Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

1,3-bis(1-isocyanato-1-methylethyl)benzene

EC Number: 220-474-4
CAS Number: 2778-42-9

CLH-O-0000006861-70-01/F

Adopted

17 September 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1,3-BIS(1-ISOCYANATO-1-METHYLETHYL)BENZENE; [M-TMXDI]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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: 1,3-bis(1-isocyanato-1-methylethyl)benzene; [m-TMXDI]
EC number: 220-474-4
CAS number: 2778-42-9
Dossier submitter: Germany

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
25.10.2019	France		MemberState	1
Comment received				
Despite the lack of clear evidence of respiratory sensitization from data with TMXDI, the current knowledge on hypersensitivity induced by isocyanates can allow proposing a classification for TMXDI. It is noted in page 13 that numerous studies demonstrate the ability of diisocyanates to cause RS also after dermal route. This type of data, if available on TMXDI, may also be used to support the proposed classification, considering the few studies with this substance.				
Dossier Submitter's Response				
We thank the FR CA for their support. Unfortunately studies demonstrating RS in animals after exposure via the dermal route are available for other diisocyanates (cf. Table 1-3 in the annex to the German diisocyanate restriction proposal, https://echa.europa.eu/documents/10162/66913681-1e1d-85ac-2314-997ed0a673c9), but not for m-TMXDI.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	Finland		MemberState	2
Comment received				
FI CA is of the opinion that category approach based on structural similarity to monomeric diisocyanates, consistency of the effects, reliability and adequacy of the source data and common underlying mechanism etc. is justified for the substance with limited test data available for itself. It has been shown that the respiratory sensitization property depends on the diisocyanate groups in the structure of the molecule. We agree that data rich diisocyanates HDI, MDI and TDI with have harmonized classifications for sensitization as Resp. Sens 1 can be used as source substances. Also, we agree that the three animal				

studies are unreliable in as-sessing the respiratory sensitizing potential of the substance in humans. The proposed classification as Resp. Sens 1, H334 is supported for 1,3-Bis(1-isocyanato-1-methylethyl)benzene.
Dossier Submitter's Response
We thank the FI CA for their support.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
24.10.2019	Sweden		MemberState	3
Comment received				
As stated in section 3.4.2.1 of Annex I to the CLP Regulation, classification for respiratory sensitisation is typically based on human data with supportive evidence from e.g. animal data. Human data (specific antibody formation) is available for m-TMXDI but is on its own not sufficient to warrant classification for respiratory sensitisation. Although the CLP criteria cannot directly be applied to XDI, the Swedish CA supports the WoE approach taken by the DS. Hence, classification of m-TMXDI as Resp. Sens. 1, H334 is supported based on sufficient evidence of the hazardous property, including the following pieces of information; 1) general mechanistic knowledge on the biological effects of diisocyanates. For example, the diisocyanate structure is an alert for respiratory sensitisation (REACH guidance on IR/CSA, Table R.7.3-3, and OECD QSAR toolbox v.4.3), 2) evidence of specific antibody formation in animals as well as in workers exposed to m-TMXDI, 3) read-across of human and non-human data of the hazardous property from structural analogue diisocyanates HDI, MDI and TDI. All three source substances have harmonised classifications as Resp Sens. 1., H334 and, 3) evidence of skin sensitisation by m-TMXDI which demonstrate the potential of the substance to initiate an immunological response.				
Dossier Submitter's Response				
We thank the SE CA for their support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
25.10.2019	France		MemberState	4
Comment received				
Skin Sensitization: We agree with the proposal despite the serious limitations of the available Buehler test with TMXDI. The classification is supported by the clear effects reported after the first challenge in this study in the light of the well-known skin sensitisation properties of isocyanates.				
Dossier Submitter's Response				
We thank the FR CA for their support.				
RAC's response				
Thank you for your comment. RAC agrees with the Dossier Submitter's proposal for classification (Skin Sens. 1A), but uses a weight-of-evidence approach, due to significant limitations of the available animal study (BRC, 1981). For details, please see the Opinion.				

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Date	Country	Organisation	Type of Organisation	Comment number
11.10.2019	Finland		MemberState	5
Comment received				
Regarding skin sensitisation endpoint one GPMT study is presented in the CLH report. The reported results show strong sensitisation potential of the substance. Thus, suggested classification of Skin Sens. 1A, H317 is supported.				
Dossier Submitter's Response				
We thank the FI CA for their support.				
RAC's response				
Thank you for your comment. RAC agrees with the Dossier Submitter's proposal for classification (Skin Sens. 1A), but uses a weight-of-evidence approach, due to significant limitations of the available animal study (BRC, 1981). For details, please see the Opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.10.2019	Sweden		MemberState	6
Comment received				
The proposal for harmonised classification as Skin Sens 1A is based on a skin sensitization test on the substance itself (BRC, 1981). According to the DS, the study resembles the protocol followed in a Buehler test. In the CLH-report it is stated that a primary irritation study with doses of 0, 0.00625, 0.0125, 0.025, 0.05 and 0.1 % (also used as challenge doses) was performed. In Annex I to the CLH-report and at ECHAs dissemination site, these doses are not given as % but as "% molar equivalents" or "molar dilutions" in relation to the positive control substance. Could the DS elaborate on the comparability of these dose measures to % w/v? The primary irritation study was performed prior to the skin sensitisation assay (BRC, 1981). Of the doses tested, the three highest ones (0.025, 0.05 and 0.1 %) seem to have caused irritation reactions, however very slight. The same doses caused more marked irritation during challenge. The induction dose selected for the skin sensitization assay was 9%, i.e. seemingly 90 times the highest dose in the primary irritation study. Hence, the choice of induction dose cannot have been made based on the primary irritation study results, nor has it been justified by other means. Consulting the OECD TG 406, the induction dose in a Buehler test should be the highest dose causing mild irritation. Does the DS have any more information about the basis for the choice of 9% as induction dose, or the degree of skin irritation to which 9% m-TMXDI gives rise? Although the induction dose used in this particular case (9%) is likely higher than what is recommended by the OECD TG 406, it is still low enough to enable sub-categorisation. Hence, the Swedish CA considers the lack of justification as an acceptable deficiency for classification purposes. Overall, the Swedish CA supports classification of m-TMXDI as Skin Sens. in Category 1A based on that ≥ 60 % of the animals had positive reactions at a > 0.2 - ≤ 20 % topical induction dose.				
Dossier Submitter's Response				
We thank the SE CA for their support. As noted in Annex I, the summary provided there for this study is a direct reproduction of the text submitted by the registrant. The DE CA did not have access to the original study report. Use of the word "molar" is believed to be a typing error, as it does not make sense here and is not used in a comparable context anywhere else.				
RAC's response				
Thank you for your comment. RAC agrees with the Dossier Submitter's proposal for				

classification (Skin Sens. 1A), but uses a weight-of-evidence approach, due to significant limitations of the available animal study (BRC, 1981). For details, please see the Opinion.