Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals

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Listing, classification and packing

Classification of UN 2290 ISOPHORONE DIISOCYANATE

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Introduction

1. The currently known studies on the substance UN 2290 ISOPHORONE DIISOCYANATE show that, in addition to its acute toxicity, it also has corrosive effects on the skin, but these are not reflected in the current classification in the Model Regulations.

2. Various in-vivo studies on corrosive effects on the skin were carried out with undiluted isophorone diisocyanate according to OECD TG 404.

In a study by Hüls AG (Hüls AG, 1984) with three rabbits per sex, which were occlusively exposed for 4 hours, an irritation index of 6.87 out of 8 could be determined. The overall result is to be considered as "Corrosive to the skin", since extensive, irreversible tissue damage such as necrosis, ulceration or scarring occurred in all animals within the observation period of 14 days (exposure time 4 hours).

In another study by Bayer AG (Bayer AG, 1994), a rabbit was half-exposed for 4 hours. An irritation index of 4.5 out of 8 was determined. After an observation period of 14 days (exposure time 4 hours), strong erythematous and exudative reactions of the skin were observed, so that the overall result must also be rated here as "Corrosive to the skin".

The study results are supported by another study (FHITA, 1981) in which 6 rabbits were exposed to the substance for 4 hours. After an observation period of 8 days (exposure time 4 hours), severe thickening and cracked sclerosis were observed on the surface of the skin. The irritation index resulted in a value of 5.71 out of 8, so that the result has to be rated as "Severe Irritation/Corrosive". As there is only an observation period of 8 days, this study can only serve as supportive.

In the Hüls AG study, an additional exposure time of 3 minutes was considered. No necroses were observed.

Through these studies, classification in packing group I (according to Table 2.8.3.4 of the UN Model Regulations) / according to the CLP criteria in category 1A can be safely excluded. However, a differentiation between packing groups II or III (according to Table 2.8.3.4) of the UN Model Regulations / according to the CLP criteria to categories 1B or 1C cannot be carried out, as the further exposure period of the studies was only 4 hours and not additionally 1 hour.

The corrosive effects on the skin are confirmed by a proposal to amend the European CLP legal classification (CLH dossier). However, only category 1 according to CLP is proposed, which is not reflected in a packing group in the UN Model Regulations (Table 2.8.3.4). The applicant of the CLH dossier has decided in favour of this category, as a differentiation into categories 1B or 1C (packing group II or III) is not possible without doubt. However, category 1A and thus packing group I can be definitely excluded.

Further in-vivo tests are not possible for reasons of animal protection. In-vitro tests are not expedient due to the substance's properties.

For reasons of safety and the precautionary principle, with the current data situation, an assignment of Class 8 (Corrosive substances) with packing group II (Table 2.8.3.4 of the UN Model Regulations) / according to the CLP criteria as Category 1B appears necessary.

3. Two studies according to OECD TG 403 are available for acute inhalation toxicity. In both studies, severe clinical effects were observed on respiration (dyspnoea, abnormal breathing, rales), motor function (spasms, tremor), skin/fur and eyes (exophthalmos, miosis) as well as emaciation, diarrhoea and distended abdomen.

One study (Bayer AG, 1995) gave an LC50 value (4 hours, rat) of 40 mg/m³. The other study (RCC Research & Consulting Company AG, 1988) gave an LC50 value of 31 mg/m³. In the Bayer AG study, however, only one pair of values was below the 100 % lethality, so that the LC50 value was calculated using the geometric mean. The value of 40 mg/m³ is thus to be regarded as less reliable than the value of 31 mg/m³ from the study by RCC Research & Consulting Company AG, which was calculated using the LOGIT model. Thus, this value is leading and should be used.

The acute inhalation toxicity values (LC50: 0.031 mg/l - 4 hours) indicate that classification in packing group I, class 6.1 (equivalent to 1 hour (LC50) value for classification is 0.124 mg/l) is required (see 2.6.2.2.4.1 and 2.6.2.2.4.2 of the UN Model Regulations). The other toxicological values (LD 50, oral: 4,814 mg/kg and LD50, dermal: > 7,000 mg/kg) do not require classification in Class 6.1.

4. For the definition of the division and subsidiary hazards, 2.0.3.1, point g, footnote 3 of the UN Model Regulations must be observed. Due to the weaker toxicity on the oral and dermal routes of exposure, this results in a major hazard of Class 8 and a minor hazard of Class 6.1, in packing group II.

Proposal

Amend the entry for UN 2290 in the Dangerous Goods list as follows (new text is shown in **red, bold, underlined**, deleted text is marked as strikethrough):

UN No.	Name and description	Class or division	Sub-sidiary hazard	UN packing group	Special provi-sions	Limited and excepted quantities		Packagings and IBCs		Portable tanks and bulk containers	
								Packing instruction	Special packing provisions	Instruc-tions	Special provisions
(1)	(2)	(3)	(4)	(5)	(6)	(7a)	(7b)	(8)	(9)	(10)	(11)
2290	ISOPHORONE DIISOCYANATE	~~6.1~~ **8**	**6.1**	~~III~~ **II**	-	~~5L~~ **1L**	~~E1~~ **E2**	P001 ~~IBC03~~ ~~LP01~~ **IBC02**	-	~~T4~~ **T7**	TP2

Justification

5. The current data situation shows that the current entry in the UN Model Regulations does not correctly reflect all existing hazards of the substance. The proposed amendment will communicate the existing hazards clearly and completely for all participants in the supply chain as well as for those involved in emergency response (fire brigade, etc.).

6. The proposed amendments in the area of limited and excepted quantities and in the area of IBCs and tank containers are required because there is a greater potential hazard due to the proposed changes in division and subsidiary hazard. Substances with the same hazard characteristics in the UN Model Regulations show the same instructions.

Annex

Corrosive effect on the skin

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. **<u>Corrosive to the skin.</u>** <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-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 Oedema, not reversible	Hüls AG, 1984a

Method, Guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Results	Reference
				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. **<u>Corrosive to the skin.</u>** 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

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 LC50	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	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)	LC50 (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 LC50.	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	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)	LC50 (4 h): 31.0 mg/m³ air * (male/female) * LOGIT-Model was used to calculate the LC50	RCC Research & Consulting Company AG, 1988

Further information

For further information, please consult:

CLH-Dossier
https://echa.europa.eu/de/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e1870dac07

REACH-Dossier
https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14516