Derek Nexus Report

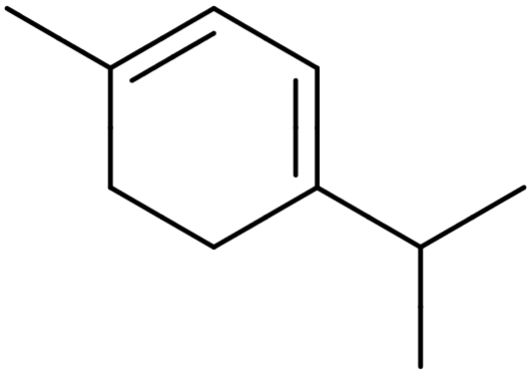
Report Information

Author	Report date	Prediction date	Program version
uieuc	20 June 2018 10:54:01	20 June 2018 10:49:21	Derek Nexus: 6.0.1, Nexus: 2.2.1

Processing Options

Selected Species	Selected Knowledge Base(s)	Reasoning Level
bacterium, mammal	Derek KB 2018 1.1	At least IMPOSSIBLE
Perceive tautomers	**Perceive mixtures**	**Match alerts without rules**
Yes	Yes	No
Show Open likelihood	**Show Negative Predictions**	**Show Rapid Prototypes**
No	Yes	Yes
Filter nearest neighbours on misclassified features		
Yes		

Submitted Compound - Structure



Smiles: C=1(C(C)C)CCC(C)=CC=1

Exact Mol Mass	136.1252
Average Mol Mass	136.23 (Source: Lhasa Limited, version 1.0)
Log Kp	-0.42 (Source: Potts & Guy, version 1.0)
Log P	4.41 (Source: BioByte Corp., version 5.9)

Predictions

Knowledge Base: Derek KB 2018 1.1

Version	Last Modified Date	Certified by
1.1	23/11/2017 10:38:05	Lhasa Limited, Leeds, Yorkshire, UK

Reasoning Summary

◆ **Mutagenicity in vitro in bacterium is INACTIVE**
- No misclassified or unclassified features

◆ **Skin sensitisation in bacterium is IMPOSSIBLE**
- Alert matched: 698 Conjugated diene
- **Exact example match:** alpha-terpinene

◆ **Skin sensitisation in mammal is PROBABLE**
- Alert matched: 698 Conjugated diene
- **Exact example match:** alpha-terpinene

Endpoints not firing any alerts at the selected reasoning level (59)

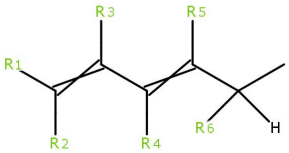
5alpha-Reductase inhibition
Adrenal gland toxicity
alpha-2-mu-Globulin nephropathy
Anaphylaxis
Androgen receptor modulation
Bladder disorders
Bladder urothelial hyperplasia
Lachrymation
Methaemoglobinaemia
Mitochondrial dysfunction
Mutagenicity in vivo
Nephrotoxicity
Neurotoxicity
Non-specific genotoxicity in vitro

Blood in urine
Bone marrow toxicity
Bradycardia
Carcinogenicity
Cardiotoxicity
Cerebral oedema
Chloracne
Cholinesterase inhibition
Chromosome damage in vitro
Chromosome damage in vivo
Cumulative effect on white cell count and immunology
Cyanide-type effects
Developmental toxicity
Glucocorticoid receptor agonism
Hepatotoxicity
HERG channel inhibition in vitro
High acute toxicity
Irritation (of the eye)
Irritation (of the gastrointestinal tract)
Irritation (of the respiratory tract)
Irritation (of the skin)
Kidney disorders
Kidney function-related toxicity
Non-specific genotoxicity in vivo
Occupational asthma
Ocular toxicity
Oestrogen receptor modulation
Oestrogenicity
Peroxisome proliferation
Phospholipidosis
Photo-induced chromosome damage in vitro
Photo-induced non-specific genotoxicity in vitro
Photo-induced non-specific genotoxicity in vivo
Photoallergenicity
Photocarcinogenicity
Photomutagenicity in vitro
Phototoxicity
Pulmonary toxicity
Respiratory sensitisation
Splenotoxicity
Teratogenicity
Testicular toxicity
Thyroid toxicity
Uncoupler of oxidative phosphorylation
Urolithiasis

Alert Descriptions

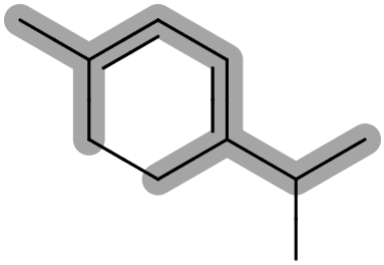
Alert: 698 Conjugated diene (from KB: Derek KB 2018 1.1)

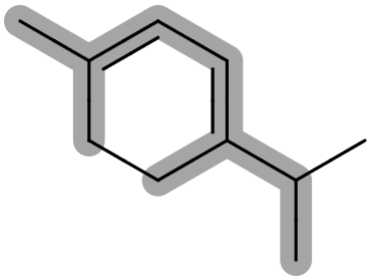
Alert Description Image



R1-R5 = H, C (not doubly bonded to O or triply bonded to N)
R6 = H, C
At least one double bond must be part of an alicyclic ring

Match with query compound





Comments

Skin sensitisation: murine local lymph node assay (LLNA)
Potential mechanism (epoxide): Pre/prohapten producing an SN2-reactive electrophile [Aptula and Roberts]
Potential mechanism (alkoxy radical): Prehapten producing a free radical generator [Payne and Walsh]

This alert describes the skin sensitisation of conjugated dienes.

beta-Phellandrene and alpha-terpinene have shown moderate sensitisation potential in the LLNA [Bergstrom et al 2006]. They are considered to sensitise by forming antigenic adducts with skin proteins through either i) an SN2 mechanism after their metabolic activation to an alpha,beta-unsaturated epoxide [Nilsson et al] or ii) an autoxidation mechanism at the allylic position forming a hydroperoxide species as has been shown for abietic acid [Karlberg et al 1988].

In vitro studies with (5R)-5-isopropenyl-2-methyl-1-methylene-2-cyclohexene (IMMC) have demonstrated that it is not electrophilic enough to readily react with nucleophilic sites on a model peptide [Nilsson et al]. However, the incubation of IMMC with human liver microsomes leads to the formation of endocyclic and exocyclic alpha,beta-unsaturated epoxide metabolites [Nilsson et al]. These have been shown to be strong sensitisers in the LLNA and cross-reacted with IMMC itself in Freund's complete adjuvant test [Nilsson et al]. IMMC forms the same alpha,beta-unsaturated epoxides after its incubation in a CYP450 cocktail modelling the enzymatic activity of the skin [Bergstrom et al 2007].

Purified abietic acid is negative in patch tests on humans sensitised to Portuguese colophony, in the GPMT and Freund's complete adjuvant test [Karlberg et al 1985]. In contrast, the hydroperoxide derivative 15-hydroperoxyabietic acid (15-HPA) is a strong skin sensitiser in guinea pigs and humans [Karlberg et al 1988]. The skin sensitisation potential derives from the formation of specific antigenic adducts with skin protein via i) direct radical reaction with the alkoxy radical intermediate, subsequent to the homolytic cleavage of its O-O bond or ii) the rearranged alpha,beta-unsaturated epoxide species [Karlberg et al 2008, Gafvert et al].

The scope of this alert covers conjugated dienes where the double bond must be in an aliphatic ring [Bergstrom et al 2006] and excludes alpha,beta-unsaturated nitriles or alpha,beta-unsaturated carbonyl derivatives which are covered elsewhere in the knowledge base.

References

- Karlberg AT, Bergstedt E, Boman A, Bohlinder K, Liden C, Nilsson JLG and Wahlberg JE. (1985)
  Is abietic acid the allergenic component of colophony?, *Contact Dermatitis*, 13 , 209-215
  DOI: 10.1111/j.1600-0536.1985.tb02552.x
- Bergstrom MA, Luthman K, Nilsson JLG and Karlberg AT. (2006)
  Conjugated dienes as prohaptens in contact allergy: in vivo and in vitro studies of structure-activity relationships, sensitizing capacity and metabolic activation., *Chemical Research in Toxicology*, 19 , 760-769
  DOI: 10.1021/tx060006n
- Nilsson AM, Bergstrom MA, Luthman K, Nilsson JLG and Karlberg AT. (2005)
  A conjugated diene identified as a prohapten: contact allergenic activity and chemical reactivity of proposed epoxide metabolites., *Chemical Research in Toxicology*, 18 , 308-316
  DOI: 10.1021/tx049758c
- Bergstrom MA, Ott H, Carlsson A, Neis M, Zwadlo-Klarwasser G, Jonsson CAM, Merk HF, Karlberg AT and Baron JM. (2007)
  A skin-like cytochrome P450 cocktail activates prohaptens to contact allergenic metabolites., *Journal of Investigative Dermatology*, 127 , 1145-1153
  DOI: 10.1038/sj.jid.5700638
- Karlberg AT, Bohlinder K, Boman A, Hacksell U, Hermansson J, Jacobsson S and Nilsson JLG. (1988)
  Identification of 15-hydroperoxyabietic acid as a contact allergen in Portuguese colophony., *Journal of Pharmacy and Pharmacology*, 40 , 42-47
  DOI: 10.1111/j.2042-7158.1988.tb05147.x
- Karlberg AT, Bergstrom MA, Borje A, Luthman K and Nilsson JLG. (2008)
  Allergic contact dermatitis - formation, structural requirements, and reactivity of skin sensitizers., *Chemical Research in Toxicology*, 21 , 53-69
  DOI: 10.1021/tx7002239
- Gafvert E, Shao LP, Karlberg AT, Nilsson U and Nilsson JLG. (1994)
  Contact allergy to resin acid hydroperoxides. Hapten binding via free radicals and epoxides., *Chemical Research in Toxicology*, 7 , 260-266
  DOI: 10.1021/tx00038a020
- Aptula AO and Roberts DW. (2006)
  Mechanistic applicability domains for nonanimal-based prediction of toxicological end points: general principles and application to reactive toxicity., *Chemical Research in Toxicology*, 19 , 1097-1105
  DOI: 10.1021/tx0601004
- Payne MP and Walsh PT. (1994)
  Structure-activity relationships for skin sensitization potential: development of structural alerts for use in knowledge-based toxicity prediction systems., *Journal of Chemical Information and Computer Sciences*, 34 , 154-161
  DOI: 10.1021/ci00017a019

Validation comments

Skin sensitisation: guinea pig maximisation test, local lymph node assay

The alert has demonstrated the following predictive performance:

1) Cronin and Basketter data set: 1 compound activates this alert of which 1 is reported positive (positive predictivity: 100%)
2) Gerberick et al data set: 5 compounds activate this alert of which 5 are reported positive (positive predictivity: 100%)
3) Contact Dermatitis data set: 0 compounds activate this alert

1) A collection of guinea pig maximisation test data for 216 compounds from the following reference: Cronin MTD and Basketter DA. Multivariate QSAR analysis of a skin sensitization database. SAR and QSAR in Environmental Research, 1994, 2, 159-179, available at "http://dx.doi.org/10.1080/10629369408029901".

2) A collection of local lymph node assay data for 318 compounds derived from the following references: (i) Gerberick GF, Ryan CA, Kern PS, Schlatter H, Dearman RJ, Kimber I, Patlewicz GY and Basketter DA. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis, 2005, 16, 157-202. Downloaded from "http://www.inchemicotox.org/results/" (3 September 2010); (ii) Kern PS, Gerberick GF, Ryan CA, Kimber I, Aptula A and Basketter DA. Local lymph node data for the evaluation of skin sensitization alternatives: a second compilation. Dermatitis, 2010, 21, 8-32, available at "http://dx.doi.org/10.2310/6620.2009.09038".

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).

In assessing predictive performance, it should be noted that:

- Mammalian skin sensitisation predictions in Derek associated with a reasoning level of equivocal or above have been considered positive;

- Predictions do not take into account (i) the tautomeric forms of compounds or (ii) the individual components of mixtures;

- Compounds have been considered positive for skin sensitisation if they have been classified as extreme, strong or moderate sensitisers;

- Compounds classified as weak sensitisers have been excluded from the analysis;

- No account has been taken of other skin sensitisation alerts which may also be present in some compounds;

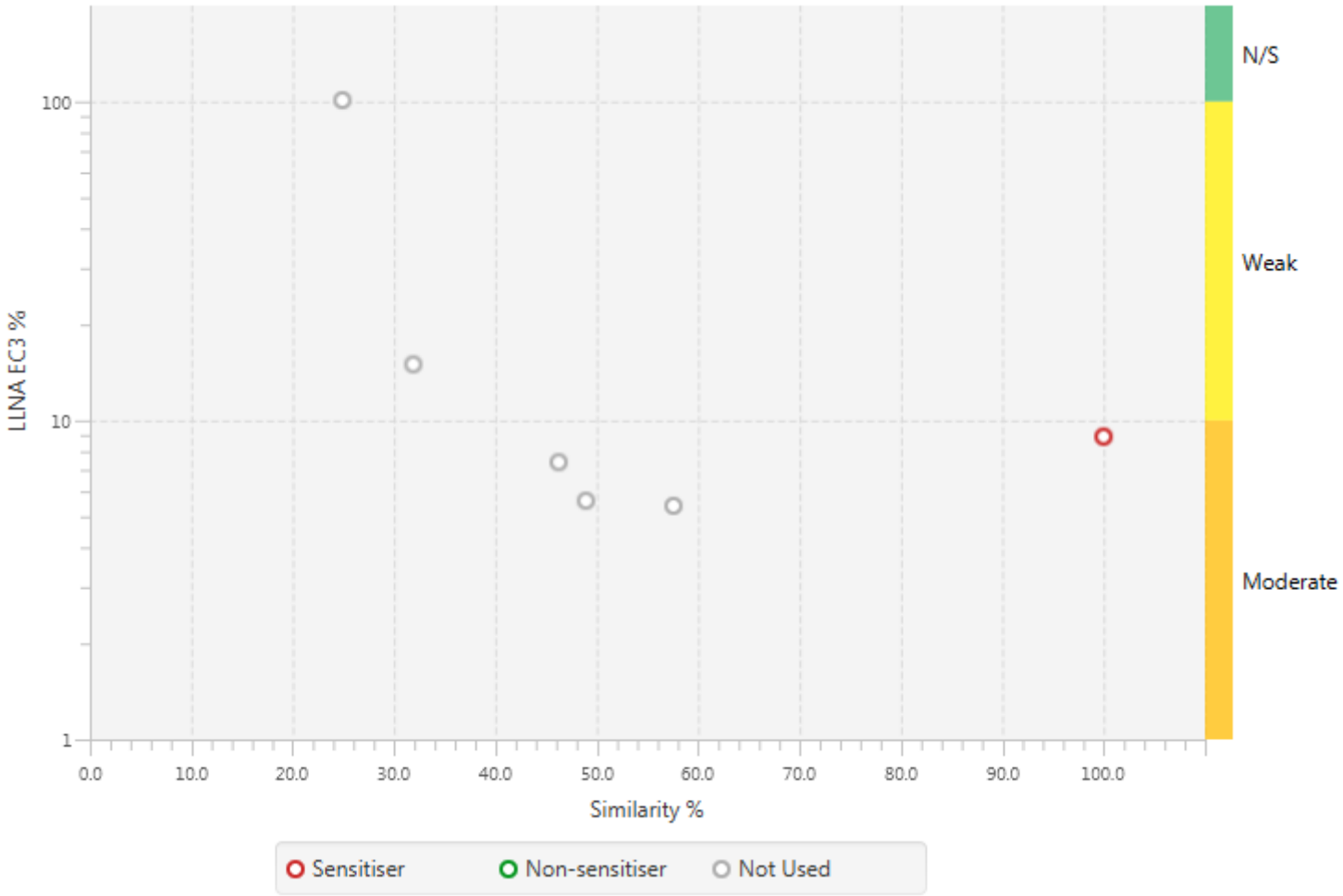
- Information from the data sets may have been used previously as supporting evidence for the derivation of some alerts;

- Some compounds may be present in more than one of the data sets analysed.

EC3 Results

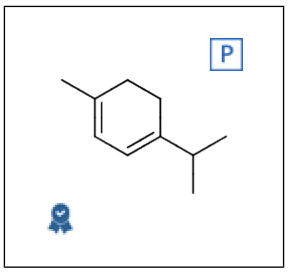
EC3 Result for Derek EC3 Model - 1.2.0

Species:	mammal
Alert:	698 Conjugated diene
Dataset Name:	Derek EC3 Model - 1.2.0
Dataset Certified:	Yes
Predicted LLNA EC3:	8.9% (moderate sensitiser)
Experimental Match:	Exact Match only used as prediction result
Compounds used in calculation:	1/6



Similar Compounds

Structure

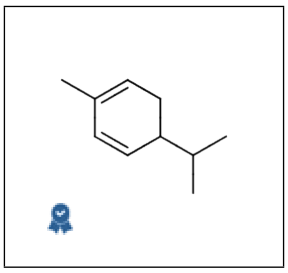


LLNA EC3 % Median: **8.9% (moderate sensitiser)**
Similarity: **100%**
Lhasa Certified: Yes
Used in Calculation: Yes
Number of Studies: 1
Molecular Weight Changed: No
Comments:

Studies

Structure ID	LLNA EC3 % Value	Reference	MWt Changed for Standardisation	Lhasa Certified
Structure-497	8.9	Bergstrom, Chemical Research in Toxicology, 2006, 19, 760-769.	No	Yes

Structure

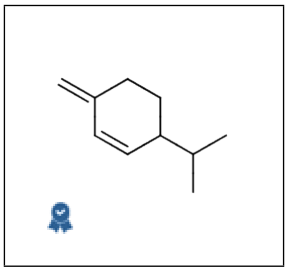


LLNA EC3 % Median: **5.4% (moderate sensitiser)**
Similarity: **58%**
Lhasa Certified: Yes
Used in Calculation: No
Number of Studies: 1
Molecular Weight Changed: No
Comments:

Studies

Structure ID	LLNA EC3 % Value	Reference	MWt Changed for Standardisation	Lhasa Certified
Structure-498	5.4	Bergstrom, Chemical Research in Toxicology, 2006, 19, 760-769.	No	Yes

Structure

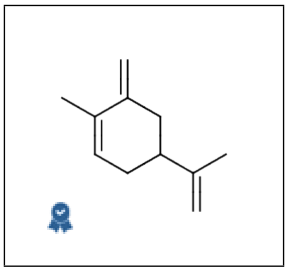


LLNA EC3 % Median: **5.6% (moderate sensitiser)**
Similarity: **49%**
Lhasa Certified: Yes
Used in Calculation: No
Number of Studies: 1
Molecular Weight Changed: No
Comments:

Studies

Structure ID	LLNA EC3 % Value	Reference	MWt Changed for Standardisation	Lhasa Certified
Structure-496	5.6	Bergstrom, Chemical Research in Toxicology, 2006, 19, 760-769.	No	Yes

Structure

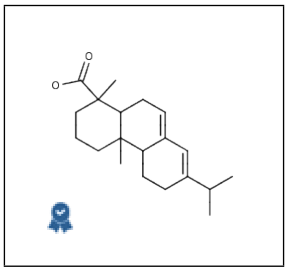


LLNA EC3 % Median: **7.4% (moderate sensitiser)**
Similarity: **46%**
Lhasa Certified: Yes
Used in Calculation: No
Number of Studies: 1
Molecular Weight Changed: No
Comments:

Studies

Structure ID	LLNA EC3 % Value	Reference	MWt Changed for Standardisation	Lhasa Certified
Structure-536	7.4	Nilsson, Chemical Research in Toxicology, 2005, 18, 308-316.	No	Yes

Structure

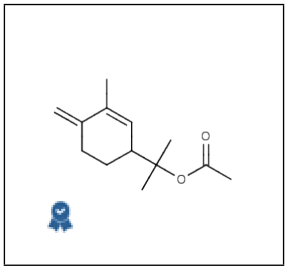


LLNA EC3 % Median: **15% (weak sensitiser)**
Similarity: **32%**
Lhasa Certified: Yes
Used in Calculation: No
Number of Studies: 1
Molecular Weight Changed: No
Comments:

Studies

Structure ID	LLNA EC3 % Value	Reference	MWt Changed for Standardisation	Lhasa Certified
Structure-789	15	Gerberick, Dermatitis, 2005, 16, 157-202.	No	Yes

Structure



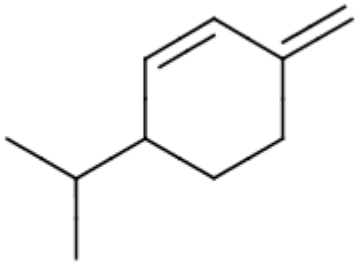
LLNA EC3 % Median: **non-sensitiser**
Similarity: **25%**
Lhasa Certified: Yes
Used in Calculation: No
Number of Studies: 1
Molecular Weight Changed: No
Comments:

Studies

Structure ID	LLNA EC3 % Value	Reference	MWt Changed for Standardisation	Lhasa Certified
Structure-1044	non-sensitiser	Kern, Dermatitis, 2010, 21, 8-32.	No	Yes

Examples for Alert 698 Conjugated diene

Example 1: beta-phellandrene



CAS Number: 555-10-2

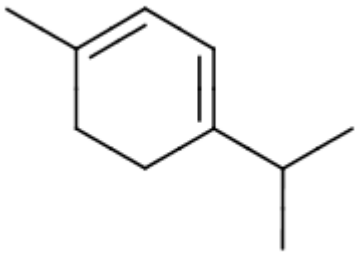
Test Data (beta-phellandrene)

1)	Species	Assay	Endpoint(s)	Result
	mouse	local lymph node assay	Skin sensitisation	positive

References

- Bergstrom MA, Luthman K, Nilsson JLG and Karlberg AT. (2006)
  Conjugated dienes as prohaptens in contact allergy: in vivo and in vitro studies of structure-activity relationships, sensitizing capacity and metabolic activation., *Chemical Research in Toxicology*, 19 , 760-769
  DOI: 10.1021/tx060006n

Example 2: alpha-terpinene **(Exact match with Query Compound)**



CAS Number: 99-86-5

Test Data (alpha-terpinene)

1)	Species	Assay	Endpoint(s)	Result
	mouse	local lymph node assay	Skin sensitisation	positive

References

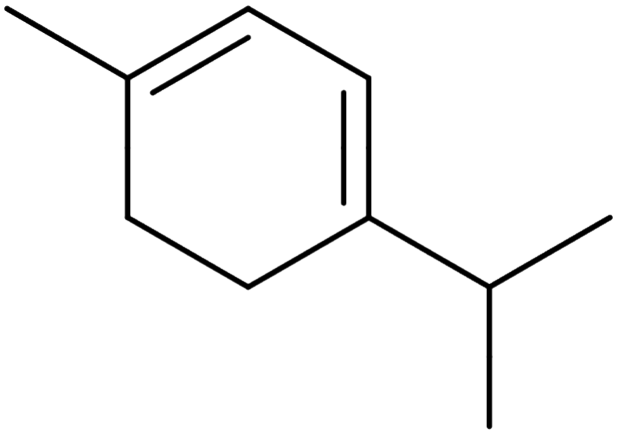
- Bergstrom MA, Luthman K, Nilsson JLG and Karlberg AT. (2006)
  Conjugated dienes as prohaptens in contact allergy: in vivo and in vitro studies of structure-activity relationships, sensitizing capacity and metabolic activation., *Chemical Research in Toxicology*, 19 , 760-769
  DOI: 10.1021/tx060006n

Reasoning Details

Mutagenicity in vitro in bacterium is INACTIVE (from KB: Derek KB 2018 1.1)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause mutagenicity; your selected species, which is bacterium.

Overview
No misclassified or unclassified features



Details
The query structure does not match any structural alerts or examples for (bacterial in vitro) mutagenicity in Derek. Additionally, the query structure does not contain any unclassified or misclassified features and is consequently predicted to be inactive in the bacterial in vitro (Ames) mutagenicity test.

Skin sensitisation in bacterium is IMPOSSIBLE (from KB: Derek KB 2018 1.1)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause skin sensitisation; your selected species, which is bacterium.

Rule 259: If [species bacterium] is [certain] then [Species dependent variable 4] is [impossible]
- species bacterium **is** CERTAIN

In bacteria the variable "Species dependent variable 4" is impossible.

Rule 5: If [known local lymph node assay positive in mouse] is [certain] then [Skin sensitisation] is [Species dependent variable 4]

- known local lymph node assay positive in mouse **is** CERTAIN
- Species dependent variable 4 **is** IMPOSSIBLE

If a chemical is known to give a positive response in the local lymph node assay in the mouse then it is considered certain that the chemical will cause skin sensitisation in mice, probable in mammals other than the mouse and impossible in bacteria. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 4".

Rule 267: If [species bacterium] is [certain] then [Species dependent variable 8] is [impossible]

- species bacterium **is** CERTAIN

In bacteria the variable "Species dependent variable 8" is impossible.

Rule 1000: If [alert 698] is [certain] then [Skin sensitisation] is [Species dependent variable 8]

- alert 698 **is** CERTAIN
- Species dependent variable 8 **is** IMPOSSIBLE

If a chemical contains alert 698 then it is considered equivocal that the chemical will cause skin sensitisation in mammals and impossible in bacteria. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 8".

Skin sensitisation in mammal is PROBABLE (from KB: Derek KB 2018 1.1)

The parameters that have influenced your prediction are: substructures in the input structure, which have the potential to cause skin sensitisation; your selected species, which is mammal.

Rule 266: If [species mammal] is [certain] then [Species dependent variable 8] is [equivocal]

- species mammal **is** CERTAIN

In mammals the variable "Species dependent variable 8" is equivocal.

Rule 1000: If [alert 698] is [certain] then [Skin sensitisation] is [Species dependent variable 8]

- alert 698 **is** CERTAIN
- Species dependent variable 8 **is** EQUIVOCAL

If a chemical contains alert 698 then it is considered equivocal that the chemical will cause skin sensitisation in mammals and impossible in bacteria. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 8".

Rule 222: If [species mouse] is [certain] then [Species dependent variable 4] is [certain]

- species mouse **is** PLAUSIBLE

In the mouse the variable "Species dependent variable 4" is certain.

Rule 261: If [mammal other than mouse] is [plausible] then [Species dependent variable 4] is [probable]

- mammal other than mouse **is** PLAUSIBLE

In mammals other than the mouse the variable "Species dependent variable 4" is probable.

Rule 5: If [known local lymph node assay positive in mouse] is [certain] then [Skin sensitisation] is [Species dependent variable 4]

- known local lymph node assay positive in mouse **is** CERTAIN
- Species dependent variable 4 **is** PROBABLE

If a chemical is known to give a positive response in the local lymph node assay in the mouse then it is considered certain that the chemical will cause skin sensitisation in mice, probable in mammals other than the mouse and impossible in bacteria. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 4".

Glossary

Certain
There is proof that the proposition is true.

Probable
There is at least one strong argument that the proposition is true and there are no arguments against it.

Plausible
The weight of evidence supports the proposition.

Equivocal
There is an equal weight of evidence for and against the proposition.

Doubted
The weight of evidence opposes the proposition.

Improbable
There is at least one strong argument that the proposition is false and there are no arguments that it is true.

Impossible
There is proof that the proposition is false.

Open
There is no evidence that supports or opposes the proposition.

Contradicted
There is proof that the proposition is both true and false.

Inactive, no misclassified or unclassified features
The query structure does not match any structural alerts or examples in Derek which show activity in a bacterial reverse mutation assay (Ames test). Additionally, the query structure does not contain any unclassified or misclassified features.

Inactive, contains misclassified features
Features in the molecule are found in non-alerting mutagens in the Lhasa reference set. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains unclassified features
Some features in the molecule have not been found in the Lhasa reference set. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Inactive, contains misclassified and unclassified features
The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.

Non-sensitiser, no misclassified or unclassified features
The query structure does not match any structural alerts or examples for skin sensitisation in Derek. Additionally, the query structure does not contain any unclassified or misclassified features.

Non-sensitiser, contains misclassified features
Features in the molecule are found in non-alerting sensitisers in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the misclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains unclassified features
Some features in the molecule have not been found in the Lhasa skin sensitisation negative prediction dataset. The prediction remains negative and the unclassified features are highlighted to enable the negative prediction to be verified by expert assessment.

Non-sensitiser, contains misclassified and unclassified features
The query structure contains features that are misclassified and features that are unclassified. These are highlighted on the structure.