Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

3-aminomethyl-3,5,5-trimethylcyclohexylamine

EC Number: 220-666-8
CAS Number: 2855-13-2

CLH-O-0000001412-86-284/F

Adopted

13 June 2019

13 June 2019

CLH-O-0000001412-86-284/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-aminomethyl-3,5,5-trimethylcyclohexylamine**

EC Number: **220-666-8**

CAS Number: **2855-13-2**

The proposal was submitted by **Germany** and received by RAC on **30 August 2018.**

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 October 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 December 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Normunds Kadiķis**

Co-Rapporteur, appointed by RAC: **Anja Menard Srpčič**

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 **13 June 2019** 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	612-067-00-9	3-aminomethyl-3,5,5-trimethylcyclohexylamine	220-666-8	2855-13-2	Acute Tox. 4 * Acute Tox. 4 * Skin Corr. 1B Skin Sens. 1 Aquatic Chronic 3	H312 H302 H314 H317 H412	GHS05 GHS07 Dgr	Add what is in Annex VI			
Dossier submitters proposal	612-067-00-9	3-aminomethyl-3,5,5-trimethylcyclohexylamine	220-666-8	2855-13-2	**Retain** Skin Corr. 1B **Add** Eye Dam. 1 **Modify** Acute Tox. 4 Skin Sens. 1A **Remove** Acute Tox. 4 * Aquatic Chronic 3	**Retain** H314 H302 H317 **Add** H318 **Remove** H312 H412	**Retain** GHS05 GHS07 Dgr	**Retain** H314 H302 H317 **Remove** H312 H412		oral: ATE = 1030 mg/kg bw	
RAC opinion	612-067-00-9	3-aminomethyl-3,5,5-trimethylcyclohexylamine	220-666-8	2855-13-2	**Retain** Skin Corr. 1B **Add** Eye Dam. 1 **Modify** Acute Tox. 4 Skin Sens. 1A **Remove** Acute Tox. 4 * Aquatic Chronic 3	**Retain** H314 H302 H317 **Add** H318 **Remove** H312 H412	**Retain** GHS05 GHS07 Dgr	**Retain** H314 H302 H317 **Remove** H312 H412		oral: ATE = 1030 mg/kg bw Skin Sens. 1A; H317: C ≥ 0.001%	
Resulting Annex VI entry if agreed by COM	612-067-00-9	3-aminomethyl-3,5,5-trimethylcyclohexylamine	220-666-8	2855-13-2	Acute Tox. 4 Skin Corr. 1B Eye Dam. 1 Skin Sens. 1A	H302 H314 H318 H317	GHS05 GHS07 Dgr	H302 H314 H317		oral: ATE = 1030 mg/kg bw Skin Sens. 1A; H317: C ≥ 0.001%	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

3-aminomethyl-3,5,5-trimethylcyclohexylamine, or isophorone diamine (IPD), is a substance that is used as a hardener, raw material for production of isocyanates and polyamides, as a components for chain extension in PUR systems and an intermediate product for organic syntheses. IPD is currently listed in Annex VI of the CLP Regulation and the Dossier Submitter (DS) proposed to revise the current classification.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Regarding acute toxicity, the DS suggested to remove the asterisk "*" denoting the current minimum classification as Acute Tox. 4*; H302 (oral toxicity) and to remove the existing classification as Acute Tox. 4*; H312 (dermal toxicity).

The DS provided one acute oral toxicity study (Institut für Pharmakologie, 1965) with Sprague-Dawley rats that was available in the REACH registration dossier. In this study the test substance (50% (v/v) solution in water) was administered to male rats (5 animals per dose) by oral gavage - 0.5; 1.0; 1.5; 2.0; 2.5 mL/kg bw corresponding to 230; 460; 690; 920; 1150 mg/kg bw, respectively. A post dosing observation period of 14 days was carried out. Clinical signs observed from 1 hour after dosing were restlessness, thirst, rough fur and tiredness. At necropsy, irritation of the intestinal mucosa was observed. A few animals showed a slight increase in kidney weight and protein in the urine, which may indicate that the kidney is a target organ. The DS acknowledged that this study has deficiencies in reporting important aspects, such as purity of the test substance and mortality rates, as well as the fact that male animals only were used.

The DS also noted that the lead registrant referred to repeated dose studies where a LOAEL of 150 mg/kg bw/day (actually, 160 mg/kg bw/day) was determined and proving that there is no significant difference in sensitivity between male and female rats (cited from SIAR for SIAM 18 (Paris, April 2004)). The DS concluded that the acute oral toxicity should not differ by an order of magnitude or more between the sexes, and thus the existing evidence taken together allows the acute oral toxicity classification to be reassessed.

Comments received during public consultation

One MSCA agreed with the proposal to classify the substance as Acute Tox. 4; H302 and to remove the classification for acute dermal toxicity.

One company, a downstream user, expressed some doubts about changing of the minimum classification due to insufficient additional data when compared with real human health experience. However, this comment was deemed unclear by both the DS and RAC as to which additional data was referred to.

Assessment and comparison with the classification criteria

Acute oral toxicity

The DS claimed that the study was carried out according to a protocol equivalent or similar to OECD TG 401. Nevertheless, significant deficiencies are present: missing information on the purity of the test substance, details on the examinations performed, mortality rates per group, information on the statistical methodology used, etc. Despite the study provided is old and lacking in detail, the acute oral LD50 obtained was 1030 mg/kg bw.

According to Table 3.1.1 of the CLP Regulation, the Acute Toxicity Estimate (ATE) of 1030 mg/kg bw confirms the classification for Acute Tox. 4; H302 (300 < ATE ≤ 2000 mg/kg bw).

RAC agrees with the argumentation provided by the DS in relation to **classification as Acute Tox. 4; H302 (Harmful if swallowed) and with setting an ATE value of 1030 mg/kg bw.**

Acute dermal toxicity

With respect to acute dermal toxicity, the DS provided one animal study on Sprague-Dawley and Crl:CD(SD) specific-pathogen-free rats performed according to OECD TG 402 and assessed as "reliable" (Biotoxtech, 2010). Five animals per sex and per group were treated with 2000 mg/kg bw of the test substance (purity > 99%) using occlusive exposure. All animals survived the duration of the study up to 14 days after dosing showing discolouration of skin, crusts formation from days 1 to 14, and scars from days 11 to 14 on the treated sites. No test substance-related effects on body weights were observed. The acute dermal LD50 was determined to be > 2000 mg/kg bw.

According to Table 3.1.1 of the CLP Regulation, the criterion for classification as Acute Tox. 4; H312 is 1000 < ATE ≤ 2000 mg/kg bw, and based on the results of the acute dermal study, this is not fulfilled, resulting in no classification for acute dermal toxicity. Thus, RAC agrees with the DS **to remove the existing classification Acute Tox. 4*; H312**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed to add the classification as Eye Dam. 1; H318 (causes serious eye damage) based on the eye damage/irritation study available (Hüls, 1983b).

Comments received during public consultation

One MSCA and one company - downstream user agreed to classify as Eye Dam. 1; H318.

Assessment and comparison with the classification criteria

No human data are available. The DS evaluated one animal eye damage/irritation study with a small white Russian rabbit (female) performed according to OECD TG 405 and assessed as "reliable with restrictions" (Hüls, 1983b). Details on purity of the test material were not provided. Undiluted test substance (0.1 mL) was instilled in rabbit's eye. Serious injury occurred almost immediately after application, expressed as corrosive effects and opalescence. Conjunctiva showed necrosis 24 hours after treatment. Due to the corrosive effect of the test material, only 1 animal was used and the experiment was terminated after 24 hours since these effects were not expected to fully reverse within 21 days.

According to criteria in the Table 3.3.1 of the CLP Regulation, classification for Eye Dam. 1 is justified: the substance produced effects on the cornea, iris or conjunctiva in at least one animal that are not expected to reverse within an observation period of 21 days.

RAC agrees to the DS' proposal to **classify the substance as Eye Dam. 1; H318**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed to modify the current Annex VI classification for skin sensitisation from Skin. Sens. 1 to Skin. Sens 1A. The DS assessed three Guinea Pig Maximisation Test (GPMT) studies:

- Dunkin-Hartley male Guinea pigs were treated with IDP in 10% ethanol as a vehicle (20 animals per dose group; 10 animals per negative (vehicle) control group) (Hüls, 1983b):
    - 1st application: intradermal induction with 0.1% of the substance; control animals were treated with the vehicle only;
    - 2nd application after one week: epicutaneous induction (occlusive administration) of 7.5% of the substance for 48 hours; control animals were treated with the vehicle only;
    - 3rd application after two weeks from 2nd application for all animals including control group: challenge (epicutaneous occlusive administration) with 2.5% and 5% of the substance and with vehicle for 24 hours.

Detailed summary of studies performed by Hüls (1983b):

Group	**Challenge concentration**	**Number of animals with positive reactions**			**Classif. acc. to CLP regulation for intradermal induction concentration <=0,1 %**
		24 h	**48 h**	**72 h**	
Control	2.5 %	0/9 (0 %)	0/9 (0 %)	0/9 (0 %)	-
Test group	2.5 %	7/20 (35 %)	5/20 (25 %)	2/20 (10 %)	Skin Sens. 1 A
Control	5 %	0/9 (0 %)	0/9 (0 %)	0/9 (0 %)	
Test group	5 %	18/20 (90 %)	15/20 (75 %)	10/20 (50 %)	Skin Sens. 1 A

The study was performed according to OECD TG 406 and considered as "reliable with restriction". The missing positive control was not required by the 1981 version of the guideline. A sensitisation response was observed in 7/20, 5/20 and 2/20 animals after 24h, 48h and 72h, respectively, from the challenge at concentration of 2.5%. When the challenge was conducted with a concentration of 5%, 18/20, 15/20 and 10/20 animals showed a sensitisation response after 24h, 48h and 72h, respectively. No animals on the control group showed any positive reaction.

- Dunkin-Hartley female Guinea pigs were treated with the test substance in distilled water as a vehicle (20 animals per dose group; 10 animals per negative (vehicle) control group) (Inveresk, 1981):

- 1st application: intradermal induction of 1% of the substance; control animals were treated with the vehicle only;
- 2nd application after one week: epicutaneous induction (occlusive administration) of 1% of the substance for 48 hours; control animals were treated with the vehicle only;
- 3rd application after two weeks from 2nd application for all animals including control group: challenge (epicutaneous occlusive administration) with 5% and 10% of the substance and with vehicle for 24 hours.

Detailed summary of studies performed by Inveresk (1981):

Group	**Challenge concentration**	**Number of animals with positive reactions**	**Classif. acc. to CLP regulation for intradermal induction concentration**
		24 h	**<=0,1 %**
Control	5 %	0/10 (0 %)	-
Test group	5 %	0/20 (0 %)	-
Control	10 %	0/10 (0 %)	-
Test group	10 %	12/20 (60 %)	Skin Sens. 1 A

The study was performed according to a protocol equivalent to OECD TG 406 and considered "reliable with restriction". The missing positive control was not required by 1981 version of the guideline.

No animals on the control group showed erythema at either 5 or 10% challenge concentration. No erythema was noted in the test group animals after challenge with 5% IPD, however in the test group challenged with 10% IPD, 12/20 animals showed erythema.

- Guinea pigs (no information on strain and number of animals) were intradermally injected with 0.5% of the test substance in acetone and later epidermally exposed in occlusive conditions to a 0.5% IPD. Control animals were similarly treated (intradermal injection and later occlusive epidermal exposure), but with vehicle alone. Two weeks after the epidermal application all animals were challenged with 2% test substance (24 hours occlusive). All test animals showed positive reactions (Thorgeirsson, 1978).

This third study was not performed according to OECD guidelines, however it was considered as "reliable with restriction" and used as supportive study by the DS.

Comments received during public consultation

One MSCA generally supported the DS' proposal while indicating that the results are borderline between sub-categorisation 1A and 1B.

One company – a downstream user supported the proposed classification for Skin Sens. 1A.

One international non-Governmental Organisation (European Environmental and Contact Dermatitis Research Group) supported the classification for Skin Sens. 1A and provided additional clinical human data (these are summarised in the Background Document under Additional Key Elements).

Assessment and comparison with the classification criteria

Based on the GPMT studies summarised above, the DS concluded that the substance is a strong dermal sensitiser. The CLP criteria for classification as Skin Sens. 1A and 1B for GPMT studies are provided in Tables 3.4.3 and 3.4.4 of the CLP Regulation. RAC agrees with the DS to modify the existing classification as Skin Sens. 1A; H317.

All three studies fit with the CLP classification criteria for Skin Sens. 1A, however the study performed by Inveresk (1981) showed a positive outcome at the highest challenge concentration of 10% only. Thus, one study indicates extreme potency (Hüls, 1983b) and the other two studies indicate a strong potency for skin sensitisation (Thorgeirsson, 1978; Inveresk, 1981); the Thorgeirsson (1978) study does not contradicting extreme potency since 100% of the tested animals were sensitised with challenge a concentration of 2% after 24h.

In conclusion, RAC proposes a SCL of 0.001% w/v in line with the CLP criteria, taking into account the potential for extreme potency determined in the study by Hüls (1983b) with challenge a concentration of 5% after 24 h, and supported by the Thorgeirsson (1978) study.

The human data provided during the Public Consultation qualitatively support the classification of the substance as a skin sensitiser, but do not allow for any quantitative analysis, i.e. cannot provide evidence for Skin. Sens 1A, because only a low number of cases are reported and/or the level and frequency of exposure in most cases are unknown. Overall, RAC considers that **classification as Skin Sens. 1A; H317 with an SCL of 0.001% w/v is warranted**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

IPD is currently listed in Annex VI of the CLP Regulation with a classification for environmental hazards as Aquatic Chronic 3; H412. The DS proposed to remove the classification as hazardous to the aquatic environment due to new interpretation/evaluation of existing data for aquatic chronic toxicity.

Degradation

In the preliminary test performed following OECD TG 111 and EU method C.7, less than 10% of the IPD was observed to hydrolyse at 50°C at pH 4, 7 and 9 after 5 days.

A ready biodegradation test according to EU Method C.4-A (Dissolved Organic Carbon (DOC) Die-Away Test) using activated sludge (adaptation not specified) resulted in 8% degradation after 28 days. The substance is therefore not readily biodegradable.

Based on this, the DS concluded that IPD is not considered rapidly degradable.

Bioaccumulation

The experimentally derived log K_{OW} is 0.99 at 23°C (OECD TG 107 and EU method A.8).

QSAR calculations with EPIWIN v3.10 resulted in a BCF value of 3.16.

Based on available data, the DS concluded that IPD has a low potential for bioaccumulation.

Aquatic toxicity

A summary of the relevant information on aquatic toxicity is provided in the following table. The results of the studies are expressed in terms of nominal concentrations.

Table: *Summary of relevant information on aquatic toxicity*

Method/Exposure	Test organism	Endpoint	Toxicity values in mg/L	Reliability/Reference
Short-term toxicity				
EU Method C.1 (Cited as Directive 84/449/EEC, C.1, 1984) semi-static	*Leuciscus idus*	96h LC_{50}	110*	Rel. 1 Hüls, 1993b
OECD TG 202, EU Method C.2 static	*Daphnia magna*	48h EC_{50}	23*	Rel. 1 Infracor, 2002
OECD TG 202 static	*Daphnia magna*	48h EC_{50}	17.4	Rel. 2 Danish Environmental Protection Agency, 2000
DIN 38412, part 11 static	*Daphnia magna*	24h EC_{50}	44	Rel. 2 Hüls, 1996a
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail semi-static	*Chaetogammarus marinus*	96h LC_{50}	324	Rel. 1 Adema, 1982
EU Method C.3 (Cited as Directive 87/302/EEC, part C, p. 89) static	*Desmodesmus subspicatus*	72h EC_{50} 72h E_rC_{50}	37 > 50	Rel. 2 Hüls, 1993d
Long-term toxicity				
OECD TG 202, part 2 semi-static	*Daphnia magna*	21d NOEC	3*	Rel. 1 Hüls, 1993c
EU method C.3 (Cited as Directive 87/302/EEC, part C, p. 89) static	*Desmodesmus subspicatus*	72h NOEC 72h EC_{10} 72h E_rC_{10}	1.5 3.1 11.2	Rel. 2 Hüls, 1993d

Note: * - Studies in which the analytical verification of the test concentrations was carried out. In these studies, all analytical measurements were within the 20% range accepted for the use of nominal concentrations.

Additional information related to maintenance of the test concentrations is provided for the acute fish study (Hüls 1993b) in the Background Document.

Acute toxicity

Acute aquatic toxicity data on IPD are available for fish, invertebrates and algae, with invertebrates being the most sensitive trophic level (48h LC_{50} = 17.4 mg/L for *D. magna*). The DS proposed not to classify the substance IPD as acutely hazardous to the aquatic environment. The

basis for this proposal is that the short-term (acute) aquatic ecotoxicity test results showed no toxicity effects to aquatic organisms (algae, daphnia and fish) at concentrations ≤ 1 mg/L.

Chronic toxicity

Long-term aquatic toxicity data on IPD are available for aquatic invertebrates and algae, whilst data for fish are lacking. Based on the available aquatic chronic toxicity data for invertebrate (21d NOEC of 3 mg/L for *D. magna*) and algae (72h E_rC_{10} of 11.2 mg/L for *D. subspicatus*), the DS concluded that IPD does not meet the classification criteria for aquatic chronic hazard. Due to the lack of chronic toxicity data for the fish, the DS used the surrogate approach. Considering that IPD is not rapidly degradable this resulted in a no classification for aquatic chronic hazard.

Comments received during public consultation

Two Member States (MS) and one company submitted comments on the environmental part of the DS's proposal during the Public Consultation (PC). One MS and the company agreed with the proposal to remove the existing classification (Aquatic Chronic 3, H412) for IPD. The second commenting MS asked for clarifications regarding analytical verification of the test item concentrations.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS that IPD does not meet the criteria for rapid degradability. This outcome is based on available hydrolysis data (stable to hydrolysis at acidic, neutral and alkaline conditions at 50°C) and the results obtained in a biodegradation study (8% degradation after 28 days).

Bioaccumulation

RAC agrees with the DS that IPD has a low potential for bioaccumulation in aquatic organisms. The basis for this is that log K_{OW} value of 0.99 is below the CLP Regulation threshold of 4.

Aquatic toxicity

Aquatic acute toxicity data on IPD are available for fish, invertebrates and algae. Since no effects on aquatic organisms were observed at or below the threshold value of 1 mg/L, IPD does not meet the criteria for classification for acute aquatic hazard. Therefore, RAC supports the DS´s proposal that no classification for acute aquatic hazards is warranted.

Chronic toxicity

Aquatic chronic toxicity data on IPD are available for two trophic levels, invertebrate and algae. In the absence of adequate chronic toxicity data for fish, the surrogate method is applied (CLP Regulation, Annex I Table 4.1.0(b)(iii)). The substance is considered non-rapidly degradable and does not fulfil the criteria for bioaccumulation potential.

- Classification based on adequate chronic toxicity data: Invertebrate *D. magna* long-term testing provided a 21d NOEC of 3 mg/L, while algae long-term testing provide a 72h E_rC_{10} of 11.2 mg/L. Both values are above threshold value of 1 mg/L and the substance is not rapidly degradable. IPD does not fulfil the criteria for chronic hazard classification, based on Table 4.1.0 (b)(i).
- Classification based on surrogate data for fish. The acute toxicity value is a 96h LC_{50} of 110 mg/L for fish *Leuciscus idus*. The 96h LC_{50} value is above 100 mg/L and the substance is not

rapidly degradable. IPD does not fulfil the criteria for chronic hazard classification, based on Table 4.1.0(b)(iii).

- **Overall conclusion**: No classification for aquatic chronic toxicity

In summary, on the basis of the available data, RAC supports the DS proposal that **no classification for environmental hazards is warranted**.

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).