Q)SAR Model Reporting Format (QMRF)

(The present QMRF v.2.1 is prepared in accordance with (Q)SAR Assessment Framework (QAF) document developed by OECD)

(https://one.oecd.org/document/ENV/CBC/MONO(2023)32/ANN1/en/pdf)

Welcome

Model version: Skin sensitization DST v.02.05
Platform version: OASIS TIMES v.2.34.1
Name: Skin sensitization DST
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Section 1. QSAR identifier

1.1 QSAR identifier (title)

Skin sensitization DST (Dermal Sensitization Threshold) model v.02.05

1.2 Other related models

Not applicable

1.3 Software coding the model

Model version: Skin sensitization DST v.02.05
Platform version: OASIS TIMES v.2.34.1
Name: Skin sensitization DST
Developer: LMC, University "Prof. As. Zlatarov", Bourgas, Bulgaria
Coding language: Delphi 10.2

Section 2. General information

2.0. Abstract

Skin sensitization DST model discriminates HPC (High Potency Category) from non-HPC chemicals with respect to dermal sensitization threshold [1] accounting for (a)biotic activation of chemicals. 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). The skin sensitization 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). Depending of the applied protein binding alert skin sensitization DST model predicts compounds as HPC chemicals and non-HPC chemicals. The model also will assign HPC for compounds having special usage or uncertainty about their protein binding mechanism and reactivity. Compounds for which no protein binding alert is found are predicted by the model as Weak/Non sensitizers.

2.1. Date of QMRF

18 June 2025

2.2. QMRF author(s) and contact details

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2.3. Date of QMRF update(s)

September 2016, June 2017; January 2020; January 2022; March 2023; April 2024; June 2025

2.4. QMRF update(s)

Information which has been modified:
Section 1.1 QSAR identifier (title) **Section 1.3** Software coding the model; **Section 2.1** Date of QMRF; **Section 2.2** QMRF author(s) and contact details; **Section 2.3** Date of QMRF update(s); **Section 2.5** Model developer(s) and contact details; **Section 2.8** Availability of information about the model; **Section 4.6** Software name and version for descriptor generation;

2.5. Model developer(s) and contact details

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

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2.6. Date of model development and/or publication

Date of the model development: 2016 September

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

2.8. Availability of information about the model

Skin Sensitization DST model is proprietary and its use is subject of licence agreement.
Information that cannot be disclosed:

- External validation sets,
- Proprietary chemicals,
- Source code.

For more details, please contact Professor Ovanes Mekenyan:
ovanes.mekenyan@oasis-lmc.org
Details of the model are provided in the sections bellow as well as in the following link: http://oasis-lmc.org/products/models/human-health-endpoints/skin-sensitization-dst.aspx

2.9. Availability of another QMRF for exactly the same model

Not available.

Section 3. Defining the endpoint – OECD Principle

3.1. Species

mouse – used in Local Lymph Node Assay;
human – used in Human Repeat Insult Patch Test

3.2. Endpoint

In vivo: Skin sensitization according to

- OECD TG 429 (LLNA) https://www.oecd-ilibrary.org/environment/test-no-429-skin-sensitisation_9789264071100-en
- 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, $\mu g/cm^2$

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

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.

Section 4. Defining the algorithm – OECD Principle 2

4.1. Type of model

Structural alerts based model

4.2. Explicit algorithm

Skin sensitization 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 Skin sensitization 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 Skin sensitization DST model v.02.05

4.7. Chemicals/Descriptors ratio

Section 5. Defining the applicability domain of the model – OECD Principle 3

5.1. Description of the applicability domain of the model

The applicability domain of Skin sensitization DST model consists of the following layers:

1. General parametric requirements

The variations of molecular parameters that may affect the quality of the measured endpoint significantly are included here (such as molecular weight, etc.). The domain of general parametric includes the range of variation of hydrophobicity (log KOW) and Molecular weight (MW) of chemicals in training set.

2. Structural domain.

The structural component of the model is based on the structural similarity between chemicals in the training set which were correctly predicted by the model. The structural neighborhood of atom-centered fragments (accounting for the first neighbours) extracted from correctly and incorrectly predicted parent structures from the training set is used to determine this similarity.

The target chemical could contain the following types of ACF:

- Fragments present in correctly predicted training chemicals only (i.e. correct fragments),
- Fragments found both in correctly and non-correctly predicted training chemicals (i.e. fuzzy fragments). These fragments are treated as correct fragments,
- Fragments present in non-correctly predicted training chemicals only (i.e. incorrect fragments),
- Fragments not present in the training chemicals (i.e. unknown fragments).

A chemical belongs to the structural domain of the model if it could be partitioned only on correct fragments. The user is able to analyse how important are unknown and incorrect fragments (if present in the target) and to make a decision about their effect on the quality of prediction. The distribution of structural characteristics of the target chemical and accepted thresholds is used as a criterion to determine how well the target is represented in the structural space of correctly predicted chemicals. The accepted domain thresholds for Skin sensitization model are as follows:

- Correct = 100%
- Incorrect = 0%

A chemical is considered In Domain if it is classified to belong to all sub-domain levels. The information implemented in the applicability domain is extracted from the correctly predicted training chemicals used to build the model and in this respect the applicability domain determines practically the interpolation space of the model.

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

The LMC software OASIS Domain Manager v.1.13 (which is embedded in OASIS platform) is used to determine the applicability domain.

http://oasis-lmc.org/products/software/domain-manager.aspx

5.4. Limits of applicability

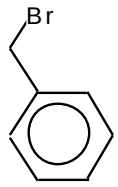
Applicability domain of the DST model includes the following sub-domain layers: general parametric requirements, structural features and alerts reliability.

- 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 EPIWin

The values of *logKow* 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:

- 3 089 correct fragments,
- 615 fuzzy fragments (treated as correct fragments),
- 673 incorrect fragments.

- Alert reliability

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).

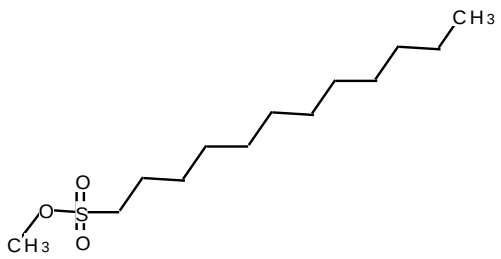
Example of a chemical belonging to alert with “High reliability”:

Chemical ID:

CAS: 2374-65-4

Name: 4-Methyl dodecane sulphonate

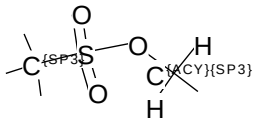
Depiction:



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.

Section 6. Defining goodness-of-fit and robustness (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). The training set was QA-ed applying the following criteria:

- LLNA (EC3, %) data:
  - ✓ all of the LLNA data are obtained according to **OECD TG 429** or equivalent studies
  - ✓ the original data source was identified and included as metadata information
  - ✓ chemicals with anomalous LLNA results (due to irritating properties, impurities) were excluded from the training set after expert assessment
- HRIPT (NOEL, μg/cm2) data
  - ✓ data from HRIPT were revised and added to the updated training set when LLNA data is not available

All available skin sensitization data (EC3 and NOEL values in μg/cm2) 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**
		≤ 64 μg/cm2 (≤ 0.256 %)	**< 64 μg/cm2 - ≤ 2500 μg/cm2** (< 0.256 % - ≤ 10 %)	**> 2500 μg/cm2** (> 10%)
# of chemicals from	**HRIPT**	-	28	16
	LLNA	49	249	869

6.6. Pre-processing of data before modeling

Not available

6.7. Statistics for goodness-of-fit

Statistic of model:

Skin sensitization 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

Not provided

6.10. Robustness – Statistics obtained by Y-scrambling

Not provided

6.11. Robustness – Statistics obtained by bootstrap

Not provided

6.12. Robustness – Statistics obtained by other methods

Not provided

6.13. Comment on the internal validation of the model

Not provided

Section 7. Defining predictivity (external validation) – OECD Principle 4

7.1. Availability of the external validation set

Not provided

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

Not provided

7.6. Experimental design of test set

Not provided

7.7. Predictivity – Statistics obtained by external validation

Not provided

7.8. Predictivity – Assessment of the external validation set

Not provided

7.9. Comments on the external validation of the model

Not provided

Section 8. Providing a mechanistic interpretation – OECD Principle 5

8.1. Mechanistic basis of the model

TIMES Skin sensitization DST model includes a list of protein binding alerts specified as Higly 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

The model building followed the traditional approach:

a. Building a hypothesis for the modelled event,
b. Defining the alerting groups based on parent structures,
c. Fitting of model variable to the observed data,
d. Verification of model quality,
e. Depending on the results found in step *d* model building could continue with step *a, b* or *f,*
f. Determination of the applicability domain and practical application of the model.

8.3. Other information about the mechanistic interpretation

Not provided

Section 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

Additional supporting information is not provided.