Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

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

EC Number: 223-861-6
CAS Number: 4098-71-9

CLH-O-0000007311-84-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

8 June 2023

CLH report

Proposal for Harmonised Classification and Labelling

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

Chemical name:

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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Version number: **2.0** **Date:** **June 2022**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON -ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE; ISOPHORONE DI-ISOCYANATE

Cover Note

The DE CA received a proposal for harmonised classification and labelling of the substance *3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate* from industry for an update of an existing entry in Annex VI to CLP. The CLH proposal included the CLH report and Annex I to the CLH report.

The indicated hazard classes for which the classification was proposed and the information basis provided were assessed by the DE CA. The industry proposal had some deficiencies and was therefore revised at the appropriate parts.

The proposal submitted by the DE CA is based on the data from study reports, the CLH report and the Annex I to the CLH report provided by industry.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON -ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE; ISOPHORONE DI-ISOCYANATE

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ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON -ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE; ISOPHORONE DI-ISOCYANATE

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

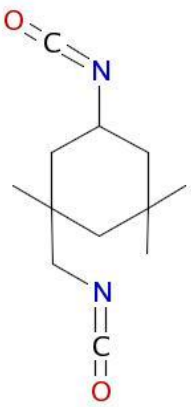
Name(s) in the IUPAC nomenclature or other international chemical name(s)	5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane
Other names (usual name, trade name, abbreviation)	Isophorone diisocyanate
ISO common name (if available and appropriate)	Not applicable
EC number (if available and appropriate)	223-861-6
EC name (if available and appropriate)	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
CAS number (if available)	4098-71-9
Molecular formula	C12H18N2O2
Structural formula	
SMILES notation (if available)	CC1(C)CC(CC(C)(CN=C=O)C1)N=C=O
Molecular weight or molecular weight range	222.2835
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant for entry in Annex VI

Figure 1 shows the number of matching substance classifications (hazard class, categories and hazard statements) provided by manufacturers and importers under REACH and CLP notifications, as well as whether the substance is defined under harmonised classification and labelling (CLH).

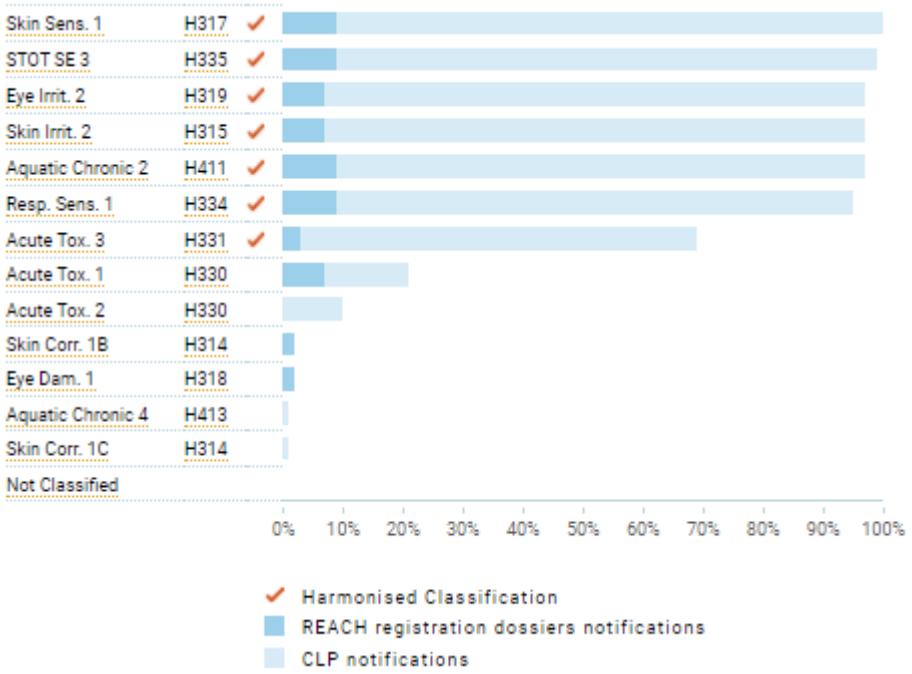


Figure 1: Breakdown of all 1044 C&L notifications for IPDI submitted to ECHA, C&L Inventory database, https://echa.europa.eu/de/brief-profile/-/briefprofile/100.021.692 [assessed 05/2022]

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP) in REACH registration (update 29/07/2021)
3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate EC no.: 223-861-6	≥ 99.5 — ≤ 99.9	Acute Tox. 3 *, H331 STOT SE 3, H335 Skin Irrit. 2, H315 Eye Irrit. 2, H319 Resp. Sens. 1, H334 Skin Sens. 1, H317 Aquatic Chronic 2, H411	Acute Tox. 1, H330 STOT SE 3, H335 Skin Corr. 1B, H314 Eye Dam. 1, H318 Resp. Sens. 1, H334 Skin Sens. 1, H317 Aquatic Chronic 2, H411

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3: For substance with an existing entry in Annex VI of CLP

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	615-008-00-5	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate; isophorone di-isocyanate	223-861-6	4098-71-9	Acute Tox. 3 * STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1 Aquatic Chronic 2	H331 H335 H315 H319 H334 H317 H411	GHS06 GHS08 GHS09 Dgr	H331 H335 H315 H319 H334 H317 H411		* Resp. Sens. 1; H334: C ≥ 0.5 % Skin Sens.1; H317: C ≥ 0.5%	2
Dossier submitters proposal					**Modify** Acute Tox 1 Skin Corr. 1 Eye Dam. 1 Skin Sens. 1A **Remove** STOT SE 3	 H330 H314 H318 H317 H335	GHS06 GHS05 GHS08 GHS09 Dgr	H330 H314 H317	**Add:** EUH071	**Add:** Inhalation: ATE = 0.031 mg/l (dust/mists) **Modify** Skin Sens.1A; H317:C ≥ 0.05 %	
Resulting Annex VI entry if agreed by RAC and COM					Acute Tox. 1 Skin Corr. 1 Eye Dam.1 Resp. Sens. 1 Skin Sens. 1A Aquatic Chronic 2	H330 H314 H318 H334 H317 H411	GHS06 GHS05 GHS08 GHS09 Dgr.	H330 H314H334 H317 H411	EUH071	Inhalation: ATE = 0.031 mg/l (dust / mist) Resp. Sens. 1; H334: C ≥ 0.5 % Skin Sens.1A; H317: C ≥ 0.05 %	2

Note 2: The concentration of isocyanate stated is the percentage by weight of the free monomer calculated with reference to the total weight of the mixture.

It should be noted that IPDI is proposed here to be classified as Skin corrosion Category 1 and thus serious damage to the eye is implicitly reflected in the hazard statement H314. To avoid redundancy with regard to labelling, the hazard statement H318 is therefore not indicated on the label.

Table 4: Reason for not proposing harmonised classification and status under consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	not evaluated in this report	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route		
Acute toxicity via dermal route		
Acute toxicity via inhalation route	**harmonised classification proposed**	**Yes**
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation	not evaluated in this report	No
Skin sensitisation	**harmonised classification proposed**	**Yes**
Germ cell mutagenicity	not evaluated in this report	No
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure	**harmonised classification proposed**	**Yes**
Specific target organ toxicity-repeated exposure	not evaluated in this report	No
Aspiration hazard		
Hazardous to the aquatic environment		
Hazardous to the ozone layer		

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance has been evaluated by EU authorities and inserted to Annex I of Dangerous Substances Directive 67/548/EEC via its 19th Adaptation to the Technical Progress (93/72/EEC) with the following classification and labelling:

Classification: T; R 23, Xi; R 36/37/38, R 42/43

Labelling: T; 23-36/37/38-42/43; S: (l /2-)26-28-38-45

This classification and labelling was extended by Symbol N and R-Phrases 51 and 53 with the 29th Adaptation to the Technical Progress (2004/73/EC) of Dangerous Substances Directive 67/548/EEC. This classification and labelling is as follows:

Classification: T; R 23, Xi; R 36/37/38, R 42/43, N; R 51-53
Labelling: T, N; R: 23-36/37/38-42-43-51/53; S: (l /2-)26-28-38-45-61

Specific concentration limits
T; R23: $C \geq 2$ %
Xn; R20: $0.5 \% \leq C < 2$ %
R42/43: $C \geq 0.5$ %

Therefore, it has been inserted into Annex VI, Table 3.1 and 3.2 of the original CLP Regulation 1272/2008.

Classification, Table 3.1: Acute Tox. 3 * H331, Eye Irrit. 2 H319, STOT SE 3 H335, Skin Irrit. 2 H315, Resp. Sens. 1 H334, Skin Sens. 1 H317, Aquatic Chronic 2 H411
Labelling, Table 3.1: GHS06, GHS08, GHS09, Dgr; H331, H319, H335, H315, H334, H317, H411

Specific concentration limits, Multiplying factor (M-factor) and Acute Toxicity Estimates (ATEs):
Resp. Sens. 1; H334: $C \geq 0.5$ %
Skin Sens.1; H317: $C \geq 0.5$ %

RAC general comment
3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (IPDI) is a liquid (the technical product is a liquid with a light yellowish colour) with a low vapour pressure under ambient conditions. Based on these characteristics, the test substance is expected to occur at temperatures close to room temperature as liquid aerosol droplets at higher concentrations and as vapour at low concentrations. It is hydrolytically unstable with a half-life of less than 12 hours.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Action is needed at Community level.

- Change in existing entry due to new data (acute inhalation toxicity, skin irritation)
- Change in existing entry due to changes in the criteria (specific target organ toxicity-single exposure, eye irritation)

Related to the hazard respiratory sensitisation, a restriction to limit the use of diisocyanates, including IPDI, in industrial and professional applications was adopted and came into force 24/08/2020.

5 IDENTIFIED USES

- Raw material for the industrial manufacture of resins/hardeners for coating materials, adhesives, sealants, elastomers, polyurethanes.

For detailed information please refer to the registration dossier of the substance.

6 DATA SOURCES

For data sources, please refer to the registration dossier of the substance.

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20 °C and 101.3 kPa	liquid at 20 °C and 101.3 kPa	Degussa AG, 2006	
Melting/freezing point	-60 °C	Sax and Lewis, 1987	
Boiling point	310 °C at 1013 hPa	Auergesellschaft GmbH, 1988, INRS, 2009	
Relative density	1.058 g/cm3 at 20 °C	Auergesellschaft GmbH, 1988, INRS, 2009	
Vapour pressure	0.000635 hPa at 20 °C, 0.00117 hPa at 25 °C 0.0212 hPa at 50 °C	Bayer AG, 1994	
Surface tension			Surface activity is not a desired property of the substance and is not expected based on structure. Therefore, a test is not required according to REACH Annex VII, 7.6, column 2.
Water solubility	Approx. 15 mg/l at 23 °C	Infracor GmbH, 2000	
Partition coefficient n-octanol/water	log Kow = 4.75 at 20 °C	Degussa AG, 2006	Estimated (QSAR)
Flash point	150.5 °C at 1013 hPa	AQura GmbH, 2010	
Flammability			The substance is a liquid. The EU method is not applicable for liquids.
Explosive properties	non explosive	AQura GmbH 2009	
Self-ignition temperature	430 °C	Auergesellschaft GmbH, 1988,	

Property	Value	Reference	Comment (e.g. measured or estimated)
		INRS, 2009, Hommel, 1991, Morel et al., 1982	
Oxidising properties			Based on the chemical structure, the substance is incapable of reacting exothermically with combustible materials. The substance contains oxygen atoms (no halogen atoms), but the oxygen atoms are not bonded directly to nitrogen atoms or other oxygen atoms. Therefore, according to REACH Annex VII, 7.13, column 2 testing is not required.
Granulometry	Not applicable (liquid)		
Stability in organic solvents and identity of relevant degradation products			The stability of the substance is not considered to be critical. This is confirmed by data in chapter 4.9 stating that the substance is completely miscible with esters, ketones, ethers, and aromatic and aliphatic hydrocarbons. Therefore, testing is not required according to REACH Annex IX, 7.15, column 1.
Dissociation constant			The substance is hydrolytically unstable (half-life less than 12 hours). Therefore, a test is not required according to REACH Annex IX, 7.16, column 2.
Viscosity	14.2 mPa s at 20 °C (dynamic)	Ibacon GmbH, 2012	

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this report.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this report.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Not evaluated in this report.

10.2 Acute toxicity - dermal route

Not evaluated in this report.

10.3 Acute toxicity - inhalation route

Table 6: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD), dose levels, duration of exposure	Mortality	Value LC_{50}	Reference
Acute Inhalation Toxicity OECD TG 403 EU Method B.2 inhalation: aerosol (nose only) acc. GLP Klimisch 1 (reliable without restriction)	Rat (Wistar) male/ female 5 animals per sex per dose	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate Purity > 99 % Particle size: Mass Median Aerodynamic Diameter (MMAD) 1.6 - 2.1 µm geometric standard deviation: approx. 1.7 µm unchanged (no vehicle) Type of exposure: nose-only using the dynamic directed-flow principle 20.4, 53.3; 73.8; 104.6; 410.3 mg/m³ + control 0 mg/m³ (analytical); Exposure duration: 4 h Post-exposure observation: 4 weeks	0 mg/m³: no mortality 20.4 mg/m³: no mortality 53.3 mg/m³: 3/5 ♂ (16 d – 28 d) 3/5 ♀ (11 d – 25 d) 73.8 mg/m³: 5/5 ♂ (1 d - 12 d) 5/5 ♀ (3 d – 9 d) 104.6 mg/m³: 5/5 ♂ (1 d - 10 d) 5/5 ♀ (1 d – 20 d) 410.3 mg/m³: 5/5 ♂ (≤ 4 h) 5/5 ♀ (≤ 4 h – 6 h)	LC_{50} (4 h): ca. 40 mg/m³ air * (male/female) * Since only test concentration (53.3 mg/m³) was within 0 % and 100 % lethality, the geometric mean of the next concentrations (20.4 and 73.8 mg/m³) was chosen by the registrant to calculate the LC_{50}.	Bayer AG, 1995
Acute Inhalation Toxicity OECD TG 403 inhalation: aerosol (nose only) acc. GLP Klimisch 2 (reliable with restriction): no air control animals; exposure concentrations spaced suboptimal, acclimation less than 7 days for group 1 to 3, body weight range for males exceeds ± 20 %	Rat (Wistar) male/ female 5 animals per sex per dose	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate Purity > 99 % 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 % ≤ 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 unchanged (no vehicle) Type of exposure: flow-past nose-only inhalation 18; 22; 70; 450 mg/m³ (analytical) Exposure duration: 4 h Post-exposure observation: 4 weeks	18 mg/m³: no mortality 22 mg/m³: 3/5 ♂(2 d -9 d) 1/5 ♀ (19 d) 70 mg/m³: 5/5 ♂(day 1/2), 4/5 ♀ (5 d – 9 d) 450 mg/m³: 5/5 ♂ (4 h – 24 h) 5/5 ♀ (4 h – 24 h)	LC_{50} (4 h): 31.0 mg/m³ air * (male/female) * LOGIT-Model was used to calculate the LC_{50}	RCC Research & Consulting Company AG, 1988

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (IPDI) is a liquid with a low vapour pressure under ambient conditions. Based on these characteristics, the test substance is expected to occur at temperatures close to room temperature as liquid aerosol droplets at higher concentrations and as vapour at low concentrations.

Two acute inhalation toxicity studies in rats according to OECD TG 403 and GLP are available.

LC50-values (4 h, rat) of approximately 40 mg/m^3 and 31 mg/m^3 were calculated, respectively. Since, there was just one pair of values below 100 % lethality in the study conducted by Bayer AG (Bayer AG, 1995) the LC50 was calculated using the geometric mean and should be regarded less reliable than the LC50 calculated using the LOGIT model in the study conducted by (RCC Research & Consulting Company AG, 1988)).

Animals of all dose groups above 20.4 mg/m³ exhibited clinical effects on respiration (such as dyspnoea, abnormal respiration, rales) and macroscopic findings, such as effects on the nose/muzzle (red incrustation, mucous membrane of the nose with reddening), the pleural cavity (filled with liquid), and the lung (less collapsed, dark-red foci, emphysematous, spongy, with escape of liquid at the cut part at gross pathology). Macroscopic findings were considered to reflect local irritant effects to the respiratory tract (Bayer AG, 1995).

10.3.2 Comparison with the CLP criteria

Based on the data presented above (LC50 values for acute inhalation toxicity were determined as 31.0 mg/m^3 air and approximately 40 mg/m^3 air) the test substance IPDI has to be considered as very toxic for rats after inhalative exposure. According to the criteria given by the CLP regulation the classification criteria for acute inhalation toxicity Category 1 are fulfilled.

Table 7: Comparison of study results with the CLP criteria

Study	Study results	Classification criteria acc. CLP	Conclusion on classification/ ATE
OECD TG 403 inhalation: aerosol (nose only) (Bayer AG, 1995)	LC_{50} (4 h): approx. 40 mg/m³ = 0.040 mg/l air	Category 1: ≤ 0.05 mg/l (dust/mist)	Acute Tox. 1, H330
OECD TG 403 inhalation: aerosol (nose only) (RCC Research & Consulting Company AG, 1988)	LC_{50} (4 h): 31.0 mg/m³ = 0.031 mg/l air	Category 1: ≤ 0.05 mg/l (dust/mist)	Acute Tox. 1, H330 ATE = 0.031 mg/l (dust / mist)

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the available data the current Annex VI entry should be modified from Acute Tox. 3 (Minimum classification) with H331 to Acute Tox. 1 with H330. The ATE (dust / mist) for inhalation corresponds to the LC50 of 0.031 mg/l.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute inhalation toxicity

Based on data available, the dosser submitter (DS) proposed to modify the harmonised classification for acute inhalation toxicity from Acute Tox. 3*, H331 (minimum classification) to Acute Tox. 1, H330 with the ATE (dust / mist) for inhalation corresponding to the LC_{50} of 0.031 mg/L.

***Table**: Summary of acute inhalation toxicity studies*

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD), dose levels, duration of exposure	Mortality	Value LC_{50}	Reference
Acute Inhalation Toxicity OECD TG 403 EU Method B.2 inhalation: aerosol (nose only) acc. GLP Klimisch 1	Rat (Wistar) 5/sex/dose	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, Purity > 99 % Particle size: MMAD) 1.6 - 2.1 µm geometric standard deviation: approx. 1.7 µm unchanged (no vehicle) Type of exposure: nose-only using the dynamic directed-flow principle 20.4, 53.3; 73.8; 104.6; 410.3 mg/m³ + control 0 mg/m³ (analytical); Exposure duration: 4 h	0 mg/m³: no mortality 20.4 mg/m³: no mortality 53.3 mg/m³: 3 ♂ (16 d – 28 d) 3 ♀ (11 d – 25 d) 73.8 mg/m³: 5 ♂ (1 d - 12 d) 5 ♀ (3 d – 9 d) 104.6 mg/m³: 5 ♂ (1 d - 10 d) 5 ♀ (1 d – 20 d) 410.3 mg/m³: 5 ♂ (≤ 4 h) 5 ♀ (≤ 4 h – 6 h)	LC_{50} (4 h): ca. 40 mg/m³ air* (male/female) * Since only test concentration (53.3 mg/m³) was within 0 % and 100 % lethality, the geometric mean of the next concentrations (20.4 and 73.8 mg/m³) was chosen by the registrant to calculate the LC_{50}.	Bayer AG, 1995
Acute Inhalation Toxicity OECD TG 403 inhalation: aerosol (nose only) acc. GLP Klimisch 2: no air control animals; exposure concentrations spaced suboptimal, acclimation less than 7	Rat (Wistar) male/ female 5 animals per sex per dose	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate Purity > 99 % 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 % ≤ 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 unchanged (no vehicle)	18 mg/m³: no mortality 22 mg/m³: 3 ♂ (2 d -9 d) 1 ♀ (19 d) 70 mg/m³: 5 ♂ (day 1/2), 4 ♀ (5 d – 9 d) 450 mg/m³: 5 ♂ (4 h – 24 h) 5 ♀ (4 h – 24 h)	LC_{50} (4 h): 31.0 mg/m³ air * (male/female) * LOGIT-Model was used to calculate the LC_{50}	RCC Research & Consulting Company AG, 1988

days for group 1 to 3, body weight range for males exceeds ± 20 %		Type of exposure: flow-past nose-only inhalation 18; 22; 70; 450 mg/m^3 (analytical) Exposure duration: 4 h			

Comments received during consultation

There were two comments submitted during the consultation, one by a Member State Competent Authority (MSCA) and one by an Industry/Trade Association, both supported the DS' proposal to modify the classification from Acute Tox. 3 with H331 to Acute Tox. 1 with H330.

The MSCA noted that the methodology used by the registrant to calculate the LC_{50} is not adequate in the Bayer (1995) study and recommended to re-calculate this LC_{50} (according to recommendations set out in OECD GD 39) for setting the ATE, since this study is the most reliable one.

RAC agrees with the DS reply that the classification is based on the lowest ATE value available. The LC_{50} value of 0.031 mg/L was determined in an acute inhalation toxicity study (RCC, 1988) of good quality (Klimisch 2). In addition, in this study two dose levels of test item were tested in the range of category 1 (0.018 mg/L and 0.022 mg/L) instead of one dose <0.05 mg/L as in the study by Bayer AG (1995). Therefore, the data from RCC (1988) study are considered more appropriate to estimate LC_{50} value than these from the Bayer AG (1995) study.

The re-calculated LC_{50} with LogProbit Model is higher than the LC_{50} calculated by the registrant e.g. approximately 0.052 mg/L, thus very close to lethal concentration for 60 % animals (0.0533 mg/L). Therefore, LogProbit Model is deemed not appropriate to calculate LC_{50} in case of data available from the study by Bayer AG (1995).

Assessment and comparison with the classification criteria

Two acute inhalation toxicity studies in rats (Wistar) according to OECD TG 403 and GLP are available.

In the Bayer AG (1995) study, the LC_{50} (aerosol, 4 h, rat) was between 0.0204 and 0.0533 mg/L air for both sexes and calculated (geometric mean) value of LC_{50} was 0.04 mg/L. In RCC (1988) study LC_{50} (aerosol, 4 h, rat) was below 0,022 and 0.07 mg/L air for male and female rats, respectively, and calculated with LOGIT Model value of LC_{50} was 0.031 mg/L air. Thus results of both relevant studies meet classification criteria of CLP Regulation for acute inhalation toxicity, Category 1 (inhalation (dust/mist) $LC_{50} \leq$ 0.05 mg/L). Concerning the acute toxicity estimate (ATE), RAC supports the proposed ATE of 0.031 mg/L as the lowest reliable LC_{50} value, based on the data from the RCC (1988) study. However, due to uncertainties in setting the exact concentration LC_{50} (based on less reliable study and older than Bayer AD, 1995 study), the ATE value should be rounded to 0.03 mg/L (dust/mist).

In conclusion, RAC agrees with the DS's proposal to **classify Isophorone di-isocyanate as Acute Tox. 1, H330: Fatal if inhaled, with ATE of 0.03 mg/L (dust/mist).**

10.4 Skin corrosion/irritation

Table 8: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
Acute Dermal Irritation / Corrosion OECD TG 404 Coverage: semi occlusive (shaved) acc. GLP Klimisch 1 (reliable without restriction)	Rabbit, (New Zealand White) one female (due to expected irritant potency of the test substance, according to TG 404)	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate Purity >99 % unchanged (no vehicle)	0.5 ml undiluted solution 4 h exposure time	Observation time after exposure: 1 h; 24 h; 48 h; 72 h and 7 d, 14 d Strong erythematous and exudative reactions observed. Corrosive to the skin. <u>Grading of skin reaction</u> Erythema - 1 h: 2 of 4 (max), well-defined erythema - 24 h, 48 h, 72 h (mean) : 2.7 of 4 (max), moderate to severe erythema, not reversible Oedema -1 h: 3 of 4 (max), moderate oedema - 24 h, 48 h, 72 h (mean): 1.7 of 4 (max), slight oedema, not reversible From day 7: white to yellowish squamous coat (on day 14 the coat was white) and eschar formation On day 14: epidermis partly removed and in this area wound with incrustation (1 x 1 cm) Reversibility: not reversible 14 days post exposure period	Bayer AG, 1994
Acute Dermal Irritation / Corrosion OECD TG 404 Coverage: occlusive (shaved) non GLP Klimisch 2 (reliable with	Rabbit, (New Zealand White) male/ female 3 animals per sex	3-isocyanatomethyl- 3,5,5-trimethylcyclohexyl isocyanate Purity >99 % unchanged (no vehicle)	0.5 ml undiluted solution 4 h exposure time	Observation time after exposure: 1 h; 24 h; 48 h;72 h and 6 d; 8 d; 10 d; 14 d <u>Grading of skin reaction</u> Erythema - 24 h, 48 h, 72 h (mean): 3.61 of 4 (max), severe erythema, not reversible Oedema 24 h, 48 h, 72 h (mean): 3.33 of 4 (max), moderate to severe	Hüls AG, 1984a

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
restrictions)				Oedema, not reversible Overall irritation index: 6.87/8.0 Extensive irreversible tissue damage such as necrosis, ulceration, or scarring within the 14 days observation period in all animals. Reversibility: not reversible 14 days post exposure period	
Acute Dermal Irritation / Corrosion OECD TG 404 Coverage: occlusive (shaved) non GLP Klimisch 2 (reliable with restrictions)	Rabbit, (New Zealand White) 6 male animals	3,5,5-trimethylcyclohexyl isocyanate No data on purity unchanged (no vehicle)	0.5 ml undiluted solution 4 h exposure time	Observation time after exposure: 4 h*, 24 h, 48 h, 72 h, 8 d <u>Grading of skin reaction (all animals, right and left flank)</u> Erythema - 4 h*: 1.17 (mean) - 24 h: 1.67 (mean) - 48 h: 1.67 (mean) - 72 h: 1.75 (mean) - 8 d: 3.25 (mean) Oedema - 4 h*: 3.0 (mean) - 24 h: 4.0 (mean) - 48 h, 72 h, 8 d: Severe irritation of the skin with severe thickening and cracked sclerosis on the surface, grading not applied Dermal irritation index: 5.71 / 8.0, “severely irritating / corrosive" Reversibility: not reversible 8 days post exposure period * immediately after the end of exposure and washing of the application area	FHITA, 1981a

Additional information on Acute Dermal Irritation / Corrosion OECD TG 404 Hüls AG (1984a)

In the study report (Hüls AG, 1984a), the following experimental procedure is documented: 0.5 ml of IPDI is applied to 6 cm^2 of skin, over which a gauze flap is placed, which is covered with a polyethylene film. The application site is then fixed with an elastic bandage. After a 4-hour exposure time, the bandage is removed. One and 24 hours after removal of the bandage, as well as after 48 and 72 hours and after 6, 8, 10 and 14 days, skin reactions are assessed according to OECD TG 404. In the study report, the results were documented in a table, which is transcribed here (Table 9).

Table 9: Numerical evaluation of reactions, individual values, mean values (Hüls AG, 1984a)

Animal	Ear tag	Sex	1 hr		24 hrs		48 hrs		72 hrs		6 d		8 d		10 d		12 d
No.		♂♀	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A B
1	11785	♂	**3**	**4**	**3**	**4**	x**3**	**4**	x**3**	**3**	x**3**	**2**	I+**3**	**2**	SI+**3**	**2**	KR scars
2	11791	♂	**2**	**4**	x**3**	**4**	**+4**	**3**	**+-4**	**3**	+-**3**	**2**	SI+**3**	**2**	K+**3**	**2**	W scars
3	11829	♂	**3**	**4**	**3**	**4**	**3**	**4**	x**3**	**3**	+**3**	**2**	I+**3**	**2**	RI+**3**	**2**	KRW scars
4	11704	♀	**3**	**4**	***4**	**4**	***4**	**3**	***4**	**3**	***4**	**1**	***4**	**1**	-SR**4**	**1**	KRW
5	11800	♀	**3**	**4**	***4**	**4**	***4**	**3**	***4**	**2**	***4**	**1**	x**I*4**	**1**	-SR**4**	**1**	KRW
6	11912	♀	**3**	**4**	***4**	**3**	***4**	**3**	***4**	**2**	***4**	**1**	-+**4**	**1**	SI+**3**	**1**	K
Mean values			6,83		7,33		7,0		6,33		5,0		5,0		4,83		

6,83 + 7,33 + 7,0 + 6,33 = 27,49

27,49 : 4 = **6,87 (irritation index)**

A= Redness	B= Swelling	I= hardening	K= crust
R= cracked, bloody	S= scab	W= wound	x= slight yellow color
*= red-brown color	+ = yellow color	- = slight hardening	

The report states: “Necrosis formation after an exposure time of 4 hours, but not after 3 minutes.” No further information is given in addition to this single sentence. Neither in the experimental procedure nor in the results table a three minutes exposure and/or observation is documented. Thus, this information is not assignable.

Table 10: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Corrositex™ In Vitro Membrane Barrier Test Method for Skin Corrosion OECD TG 435 acc. GLP 3 (not reliable)	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate Purity is known to the DS and judged as high purity 500 µL of the neat test item was dispensed directly atop the bio-barrier. unchanged (no vehicle)	Corrositex™ - Positive control: Sulphuric acid (95-97 %) - Negative control: Citric acid (10 % (w/v)) solution in deionised water) - Reference Item: acetic acid (10 % (v/v)) Deficiencies in the test design and performance (precipitation in the chemical detection system instead of colour change; unclear differences in colour change after use of confirmation reagent for the test- and reference substance; strong corrosive positive control rather than medium corrosive substance)	*Compatibility Test (Test Item):* The test item induced a detectable precipitation (instead of a colour change) in the chemical detection system after 1 minute incubation. *Compatibility Test (Reference Item)* The reference item induced a change in colour in the chemical detection system after 1 minute incubation. ***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, which corresponds to Corrositex® category 2 test chemicals according to the study report. ***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, which corresponds to Corrositex® category 2 test chemicals according to the study report. ***Classification Test*** (membrane barrier penetration) - ***Test Item:*** > 60 min, UN GHS prediction "non-corrosive" - ***Reference Item:*** > 30-60 min, UN GHS prediction "Corrosive, Sub-Category1C" - ***Negative control***: > 60 min - ***Positive control***: 53 seconds **Dossier submitter concluded that results are not reliable due to deficiencies in the test design and performance**	Envigo CRS GmbH, 2016

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

Three animal studies on the skin irritating/ corrosive properties of IPDI were performed according to OECD TG 404. Undiluted test substance was applied in these studies.

In one study with three rabbits per sex exposed occlusively for 4 hours, the irritation index was 6.9 of max. 8.0 (Hüls AG, 1984a). Extensive irreversible tissue damage such as necrosis, ulceration, or scarring within the observation period of 14 days was observed in all animals. This overall assessment was confirmed by another study with one rabbit exposed semiocclusively for 4 hours. The results indicate corrosive properties of IPDI with an irritation index of 4.5 of max. 8.0 (Bayer AG, 1994). Non-reversible corrosive effects were observed during 14 d post exposure. In one study with six male rabbits exposed occlusively for 4 hours, strong thickening and cracked sclerosis on the skin surface were observed (FHITA, 1981a). The skin tissue damage was irreversible. Exposure times less than 4 hours were not applied in any of the three OECD TG 404 studies available.

The *in vitro* membrane barrier test method OECD TG 435, as recommended for use as part of a tiered testing strategy for assessing the dermal corrosion hazard potential of chemicals, was performed with IPDI using the Corrositex™ test kit (Envigo CRS GmbH, 2016). Under the experimental conditions reported, the test item IPDI was considered to be skin irritant but not corrosive to skin. However, the test item induced a detectable precipitation (instead of a colour change) in the compatibility test after 1 minute incubation. OECD TG 435 states as limitation that "test chemicals not causing a detectable change in the compatibility test (*i.e.*, colour change in the Chemical Detection System (CDS) of the validated reference test method) cannot be tested with the membrane barrier test method and should be tested using other test methods." Further deficiencies in the test design and performance (strong corrosive positive control rather than medium corrosive substance; unclear differences in colour change after use of confirmation reagent for the test- and reference substance) lead to the overall assessment by the dossier submitter (DS) of the study as not reliable.

Adequate, reliable and representative animal data are available for the assessment of IPDI and indicate corrosive properties of IPDI. Reliable *in vitro* data are not available.

10.4.2 Comparison with the CLP criteria

Based on the data presented above (corrosive responses in animals following 4 hours of exposure within the 14 days of observation) the test substance IPDI has to be considered as corrosive to the skin. Exposure up to 1 hour was not performed in any of the studies available. Therefore, a distinction between Sub-Category 1B and 1C is not feasible. It should be assumed that a corrosive effect that is detectable after 3 min of exposure and 1 hour of observation is also visible 1 hour (or immediately) after 4 hours of exposure. Destruction of the skin tissue 1 hour (or immediately) after 4 hours of exposure was not observed. Thus, Sub-Category 1A is not appropriate. Based on the data available classification in Sub-Category 1B would represent a conservative approach.

Table 11: CLP criteria Category 1 "Corrosive"

Category	Criteria
1	Destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after **exposure ≤ 4 h**
1A	Corrosive responses in at least one animal following **exposure ≤ 3 min** during an **observation period ≤ 1 h**
1B	Corrosive responses in at least one animal following **exposure > 3 min and ≤ 1 h** and **observations ≤ 14 d**
1C	Corrosive responses in at least one animal after **exposures > 1 h and ≤ 4 h** and **observations ≤ 14 d**

Table 12: CLP criteria Category 2 “Irritation”

Category	Criteria
2 irritant	(1) Mean score of ≥ 2.3 - ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

Table 13: Comparison of study results with the CLP criteria

Study	Application, Number of animals	Exposure time [h]	Post exposure observation [d]	Study results	Conclusion on Classification
OECD TG 404 Klimisch 1 (reliable without restriction) (Bayer AG, 1994)	Semi-occlusive, n=1	4	14	not reversible, effects after 14 d	Skin Corr. 1; *Skin Corr. 1A not appropriate; distinction between 1B/1C not feasible due to an exposure time of 4 h*
OECD TG 404 Klimisch 2 (reliable with restrictions) (Hüls AG, 1984a)	Occlusive, n=6	4	14	not reversible, effects after 14 d	Skin Corr. 1; *Skin Corr. 1A not appropriate; distinction between 1B/1C not feasible due to an exposure time of 4 h*
OECD TG 404 Klimisch 2 (reliable with restrictions) (FHITA, 1981a)	Occlusive, n=6	4	8	not reversible, effects after 8 d	Skin Corr. 1; *Skin Corr. 1A not appropriate; distinction between 1B/1C not feasible due to an exposure time of 4 h*

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Based on available *in vivo* data, IPDI is corrosive to the skin and needs to be classified in Category 1 “Corrosive”. Sub-Category 1A is not appropriate. The distinction between 1B/1C is not feasible due to an exposure time of 4 h. Data are neither sufficient for sub-categorisation nor for the assessment of SCL setting.

The current Annex VI entry should be modified from Skin Irrit. 2 with H315 to Skin Corr. 1 with H314.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Based on available *in vivo* studies, the DS proposed to modify harmonised classification for skin effects from Skin Irrit. 2, H315 to Skin Corr. 1, H314.

Animal data

Table*: Summary of animal studies on skin corrosion/irritation*

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
Acute Dermal Irritation / Corrosion OECD TG 404 Coverage: semi occlusive (shaved) acc. GLP Klimisch 1 (reliable without restriction)	Rabbit, (New Zealand White) one female (due to expected irritant potency of the test substance, according to TG 404)	3-isocyanato-methyl-3,5,5-trimethy-lcyclohexyl isocyanate Purity >99 % unchanged (no vehicle)	0.5 mL undiluted solution 4 h exposure time	Observation time after exposure: 1 h; 24 h; 48 h; 72 h and 7 d, 14 d Strong erythematous and exudative reactions observed. Corrosive to the skin. <u>Grading of skin reaction</u> Erythema - 1 h: 2 of 4 (max), well-defined erythema - 24 h, 48 h, 72 h (mean) : 2.7 of 4 (max), moderate to severe erythema, not reversible Oedema -1 h: 3 of 4 (max), moderate oedema - 24 h, 48 h, 72 h (mean): 1.7 of 4 (max), slight oedema, not reversible From day 7: white to yellowish squamous coat (on day 14 the coat was white) and eschar formation On day 14: epidermis partly removed and in this area wound with incrustation (1 x 1 cm) Reversibility: not reversible 14 days post exposure period	Bayer AG, 1994
Acute Dermal Irritation / Corrosion OECD TG 404 Coverage: occlusive (shaved) non GLP Klimisch 2 (reliable with restrictions)	Rabbit, (New Zealand White) male/ female 3 animals per sex	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate Purity >99 % unchanged (no vehicle)	0.5 mL undiluted solution 4 h exposure time	Observation time after exposure: 1 h; 24 h; 48 h;72 h and 6 d; 8 d; 10 d; 14 d <u>Grading of skin reaction</u> Erythema - 24 h, 48 h, 72 h (mean): 3.61 of 4 (max), severe erythema, not reversible Oedema 24 h, 48 h, 72 h (mean): 3.33 of 4 (max), moderate to severe Oedema, not reversible Overall irritation index: 6.87/8.0 Extensive irreversible tissue damage such as necrosis, ulceration, or scarring within the 14 days observation period in all animals. Reversibility: not reversible <u>14 days post exposure period</u>	Hüls AG, 1984a

Acute Dermal Irritation / Corrosion OECD TG 404 Coverage: occlusive (shaved) non GLP Klimisch 2 (reliable with restrictions)	Rabbit, (New Zealand White) 6 male animals	3,5,5-trimethyl-cyclohexyl isocyanate No data on purity unchanged (no vehicle)	0.5 mL undiluted solution 4 h exposure time	Observation time after exposure: 4 h*, 24 h, 48 h, 72 h, 8 d <u>Grading of skin reaction (all animals, right and left flank)</u> Erythema - 4 h*: 1.17 (mean) - 24 h: 1.67 (mean) - 48 h: 1.67 (mean) - 72 h: 1.75 (mean) - 8 d: 3.25 (mean) Oedema - 4 h*: 3.0 (mean) - 24 h: 4.0 (mean) - 48 h, 72 h, 8 d: Severe irritation of the skin with severe thickening and cracked sclerosis on the surface, grading not applied Dermal irritation index: 5.71 / 8.0, "severely irritating / corrosive" Reversibility: not reversible 8 days post exposure period * immediately after the end of exposure and washing of the application area	FHITA, 1981a

In vitro data

***Table**: Summary of in vitro study relevant for skin corrosion/irritation*

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Corrositex™ *In Vitro* Membrane Barrier Test Method for Skin Corrosion OECD TG 435 acc. GLP 3 (not reliable)	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate Purity is known to the DS and judged as high purity 500 µL of the neat test item was dispensed directly atop the bio-barrier. Unchanged (no vehicle)	Corrositex™ - Positive control: Sulphuric acid (95-97 %) - Negative control: Citric acid (10 % (w/v)) solution in deionised water) - Reference Item: acetic acid (10 % (v/v)) Deficiencies in the test design and performance (precipitation in the chemical detection system instead of colour change; unclear differences in colour change after use of confirmation reagent for the test- and	*Compatibility Test (Test Item):* The test item induced a detectable precipitation (instead of a colour change) in the chemical detection system after 1 minute incubation. *Compatibility Test (Reference Item)* The reference item induced a change in colour in the chemical detection system after 1 minute incubation. ***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, which corresponds to Corrositex® Category 2 test chemicals according to the study report. ***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, which corresponds to Corrositex® Category 2 test chemicals according to the study report. ***Classification Test* (Membrane Barrier**	Envigo CRS GmbH, 2016

		reference substance; strong corrosive positive control rather than medium corrosive substance)	**Penetration):** - *Test Item:* > 60 min, UN GHS prediction "non-corrosive" - *Reference Item:* > 30-60 min, UN GHS prediction "Corrosive, Sub-Category1C" - *Negative control*: > 60 min - *Positive control*: 53 seconds DS concluded that the results are not reliable due to deficiencies in the test design and performance	

Comments received during consultation

There were two comments submitted during the consultation, one by a MSCA and one by an Industry/Trade Association, both supported the proposal of the DS to modify the classification from Skin Irrit. 2, H315 to Skin Corr. 1, H314. However, the Industry/Trade Association considered that Category 1 without sub-categorisation corresponds to an over classification.

Sub-categorisation must be based on data and in line with the CLP criteria, however, as no shorter exposure duration than 4h was used in the available *in vivo* studies, sub-categories 1A & 1B cannot be excluded and Category 1 should then be applied. In addition, RAC notes that according to the CLP Regulation (Annex I: 3.2.4.1) the same labelling elements are assigned to Sub-Category 1A/1B/1C and Category 1 of skin corrosion.

Assessment and comparison with the classification criteria

Three animal studies on the skin irritating/corrosive properties of IPDI were performed according to OECD TG 404.

In most reliable, GLP study (Bayer AG, 1994) with one female rabbit exposed semiocclusively for 4 hours, the results indicate corrosive properties of IPDI with strong erythematous and exudative reactions. On day 14 white squamous coat epidermis partly removed and in this area wound with incrustation (1 x 1 cm) were observed. Non-reversible corrosive effects were observed during 14 days post exposure.

In the second study (Hüls AG, 1984a), non GLP, with three rabbits per sex exposed occlusively for 4 hours, extensive irreversible tissue damage such as necrosis, ulceration, or scarring within the observation period of 14 days was observed in all animals.

In the third study (FHITA, 1981a) with six male rabbits exposed occlusively for 4 hours, strong thickening and cracked sclerosis on the skin surface were observed. The skin tissue damage was irreversible.

Only one available animal study was performed under semi-occlusive conditions (as recommended in the OECD TG 404). The occlusive condition used in the 2 other assays represent a worst-case situation.

Exposure times less than 4 hours were not applied in any of the three OECD TG 404 studies available.

The *in vitro* membrane barrier test method, OECD TG 435, was performed with IPDI using the Corrositex™ test kit (Envigo CRS GmbH, 2016). Under the experimental conditions

reported, the test item IPDI was considered to be a skin irritant but not corrosive to skin. However, the test item induced a detectable precipitation (instead of a colour change) in the compatibility test after 1 minute incubation. The OECD TG 435 states as limitation that "test chemicals not causing a detectable change in the compatibility test (i.e., colour change in the Chemical Detection System of the validated reference test method) cannot be tested with the membrane barrier test method and should be tested using other test methods." In addition, the membrane barrier method has been endorsed as a scientifically validated test for a limited range of substances – mainly acids, bases and their derivatives, however IPDI is not such a substance. Therefore, the OECD TG 435 test method should not be used to make decisions on the corrosivity and non-corrosivity of IPDI.

RAC agrees with DS that study by Envigo CRS GmbH (2016) could not be considered as reliable due to deficiencies in the test design and performance.

According to Annex I: 3.2.1.1. of CLP Regulation "skin corrosion means the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discolouration due to blanching of the skin, complete areas of alopecia, and scars."

Based on the adequate and reliable animal data (corrosive responses in animals following 4 hours of exposure within the 14 days of observation), the test substance IPDI has to be considered as corrosive to the skin. Exposure up to 1 hour was not performed in any of the studies available. Therefore, a distinction between Sub-Category 1B and 1C is not feasible. Destruction of the skin tissue 1 hour (or immediately) after 4 hours of exposure was not observed. Thus, Sub-Category 1A is not appropriate since ≤ 3 minutes exposure and observation during period ≤ 1 h was not documented. However Sub-Category 1C could not be assigned taking into account that Sub-Category 1A and 1B could not be excluded due to absence of examination after 3 minutes and 1 hour.

In conclusion RAC agrees with DS that **classification of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate as Skin Corr. 1, H314 is warranted**. Data are neither sufficient for sub-categorisation nor for the offsetting of an SCL.

10.5 Serious eye damage/eye irritation

Table 14: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Eye Irritation / Serious Eye Damage OECD TG 405 non GLP Klimisch 2 (reliable with restrictions)	Rabbit, (New Zealand White) 6 male animals	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate No data on purity unchanged (no vehicle)	0.1 ml, undiluted 30 s exposure time Rinsing: - right eye rinsed for 3 min with physiol. sodium chloride solution subsequently after exposure - left eye was not rinsed.	Irritating effects, not reversible Average score per animal (Time points: 24 h, 48 h, 72 h) - 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 (Exudation) (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 The irritation score was 36.4/110 (not rinsed) or 26.4/110 (rinsed eye). There was a constantly high degree of chemosis (mean score of 4.0 for 6/6 animals) 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 regression within 8 days. An observation up to 21 days was not reported.	FHITA, 1981b
Eye Irritation / Serious Eye Damage OECD TG 405 non GLP Klimisch 1 (reliable without	Rabbit, (New Zealand White) male/ female 3 animals per sex	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate Purity >99 % unchanged (no vehicle)	0.1 ml, undiluted Without rinsing one eye per animal treated	Mild irritating effects observed. Average score per animal (Time points: 24 h, 48 h, 72 h) - Cornea (opacity) (max. 4.0): 0.3; 0.3; 0.0; 0.0; 0.7; 0.7 - Cornea (area) (max. 4.0): 0.3; 0.3; 0.0; 0.0; 0.7; 0.3; - Iris (max. 2): 0.0; 0.0; 0.3; 0.3; 0.0; 0.3; - Conjunctivae (max. 3) 1.3; 2.0; 1.0; 1.3; 1.7; 2.3; (reversible within 15 days)	Hüls AG, 1984b

restriction)				- Chemosis (max. 4) 0.7; 0.7; 0.7; 0.7; 0.7; 0.7; (reversible) - Exudation (max. 3) 1.0; 1.3; 1.3; 1.3; 1.3; 1.3; (reversible) The irritation index was 9.96 of max. 110 Significant exsudation at 1 h and 24 h observation time point Ten days after treatment all animals showed loss of hair around treated eye, incrustation at the eye lid, mostly associated with thickening on day 13, which is not reflected in the scores.	

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

Two studies performed according to OECD TG 405 on serious eye damage/eye irritation of IPDI.

In the study of (FHITA, 1981b), where both eyes were treated (0.1 ml undiluted per eye) and only one eye was rinsed, severe conjunctiva effects were observed. There was a constant high degree of chemosis, exudation and conjunctivae redness throughout the 8 days observation period both on rinsed and non-rinsed eyes in all animals, and slight cornea damage, to a lesser degree on the rinsed eye, with significant retrogression within 8 days. An observation period of 21 days was not reported. Thus, it remains unclear whether the observed effects and the slight cornea damage (no incidence reported) were fully reversed within an observation period of 21 days.

In the study of (Hüls AG, 1984b), where one eye of each animal was treated (0.1 ml test item undiluted) and the other eye was untreated, mild irritating effects were observed. The exudation observed in the study of (Hüls AG, 1984b) may have contributed to the avoidance of damage to the eye. Ten days after treatment with 0.1 ml undiluted test item all animals in this study showed loss of hair around the eye and incrustation at the eye lid, mostly associated with thickening on day 13.

10.5.2 Comparison with the CLP criteria

Based on the data presented above (irritating effects in eyes of rabbits, which are not reversible within 8 days observation period), the test substance IPDI has the potential to induce eye irritation and cornea damage. An observation period of 21 days was not reported. According to the criteria given by the CLP Regulation, the classification criteria for Eye irritation Category 2 are fulfilled, however Category 1 cannot be excluded. No reasons could be identified to explain differences in the outcome of both studies.

All results are assembled together in a single weight-of-evidence assessment. Animal data on eye damage/eye irritation are inconclusive for classification. Based on animal data on skin corrosion, IPDI has to be considered as corrosive to the skin. IPDI is proposed here to be classified as Skin corrosion Category 1. Considering the totality of existing information, IPDI is deemed to cause serious eye damage.

According to CLP Regulation, Annex I, 3.3.2.2.2.: “Skin corrosive substances shall be considered as leading to serious eye damage (Category 1) as well, while skin irritant substances may be considered as leading to eye irritation (Category 2).“

Table 15: CLP criteria Category 1 "Serious eye damage" and Category 2 "Eye irritation"

Category	Criteria
Serious eye damage (Category 1)	Substance that produces: (a) in at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or (b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1.5; calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.
Eye irritation (Category 2)	Substance that produces in at least in 2 of 3 tested animals, a positive response of: (a) corneal opacity ≥ 1; and/or (b) iritis ≥ 1; and/or (c) conjunctival redness ≥ 2; and/or (d) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

Table 16: Comparison of study results with the CLP criteria

Study	Classification criteria acc. CLP	Study results / ATE
OECD TG 405 Klimisch 2 (reliable with restrictions) (FHITA, 1981b)	Inconclusive, *Category 1 cannot be excluded*	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. Irritating effects, not reversible within 8 days. An observation period of 21 days was not reported.
OECD TG 405 Klimisch 1 (reliable without restriction) (Hüls AG, 1984b)	No classification	Exudation observed, avoidance of damage to the eye. Ten days after treatment with 0.1 ml undiluted test substance all animals in this study showed loss of hair around the eye and incrustation at the eye lid, mostly associated with thickening on day 13, which is not reflected in the scores.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Based on available data and the proposal here to classify IPDI as corrosive, Skin Corrosion Category 1, Annex VI entry should be modified from Eye irritation, Category 2 with H319 to Serious eye damage, Category 1 with H 318.

Serious damage to the eye is implicitly reflected in the hazard statement H314. To avoid redundancy with regard to labelling, the hazard statement H318 is therefore not indicated on the label.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed to modify harmonised classification for eye effects from Eye Irrit. 2, H319 to Eye Dam. 1, H318, based on the following criterion of CLP Regulation: "Skin corrosive substances shall be considered as leading to serious eye damage (Category 1)".

Table: *Summary of available animal studies on serious eye damage/eye irritation*

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Eye Irritation / Serious Eye Damage OECD TG 405 non GLP Klimisch 2 (reliable with restrictions)	Rabbit, (New Zealand White) 6 male animals	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate No data on purity unchanged (no vehicle)	0.1 mL, undiluted 30 s exposure time Rinsing: - right eye rinsed for 3 min with physiol. sodium chloride solution subsequently after exposure - left eye was not rinsed.	Irritating effects, not reversible Average score per animal (Time points: 24 h, 48 h, 72 h) - 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 (Exudation) (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 The irritation score was 36.4/110 (not rinsed) or 26.4/110 (rinsed eye). There was a constantly high degree of chemosis (mean score of 4.0 for 6/6 animals) 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 regression within 8 days.	FHITA, 1981b
Eye Irritation / Serious Eye Damage OECD TG 405 non GLP Klimisch 1 (reliable without restriction)	Rabbit, (New Zealand White) male/ female 3 animals per sex	3-isocyanato-methyl-3,5,5-trimethy-lcyclohexyl isocyanate Purity > 99 % unchanged (no vehicle)	0.1 mL, undiluted Without rinsing one eye per animal treated	Mild irritating effects observed. Average score per animal (Time points: 24 h, 48 h, 72 h) - Cornea (opacity) (max. 4.0): 0.3; 0.3; 0.0; 0.0; 0.7; 0.7 - Cornea (area) (max. 4.0): 0.3; 0.3; 0.0; 0.0; 0.7; 0.3; - Iris (max. 2): 0.0; 0.0; 0.3; 0.3; 0.0; 0.3; - Conjunctivae (max. 3) 1.3; 2.0; 1.0; 1.3; 1.7; 2.3; (reversible within 15 days) - Chemosis (max. 4) 0.7; 0.7; 0.7; 0.7; 0.7; 0.7; (reversible)	Hüls AG, 1984b

				- Exudation (max. 3) 1.0; 1.3; 1.3; 1.3; 1.3; 1.3; (reversible) The irritation index was 9.96 of max. 110 Significant exudation at 1 h and 24 h observation time point. Ten days after treatment all animals showed loss of hair around treated eye, incrustation at the eye lid, mostly associated with thickening on day 13, which is not reflected in the scores.	

Comments received during consultation

There were two comments submitted during the consultation, one by a MSCA and one by an Industry/Trade Association, both supported the proposal of DS to modify the classification from Eye Irrit. 2, H319 to Eye Dam. 1, H318.

Assessment and comparison with the classification criteria

Two studies on serious eye damage/eye irritation in rabbits (New Zealand White) according to OECD TG 405, non GLP, are available.

In the study of (FHITA, 1981b), where both eyes were treated (0.1 mL undiluted per eye) and only one eye was rinsed, severe irritation of the conjunctiva was observed. There was a constant 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. An observation period of 21 days was not reported.

In the study of Hüls AG (1984b), where one eye of each animal was treated (0.1 mL test item undiluted) and the other eye was untreated, mild irritating effects were observed. The exudation observed in this study (Hüls AG, 1984b) may have contributed to the avoidance of damage to the eye. Ten days after the treatment, mLall animals showed loss of hair around the eye and incrustation at the eye lid, mostly associated with thickening on day 13.

Based on the data presented above (irritating effects in eyes of rabbits, which are not reversible within the 8 days observation period), the IPDI has the potential to induce eye irritation and cornea damage. An observation period of 21 days was not reported. According to the criteria given by the CLP Regulation, the classification criteria for eye irritation Category 2 are fulfilled, however Category 1 cannot be excluded. No reasons could be identified to explain the differences in the outcome of both studies.

All results are assembled together in a single weight-of-evidence assessment. Animal data on eye damage/eye irritation are inconclusive for classification due to a too short observation period for reversibility in the first study where Category 1 cannot be excluded and due to inconsistencies in results between the two studies. However, the eye data can be used a supportive for the conclusion for classification as Category 1 which is based on skin corrosion data in animals. IPDI is proposed here to be classified as skin corrosion Category 1. Considering the totality of existing information, IPDI is deemed to cause serious eye damage.

In addition, RAC notes that according to CLP Regulation, Annex I:, 3.3.2.2.2.: "Skin corrosive substances shall be considered as leading to serious eye damage (Category 1) as well, while skin irritant substances may be considered as leading to eye irritation (Category 2)."

In conclusion RAC agrees that **classification of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate as Eye Dam. 1, H318 is warranted**.

10.6 Respiratory sensitisation

Not evaluated in this report.

(Harmonised classification: Resp. Sens. 1; H334: C ≥ 0.5 %)

10.7 Skin sensitisation

Table 17: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	Results	**Reference**
Guinea pig maximisation test OECD TG 406 non GLP Klimisch 2 (reliable with restrictions)	Guinea pig; Pirbright White; Sex not specified; Treatment: 20 animals, Control: 20 animals	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate No data on purity	1st application: Induction intracutaneous - test item 10 % (in paraffin; FCA diluted 1:1 with Oleum rachaidis prior to mixing with the test item) - control: FCA undiluted; paraffin undiluted; 10 % paraffin in FCA diluted 1:1 with Oleum rachaidis 2nd application: Induction occlusive epicutaneous - test item undiluted - control: paraffin undiluted 3rd application: Challenge occlusive epicutaneous - test item undiluted - control: paraffin undiluted	Positive response 24 h and 48 h after epicutaneous challenge with undiluted test item Number with positive reactions: *1st reading* 24 h after challenge: - 17 / 20 of test group (dose: undiluted), mean score 1.15/3 - 0 / 20 of negative control (dose: vehicle) *2nd reading* 48 h after challenge: - 16 / 20 of test group (dose: undiluted), mean score 0.85/3 - 0 / 20 of negative control (dose: vehicle)	IBR, 1983
Local Lymph Node Assay similar to OECD TG 429 (study performed before TG was adopted) GLP not	Mouse; BALB/c; 4 females per dose	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate No data on purity	0; 0.05; 0.1; 0.25; 0.5; 0.5; 1.0; 2.5; 0.5 % (w/v) in 4:1 acetone: olive oil; Controls: vehicle, acetone: olive oil (4:1 v/v) 25 µl, topically on the dorsum of both ears, 3 consecutive days (day 1 to day 3) on day 6: all mice injected intravenously via the tail vein with 20 µCi of	Strong skin sensitisation EC_3: 0.073 % (stated in study report) Conc. (% w/v) / Stimulation index (mean cpm/ node x 10^{-2}) 0.05 / 1.81 0.1 / 4.39 0.25 / 23.21	Dearman et al., 1992

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
specified Klimisch 2 (reliable with restrictions)			[^{3}H]methylthymidine (sp act 2 Ci/mmol) in 250 µl of phosphate-buffered saline. Five hours after injection: mice killed and the draining auricular lymph nodes excised. Incorporation of [^{3}H]thymidine (^{3}HTdR) was measured by β-scintillation. Results were expressed as mean cpm per node	0.5 30.58 1.0 40.16 2.5 54.91	
Buehler test EU Method B.6 (Cited as Directive 84/449/EEC, B.6) GLP not specified Klimisch 2 (reliable with restrictions)	Guinea pig (Dunkin-Hartley) Female Treatment: 20 animals, Control: 10 animals	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate Purity >99 %	Induction: epicutaneous, occlusive, 5 % (w/v) in petrolatum, 0.5 ml Challenge: epicutaneous, occlusive, 1 % (w/v) in petrolatum (14 days after induction), 0.5 ml Vehicle control Assessment: 30 h after challenge Positive control: neomycin sulphate (CAS 1405-10-3) Positive reference substance: HMDI (CAS: 5124-30-1)	Strong skin sensitisation Number with positive reactions: - treatment group: 16 /20 (80 % responding) upon occlusive epicutaneous challenge with 1% test substance - neomycin sulphate: 10/19 (53 % responding) - HMDI: 19/20 (95 % responding) - vehicle control: no irritation and/or sensitization	Zissu et al., 1998

Table 18: Summary table of human data on skin sensitisation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Publication	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	Potency ranking of chemicals with contact allergenic properties using clinical and experimental data on humans and results of animal tests. Category A: substances having significant allergenic properties. Category B: substances with a solid-based indication of a contact allergenic potential and substances with the capacity of cross-reactions. Category C: substances with insignificant or questionable allergenic effects.	IPDI was allocated in Category B Experience with humans indicate a sensitising effect of IPDI by skin contact. Animal experiments showed a clear sensitising potential.	Schlede et al., 2003
Publication/ Evaluating compilation	3-isocyanatomethyl-3,5,5-	Cross-reference to (Schlede et al, 2003) Evaluation of clinical and experimental data	Skin sensitisation in humans after skin contact;	Kayser and Schlede, 2001

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
(in German)	trimethylcyclohexyl isocyanate	on humans and results of animal tests on 244 substances published as a loose-leaf-book (Kayser and Schlede, 2001) in German	clearly sensitising in experiments with animals	
Report	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate	IVDK[1]data of the years 2007 to 2016 from 120,977 patients, who are routinely patch tested 2/ 111 IPDI patch tested occupational dermatitis (OD) patients with positive reactions, 1.8 % positive [95 %-CI, 0.2 -6.4] 2/ 56 IPDI patch tested Non-OD patients with positive reactions, 3.6 % positive [95 %-CI, 0.4 - 12.3] 4/195 IPDI patch tested patients with positive reactions, 2.1 % positive [95 %-CI, 0.6 - 5.2] Note: IPDI being a highly reactive compound, no stable patch test preparation is available. Validity of patch test results is doubtful.	May cause allergic reactions of the skin and the airways (asthma).	Geier and Schubert, 2021

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

For skin sensitisation various studies are available. Three are similar/according to guidelines and can be used for classification. The results are all clearly positive indicative of sensitising properties.

In the Guinea pig maximisation test (IBR, 1983) with IPDI (10 % intradermal induction dose) 17 out of 20 (85 %) animals were positive 24 hours after challenge, having an overall mean score of 1.15 (max. 3). After 48 hours, 16 out of 20 (80 %) animals were positive having an overall mean score of 0.85 (max. 3). Overall, 24 and 48 hours after the challenge 19 out of 20 (95 %) animals showed a positive reaction whereas no animal in the control group showed a positive response. IPDI was not tested in this study at ≤ 1 % intradermal induction dose. There was no indication of primary irritation in the range finding study in concentrations up to 100 % IPDI.

Dearman et al. (1992) tested immunological responses in mice exposed to three diisocyanates; IPDI, diphenylmethane- 4,4'-diisocyanat and dicyclohexylmethane-4,4'-diisocyanate. Prior to coming into force of the OECD TG 429 and consequently with minor deviations from this guideline, the lymphocyte proliferative responses in draining lymph nodes were measured 3 days following exposure of mice to various concentrations (0.0; 0.05; 0.1; 0.25; 0.5; 1.0; 2.5 %) of IPDI. IPDI caused a concentration-related increase in lymph node cell proliferation. Stimulation indices increased from 1.81 after treatment with 0.05 % IPDI up to 54.91 after treatment with 2.5 %. The EC3 is 0.073 %. Additionally, in the mouse ear swelling test performed within this study, ear thickness was evaluated 24 hours after the challenge by epicutaneous application of 25 µl of 0.5 % solution. The results showed a concentration-dependent increase of ear thickness relative to pre-challenge values (Induction 0.1 %; 0.25 %; 0.5 %; 1.0 %; 2.5 % (w/v) / 50 µl). The optimum response was observed at 1.0 % induction concentration.

[1] Information network of departments of dermatology (Informationsverbund Dermatologischer Kliniken-IVDK) (currently 56) for the surveillance and scientific evaluation of contact allergies

Zissu et al. (1998) conducted Buehler tests with various diisocyanates, including IPDI. After occlusive epicutaneous induction with 0.5 ml of a solution of 5 % (w/v) IPDI in petrolatum, 16 out of 20 (80 %) animals showed positive response upon occlusive epicutaneous challenge with 1 % test substance.

Schlede et al. (2003) developed a ranking system on skin sensitising potency for 244 chemicals. Available clinical and experimental data on humans and results of animal tests were evaluated. 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 three out of four workers led to occurrence of eczema. Only one of these workers have had previously contact to IPDI, the three others have been exposed to different diisocyanates beforehand. Additionally, in a patch test, four workers were tested for 48 hours with 1 % IPDI in ethanol. Two workers already had an allergy to isophorondiamine and two have been sensitised with isophorondiamine. All four workers responded positively to IPDI. Five control persons had no positive reaction. The authors cite another publication (Deutsche Forschungsgemeinschaft, 1995), which reports a sensitisation to IPDI and other diisocyanates in three out of six patients after exposure to polyurethane chemicals. It has to be noted that the human data cited by (Kayser and Schlede, 2001) are poorly documented occupational studies with very small selected groups. Kayser and Schlede (2001) conclude that there is indication of IPDI causing skin sensitisation in humans after skin contact and that IPDI is clearly sensitising in experiments with animals. Within three defined categories of the described ranking system, IPDI was listed in (the mid-) Category B for substances with a solid-based indication of a contact allergenic potential and substances with the capacity of cross-reactions. However, the ranking system criteria do not reflect the CLP criteria for the hazard Category and Sub-Categories for skin sensitisers.

Human diagnostic patch test data of the years 2007 to 2016 are presented in the IVDK report by (Geier and Schubert, 2021). More than 400 allergens were patch tested in patients, who are routinely patch tested (n = 120,977), patients with occupational dermatitis (OD patients; n = 18,877) and/or patients without OD (Non-OD patients; n = 87,966) and elicited positive reactions. In all three groups, exposure to IPDI induced positive reactions with high frequency in the patch tests: 1.8 % of OD patients, 3.6 % of non-OD patients and 2.1 % of patch tested patients. However, the authors stated that IPDI being a highly reactive compound, no stable patch test preparation is available. Validity of patch test results is doubtful. Information on exposure concentration, repeated exposure or number of exposures is not given in the IVDK report.

10.7.2 Comparison with the CLP criteria

Table 19: Hazard Category and Sub-Categories for skin sensitisers

Category	Criteria
Category 1	Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub- categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or (b) if there are positive results from an appropriate animal test (see specific criteria in section 3.4.2.2.4.1).
Sub-Category 1A	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.
Sub-Category 1B	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered.

Table 20: Animal test results for Sub-Category 1A or Sub-Category 1B

Assay	Criteria Sub-Category 1A	Criteria Sub-Category 1B
Local lymph node assay	EC_3 value ≤ 2 %	EC_3 value > 2 %
Guinea pig maximisation test	≥ 30 % responding at ≤ 0.1 % intradermal induction dose or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose	≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose
Buehler assay	≥ 15 % responding at ≤ 0.2 % topical induction dose or ≥ 60 % responding at > 0.2 % to ≤ 20 % topical induction dose	≥ 15 % to < 60 % responding at > 0.2 % to ≤ 20 % topical induction dose or ≥ 15 % responding at > 20 % topical induction dose

Table 21: Comparison of study results with the CLP criteria

Animal data	CLP Sub-Category
Local lymph node assay EC_3 0.073 % Extreme potency (< 0.2 %)	1A
Guinea pig maximisation test ≥ 80 % responding at 10 % intradermal induction dose Moderate potency (criteria ≥ 30 % responders) (**Table 3.7, CLP guidance, 2017 notes "If the concentration used for intradermal induction or the incidence of sensitised guinea pigs is very high, care should be taken to exclude the possibility of the substance being a Cat 1A (a strong or an extreme) sensitiser.")	1B **(1A)
Buehler test 80 % responding at 5 % topical induction dose Strong potency	1A
Human data	**CLP (Sub-)Category**
(Schlede et al., 2003): proven contact allergenic effect and cross-reactivity	1
(Geier and Schubert, 2021): 1.8 % of OD patients, 3.6 % of Non-OD patients and 2.1 % of patch tested patients high frequency of occurrence of skin sensitisation in humans, information on exposure not available (Table 3.2 and 3.4 CLP guidance, 2017)	1

The results from the local lymph node assay as well as the Buehler test meet the critical values for a classification in Sub-Category 1A according to the CLP classification criteria.

The results of the guinea pig maximisation test fulfil the criteria for classification to Sub-Category 1B. IPDI was not tested at ≤ 1 % intradermal induction dose in the guinea pig maximisation test. Therefore, a classification for Sub-Category 1A cannot be excluded.

Evidence in humans is given that IPDI can lead to sensitisation by skin contact in a substantial number of persons. Kayser and Schlede (2001) conclude a solid-based indication of a contact allergenic potential and

the capacity of cross-reactions. Human diagnostic patch test data reveal a high frequency of occurrence of skin sensitisation, however, information on exposure is not available (Geier and Schubert, 2021). Based on human data IPDI shall be classified as skin sensitiser Category 1. Due to the lack of exposure data, sub-categorisation on the basis of human data is not feasible.

Overall, sufficient evidence from reliable animal studies is provided to warrant classification in Sub-Category 1A according to the CLP classification criteria.

Specific concentration limit

The LLNA results indicate that the substance is an extreme sensitiser (EC3 of 0.073 %, see Table 3.9, CLP guidance, 2017). Based on this low effect level the (CLP guidance, 2017) recommends an SCL of 0.001 % for extremely potent sensitisers. The GPMT tests indicated a moderate potency that, however, should be modified to a strong potency taking the high % of responders into account (80 % at 24 h, 95 % at 48 h). A strong potency derived from this GPMT study and of the Buehler study would justify a GCL of 0.1 %.

From a conservative perspective, an SCL of 0.001 % would be justifiable according to the CLP criteria, the EC3 value of 0.073 % from the LLNA and taking into account the concern on cross-reactivity to other di-isocyanates. In a weight of evidence taking all data into account, 0.05 % is considered as appropriate by the DS. It is assumed that IPDI holds similar sensitising properties as other diisocyanates (data are presented in the Annex to the Background document[2] of the restriction proposal for the diisocyanates). It is noted that the SCL based on the LLNA of IPDI is lower than SCLs for other diisocyanates (Table 7 in Annex to the Background document of the restriction proposal of diisocyanates).

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the available data, classification as Skin Sens. 1A with H317 (may cause an allergic skin reaction) is warranted for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

Additional labelling

According to the CLP Regulation, Annex II, section 2.4 the following special rule for supplemental label elements shall apply for mixtures containing 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. "Unless already identified on the label of the packaging, mixtures containing isocyanates (as monomers, oligomers, prepolymers, etc. or as mixture thereof) shall bear the following statement: EUH204 – Contains isocyanates. May produce an allergic reaction.".

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Based on available data the DS proposed to modify harmonised classification for skin sensitisation from Skin Sens. 1 to Skin Sens. 1A, with SCL = 0.05 %.

***Table**: Summary of animal studies on skin sensitisation*

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Guinea pig maximisation test	Guinea pig; Pirbright White; Sex not	3-isocyanato-methyl-	1st application: Induction intracutaneous - test item 10 %	Positive response 24 h and 48 h after epicutaneous challenge	IBR, 1983

[2] https://echa.europa.eu/documents/10162/708cca92-3d8b-316b-a814-18d85288676d

<table>
<tr>
<td>OECD TG 406
non GLP
Klimisch 2 (reliable with restrictions)</td>
<td>specified;
Treatment: 20 animals;
Control:
20 animals</td>
<td>3,5,5-trimethyl-cyclohexyl isocyanate
No data on purity</td>
<td>(in paraffin; FCA diluted 1:1 with Oleum rachaidis prior to mixing with the test item)
- control: FCA undiluted; paraffin undiluted; 10 % paraffin in FCA diluted 1:1 with Oleum rachaidis

2nd application: Induction occlusive epicutaneous
- test item undiluted
- control: paraffin undiluted

3rd application: Challenge occlusive epicutaneous
- test item undiluted
- control: paraffin undiluted</td>
<td>with undiluted test item

Number with positive reactions:
1st reading 24 h after challenge:
- 17 / 20 of test group (dose: undiluted), mean score 1.15/3
- 0 / 20 of negative control (dose: vehicle)
2nd reading 48 h after challenge:
- 16 / 20 of test group (dose: undiluted), mean score 0.85/3
- 0 / 20 of negative control (dose: vehicle)</td>
<td></td>
</tr>
<tr>
<td>Local Lymph Node Assay

similar to OECD TG 429 (study performed before TG was adopted)

GLP not specified

Klimisch 2 (reliable with restrictions)</td>
<td>Mouse;
BALB/c;
4 females per dose</td>
<td>3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate
No data on purity</td>
<td>0; 0.05; 0.1; 0.25; 0.5; 0.5; 1.0; 2.5; 0.5 % (w/v) in 4:1 acetone: olive oil;
Controls: vehicle, acetone: olive oil (4:1 v/v)
25 µl, topically on the dorsum of both ears,
3 consecutive days (day 1 to day 3)

on day 6:
all mice injected intravenously via the tail vein with 20 µCi of [^{3}H]methylthymidine (sp act 2 Ci/mmol) in 250 µl of phosphate-buffered saline.
Five hours after injection: mice killed and the draining auricular lymph nodes excised. Incorporation of [^{3}H]thymidine (^{3}HTdR) was measured by β-scintillation.
Results were expressed as mean cpm per node</td>
<td>Strong skin sensitisation

EC_3: 0.073 % (stated in study report)

<table>
<tr><th>Conc. (% w/v)</th><th>Stimulation index (mean cpm/ node x 10^{-2})</th></tr>
<tr><td>0.05</td><td>1.81</td></tr>
<tr><td>0.1</td><td>4.39</td></tr>
<tr><td>0.25</td><td>23.21</td></tr>
<tr><td>0.5</td><td>30.58</td></tr>
<tr><td>1.0</td><td>40.16</td></tr>
<tr><td>2.5</td><td>54.91</td></tr>
</table>
</td>
<td>Dearman et al., 1992</td>
</tr>
<tr>
<td>Buehler test
EU Method B.6 (Cited as Directive 84/449/EEC, B.6)
GLP not specified
Klimisch 2 (reliable with restrictions)</td>
<td>Guinea pig (Dunkin-Hartley)
Female
Treatment: 20 animals,
Control:
10 animals</td>
<td>3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate
Purity > 99 %</td>
<td>Induction: epicutaneous, occlusive, 5 % (w/v) in petrolatum, 0.5 mL

Challenge: epicutaneous, occlusive, 1 % (w/v) in petrolatum (14 days after induction), 0.5 mL

Vehicle control

Assessment: 30h after challenge

Positive control: neomycin sulphate (CAS 1405-10-3)
Positive reference substance: HMDI (CAS: 5124-30-1)</td>
<td>Strong skin sensitisation

Number with positive reactions:
- treatment group: 16 /20 (80 % responding) upon occlusive epicutaneous challenge with 1 % test substance
- neomycin sulphate: 10/19 (53 % responding)
- HMDI: 19/20 (95 % responding)
- vehicle control: no irritation and/or sensitization</td>
<td>Zissu et al., 1998</td>
</tr>
</table>

Table: *Summary of human data on skin sensitisation*

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Publication	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate	Potency ranking of chemicals with contact allergenic properties using clinical and experimental data on humans and results of animal tests. Category A: substances having significant allergenic properties. Category B: substances with a solid-based indication of a contact allergenic potential and substances with the capacity of cross-reactions. Category C: substances with insignificant or questionable allergenic effects.	IPDI was allocated in Category B Experience with humans indicate a sensitising effect of IPDI by skin contact. Animal experiments showed a clear sensitising potential.	Schlede et al., 2003
Publication/ Evaluating compilation (in German)	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate	Cross-reference to (Schlede et al., 2003) Evaluation of clinical and experimental data on humans and results of animal tests on 244 substances published as a loose-leaf-book (Kayser and Schlede, 2001) in German	Skin sensitisation in humans after skin contact; clearly sensitising in experiments with animals	Kayser and Schlede, 2001
Report	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl isocyanate	IVDK[3]data of the years 2007 to 2016 from 120977 patients, who are routinely patch tested 2/111 IPDI patch tested occupational dermatitis (OD) patients with positive reactions, 1.8 % positive [95 %-CI, 0.2 - 6.4] 2/56 IPDI patch tested Non-OD patients with positive reactions, 3.6 % positive [95 %-CI, 0.4 - 12.3] 4/195 IPDI patch tested patients with positive reactions, 2.1 % positive [95 %-CI, 0.6 - 5.2] Note: IPDI being a highly reactive compound, no stable patch test preparation is available. Validity of patch test results is doubtful.	May cause allergic reactions of the skin and the airways (asthma).	Geier and Schubert, 2021

Specific concentration limit

An SCL of 0.001 % would be justifiable according to the CLP criteria, based on the EC_3 value of 0.073 % from the Local Lymph Node Assay (LLNA) and taking into account the concern on cross-reactivity to other di-isocyanates. A value of 0.05 % is considered as appropriate by DS. It is assumed that IPDI holds similar sensitising properties as other diisocyanates (data are presented in the annex to the background document of the restriction proposal for the diisocyanates[4]). It is noted that the SCL based on the LLNA of IPDI is lower than SCLs for some other diisocyanates (Table 7 in the annex to the background document of the restriction proposal of diisocyanates) However, RAC notes that the classification of these other isocyanates with higher SCLs originated from the time before the CLP Regulation. In the more recent RAC opinions on isocyanates the SCL was not set due to incompleteness of data to allow potency estimation in such a detail.

[3] *Information network of departments of dermatology (Informationsverbund Dermatologischer Kliniken-IVDK) (currently 56) for the surveillance and scientific evaluation of contact allergies*

[4] *https://echa.europa.eu/documents/10162/708cca92-3d8b-316b-a814-18d85288676d*

Comments received during consultation

There were two comments submitted during the consultation, one by a MSCA and one by an Industry/Trade Association. MSCA supported the DS' proposal to modify the classification from Skin Sens. 1 to Skin Sens. 1A. Industry/Trade Association supported classification of IPDI as skin sensitiser, but did not agree with sub-categorisation as 1A and the SCL setting. Industry/Trade Association is of the opinion that data are not sufficient for a clear discrimination between Sub-Categories as the data on potency of IPDI are limited and human and animal data are not fully consistent and the available data currently do not allow a solid assessment of the potency.

The industry/Trade Association cited an NIH Publication (No. 11-7709): "LLNA cannot be considered a stand-alone assay to determine skin sensitization potency categories…". However, this statement refers to skin sensitisers with an EC_3 > 2 %. For skin sensitisers with EC_3 of ≤ 2 %, the ICCVAM-recommendation is: "ICCVAM concludes that the LLNA, using the GHS classification criteria, can be used to categorise substances as strong sensitisers (GHS Sub-Category 1A) when the estimated concentration that produces a positive LLNA result (i.e., EC_3) is ≤ 2 %."

RAC agrees with DS that sufficient evidence from reliable animal studies is provided to warrant classification in Sub-Category 1A according to the CLP classification criteria.

Assessment and comparison with the classification criteria

For skin sensitisation, various studies are available. Three were performed according or similar to guidelines and can be used for classification. The results are all clearly positive and indicative of sensitising properties.

Animal data

In the Guinea pig maximisation test (IBR, 1983) with IPDI (10 % intradermal induction dose) 17 out of 20 (85 %) animals were positive 24 hours after challenge. After 48 hours, 16 out of 20 (80 %) animals were positive. Overall, 24 and 48 hours after the challenge 19 out of 20 (95 %) animals showed a positive reaction whereas no animal in the control group showed a positive response. IPDI was not tested in this study at ≤ 1 % intradermal induction dose. The lack of indication of primary irritation in the range finding study in concentrations up to 100 % IPDI (skin corrosive substance) raises doubt on reliability of this study.

Dearman et al. (1992) tested immunological responses in mice exposed to three diisocyanates; IPDI, diphenylmethane- 4,4'-diisocyanat and dicyclohexylmethane-4,4'-diisocyanate. Prior to coming into force of the OECD TG 429 and consequently with minor deviations from this guideline, the lymphocyte proliferative responses in draining lymph nodes were measured 3 days following exposure of mice to various IPDI concentrations (0.0; 0.05; 0.1; 0.25; 0.5; 1.0; 2.5 %). IPDI caused a concentration-related increase in lymph node cell proliferation. Stimulation indices increased from 1.81 after treatment with 0.05 % IPDI up to 54.91 after treatment with 2.5 %. The EC3 is 0.073 %. Additionally, in the mouse ear swelling test performed within this study, ear thickness was evaluated 24 hours after the challenge by epicutaneous application of 25 µL of 0.5 % solution. The results showed a concentration-dependent increase of ear thickness relative to pre-challenge values (induction 0.1 %; 0.25 %; 0.5 %; 1.0 %; 2.5 % (w/v) / 50 µL). The

optimum response was observed at 1.0 % induction concentration.

Zissu et al. (1998) conducted Buehler tests with various diisocyanates, including IPDI. After occlusive epicutaneous induction with 0.5 mL of a solution of 5 % (w/v) IPDI in petrolatum, 16 out of 20 (80 %) animals showed positive response upon occlusive epicutaneous challenge with 1 % test substance.

Human data

Schlede et al. (2003) developed a ranking system on skin sensitising potency for 244 chemicals. Available clinical and experimental data on humans and results of animal tests were evaluated. In the detailed conclusion for IPDI, the authors (Kayser and Schlede, 2001) cited an open epicutaneous test, in which the 1-hour exposure of IPDI in three out of four workers led to occurrence of eczema. Only one of these workers have had previously contact to IPDI, the three others have been exposed to different diisocyanates beforehand. Additionally, in a patch test, four workers were tested for 48 hours with 1 % IPDI in ethanol. Two workers already had an allergy to isophorondiamine and two have been sensitised with isophorondiamine. All four workers responded positively to IPDI. Five control persons had no positive reaction. The authors cite another publication (Deutsche Forschungsgemeinschaft, 1995), which reports a sensitisation to IPDI and other diisocyanates in three out of six patients after exposure to polyurethane chemicals. It has to be noted that the human data cited by (Kayser and Schlede, 2001) are poorly documented occupational studies with very small selected groups. Kayser and Schlede (2001) concluded that there is indication of IPDI causing skin sensitisation in humans after skin contact and that IPDI is clearly sensitising in experiments with animals. Within three defined categories of the described ranking system, IPDI was listed in (the mid-) Category B for substances with a solid-based indication of a contact allergenic potential and substances with the capacity of cross-reactions. However, the ranking system criteria do not reflect the CLP criteria for the hazard Category and Sub-Categories for skin sensitisers.

Human diagnostic patch test data of the years 2007 to 2016 are presented in the IVDK report (Geier and Schubert, 2021). More than 400 allergens were patch tested in patients, who are routinely patch tested (n = 120 977), patients with occupational dermatitis (OD patients; n = 18 877) and/or patients without OD (non-OD patients; n = 87 966) and elicited positive reactions. In all three groups, exposure to IPDI induced positive reactions with high frequency in the patch tests: 1.8 % of OD patients, 3.6 % of non-OD patients and 2.1 % of patch tested patients. However, the authors stated that IPDI being a highly reactive compound, no stable patch test preparation is available. Therefore, the validity of the patch test results is doubtful. Information on exposure concentration, repeated exposure or number of exposures is not given in the IVDK report.

The results from the local lymph node assay as well as the Buehler test meet the criteria for classification in Sub-Category 1A according to the CLP Regulation.

The results of the guinea pig maximisation test fulfil the criteria for classification to Sub-Category 1B. IPDI was not tested at ≤ 1 % intradermal induction dose in the guinea pig maximisation test. Therefore, a classification for Sub-Category 1A cannot be excluded.

Evidence in humans is given that IPDI can lead to sensitisation by skin contact in a substantial number of people. Kayser and Schlede (2001) concluded that IPDI has a clear indication of a contact allergenic potential and a capacity for cross-reactions with other

sensitisers. The human diagnostic patch test data revealed a high frequency of occurrence of skin sensitisation, however, information on exposure is not available (Geier and Schubert, 2021). Based on human data, IPDI shall be classified as skin sensitiser Category 1. Due to the lack of exposure data, sub-categorisation on the basis of human data is not feasible.

Overall, sufficient evidence from reliable animal studies is provided to warrant classification in Sub-Category 1A according to the CLP classification criteria.

Specific concentration limit

The LLNA results indicate that the substance is an extreme sensitiser (EC3 of 0.073 %, see Table 3.9, CLP guidance, 2017). Based on this low EC3 value the CLP guidance (2017) recommends an SCL of 0.001 % for extremely potent sensitisers. The Guinea Pig Maximisation Test (GPMT) tests indicated a moderate potency that, however, should be modified to a strong potency taking the high % of responders into account (80 % at 24 h, 95 % at 48 h). A strong potency derived from this GPMT study and of the Buehler study would justify a GCL of 0.1 %.

Given the low reliability of the GPMT study and lack of test with concentrations (for topical induction) ≤ 0.2 % in the Buehler study, the SCL of 0.001 %, based on the most reliable LLNA study (Dearman et al., 1992), is set by RAC.

In conclusion, RAC considers a **classification as Skin Sens. 1A, H317 (may cause an allergic skin reaction) with an SCL = 0.001 %** to be warranted for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

10.8 Germ cell mutagenicity

Not evaluated in this report.

10.9 Carcinogenicity

Not evaluated in this report.

10.10 Reproductive toxicity

Not evaluated in this report.

10.11 Specific target organ toxicity-single exposure

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

The substance IPDI is currently bears a harmonised classification as STOT SE 3 according to CLP Regulation.

Because the substance is proposed to be classified as Skin. Corr. 1 and Acute Tox. 1 for the inhalation route and is already classified as Resp. Sens. 1, additional classification as STOT SE 3 is not needed according to the "Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures" (version 5.0; 07/2017) which reads "It is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this, then Category 3 may be appropriate. In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier."

In the acute inhalation toxicity study (Bayer AG, 1995), examinations revealed that animals of all dose groups above 20.4 mg/m³ that died up to 28 d after exposure showed macroscopic findings such as nose/muzzle with red incrustations, mucous membrane of the nose with reddening, lung with dark-red foci, pleural cavity filled with liquid, lung less collapsed emphysematous, and spongy. Microscopic examinations were not conducted. Except for two animals of each sex of the 53.3 mg/m³ groups that were sacrificed on day 28, all other animals of this dose level and higher died spontaneously. The observed lung effects were noted in almost all of them and are considered as perimortal effects.

Available data indicate that there is a likelihood that the mechanism of toxicity is corrosivity. Thus, in addition to classification for inhalation toxicity it is proposed to label IPDI also as 'corrosive to the respiratory tract'.

10.11.2 Comparison with the CLP criteria

Already classified.

10.11.3 Conclusion on classification and labelling for STOT SE

Based on the CLP regulation including the Guidance mentioned in 10.11.1 and the proposed classification as Skin. Corr. Category 1, Acute Tox. Category 1 for inhalation as well as Resp. Sens. Category 1, the Classification "STOT-SE" should be modified from Category 3 to "not classified" because classification STOT SE 3 is also implicit with the aforementioned classifications. It is recommended to include the supplemental hazard statement EUH071: Corrosive to the respiratory tract.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

DS proposed to delete the current classification as STOT SE 3 considering the proposed classification as corrosive to skin, with the adding of EUH071: corrosive to the respiratory tract.

Comments received during consultation

There were two comments submitted during the consultation, one by a MSCA and one by an Industry/Trade Association. The MSCA agreed with the approach to delete the current classification as STOT SE 3 considering the proposed classification as corrosive to skin, with the addition of EUH071. The Industry/Trade Association agreed with no classification for STOT SE 3, but disagreed with additional labelling "corrosive to the respiratory tract" as no histological examinations have been conducted to differentiate between local

irritation and corrosion to the respiratory tract. Consequently, effects on the respiratory tract are not sufficiently examined to justify additional labelling.

However, according to the criteria in section 1.2.6 of Annex I to the CLP Regulation, no specific study is required for the assignment of EUH071.

Assessment and comparison with the classification criteria

Because the substance is proposed to be classified as Skin. Corr. 1 and Acute Tox. 1 for the inhalation route and is already classified as Resp. Sens. 1, additional classification as STOT SE 3 is not needed according to the "Guidance on the Application of the CLP Criteria" (hereafter CLP guidance, version 5.0; 07/2017) which reads "It is a reasonable assumption that corrosive substances may also cause respiratory tract irritation (RTI) when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this, then Category 3 may be appropriate. In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier."

In the acute inhalation toxicity study (Bayer AG, 1995), examinations revealed that animals of all dose groups above 20.4 mg/m³ that died up to 28 d after exposure showed macroscopic findings such as nose/muzzle with red incrustations, mucous membrane of the nose with reddening, lung with dark-red foci, pleural cavity filled with liquid, lung less collapsed emphysematous, and spongy. Microscopic examinations were not conducted. Except for two animals of each sex of the 53.3 mg/m³ groups that were sacrificed on day 28, all other animals of this dose level and higher died spontaneously. The observed lung effects were noted in almost all of them and are considered as perimortal effects.

The available data indicate that there is a likelihood that the mechanism of toxicity is corrosivity. Thus, in addition to classification for inhalation toxicity it is proposed to label IPDI also as 'corrosive to the respiratory tract'.

Based on the CLP Regulation, the CLP guidance and the proposed classification as Skin. Corr. Category 1, Acute Tox. Category 1 for inhalation as well as Resp. Sens. Category 1, RAC agrees that the **Classification "STOT SE" should be modified from Category 3 to "no classification"**. RAC considers the inclusion of the supplemental hazard statement **EUH071: Corrosive to the respiratory tract** to be warranted according to the criteria in section 1.2.6 of Annex I to the CLP Regulation.

10.12 Specific target organ toxicity-repeated exposure

Not evaluated in this report.

10.13 Aspiration hazard

Not evaluated in this report.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this report.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this report.

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