

Committee for Risk Assessment
RAC

Annex 2
Response to comments document (RCOM)
to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 3-AMINOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYLAMINE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 3-aminomethyl-3,5,5-trimethylcyclohexylamine

EC number: 220-666-8

CAS number: 2855-13-2

Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2018	Germany	<confidential>	Company-Downstream user	1
Comment received				
The test data submitted is not sufficiently reliable for any reclassification - too many conclusions drawn which appear to be inconclusive or invalid				
Dossier Submitter's Response				
The comment is unfortunately too general and too unspecific to be addressed.				
RAC's response				
All data submitted are evaluated in relation to specific endpoint.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
07.12.2018	France		MemberState	2
Comment received				
France agrees with the classification as Acute tox. 4 (H302) for oral toxicity. However, considering the limits and lack of information on the study available, we would propose the generic ATE of the category, i.e. 500 mg/kg instead of 1030 mg/kg bw.				
France agrees with the removal of the classification for acute dermal toxicity.				
Dossier Submitter's Response				
Acute oral toxicity				
The available acute oral toxicity study is indeed associated with considerable uncertainty. The French proposal should be discussed by RAC against the background of previous decisions in similar cases.				

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Acute dermal toxicity
The DS is grateful to France for supporting the proposal.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2018	Germany	<confidential>	Company-Downstream user	3
Comment received				
insufficient additional data to substantiate making the transitional classification permanent when compared with real human health experience.				
Dossier Submitter's Response				
Making a transitional classification permanent does not necessarily require additional data. It may also mean a re-evaluation of existing data which was not possible when translating the previous DSD into CLP classifications. Moreover, since no specific data regarding "real human health experience" have been submitted, this comment cannot be addressed.				
RAC's response				
The DS remarked in the dossier that it is not possible to follow-up what data served for transitional classification Acute Tox. 4*, H312 (dermal toxicity). The new study dated to 2010 allows to remove this classification. If the comment from downstream user relates to oral toxicity, RAC agrees with explanation given by DS.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
07.12.2018	France		MemberState	4
Comment received				
France agrees with the classification as Eye dam. 1, H318.				
Dossier Submitter's Response				
The DS is grateful to France for supporting the proposal.				
RAC's response				
Noted and supported.				

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2018	Germany	<confidential>	Company-Downstream user	5
Comment received				
Satisfactory				
Dossier Submitter's Response				
The DS is grateful for the support.				
RAC's response				
Noted and supported.				

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OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2018	Germany	<confidential>	Company-Downstream user	6
Comment received				
Satisfactory although human health experience shows less sensitisation.				
Dossier Submitter's Response				
The DS is grateful for the general support. No specific data regarding the "human health experience" are submitted and therefore no further evaluation of the statement that those data would show "less sensitisation" is possible. Moreover, it is generally difficult to derive skin sensitisation potency from human data. All in all the comment cannot be further addressed.				
RAC's response				
RAC agrees that human data are not available and the classification is based on satisfactory animal data.				

Date	Country	Organisation	Type of Organisation	Comment number
07.12.2018	France		MemberState	7
Comment received				
France agrees with the conclusion of the first study described (Hüls, 1983). For the second study (Inveresk, 1981), there is a mistake in the table 14, the induction concentration being 1% instead of 0.1%. The results are borderline with a classification 1B, and we are of the opinion that this point should have been discussed in the CLH report.				
Dossier Submitter's Response				
The DS is grateful to France for pointing out the error in the sub-table heading. The DS acknowledges that with an intradermal induction concentration of 1% and a response of exactly 60%, this is indeed a borderline result. Overall, however, with two clear 1A and one borderline 1A/1B result, the conclusion 1A remains the same.				
RAC's response				
RAC supports the DS in so that, as the results from two studies fulfil the criteria for classification as Skin Sens. 1A, and one study showed borderline 1A/1B results, the conclusion 1A is justified.				

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2018	Finland	European Environmental and Contact Dermatitis Research Group (EECDRG)	International NGO	8
Comment received				
We want to endorse the harmonised classification as a skin sensitizer in Category 1A and point out the extensive clinical human data on the subject.				
ECHA note – An attachment was submitted with the comment above. Refer to public attachment EECDRG statement_to_Proposal for Harmonised Classification and Labelling of IPDA 2018_2.pdf				

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Dossier Submitter's Response

The DS is grateful for the support of the classification proposal.

In order to use human data for potency sub-categorisation, section 3.4.2.2.3.1 of the ECHA "Guidance on the Application of the CLP criteria" asks for the frequency and level of exposure of the affected patients. However, while case reports may demonstrate sensitisation in individual patients and clinical patch-test data may give information on the frequency of occurrence of allergic reactions within a larger patient collective, both data types are in most cases not suitable to identify whether these patients had been exposed to the agent in question at a relatively low or high level.

IPD already has a harmonised classification as Skin Sens. 1. With respect to this endpoint, it was the purpose of the CLH dossier to present data supporting sub-categorisation. The data submitted by EECDRG certainly qualitatively support the classification of IPDA as a skin sensitizer and in most cases are not in conflict with a classification as 1A, but they cannot positively support or provide proof for 1A, because only a low number of cases is reported and/or level and frequency of exposure are unknown in most cases.

In the table below it is briefly shown that none of the reports submitted by EECDRG was able to demonstrate a high frequency of sensitised patients in a sufficiently large collective, while at the same time providing proof of a relatively low exposure.

Ref.	Type of study	No. positive to IPD/no. tested (%)	Conclusion on frequency [§]	Conclusion on exposure [§]
(Dahlquist and Fregert, 1979)	Case report of two workers exposed to IPD and other epoxy resin-related substances	2/2 (100)	High, but only two cases	Presumably high
(van Putten et al., 1984)	Patch testing in 23 males with eczema exposed to epoxy resin	0/23 (0)	Not applicable	Not possible
	Patch testing in 112 males without eczema exposed to epoxy resin	3/112 (2.7)	High	
(Guerra et al., 1992)	Case report of three workers exposed to IPD and other epoxy resin-related substances	3/3 (100)	High, but only three cases	Presumably high
(Lodi et al., 1993)	Case report of two parquet layers exposed to two-component glues containing, inter alia, IPD	2/2 (100)	High, but only two cases	Presumably high
(Patussi et al., 1995)	Case report of a parquet layer	1/1 (100)	High, but only one case	Presumably high
(Kanerva et al., 1996)	Case report of a car painter; unclear whether IPD was tested at all; only one case			
(Tarvainen et al., 1998)	Case report of one worker exposed to IPD	1/1 (100)	High, but only one case	Presumably high
(Kelterer et al., 2000)	Case report of one worker exposed to two-component epoxy resin glue including IPD	1/1 (100)	High, but only one case	Presumably high
(Rademaker, 2000)	Case report of 16 cases of occupational allergy to epoxy resins over a period of 5 years	1/16	Unclear, how many patients had been exposed to IPD (and, if so, at what level).	

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(Geier et al., 2004)	Multi-centre study in patients with suspected ER allergy and patients with previous positive patch test to ER in standard series (including IPD)	5/87 (5.7)	High	Unknown
(Foti et al., 2010)	Case study of a brick layer using two-component grout containing IPD	1/1 (100)	High, but only one case	Presumably high
(Canelas et al., 2010)	Review of patch test data base of a dermatological clinic between 1999 and 2008	4/2440 (0.16)	Low/moderate	Unknown
(Aalto-Korte et al., 2014)	Review of patch test data base of a dermatological clinic between 1992 and 2014	12/642 (1.9)	High	Unknown
(Aalto-Korte et al., 2015)	Patch testing of male sewage repair workers applying ER	2/8 (25)	High, but small number of cases	Presumably high
(Geier et al., 2016)	Multi-centre review of allergic reactions to ER hardeners 2002-2011	56/580	High	Unknown, possibly high

[§]In line with the ECHA Guidance on the Application of the CLP Criteria, section 3.4.2.2.3.1

References

- Aalto-Korte K., Pesonen M., and Suuronen K. (2015): Occupational allergic contact dermatitis caused by epoxy chemicals: occupations, sensitizing products, and diagnosis. *Contact Dermatitis* 73 (6), 336-342. DOI: doi:10.1111/cod.12445
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- Canelas M.M., Gonçalo M., and Figueiredo A. (2010): Contact allergy to epoxy resins—a 10-year study. *Contact Dermatitis* 62 (1), 55-55. DOI: doi:10.1111/j.1600-0536.2009.01652.x
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- Foti C., Bonamonte D., Antelmi A., Nettis E., Cassano N., Vena G.A., and Angelini G. (2010): Airborne allergy to isophoronediamine and epoxy resin. *Immunopharmacology and Immunotoxicology* 32 (3), 528-529. DOI: 10.3109/08923970903468839
- Geier J., Lessmann H., Hillen U., Jappe U., Dickel H., Koch P., Frosch P.J., Schnuch A., and Uter W. (2004): An attempt to improve diagnostics of contact allergy due to epoxy resin systems. First results of the multicentre study EPOX 2002. *Contact Dermatitis* 51 (5-6), 263-272. DOI: doi:10.1111/j.0105-1873.2004.00465.x
- Geier J., Lessmann H., Hillen U., Skudlik C., and Jappe U. (2016): Sensitization to reactive diluents and hardeners in epoxy resin systems. IVDK data 2002–2011. Part I: reaction frequencies. *Contact Dermatitis* 74 (2), 83-93. DOI: doi:10.1111/cod.12491
- Guerra L., Vincenzi C., Bardazzi F., and Tosti A. (1992): Contact sensitization due to isophoronediamine. *Contact Dermatitis* 27 (1), 52-53. DOI: doi:10.1111/j.1600-0536.1992.tb05200.x
- Kanerva L., Estlander T., and Jolanki R. (1996): Occupational allergic contact dermatitis caused by 2,4,6-tris-(dimethylaminomethyl)phenol, and review of sensitizing epoxy resin hardeners. *International Journal of Dermatology* 35 (12), 852-856. DOI: doi:10.1111/j.1365-4362.1996.tb05050.x

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Kelterer D., Bauer A., and Elsner P. (2000): Short communications. Contact Dermatitis 43 (2), 110-126. DOI: doi:10.1034/j.1600-0536.2000.043002110.x

Lodi A., Mancini L.L., Pozzi M., Chiarelli G., and Crosti C. (1993): Occupational airborne allergic contact dermatitis in parquet layers. Contact Dermatitis 29 (5), 281-282. DOI: doi:10.1111/j.1600-0536.1993.tb03573.x

Patussi V., Kokeli F., and Buttazzi P. (1995): Occupational airborne allergic contact dermatitis due to 3-amino-methyl-3,5,5-trimethylcyclohexylamine. Contact Dermatitis 32 (4), 239-239. DOI: doi:10.1111/j.1600-0536.1995.tb00676.x

Rademaker M. (2000): Occupational epoxy resin allergic contact dermatitis. Australasian Journal of Dermatology 41 (4), 222-224. DOI: doi:10.1046/j.1440-0960.2000.00441.x

Tarvainen K., Jolanki R., Eckerman M.-L.H., and Estlander T. (1998): Occupational allergic contact dermatitis from isophoronediamine (IPDA) in operative-clothing manufacture. Contact Dermatitis 39 (1), 46-47. DOI: doi:10.1111/j.1600-0536.1998.tb05826.x

van Putten P.B., Coenraads P.J., and Nater J.P. (1984): Hand dermatoses and contact allergic reactions in construction workers exposed to epoxy resins. Contact Dermatitis 10 (3), 146-150. DOI: doi:10.1111/j.1600-0536.1984.tb00020.x

RAC's response

RAC agrees that the data submitted by EECDRG qualitatively support the classification of the substance as a skin sensitiser and generally are not in conflict with a classification as Skin Sens. 1A.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
21.10.2018	Germany	<confidential>	Company-Downstream user	9
Comment received				
Satisfactory				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you for your comment. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.12.2018	United Kingdom		MemberState	10
Comment received				
3-aminomethyl-3,5,5-trimethylcyclohexylamine (EC: 220-666-8; CAS: 2855-13-2)				
Please can you confirm if the studies with endpoints based on nominal concentrations include analytical verification of fresh and expired treatments to support the use of nominal endpoints? It is currently unclear if the measured data refers to initial fresh exposure treatments or both fresh and aged treatments.				

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Dossier Submitter's Response
<p>In the acute fish toxicity study, the concentration of the test item was measured 0, 24, 48 and 72 hours after the test item application. The measured values were within the 20% range accepted for the use of nominal concentrations.</p> <p>In the first acute aquatic invertebrate study, the analytical verification of the test item concentrations was carried out after 0 and 48 hours and did also not vary more than 20% from the nominal concentrations. For the other three acute aquatic invertebrate studies no analytical verification of the test concentrations were carried out.</p> <p>In the algae study no analytical verification of the test item concentrations was carried out.</p> <p>For the long-term toxicity study to aquatic invertebrates the test item concentration was analytically verified for the concentrations 1.0, 3.0 and 10.0 mg/L at day 0, 2, 9, 12, 14 and 16. The measured concentrations laid within the accepted 20% of the nominal concentrations.</p>
RAC's response
<p>Thank you for your comment. RAC appreciates the clarification provided by the Dossier Submitter regarding the analytical verifications of the test item concentrations.</p>

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	Finland		MemberState	11
Comment received				
<p>FI CA supports the conclusion to remove classification of Aquatic Chronic 3, H412 for 3-aminomethyl-3,5,5-trimethylcyclohexylamine based on chronic NOEC values > 1 mg/L for aquatic invertebrates and algae and acute LC50 value > 100 mg/L for fish.</p>				
Dossier Submitter's Response				
<p>Thank you for your support.</p>				
RAC's response				
<p>Thank you for your comment. RAC notes the support for the proposal to remove the existing environmental classification (Aquatic Chronic 3; H412) for the isophorone diamine.</p> <p>RAC agrees with the Dossier Submitter and commenting Member State that the substance should not be classified for environmental hazard.</p>				

PUBLIC ATTACHMENTS

1. EECDRG statement_to_Proposal for Harmonised Classification and Labelling of IPDA 2018_2.pdf [Please refer to comment No. 8]