Committee for Risk Assessment

RAC

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

Adopted

8 June 2023

8 June 2023

CLH-O-0000007311-84-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate; isophorone di-isocyanate**

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

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

The proposal was submitted by **Germany** and received by RAC on **24 June 2022.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **8 August 2022**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 October 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Beata Pęczkowska**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **8 June 2023** by **consensus.**

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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	223-861-6	4098-71-9	Acute Tox. 3* Skin Irrit. 2 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1 STOT SE 3 Aquatic Chronic 2	H331 H315 H319 H334 H317 H335 H411	GHS08 GHS09 GHS06 Dgr	H331 H315 H319 H334 H317 H335 H411	-	Resp. Sens. 1; H334: C ≥ 0.5 % Skin Sens.1; H317: C ≥ 0.5 %	Note 2
Dossier submitters proposal	615-008-00-5	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate; isophorone di-isocyanate	223-861-6	4098-71-9	**Modify** Acute Tox. 1 Skin Corr. 1 Eye Dam. 1 Skin Sens. 1A **Remove** STOT SE 3	**Modify** H330 H314 H318 H317 **Remove** H335	GHS05 GHS06 GHS08 GHS09 Dgr	H330 H314 H317	**Add** EUH071	**Add** inhalation: ATE = 0,031 mg/l (dusts or mists) **Modify** Skin Sens. 1A: H317: C ≥ 0.05 %	
RAC opinion	615-008-00-5	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate; isophorone di-isocyanate	223-861-6	4098-71-9	**Modify** Acute Tox. 1 Skin Corr. 1 Eye Dam. 1 Skin Sens. 1A **Remove** STOT SE 3	**Modify** H330 H314 H318 H317 **Remove** H335	GHS05 GHS06 GHS08 GHS09 Dgr	H330 H314 H317	**Add** EUH071	**Add** inhalation: ATE = 0,03 mg/l (dusts or mists) **Modify** Skin Sens. 1A: H317: C ≥ 0.001 %	**Retain** Note 2
Resulting Annex VI entry if agreed by COM	615-008-00-5	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate; isophorone di-isocyanate	223-861-6	4098-71-9	Acute Tox. 1 Skin Corr. 1 Eye Dam. 1 Resp. Sens. 1 Skin Sens. 1A Aquatic Chronic 2	H330 H314 H318 H334 H317 H411	GHS05 GHS06 GHS08 GHS09 Dgr	H330 H314 H318 H334 H317 H411	EUH071	inhalation: ATE = 0,03 mg/l (dusts or mists) Resp. Sens. 1; H334: C ≥ 0.5 % Skin Sens.1A; H317: C ≥ 0.001 %	Note 2

GROUNDS FOR ADOPTION OF THE OPINION

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.

HUMAN HEALTH HAZARD EVALUATION

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	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	18 mg/m³: no mortality 22 mg/m³: 3 ♂ (2 d -9 d) 1 ♀ (19 d) 70 mg/m³:	LC_{50} (4 h): 31.0 mg/m³ air * (male/female) * LOGIT-Model was used to	RCC Research & Consulting Company AG, 1988

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
Klimisch 2: 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 %		- 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	5 ♂ (day 1/2), 4 ♀ (5 d – 9 d) 450 mg/m³: 5 ♂ (4 h – 24 h) 5 ♀ (4 h – 24 h)	calculate the LC_{50}	

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} ≤ 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).**

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.

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 <u>14 days post exposure period</u>	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.	Hüls AG, 1984a

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
				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-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	*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	Envigo CRS GmbH, 2016

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		colour change after use of confirmation reagent for the test- and reference substance; strong corrosive positive control rather than medium corrosive substance)	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 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.

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) - 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.	Hüls AG, 1984b

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**.

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 OECD TG 406 non GLP Klimisch 2 (reliable with restrictions)	Guinea pig; Pirbright White; Sex not specified; Treatment: 20 animals; Control: 20 animals	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl 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 specified Klimisch 2 (reliable with restrictions)	Mouse; BALB/c; 4 females per dose	3-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl 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 [^{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	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 0.5 / 30.58 1.0 / 40.16 2.5 / 54.91	Dearman et al., 1992
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-isocyanato-methyl-3,5,5-trimethyl-cyclohexyl 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: 30h 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: *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[1]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[2]). 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.

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

[2] 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

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).