

(Q)SAR Model Reporting Format – QMRF

Welcome

Model version: Skin sensitization DST v.02.03

Platform version: OASIS TIMES v.2.32.1

Name: Skin sensitization DST

Author: LMC, University "Prof. As. Zlatarov", Bourgas, Bulgaria

Date: March, 2023

e-mail: omekenya@btu.bg

www: <http://www.oasis-lmc.org/>

1. QSAR Identifier

1.1 QSAR Identifier (title)

Skin sensitization DST (Dermal Sensitization Threshold) model

1.2 Other related models

1.3 Software coding the model

Model version: Skin sensitization DST v.02.03

Platform version: OASIS TIMES v.2.32.1

Name: Skin sensitization DST

Developer: Laboratory of Mathematical Chemistry, University "Prof. Assen Zlatarov, " 1 Yakimov Str., Bourgas 8010, BULGARIA

<http://oasis-lmc.org>

Coding language: Delphi XE3

2. General information

2.1 Date of QMRF

March 2023

2.2 QMRF author(s) and contact details

Gergana Dimitrova (geri_d@btu.bg)

Laboratory of Mathematical Chemistry, University "Prof. Assen Zlatarov, " 1 Yakimov Str., Bourgas 8010, BULGARIA

<http://oasis-lmc.org>

2.3 Date of QMRF update(s)

September 2016, June 2017; January 2020; January 2022; March 2023

2.4 QMRF update(s)

Information which has been modified:

- Information in **section 1. QSAR Identifier**, field **1.3 Software coding the model**

- Information in **Section 2. General information**, field **2.1 Date of QMRF**; **2.3 Date of QMRF update(s)**
- Information in **Section 3. Defining the endpoint – OECD Principle 1**, fields **3.7. Endpoint data quality and variability**
- Information in **Section 4. Defining the algorithm – OECD Principle 2**, fields **4.3. Descriptors in the model**; **4.4. Descriptor section**; **4.5. Algorithm and descriptor generation**; **4.6. Software name and version for descriptor generation**
- Information in **Section 5. Defining the applicability domain of the model – OECD Principle 3**, fields **5.2. Method used to assess the applicability domain**; **5.4. Limits of applicability**
- Information in **Section 6. Internal validation - OECD Principle 4**, fields **6.1. Availability of the training set**; **6.2. Available information for the training set**; **6.3. Data for each descriptor variable for the training set**; **6.5 Other information about the training set**; **6.7 Statistics for goodness-of-fit**
- Information in **Section 8. Providing a mechanistic interpretation – OECD Principle 5**, fields **8.1. Mechanistic basis of the model**

2.5 Model developer(s) and contact details

The TIMES DST model was developed by the Laboratory of Mathematical Chemistry using funding from RIFM and with participation of Dr. David Roberts as reviewing expert.

- 1) Gergana Dimitrova, Laboratory of Mathematical Chemistry, University "Prof. Assen Zlatarov, " 1 Yakimov Str., Bourgas 8010, BULGARIA
- 2) Saby Dimitrov, Laboratory of Mathematical Chemistry, University "Prof. Assen Zlatarov, " 1 Yakimov Str., Bourgas 8010, BULGARIA
- 3) Ovanes Mekenyan, Laboratory of Mathematical Chemistry, University "Prof. Assen Zlatarov, " 1 Yakimov Str., Bourgas 8010, BULGARIA

2.6 Date of model development and/or publication

2016 September

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

2.8 Availability of information about the model

<http://oasis-lmc.org/products/models/human-health-endpoints/skin-sensitization-dst.aspx>

2.9 Availability of another QMRF for exactly the same model

3. Defining the endpoint – OECD Principle 1

3.1 Species

Mouse; human

3.2 Endpoint

In vivo: skin sensitization – LLNA and HRIPT

3.3 Comment on endpoint

Skin sensitization resulting in allergic contact dermatitis is a common occupational and environmental health issue. Many hundreds of chemicals have been implicated as skin sensitizers, and allergic contact dermatitis is without doubt the most common manifestation of immunotoxicity in humans. The sensitization potency, coupled with information on exposure levels, can be used in a Quantitative Risk Assessment (QRA) to determine an acceptable level of a given chemical in a given product. Where consumer skin exposure is low, a risk assessment can be conducted using the Dermal Sensitization Threshold (DST) approach, avoiding the need to determine potency experimentally [1].

3.4 Endpoint units

LLNA – EC₃, $\mu\text{g}/\text{cm}^2$

HRIPT - NOEL, $\mu\text{g}/\text{cm}^2$

3.5 Dependent variable

Obs. Skin Sensitization potency

3.6 Experimental protocol

LLNA (the murine local lymph node assay) - test Guidelines 429; HRIPT (the human repeat insult patch test)

3.7 Endpoint data quality and variability

High quality. The model was derived from a data set compiled from chemicals tested in the LLNA and HRIPT. Detailed information is provided in [Appendix 1](#).

4. Defining the algorithm – OECD Principle 2

4.1 Type of model

Structural alerts based model

4.2 Explicit algorithm

TIMES DST model aims to encode structure toxicity and structure metabolism relationships through a number of transformations simulating skin metabolism and interaction of the generated reactive metabolites with skin proteins. The skin metabolism simulator mimics metabolism using 2D structural information. The autoxidation (abiotic oxidation) of chemicals is also accounted for. A training set of diverse chemicals was compiled and their skin sensitization potency assigned to one of three classes. These three classes were High potent, Potent or Weak/Non sensitizing chemicals.

4.3 Descriptors in the model

Descriptors in the model are structural alerts related to interactions with skin Proteins. Each alert is supported by detailed mechanistic description of the interaction with proteins provided as additional explanatory textual information. To assess the reactivity of some specific alerts addition requirements for logKow were set in the model.

4.4 Descriptor selection

The main characteristics of each Protein binding alerts in the TIMES DST model are as follows:

- Alert name (corresponding to the name of the chemical class which is addressed);
- Performance of alert (correct/incorrect predictions) which is estimated based on proportion of observed positive chemicals from all chemicals captured by the alert. Performance of each alert is provided with its confidence range. As smaller is the size of local training sets as wider are the confidence ranges and vice versa.
- P-values addressing the reliability of alert performance estimation and taking into account possible bias of positive/negative chemicals in the training set of the model. Low p-values could be obtained only if both are satisfied:
 - The number of chemicals in local training set is high enough;

- The alert performance is significantly higher than the proportion of positive/negative chemicals in the model training set, i.e. so-called naïve alert.

Analogically, high p-values could be obtained in case of:

- Small number of local training set chemicals (1-2 chemicals); or
- Performance comparable to the performance of the naïve alert.

High performance associated with low p-values indicates for High Reliability of alerts.

4.5 Algorithm and descriptor generation

For derivation of each alert mechanistically justifiable structural fragment for interaction with skin proteins are identified from the chemicals having positive data in the training set and/or suggested by experts.

4.6 Software name and version for descriptor generation

TIMES DST model v.02.03

4.7 Chemicals/Descriptors ratio

5. Defining the applicability domain – OECD Principle 3

5.1 Description of the applicability domain of the model

The applicability domain of TIMES DST model consists of the following layers:

1. General parametric requirements - includes ranges of variation of $\log K_{OW}$ and MW . It specifies in the domain only those chemicals that fall in the range of variation of the MW and $\log Kow$ defined on the bases of the correctly predicted training set chemicals.

This layer of the domain is applied only on parent chemicals.

2. Structural domain - it is represented by list of atom - centered fragments extracted from the chemicals in the training set. The training chemicals were split into two subsets: chemicals correctly predicted by the model and incorrectly predicted chemicals. These two subsets of chemicals were used to extract characteristics determining the "good" and "bad" space of the domain. Extracted characteristics were split into three categories: unique characteristics of correct and incorrect chemicals

(presented only in one of the subsets) and fuzzy characteristics presented in both subsets of chemicals.

Structural domain is applied on parent chemicals, only.

5.2 Methods used to assess the applicability domain

The approach used to determine and assess the domain is described in:

Dimitrov S, Dimitrova G., Pavlov T., Dimitrova N., Patlewicz G., Niemela J., Mekenyan O., A stepwise approach for defining the applicability domain of SAR and QSAR models, *J. Chem. Inf. Model.*, 45, 839-849 (2005).

5.3 Software name and version for applicability domain assessment

Domain Manager v.1.13 developed at Laboratory of Mathematical Chemistry University, "Prof. Assen Zlatarov," 1 Yakimov Str., Bourgas 8010, BULGARIA

5.4 Limits of applicability

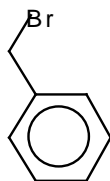
Applicability domain of the DST model includes the following sub-domain layers: general parametric requirements and structural features.

- General properties requirements:

As described in the Section 5.1.1, parametric domain of the model is derived based on Log *Kow* and *MW*. Example demonstrating belonging of a training set chemical to the parametric layer of the model domain is provided below:

Example chemical:

- CAS: 100-39-0
- Name: Benzyl bromide
- 2D Depiction:



Property	Domain	Example chemical
$\log K_{OW}$	[-13.7; 33.5]	2.88
MW, Da	[16.03; 1353.42]	171.03

* K_{OW} is calculated by EPI Suite

The values of $\log K_{OW}$ and MW of the example chemical are within the ranges of these parameters extracted from the whole training set of the model. Hence, with respect to the general parametric requirements, the target chemical is estimated to be *In Domian*.

- Structural features

Structural domain of the model is extracted from 1211 training chemicals containing:

- 3 107 correct fragments,
- 614 fuzzy fragments (treated as correct fragments),
- 655 incorrect fragments.

Additional information for alerts reliability is provided in the model reports. Reliability of alerts is estimated based on:

- Performance (Concordance) within the local training set chemicals (C);
- Number of the local training sets (N);
- Mechanistic justification (M).

According to these criteria, there are four reliability estimates for the alerts in the models:

- High reliability alerts ($C \geq 0.6, N \geq 5, M$)
- Low reliability alerts ($C \leq 0.6, N \geq 5, M$)
- Undetermined alerts ($1 < N < 5, M$)
- Undetermined theoretical alerts (M).

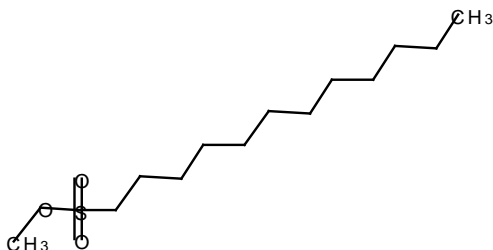
Example of a chemical belonging to alert with “High reliability”:

Chemical ID:

CAS: 2374-65-4

Name: 4-Methyl dodecane sulphonate

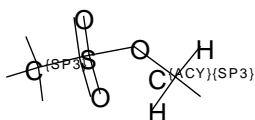
Depiction:



Belonging to alert:

Name: Sulfonates

Structural boundaries:



Reliability:

“High reliability” based on C=1; N=6 and M.

Currently, information for alerts reliability is provided in the model reports.

6. Internal validation - OECD Principle 4

6.1 Availability of the training set

The training set of the model contains 1211 chemicals, including 49 HPC; 277 non HPC and 885 weak/non sensitizers.

6.2 Available information for the training set

Chemical names, CAS numbers, SMILES, documented data and literature sources are available for each compound in the model training set.

6.3 Data for each descriptor variable for the training set

Descriptors in the models are structural alerts.

6.4 Data for the dependent variable for the training set

No provided

6.5 Other information about the training set

The model was developed using a dataset of 1211 unique chemicals tested by Local Lymph Node Assay (LLNA) and Human Repeat Insult Patch Test (HRIPT). All available skin sensitization data (EC3 and NOEL values in $\mu\text{g}/\text{cm}^2$) from both tests were stored in the DST training set. In case of multiple data the worst case scenario (or expert judgement) is applied. Most potent data (EC3, NOEL) is selected to represent the chemical in the training set. As a result the DST database includes 1211 unique chemicals distributed in three classes:

- HPC
- Non HPC (but positive sensitizers)
- Weak/Non sensitizers

The distribution of chemicals into three classes is given below:

		HPC	non HPC (but positive sensitizers)	Weak/Non sensitizers
		$\leq 64 \mu\text{g}/\text{cm}^2$ ($\leq 0.256\%$)	$< 64 \mu\text{g}/\text{cm}^2 - \leq 2500 \mu\text{g}/\text{cm}^2$ ($< 0.256\% - \leq 10\%$)	$> 2500 \mu\text{g}/\text{cm}^2$ ($> 10\%$)
# of chemicals from	HRIPT	-	28	16
	LLNA	49	249	869

6.6 Pre-processing of data before modeling

6.7 Statistics for goodness-of-fit

Statistic of model:

TIMES DST model was able to predict correctly 96% of HPC chemicals and 77% of non HPC chemicals, i.e., an overall performance of 80%.

6.8 Robustness – Statistics obtained by leave-one-out cross-validation

Not provided

6.9 Robustness – Statistics obtained by leave-many-out cross-validation

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

7.2 Available information for the external validation set

CAS RN:

Chemicals Name:

SMILES:

Formula:

INChi:

MOL file:

7.3 Data for each descriptor variable for the external validation set

Not provided

7.4 Data for the dependent variable for the external validation set

Not provided

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

TIMES DST model includes a list of protein binding alerts specified as Highly potent or Potent. The alerts are applied in combination with the TIMES simulators for abiotic oxidation (pre-electrophilic activation) and skin metabolism (pro-electrophilic activation). Because of the paucity of reported skin metabolism data, initially the simulator transformations were developed based on empirical and theoretical knowledge. The transformation probabilities (defining the priority of their execution) were parameterized to reproduce skin sensitization data. Currently, the simulator was upgraded and adjusted to simulate the documented in vitro metabolism presented in 206 maps. The simulator comprises about 440 transformations, which can be divided into four main types: abiotic transformations; covalent interactions of alerts with proteins; Phase I and Phase II reactions. Interactions with skin proteins are presented by 188 transformations grouped into two types: highly potent and potent.

Reliability of alerts in the TIMES DST model has been also evaluated to provide transparent mechanistic reasoning for predicting sensitization potential. Alert performance was defined as

the ratio between the number of correct (positive and negative) predictions and the total number of chemicals within the local training set that triggered the alert. The alert performance was assessed based on the predictions on parents, autoxidation products simulated by the external AU simulator and metabolites as simulated by the skin metabolism simulator embedded in TIMES DST model. Four different categories of reliability were defined:

- High reliability – alert performance higher than 60% and more than 5 chemical in local (transformation/alert) training set
- Low reliability – performance less than 60% and more than 5 chemicals in training set
- Undetermined reliability – less than 5 chemicals in training set
- Undetermined (theoretical) – there are no chemicals supporting the alert in the local training set

8.2 A priori or a posteriori mechanistic interpretation

8.3 Other information about the mechanistic interpretation

9. Miscellaneous information

9.1 Comments

The model can be used to discriminate HPC (High Potency Category) from non-HPC chemicals with respect to dermal sensitization threshold accounting for (a)biotic activation of chemicals.

9.2 Bibliography

1. Roberts, D., Api, A.M., Safford, R., Lalko, J. *Reg. Toxicol. Pharm.* 72 (2015) 683–693.
2. Dimitrov, S., Dimitrova, G., Pavlov, T., Dimitrova, N., Patlevisz, G., Niemela, J. and Mekemyan, O. *J. Chem. Inf. Model.* 45 (2005), pp. 839-849.

9.3 Supporting information