	QMRF identifier (JRC Inventory): **To be entered by JRC**
	QMRF Title: **Derek Nexus - skin sensitisation**
	Printing Date: **30 Oct 2023**

1.QSAR identifier

1.1.QSAR identifier (title):

Derek Nexus - skin sensitisation

1.2.Other related models:

Derek Nexus contains alerts for multiple endpoints, including mutagenicity, chromosome damage, carcinogenicity, hepatotoxicity, teratogenicity and skin irritation

1.3.Software coding the model:

Derek Nexus v6.3.0 contains 132 alerts for skin sensitisation, together with reasoning rules encoding physicochemical descriptors. In addition to a prediction of skin sensitisation potency for alerting query compounds, Derek evaluates potentially misclassified and unclassified features in compounds that do not activate skin sensitisation alerts or examples.

2.General information

2.1.Date of QMRF:

26 July 2010

2.2.QMRF author(s) and contact details:

Kate Langton Lhasa Limited 22-23 Blenheim Terrace, Woodhouse Lane, Leeds, LS2 9HD, UK

2.3.Date of QMRF update(s):

30 October 2023

2.4.QMRF update(s):

Rachael Tennant, Lhasa Limited, Granary Wharf House, 2 Canal Wharf, Leeds, LS11 5PS, UK

1.3, 2.3, 2.4, 2.6, 4.5

2.5.Model developer(s) and contact details:

Lhasa Limited Granary Wharf House, 2 Canal Wharf, Leeds, LS11 5PS

2.6.Date of model development and/or publication:

Derek Nexus 6.3.0 was released on 27 October 2023

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

[1]Sanderson DM & Earnshaw CG (1991). Computer prediction of possible toxic action from chemical structure; The DEREK system. Human and Experimental Toxicology 10, 261-273.

[2]Judson PN, Marchant CA & Vessey JD (2003). Using argumentation for absolute reasoning about the potential toxicity of chemicals. Journal of Chemical Information and Computer Sciences 43, 1364-1370.

[3]Marchant CA, Briggs KA & Long A (2003). In silico tools for sharing data and knowledge on toxicity and metabolism: Derek for Windows, Meteor, and Vitic. Toxicology Mechanisms and Methods 18, 177–187.

[4]Judson PN, Stalford SA & Vessey J (2013). Assessing confidence in predictions made by knowledge-based systems. Toxicology Research 2, 70-79.

[5]Canipa SJ, Chilton ML, Hemingway R, Macmillan DS, Myden A, Plante JP, Tennant RE, Vessey JD, Steger-Hartmann T, Gould J, Hillegass J, Etter S, Smith BPC, White A, Sterchele P, De Smedt

A, O'Brien D, Parakhia R (2017). A quantitative in silico model for predicting skin sensitization using a nearest neighbours approach within expert-derived structure-activity alert spaces.
[6]Chilton ML, Macmillan DS, Steger-Hartmann T, Hillegass J, Bellion P, Vuorinen A, Etter S, Smith BPC, White A, Sterchele P, De Smedt A, Glogovac M, Glowienke S, O'Brien D, Parakhia R (2018). Making reliable negative predictions of human skin sensitisation using an in silico fragmentation approach. Regulatory Toxicology and Pharmacology 95, 227-235.

2.8.Availability of information about the model:

Derek Nexus is a proprietary, rule-based expert system for the prediction of toxicity. Its knowledge base is composed of alerts, examples and reasoning rules which may each contribute to the predictions made by the system. Each alert in Derek describes a chemical substructure believed to be responsible for inducing a specific toxicological outcome (often referred to as a toxicophore). Alerts are derived by experts, using toxicological data and information regarding the biological mechanism of action. Where relevant, metabolism data may be incorporated into an alert, enabling the prediction of compounds which are not directly toxicity but are metabolised to an active species. The derivation of each alert is described in the alert comments along with supporting references and example compounds where possible. By reporting this information to the user, Derek provides highly transparent predictions. Furthermore, Derek Nexus gives quantitative EC3 predictions for alerting compounds and negative predictions when no alert is fired for the skin sensitisation endpoint. The use of structural alerts for the prediction of toxicity is both widely understood and the subject of many publications.

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

No

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Predictions are made for the class of mammals and can be broken down into species (e.g. mouse, human, guinea pig).

3.2.Endpoint:

TOX 7.4.1. Skin sensitisation

3.3.Comment on endpoint:

The Derek Nexus model for skin sensitisation is developed from several sources of data. Sources of primary data used for alert development include [1] guinea pig data, such as the Buehler and maximisation tests, [2] human data from maximisation and patch tests, [3] mouse data, mostly from the local lymph node assay. Secondary data sources of toxicity such as [4] BgVV categories, [5] R43 classifications, [6] HRIPT data and [7] human potency classifications have also been used. Additionally, alert writers consider both mechanistic evidence and chemical properties (such as reactivity).

3.4.Endpoint units:

Derek Nexus makes predictions for toxicity through reasoning. For the endpoint of skin sensitisation, predictions for toxicity decrease in confidence in the following order: certain> probable>plausible>equivocal [Judson et al 2013]. Predictions against toxicity increase in confidence in the following order: non-sensitiser (with unclassified and/or misclassified features)<non-sensitiser<improbable [Chilton et al]. These likelihood levels have been shown to correlate with predictivity. Multiple data sources (e.g. toxicity data from multiple assays and mechanistic evidence) are synthesised into the structure-activity relationships that underpins Derek Nexus predictions. Units are considered by the alert writers when building the alert training set, however, as predictions are made using data from multiple assays these do not include units as default - with the exception of the EC3 predictions which are given in % units.

3.5.Dependent variable:

Data from several toxicity assays (e.g. local lymph node assay (LLNA), guinea pig maximisation test (GPMT), human repeat insult patch test (HRIPT)) and mechanistic studies (e.g. direct peptide reactivity assay (DPRA)) are synthesised to arrive at an expert conclusion of whether compounds within the model training set is likely to be a skin sensitiser.

3.6.Experimental protocol:

The model is based primarily on data from Guinea Pig Maximisation Test or Local Lymph Node Assay conducted following standard test protocol (GPMT: OECD Test Guideline 406; LLNA: OECD Test Guideline 429). If activity is observed in a non-standard assay or protocol this will be mentioned in the comments. The process of alert development for skin sensitisation has been published [Langton et al].

3.7.Endpoint data quality and variability:

Alert writers use all available and relevant information in the public domain (and proprietary data, where available) for alert development. Wherever possible, primary references are used as data sources: (i) the data are subject to expert assessment prior to inclusion in the alert training set using, amongst other criteria, OECD test guidelines and (ii) the references themselves are cited in the alert comments enabling users to conduct their own expert assessments on data quality.

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

Expert derived structural alerts for skin sensitisation (2D SARs), physicochemical properties and associated reasoning. Following alert evaluation, Derek will make a prediction of skin sensitisation potency for alerting query compounds, where possible [Canipa et al]. This is based on the activity (EC3 values) for nearest neighbours derived from a local lymph node assay data set. In addition Derek evaluates whether non-alerting query compounds contain any features that are either (i)

also present in non-alerting skin sensitisers in a large Skin Sensitisation reference set (misclassified features) or (ii) not present in a large Skin Sensitisation reference set (unclassified features) [Chilton et al].

4.2.Explicit algorithm:

Structural alerts

logic of argumentation

feature-based database search

nearest neighbours (within same alert as query compound) based on Tanimoto similarity

4.3.Descriptors in the model:

[1]Markush structures encoding activating and deactivating features (known as patterns in the Derek Nexus knowledge base)

[2]2D structural fragments

4.4.Descriptor selection:

There is an a priori assumption that patterns and associated reasoning will be used to model skin sensitisation potential within Derek Nexus. Further, experts identified that 1) predictions of potency (LLNA EC3) could be made using nearest neighbours within the same alert [Canipa et al], and 2) misclassified and unclassified features were useful descriptors for determining the reliability of negative predictions for non-alerting compounds [Chilton et al].

4.5.Algorithm and descriptor generation:

Alert writers design the patterns to describe the activating and deactivating features found during expert assessment of the alert training set. Structural fingerprints are generated using Derek EC3 model 2023.0 from 720 compounds (comprising 600 sensitisers and 120 non-sensitisers) in the local lymph node data set [Canipa et al]. Misclassified and unclassified features are generated by processing a large Skin Sensitisation reference set of 3248 compounds (comprising 1522 sensitisers and 1726 non-sensitisers) against Derek Nexus (v6.3.0) and fragmenting [Chilton et al].

4.6.Software name and version for descriptor generation:

Alert writers use the Derek Knowledge Editor (v2.0) for the implementation of patterns. Structural fingerprints and fragmentation are generated using an in-house algorithm.

4.7.Chemicals/Descriptors ratio:

This is not applicable to structural alerts as these are knowledge-based rather than statistically based.

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

The scopes of the structure-activity relationships describing the skin sensitisation endpoint are defined by the developer to be the applicability domain for the model. Therefore, if a chemical activates an alert describing a structure-activity for skin sensitisation it can be considered to be within the applicability domain. The applicability of potency predictions may be judged, and modified, by the user based on the displayed data for nearest neighbours. If a compound does not activate an alert or reasoning rule then Derek makes a negative prediction. The applicability of the negative prediction to the query compounds can be determined by an expert, if required, by investigating the presence (or absence) of misclassified and/or unclassified features.

5.2.Method used to assess the applicability domain:

The applicability domain of each alert is defined by the alert developer on the basis of the training set data and expert judgement on the chemical and biological factors which affect the mechanism of action for each alert. For potency predictions, at least three nearest neighbours are required within alerting space to make a prediction. For non-alerting compounds, users should determine the applicability of negative predictions by evaluating the information supplied by Derek (i.e. the presence or absence of misclassified and/or unclassified features).

5.3.Software name and version for applicability domain assessment:

This is not applicable.

5.4.Limits of applicability:

Limits for individual alerts are mainly defined by restrictions in the scope of the alerts which are available for inspection within the software.

6.Internal validation - OECD Principle 4

6.1.Availability of the training set:

No

6.2.Available information for the training set:

CAS RN: No

Chemical Name: No

Smiles: No

Formula: No

INChI: No

MOL file: No

NanoMaterial: No

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

No

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

No

6.5.Other information about the training set:

Non-proprietary elements of the training set are available through the references, and illustrated by the examples, within Derek Nexus. The illustrative examples are not available, due to the proprietary nature of Derek Nexus.

6.6.Pre-processing of data before modelling:

This is not applicable.

6.7.Statistics for goodness-of-fit:

This is not applicable.

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

This is not applicable.

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

This is not applicable.

6.10.Robustness - Statistics obtained by Y-scrambling:

This is not applicable.

6.11.Robustness - Statistics obtained by bootstrap:

This is not applicable.

6.12.Robustness - Statistics obtained by other methods:

This is not applicable.

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: No

Chemical Name: No

Smiles: No

Formula: No

INChI: No

MOL file: No

NanoMaterial: No

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

No

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

No

7.5.Other information about the external validation set:

Three published data sets have been used for alert validation: [1] Cronin and Basketter (216 compounds), [2] Gerberick et al and Kern et al (a combined data set of 318 compounds) and [3] a collection of local lymph node assay data (137 compounds) published in Contact Dermatitis which have been extracted from Vitic Nexus (13 September 2012). Further, the relationship between likelihood levels and prediction accuracy has been assessed [Judson et al 2013]. Validation studies of the EC3 model and negative prediction model have been published [Canipa et al, Chilton et al]. Finally, several external evaluations have been published [Rorije et al, Nukada et al, Golden et al].

7.6.Experimental design of test set:

Proprietary data sets were sought.

7.7.Predictivity - Statistics obtained by external validation:

The software reports the number of positive and negative compounds from the validation data sets that activate each alert and calculates positive predictivity using this data.

7.8.Predictivity - Assessment of the external validation set:

Alerts are validated using data derived from LLNA and guinea pig assays covering 516 unique compounds. The compounds in the data sets are primarily small chemicals and so are representative of the structures used to build the model.

7.9.Comments on the external validation of the model:

This is not applicable.

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

All alerts describing structure-activity relationships for the skin sensitisation endpoint have a mechanistic basis wherever possible. Mechanistic information is detailed in the comments associated with an alert and can include information on both the mechanism of action and biological target.

8.2.A priori or a posteriori mechanistic interpretation:

The mechanistic basis of the model was developed a priori by examining the toxicological and mechanistic evidence before developing the structure-activity relationship.

8.3.Other information about the mechanistic interpretation:

All references supporting the mechanistic basis of an alert are detailed and available for inspection within the software.

9.Miscellaneous information

9.1.Comments:

Derek Nexus may be used to assess the toxicity of a wide range of chemical classes, including food, drug, cosmetic, and industrial chemicals, and the system provides predictions for over 50 toxicological endpoints, including mutagenicity, chromosome damage, carcinogenicity, skin sensitisation and reproductive toxicity. Skin sensitisation predictions from Derek have shown potential utility when used as part of a weight of evidence assessments [Goebel et al] and integrated testing strategies/defined approaches for skin sensitisation [Rorije et al, Nukada et al, Macmillan and Chilton].

9.2.Bibliography:

[1]Sanderson DM & Earnshaw CG (1991). Computer prediction of possible toxic action from chemical structure; The DEREK system. Human and Experimental Toxicology 10, 261-273.

[2]Judson PN, Marchant CA & Vessey JD (2003). Using argumentation for absolute reasoning about the potential toxicity of chemicals. Journal of Chemical Information and Computer Sciences 43, 1364-1370.

[3]Marchant CA, Briggs KA & Long A (2003). In silico tools for sharing data and knowledge on toxicity and metabolism: Derek for Windows, Meteor, and Vitic. Toxicology Mechanisms and Methods 18, 177–187.
[4]Judson PN, Stalford SA & Vessey J (2013). Assessing confidence in predictions made by knowledge-based systems. Toxicology Research 2, 70-79.
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[6]Chilton ML, Macmillan DS, Steger-Hartmann T, Hillegass J, Bellion P, Vuorinen A, Etter S, Smith BPC, White A, Sterchele P, De Smedt A, Glogovac M, Glowienke S, O'Brien D, Parakhia R (2018). Making reliable negative predictions of human skin sensitisation using an in silico fragmentation approach. Regulatory Toxicology and Pharmacology 95, 227-235.
[7]Langton K, Patlewicz GY, Long A, Marchant CA, Basketter DA (2006). Structure-activity relationships for skin sensitization: recent improvements to Derek for Windows. Contact Dermatitis 55, 342-347.
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[12]Rorije E, Aldenberg T, Buist H, Kroese D & Schüürmann G (2013). The OSIRIS Weight of Evidence approach: ITS for skin sensitisation. Regulatory Toxicology and Pharmacology 67, 146-156.
[13]Nukada Y1, Miyazawa M, Kazutoshi S, Sakaguchi H & Nishiyama N (2013). Data integration of non-animal tests for the development of a test battery to predict the skin sensitizing potential and potency of chemicals. Toxicology in Vitro 27, 609-618.
[14]Golden E, Macmillan DS, Dameron G, Kern P, Hartung T & Maertens A (2020). Evaluation of the global performance of eight in silico skin sensitization models using human data. ALTEX - Alternatives to animal experimentation.
[15]Macmillan DS & Chilton ML. (2019). A defined approach for predicting skin sensitisation hazard and potency based on the guided integration of in silico, in chemico and in vitro data using exclusion criteria. Regulatory Toxicologoy and Pharmacology 101, 35-47.

9.3.Supporting information:

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