Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

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English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ADDENDUM TO WEIGHT OF EVIDENCE ASSESSMENT FOR THE SKIN SENSITISATION POTENTIAL OF 4-ISOPROPYLANILINE (CUMIDINE, CAS 99-88-7)

Series on Testing and Assessment
No. 199

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OECD Environment, Health and Safety Publications
Series on Testing and Assessment

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ADDENDUM TO WEIGHT OF EVIDENCE ASSESSMENT FOR THE SKIN SENSITISATION POTENTIAL OF 4-ISOPROPYLANILINE (CUMIDINE, CAS 99-88-7)

IOMC
INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2014

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This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organisations.

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This publication is available electronically, at no charge.

Also published in the Series on Testing and Assessment link

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or contact:

OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

FOREWORD

This Weight of Evidence case study has been prepared by experts from the Netherlands and Denmark, with support from the OECD Secretariat.

A hazard assessment of the industrial chemical 4-isopropylaniline (CAS 99-88-7) prepared by the Japanese authorities was discussed by OECD member countries at an OECD Cooperative Chemicals Assessment Meeting (CoCAM) on 16-18 October 2012.

Skin sensitisation is not a mandatory OECD SIDS endpoint, which means that there are no formal requirements for evaluation or generation of test data to conclude on this endpoint in a chemical hazard assessment of the OECD. However, if any data are available for this endpoint, it should be included in the assessment.

No experimental test data on skin sensitisation were available for 4-isopropylaniline. However, the chemical structure of this substance is similar to substances known to be potent skin sensitisers, including some well-known hair colouring agents such as *p*-phenylenediamine, *p*-toluenediamine and *p*-aminophenol. Therefore, it was decided that a case study with non-test information on skin sensitisation of 4-isopropylaniline would be prepared.

This case study aims to provide all available and relevant (non-testing) evidence on the skin sensitisation potential for 4-isopropylaniline, and subsequently uses a Weight of Evidence (WoE) approach to arrive at a conclusion. Although some evidence on its own may be considered insufficient (e.g. a QSAR prediction that has an out-of-applicability domain warning) to reach a conclusion, this information can still be taken into account in a WoE approach, especially if the information confirms other (equally or more reliable) sources of information. The WoE assessment presents a hypothesis on skin metabolism and mechanism through which the substance of interest can cause skin sensitisation. Five structural analogues for which experimental skin sensitisation data are available were selected based on hypothesised mechanism and the other selection criteria that are detailed in the document. Furthermore, positive predictions for the substance of interest from five independent QSAR models are presented, and the QSAR predictions for the selected structural analogues by these same QSAR models show the ability of the QSARs to (correctly) predict skin sensitisation potential for this type of substance. All this information points to the same conclusion: 4-isopropylaniline would very likely be a skin sensitiser.

This document is an accompanying document to *Weight of Evidence Assessment for the Skin Sensitisation Potential Of 4-Isopropylaniline (Cumidine, CAS 99-88-7)* [ENV/JM/MONO(2014)5], and includes appendices 1-7. This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

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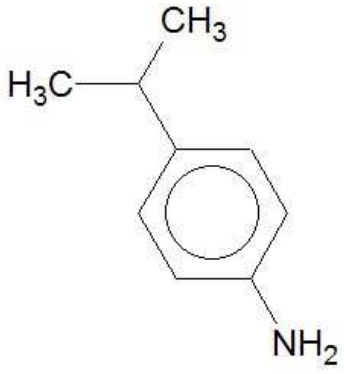
APPENDIX 1

CAS: 99-88-7



EINECS No: 202-797-2 REACH EC Number:202-797-2 Found in: METI_Japan; TSCA; IUCLID; HPVC_EU

DK EPA Advisory list classifications 2010:

CLP: Carc2 AcuteTox4 SkinSens1 Chron2 DSD: Carc3;R40 Xn;R22 R43 N;R51/53

Physico chemical properties:

Molecular wt.:	135,21	Melting point (C)	23,17	Boiling point (C):	230,83
Vapour press. mmHG:	0,101	Henry's const. atm-m3/Mole:	3,7E-6		
Solubility mg/l:	1150	LogP oct/water:	2,53	LogKoc	2,3447
Max.sat.vap.conc. mg/l@20C:	0,7344955	Dermal abs.mg/cm2/event:	0,012	(Moderate)	
Bioavail. (Rule of 5):	0	% G.I. abs. /dose 1 m	95	Reactive groups:	-
Log blood-brain:	0,3098	% G.I. abs./dose 1000mg:	90		
Energy HOMO:	-8,3896	Energy LUMO:	0,62908	T95, days:	1,133813
Ionization, pH=7.4	pKa Acid:	999		pKa Base:	4,9
LogD: 2,28	Reliability, pKa Acid:	0		Reliability, pKa Base:	0,4

ESTIMATED HALF-LIFE IN DAYS:

Hydrolysis: 0 Atmosph. oxidation (OH): 0,08114494 Atmosph. ox. (Ozone): -

ENVIRONMENTAL PARTITIONING (McKay):

	Air (%)	Water (%)	Soil (%)	Sediment (%)	
(I):	34,61335	62,16645	1,665619	1,554578	
(III):	0,107	23,3	76,4	0,188	Persistence time (hr): 909
(III), Half life:	1,95	900	1800	8100	

BIODEGRADATION I:	Linear (A):	Non linear (A):	Ultimate (B:)	Primary (B):
Syracure BPP:	0,5041	0,44	2,6906	3,4758
Syracuse MITI:	0,1761	0,1392	----------	----------

A) >= 0.5 degrades fast. B) 4= Hours 3 = Weeks 2= Months 1= Years

BIODEGRADATION II:	Test	QSAR	QSAR Quality	Percent
DEPA Multicase READY	4	EQU	WRN	75

BIOCONCENTRATION FACTOR: LogBCF1 (Bintein): 1,516102 LogBCF2 (Syracuse): 1,22

LBB1 (LC-50) Fish (mg/l):	Non polar narc.: 33,57872	Non-polar narc.:	66,39974
LBB2 (LC-50) Fish (mg/l):	Polar narc.: 8,240175	Polar narc.:	16,29442

MULTICASE Aq. Tox	Test	QSAR	QSAR Quality	Percent	Disc. score	Cover	Alert
Fath. minn. LC50 mg/l	-	16,69	AOK	97	POS	-	2B
Daphnia m. LC50 mg/l	-	2,11	AOK	88	POS	-	B
Algae (Selen.) EC50 mg/l		70,97585	AOK	24	NEG	-	-
Tetrahym p. IG50 mg/l	81,86	51,41843	WRN	85	EQU	-	BM

MCASEQSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

Cytochrome P450

2D6 substrate	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Multicase	-	NEG	AOK	18	-	-
Leadscope		0	Predicted	0,268		
2D6 inhibitor, PASS		0,086				
2D6 S/I, Leadscope		0,459	-			
3A4 substrate	-	NEG	AOK	N/A	-	-
3A4 inhibitor, PASS		0,1289				
3A4 S/I, Leadscope		0,107	-			

2C9 substrate

SciQSAR 0,13932 PASS -0,4286

2C9 inhibitor, PASS 0,6223

2C9 S/I, Leadscope	0,202	-
1A2 substrate, Leadscope	0,884	-
1A2 inhibitor, PASS	0,1063	
1A2 S/I, Leadscope	0,725	-

2C19 substrate
SciQSAR 0,24075 PASS 0,3732
2C19 S/I, Leadscope 0,382 -

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

	Pharma LD50 [mg]	Pharma Reliability	RTECS LD50 [mg]
Rat, oral:	870	0,85	-
Mouse, oral:	560	0,72	-
Rat, intraperitoneal:	280	0,69	-
Mouse, intraperitoneal:	200	0,55	-
Rat, intravenous:			-
Mouse, intravenous:	72,15	0,78	-
Mouse, subcutaneous:	200	0,72	

Pharma Probabilities	LD50 <= 5 mg/kg	LD50 <= 50 mg/k	LD50 <= 300 mg/k	LD50 <= 3000 mg/kg
	0,001	0,007	0,084	0,831

LD50, other tests: - -

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Skin irritation						
MC (severe):	-	POS	WRN	66	-	b
		Strong	Moderate	Weak	Inactive	Effect
PASS		0,1911	0,5291	0,4861	0,5165	0,4891
PASS Eye irritation		0,4089	0,6097	0,6398	0,5994	
Sensitization (GPM+H)	-	POS	AOK	90	-	B
Respiratory allergy:	-	NEG	AOK	23	-	-
MC Teratogenicity (Hum.):	-	NEG	AOK	21	-	-
PASS Teratogenicity		0,2908				
Estrogen RB (Hum.) I:	-	NEG	AOK	23	-	-
Estrogen RB (Hum.) II:	-	NEG	AOK	19	-	-
Estr. Reporter (Hum.):	-	NEG	AOK	21	-	-
Antiandrogen in vitro:	-	NEG	AOK	22	-	-
MC ArH receptor binding:		EQU	AOK	60	-	b
SciQSAR ArH:		N/A				

MCASEQSAR Quality: AOK, A1B = Good prediction, FRG = Unknown fragment, WRN = P

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
DNA react. (Ashby):	-	POS	AOK	96	-	B
Mutagenicity II (Ames):	-	NEG+	PRB	78	-	Bd
Mutagenicity II (Ames), old:		EQU-	AOK	78	-	Bd
Direct, S9 (Ames):	-	NEG-	AOK	22	-	d
Base pair (Ames):	-	NEG	AOK	23	-	-
Frame shift (Ames):	-	EQU	AOK	73	-	B
Rev. > 10xCtrl (Ames):	-	EQU	AOK	80	-	B
Chrom. aberration (CHO):		NEG	AOK	21	-	-
Chrom. aberration (CHL):		POS	AOK	85	-	B
Mouse lymphoma (GTX):		EQU	AOK	72	-	B
CHO - HGPRT (GTX)	-	NEG-	AOK	25	-	d
UDS - Rat hepatocyte:	-	NEG	AOK	23	-	-
SHE - Cell transformation:		EQU	AOK	70	-	B
Dros. SI-Rec. Lethal:	-	NEG	AOK	23	-	-
Mouse micronucleus II:	-	NEG	AOK	22	-	-
Rodent, Dom. Lethal:	-	EQU	AOK	60	-	B?
Mouse, SCE bone marrow:		EQU	AOK	73	-	B
Mouse, COMET assay:	-	EQU	AOK	77	-	B

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
FDA Cancer male Rat:	-	EQU	AOK	78	-	B
- CDER Proprietary:	-	POS	AOK	84	-	B
- CDER Proprietary new:	-	POS	AOK	78	-	B

FDA Cancer female Rat:	-	EQU	AOK	75	-	B	
- CDER Proprietary:	-	EQU	AOK	75	-	B	
- CDER Proprietary new:	-	POS	AOK	84	-	B	
FDA Cancer male Mouse:	-	EQU	AOK	78	-	B	
- CDER Proprietary:	-	NEG	AOK	23	-	-	
- CDER Proprietary new:	-	POS	AOK	84	-	B	
FDA Cancer fem. Mouse:	-	EQU	AOK	75	-	B	
- CDER Proprietary:	-	NEG	AOK	22	-	-	
- CDER Proprietary new:	-	POS	AOK	75	-	B	Disc. score
CPDB Rat TD50 mg/k	-	15,68	AOK	95	-	B	POS
CPDB Mouse TD50 mg/l	-	19,02	AOK	95	-	B	POS
CPDB Liver specif	-	NEG	AOK	19	-	-	

FDA ICSAS: + SSA: 4 Comment: -
AG1: + AG2: + AG3: + AG4: (+)

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

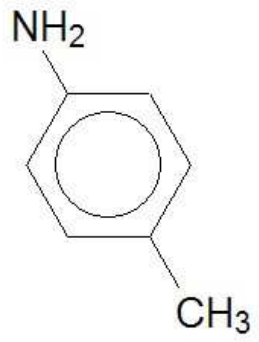
Test	QSAR	Domain error
Leadscope Developmental Toxicity		
Fetal_death_mouse:	0,2385	-
Fetal_death_rabbit:	0,177	-
Fetal_death_rat:	0,1915	-
Fetal_death_rodent:	0,2015	-
Post_impl_mouse_(AG6):	0,225	-
Post_impl_rodent_(AG1):	0,26	-
Post_impl._loss_rabbit:	0,134	-
Post_impl._loss_rat:	0,267	-
Pre_impl._loss_mouse:	0,415	-
Pre_impl._loss_rabbit:	0,127	-
Pre_impl._loss_rat:	0,1705	-
Pre_impl._loss_rodent:	0,216	-
Retard_rodent_(AH1):	0,168	-
Retardation_mouse:	0,2785	-
Retardation_rabbit:	0,282	-
Retardation_rat:	0,1163	-
Struct_mouse_(AL6):	0,268	-
Struct_rodent_(AL1):	0,381	-
Structural_rabbit:	0,192	-
Structural_rat:	0,4265	-
Visceral_mouse:	0,411	-
Visceral_rat:	0,261	-
Visceral_rodent:	0,3148	-
Weight_dec._mouse:	0,335	-
Weight_dec._rabbit:	0,096	-
Weight_dec._rat:	0,257	-
Wt_dec_rodent_(Al1):	0,208	-
PASS Embryotoxicity:	0,3426	

Test	QSAR	Domain error
Leadscope Cardiac effects		
Arrhythmia:	0,173	-
Bradycardia:	0,152	-
Conduction:	0,0963	-
Coronary artery:	0,108	-
Electrocardiogram:	0,147	-
Heart failure:	0,125	-
Myocardial:	0,0429	-
Myocardial infarct:	0,131	-
Palpitations:	0,175	-
QT prolongation:	0,1456	-
Rate rhythm:	0,296	-
Tachycardia:	0,25	-
Torsades:	0,135	-
Leadscope Reproductive Toxicity		
Repro_mouse_female:	-	Not in Domain
Repro_mouse_male:	-	Not in Domain
Repro_rat_female:	0,2173	-
Repro_rat_male:	0,33	-
Repro_rodent_female:	0,323	-

Test	QSAR	Domain error
Hepatobiliary effects		
Bile duct:	-	Not in Domain
Enzyme release:	0,126	-
Gall bladder:	-	Not in Domain
Jaundice:	0,1723	-
Liver acute:	0,439	-
PASS Hepatotoxicity	0,6875	
Urinary tract effects		
Bladder:	0,257	-
Blood urine:	-	Not in Domain
Kidney:	-	Not in Domain
Kidney function:	-	Not in Domain
Nephropathy:	-	Not in Domain
Urolithiasis:	0,1355	-
PASS Nephrotoxicity:	0,6014	

Repro_rodent_male:	0,351	-
Sperm_mouse(AP5):	0,0324	-
Sperm_rat:	0,445	-
Sperm_rodent:	0,5295	-

CAS: 106-49-0



EINECS No: 203-403-1 REACH EC Number:203-403-1 Found in: DSL; TSCA; IUCLID; HPVC_EU; METI_Japan; HPVC_USEPA
DK EPA Advisory list classifications 2010:
CLP: - DSD: -

Physico chemical properties:

Molecular wt.:	107,16	Melting point (C)	11,62	Boiling point (C):	204,16
Vapour press. mmHG:	0,219	Henry's const. atm-m3/Mole:	2,1E-6		
Solubility mg/l:	6449	LogP oct/water:	1,62	LogKoc	1,8605
Max.sat.vap.conc. mg/l@20C:	1,262222	Dermal abs.mg/cm2/event:	0,026	(Moderate)	
Bioavail. (Rule of 5):	0	% G.I. abs. /dose 1 m	90	Reactive groups:	-
Log blood-brain:	0,1278	% G.I. abs./dose 1000mg:	90		
Energy HOMO:	-8,35587	Energy LUMO:	0,61676	T95, days:	0,476213
Ionization, pH=7.4	pKa Acid:	999		pKa Base:	4,9
LogD: 1,46	Reliability, pKa Acid:	0		Reliability, pKa Base:	0,4

ESTIMATED HALF-LIFE IN DAYS:
Hydrolysis: 0 Atmosph. oxidation (OH): 0,08097176 Atmosph. ox. (Ozone): -

ENVIRONMENTAL PARTITIONING (McKay):

	Air (%)	Water (%)	Soil (%)	Sediment (%)	
(I):	14,49654	84,96202	0,2800557	0,2613853	
(III):	0,265	40,1	59,5	0,0905	Persistence time (hr): 968
(III), Half life:	1,94	360	720	3240	

BIODEGRADATION I:	Linear (A):	Non linear (A):	Ultimate (B:)	Primary (B):
Syracure BPP:	0,5175	0,5392	2,7526	3,5162
Syracuse MITI:	0,31	0,2677	----------	----------

A) >= 0.5 degrades fast. B) 4= Hours 3 = Weeks 2= Months 1= Years

BIODEGRADATION II:	Test	QSAR	QSAR Quality	Percent
DEPA Multicase READY	4	NEG	AOK	25

BIOCONCENTRATION FACTOR: LogBCF1 (Bintein): 0,6881757 LogBCF2 (Syracuse): 0,37

LBB1 (LC-50) Fish (mg/l):	Non polar narc.: 179,0666	Non-polar narc.:	372,5549
LBB2 (LC-50) Fish (mg/l):	Polar narc.: 43,94273	Polar narc.:	91,42452

MULTICASE Aq. Tox	Test	QSAR	QSAR Quality	Percent	Disc. score	Cover	Alert
Fath. minn. LC50 mg/l	171	171	AOK	89	EQU	-	BM
Daphnia m. LC50 mg/l	0,12	0,12	AOK	88	POS	-	BA
Algae (Selen.) EC50 mg/l	3,900001	3,900001	AOK	75	POS	-	B?A
Tetrahym p. IG50 mg/l	119,56	108,9915	WRN	85	EQU	-	BM

MCASEQSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

Cytochrome P450

2D6 substrate	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Multicase	-	NEG	AOK	18	-	-
Leadscope		0	Predicted	0,267		
2D6 inhibitor, PASS		0,0939				
2D6 S/I, Leadscope		0,38	-			
3A4 substrate	-	NEG	AOK	N/A	-	-
3A4 inhibitor, PASS		0,0651				
3A4 S/I, Leadscope		0,138	-			

2C9 substrate
SciQSAR 0,071785 PASS -0,4308
2C9 inhibitor, PASS 0,5606

2C9 S/I, Leadscope	0,209	-
1A2 substrate, Leadscope	0,947	-
1A2 inhibitor, PASS	0,1973	
1A2 S/I, Leadscope	-	Not in Domain

2C19 substrate
SciQSAR 0,18987 PASS 0,3546
2C19 S/I, Leadscope 0,344 -

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

	Pharma LD50 [mg]	Pharma Reliability	RTECS LD50 [mg]
Rat, oral:	500	0,78	-
Mouse, oral:	550	0,81	330
Rat, intraperitoneal:	300	0,67	-
Mouse, intraperitoneal:	120	0,78	50
Rat, intravenous:			-
Mouse, intravenous:	100	0,7	-
Mouse, subcutaneous:	110	0,64	

Pharma Probabilities	LD50 <= 5 mg/kg	LD50 <= 50 mg/k	LD50 <= 300 mg/k	LD50 <= 3000 mg/kg
	0,002	0,02	0,237	0,946

LD50, other tests: 336 mg/kg orl-rat

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Skin irritation						
MC (severe):	POS	POS	AOK	66	-	B?A
		Strong	Moderate	Weak	Inactive	Effect
PASS		0,3277	0,3969	0,4191	0,7011	0,4018
PASS Eye irritation		0,3983	0,7273	0,5418	0,6931	
Sensitization (GPM+H)	-	POS	AOK	90	-	B
Respiratory allergy:	-	NEG	AOK	23	-	-
MC Teratogenicity (Hum.):	-	NEG	AOK	21	-	-
PASS Teratogenicity		0,3897				
Estrogen RB (Hum.) I:	-	NEG	AOK	23	-	-
Estrogen RB (Hum.) II:	-	NEG	AOK	19	-	-
Estr. Reporter (Hum.):	-	NEG	AOK	21	-	-
Antiandrogen in vitro:	-	NEG	AOK	22	-	-
MC ArH receptor binding:		EQU	AOK	60	-	b
SciQSAR ArH:		N/A				

MCASEQSAR Quality: AOK, A1B = Good prediction, FRG = Unknown fragment, WRN = P

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
DNA react. (Ashby):	POS	POS	AOK	96	-	BA
Mutagenicity II (Ames):	-	POS	AOK	78	-	B
Mutagenicity II (Ames), eld:		EQU	AOK	78	-	B
Direct, S9 (Ames):	NEG	NEG	AOK	22	-	dI
Base pair (Ames):	NEG	NEG	AOK	23	-	I
Frame shift (Ames):	NEG	NEG	AOK	73	-	BI
Rev. > 10xCtrl (Ames):	-	EQU	AOK	80	-	B
Chrom. aberration (CHO):		NEG-	AOK	21	-	d
Chrom. aberration (CHL):	POS	POS	AOK	85	-	BA
Mouse lymphoma (GTX):		EQU	AOK	72	-	B
CHO - HGPRT (GTX)	-	NEG	AOK	25	-	-
UDS - Rat hepatocyte:	-	NEG	AOK	23	-	-
SHE - Cell transformation:		EQU	AOK	70	-	B
Dros. SI-Rec. Lethal:	-	NEG	AOK	23	-	-
Mouse micronucleus II:	-	NEG	AOK	22	-	-
Rodent, Dom. Lethal:	-	NEG	AOK	21	-	-
Mouse, SCE bone marrow:		EQU	AOK	73	-	B
Mouse, COMET assay:	-	EQU	AOK	77	-	B

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
FDA Cancer male Rat:	NEG	NEG	AOK	78	-	BI
- CDER Proprietary:	POS	POS	AOK	84	-	BA
- CDER Proprietary new:	NEG	NEG	AOK	78	-	BI

FDA Cancer female Rat:	POS	POS	AOK	75	-	BA	
- CDER Proprietary:	POS	POS	AOK	75	-	BA	
- CDER Proprietary new:	-	POS	AOK	84	-	B	
FDA Cancer male Mouse:	NEG	NEG	AOK	78	-	BI	
- CDER Proprietary:	NEG	NEG	AOK	23	-	I	
- CDER Proprietary new:	POS	POS	AOK	84	-	BA	
FDA Cancer fem. Mouse:	POS	POS	AOK	75	-	BA	
- CDER Proprietary:	POS	POS	AOK	66	-	bA	
- CDER Proprietary new:	POS	POS	AOK	75	-	BA	Disc. score
CPDB Rat TD50 mg/k	-	380,28	AOK	95	-	BI	NEG
CPDB Mouse TD50 mg/l	-	49,94	AOK	95	-	BA	POS
CPDB Liver specif	POS	POS	AOK	66	-	bA	

FDA ICSAS: +A SSA: 4 Comment:-
AG1: - AG2: + AG3: + AG4: +

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

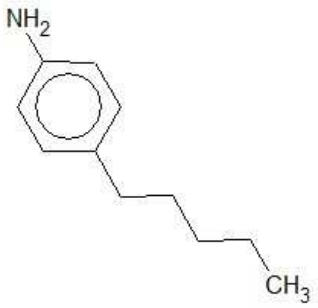
Test	QSAR	Domain error
Leadscope Developmental Toxicity		
Fetal_death_mouse:	0,2385	-
Fetal_death_rabbit:	0,164	-
Fetal_death_rat:	0,197	-
Fetal_death_rodent:	0,1855	-
Post_impl_mouse_(AG6):	0,154	-
Post_impl_rodent_(AG1):	0,267	-
Post_impl._loss_rabbit:	0,121	-
Post_impl._loss_rat:	0,256	-
Pre_impl._loss_mouse:	0,338	-
Pre_impl._loss_rabbit:	0,123	-
Pre_impl._loss_rat:	0,169	-
Pre_impl._loss_rodent:	0,199	-
Retard_rodent_(AH1):	0,151	-
Retardation_mouse:	0,264	-
Retardation_rabbit:	0,284	-
Retardation_rat:	0,117	-
Struct_mouse_(AL6):	0,313	-
Struct_rodent_(AL1):	0,4	-
Structural_rabbit:	0,208	-
Structural_rat:	0,4615	-
Visceral_mouse:	0,3967	-
Visceral_rat:	0,2715	-
Visceral_rodent:	0,3033	-
Weight_dec._mouse:	0,2664	-
Weight_dec._rabbit:	0,0978	-
Weight_dec._rat:	0,254	-
Wt_dec_rodent_(AI1):	0,163	-
PASS Embryotoxicity:	0,401	

Test	QSAR	Domain error
Leadscope Cardiac effects		
Arrhythmia:	0,153	-
Bradycardia:	0,15	-
Conduction:	0,0984	-
Coronary artery:	0,0913	-
Electrocardiogram:	0,126	-
Heart failure:	0,131	-
Myocardial:	0,0147	-
Myocardial infarct:	0,125	-
Palpitations:	0,116	-
QT prolongation:	0,1192	-
Rate rhythm:	0,281	-
Tachycardia:	0,246	-
Torsades:	0,103	-
Leadscope Reproductive Toxicity		
Repro_mouse_female:	-	Not in Domain
Repro_mouse_male:	-	Not in Domain
Repro_rat_female:	0,209	-
Repro_rat_male:	0,335	-
Repro_rodent_female:	0,2837	-

Test	QSAR	Domain error
Hepatobiliary effects		
Bile duct:	-	Not in Domain
Enzyme release:	0,1445	-
Gall bladder:	-	Not in Domain
Jaundice:	-	Not in Domain
Liver acute:	-	Not in Domain
PASS Hepatotoxicity	0,6226	
Urinary tract effects		
Bladder:	0,24	-
Blood urine:	-	Not in Domain
Kidney:	-	Not in Domain
Kidney function:	-	Not in Domain
Nephropathy:	-	Not in Domain
Urolithiasis:	-	Not in Domain
PASS Nephrotoxicity:	0,4985	

Repro_rodent_male:	0,375	-
Sperm_mouse(AP5):	0,0266	-
Sperm_rat:	0,9415	-
Sperm_rodent:	0,4835	-

CAS: 33228-44-3



EINECS No: - REACH EC Number:- Found in: TSCA; IUCLID; METI_Japan

DK EPA Advisory list classifications 2010:

CLP: - DSD: -

Physico chemical properties:

Molecular wt.:	163,26	Melting point (C)	55,08	Boiling point (C):	275,81
Vapour press. mmHG:	0,0037	Henry's const. atm-m3/Mole:	1E-5		
Solubility mg/l:	69,87	LogP oct/water:	3,59	LogKoc	2,9441
Max.sat.vap.conc. mg/l@20C:	0,03248931	Dermal abs.mg/cm2/event:	0,0053	(Moderate)	
Bioavail. (Rule of 5):	0	% G.I. abs. /dose 1 m	100	Reactive groups:	-
Log blood-brain:	0,5218	% G.I. abs./dose 1000mg:	90		
Energy HOMO:	-8,36648	Energy LUMO:	0,6198	T95, days:	3,114449
Ionization, pH=7.4	pKa Acid:	999		pKa Base:	4,9
LogD: 3,55	Reliability, pKa Acid:	0		Reliability, pKa Base:	0,4

ESTIMATED HALF-LIFE IN DAYS:

Hydrolysis: 0 Atmosph. oxidation (OH): 0,07839421 Atmosph. ox. (Ozone):-

ENVIRONMENTAL PARTITIONING (McKay):

	Air (%)	Water (%)	Soil (%)	Sediment (%)	
(I):	20,26718	49,99741	15,38038	14,35502	
(III):	0,199	24,3	74,6	0,864	Persistence time (hr): 458
(III), Half life:	1,88	360	720	3240	

BIODEGRADATION I:	Linear (A):	Non linear (A):	Ultimate (B:)	Primary (B):
Syracure BPP:	0,5992	0,7693	2,9269	3,7043
Syracuse MITI:	0,1946	0,148	----------	----------

A) >= 0.5 degrades fast. B) 4= Hours 3 = Weeks 2= Months 1= Years

BIODEGRADATION II:	Test	QSAR	QSAR Quality	Percent
DEPA Multicase READY	4	EQU	AOK	84

BIOCONCENTRATION FACTOR: LogBCF1 (Bintein): 2,478634 LogBCF2 (Syracuse:) 1,91

LBB1 (LC-50) Fish (mg/l):	Non polar narc.:	4,41981	Non-polar narc.:	16,36958
LBB2 (LC-50) Fish (mg/l):	Polar narc.:	1,084616	Polar narc.:	4,017074

MULTICASE Aq. Tox	Test	QSAR	QSAR Quality	Percent	Disc. score	Cover	Alert
Fath. minn. LC50 mg/l	-	7,55	AOK	89	POS	-	B
Daphnia m. LC50 mg/l	-	1,26	AOK	88	POS	-	B
Algae (Selen.) EC50 mg/l		1,220821	AOK	83	POS	-	B
Tetrahym p. IG50 mg/l	3,21	12,09595	AOK	97	POS	-	2BA

MCASEQSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

Cytochrome P450

2D6 substrate	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Multicase	-	NEG	AOK	18	-	-
Leadscope		0	Predicted	0,293		
2D6 inhibitor, PASS		0,1539				
2D6 S/I, Leadscope		-	-			
3A4 substrate	-	NEG	AOK	N/A	-	-
3A4 inhibitor, PASS		0,0492				
3A4 S/I, Leadscope		-	-			

2C9 substrate

SciQSAR - PASS -0,2345

2C9 inhibitor, PASS 0,598

2C9 S/I, Leadscope	-	-
1A2 substrate, Leadscope	-	-
1A2 inhibitor, PASS	0,2522	
1A2 S/I, Leadscope	-	-
2C19 substrate		
SciQSAR -		PASS 0,3272
2C19 S/I, Leadscope	-	-

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

	Pharma LD50 [mg]	Pharma Reliability	RTECS LD50 [mg]
Rat, oral:	1700	0,3	-
Mouse, oral:	410	0,75	-
Rat, intraperitoneal:	230	0,53	-
Mouse, intraperitoneal:	130	0,45	-
Rat, intravenous:			-
Mouse, intravenous:	34,88	0,34	-
Mouse, subcutaneous:	310	0,32	

Pharma Probabilities	LD50 <= 5 mg/kg	LD50 <= 50 mg/k	LD50 <= 300 mg/k	LD50 <= 3000 mg/kg
	0,006	0,028	0,12	0,632

LD50, other tests: - -

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Skin irritation						
MC (severe):	-	POS	WRN	87	-	B
		Strong	Moderate	Weak	Inactive	Effect
PASS		0,3419	0,4687	0,4374	0,6076	0,4351
PASS Eye irritation		0,4545	0,6682	0,5235	0,6906	
Sensitization (GPM+H)	-	POS	AOK	90	-	B
Respiratory allergy:	-	NEG-	AOK	23	-	d
MC Teratogenicity (Hum.):		NEG	AOK	21	-	-
PASS Teratogenicity		0,3861				
Estrogen RB (Hum.) I:	-	NEG	AOK	23	-	-
Estrogen RB (Hum.) II:	NEG	NEG	AOK	19	-	dI
Estr. Reporter (Hum.):	NEG	NEG	AOK	21	-	I
Antiandrogen in vitro:	-	NEG	AOK	22	-	-
MC ArH receptor binding:		EQU	AOK	60	-	b
SciQSAR ArH:		N/A				

MCASEQSAR Quality: AOK, A1B = Good prediction, FRG = Unknown fragment, WRN = P

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
DNA react. (Ashby):	-	POS	AOK	96	-	B
Mutagenicity II (Ames):	-	POS	AOK	78	-	B
Mutagenicity II (Ames), old:		EQU	AOK	78	-	B
Direct, S9 (Ames):	-	EQU-	AOK	60	-	Bd
Base pair (Ames):	-	POS	WRN	80	-	B?
Frame shift (Ames):	-	EQU	AOK	73	-	B
Rev. > 10xCtrl (Ames):	-	EQU	AOK	80	-	B
Chrom. aberration (CHO):		NEG	AOK	21	-	-
Chrom. aberration (CHL):		POS	AOK	85	-	B
Mouse lymphoma (GTX):		EQU	AOK	72	-	B
CHO - HGPRT (GTX)	-	NEG	AOK	25	-	-
UDS - Rat hepatocyte:	-	POS	AOK	87	-	B
SHE - Cell transformation:		EQU-	AOK	70	-	BD
Dros. SI-Rec. Lethal:	-	POS	WRN	91	-	B
Mouse micronucleus II:	-	NEG	AOK	22	-	-
Rodent, Dom. Lethal:	-	NEG	AOK	21	-	-
Mouse, SCE bone marrow:		EQU	AOK	73	-	B
Mouse, COMET assay:	-	EQU-	AOK	77	-	Bd

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
FDA Cancer male Rat:	-	EQU	AOK	78	-	B
- CDER Proprietary:	-	POS	AOK	84	-	B
- CDER Proprietary new:	-	POS	AOK	78	-	B

FDA Cancer female Rat:	-	EQU	AOK	75	-	B	
- CDER Proprietary:	-	EQU	AOK	75	-	B	
- CDER Proprietary new:	-	POS	AOK	84	-	B	
FDA Cancer male Mouse:	-	EQU	AOK	78	-	B	
- CDER Proprietary:	-	NEG	AOK	23	-	-	
- CDER Proprietary new:	-	POS	AOK	84	-	B	
FDA Cancer fem. Mouse:	-	EQU	AOK	75	-	B	
- CDER Proprietary:	-	NEG	AOK	22	-	-	
- CDER Proprietary new:	-	POS	AOK	75	-	B	Disc. score
CPDB Rat TD50 mg/k	-	12,78	AOK	95	-	B	POS
CPDB Mouse TD50 mg/l	-	16,6	AOK	95	-	B	POS
CPDB Liver specif	-	NEG	AOK	19	-	-	

FDA ICSAS: + SSA: 4 Comment: -
AG1: + AG2: + AG3: + AG4: (+)

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

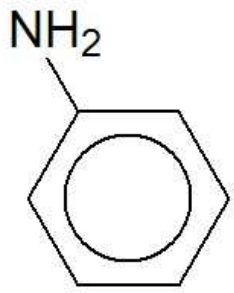
Test	QSAR	Domain error
Leadscope Developmental Toxicity		
Fetal_death_mouse:	-	-
Fetal_death_rabbit:	-	-
Fetal_death_rat:	-	-
Fetal_death_rodent:	-	-
Post_impl_mouse_(AG6):	-	-
Post_impl_rodent_(AG1):	-	-
Post_impl._loss_rabbit:	-	-
Post_impl._loss_rat:	-	-
Pre_impl._loss_mouse:	-	-
Pre_impl._loss_rabbit:	-	-
Pre_impl._loss_rat:	-	-
Pre_impl._loss_rodent:	-	-
Retard_rodent_(AH1):	-	-
Retardation_mouse:	-	-
Retardation_rabbit:	-	-
Retardation_rat:	-	-
Struct_mouse_(AL6):	-	-
Struct_rodent_(AL1):	-	-
Structural_rabbit:	-	-
Structural_rat:	-	-
Visceral_mouse:	-	-
Visceral_rat:	-	-
Visceral_rodent:	-	-
Weight_dec._mouse:	-	-
Weight_dec._rabbit:	-	-
Weight_dec._rat:	-	-
Wt_dec_rodent_(AI1):	-	-
PASS Embryotoxicity:	0,381	

Test	QSAR	Domain error
Leadscope Cardiac effects		
Arrhythmia:	-	-
Bradycardia:	-	-
Conduction:	-	-
Coronary artery:	-	-
Electrocardiogram:	-	-
Heart failure:	-	-
Myocardial:	-	-
Myocardial infarct:	-	-
Palpitations:	-	-
QT prolongation:	-	-
Rate rhythm:	-	-
Tachycardia:	-	-
Torsades:	-	-
Leadscope Reproductive Toxicity		
Repro_mouse_female:	-	-
Repro_mouse_male:	-	-
Repro_rat_female:	-	-
Repro_rat_male:	-	-
Repro_rodent_female:	-	-

Test	QSAR	Domain error
Hepatobiliary effects		
Bile duct:	-	-
Enzyme release:	-	-
Gall bladder:	-	-
Jaundice:	-	-
Liver acute:	-	-
PASS Hepatotoxicity	0,4842	
Urinary tract effects		
Bladder:	-	-
Blood urine:	-	-
Kidney:	-	-
Kidney function:	-	-
Nephropathy:	-	-
Urolithiasis:	-	-
PASS Nephrotoxicity:	0,4043	

Repro_rodent_male:	-	-
Sperm_mouse(AP5):	-	-
Sperm_rat:	-	-
Sperm_rodent:	-	-

CAS: 62-53-3



EINECS No: 200-539-3 REACH EC Number:200-539-3 Found in: HPVC_EU; HPVC_USEPA; DSL; IUCLID; METI_Japan; PEST_Inert; TSCA
DK EPA Advisory list classifications 2010:
CLP: - DSD: -

Physico chemical properties:

Molecular wt.:	93,13	Melting point (C)	-6,16	Boiling point (C):	183,99
Vapour press. mmHG:	0,791	Henry's const. atm-m3/Mole:	1,9E-6		
Solubility mg/l:	18790	LogP oct/water:	1,08	LogKoc	1,6511
Max.sat.vap.conc. mg/l@20C:	3,962096	Dermal abs.mg/cm2/event:	0,037	(Moderate)	
Bioavail. (Rule of 5):	0	% G.I. abs. /dose 1 m	90	Reactive groups:	-
Log blood-brain:	0,0198	% G.I. abs./dose 1000mg:	90		
Energy HOMO:	-8,52005	Energy LUMO:	0,64066	T95, days:	0,2846042
Ionization, pH=7.4	pKa Acid:	999		pKa Base:	4,6
LogD: 1,13	Reliability, pKa Acid:	0		Reliability, pKa Base:	0,4

ESTIMATED HALF-LIFE IN DAYS:
Hydrolysis: 0 Atmosph. oxidation (OH): 0,09936214 Atmosph. ox. (Ozone): -

ENVIRONMENTAL PARTITIONING (McKay):

	Air (%)	Water (%)	Soil (%)	Sediment (%)	
(I):	15,50368	84,34131	0,08017888	0,07483362	
(III):	0,336	45	54,6	0,0886	Persistence time (hr): 946
(III), Half life:	2,29	360	720	3240	

BIODEGRADATION I:	Linear (A):	Non linear (A):	Ultimate (B:)	Primary (B):
Syracure BPP:	0,5975	0,829	2,8804	3,6099
Syracuse MITI:	0,3185	0,3125	----------	----------

A) >= 0.5 degrades fast. B) 4= Hours 3 = Weeks 2= Months 1= Years

BIODEGRADATION II:	Test	QSAR	QSAR Quality	Percent
DEPA Multicase READY	2	NEG	AOK	25

BIOCONCENTRATION FACTOR: LogBCF1 (Bintein): 0,196793 LogBCF2 (Syracuse): 0,5

LBB1 (LC-50) Fish (mg/l):	Non polar narc.:	482,4521	Non-polar narc.: 240,0199
LBB2 (LC-50) Fish (mg/l):	Polar narc.:	118,3931	Polar narc.: 58,90058

MULTICASE Aq. Tox	Test	QSAR	QSAR Quality	Percent	Disc. score	Cover	Alert
Fath. minn. LC50 mg/l	75,5	75,5	AOK	25	EQU	-	M
Daphnia m. LC50 mg/l	0,16	0,16	AOK	99	POS	-	2BA
Algae (Selen.) EC50 mg/l	70	70	AOK	24	EQU	-	M
Tetrahym p. IG50 mg/l	72,42	170,7024	WRN	85	EQU	-	BM

MCASEQSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

Cytochrome P450

2D6 substrate	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Multicase	NEG	NEG	AOK	18	-	-
Leadscope		0	Predicted	0,241		
2D6 inhibitor, PASS		0,1565				
2D6 S/I, Leadscope		0,312	-			
3A4 substrate	NEG	NEG	AOK	N/A	-	I
3A4 inhibitor, PASS		0,1131				
3A4 S/I, Leadscope		0,0387	-			

2C9 substrate
SciQSAR 0,068396 PASS -0,5267
2C9 inhibitor, PASS 0,5259

2C9 S/I, Leadscope	0,128	-
1A2 substrate, Leadscope	0,908	-
1A2 inhibitor, PASS	0,2134	
1A2 S/I, Leadscope	-	Not in Domain

2C19 substrate
SciQSAR 0,15525 PASS 0,3371
2C19 S/I, Leadscope 0,334 -

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

	Pharma LD50 [mg]	Pharma Reliability	RTECS LD50 [mg]
Rat, oral:	490	0,78	250
Mouse, oral:	510	0,86	464
Rat, intraperitoneal:	220	0,44	420
Mouse, intraperitoneal:	150	0,7	492
Rat, intravenous:			-
Mouse, intravenous:	93,21	0,71	-
Mouse, subcutaneous:	110	0,61	

Pharma Probabilities	LD50 <= 5 mg/kg	LD50 <= 50 mg/k	LD50 <= 300 mg/k	LD50 <= 3000 mg/kg
	0,002	0,021	0,247	0,948

LD50, other tests: 250 mg/kg orl-rat

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Skin irritation						
MC (severe):	-	NEG-	AOK	23	-	d
		Strong	Moderate	Weak	Inactive	Effect
PASS		0,2538	0,2667	0,3485	0,6336	0,2875
PASS Eye irritation		0,3436	0,5863	0,4494	0,7076	
Sensitization (GPM+H)	POS	POS	AOK	90	-	BA
Respiratory allergy:	-	NEG	AOK	23	-	-
MC Teratogenicity (Hum.):	-	NEG	AOK	21	-	-
PASS Teratogenicity		0,4227				
Estrogen RB (Hum.) I:	-	NEG	AOK	23	-	-
Estrogen RB (Hum.) II:	-	NEG-	AOK	19	-	2d
Estr. Reporter (Hum.):	-	NEG	AOK	21	-	-
Antiandrogen in vitro:	-	NEG	AOK	22	-	-
MC ArH receptor binding:		NEG	AOK	22	-	-
SciQSAR ArH:		N/A				

MCASEQSAR Quality: AOK, A1B = Good prediction, FRG = Unknown fragment, WRN = P

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
DNA react. (Ashby):	POS	POS	AOK	96	-	BA
Mutagenicity II (Ames):	-	EQU	WRN	78	-	B
Mutagenicity II (Ames), eld:		EQU	AOK	78	-	B
Direct, S9 (Ames):	-	NEG	AOK	22	-	-
Base pair (Ames):	-	NEG	AOK	23	-	-
Frame shift (Ames):	-	EQU	AOK	73	-	B
Rev. > 10xCtrl (Ames):	-	EQU	AOK	95	-	2B
Chrom. aberration (CHO):	POS	POS	AOK	81	-	BA
Chrom. aberration (CHL):	NEG	NEG	AOK	85	-	BI
Mouse lymphoma (GTX):	POS	POS	AOK	72	-	BA
CHO - HGPRT (GTX)	-	NEG	AOK	25	-	-
UDS - Rat hepatocyte:	NEG	NEG	AOK	23	-	dI
SHE - Cell transformation	NEG	NEG	AOK	23	-	I
Dros. SI-Rec. Lethal:	-	NEG	AOK	23	-	-
Mouse micronucleus II:	POS	POS	AOK	66	-	bA
Rodent, Dom. Lethal:	-	NEG	AOK	21	-	-
Mouse, SCE bone marrow:	POS	POS	AOK	73	-	BA
Mouse, COMET assay:	POS	POS	AOK	69	-	BA

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
FDA Cancer male Rat:	POS	POS	AOK	66	-	bA
- CDER Proprietary:	NEG	NEG	AOK	22	-	I
- CDER Proprietary new:	POS	POS	AOK	66	-	bA

FDA Cancer female Rat:	NEG	NEG	AOK	23	-	I	
- CDER Proprietary:	NEG	NEG	AOK	22	-	I	
- CDER Proprietary new:	POS	POS	AOK	66	-	bA	
FDA Cancer male Mouse:	POS	POS	AOK	66	-	bA	
- CDER Proprietary:	POS	POS	AOK	66	-	bA	
- CDER Proprietary new:	NEG	NEG	AOK	21	-	I	
FDA Cancer fem. Mouse:	NEG	NEG	AOK	23	-	I	
- CDER Proprietary:	NEG	NEG	AOK	22	-	I	
- CDER Proprietary new:	NEG	NEG	AOK	22	-	I	Disc. score
CPDB Rat TD50 mg/k	-	330,5	AOK	0	-	2BA	POS
CPDB Mouse TD50 mg/l	-	750,38	AOK	95	-	BI	NEG
CPDB Liver specif	NEG	NEG	AOK	19	-	I	

FDA ICSAS: ?A SSA: 2 Comment:-
AG1: + AG2: + AG3: - AG4: -

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

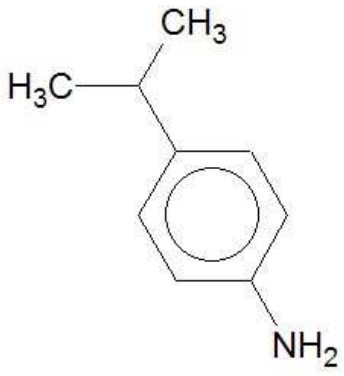
Test	QSAR	Domain error
Leadscope Developmental Toxicity		
Fetal_death_mouse:	0,1205	-
Fetal_death_rabbit:	-	Not in Domain
Fetal_death_rat:	0,1985	-
Fetal_death_rodent:	0,186	-
Post_impl_mouse_(AG6):	0,197	-
Post_impl_rodent_(AG1):	0,248	-
Post_impl._loss_rabbit:	-	Not in Domain
Post_impl._loss_rat:	0,257	-
Pre_impl._loss_mouse:	0,1344	-
Pre_impl._loss_rabbit:	-	Not in Domain
Pre_impl._loss_rat:	0,1595	-
Pre_impl._loss_rodent:	0,1925	-
Retard_rodent_(AH1):	0,158	-
Retardation_mouse:	0,0886	-
Retardation_rabbit:	-	Not in Domain
Retardation_rat:	0,156	-
Struct_mouse_(AL6):	0,242	-
Struct_rodent_(AL1):	0,275	-
Structural_rabbit:	-	Not in Domain
Structural_rat:	0,304	-
Visceral_mouse:	0,2142	-
Visceral_rat:	0,264	-
Visceral_rodent:	0,236	-
Weight_dec._mouse:	0,06425	-
Weight_dec._rabbit:	-	Not in Domain
Weight_dec._rat:	0,234	-
Wt_dec_rodent_(AI1):	0,172	-
PASS Embryotoxicity:	0,4301	

Test	QSAR	Domain error
Leadscope Cardiac effects		
Arrhythmia:	-	Not in Domain
Bradycardia:	0,571	-
Conduction:	0,096	-
Coronary artery:	0,0691	-
Electrocardiogram:	0,12	-
Heart failure:	0,126	-
Myocardial:	0,0291	-
Myocardial infarct:	0,0938	-
Palpitations:	-	Not in Domain
QT prolongation:	0,1151	-
Rate rhythm:	0,469	-
Tachycardia:	-	Not in Domain
Torsades:	0,152	-
Leadscope Reproductive Toxicity		
Repro_mouse_female:	-	Not in Domain
Repro_mouse_male:	-	Not in Domain
Repro_rat_female:	0,1965	-
Repro_rat_male:	-	Not in Domain
Repro_rodent_female:	0,2595	-

Test	QSAR	Domain error
Hepatobiliary effects		
Bile duct:	-	Not in Domain
Enzyme release:	-	Not in Domain
Gall bladder:	-	Not in Domain
Jaundice:	0,161	-
Liver acute:	-	Not in Domain
PASS Hepatotoxicity	0,6077	
Urinary tract effects		
Bladder:	0,236	-
Blood urine:	-	Not in Domain
Kidney:	-	Not in Domain
Kidney function:	-	Not in Domain
Nephropathy:	-	Not in Domain
Urolithiasis:	-	Not in Domain
PASS Nephrotoxicity:	0,5112	

Repro_rodent_male:	-	Not in Domain
Sperm_mouse(AP5):	0,0318	-
Sperm_rat:	0,474	-
Sperm_rodent:	0,193	-

CAS: 99-88-7



EINECS No: 202-797-2 REACH EC Number:202-797-2 Found in: METI_Japan; TSCA; IUCLID; HPVC_EU

DK EPA Advisory list classifications 2010:

CLP: Carc2 AcuteTox4 SkinSens1 Chron2 DSD: Carc3;R40 Xn;R22 R43 N;R51/53

Physico chemical properties:

Molecular wt.:	135,21	Melting point (C)	23,17	Boiling point (C):	230,83
Vapour press. mmHG:	0,101	Henry's const. atm-m3/Mole:	3,7E-6		
Solubility mg/l:	1150	LogP oct/water:	2,53	LogKoc	2,3447
Max.sat.vap.conc. mg/l@20C:	0,7344955	Dermal abs.mg/cm2/event:	0,012	(Moderate)	
Bioavail. (Rule of 5):	0	% G.I. abs. /dose 1 m	95	Reactive groups:	-
Log blood-brain:	0,3098	% G.I. abs./dose 1000mg:	90		
Energy HOMO:	-8,3896	Energy LUMO:	0,62908	T95, days:	1,133813
Ionization, pH=7.4	pKa Acid:	999		pKa Base:	4,9
LogD: 2,28	Reliability, pKa Acid:	0		Reliability, pKa Base:	0,4

ESTIMATED HALF-LIFE IN DAYS:

Hydrolysis: 0 Atmosph. oxidation (OH): 0,08114494 Atmosph. ox. (Ozone): -

ENVIRONMENTAL PARTITIONING (McKay):

	Air (%)	Water (%)	Soil (%)	Sediment (%)	
(I):	34,61335	62,16645	1,665619	1,554578	
(III):	0,107	23,3	76,4	0,188	Persistence time (hr): 909
(III), Half life:	1,95	900	1800	8100	

BIODEGRADATION I:	Linear (A):	Non linear (A):	Ultimate (B:)	Primary (B):
Syracure BPP:	0,5041	0,44	2,6906	3,4758
Syracuse MITI:	0,1761	0,1392	----------	----------

A) >= 0.5 degrades fast. B) 4= Hours 3 = Weeks 2= Months 1= Years

BIODEGRADATION II:	Test	QSAR	QSAR Quality	Percent
DEPA Multicase READY	4	EQU	WRN	75

BIOCONCENTRATION FACTOR: LogBCF1 (Bintein): 1,516102 LogBCF2 (Syracuse:): 1,22

LBB1 (LC-50) Fish (mg/l):	Non polar narc.:	33,57872	Non-polar narc.: 66,39974
LBB2 (LC-50) Fish (mg/l):	Polar narc.:	8,240175	Polar narc.: 16,29442

MULTICASE Aq. Tox	Test	QSAR	QSAR Quality	Percent	Disc. score	Cover	Alert
Fath. minn. LC50 mg/l	-	16,69	AOK	97	POS	-	2B
Daphnia m. LC50 mg/l	-	2,11	AOK	88	POS	-	B
Algae (Selen.) EC50 mg/l		70,97585	AOK	24	NEG	-	-
Tetrahym p. IG50 mg/l	81,86	51,41843	WRN	85	EQU	-	BM

MCASEQSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

Cytochrome P450

2D6 substrate	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Multicase	-	NEG	AOK	18	-	-
Leadscope		0	Predicted	0,268		
2D6 inhibitor, PASS		0,086				
2D6 S/I, Leadscope		0,459	-			
3A4 substrate	-	NEG	AOK	N/A	-	-
3A4 inhibitor, PASS		0,1289				
3A4 S/I, Leadscope		0,107	-			

2C9 substrate

SciQSAR 0,13932 PASS -0,4286

2C9 inhibitor, PASS 0,6223

2C9 S/I, Leadscope	0,202	-
1A2 substrate, Leadscope	0,884	-
1A2 inhibitor, PASS	0,1063	
1A2 S/I, Leadscope	0,725	-

2C19 substrate
SciQSAR 0,24075 PASS 0,3732
2C19 S/I, Leadscope 0,382 -

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

	Pharma LD50 [mg]	Pharma Reliability	RTECS LD50 [mg]
Rat, oral:	870	0,85	-
Mouse, oral:	560	0,72	-
Rat, intraperitoneal:	280	0,69	-
Mouse, intraperitoneal:	200	0,55	-
Rat, intravenous:			-
Mouse, intravenous:	72,15	0,78	-
Mouse, subcutaneous:	200	0,72	

Pharma Probabilities	LD50 <= 5 mg/kg	LD50 <= 50 mg/k	LD50 <= 300 mg/k	LD50 <= 3000 mg/kg
	0,001	0,007	0,084	0,831

LD50, other tests: - -

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Skin irritation						
MC (severe):	-	POS	WRN	66	-	b

	Strong	Moderate	Weak	Inactive	Effect
PASS	0,1911	0,5291	0,4861	0,5165	0,4891
PASS Eye irritation	0,4089	0,6097	0,6398	0,5994	

Sensitization (GPM+H)	-	POS	AOK	90	-	B
Respiratory allergy:	-	NEG	AOK	23	-	-
MC Teratogenicity (Hum.):	-	NEG	AOK	21	-	-
PASS Teratogenicity		0,2908				
Estrogen RB (Hum.) I:	-	NEG	AOK	23	-	-
Estrogen RB (Hum.) II:	-	NEG	AOK	19	-	-
Estr. Reporter (Hum.):	-	NEG	AOK	21	-	-
Antiandrogen in vitro:	-	NEG	AOK	22	-	-
MC ArH receptor binding:		EQU	AOK	60	-	b
SciQSAR ArH:		N/A				

MCASEQSAR Quality: AOK, A1B = Good prediction, FRG = Unknown fragment, WRN = P

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
DNA react. (Ashby):	-	POS	AOK	96	-	B
Mutagenicity II (Ames):	-	NEG+	PRB	78	-	Bd
Mutagenicity II (Ames), eld:		EQU-	AOK	78	-	Bd
Direct, S9 (Ames):	-	NEG-	AOK	22	-	d
Base pair (Ames):	-	NEG	AOK	23	-	-
Frame shift (Ames):	-	EQU	AOK	73	-	B
Rev. > 10xCtrl (Ames):	-	EQU	AOK	80	-	B
Chrom. aberration (CHO):		NEG	AOK	21	-	-
Chrom. aberration (CHL):		POS	AOK	85	-	B
Mouse lymphoma (GTX):		EQU	AOK	72	-	B
CHO - HGPRT (GTX)	-	NEG-	AOK	25	-	d
UDS - Rat hepatocyte:	-	NEG	AOK	23	-	-
SHE - Cell transformation:		EQU	AOK	70	-	B
Dros. SI-Rec. Lethal:	-	NEG	AOK	23	-	-
Mouse micronucleus II:	-	NEG	AOK	22	-	-
Rodent, Dom. Lethal:	-	EQU	AOK	60	-	B?
Mouse, SCE bone marrow:		EQU	AOK	73	-	B
Mouse, COMET assay:	-	EQU	AOK	77	-	B

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
FDA Cancer male Rat:	-	EQU	AOK	78	-	B
- CDER Proprietary:	-	POS	AOK	84	-	B
- CDER Proprietary new:	-	POS	AOK	78	-	B

FDA Cancer female Rat:	-	EQU	AOK	75	-	B	
- CDER Proprietary:	-	EQU	AOK	75	-	B	
- CDER Proprietary new:	-	POS	AOK	84	-	B	
FDA Cancer male Mouse:	-	EQU	AOK	78	-	B	
- CDER Proprietary:	-	NEG	AOK	23	-	-	
- CDER Proprietary new:	-	POS	AOK	84	-	B	
FDA Cancer fem. Mouse:	-	EQU	AOK	75	-	B	
- CDER Proprietary:	-	NEG	AOK	22	-	-	
- CDER Proprietary new:	-	POS	AOK	75	-	B	Disc. score
CPDB Rat TD50 mg/k	-	15,68	AOK	95	-	B	POS
CPDB Mouse TD50 mg/l	-	19,02	AOK	95	-	B	POS
CPDB Liver specif	-	NEG	AOK	19	-	-	

FDA ICSAS: + SSA: 4 Comment: -
AG1: + AG2: + AG3: + AG4: (+)

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

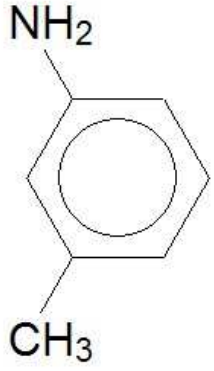
Test	QSAR	Domain error
Leadscope Developmental Toxicity		
Fetal_death_mouse:	0,2385	-
Fetal_death_rabbit:	0,177	-
Fetal_death_rat:	0,1915	-
Fetal_death_rodent:	0,2015	-
Post_impl_mouse_(AG6):	0,225	-
Post_impl_rodent_(AG1):	0,26	-
Post_impl._loss_rabbit:	0,134	-
Post_impl._loss_rat:	0,267	-
Pre_impl._loss_mouse:	0,415	-
Pre_impl._loss_rabbit:	0,127	-
Pre_impl._loss_rat:	0,1705	-
Pre_impl._loss_rodent:	0,216	-
Retard_rodent_(AH1):	0,168	-
Retardation_mouse:	0,2785	-
Retardation_rabbit:	0,282	-
Retardation_rat:	0,1163	-
Struct_mouse_(AL6):	0,268	-
Struct_rodent_(AL1):	0,381	-
Structural_rabbit:	0,192	-
Structural_rat:	0,4265	-
Visceral_mouse:	0,411	-
Visceral_rat:	0,261	-
Visceral_rodent:	0,3148	-
Weight_dec._mouse:	0,335	-
Weight_dec._rabbit:	0,096	-
Weight_dec._rat:	0,257	-
Wt_dec_rodent_(Al1):	0,208	-
PASS Embryotoxicity:	0,3426	

Test	QSAR	Domain error
Leadscope Cardiac effects		
Arrhythmia:	0,173	-
Bradycardia:	0,152	-
Conduction:	0,0963	-
Coronary artery:	0,108	-
Electrocardiogram:	0,147	-
Heart failure:	0,125	-
Myocardial:	0,0429	-
Myocardial infarct:	0,131	-
Palpitations:	0,175	-
QT prolongation:	0,1456	-
Rate rhythm:	0,296	-
Tachycardia:	0,25	-
Torsades:	0,135	-
Leadscope Reproductive Toxicity		
Repro_mouse_female:	-	Not in Domain
Repro_mouse_male:	-	Not in Domain
Repro_rat_female:	0,2173	-
Repro_rat_male:	0,33	-
Repro_rodent_female:	0,323	-

Test	QSAR	Domain error
Hepatobiliary effects		
Bile duct:	-	Not in Domain
Enzyme release:	0,126	-
Gall bladder:	-	Not in Domain
Jaundice:	0,1723	-
Liver acute:	0,439	-
PASS Hepatotoxicity	0,6875	
Urinary tract effects		
Bladder:	0,257	-
Blood urine:	-	Not in Domain
Kidney:	-	Not in Domain
Kidney function:	-	Not in Domain
Nephropathy:	-	Not in Domain
Urolithiasis:	0,1355	-
PASS Nephrotoxicity:	0,6014	

Repro_rodent_male:	0,351	-
Sperm_mouse(AP5):	0,0324	-
Sperm_rat:	0,445	-
Sperm_rodent:	0,5295	-

CAS: 108-44-1



EINECS No: 203-583-1 REACH EC Number:203-583-1 Found in: DSL; TSCA; IUCLID; HPVC_EU; METI_Japan; HPVC_USEPA
DK EPA Advisory list classifications 2010:
CLP: - DSD: -

Physico chemical properties:

Molecular wt.:	107,16	Melting point (C)	11,62	Boiling point (C):	204,16
Vapour press. mmHG:	0,306	Henry's const. atm-m3/Mole:	2,1E-6		
Solubility mg/l:	6449	LogP oct/water:	1,62	LogKoc	1,8605
Max.sat.vap.conc. mg/l@20C:	1,763653	Dermal abs.mg/cm2/event:	0,026	(Moderate)	
Bioavail. (Rule of 5):	0	% G.I. abs. /dose 1 m	90	Reactive groups:	-
Log blood-brain:	0,1278	% G.I. abs./dose 1000mg:	90		
Energy HOMO:	-8,48259	Energy LUMO:	0,60397	T95, days:	0,476213
Ionization, pH=7.4	pKa Acid:	999		pKa Base:	4,6
LogD: 1,46	Reliability, pKa Acid:	0		Reliability, pKa Base:	0,4

ESTIMATED HALF-LIFE IN DAYS:
Hydrolysis: 0 Atmosph. oxidation (OH): 0,0534436 Atmosph. ox. (Ozone): -

ENVIRONMENTAL PARTITIONING (McKay):

	Air (%)	Water (%)	Soil (%)	Sediment (%)	
(I):	19,15247	80,33557	0,2648058	0,2471521	
(III):	0,176	40	59,7	0,0907	Persistence time (hr): 969
(III), Half life:	1,28	360	720	3240	

BIODEGRADATION I:	Linear (A):	Non linear (A):	Ultimate (B:)	Primary (B):
Syracure BPP:	0,5175	0,5392	2,7526	3,5162
Syracuse MITI:	0,31	0,2677	----------	----------

A) >= 0.5 degrades fast. B) 4= Hours 3 = Weeks 2= Months 1= Years

BIODEGRADATION II:	Test	QSAR	QSAR Quality	Percent
DEPA Multicase READY	0	POS	AOK	75

BIOCONCENTRATION FACTOR: LogBCF1 (Bintein): 0,6881757 LogBCF2 (Syracuse): 0,38

LBB1 (LC-50) Fish (mg/l):	Non polar narc.: 179,0666	Non-polar narc.:	364,0746
LBB2 (LC-50) Fish (mg/l):	Polar narc.: 43,94273	Polar narc.:	89,34345

MULTICASE Aq. Tox	Test	QSAR	QSAR Quality	Percent	Disc. score	Cover	Alert
Fath. minn. LC50 mg/l	-	437,97	AOK	25	NEG	-	-
Daphnia m. LC50 mg/l	0,73	0,73	AOK	99	POS	-	4BA
Algae (Selen.) EC50 mg/l		1,263553	AOK	92	POS	-	B
Tetrahym p. IG50 mg/l	284,89	539,5016	WRN	24	EQU	-	M

MCASEQSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

Cytochrome P450

2D6 substrate	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Multicase	-	POS	AOK	80	-	B?
Leadscope		-	Not in domain	-		
2D6 inhibitor, PASS		0,0746				
2D6 S/I, Leadscope		-	Not in Domain			
3A4 substrate	-	NEG	AOK	N/A	-	-
3A4 inhibitor, PASS		0,0129				
3A4 S/I, Leadscope		0,14	-			

2C9 substrate
SciQSAR 0,089145 PASS -0,3921
2C9 inhibitor, PASS 0,5261

2C9 S/I, Leadscope	0,192	-
1A2 substrate, Leadscope	0,947	-
1A2 inhibitor, PASS	0,1658	
1A2 S/I, Leadscope	-	Not in Domain

2C19 substrate
SciQSAR 0,24293 PASS 0,2726
2C19 S/I, Leadscope 0,498 -

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WRN =

	Pharma LD50 [mg]	Pharma Reliability	RTECS LD50 [mg]
Rat, oral:	500	0,78	450
Mouse, oral:	550	0,81	740
Rat, intraperitoneal:	300	0,67	-
Mouse, intraperitoneal:	120	0,78	116
Rat, intravenous:			-
Mouse, intravenous:	100	0,7	-
Mouse, subcutaneous:	110	0,64	

Pharma Probabilities	LD50 <= 5 mg/kg	LD50 <= 50 mg/k	LD50 <= 300 mg/k	LD50 <= 3000 mg/kg
	0,002	0,02	0,237	0,946

LD50, other tests: 450 mg/kg orl-rat

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
Skin irritation						
MC (severe):	NEG	NEG	AOK	23	-	dI

	Strong	Moderate	Weak	Inactive	Effect
PASS	0,3027	0,4236	0,4342	0,7856	0,416
PASS Eye irritation	0,3936	0,7535	0,5233	0,7071	

Sensitization (GPM+H)	-	POS	AOK	90	-	B
Respiratory allergy:	-	NEG	AOK	23	-	-
MC Teratogenicity (Hum.):	-	NEG	AOK	21	-	-
PASS Teratogenicity		0,3471				
Estrogen RB (Hum.) I:	-	NEG	AOK	23	-	-
Estrogen RB (Hum.) II:	-	NEG-	AOK	19	-	d
Estr. Reporter (Hum.):	-	NEG	AOK	21	-	-
Antiandrogen in vitro:	-	NEG	AOK	22	-	-
MC ArH receptor binding:		NEG	AOK	22	-	-
SciQSAR ArH:		N/A				

MCASEQSAR Quality: AOK, A1B = Good prediction, FRG = Unknown fragment, WRN = P

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
DNA react. (Ashby):	POS	POS	AOK	96	-	BA
Mutagenicity II (Ames):	NEG	NEG	AOK	78	-	BI
Mutagenicity II (Ames), dM	NEG	NEG	AOK	78	-	BI
Direct, S9 (Ames):	-	NEG	AOK	22	-	-
Base pair (Ames):	-	NEG-	AOK	23	-	d
Frame shift (Ames):	-	EQU	AOK	73	-	B
Rev. > 10xCtrl (Ames):	-	EQU	WRN	66	-	b
Chrom. aberration (CHO):		NEG-	AOK	21	-	d
Chrom. aberration (CHL):	NEG	NEG	AOK	85	-	BI
Mouse lymphoma (GTX):		EQU	AOK	72	-	B
CHO - HGPRT (GTX)	-	EQU	WRN	75	-	b
UDS - Rat hepatocyte:	-	NEG-	AOK	23	-	d
SHE - Cell transformation:		POS	AOK	94	-	2B
Dros. SI-Rec. Lethal:	-	NEG-	AOK	23	-	d
Mouse micronucleus II:	-	NEG	AOK	22	-	-
Rodent, Dom. Lethal:	-	EQU	WRN	66	-	b
Mouse, SCE bone marrow:		POS	AOK	95	-	2B
Mouse, COMET assay:	-	NEG	AOK	23	-	-

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

	Test	QSAR	QSAR Quality	Percent	Cover	Alert
FDA Cancer male Rat:	NEG	NEG	AOK	23	-	I
- CDER Proprietary:	-	EQU	WRN	22	-	dM
- CDER Proprietary new:	NEG	NEG	AOK	22	-	dI

FDA Cancer female Rat:	NEG	NEG	AOK	23	-	dI	
- CDER Proprietary:	NEG	NEG	AOK	22	-	dI	
- CDER Proprietary new:	-	NEG-	AOK	21	-	d	
FDA Cancer male Mouse:	NEG	NEG	AOK	23	-	dI	
- CDER Proprietary:	NEG	NEG	AOK	23	-	dI	
- CDER Proprietary new:	-	-	WRN	21	-	dM	
FDA Cancer fem. Mouse:	NEG	NEG	AOK	23	-	dI	
- CDER Proprietary:	NEG	NEG	AOK	22	-	dI	
- CDER Proprietary new:	NEG	NEG	AOK	22	-	dI	Disc. score
CPDB Rat TD50 mg/k	-	999,99	AOK	95	-	BI	NEG
CPDB Mouse TD50 mg/l	-	999,99	AOK	95	-	BA	POS
CPDB Liver specif	POS	POS	AOK	87	-	BA	

FDA ICSAS: -M SSA: 0 Comment:-
AG1: - AG2: - AG3: m AG4: -

MCASE QSAR Quality: AOK = Good prediction, FRG = Unknown fragment, WR

Test	QSAR	Domain error
Leadscope Developmental Toxicity		
Fetal_death_mouse:	0,1545	-
Fetal_death_rabbit:	0,0886	-
Fetal_death_rat:	0,197	-
Fetal_death_rodent:	0,1149	-
Post_impl_mouse_(AG6):	0,154	-
Post_impl_rodent_(AG1):	0,267	-
Post_impl._loss_rabbit:	0,122	-
Post_impl._loss_rat:	0,256	-
Pre_impl._loss_mouse:	0,108	-
Pre_impl._loss_rabbit:	0,0733	-
Pre_impl._loss_rat:	0,169	-
Pre_impl._loss_rodent:	0,199	-
Retard_rodent_(AH1):	0,151	-
Retardation_mouse:	0,1375	-
Retardation_rabbit:	0,178	-
Retardation_rat:	0,156	-
Struct_mouse_(AL6):	0,313	-
Struct_rodent_(AL1):	0,294	-
Structural_rabbit:	0,208	-
Structural_rat:	0,3035	-
Visceral_mouse:	0,2447	-
Visceral_rat:	0,1846	-
Visceral_rodent:	0,1667	-
Weight_dec._mouse:	0,1014	-
Weight_dec._rabbit:	0,0978	-
Weight_dec._rat:	0,254	-
Wt_dec_rodent_(AI1):	0,163	-
PASS Embryotoxicity:	0,3723	

Test	QSAR	Domain error
Leadscope Cardiac effects		
Arrhythmia:	0,174	-
Bradycardia:	0,222	-
Conduction:	0,074	-
Coronary artery:	0,127	-
Electrocardiogram:	0,0925	-
Heart failure:	0,131	-
Myocardial:	0,058	-
Myocardial infarct:	0,22	-
Palpitations:	0,078	-
QT prolongation:	0,0874	-
Rate rhythm:	0,247	-
Tachycardia:	0,153	-
Torsades:	0,0204	-
Leadscope Reproductive Toxicity		
Repro_mouse_female:	-	Not in Domain
Repro_mouse_male:	-	Not in Domain
Repro_rat_female:	0,1685	-
Repro_rat_male:	0,335	-
Repro_rodent_female:	0,1505	-

Test	QSAR	Domain error
Hepatobiliary effects		
Bile duct:	-	Not in Domain
Enzyme release:	0,128	-
Gall bladder:	-	Not in Domain
Jaundice:	-	Not in Domain
Liver acute:	-	Not in Domain
PASS Hepatotoxicity	0,6187	
Urinary tract effects		
Bladder:	0,229	-
Blood urine:	-	Not in Domain
Kidney:	-	Not in Domain
Kidney function:	-	Not in Domain
Nephropathy:	-	Not in Domain
Urolithiasis:	-	Not in Domain
PASS Nephrotoxicity:	0,476	

Repro_rodent_male:	0,375	-
Sperm_mouse(AP5):	0,0266	-
Sperm_rat:	0,436	-
Sperm_rodent:	0,0935	-

APPENDIX 2

Derek Nexus Report

Author
rorijee
Report Date
09 August 2013 10:36:05
Prediction Date
09 August 2013 10:23:53
Program version
Derek Nexus: 3.0.1, Nexus: 1.5.0
Compound name
Structure
Constraints
Perceive alerts without rules false
Average molecular mass
135.21 (Lhasa Limited, version 1.0)
Exact molecular mass
135.1048 (Lhasa Limited, version 1.0)
Log Kp
-1.88 (Potts & Guy, version 1.0 (LogP: BioByte Corp., version 5.3; Average Molecular Mass: Lhasa Limited, version 1.0))
Log P
2.34 (BioByte Corp., version 5.3)

Submitted compound

Predictions

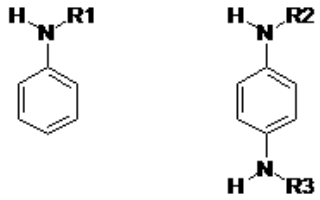
Derek KB 2012 1.0

KnowledgeBase name
Derek KB 2012 1.0
KnowledgeBase location
C:/Program Files/Lhasa Limited/Lhasa Knowledge Suite - Nexus 1.5/KnowledgeBases/org.lhasalimited.pluto.knowledge.derek_1.0.7
KnowledgeBase version
1.0
KnowledgeBase last modified
29 November 2012 11:56:30
KnowledgeBase certified by
Lhasa Limited, Leeds, Yorkshire, UK

Reasoning summary and alerts found

Skin sensitisation in mammal is PLAUSIBLE
427 Aromatic primary or secondary amine

Alert overview: 427 Aromatic primary or secondary amine



(I) (II)

R1 = H, CH3, CH2CH3, CH2CH=CH2, CH2C≡CH
R2, R3 = H, C
Amino substituted coumarins are excluded

Comments

This alert describes the skin sensitisation of aromatic amines and their N-protonated forms according to the toxicophores shown.

In order to elicit a sensitisation response aromatic amines require transformation to a species capable of reacting with a skin protein nucleophilic group. Three key mechanisms through which this could be achieved have been postulated, all of which may have a role to play.

Mechanism 1:
By analogy with the generally accepted mechanism for Ames test mutagenicity, it has been suggested that N-hydroxylation occurs, possibly mediated by cytochrome P450 enzymes [Westphal et al]. Subsequent O-esterification is thought to involve two principal processes; acetylation mediated by N-acetyltransferase, or sulphation mediated by sulphotransferase. Non-enzymatic cleavage can then give rise to a reactive nitrenium ion. The bioactivation of aromatic amines to the hydroxylamine has been confirmed within human keratinocytes [Reilly et al], while O-acetylation has been demonstrated in rodent skin [Kawakubo et al]. Sulphotransferases have been detected in human and rodent skin, although O-sulphation of the hydroxylamine has not been confirmed [Smith and Hotchkiss].

Mechanism 2:
In an alternative proposal, the protein-reactive species is a nitroso compound, formed by non-enzymic autoxidation of a hydroxylamine [Naisbitt et al 2001]. Nitroso compounds have been shown to be highly reactive with thiol groups (glutathione), but unreactive towards amine groups (lysine, aniline) [Naisbitt et al 1996].

Mechanism 3:
In a further hypothesis, certain p-substituted aromatic amines are metabolised to p-benzoquinone, which it has been proposed acts as a common hapten resulting in cross-reactivity between such compounds [Mayer, Dupuis and Benezra]. However, studies on a series of p-substituted aromatic amines in both guinea pig and man have shown limited cross-reactivity, suggesting benzoquinone is not the principal hapten for these compounds. Instead, a range of electrophilic reaction intermediates able to bind to epidermal proteins have been proposed [Basketter and Goodwin, Basketter and Liden, Lisi and Hansel].

The scope of this alert is based on the mechanistic considerations outlined above, as well as data contributed by a Lhasa Limited member and from published collections including Unilever in-house data [Cronin and Basketter] and the BgVV list of contact allergens [Kayser and Schlede]. It is assumed that p-diamine structures have the potential to react by mechanism 3 (toxicophore II), and that both p-diamines and other aromatic amines have the potential to react by mechanisms 1 and 2 provided that they are either a primary aromatic amine or can be readily metabolised to one (toxicophore I). It has been demonstrated that N-methyl and N-ethyl substituents are more readily cleaved by N-dealkylation than larger alkyl groups [Testa], and it is therefore assumed that secondary aromatic amines which bear such small alkyl substituents are more likely to exhibit skin sensitisation than those in which larger N-alkyl substituents are present. In addition to saturated methyl and ethyl groups, small unsaturated substituents such as allyl and propargyl are also readily removed by N-dealkylation [Testa], and are therefore also considered within the scope of the alert. Aromatic amides, tertiary amines, heteroaromatic compounds and coumarins are excluded from the alert as there is generally little evidence for the activity of such compounds from the sources examined. In the literature, the absence of sensitising ability of the amino substituted coumarins 7-ethylamino-4,6-dimethylcoumarin and 7-amino-4-methylcoumarin has been reported in a modified guinea pig maximisation assay [Hausen and Berger].

The presence of a skin sensitisation structural alert within a molecule indicates the molecule has the potential to cause skin sensitisation. Whether or not the molecule will be a skin sensitiser will also depend upon its percutaneous absorption. Generally, small lipophilic molecules are more readily absorbed into the skin and are therefore more likely to cause sensitisation.

References

Title	A role for bioactivation and covalent binding within epidermal keratinocytes in sulfonamide-induced cutaneous drug reactions.
Author	Reilly TP, Lash LH, Doll MA, Hein DW, Woster PM and Svensson CK.
Source	Journal of Investigative Dermatology
Year	2000
Volume	114
Pages	1164-1173
Additional Content	
DOI	10.1046/j.1523-1747.2000.00985.x
Issue Number	
Supplemental	Note: available at "http://dx.doi.org/10.1046/j.1523-1747.2000.00985.x"., DOI: 10.1046/j.1523-1747.2000.00985.x

Title	Allergic Contact Dermatitis to Simple Chemicals: A Molecular Approach.
Author	Dupuis G and Benezra C.
Source	Allergic Contact Dermatitis to Simple Chemicals: A Molecular Approach, Dupuis G and Benezra C, Marcel Dekker, New York
Year	1982
Volume	
Pages	83
Additional Content	
DOI	

Issue Number
Supplemental

Title Antigenicity and immunogenicity of sulphamethoxazole: demonstration of metabolism-dependent haptenation and T-cell proliferation in vivo.
Author Naisbitt DJ, Gordon SF, Pirmohamed M, Burkhart C, Cribb AE, Pichler WJ and Park BK.
Source British Journal of Pharmacology
Year 2001
Volume 133
Pages 295-305
Additional Content
DOI 10.1038/sj.bjp.0704074
Issue Number
Supplemental Note: available at "http://dx.doi.org/10.1038/sj.bjp.0704074"., DOI: 10.1038/sj.bjp.0704074

Title Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung.
Author Kayser D and Schlede E (editors).
Source Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung, Kayser D and Schlede E (editors), Urban & Vogel Medien und Medizin Verlagsgesellschaft, Munich
Year 2001
Volume
Pages
Additional Content
DOI
Issue Number
Supplemental

Title Further investigation of the prohapten concept: reactions to benzene derivatives in man.
Author Basketter DA and Liden C.
Source Contact Dermatitis
Year 1992
Volume 27
Pages 90-97
Additional Content
DOI 10.1111/j.1600-0536.1992.tb05216.x
Issue Number
Supplemental Note: available at "http://dx.doi.org/10.1111/j.1600-0536.1992.tb05216.x"., DOI: 10.1111/j.1600-0536.1992.tb05216.x

Title Group sensitization to compounds of quinone structure and its biochemical base.
Author Mayer RL.
Source Progress in Allergy
Year 1954
Volume 4
Pages 79-82
Additional Content
DOI
Issue Number
Supplemental

Title Investigation of the prohapten concept. Cross reactions between 1,4-substituted benzene derivatives in the guinea pig.
Author Basketter DA and Goodwin BFJ.
Source Contact Dermatitis
Year 1988
Volume 19
Pages 248-253
Additional Content
DOI 10.1111/j.1600-0536.1988.tb02921.x
Issue Number
Supplemental Note: available at "http://dx.doi.org/10.1111/j.1600-0536.1988.tb02921.x"., DOI: 10.1111/j.1600-0536.1988.tb02921.x

Title Is benzoquinone the prohapten in cross-sensitivity among aminobenzene compounds?
Author Lisi P and Hansel K.
Source Contact Dermatitis
Year 1998
Volume 39
Pages 304-306
Additional Content
DOI 10.1111/j.1600-0536.1998.tb05945.x
Issue Number
Supplemental Note: available at "http://dx.doi.org/10.1111/j.1600-0536.1998.tb05945.x"., DOI: 10.1111/j.1600-0536.1998.tb05945.x

Title Monooxygenase-catalyzed N-C cleavage.
Author Testa B.

Source	The Metabolism of Drugs and other Xenobiotics: Biochemistry of Redox Reactions, Testa B, Academic Press, London
Year	1995
Volume	
Pages	210-212
Additional Content	
DOI	
Issue Number	
Supplemental	

Title	Multivariate QSAR analysis of a skin sensitization database.
Author	Cronin MTD and Basketter DA.
Source	SAR and QSAR in Environmental Research
Year	1994
Volume	2
Pages	159-179
Additional Content	
DOI	10.1080/10629369408029901
Issue Number	
Supplemental	Note: dataset available at "http://www.inchemicotox.org/results/"., DOI: 10.1080/10629369408029901, PMID: 8790644

Title	N-Acetyltransferase 1 and 2 polymorphisms in para-substituted arylamine-induced contact allergy.
Author	Westphal GA, Reich K, Schulz TG, Neumann C, Hallier E and Schnuch A.
Source	British Journal of Dermatology
Year	2000
Volume	142
Pages	1121-1127
Additional Content	
DOI	10.1046/j.1365-2133.2000.03536.x
Issue Number	
Supplemental	Note: available at "http://dx.doi.org/10.1046/j.1365-2133.2000.03536.x"., DOI: 10.1046/j.1365-2133.2000.03536.x

Title	Properties of cutaneous acetyltransferase catalyzing N- and O-acetylation of carcinogenic arylamines and N-hydroxylarylamine.
Author	Kawakubo Y, Manabe S, Yamazoe Y, Nishikawa T and Kato R.
Source	Biochemical Pharmacology
Year	1988
Volume	37
Pages	265-270
Additional Content	
DOI	10.1016/0006-2952(88)90728-9
Issue Number	
Supplemental	Note: available at "http://dx.doi.org/10.1016/0006-2952(88)90728-9"., DOI: 10.1016/0006-2952(88)90728-9

Title	Synthesis and reactions of nitroso sulphamethoxazole with biological nucleophiles: implications for immune mediated toxicity.
Author	Naisbitt DJ, O'Neill PM, Pirmohamed M and Park BK.
Source	Bioorganic and Medicinal Chemistry Letters
Year	1996
Volume	6
Pages	1511-1516
Additional Content	
DOI	10.1016/S0960-894X(96)00260-0
Issue Number	
Supplemental	Note: available at "http://dx.doi.org/10.1016/S0960-894X(96)00260-0"., DOI: 10.1016/S0960-894X(96)00260-0

Title	The sensitizing capacity of coumarins (III).
Author	Hausen BM and Berger M.
Source	Contact Dermatitis
Year	1989
Volume	21
Pages	141-147
Additional Content	
DOI	10.1111/j.1600-0536.1989.tb04726.x
Issue Number	
Supplemental	Note: available at "http://dx.doi.org/10.1111/j.1600-0536.1989.tb04726.x"., DOI: 10.1111/j.1600-0536.1989.tb04726.x

Title	Xenobiotics as skin sensitisers: metabolic activation and detoxication, and protein-binding mechanisms.
Author	Smith CK and Hotchkiss SAM.
Source	Allergic Contact Dermatitis: Chemical and Metabolic Mechanisms, Smith CK and Hotchkiss SAM, Taylor and Francis, London
Year	2001
Volume	
Pages	119-205

Additional Content
DOI
Issue Number
Supplemental

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: 13 compounds activate this alert of which 12 are reported positive (positive predictivity = 92%)
2) Gerberick et al data set: 23 compounds activate this alert of which 19 are reported positive (positive predictivity = 83%)
3) Contact Dermatitis data set: 10 compounds activate this alert of which 3 are reported positive (positive predictivity = 30%)

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 â€œhttp://dx.doi.org/10.2310/6620.2009.09038â€□.

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.

Examples: (427 Aromatic primary or secondary amine)

Example 1. 4-chloroaniline

CAS Number: 106-47-8

Test Data: (4-chloroaniline)

1.

Species	guinea pig
Assay	maximisation test
Result	moderate
Endpoint(s)	Skin sensitisation

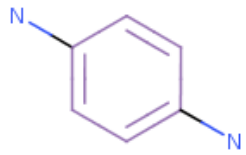
References

Title	Multivariate QSAR analysis of a skin sensitization database.
Author	Cronin MTD and Basketter DA.
Source	SAR and QSAR in Environmental Research
Year	1994
Volume	2
Pages	159-179
Additional Content	
DOI	10.1080/10629369408029901

Issue Number	
Supplemental	Note: dataset available at "http://www.inchemicotox.org/results/"., DOI: 10.1080/10629369408029901, PMID: 8790644

Example 2. p-phenylenediamine

CAS Number: 106-50-3



Comments:
Ames test data reported by Zeiger et al 1988 relate to testing of the dihydrochloride salt.
In vitro chromosome aberration test reported by NTP 1983 relate to testing of the dihydrochloride salt (CAS number = 624-18-0).

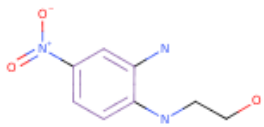
Test Data: (p-phenylenediamine)

1.

Species	guinea pig
Assay	maximisation test
Result	strong
Endpoint(s)	Skin sensitisation
References	
Title	Multivariate QSAR analysis of a skin sensitization database.
Author	Cronin MTD and Basketter DA.
Source	SAR and QSAR in Environmental Research
Year	1994
Volume	2
Pages	159-179
Additional Content	
DOI	10.1080/10629369408029901
Issue Number	
Supplemental	Note: dataset available at "http://www.inchemicotox.org/results/"., DOI: 10.1080/10629369408029901, PMID: 8790644

Example 3. 2-(2-amino-4-nitroanilino)ethanol

CAS Number: 56932-44-6



Test Data: (2-(2-amino-4-nitroanilino)ethanol)

1.

Species	guinea pig
Assay	maximisation test
Result	strong
Endpoint(s)	Skin sensitisation
References	
Title	Multivariate QSAR analysis of a skin sensitization database.
Author	Cronin MTD and Basketter DA.
Source	SAR and QSAR in Environmental Research
Year	1994
Volume	2
Pages	159-179

Additional Content	
DOI	10.1080/10629369408029901
Issue Number	
Supplemental	Note: dataset available at "http://www.inchemicotox.org/results/"., DOI: 10.1080/10629369408029901, PMID: 8790644

Locations

Reasoning details

Skin sensitisation is PLAUSIBLE

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

Rule 243: If [species mammal] is [certain] then [Species dependent variable 22] is [plausible]
species mammal is CERTAIN

Rule 903: If [alert 427] is [certain] then [Skin sensitisation] is [Species dependent variable 22]
alert 427 is CERTAIN
Species dependent variable 22 is PLAUSIBLE

Rule 243
If [species mammal] is [certain] then [Species dependent variable 22] is [plausible]

Comments:
In mammals the variable "Species dependent variable 22" is plausible.

References:

Rule 903
If [alert 427] is [certain] then [Skin sensitisation] is [Species dependent variable 22]

Comments:
If a chemical contains alert 427 then it is considered plausible 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 22".

References:

Reasoning 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.

1 of 1

Derek Nexus Report

Author
rorijee
Report date
09 August 2013 10:39:35
Prediction date
09 August 2013 10:39:19
Program version
Derek Nexus: 3.0.1, Nexus: 1.5.0

Submitted compound

Predictions

Derek KB 2012 1.0

KnowledgeBase name
Derek KB 2012 1.0
KnowledgeBase version
1.0
KnowledgeBase last modified
29 November 2012 11:56:30
KnowledgeBase location
C:/Program Files/Lhasa Limited/Lhasa Knowledge Suite - Nexus 1.5/KnowledgeBases/org.lhasalimited.pluto.knowledge.derek_1.0.7
KnowledgeBase certified by
Lhasa Limited, Leeds, Yorkshire, UK

Reasoning summary and alerts found

Skin sensitisation in mammal is PLAUSIBLE
427 Aromatic primary or secondary amine

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Open

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Contradicted

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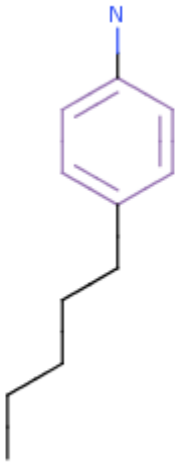
Derek Nexus Report

Author
rorijee
Report date
09 August 2013 10:46:04
Prediction date
09 August 2013 10:44:06
Program version
Derek Nexus: 3.0.1, Nexus: 1.5.0

Submitted compound



Predictions

Derek KB 2012 1.0

KnowledgeBase name
Derek KB 2012 1.0
KnowledgeBase version
1.0
KnowledgeBase last modified
29 November 2012 11:56:30
KnowledgeBase location
C:/Program Files/Lhasa Limited/Lhasa Knowledge Suite - Nexus 1.5/KnowledgeBases/org.lhasalimited.pluto.knowledge.derek_1.0.7
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Derek Nexus Report

Author
rorijee
Report date
09 August 2013 11:44:53
Prediction date
09 August 2013 11:44:43
Program version
Derek Nexus: 3.0.1, Nexus: 1.5.0

Submitted compound

Predictions

Derek KB 2012 1.0

KnowledgeBase name
Derek KB 2012 1.0
KnowledgeBase version
1.0
KnowledgeBase last modified
29 November 2012 11:56:30
KnowledgeBase location
C:/Program Files/Lhasa Limited/Lhasa Knowledge Suite - Nexus 1.5/KnowledgeBases/org.lhasalimited.pluto.knowledge.derek_1.0.7
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Open

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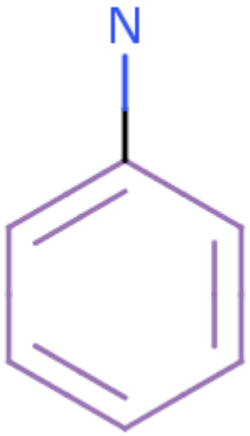
Contradicted

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

Derek Nexus Report

Author
rorijee
Report date
09 August 2013 11:46:29
Prediction date
09 August 2013 11:46:15
Program version
Derek Nexus: 3.0.1, Nexus: 1.5.0

Submitted compound



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Derek KB 2012 1.0

KnowledgeBase name
Derek KB 2012 1.0
KnowledgeBase version
1.0
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29 November 2012 11:56:30
KnowledgeBase location
C:/Program Files/Lhasa Limited/Lhasa Knowledge Suite - Nexus 1.5/KnowledgeBases/org.lhasalimited.pluto.knowledge.derek_1.0.7
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Open

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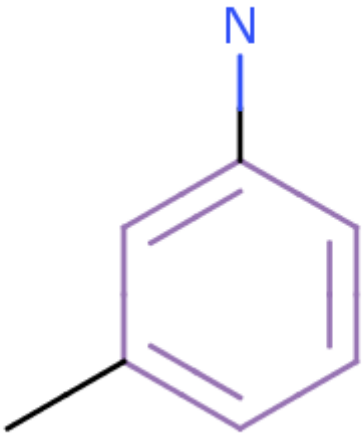
Contradicted

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

Derek Nexus Report

Author
rorijee
Report date
09 August 2013 11:47:15
Prediction date
09 August 2013 11:47:10
Program version
Derek Nexus: 3.0.1, Nexus: 1.5.0

Submitted compound



Predictions

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Reasoning summary and alerts found

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APPENDIX 3

Report

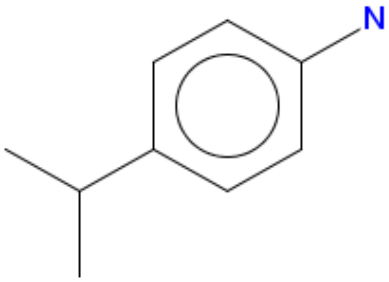
Prediction and Applicability Domain analysis for models:

Skin Sensitisation model (CAESAR) (version 2.1.5)

Calculation core version: 1.1.1

1. Prediction Summary

Prediction for compound 1 (Molecule 1)

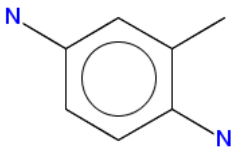


Prediction: Reliability:

Model assessment: Prediction is Sensitizer, but the result shows some critical aspects, which require to be checked:
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments

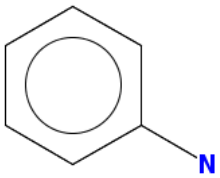
Compound: 1
Compound SMILES: Nc1ccc(cc1)C(C)C
Experimental value: -
Prediction: Sensitizer
O(Active): 0.88
O(Inactive): 0.12
Reliability: Compound could be out of model Applicability Domain
Remarks for the prediction:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



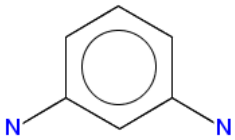
CAS: 95-70-5
Dataset id: 140 (training set)
SMILES: Nc1ccc(N)c(c1)C
Similarity: 0.865

Experimental value: Sensitizer
Predicted value: Sensitizer



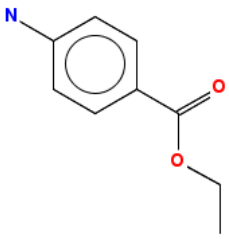
CAS: 62-53-3
Dataset id: 11 (training set)
SMILES: Nc1ccccc1
Similarity: 0.863

Experimental value: Sensitizer
Predicted value: Sensitizer



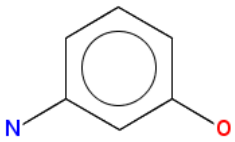
CAS: 108-45-2
Dataset id: 178 (training set)
SMILES: Nc1cccc(N)c1
Similarity: 0.823

Experimental value: Sensitizer
Predicted value: Sensitizer



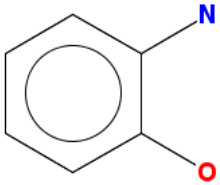
CAS: 94-09-7
Dataset id: 16 (training set)
SMILES: O=C(OCC)c1ccc(N)cc1
Similarity: 0.805

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



CAS: 591-27-5
Dataset id: 7 (training set)
SMILES: Oc1cccc(N)c1
Similarity: 0.805

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 95-55-6
Dataset id: 6 (training set)
SMILES: Oc1ccccc1(N)
Similarity: 0.805

Experimental value: Sensitizer
Predicted value: Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD Index = 0.79 Explanation: predicted substance could be out of the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.864 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✓	**Concordance for similar molecules** Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
✓	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
⚠	**Atom Centered Fragments similarity check** ACF matching index = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments.
✓	**Model descriptors range check** Descriptors range check = true Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Symbols explanation:

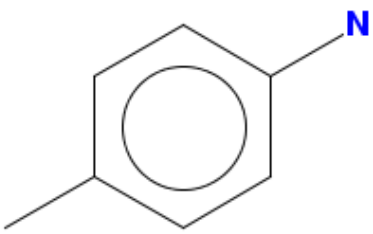
✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✗ The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound 2 (Molecule 2)

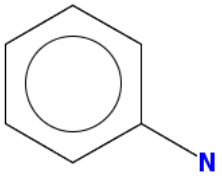


Prediction: Reliability:

Model assessment: Prediction is Sensitizer, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

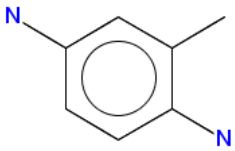
Compound: 2
Compound SMILES: Nc1ccc(cc1)C
Experimental value: -
Prediction: Sensitizer
O(Active): 0.88
O(Inactive): 0.12
Reliability: Compound is in model Applicability Domain
Remarks for the prediction:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



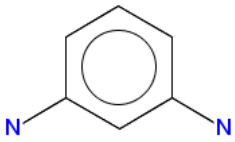
CAS: 62-53-3
Dataset id: 11 (training set)
SMILES: Nc1ccccc1
Similarity: 0.928

Experimental value: Sensitizer
Predicted value: Sensitizer



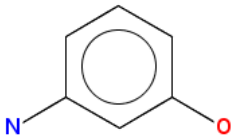
CAS: 95-70-5
Dataset id: 140 (training set)
SMILES: Nc1ccc(N)c(c1)C
Similarity: 0.895

Experimental value: Sensitizer
Predicted value: Sensitizer



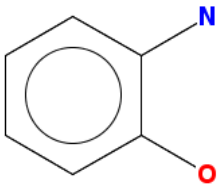
CAS: 108-45-2
Dataset id: 178 (training set)
SMILES: Nc1cccc(N)c1
Similarity: 0.879

Experimental value: Sensitizer
Predicted value: Sensitizer



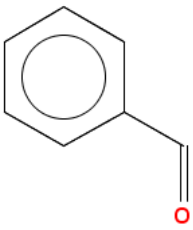
CAS: 591-27-5
Dataset id: 7 (training set)
SMILES: Oc1cccc(N)c1
Similarity: 0.856

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 95-55-6
Dataset id: 6 (training set)
SMILES: Oc1ccccc1(N)
Similarity: 0.856

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 100-52-7
Dataset id: 12 (training set)
SMILES: O=Cc1ccccc1
Similarity: 0.793

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD Index = 0.954
Explanation: predicted substance is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.911
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Atom Centered Fragments similarity check
ACF matching index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Model descriptors range check
Descriptors range check = true
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Symbols explanation:

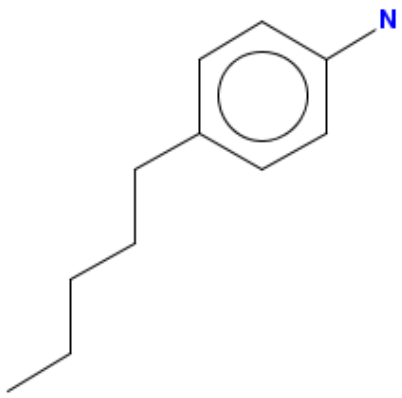
The feature has a good assessment, model is reliable regarding this aspect.

The feature has a non optimal assessment, this aspect should be reviewed by an expert.

The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound 3 (Molecule 3)

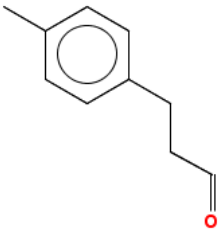


Prediction: Reliability:

Model assessment: Prediction is Sensitizer, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

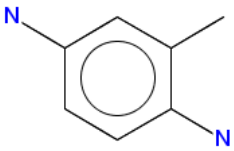
Compound: 3
Compound SMILES: Nc1ccc(cc1)CCCCC
Experimental value: -
Prediction: Sensitizer
O(Active): 0.88
O(Inactive): 0.12
Reliability: Compound is in model Applicability Domain
Remarks for the prediction:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



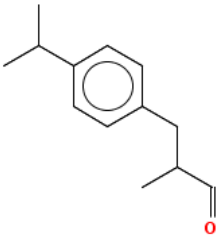
CAS: 5406-12-2
Dataset id: 147 (training set)
SMILES: O=CCCc1ccc(cc1)C
Similarity: 0.802

Experimental value: Sensitizer
Predicted value: Sensitizer



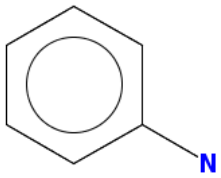
CAS: 95-70-5
Dataset id: 140 (training set)
SMILES: Nc1ccc(N)c(c1)C
Similarity: 0.8

Experimental value: Sensitizer
Predicted value: Sensitizer



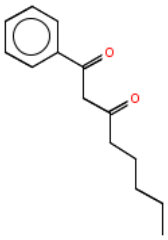
CAS: 103-95-7
Dataset id: 67 (training set)
SMILES: O=CC(C)Cc1ccc(cc1)C(C)C
Similarity: 0.792

Experimental value: Sensitizer
Predicted value: Sensitizer



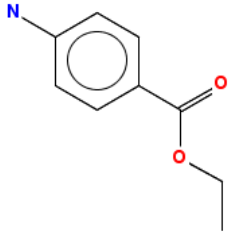
CAS: 62-53-3
Dataset id: 11 (training set)
SMILES: Nc1ccccc1
Similarity: 0.792

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 55846-68-1
Dataset id: 180 (training set)
SMILES: O=C(c1ccccc1)CC(=O)CCCCC
Similarity: 0.767

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 94-09-7
Dataset id: 16 (training set)
SMILES: O=C(OCC)c1ccc(N)cc1
Similarity: 0.766

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD Index = 0.895
Explanation: predicted substance is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.801
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Atom Centered Fragments similarity check
ACF matching index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Model descriptors range check
Descriptors range check = true
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Symbols explanation:

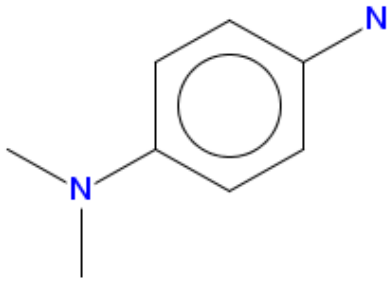
The feature has a good assessment, model is reliable regarding this aspect.

The feature has a non optimal assessment, this aspect should be reviewed by an expert.

The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound 4 (Molecule 4)

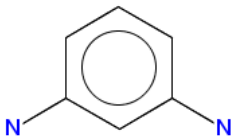


Prediction: Reliability:

Model assessment: Prediction is Sensitizer, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
Anyway some issues could be not optimal:
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments

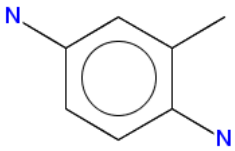
Compound: 4
Compound SMILES: Nc1ccc(cc1)N(C)C
Experimental value: -
Prediction: Sensitizer
O(Active): 0.9
O(Inactive): 0.1
Reliability: Compound is in model Applicability Domain
Remarks for the prediction:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



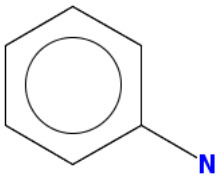
CAS: 108-45-2
Dataset id: 178 (training set)
SMILES: Nc1cccc(N)c1
Similarity: 0.899

Experimental value: Sensitizer
Predicted value: Sensitizer



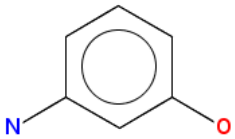
CAS: 95-70-5
Dataset id: 140 (training set)
SMILES: Nc1ccc(N)c(c1)C
Similarity: 0.883

Experimental value: Sensitizer
Predicted value: Sensitizer



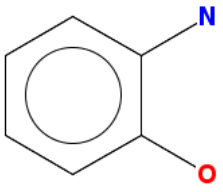
CAS: 62-53-3
Dataset id: 11 (training set)
SMILES: Nc1ccccc1
Similarity: 0.856

Experimental value: Sensitizer
Predicted value: Sensitizer



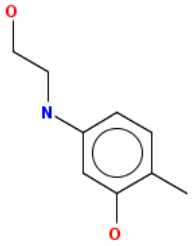
CAS: 591-27-5
Dataset id: 7 (training set)
SMILES: Oc1cccc(N)c1
Similarity: 0.844

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 95-55-6
Dataset id: 6 (training set)
SMILES: Oc1ccccc1(N)
Similarity: 0.844

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 55302-96-0
Dataset id: 149 (training set)
SMILES: Oc1cc(ccc1C)NCCO
Similarity: 0.782

Experimental value: Sensitizer
Predicted value: Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD Index = 0.802
Explanation: predicted substance is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.891
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Atom Centered Fragments similarity check
ACF matching index = 0.85
Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments.

Model descriptors range check
Descriptors range check = true
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Symbols explanation:

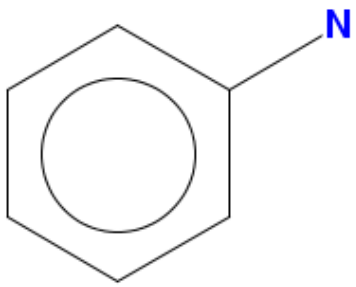
The feature has a good assessment, model is reliable regarding this aspect.

The feature has a non optimal assessment, this aspect should be reviewed by an expert.

The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound 5 (Molecule 5)

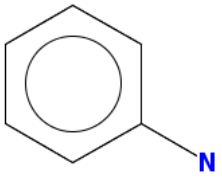


EXPERIMENTAL DATA

Model assessment: Experimental activity is Sensitizer.
Model prediction is Sensitizer (good reliability).

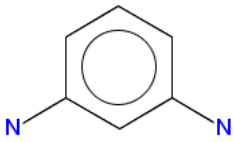
Compound: 5
Compound SMILES: Nc1ccccc1
Experimental value: Sensitizer
Prediction: Sensitizer
O(Active): 0.88
O(Inactive): 0.11
Reliability: Compound is in model Applicability Domain
Remarks for the prediction:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



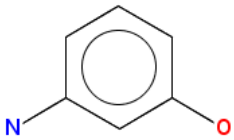
CAS: 62-53-3
Dataset id: 11 (training set)
SMILES: Nc1ccccc1
Similarity: 1

Experimental value: Sensitizer
Predicted value: Sensitizer



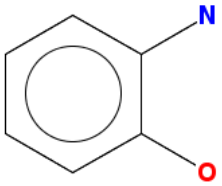
CAS: 108-45-2
Dataset id: 178 (training set)
SMILES: Nc1cccc(N)c1
Similarity: 0.903

Experimental value: Sensitizer
Predicted value: Sensitizer



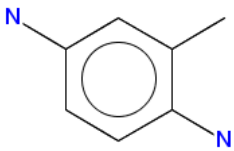
CAS: 591-27-5
Dataset id: 7 (training set)
SMILES: Oc1cccc(N)c1
Similarity: 0.88

Experimental value: Sensitizer
Predicted value: Sensitizer



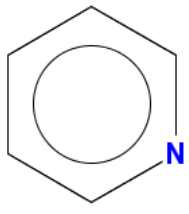
CAS: 95-55-6
Dataset id: 6 (training set)
SMILES: Oc1ccccc1(N)
Similarity: 0.88

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 95-70-5
Dataset id: 140 (training set)
SMILES: Nc1ccc(N)c(c1)C
Similarity: 0.837

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 110-86-1
Dataset id: 187 (training set)
SMILES: n1ccccc1
Similarity: 0.793

Experimental value: Sensitizer
Predicted value: Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD Index = 1
Explanation: predicted substance is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 1
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Atom Centered Fragments similarity check
ACF matching index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Model descriptors range check
Descriptors range check = true
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Symbols explanation:

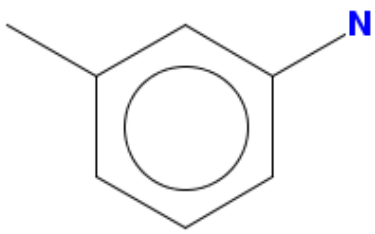
The feature has a good assessment, model is reliable regarding this aspect.

The feature has a non optimal assessment, this aspect should be reviewed by an expert.

The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound 6 (Molecule 6)

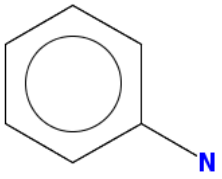


Prediction: Reliability:

Model assessment: Prediction is Sensitizer, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

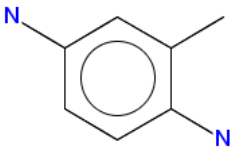
Compound: 6
Compound SMILES: Nc1cccc(c1)C
Experimental value: -
Prediction: Sensitizer
O(Active): 0.88
O(Inactive): 0.12
Reliability: Compound is in model Applicability Domain
Remarks for the prediction:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



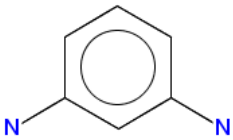
CAS: 62-53-3
Dataset id: 11 (training set)
SMILES: Nc1ccccc1
Similarity: 0.923

Experimental value: Sensitizer
Predicted value: Sensitizer



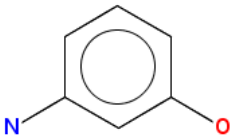
CAS: 95-70-5
Dataset id: 140 (training set)
SMILES: Nc1ccc(N)c(c1)C
Similarity: 0.907

Experimental value: Sensitizer
Predicted value: Sensitizer



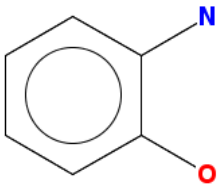
CAS: 108-45-2
Dataset id: 178 (training set)
SMILES: Nc1cccc(N)c1
Similarity: 0.875

Experimental value: Sensitizer
Predicted value: Sensitizer



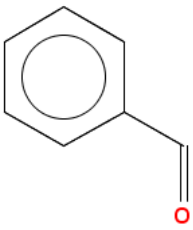
CAS: 591-27-5
Dataset id: 7 (training set)
SMILES: Oc1cccc(N)c1
Similarity: 0.853

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 95-55-6
Dataset id: 6 (training set)
SMILES: Oc1ccccc1(N)
Similarity: 0.853

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 100-52-7
Dataset id: 12 (training set)
SMILES: O=Cc1ccccc1
Similarity: 0.79

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD Index = 0.956
Explanation: predicted substance is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.915
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Atom Centered Fragments similarity check
ACF matching index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Model descriptors range check
Descriptors range check = true
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.

The feature has a non optimal assessment, this aspect should be reviewed by an expert.

The feature has a bad assessment, model is not reliable regarding this aspect.

References and Documentation

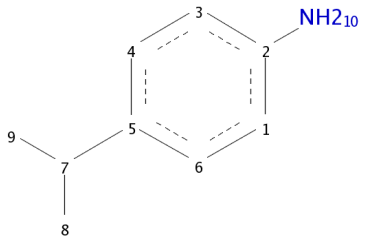
You can find complete details on each model and on how to read results in the proper model's guide, available on-line at www.vega-qsar.eu or directly in the VegaNIC application.

Skin Sensitisation model (CAESAR) (version 2.1.5)

QSAR classification model for Skin sensitisation based on a Adaptive Fuzzy Partion. The model extends the original CAESAR Skin model 1.0. The original model was developed inside the CAESAR Project (http://www.caesar-project.eu/).

APPENDIX 4

Molecule 1



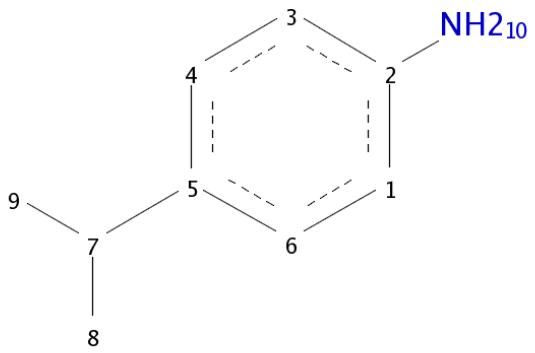
$C_9H_{13}N$
Molecular Weight: 135.20621
ALogP: 2.277
Rotatable Bonds: 1
Acceptors: 1
Donors: 1

Summary

Prediction

Model: Skin Sensitization NEG v SENS (v6.1)
Computed Probability of Sensitization = 1.000
Model: Skin Sensitization MLD/MOD v SEV (v6.1)
Probability of SEV Sensitization = 1.000

Molecule 1



$C_9H_{13}N$
Molecular Weight: 135.20621
ALogP: 2.277
Rotatable Bonds: 1
Acceptors: 1
Donors: 1

Prediction

SubModel: Aromatics SENS v NON

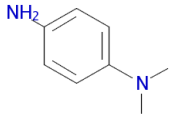
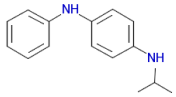
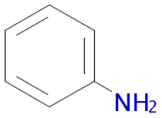
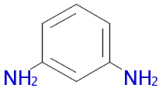
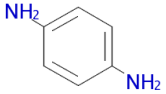
Computed Probability of Sensitization = 1.000

Discriminant Score = 16.554

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Skin Sensitization NEG v SENS (v6.1)

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	NEG	POS
Predicted Endpt	POS	POS	POS	POS	POS
Distance	0.267	0.277	0.293	0.307	0.332

OPS Summary

Within OPS: False

Within OPS Limits: True

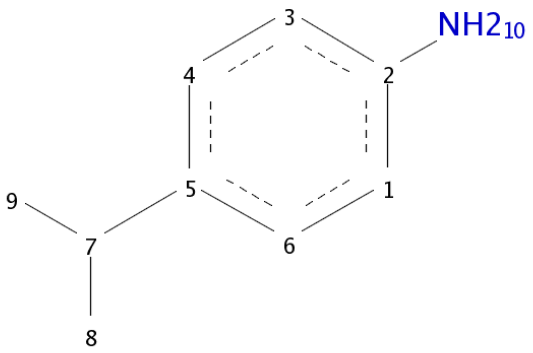
All Fragments Covered: True

Compound in Database: False

Descriptor Contribution

Descriptor	Value
[Aromatic C]	-25.713
[Aromatic C] * [Aliphatic N]	12.601
Symmetry Index #3	10.987
[*CH(*)*] * [Aromatic C]	7.004
[:cH:] : [:c(*):]	6.528

Molecule 1



$C_9H_{13}N$
Molecular Weight: 135.20621
ALogP: 2.277
Rotatable Bonds: 1
Acceptors: 1
Donors: 1

Prediction

SubModel: Aromatics MLD/MOD v SEV

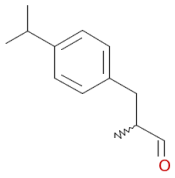
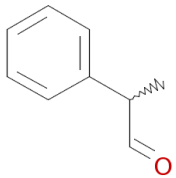
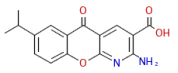
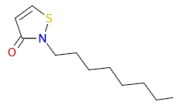
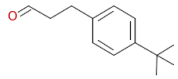
Probability of SEV Sensitization = 1.000

Discriminant Score = 14.448

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Skin Sensitization MLD/MOD v SEV (v6.1)

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	POS	POS
Predicted Endpt	POS	POS	POS	NEG	POS
Distance	0.496	0.505	0.538	0.614	0.640

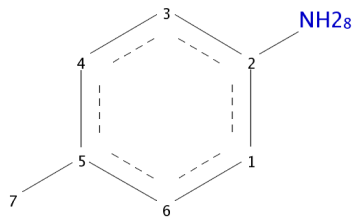
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: False

Descriptor Contribution

Descriptor	Value
[*CH(*)*] * [Aromatic C]	14.697
CONSTANT TERM	-11.986
[Aliphatic C] * [-CH3]	9.995
Symmetry Index #1	-7.025
[Aromatic C] * [Aliphatic N]	5.833

Molecule 1



C_7H_9N
Molecular Weight: 107.15306
ALogP: 1.569
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

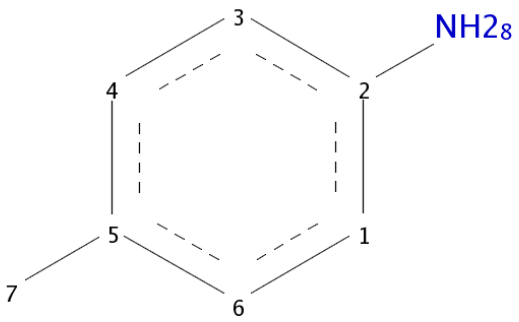
Summary

Prediction

Model: Skin Sensitization NEG v SENS (v6.1)
Computed Probability of Sensitization = 1.000
Model: Skin Sensitization MLD/MOD v SEV (v6.1)
Probability of SEV Sensitization = 0.000

Molecule 1

Skin Sensitization NEG v SENS (v6.1)



C_7H_9N
Molecular Weight: 107.15306
ALogP: 1.569
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Prediction

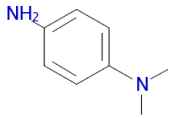
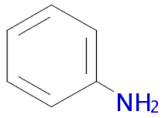
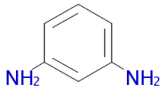
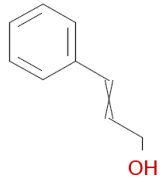
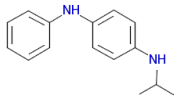
SubModel: Aromatics SENS v NON

Computed Probability of Sensitization = 1.000

Discriminant Score = 14.166

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	NEG	POS	POS
Predicted Endpt	POS	POS	POS	POS	POS
Distance	0.267	0.295	0.304	0.326	0.333

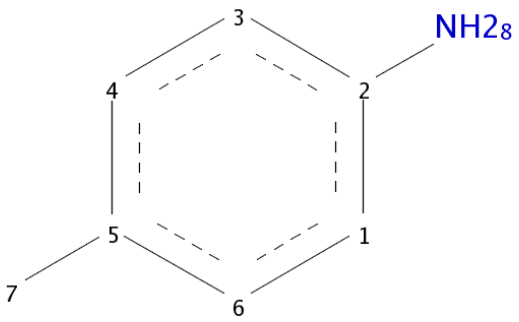
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: False

Descriptor Contribution

Descriptor	Value
[Aromatic C]	-24.875
[Aromatic C] * [Aliphatic N]	12.387
Symmetry Index #3	11.771
[Aliphatic C] * [Aromatic C]	11.008
[:cH:] : [:c(*):]	6.528

Molecule 1



C_7H_9N
Molecular Weight: 107.15306
ALogP: 1.569
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Prediction

SubModel: Aromatics MLD/MOD v SEV

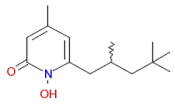
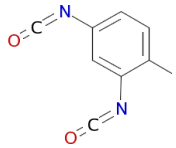
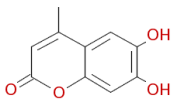
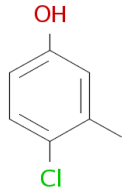
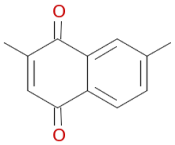
Probability of SEV Sensitization = 0.000

Discriminant Score = -17.819

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Skin Sensitization MLD/MOD v SEV (v6.1)

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	POS	POS
Predicted Endpt	NEG	NEG	NEG	NEG	NEG
Distance	0.334	0.384	0.505	0.511	0.516

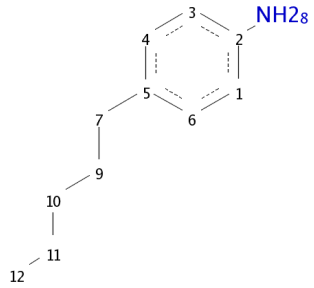
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: False

Descriptor Contribution

Descriptor	Value
CONSTANT TERM	-11.986
[-CH3] * [Aromatic C]	-6.803
Symmetry Index #1	-6.022
[Aromatic C] * [Aliphatic N]	5.833
Shape Index # 6	1.158

Molecule 1



$C_{11}H_{17}N$
Molecular Weight: 163.25937
ALogP: 3.394
Rotatable Bonds: 4
Acceptors: 1
Donors: 1

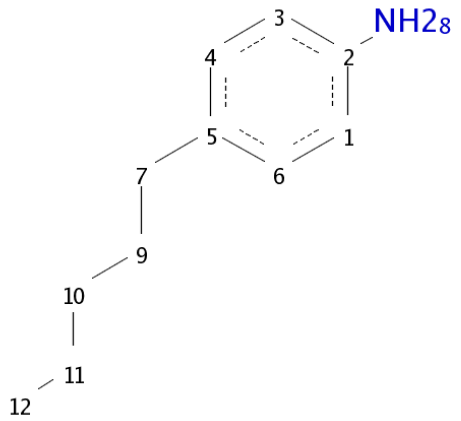
Summary

Prediction

Model: Skin Sensitization NEG v SENS (v6.1)
Computed Probability of Sensitization = 1.000
Model: Skin Sensitization MLD/MOD v SEV (v6.1)
Probability of SEV Sensitization = 0.000

Molecule 1

Skin Sensitization NEG v SENS (v6.1)



$C_{11}H_{17}N$
Molecular Weight: 163.25937
ALogP: 3.394
Rotatable Bonds: 4
Acceptors: 1
Donors: 1

Prediction

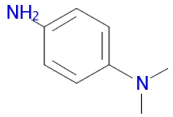
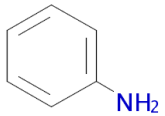
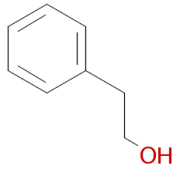
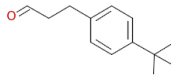
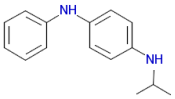
SubModel: Aromatics SENS v NON

Computed Probability of Sensitization = 1.000

Discriminant Score = 19.929

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	POS	POS
Predicted Endpt	POS	POS	POS	POS	POS
Distance	0.333	0.348	0.357	0.362	0.370

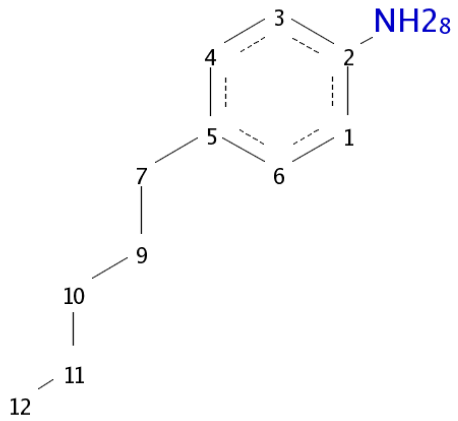
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: False

Descriptor Contribution

Descriptor	Value
[Aromatic C]	-26.312
Symmetry Index #3	13.079
[Aromatic C] * [Aliphatic N]	12.746
[-CH2-] - [-CH2-]	10.691
[Aliphatic C] * [Aromatic C]	8.662

Molecule 1



$C_{11}H_{17}N$
Molecular Weight: 163.25937
ALogP: 3.394
Rotatable Bonds: 4
Acceptors: 1
Donors: 1

Prediction

SubModel: Aromatics MLD/MOD v SEV

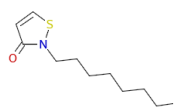
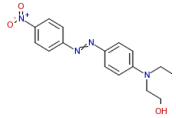
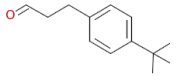
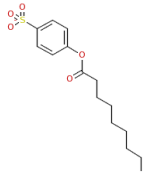
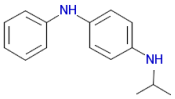
Probability of SEV Sensitization = 0.000

Discriminant Score = -10.316

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Skin Sensitization MLD/MOD v SEV (v6.1)

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	POS	POS
Predicted Endpt	NEG	POS	POS	POS	NEG
Distance	0.286	0.503	0.547	0.551	0.569

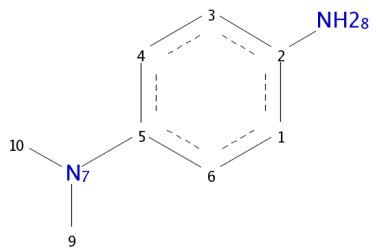
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: False

Descriptor Contribution

Descriptor	Value
[Aliphatic C] * [-CH3]	12.673
CONSTANT TERM	-11.986
Symmetry Index #1	-10.036
[-CH3] * [*CH2*]	-9.800
[Aromatic C] * [Aliphatic N]	5.833

Molecule 1



$C_8H_{12}N_2$
Molecular Weight: 136.19427
ALogP: 1.245
Rotatable Bonds: 1
Acceptors: 2
Donors: 1

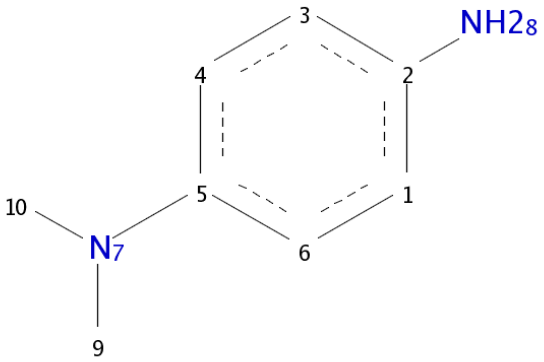
Summary

Prediction

Model: Skin Sensitization NEG v SENS (v6.1)
Computed Probability of Sensitization = 0.975
Model: Skin Sensitization MLD/MOD v SEV (v6.1)
Probability of SEV Sensitization = 1.000

Molecule 1

Skin Sensitization NEG v SENS (v6.1)



$C_8H_{12}N_2$
Molecular Weight: 136.19427
ALogP: 1.245
Rotatable Bonds: 1
Acceptors: 2
Donors: 1

Prediction

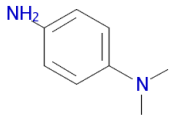
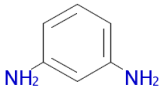
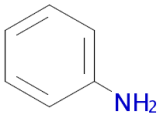
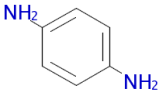
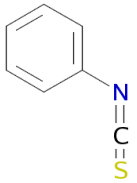
SubModel: Aromatics SENS v NON

Computed Probability of Sensitization = 0.975

Discriminant Score = 3.679

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	NEG	POS	POS	POS
Predicted Endpt	POS	POS	POS	POS	POS
Distance	0.000	0.158	0.173	0.203	0.206

OPS Summary

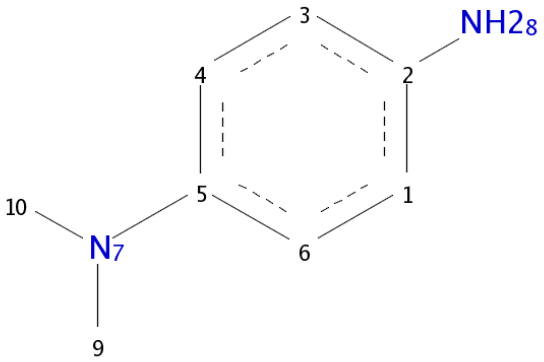
Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: True
Modeled Endpoint: POS

Descriptor Contribution

Descriptor	Value
[Aromatic C]	-24.642
Symmetry Index #3	10.987
[Aromatic C] * [Aliphatic N]	9.440
[:cH:] : [:c(*):]	6.528
[-CH3]	-4.931

Molecule 1

Skin Sensitization MLD/MOD v SEV (v6.1)



$C_8H_{12}N_2$
Molecular Weight: 136.19427
ALogP: 1.245
Rotatable Bonds: 1
Acceptors: 2
Donors: 1

Prediction

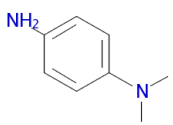
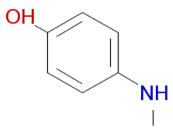
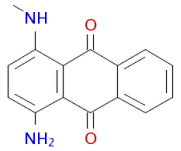
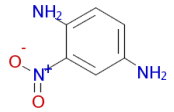
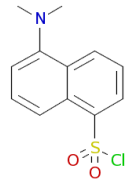
SubModel: Aromatics MLD/MOD v SEV

Probability of SEV Sensitization = 1.000

Discriminant Score = 12.241

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	POS	POS
Predicted Endpt	POS	POS	POS	POS	POS
Distance	0.000	0.395	0.535	0.545	0.562

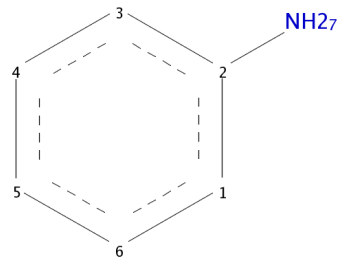
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: True
Modeled Endpoint: POS

Descriptor Contribution

Descriptor	Value
[-CH3] * [Aliphatic N]	16.655
CONSTANT TERM	-11.986
[Aromatic C] * [Aliphatic N]	11.667
Symmetry Index #1	-7.025
Shape Index # 7	2.074

Molecule 1



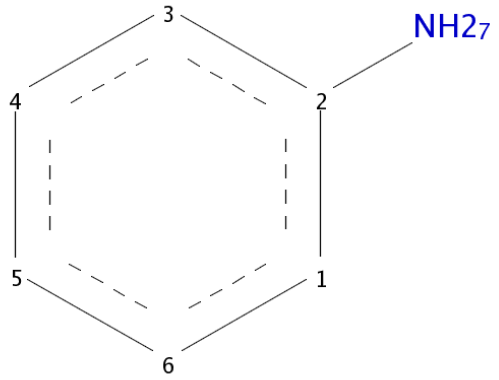
C_6H_7N
Molecular Weight: 93.12648
ALogP: 1.083
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Summary

Prediction

Model: Skin Sensitization NEG v SENS (v6.1)
Computed Probability of Sensitization = 1.000
Model: Skin Sensitization MLD/MOD v SEV (v6.1)
Probability of SEV Sensitization = 0.000

Molecule 1



C_6H_7N
Molecular Weight: 93.12648
ALogP: 1.083
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Prediction

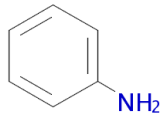
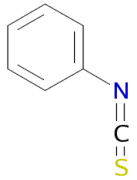
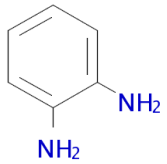
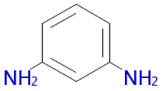
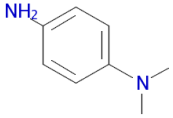
SubModel: Aromatics SENS v NON

Computed Probability of Sensitization = 1.000

Discriminant Score = 10.660

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	NEG	POS
Predicted Endpt	POS	POS	POS	POS	POS
Distance	0.000	0.155	0.158	0.162	0.173

OPS Summary

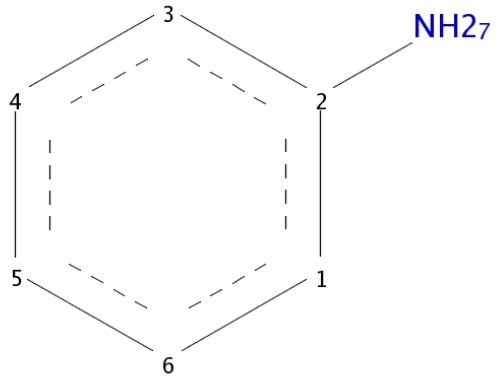
Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: True
Modeled Endpoint: POS

Descriptor Contribution

Descriptor	Value
[Aromatic C]	-25.993
[Aromatic C] * [Aliphatic N]	12.236
Symmetry Index #3	11.211
[:cH:] : [:cH:]	7.447
[:cH:] : [:c(*):]	3.264

Molecule 1

Skin Sensitization MLD/MOD v SEV (v6.1)



C_6H_7N
Molecular Weight: 93.12648
ALogP: 1.083
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Prediction

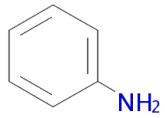
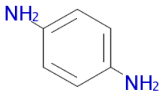
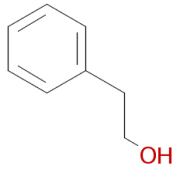
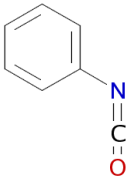
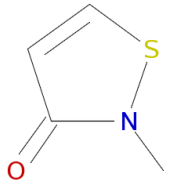
SubModel: Aromatics MLD/MOD v SEV

Probability of SEV Sensitization = 0.000

Discriminant Score = -10.013

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	POS	POS
Predicted Endpt	NEG	NEG	NEG	POS	NEG
Distance	0.000	0.277	0.412	0.421	0.432

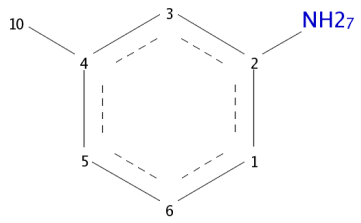
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: True
Modeled Endpoint: NEG

Descriptor Contribution

Descriptor	Value
CONSTANT TERM	-11.986
[Aromatic C] * [Aliphatic N]	5.833
Symmetry Index #1	-5.018
Shape Index # 6	1.158

Molecule 1



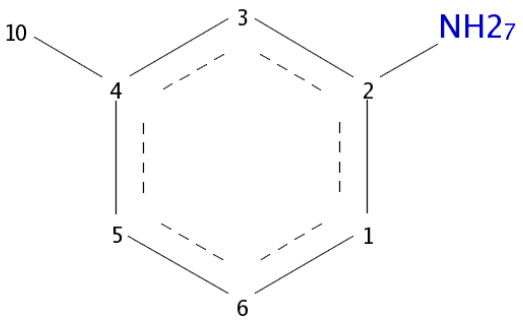
C_7H_9N
Molecular Weight: 107.15306
ALogP: 1.569
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Summary

Prediction

Model: Skin Sensitization NEG v SENS (v6.1)
Computed Probability of Sensitization = 1.000
Model: Skin Sensitization MLD/MOD v SEV (v6.1)
Probability of SEV Sensitization = 0.000

Molecule 1



C_7H_9N
Molecular Weight: 107.15306
ALogP: 1.569
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Prediction

SubModel: Aromatics SENS v NON

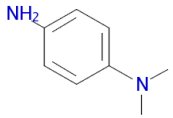
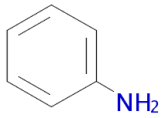
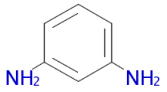
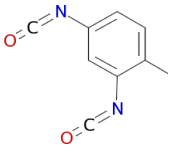
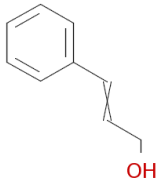
Computed Probability of Sensitization = 1.000

Discriminant Score = 18.144

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Skin Sensitization NEG v SENS (v6.1)

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	NEG	POS	POS
Predicted Endpt	POS	POS	POS	POS	POS
Distance	0.276	0.299	0.317	0.322	0.326

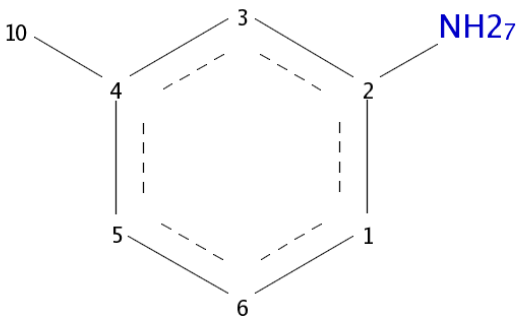
OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: False

Descriptor Contribution

Descriptor	Value
[Aromatic C]	-24.837
Symmetry Index #3	15.695
[Aromatic C] * [Aliphatic N]	12.467
[Aliphatic C] * [Aromatic C]	10.829
[:cH:] : [:c(*):]	6.528

Molecule 1



C_7H_9N
Molecular Weight: 107.15306
ALogP: 1.569
Rotatable Bonds: 0
Acceptors: 1
Donors: 1

Prediction

SubModel: Aromatics MLD/MOD v SEV

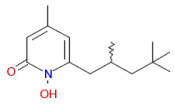
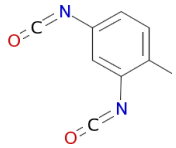
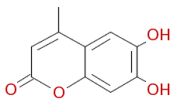
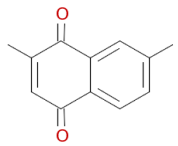
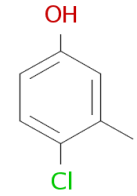
Probability of SEV Sensitization = 0.000

Discriminant Score = -20.133

Probability values from 0.0 to 0.30 are considered low probabilities, and are likely to produce a negative response in an experimental assay; whereas probability values greater than 0.70 are considered high, and are likely to produce a positive response in an experimental assay. Probabilities greater than 0.30 but less than 0.70 are considered indeterminate.

Skin Sensitization MLD/MOD v SEV (v6.1)

Similar Compounds

	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
Molecule					
Actual Endpoint	POS	POS	POS	POS	POS
Predicted Endpt	NEG	NEG	NEG	NEG	NEG
Distance	0.311	0.368	0.491	0.505	0.505

OPS Summary

Within OPS: True
Within OPS Limits: True
All Fragments Covered: True
Compound in Database: False

Descriptor Contribution

Descriptor	Value
CONSTANT TERM	-11.986
Symmetry Index #1	-8.029
[-CH3] * [Aromatic C]	-6.693
[Aromatic C] * [Aliphatic N]	5.833
Shape Index # 6	0.741

APPENDIX 5

Skin sensitisation parent and metabolites information

Experimental and calculated activity of parent chemicals. Metabolites distribution; 2D view of metabolites with their quantity and predicted sensitisation potential.

Information about:

TIMES version	OASIS TIMES MIX V.2.27.5 TB
Dataset	C:\Program Files\OASIS-LMC\TIMES.2.27.5\EndPointsGDB\General mutagenicity expert v05\SS.Odb
Metabolic simulator	Skin sensitization v. 16.18 with autoxidation
Map generation options	Max tree depth in levels: 5 Probability to obtain metabolite: 0.0001 Threshold for logKOW: no threshold Max number of rival pathways: 11 Rival probability coefficient: 0.010 Count every mapping as a different way: Yes

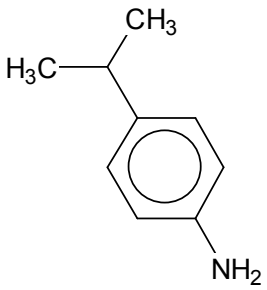
Parent information

CAS No 99-88-7

Chem Name 4-isopropylaniline

SMILES c1(C(C)C)ccc(N)cc1

1

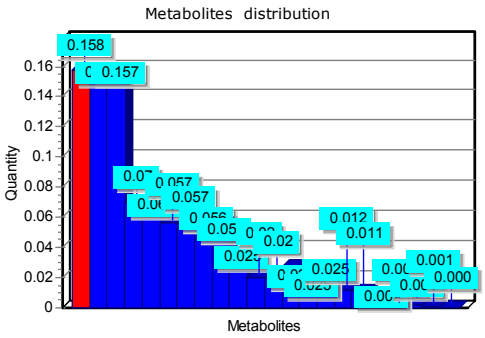


Skin sensitisation:

Experimental: No data

Predicted: Weak sensitiser

Structural Alert: M



Transformation 288, Quantity=0.1577
C(=O)(O)C1C(O)C(O)C(O)C(Nc2ccc(C(C)C)cc2)O1

Total Model Domain: Out of Domain

Domain Details

Parametric Domain: In domain

Total Structural Domain: Out of domain

Metabolites information

Parent	Metabolite 1	Metabolite 2	Metabolite 3
Quantity: 0.0119	**Quantity:** 0.0016	**Quantity:** 0.0019	**Quantity:** 0.0202
Skin sensitization: Non sensitiser	**Skin sensitization:** Weak sensitiser	**Skin sensitization:** Non sensitiser	**Skin sensitization:** Non sensitiser
Total Model Domain: Out of Domain	**Total Model Domain:** Out of Domain	**Total Model Domain:** Out of Domain	**Total Model Domain:** Out of Domain
Structural Alert:	**Structural Alert:** Peroxides/Autoxidation product	**Structural Alert:**	**Structural Alert:**

Metabolite 4	Metabolite 5	Metabolite 6	Metabolite 7
Quantity: 0.0563	**Quantity:** 0.0014	**Quantity:** 0.0002	**Quantity:** 0.0006
Skin sensitization:	**Skin sensitization:**	**Skin sensitization:**	**Skin sensitization:**
Non sensitiser	Non sensitiser	Weak sensitiser	Weak sensitiser
Total Model Domain:	**Total Model Domain:**	**Total Model Domain:**	**Total Model Domain:**
Out of Domain	Out of Domain	Out of Domain	Out of Domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**	**Structural Alert:**
		Aromatic nitroso compounds/Autoxidation	Aromatic nitroso compounds

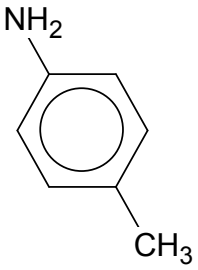
Parent information

CAS No 106-49-0

Chem Name 4-Toluidine

SMILES c1(N)ccc(C)cc1

2

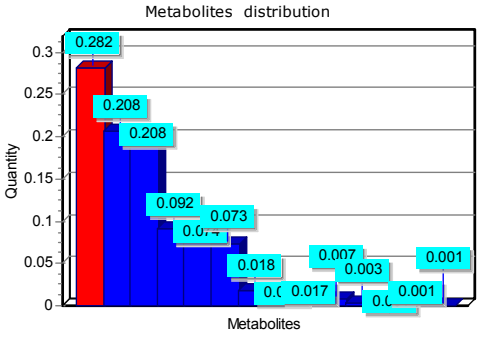


Skin sensitisation:

Experimental: No data

Predicted: Strong sensitiser

Structural Alert: M



Transformation 101, Quantity=0.2817
c1(N)ccc(CS[Pr])cc1

Total Model Domain: Out of Domain

Domain Details

Parametric Domain: In domain

Total Structural Domain: Out of domain

Metabolites information

Parent	Metabolite 1	Metabolite 2	Metabolite 3
Quantity: 0.0010	**Quantity:** 0.0028	**Quantity:** 0.0741	**Quantity:** 0.0009
Skin sensitization:	**Skin sensitization:**	**Skin sensitization:**	**Skin sensitization:**
Non sensitiser	Strong sensitiser	Non sensitiser	Non sensitiser
Total Model Domain:	**Total Model Domain:**	**Total Model Domain:**	**Total Model Domain:**
Out of Domain	Out of Domain	Out of Domain	Out of Domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**	**Structural Alert:**
	Quinone methide imines		

Metabolite 4

Quantity: 0.0007

Skin sensitization:

Weak sensitiser

Total Model Domain:

Out of Domain

Structural Alert:

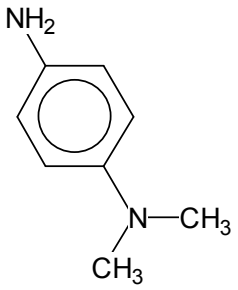
Aromatic nitroso compounds

Parent information

CAS No 99-98-9

Chem Name Dimethyl-4-phenylenediamine

3



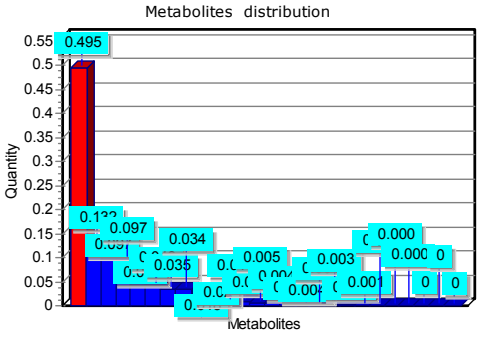
SMILES c1(N)ccc(N(C)C)cc1

Skin sensitisation:

Experimental: Strong sensitiser

Predicted: Strong sensitiser

Structural Alert: M



Transformation 102, Quantity=0.4945
c1(O)c(N[Pr])cc(N(C)C)cc1

Total Model Domain: In domain

Domain Details

Parametric Domain: In domain

Total Structural Domain: In domain

Metabolites information

Parent	Metabolite 1	Metabolite 2	Metabolite 3
			
Quantity: 0.0003	**Quantity:** 0.0050	**Quantity:** 0.0013	**Quantity:** 0.0345
Skin sensitization:	**Skin sensitization:**	**Skin sensitization:**	**Skin sensitization:**
Non sensitiser	Strong sensitiser	Strong sensitiser	Non sensitiser
Total Model Domain:	**Total Model Domain:**	**Total Model Domain:**	**Total Model Domain:**
In domain	In domain	In domain	In domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**	**Structural Alert:**
	Quinone (di)imine/Autoxidation product	Quinone (di)imine/Autoxidation product	

Metabolite 4	Metabolite 5	Metabolite 6	Metabolite 7
Quantity: 0.0001	**Quantity:** 0.0012	**Quantity:** 0.0003	**Quantity:** 0.0035
Skin sensitization:	**Skin sensitization:**	**Skin sensitization:**	**Skin sensitization:**
Non sensitiser	Non sensitiser	Weak sensitiser	Non sensitiser
Total Model Domain:	**Total Model Domain:**	**Total Model Domain:**	**Total Model Domain:**
In domain	In domain	In domain	In domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**	**Structural Alert:**
		Aromatic nitroso compounds	

Metabolite 8	Metabolite 9	Metabolite 10
Quantity: 0.0000	**Quantity:** 0.0183	**Quantity:** 0.0000
Skin sensitization:	**Skin sensitization:**	**Skin sensitization:**
Strong sensitiser	Non sensitiser	Weak sensitiser
Total Model Domain:	**Total Model Domain:**	**Total Model Domain:**
In domain	In domain	In domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**
Quinones (quinone imines)		Aromatic nitroso compounds

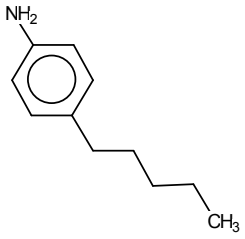
Parent information

CAS No 33228-44-3

Chem Name Benzenamine, 4-pentyl-

SMILES c1(N)ccc(CCCCC)cc1

4

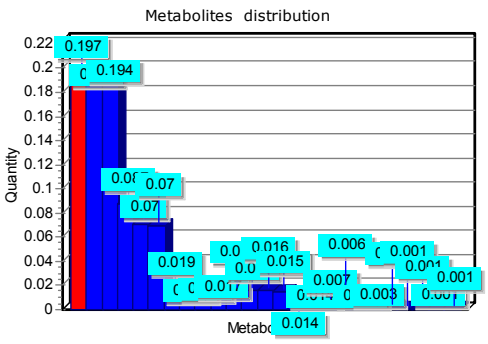


Skin sensitisation:

Experimental: No data

Predicted: Strong sensitiser

Structural Alert: M



Transformation 288, Quantity=0.197
C(=O)(O)C1C(O)C(O)C(O)C(O)C(Nc2ccc(CCCCC)cc2)O1

Total Model Domain	Out of Domain
Domain Details	
Parametric Domain	In domain
Total Structural Domain	Out of domain

Metabolites information

Parent	Metabolite 1	Metabolite 2	Metabolite 3
Quantity: 0.0008	**Quantity:** 0.0018	**Quantity:** 0.0704	**Quantity:** 0.0009
Skin sensitization: Non sensitiser	**Skin sensitization:** Strong sensitiser	**Skin sensitization:** Non sensitiser	**Skin sensitization:** Non sensitiser
Total Model Domain: Out of Domain	**Total Model Domain:** Out of Domain	**Total Model Domain:** Out of Domain	**Total Model Domain:** Out of Domain
Structural Alert:	**Structural Alert:** Quinone methide imines	**Structural Alert:**	**Structural Alert:**

Metabolite 4	Metabolite 5	Metabolite 6	Metabolite 7
Quantity: 0.0008	**Quantity:** 0.0029	**Quantity:** 0.0026	**Quantity:** 0.0007
Skin sensitization: Non sensitiser	**Skin sensitization:** Non sensitiser	**Skin sensitization:** Non sensitiser	**Skin sensitization:** Weak sensitiser
Total Model Domain: Out of Domain	**Total Model Domain:** Out of Domain	**Total Model Domain:** Out of Domain	**Total Model Domain:** Out of Domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**	**Structural Alert:** Aromatic nitroso compounds

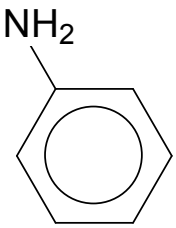
Parent information

CAS No 62-53-3

Chem Name Aniline

SMILES c1(N)ccccc1

5

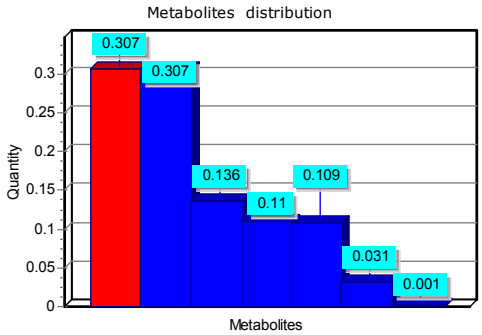


Skin sensitisation:

Experimental: Weak sensitiser

Predicted: Weak sensitiser

Structural Alert: M



Transformation 289, Quantity=0.3069
c1(NC(C)=O)ccccc1

Total Model Domain: In domain

Domain Details

Parametric Domain: In domain

Total Structural Domain: In domain

Metabolites information

Parent	Metabolite 1	Metabolite 2
		
Quantity: 0.0311	**Quantity:** 0.1096	**Quantity:** 0.0011
Skin sensitization:	**Skin sensitization:**	**Skin sensitization:**
Non sensitiser	Non sensitiser	Weak sensitiser
Total Model Domain:	**Total Model Domain:**	**Total Model Domain:**
In domain	In domain	In domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**
		Aromatic nitroso compounds

Parent information

CAS No 108-44-1

Chem Name 3-Toluidine

SMILES c1(N)cc(C)ccc1

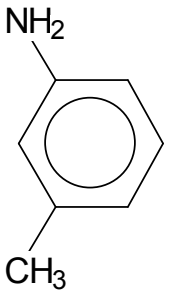
Skin sensitisation:

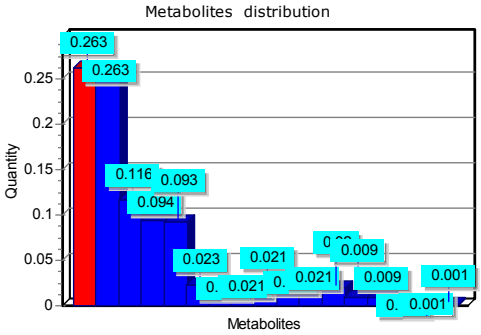
Experimental: No data

Predicted: Weak sensitiser

Structural Alert: M

6

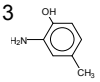




Transformation 289, Quantity=0.2629
c1(NC(C)=O)cc(C)ccc1

Total Model Domain	Out of Domain
Domain Details	
Parametric Domain	In domain
Total Structural Domain	Out of domain

Metabolites information

Parent	Metabolite 1	Metabolite 2	Metabolite 3
			
Quantity: 0.0199	**Quantity:** 0.0939	**Quantity:** 0.0012	**Quantity:** 0.0012
Skin sensitization:	**Skin sensitization:**	**Skin sensitization:**	**Skin sensitization:**
Non sensitiser	Non sensitiser	Non sensitiser	Non sensitiser
Total Model Domain:	**Total Model Domain:**	**Total Model Domain:**	**Total Model Domain:**
Out of Domain	Out of Domain	Out of Domain	Out of Domain
Structural Alert:	**Structural Alert:**	**Structural Alert:**	**Structural Alert:**

Metabolite 4 

Quantity: 0.0009

Skin sensitization:

Weak sensitiser

Total Model Domain:

Out of Domain

Structural Alert:

Aromatic nitroso compounds

APPENDIX 6

	QMRF identifier (JRC Inventory):To be entered by ECB
	QMRF Title: MultiCASE commercial model A33 for skin sensitization, Danish National Food Institute.
	Printing Date:15-12-2009

1.QSAR identifier

1.1.QSAR identifier (title):

MultiCASE commercial model A33 for skin sensitization, Danish National Food Institute.

1.2.Other related models:

1.3.Software coding the model:

MultiCASE MC4PC www.multicase.com

2.General information

2.1.Date of QMRF:

15. December 2007.

2.2.QMRF author(s) and contact details:

[1]Tine Ringsted; Danish National Food Institute; Mørkhøj Bygade 19, 2860 Søborg, Denmark; tiri@food.dtu.dk

[2]Gunde Egeskov Jensen; National Food Institute; Mørkhøj Bygade 19, 2860 Søborg, Denmark; gunje@food.dtu.dk

[3]Eva Bay Wedebye; National Food Institute; Mørkhøj Bygade 19, 2860 Søborg, Denmark; ebawe@food.dtu.dk

[4]Jay Russel Niemelä; National Food Institute; Mørkhøj Bygade 19, 2860 Søborg, Denmark; jarn@food.dtu.dk

[5]Nikolai Nikolov; National Food Institute; Mørkhøj Bygade 19, 2860 Søborg, Denmark; nign@food.dtu.dk

2.3.Date of QMRF update(s):

December 2009

2.4.QMRF update(s):

Eva Bay Wedebye and Tine Ringsted, many sections updated

2.5.Model developer(s) and contact details:

MultiCASE Inc. 23811 Chagrin Blvd Ste 305, Beachwood, OH, 44122, USA www.multicase.com

2.6.Date of model development and/or publication:

Commercial model bought in 1999.

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

[1]Software: MC4PC from MultiCASE Inc., commercial model A33

[2]Graham C, Gealy R,Macina OT,Karol MH, Rosenkranz HS. QSAR for allergic contact dermatitis. Quant.Struct.Act.Relat (1996) 15:224-229

[3]Gealy,R.; Graham,C.; Sussman,N.B.; Macina,O.T.; Rosenkranz,H.S.; Karol,M.H. Evaluating clinical case report data for SAR modeling of allergic contact dermatitis Hum.Exp.Toxicol. (1996) 15(6):489-493

[4]Rosenkranz,H.S.; Klopman,G.; Zhang,Y.P.; Graham,C.; Karol,M.H. Relationship between allergic contact dermatitis and electrophilicity

Environ.Health Perspect. (1999) 107(2):129-132

2.8.Availability of information about the model:

The data set is commercially available from MultiCASE Inc.

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

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Humans or guinea pigs.

3.2.Endpoint:

4.Human health effects 4.6.Skin sensitisation

3.3.Comment on endpoint:

GPMT tests or allergic contact dermatitis (ACD) in humans.

3.4.Endpoint units:

MultiCASE CASE units

3.5.Dependent variable:

Skin sensitisation, positive or negative

3.6.Experimental protocol:

OECD guideline 406 Skin sensitisation

3.7.Endpoint data quality and variability:

n/a

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

AI system: Fragment based statistical system which creates a number of sub models derived by multiple linear regression.

4.2.Explicit algorithm:

Multiple explicit algorithms operate within the MultiCASE model

4.3.Descriptors in the model:

[1]Fragment descriptors,
[2]Distance descriptors,
[3]Physical descriptors,
[4]Electronic descriptors,
[5]Quantum mechanical descriptors

4.4.Descriptor selection:

Automated selection.

4.5.Algorithm and descriptor generation:

MC4PC is a fragment-based statistical model system. The methodology involves breaking down the structures of the training set into all possible fragments from 2 to 10 heavy (non-hydrogen) atoms in length. Two-dimensional distances between heavy atoms are also included in the analysis. Fragments from the entire training set are combined into gross activity categories. A structural fragment is considered as a biophore if it has a statistical significant association with chemicals in the active category. It is considered a biophobe if it has a statistically significant relation with the inactive category. Within each biophore modulators of

the activity, such as substructures, molecular orbital energies and two-dimensional distance descriptors, of the biophores are identified. Statistical equations based on relevant descriptors are established within each statistical significant biophore. The program was set to maximum specificity (details available upon request).

4.6.Software name and version for descriptor generation:

MC4PC v. 2005

4.7.Descriptors/Chemicals ratio:

The model uses primarily fragment descriptors, specific to a group of structurally related chemicals from the training set, therefore estimations of the number of used descriptors may be difficult.

In general, we estimate that the model uses an order of magnitude less descriptors than there are observations. It should be noted that due to MultiCASE's complex decision making scheme,

overfitting is rare, compared to simpler linear models. Warnings are issued in case of statistically insufficient number of observations, which is not the case in the present model.

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

Applicability domain of MultiCASE models is expressed in terms of fragments unknown to the system and statistical significance of the known biophores and biophobes. Descriptors may also be taken into account. Failure to comply with the model domain is not absolute but may be graded, depending on the number and nature of the involved fragments. Thus, different applications may define the applicability domain in different ways. The Danish QSAR group has accepted the strictest possible definition of applicability domain for its MultiCASE models, namely, only chemicals without any unknown fragments are accepted. This applicability domain definition was applied when determining the validation result.

5.2.Method used to assess the applicability domain:

Only chemicals with no warnings when predicted are within the domain. Warnings are given to chemicals with unknown fragments or/and statistical insignificance.

5.3.Software name and version for applicability domain assessment:

MultiCASE v. 2005.

5.4.Limits of applicability:

Discrete organics as defined by the model. See 5.2

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

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::

1033 chemicals are in the training set: 316 positive (active), 22 marginals and 695 negative (inactive).

6.6.Pre-processing of data before modelling:

n/a

6.7.Statistics for goodness-of-fit:

98-100% concordance.

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

Not performed. (It is not a preferred measurement for evaluating large models).

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

MC4PC five-fold 2 * 50 % cross-validation performed by DK National Food Institute gave:

Sensitivity: 69.9%
Specificity: 95.4%
Concordance: 90.7%

The cross-validation is done by randomly removing 50% of the training set, where the 50% contains the same ratio of positive and negatives as the training set. Then creating a model on the remaining 50% and use it to predict the removed 50%. After making a model on remaining 50% of the training set a new model is made on the removed 50% of the training set and this model is used to predict the other 50%. Repeating this five times.

6.10.Robustness - Statistics obtained by Y-scrambling:

Not performed.

6.11.Robustness - Statistics obtained by bootstrap:

Not performed.

6.12.Robustness - Statistics obtained by other methods:

Not performed.

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

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:

Not available.

7.6.Experimental design of test set:

Not performed.

7.7.Predictivity - Statistics obtained by external validation:

Not available.

7.8.Predictivity - Assessment of the external validation set:

Not available.

7.9.Comments on the external validation of the model:

Not available.

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

The model identifies substructures (fragments) and for each set of molecules containing a specific fragment further identifies additional parameters (modulators e.g. logP and molecular orbital energies). Many predictions may indicate modes of action that are obvious for persons with expert knowledge for the endpoint.

8.2.A priori or a posteriori mechanistic interpretatio:

A posteriori mechanistic interpretation. The information in 8.1 may provide mechanistic interpretation.

8.3.Other information about the mechanistic interpretation:

9.Miscellaneous information

9.1.Comments:

The model can be used to predict sensitizing effect (ACD humans or GPMT).

9.2.Bibliography:

OECD Guidelines

9.3.Supporting information:

Training set(s)

Test set(s)

Supporting information

10.Summary (ECB Inventory)

10.1.QMRF number:

To be entered by ECB

10.2.Publication date:

To be entered by ECB

10.3.Keywords:

To be entered by ECB

10.4.Comments:

To be entered by ECB

APPENDIX 7

QMRF	*QMRF identifier (ECB Inventory):*Q13-34-36-315
	QMRF Title: Derek for Windows - Skin sensitisation
	*Printing Date:*17-dic-2012
	QMRF

1.QSAR identifier

1.1.QSAR identifier (title):

Derek for Windows - Skin sensitisation

1.2.Other related models:

No information available

1.3.Software coding the model:

Derek for Windows version 13 www.lhasalimited.org/derek

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 kate.langton@lhasalimited.org www.lhasalimited.org

2.3.Date of QMRF update(s):

2.4.QMRF update(s):

2.5.Model developer(s) and contact details:

Lhasa Limited 22-23 Blenheim Terrace, Woodhouse Lane, LS2 9HD, UK kate.langton@lhasalimited.org www.lhasalimited.org

2.6.Date of model development and/or publication:

Derek for Windows version 13 was released in December 2010 and included updates to the skin sensitisation endpoint.

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

[1]D.M. Sanderson and C.G. Earnshaw; Computer Prediction of Possible Toxic Action from Chemical Structure; The DEREK System; Human and Experimental Toxicology, 1991, 10, 261-273 http://het.sagepub.com/cgi/content/abstract/10/4/261

[2]P.N. Judson, C.A. Marchant,and J.D. Vessey; Using Argumentation for Absolute Reasoning about the Potential Toxicity of Chemicals. JCICS, 2003, 43, 1364-1370 http://pubs.acs.org/doi/abs/10.1021/ci020272g

2.8.Availability of information about the model:

The model contains multiple alerts (version 13 contains 71 skin sensitisation alerts) which each describe an SAR for a specific chemical class and is augmented by a rule to consider LogKp value. The alerts are available for inspection within the software and representative examples are provided to illustrate a given alert if available. The training set underpinning a given alert is proprietary, though generally based on publicly available data. The basis of the rule considering the effect of LogKp is publicly available and referenced within the model.

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

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Mammal (mainly Guinea Pig, Mouse and Human)

3.2.Endpoint:

4.Human health effects 4.6.Skin sensitisation

3.3.Comment on endpoint:

The model is primarily based on data from the Guinea Pig Maximisation Test (GPMT) and Local Lymph Node Assay (LLNA). Data from a number of additional assays have also been used to build the model including Human Patch Test results.

3.4.Endpoint units:

A Derek for Windows alert makes a prediction on the likelihood of a query compound causing skin sensitisation and is not restricted to a specific assay, and does not include units. Accordingly, data generated from multiple assays is used to develop an alert and an appreciation of the assay units is required when building the alert training set. The EC3 value in the LLNA is used to assign activity for skin sensitisation. Any compound with an EC3 < 100% is considered positive when developing an alert. For other assays, the author's call is generally accepted.

3.5.Dependent variable:

Data is not processed before an alert is developed, although the model predicts for skin sensitisation and the data used to develop the alerts is assay specific. A positive result in an assay (see section 3.4) is required to develop an alert, though an alert will not be built against a singe compound.

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 Guidline 406; LLNA: OECD Test Guideline 429). If activity is observed in a non-standard assay or protocol this will be mentioned in the comments.

3.7.Endpoint data quality and variability:

Alerts are developed against data generated following standard test protocols (predominantly OECD TG 406 and OECD TG 429), the data forming the basis of each alert is fully referenced within the alert. An initial dataset used to develop the endpoint (Cronin MT and Basketter DA. Multivariate QSAR analysis of a skin sensitization database. SAR and QSAR in Environmental Research, 1994, 2, 159-179) is recognised to be of high quality as the tests were run to identical protocols and generated within a single organisation. Subsequent alert (and overall endpoint) development has been against multiple sources of data from which it is hard to draw general conclusions, though all data is generated to standard protocols, and all references are available within the model.

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

Expert system based on multiple structure alerts (2D SARs).

4.2.Explicit algorithm:

Expert system

Expert system based on multiple structure alerts (2D SARs)

Alert based

4.3.Descriptors in the model:

4.4.Descriptor selection:

LogP (required for the prediction of LogKp) is generated by the reasoning engine within the model using either the Moriguchi equation (Moriguchi I et al, Chemical and Pharmaceutical Bulletin, 1992, 40, 127) or the ClogP model from BioByte. The user can select which model to use or supply their own values.

LogKp is generated using the Potts and Guy equation (Potts RO and Guy RH, Pharmaceutical Research, 1992, 9, 663-669).

4.5.Algorithm and descriptor generation:

The model comprises multiple alerts and associated reasoning rules and one physicochemical-based (LogKp) reasoning rule. The alerts have been built to each describe particular chemical class(es) based on all the available data in the public domain and any donated proprietary data, though an alert will not be written against a single compound. The likelihood and scope of an alert are defined by the developer based on the data collated. An alert is triggered when a query compound matches the scope of the alert as defined by inclusion and exclusion patterns. The LogKp value for the query compound will be considered by the physicochemical-based rule and may augment the overall reasoning level observed. A negative prediction may be generated if a query compound matches no alerts but activated the physicochemical-based reasoning rule.

4.6.Software name and version for descriptor generation:

BioByte Corp
ClogP is used to calculate LogP
None identified
http://www.biobyte.com/

Moriguchi equation
A published equation for the prediction of LogP
n/a
http://www.journalarchive.jst.go.jp/jnlpdf.php?cdjournal=cpb1958&cdvol=40&noissue=1&startpage=127&lang=en&from=jnltoc

Potts and Guy equation
A published equation for the prediction of LogKp
n/a
http://www.springerlink.com/content/u3j7325272041303/?p=612e5a80876e4cedbe325dc31f85e82d&pi=13

4.7.Descriptors/Chemicals 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 scope 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 matches an alert describing a structure-activity for skin sensitisation it can be considered to be within the applicability domain. The scope of each alerts is defined using inclusion patterns to describe the structures of the known positive compounds in the training set and also exclusion patterns which may be used to describe the structures of known negative compounds as well as limit the alert to the structure types observed in the training set and thus set the applicability domain for the alert.

A negative prediction is generated if a query compound has a value of LogKp which invokes the reasoning rule based on LogKp however LogP or LogKp values do not limit the applicability domain of the model.

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.

5.3.Software name and version for applicability domain assessment:

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, there are no limits for physicochemical descriptors.

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

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:

The training set for each alert is not available. The number of compounds upon which an alert is built can vary substantially from alert to alert depending on the amount information available in the public domain or donated proprietary data, however an alert will not be built against a single compound. No internal validation has been performed.

6.6.Pre-processing of data before modelling:

Data is not processed before an alert is developed, though an alert will not be built against a single compound, and data generated from standard test protocols is always used unless the alert comments specifically mention otherwise.

6.7.Statistics for goodness-of-fit:

Not applicable

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

Not applicable

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

Not applicable

6.10.Robustness - Statistics obtained by Y-scrambling:

Not applicable

6.11.Robustness - Statistics obtained by bootstrap:

Not applicable

6.12.Robustness - Statistics obtained by other methods:

Not applicable

7.External validation - OECD Principle 4

7.1.Availability of the external validation set:

Yes

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:

No

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

No

7.5.Other information about the external validation set:

Lhasa Limited has performed an external validation, the two datasets are publicly available but not attached.

1. Cronin MT and Basketter DA. Multivariate QSAR analysis of a skin 7.External validation - OECD Principle 4 sensitization database. SAR and QSAR in Environmental Research, 1994, 2, 159-179, available at "http://dx.doi.org/10.1080/10629369408029901".

2. 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.

Additional external validations are published in the literature but the results are not presented in the model and so the validations are not referenced here.

7.6.Experimental design of test set:

Proprietary datasets were sought

7.7.Predictivity - Statistics obtained by external validation:

The positive predictivity for each alert for the two datasets is available within the software.

7.8.Predictivity - Assessment of the external validation set:

The total number of compounds in the validation dataset is 426 and so is sufficiently large to validate the model.

The compounds in the dataset 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:

No information available

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. The mechanism of action may include chemical reactivity, electrophlic reactions, but cannot be generalised over the multiple alerts in the model. The mechanistic basis of any alert is fully referenced in the alert comments.

8.2.A priori or a posteriori mechanistic interpretation:

The mechanistic basis of the model was developed a priori by examining the active and inactive structures 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 for Windows is an knowledge-based expert system containing mechanistically-based rules which are built using all the underlying evidence available to the SAR developer. Therefore, there is no defined training or test set, and therefore there are no internal validation statistics to report. The model may be used to consider the likelihood of skin sensitisation when preparing a submission for REACH, or developing personal products.

9.2.Bibliography:

[1]Cronin MT and Basketter DA. Multivariate QSAR analysis of a skin sensitization database. SAR and QSAR in Environmental Research, 1994, 2, 159-179 http://dx.doi.org/10.1080/10629369408029901

[2]Gerberick GF, Ryan CA, Kern PS, Schlatter H, Dearman RJ, Kimber I, Patlewicz GY and Basketter DA (2005) Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis 16, 157-202 http://www.inchemicotox.org/results

9.3.Supporting information:

10.Summary (ECB Inventory)

10.1.QMRF number:

Q13-34-36-315

10.2.Publication date:

2011/06/08

10.3.Keywords:

Lhasa Limited, Derek for Windows - Skin sensitisation, Mammal (mainly Guinea Pig, Mouse and Human)

10.4.Comments: