:

The present prediction may be used for preparing the REACH Joint Registration Dossier on the Substance(s) for submission to the European Chemicals Agency ("ECHA") as required by Regulation (EC) N° 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals ("REAC H") and as required by Biocide Product Directive 98/8/EC ("98/8/EC")

4.2 Approach for regulatory interpretation of the model result

The predicted result has been presented in the formats directly usable for the intended regulatory purposes, both the numeric value and the transferred scale values have been presented.

4.3 Outcome

See section 3.2(e) for the classification of the prediction in light of the regulatory purpose described in 4.1.

4.4 Conclusion

Considering the above, the predicted result can be considered adequate for the regulatory conclusion described in 4.1.