QMRF CHAPTER TITLES	SECTION TITLES	MODEL DESCRIPTION *(Fill in this column)*
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 v5.0 contains 80 alerts for skin sensitisation, together with reasoning rules encoding physicochemical descriptors
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):	7 January 2016
	2.4. QMRF update(s):	Lilia Fisk, Lhasa Limited, Granary Wharf House, 2 Canal Wharf, Leeds, LS11 5PS, UK 1.3, 2.3, 2.4, 2.5, 2.6, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 5.1, 5.2
	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 5.0 was released on 18 January 2015
	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.
	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. 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:	4.Human health effects 4.6.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 and [5] R43 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 and against toxicity through reasoning. For the endpoint of skin sensitisation, predictions for toxicity decrease in confidence in the following order: certain> probable>plausible>equivocal. Predictions against toxicity increase in confidence in the following order: doubted<improbable. These likelihood levels have been shown to correlate with predictivity [Judson et al, 2013]. 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. An appreciation of the assay units applied by alert writers when building the alert training set. However, predictions are not restricted to a specific assay and, as a result, do not include units.
	3.5. Dependent variable:	Data from several toxicity assays (e.g. LLNA, GPMT, HRIPT) and mechanistic studies (e.g. 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. This is based on the activity (EC3 values) for nearest neighbours derived from a local lymph node assay data set.
	4.2. Explicit algorithm:	[1] Structural alerts, [2] logic of argumentation, [3] 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 fingerprints.
	4.4. Descriptor selection:	There is an a priori assumption that patterns, physicochemical properties and associated reasoning will be used to model toxicity within Derek Nexus. Further, experts identified that predictions of potency (LLNA EC3) could be made using nearest neighbours within the same alert.
	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 from the 465 compounds in the local lymph node data set.
	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 are generated using an in-house algorithm.
	4.7. Chemicals/Descriptors ratio:	This is not applicable as the structural alerts 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 in Derek, a result of 'nothing to report' is presented to the user. This can be interpreted as a negative prediction or that the query compound is outside the domain of the model. Which of these is more appropriate may depend on the endpoint of interest. For the endpoint of skin sensitisation, which features multiple alerts believed to cover most of the mechanisms and chemical classes responsible for activity, 'nothing to report' may be extrapolated to a negative prediction.
	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.
	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:	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.
	6.2. Available information for the training set:	CAS RN: No Chemical name: No Smiles: No Formula: No Inchi: No MOL file: No
	6.3. Data for each descriptor variable for the training set:	This is not applicable.
	6.4. Data for the dependent variable for the training set:	This is not applicable.
	6.5. Other information about the training set:	This is not applicable.
	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:	External validation is carried out on each knowledge base release. The data sets used for validation are available in the public domain, but the curated versions used at Lhasa are proprietary, so are not made available.
	7.2. Available information for the external validation set:	CAS RN: No Chemical name: No Smiles: No Formula: No Inchi: No MOL file: No
	7.3. Data for each descriptor variable for the external validation set:	This is not applicable.
	7.4. Data for the dependent variable for the external validation set:	This is not applicable.
	7.5. Other information about the external validation set:	Three published data sets have been used for alert validation: [1] Cronin and Basketter, [2] Gerberick et al and Kern et al and [3] a collection of local lymph node assay data for 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]. Finally, several external evaluations have been published [Rorije et al, Nukada 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:	Data derived from LLNA and guinea pig assays covering 504 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 for skin sensitisation [Rorije et al, Nukada et al]. Additionally, Derek mutagenicity predictions are submitted as part of the regulatory requirements on genotoxic impurities in pharmaceuticals [Sutter et al].
	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. [5] 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. [6] Potts RO and Guy RH (1992). Predicting skin permeability. Pharmaceutical Research 9, 663-669. [7] Cronin MT & Basketter DA (1994). Multivariate QSAR analysis of a skin sensitization database. SAR and QSAR in Environmental Research 2, 159-179. [8] Gerberick GF, Ryan CA, Kern PS, Schlatter H, Dearman RJ, Kimber I & Patlewicz GY, Basketter DA (2005). Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis 16, 157-202. [9] Kern PS, Gerberick GF, Ryan CA, Kimber I, Aptula A & Basketter DA (2010). Local lymph node data for the evaluation of skin sensitization alternatives: a second compilation. Dermatitis 21, 8-32. [10] Goebel C, Aeby P, Ade N, Alépée N, Aptula A, Araki D, Dufour E, Gilmour N, Hibatallah J, Keller D, Kern P, Kirst A, Marrec-Fairley M, Maxwell G, Rowland J, Safford B, Schellauf F, Schepky A, Seaman C, Teichert T, Tessier N, Teissier S, Weltzien HU, Winkler P & Scheel J (2012). Guiding principles for the implementation of non-animal safety assessment approaches for cosmetics: Skin sensitisation. Regulatory Toxicology and Pharmacology 63, 40-52. [11] 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. [12] 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. [13] Sutter A, Amberg A, Boyer S, Brigo A, Contrera JF, Custer LL, Dobo KL, Gervais V, Glowienke S, van Gompel J, Greene N, Muster W, Nicolette J, Reddy MV, Thybaud V, Vock E, White AT & Müller L (2013). Use of in silico systems and expert knowledge for structure-based assessment of potentially mutagenic impurities. Regulatory Toxicology and Pharmacology 67, 39-52.
	9.3. Supporting information:	No information is available.
10. Summary (JRC Inventory)		
	10.1. QMRF number:	tbc by JHRC
	10.2. Publication date:	tbc by JHRC
	10.3. Keywords:	tbc by JHRC
	10.4. Comments:	tbc by JHRC