Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate;
isophorone di-isocyanate

EC Number: **223-861-6**

CAS Number: **4098-71-9**

Index Number: **615-008-00-5**

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Not evaluated in this report.

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Not evaluated in this report.

3 HEALTH HAZARDS

Acute toxicity

3.1 Acute toxicity - oral route

Not evaluated in this report.

3.2 Acute toxicity - dermal route

Not evaluated in this report.

3.3 Acute toxicity - inhalation route

3.3.1 Animal data

3.3.1.1 [Study 1]

Study reference:

Bayer AG, Isophorondiisocyanat - study on acute inhalation toxicity in rats according to OECD 403 (1995)

Detailed study summary and results:

Test type

OECD Guideline TG 403 (Acute Inhalation Toxicity)

EU Method B.2 (Acute Toxicity (Inhalation))

acc. GLP

Guideline study with acceptable restrictions: exposure concentrations spaced suboptimal

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

>99 %

Impurities do not affect the classification

Bayer AG, batch no. 1.5/3-28

Particle size: Mass Median Aerodynamic Diameter (MMAD) 1.6 - 2.1 µm geometric standard deviation: approx. 1.7 µm

Type or preparation of particles: aerosol, generated using a two component nozzle with conditioned compressed air unchanged (no vehicle)

Test animals

rat (Wistar) male/ female

5 animals per sex per dose

Age: 2-3 months

Weight at study initiation: 193 g (males mean), 177 g (females mean)

Administration/exposure

Type of exposure: nose-only using the dynamic directed-flow principle

Duration of test/ exposure period. 48h

Nominal concentration (calculated from the ratio of the quantity of test substance sprayed into the baffle and the total th roughput of air through the inhalation chamber): 115, 289, 462, 379, 1514 mg/m3

Gravimetric concentration: 18, 55, 85, 105, 410 mg/m3

20.4, 53.3; 73.8; 104.6; 410.3 mg/m3 + control (analytical)

Analytical verification of test atmosphere concentrations: yes, HPLC, UV detection

post-exposure observation period: 4 weeks

Control group: Yes, 0 mg/ m3

Statiastical methods: geometric mean

Results and discussion

LC50 (4 h): ca. 40 mg/m³ air (male/female). Under the conditions of this study the test item is very toxic for rats after inhalative exposure.

3.3.1.2 [Study 2]

Study reference:

RCC Research & Consulting Company Ltd., 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat - 4-hour acute inhalation toxicity study in rats (1988)

Detailed study summary and results:

Test type

OECD Guideline TG 403 (Acute Inhalation Toxicity)

inhalation: aerosol (nose only)

RL 2 (reliable with restriction)

acc. GLP

Guideline study with acceptable restrictions: no air control animals; exposure concentrations spaced suboptimal

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

>99 %

Impurities do not affect the classification

Hüls AG, batch no. 87/07/11 SM1

Particle size: 18 mg/m3: 100 % <= 4.6 µm; 99.7 % <= 3 µm; 92.4 % <= 2.13 µm 22 mg/m3: 100 % <= 4.6 µm; 99.3 % <= 3 µm; 94.4 % <= 99.7 % <= 3 µm; 92.4 % <= 2.13 µm 22 mg/m3: 100 % <= 4.6 µm; 99.3 % <= 3 µm; 94.4 % <= 2.13 µm 70 mg/m3: 100 % <= 4.6 µm; 97.2 % <= 3 µm; 87.1 % <= 2.13 µm 450 mg/m3: 100 % <= 4.6 µm; 81.3 % <= 3 µm; 61.1 % <= 2.13 µm

Type or preparation of particles: Hospitak No. 950 nebulizer and dilution system (clean air), symmetrical topdown flow of aerosol to animals' noses and further unchanged (no vehicle)

Test animals

rat (Wistar) male/ female

5 animals per sex per dose

Age at study initiation: males 10-11 weeks, females 13-14 weeks

Weight at study initiation: males 221.8-326.8 g, females 202.2-266.4 g)

Administration/exposure

Type of exposure: flow-past nose-only inhalation

Duration of test/exposure period:4h

Gravimetric concentrations: 14, 23, 69, 548 mg/m3

Analytical verification of test atmosphere concentrations: yes, GC

post-exposure observation period: 27 days

No control group.

LoGIT-Model was used to calculate the LC50

Results and discussion

LC50 (4 h): 31.0 mg/m³ air (male/female), very toxic for rats after inhalative exposure.

3.3.2 Human data

Not evaluated in this report.

3.3.3 Other data

Not evaluated in this report.

3.4 Skin corrosion/irritation

3.4.1 Animal data

3.4.1.1 [Study 1]

Study reference:

Bayer AG, Isophorondiisocyanat - study for skin irritation/corrosion in rabbits, 1994

Detailed study summary and results:

Test type

OECD Guideline TG 404 (Acute Dermal Irritation / Corrosion)

Coverage: semi occlusive (shaved)

1 (reliable without restriction)

acc. GLP

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

>99 %

Impurities do not affect the classification

Bayer AG, Leverkusen, Batch/lot no. 1.5 / 3.-20

liquid at 20°C and 101.3 kPa, log Kow = 4.75 at 20 °C

Test animals

Rabbit, (New Zealand White), female

1 animal, (due to animal welfare considerations)

3,2 kg

Administration/exposure

4 hours exposure time

Total volume applied: 0.5 ml, undiluted

Post exposure observation period: 14 days

Control: untreated skin

Undiluted

Observation time after exposure: 1h; 24h; 48h; 72h

Scoring system: 83/467/EEC; Draize scores

Tests site shaved, Area of exposure: ca. 6 cm2, semiocclusive

Removal of test substance: water

Statistical methods: Mean value

Results and discussion

Erythrema score	Mean (24/48/72h)	Score:2,7	Max. Score: 4	Not reversible
Edema score	Mean (24/48/72h)	Score: 1,7	Max. Score: 4	Not reversible
primary dermal irritation index (PDII)	Mean (1h/ 24/48/72h)	Score: 4,5	Max. Score: 8	Not reversible

On the exposed skin strong erythematous and exsudative reactions were observed. From day 7 on a white to yellowish squamous coat (on day 14 the coat was white) and eschar formation were seen. On day 1, on the exposed skin area the epidermis was partly removed and in this area a wound (1 x 1 cm) with incrustation was observed.
4.5 of max. 8.0 (Krötlinger, 1994)

3.4.1.2 [Study 2]

Study reference:

Hüls AG, Prüfung der akuten Hautreizwirkung von Isophorondiisocyanat (IPDI), 1984

Detailed study summary and results:

Test type

OECD Guideline TG 404 (Acute Dermal Irritation / Corrosion)
Coverage: occlusive (shaved)
1 (reliable without restriction)
non GLP

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
>99 %
Impurities do not affect the classification
Unknown batch
liquid at 20°C and 101.3 kPa, log Kow = 4.75 at 20 °C

Test animals

Rabbit, (New Zealand White), male/ female
No. of animals per sex per dose: 3
weight at the study initiation: 3,8- 5,3 kg

Administration/exposure

4 hours exposure time
Total volume applied: 0.5 ml, undiluted

Post exposure observation: 14 days

No control

undiluted

Examination time points: 1; 24; 48; 72 hours and 6; 8; 10; 14 days after removal of patch and test substance

Scoring system: 6th Amendment = 79/831/EEC

Tests site shaved, Area of exposure: ca. 6 cm2, semiocclusive

Removal of test substance: water

Statistical methods:Mean value

Results and discussion

Tier Nr.	Ohr-marke	Geschl.	1 Std. A	1 Std. B	24 Std. A	24 Std. B	48 Std. A	48 Std. B	72 Std. A	72 Std. B	6 Tage A	6 Tage B	8 Tage A	8 Tage B	10 Tage A	10 Tage B	14 Tage A	14 Tage B
1	11785	männl.	3	4	3	4	x3	4	x3	3	x3	2	I+3	2	SI+3	2	KRNarben	
2	11791	männl.	2	4	x3	4	+4	3	+-4	3	+-3	2	SI+3	2	K+3	2	W Narben	
3	11829	männl.	3	4	3	4	3	4	x3	3	+3	2	I+3	2	RI+3	2	KRWNarben	
4	11704	weibl.	3	4	*4	4	*4	3	*4	3	*4	1	*4	1	-SR4	1	KRW	
5	11800	weibl.	3	4	*4	4	*4	3	*4	2	*4	1	xI*4	1	-SR4	1	KRW	
6	11912	weibl.	3	4	*4	3	*4	3	*4	2	*4	1	-+4	1	SI+3	1	K	
$\bar{x}$ absolut			6,83		7,33		7,0		6,33		5,0		5,0		4,83			

27,49 : 4 = 6,87 = Irritationsindex

Tier-Nr. = animal number

Männl. = male

Weibl. = female

Std. = hr

Tage = days

Narben = scars

Irritationsindex= irritation index

A= Redness

B= Swelling

X= slight yellow color

*= red-brown color

+ = yellow color

- = slight hardening

I= hardening

S= scab

K= crust

R= cracked, bloody

W= wound

Not reversible

Description of all lesions: S. table

Average score:

- Erythema: 3.61/4.0 (6th Amendment = 79/831/EEC)
- Edema: 3.33/4.0 (6th Amendment = 79/831/EEC)
- Overall: 6.87/8.0 (OECD TG) OTHER EFFECTS: necrosis after 4 hours, not after 3 minutes

3.4.1.3 [Study 3]

Study reference:

Fraunhofer ITA, Bericht über die Prüfung von Isophorondiisocyanat auf primäre Hautreizwirkung, 1981

Detailed study summary and results:

Test type

OECD Guideline TG 404 (Acute Dermal Irritation / Corrosion)

Coverage: occlusive (shaved)

2 (reliable with restrictions)

non GLP

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

No data on purity/ batch number

Impurities do not affect the classification

No data

liquid at 20°C and 101.3 kPa, log Kow = 4.75 at 20 °C

Test animals

Rabbit, (New Zealand White), male

No. of animals per sex per dose: 6

weight at the study initiation. 2,3 kg

Administration/exposure

4 hours exposure time

Total volume applied: 0.5 ml, undiluted

Post exposure observation period: 8 days

No control

undiluted

Examination time points: immediately after removal = 4 hours; 24, 48, 72 hours; 8 days

Scoring system: maximum 4 scores each for erythema and scab formation and edema formation; average of 24 h and 72 h readings

Test site: 2.5 cm x 2.5 cm flank skin on both sides; 8 cm x 8 cm shaved 24 hours in advance, Occlusion: PVC film

Removal of test substance: water

Statistical methods: Mean value

Results and discussion

		Zeit	Hautreizwirkung/Tier Nr.						–	ø
			1	2	3	4	5	6	–	
1. Hautrötung	li	4 h	1	2	1	1	1	1	7	1,17
		24 h	1	2	3	1	2	1	10	1,67
		48 h	1	2	3	1	2	1	10	1,67
		72 h	1	2	3	1	2	1	10	1,67
		8 d	4	3	3	3	3	3		
	re.	4 h	1	2	1	1	1	1	7	1,17
		24 h	2	2	2	1	2	1	10	1,67
		48 h	2	2	2	1	2	1	10	1,67
		72 h	2	2	3	1	2	1	11	1,83
		8 d	4	3	4	3	3	3		
2. Ödembildung	li.	4 h	3	3	4	4	2	3	19	3,17
		24 h	4	4	4	4	4	4	24	4,0
		48 h	*	*	*	*	*	*	--	--
		72 h	*	*	*	*	*	*	--	--
		8 d	*	*	*	*	*	*		
	re.	4 h	3	2	2	4	3	3	17	2,83
		24 h	4	4	4	4	4	4	24	4,0
		48 h	*	*	*	*	*	*	--	--
		72 h	*	*	*	*	*	*	--	--
		8 d	*	*	*	*	*	*		

Hautreizuung/ Tier Nr= skin irritation/ animal number

Zeit= time

Li= left side

Re= right side

Hautrötung= erythema

Ödembildung= edema

* = High degree of irritation of the skin with severe thickening and fissured surface hardening after 8d was observed.

Not reversible

High degree of irritation of the skin with severe thickening and fissured surface hardening after 8d was observed.

dermal irritation index 5.71 of max. 8.0, “severly irritating/corrosive" for rabbits under the conditions of the study

3.4.2 Human data

Not evaluated in this report.

3.4.3 Other data

3.4.3.1 [Study 4]

Study reference:

Envigo, Vestanat IPDI: In vitro membrane barrier test for skin corrosion, 2016

Detailed study summary and results:

Test type

OECD Guideline TG 435 (In Vitro Membrane Barrier Test Method for Skin Corrosion)

Corrositex™

2 (reliable with restrictions)

acc. GLP

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

99.9 %

Impurities do not affect the classification

Batch number unknown

Test System

Test Kit

Name: Corrositex™

Corrositex™ is a validated and accepted in vitro method to assess if a test item can produce skin corrosion, and to distinguish between GHS corrosivity categories 1A, 1B and 1C. This method has been accepted by regulatory authorities. The in vitro assay system is conducted in three consecutive steps: test qualification, categorisation and classification of the test sample.

Administration/exposure

Preparation of the Bio-barrier

- One day prior to testing the bio-barrier matrix was prepared.

- The bio-barrier powder was solved in the bio-barrier diluent and heated for 20 ± 2 minutes at 68 – 70 °C in a water bath under continuous stirring.

- The temperature did not exceed 70 °C. The mixture was allowed to cool in the turned-off water bath for another 10 minutes.

- The mixture was then filled into the membrane holders (200 µL per membrane holder). Air bubbles were avoided.
- The filled membrane holders were sealed with parafilm and were stored at 2 – 8 °C until further use.

Qualify Test

- In order to test whether the test system is suitable for the test item and reference item, 150 µL of the test item were applied into the "Qualify Test Vial". The vial was shaken until the solution appeared homogenous, and incubated for 1 minute. Afterwards, a change in consistency was noted.

Categorisation Test

- In the categorisation test the observation period of the test item and reference item after application to the bio-barrier was determined:

• Category 1: observation period after application will be 4 hours
• Category 2: observation period after application will be 1 hour

- Approximately 150 µL of the test item were applied into the "Category A Vial" as well as into the "Category B Vial". The vials were shaken until the solution appeared homogenous. After 1 minute no colour change was monitored.
- Based on the colour change obtained, a test item is assigned to a category. If an intense colour change (similar to the category 1 colour chart) is observed in "Category A Vial" or in "Category B Vial" the test item is assigned to category 1. If a less intense colour change (similar to the category 2 colour chart) is observed in "Category A Vial" or in "Category B Vial" the test item will be assigned to category 2. If no colour change is observed in either of the vials, a confirmation test is conducted. For the confirmation test two drops of the confirm reagent are added to the "Category B Vial".

The vial was shaken for 5 seconds. The colour of the solution matched one of the colours shown in the accompanying colour chart, confirming that the test item is a category 2 substance.

Classification Test

- 11 vials containing the CDS were pre-warmed to room temperature.
- 4 vials each were used for quadruplicate measurement of the test item and reference item, the vial labelled (+) was used for the positive control (single measurement), and the vial labelled (-) was used for the negative control (single measurement).
- The vial labelled C was used as colour reference for the CDS.
- Applications of the test item, reference item and the controls were performed staggered to ensure accurate reaction times to be recorded.
- The prepared bio-barriers were placed atop the CDS vials (not longer than 2 min prior to application) and 500 µL of the test item or controls, respectively, were applied per bio-barrier for 1 hour was a result from the categorisation test.
- The time interval of the possible colour change or precipitation in the CDS solution was recorded in the raw data file.

Results and discussion

Qualify Test (Test Item)
The test item induced a physical change (precipitation) in the qualify test after 1 minute incubation. Since a physical change (precipitation) was visible in the “Qualify Test Vial”, the test item was considered to be suitable for the next step.
Qualify Test (Reference Item)
The reference item induced a change in colour in the qualify test after 1 minute incubation. Since a change in colour was visible in the “Qualify Test Vial”, the test item was considered to be suitable for the next step.
Categorisation Test (Test Item)
The test item did not induce a change in colour neither Category A vial nor in the Category B vial after 1 minute incubation. A confirmation experiment was performed by adding the confirm reagent to the Category B vial. This induced a change in colour to grey. Therefore, the test item was classified as category 2.
Categorisation Test (Reference Item)
The reference item did not induce a change in colour neither Category A vial nor in the Category B vial after 1 minute incubation. A confirmation experiment was performed by adding the confirm reagent to the Category B vial. This induced a change in colour to yellow. Therefore, the test item was classified as category 2.

Classification Test

Test Group	Time Interval of Color Change	UN GHS Prediction
Negative Control	> 60 minutes	Non-corrosive
Positive Control	53 seconds	Corrosive Sub-category 1A
Reference Item	> 30 – 60 minutes	Corrosive Sub-category1C
Test Item	> 60 minutes	Non corrosive

A change of colour of the CDS reagent after treatment of the bio-barriers with the reference item could be observed in the interval from 30 to 60 minutes. According to the classification criteria given in "overall remarks" the reference item was classified as corrosive (GHS Cat 1C).

3.5 Serious eye damage/eye irritation

3.5.1 Animal data

3.5.1.1 [Study 1]

Study reference:

Fraunhofer Institut, Bericht über die Prüfung von Isophorondiisocyanat auf Schleimhautreizwirkung, 1981

Detailed study summary and results:

Test type

equivalent to OECD Guideline TG 405 (Acute Eye Irritation / Corrosion)
2 (reliable with restrictions)
non GLP

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
Unknown degree of purity/ batch number
Impurities do not affect the classification
liquid at 20°C and 101.3 kPa, log Kow = 4.75 at 20 °C
Corrosive to skin (GHS Cat 1C)

Test animals

New Zealand white rabbit, male

No. of animals per sex per dose:6

weight at the study initiation: 2.3 kg

Administration/exposure

Duration of test/exposure period: 30 s
0.1 ml into each eye
Post exposure observation period: 8 days
Control group and treatment
No control group
No vehicle
Time points at which grading/scoring took place:1; 24; 48; 72 hours; 8 days
Tool used to asses scores: ophthalmoscope; fluorescein
Grading scale: maximum 110 scores (Draize)
Removal of test substanc:rinsing for 3 min with physiol. sodium chloride solution
Post exposure observation period: 8 days
Statistical methods: Mean value

Results and discussion

AVERAGE SCORE (24; 48;72h)

- Cornea (opacity) (max. 4):

Not rinsed: 1.0; 1.0; 1.0; 1.0; 1.0; 1.0/ Rinsed: 1.0; 1.0; 1.0; 1.0; 0.7; 0.7

- Cornea (area) (max.4):

Not rinsed: 3.7; 3.0; 2.7; 3.5; 3.0; 2.7/ Rinsed: 2.3; 2.3; 1.7; 1.7; 1.0; 0.7

- Iris: (max. 2):

Not rinsed: 1.0; 0.7; 1.0; 0.5; 0.0; 0.3;/ Rinsed: 0.0; 0.0; 0.7; 0.0; 0.0; 0.0

- Conjunctivae (Redness (max. 3)

Not rinsed: 2.7; 3.0; 3.0; 2.7; 2.7; 3.0/ Rinsed: 2.7; 3.0; 3.0; 2.3; 2.7; 2.7

- Conjunctivae (Chemosis): (max. 4)

Not rinsed: 4.0; 4.0; 4.0; 4.0; 4.0; 4.0/ Rinsed: 4.0; 4.0; 4.0; 4.0; 3.7; 3.7

- Conjunctivae (Exsudation (max. 3)

Not rinsed: 3.0; 3.0; 3.0; 3.0; 2.7; 2.3/ Rinsed: 2.0; 2.7; 3.0; 2.3; 1.7; 2.0

Not reversible/ not fully reversible

There was a constantly high degree of chemosis throughout the 8 days observation period both on rinsed and non-rinsed eyes, and slight cornea damage, to a lesser degree on the rinsed eye, with significant retrogression within 8 days.

AVERAGE SCORE (not rinsed / rinsed)

- Cornea (opacity): 1.0 / 0.9 (max. 4)

- Cornea (area): 2.9 / 1.6 (max. 4)

- Iris: 0.67 / 0.1 (max. 2)
- Conjunctivae (Redness): 2.8 / 2.7 (max. 3)
- Conjunctivae (Chemosis): 3.9 / 3.9 (max. 4)
- Conjunctivae (Exsudation): 2.8 / 2.3 (max. 3)
- Overall irritation score: 36.4 / 26.4 (max. 110)

Number of animals affected: 6/6

Overall irritation score: 36.4 / 26.4 (max. 110)

3.5.1.2 [Study 2]

Study reference:

Hüls AG, Prüfung der akuten Augen- und Schleimhautreizwirkung von Isophorondiisocyanat (IPDI), 1984

Detailed study summary and results:

Test type

OECD Guideline TG 405 (Acute Eye Irritation / Corrosion)

1 (reliable without restriction)

non GLP

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

>99 %

Impurities do not affect the classification

Batch number unknown

liquid at 20°C and 101.3 kPa, log Kow = 4.75 at 20 °C

corrosive to skin (GHS Cat 1C)

Test animals

New Zealand white rabbit, male/ female

No. of animals per sex per dose: 3

weight at the study initiation: 3.7-5.4 kg

Administration/exposure

Duration of test/exposure period: 15 days

Total dose: 0.1 ml into each eye

Post exposure observation period: 15 days

No control group

No vehicle

Time points at which grading/scoring took place: 1; 24; 48; 72 hours and 6; 8; 10; 13; and 15 days after treatment

Tool used to asses scores: othersodium fluorescein plus ophthalmic lamp

Grading scale: maximum 110 scores (Draize)
unrinsed
Post exposure observation period:15 days
Statistical methods: Mean value

Results and discussion

Average score per animal (Time points: 24h, 48h, 72h)
cornea opacity score (max. 4.0): 0.3; 0.3; 0.0; 0.0; 0.7; 0.7
Cornea area score (max. 4.0): 0.3; 0.3; 0.0; 0.0; 0.7; 0.3;
iris score (max. 2): 0.0; 0.0; 0.3; 0.3; 0.0; 0.3;
conjunctivae score (max. 3): 1.3; 2.0; 1.0; 1.3; 1.7; 2.3;
chemosis score (max. 4): 0.7; 0.7; 0.7; 0.7; 0.7; 0.7
Exsudation (max. 3): 1.0; 1.3; 1.3; 1.3; 1.3; 1.3
according to the scores fully reversible within 15 days

Significant exsudation was observed at the 1 hour and 24 hour inspections. Ten days after treatment all animals showed loss of hair around the eye and incrustation at the eyelid, mostly associated with thickening on day 13, which is not ref lected in the scores.
Number of animals affected:6/6
The irritation index was 9.96 of max. 110

3.5.2 Human data

Not evaluated in this report.

3.5.3 Other data

Not evaluated in this report.

3.6 Respiratory sensitisation

Not evaluated in this report.

3.7 Skin sensitisation

3.7.1 Animal data

3.7.1.1 [Study 1]

Study reference:

IBR (International Bio-Research), Huels AG, 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat - Prüfung auf sensibilisierende Eigenschaften am Meerschweinchen nach B. Magnusson und A.M. Kligman (gemäß OECD Richtlinien), 1983

Detailed study summary and results:

Test type

Guinea pig maximisation test

Induction: intradermal and epicutaneous

Challenge: epicutaneous, occlusive

OECD GL 406

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
Degree of purity: Not reported

Impurities do not affect the classification

Batch number unknown

Test animals

Guinea pig, Strain: Dunkin-Hartley, Pirbright White, Hoe: DHPK (SPF - LAC.) /Boe., Sex: no dataNo. of animals per sex per dose: 20 test / 20 control

Weight at study initiation: mean 350 g

Administration/exposure

Controls: 20 animals, concurrent vehicle (Paraffin oil (DAB6))

Induction:

pairwise injections of 0.05 ml each on shoulders

Days 7-9: 48 hours closed patch treatment of injection sites (0.5 ml; control: vehicle)

Days 21-22: 24 hour closed patch treatment with test substance (left flank) / vehicle (right flank)

pairwise injections of 0.05 ml each on shoulders:

2 x test substance 10 % in vehicle (paraffin) (control: vehicle)

2 x test substance 10 % in 50:50 mixture of Freund's Complete Adjuvant (FCA) / oleum arachidis (control: vehicle instead of test substance)

2 x FCA / distilled water (50:50) (control: FCA undiluted)

Days 7-9: 48 hours closed patch treatment of injection sites (0.5 ml; control: vehicle)

Challenge:

Days 21-22: 24 hour closed patch treatment with test substance (left flank) / vehicle (right flank)

Days 22-23: Readings at patch removal and 24 hours later

Concentrations used for challenge: 100 % (0.5 ml)

Rechallenge: no - Positive control: none

Results and discussion

- Grading system:

0 = no skin reaction

0.5 = slight and spotted erythema

1 = slight and regular, or moderate and spotted erythema

2 = moderate erythema

3 = severe erythema or edema

The test item showed no indication of primary irritation in the range finding study in concentrations up to 100%.

24 hours after the challenge, 17 out of 20 animals were positive having an overall mean score of 1.15 (max.3). After 48 hours 16 out of 20 animals were positive having an overall mean score of 0.85 (max.3). 24 and 48 hours after the challenge 19 out of 20 animals showed a positive reaction. In the control group 0 out of 20 animals were positive at 24 and at 48 hours after the challenge.

Under the conditions of this guinea pig maximization test, the test item 3 -Isocyanatomethyl-3,3,3 - trimetylcyclohexylisocyanate exhibited the potential to produce dermal sensitization in guinea pigs. These results characterize the test substance as a dermal sensitizer under the conditions of this study.

negative control	paraffin			IPDI			
Animal	Number	24hrs	48 hrs	Animal	Number	24hrs	48 hrs
1	391	0	0	1	371	2	1
2	392	0	0	2	372	2	1
3	393	0	0	3	373	1	1
4	394	0	0	4	374	1	1
5	395	0	0	5	375	2	2
6	396	0	0	6	376	1	0
7	397	0	0	7	377	1	1
8	398	0	0	8	378	2	1
9	399	0	0	9	379	2	1
10	400	0	0	10	380	1	1
11	401	0	0	11	381	1	1
12	402	0	0	12	382	1	1

13	403	0	0	13	383	0	1
14	404	0	0	14	384	1	1
15	405	0	0	15	385	0	1
16	406	0	0	16	386	1	0
17	407	0	0	17	387	1	0
18	408	0	0	18	388	2	1
19	409	0	0	19	389	0	0
20	410	0	0	20	390	1	1
Sum		0	0	Sum		23	17

24 hours after challenge: 17/20 animals positive, overall mean score 1.15 (max.3)

48 hours after challenge: 16/20 animals positive, overall mean score 0.85 (max.3)

24 and 48 hours after challenge: 19/20 animals with positive reaction = extreme sensitization, interpreted as "slight sensitization" by the authors

Control group: 0/20 animals positive at both 24 and 48 hours

3.7.1.2 [Study 2]

Study reference:

Dearman et al, Characterization of murine immune responses to allergenic diisocyanates, 1992

Detailed study summary and results:

Test type

equivalent or similar to OECD GL 429 (Skin Sensitisation: Local Lymph Node Assay)

Groups of mice (n = 4) were exposed topically on the dorsum of both ears to 25 µl of various concentrations of the test chemical in Three days later all mice were injected intravenously via the tail vein with 20 eCi of [3 H]methylthymidine (sp act 2 Ci/mmol; in 250 l of phosphate-buffered saline (PBS). Five hours later mice were killed and the draining auricular lymph nodes excised Incorporation of [3 H]thymidine (3HTdR) was measured by scintillation

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

Degree of purity: Not reported

Impurities do not affect the classification

Batch number unknown

Test animals

Mouse; BALB/c;Sex: female

No. of animals per sex per dose:4

Age: 8-12 weeks

Administration/exposure

Controls: vehicle (acetone/olive oil (4:1 v/v))

Groups of mice (n = 4) were exposed topically on the dorsum of both ears to 25 µl of various concentrations of the test chemical in 4:1 acetone: olive oil (AOO). Control mice received an equivalent volume of vehicle alone. Three days later all mice were injected intravenously via the tail vein with 20 eCi of [3 H]methylthymidine (sp act 2 Ci/mmol; Amersham International, Amersham, Bucks, UK) in 250 "l of phosphate-buffered saline (PBS). Five hours later mice were killed and the draining auricular lymph nodes excised and pooled for each experimental group. A single cell suspension was prepared by gentle mechanical disaggregation through 200mesh stainless steel gauze. LNC were washed twice with an excess of PBS and precipitated in 5% trichloroacetic acid (TCA). Twelve hours later pellets were resuspended with I ml ofTCA and transferred to 10 ml of scintillation fluid (Optiphase MP, LKB, Flow McClean, VA). Incorporation of [3 H]thymidine (3HTdR) was measured by *scintillation and results were expressed as the mean cpm per node for each experimental group

Results and discussion

showed a dermal sensitizing potential

EC3: 0.073

Stimulation index: 1.81 (0.05)

Stimulation index: 4.39 (0.1)

Stimulation index: 23.21 (0.25)

Stimulation index: 30.58 (0.5)

Stimulation index: 40.16 (1.0)

Stimulation index: 54.91 (2.5)

3.7.1.3 [Study 2]

Study reference:

Zissu ez al, Cutaneous sensitization to some polyisocyanate prepolymers in guinea pigs, 1998

Detailed study summary and results:

Test type

Buehler test

Induction: epicutaneous, occlusive

Challenge: epicutaneous, occlusive

EU Method B.6 (Skin Sensitisation) (Cited as Directive 84/449/EEC, B.6)

Test substance

Test material: 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

Degree of purity: Not reported

Impurities do not affect the classification

Batch number unknown

Test animals

guinea pig (Dunkin-Hartley) female

20 test- / 10 control- animals

Weight on average 350 g

Administration/exposure

Negativce control: vehicle

Positive control: neomycin sulfate (CAS# 1405-10-3), HMDI (CAS: 5124-30-1) was selected as positive reference substance

epicutaneous

occlusive

Concentrations used for induction: 5 % (w/v); 0.5 ml

induction vehicle: petrolatum

Induction schedule: not reported; see guideline

Concentrations used for challenge: 1 % (w/v); 0.5 ml

vehicle: petrolatum

Results and discussion

grading system of Magnusson/Kligman:

0 = no visible change

1 = discrete or patchy erythema

2 = moderate and confluent erythema

3 = intense erythema and swelling only scores of 2 and/or 3 considered positive;

the test substance is a strong sensitizer under the conditions of this study.

Sensitization reaction:

test group treated with test substance 16/20 animals positive = strong sensitization

test group treated with vehicle: all animals negative (0-1 scores)

control groups: no irritation or sensitization

3.7.2 Human data

3.7.2.1 [Study 1]

Study reference:

Schlede et. al, Chemical substances and contact allergy—244 substances ranked according to allergenic potency, 2003

Detailed study summary and results:

Test type

Thirty experts including dermatologists from universities, representatives from the chemical industry and from

regulatory authorities elaborated and consequently decided on the potency ranking of chemicals with contact allergenic properties. Clinical and experimental data on humans and results of animal tests as documented in the scientific literature were carefully collected and evaluated. It was decided to rank the most potent contact allergens in Category A of substances having significant allergenic properties. Substances with a solid-based indication of a contact allergenic potential and substances with the capacity of cross-reactions were listed in Category B and substances with insignificant or questionable allergenic effects were listed in Category C.

IPDI was allocated in Category B for substances with a solid-based indication of a contact allergenic potential and substances with the capacity of cross-reactions :

Experience with humans indicate a sensitizing effect of IPDI by skin contact. Animal experiments showed a clear sensitizing potential.

3.7.2.2 [Study 2] etc.

Study reference:

Kayser, D., Schlede, E. (2001). Chemikalien und Kontaktallergien. [Chemicals and contact allergies] Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, 2001

Detailed study summary and results:

Test type

In the detailed conclusion for IPDI the authors Kayser and Schlede (2001) cite an open epicutaneous test, in which the 1 hour exposure of IPDI in 3 out of 4 workers led to occurrence of eczema. Only one of these workers have had previously contact to IPDI, the 3 others have been exposed to different diisocyanadate beforehand. Additionally, in a patch test, 4 workers were tested for 48 hours with 1% IPDI in ethanol. Two workers already had an allergy to Isophorondlamin and two have been sensitized with Isophorondiamine. All worker responded positively to IPDI.

3.7.3 Other data

Not evaluated in this report.

3.8 Germ cell mutagenicity

Not evaluated in this report.

3.9 Carcinogenicity

Not evaluated in this report.

3.10 Reproductive toxicity

Not evaluated in this report.

3.11 Specific target organ toxicity – single exposure

No additional Studies evaluated evaluated in this report.

3.12 Specific target organ toxicity – repeated exposure

Not evaluated in this report.

3.13 Aspiration hazard

Not evaluated in this report.

4 ENVIRONMENTAL HAZARDS

Not evaluated in this report.