Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Tetramethylene dimethacrylate

EC Number: 218-218-1
CAS Number: 2082-81-7

CLH-O-0000007058-72-01/F

Adopted

26 November 2021

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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: tetramethylene dimethacrylate
EC number: 218-218-1
CAS number: 2082-81-7
Dossier submitter: Finland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2021	France		MemberState	1
Comment received				
MMA has been recently classified by the RAC as a respiratory sensitizer. As you refer to MMA in your CLH report and considering that methacrylate compounds are an important aetiological factor in occupational asthma, it would have been interesting to assess if tetramethylene dimethacrylate should also fulfil criteria for classification as Resp. Sens (in addition to Skin Sensitisation). However, one argument against this classification may be the vapour pressure of this substance which can prevent inhalation exposure and potential respiratory sensitisation.				
Dossier Submitter's Response				
Noted.				
RAC's response				
The category Resp. Sens was not opened for evaluation by RAC as it was not proposed by Dossier Submitter				

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Belgium		MemberState	2
Comment received				
BE CA would like to thank the Finnish CA for this CLH proposal. According to the self-classification (Eye Irrit 2, Skin Irrit 2, STOT SE 3 H335, Skin Sens 1/1B), harmonised classification for eye irritation, skin irritation and STOT SE might also have been considered suitable. BE CA therefore regrets that these hazard classes were not assessed in the present CLH proposal.				

Dossier Submitter's Response
Noted
RAC's response
The hazard classes other than Skin Sensitisation were not opened for evaluation by RAC as they were not proposed by Dossier Submitter

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2021	Sweden		MemberState	3
Comment received				
The SE CA supports the proposed harmonised classification of tetramethylene dimethylacrylate as Skin Sens. 1B, H317 based on animal data (key study LLNA with EC3 = 31.4%). Human evidence further supports classification of tetramethylene dimethylacrylate as a skin sensitiser.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for comment. RAC also propose a classification Skin Sens. 1B, H317 based on animal data with human data as supportive evidence				

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2021	Germany	<confidential>	Company-Importer	4
Comment received				
With reference to the CLH dossier regarding Tetramethylene Dimethacrylate (EC number 218-218-1), we agree with the harmonised classification as Skin Sens 1B, H317, mainly based on animal data, namely LLNA data, proposed by the Finnish MSCA. We also agree to the proposed assessment on human data that this data supports the classification and labelling in a weight of evidence approach and does not allow a sub-categorisation due to the absence of exposure information. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2021-18-01_Comment on CLH Dossier 1,4-BDDMA_public.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2021-18-01_Comment on CLH dossier on 1,4-BDDMA.pdf				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for comment. RAC also propose a classification Skin Sens. 1B, H317 based on animal data with human data as supportive evidence.				

Date	Country	Organisation	Type of Organisation	Comment number
05.01.2021	Germany		MemberState	5
Comment received				
Please find our detailed comments in the attachment (DE-CA-Comments_Tetramethylene dimethacrylate.pdf)				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA-Comments_Tetramethylene dimethacrylate.pdf

Dossier Submitter's Response

Thank you for your comments.
The assessment relies on the full study report of LLNA and we do not have access to more detailed information. Acute dermal toxicity study conducted with the substance is not available. There is only a supporting study available on closely related read-across substance 1,3-BDDMA. The study is very poorly reported. No clinical signs or other effects were observed. The acute dermal LD50 of 1,3-BDDMA is reported to be >3000 mg/kg bw in rabbit. Acute oral toxicity LD50 of 1,3-BDDMA (rat, combined) is reported to be 10 066 mg/kg bw. The study has been performed according to the OECD TG 401. As the substance is not acutely toxic by the oral route this supports findings that it is not acutely toxic by the dermal route either.

The unspecific clinical symptoms: reduced spontaneous activity, ruffled fur and hunched posture may in general indicate mild systemic toxicity. These effects were observed in all treated animals on day 3 (25%: 1h after the third application; 50% and 100%: 1h before and 1h after the third application). Furthermore, the animals in mid and high dose groups showed eyelid closure and abnormal walk. No marked reduction in body weight nor mortality was observed during the study period. According to the authors, it cannot be confirmed whether these symptoms were signs of systemic toxicity or mere reactions to the irritant nature of the test substance. However, the study was considered valid by the authors. In the registration dossier the study is reliable without restrictions with klimisch score 1. Skin irritation in test animals was not excessive as the erythema scores varied between 1 and 2 (<3). It can not be concluded, if the effects observed in LLNA, were reactions to the irritant nature of the substance. Without any more detailed information on the clinical signs and taking into account that there was no relevant body weight loss, it is difficult to conclude on systemic toxicity either. Nevertheless, we note that slight clinical signs were observed in the study and they might indicate systemic toxicity.

RAC's response

Thank you for comment. RAC agrees with the opinion of Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2021	Belgium		MemberState	6

Comment received

The CLH report describes evidences of skin sensitisation in human after exposure or co-exposure to tetramethylene dimethacrylate. A total of 26 clinical studies have been identified for tetramethylene dimethacrylate. The studies comprised a total of 128 patients who tested positive to the substance. In all studies, the diagnostic method was patch testing.

In animals, five studies are described in the CLH dossier. First, a LLNA in mice (rel 1, Anon 2014) concluded that tetramethylene dimethacrylate is sensitising, based on SI values of 2.74, 3.76, and 5.72, at 25, 50 and 100% test-compound respectively. The calculated EC3 value was 31.4% (w/v). On a weight-of-evidence approach, a FCA test in Guinea pig (rel 3, Anon, 1983a) further supported the sensitising potential, showing positive results in all animals after induction with a concentration of 13% 1,4-butanediol dimethacrylate. A GPMT in Guinea pig (rel 3, Anon 1983b) also indicated ambiguous

results after induction with a concentration of 13% 1,4-butanediol dimethacrylate. In contrast, two GPMTs in guinea pig (rel 3, Anon 1984a ; rel 2, Anon 1984b) concluded that 1,4-butanediol dimethacrylate was not sensitising after induction up to 2% intradermal injection and 50% topical application. Due to the limitations in the reporting and/or the testing conditions, BE CA is of the view that these negative results are not reliable enough to base a classification on it.

Overall, BE CA considers that based on the weight-of-evidence including both human and animal data, it should be concluded that a classification as skin sensitiser is warranted for tetramethylene dimethacrylate. When it comes to the sub-categorization, BE CA is of the opinion that, when available, adequate human data should always be preferred over animal data to conclude on classification.

In the present situation, the available data allows us to make a conclusion on occurrence of skin sensitisation in human. In line with the DS, we agree that the frequency of positive reactions to tetramethylene dimethacrylate in diagnostic patch tests can be considered high, according to the CLP guideline. Regarding the exposure frequency, The DS concludes that there is no adequate information enabling the assessment of true exposure to the substance. We are of the view that sufficient information is available to conclude on exposure of the substance, at least for some categories of workers.

According to the registration dossier, tetramethylene dimethacrylate is manufactured and/or imported in the European Economic Area in 1 000-10 000 tonnes per year with a widespread use of the substance. It is used in different coating products, fillers, putties, plasters, modelling clay, paints, adhesives and sealants by consumers, by professional workers, in formulation or re-packing, at industrial sites and in manufacturing. Workers may be in direct contact with formulated products containing the substance during mixing (including by hand) or blending, and the products may be used with rollers or brushes or via dipping or pouring.

In particular, exposure to tetramethylene dimethacrylate through dental composite resins of dentists and dental technicians, leading to skin sensitisation, is well described. Literature includes e.g. Aalto-Korte et al. (2007), Goon et al. (2006), Kanerva et al. (1989), Kiec-Swierczynska et al. (1996), Peiler et al. (2000), Rustemeyer et al. (1996) and Wrangsjö et al. (2001). Although positive test reactions may also arise from cross-reactivity to other methacrylates, Peiler et al. (2000) confirmed exposure to the substance in all six dental technicians who gave a positive reaction to it. In addition, the cross-sectional studies on dental technicians mimicking workplace studies (on selected workers) showed frequency of positive patch tests of 2%, i.e. above the cut-off value of 1.0% for high frequency.

In this category of workers, it should be assumed that the exposure to the compound is more than one daily (score 2) and that the number of exposures is more than 100 (score 2). In addition, tetramethylene dimethacrylate being one of the main composants of dental composite resins, the concentration of this compound in such articles is certainly more than 1.0% (score 6). Therefore, according to the CLP guideline, the exposure of dentists and dental technicians to tetramethylene dimethacrylate should be considered of high frequency. Therefore, BE CA considers that for this category of workers, both frequency of occurrence of skin sensitisation and frequency of exposure should be concluded to be high. Similarly, workers in the field of long-lasting nail polishing might be considered highly exposed to tetramethylene dimethacrylate.

When assessing human data, the CLP guidelines states that the classification decision leads to Skin Sens 1 without sub-categorization in case of relatively high frequency of occurrence of skin sensitisation and relatively high frequency of exposure (score 5-6). Therefore BE CA supports a Skin Sens 1 classification without sub-categorization.

Finally, the DS retained the LLNA as the key study to decide on the most appropriate classification. However, BE CA notes that the LLNA was performed with high concentrations of tetramethylene dimethacrylate (25, 50 and 100%). According to the OECD 429 guidance on LLNA, the highest concentration should be selected in order to "maximise exposure while avoiding systemic toxicity and/or excessive local skin irritation". In this view, a pre-test was performed in two animals with concentrations of 50 and 100% to determine the highest non-irritant test concentration. Results of the pre-test reported erythema and scabby ears in animals treated with the undiluted test-compound. These findings are in line with the self-classification of the substance as Skin Irrit. 2. Furthermore, animals showed clinical signs indicating acute systemic toxicity from 50% concentration (eyelid closure and abnormal walk on day 3, and ruffled fur on day 4 ; reduced spontaneous activity on day 4 at the highest dose). BE CA therefore questions the dose selection of this LLNA using concentrations of 25%, 50% and 100% tetramethylene dimethacrylate in the main study.

Dossier Submitter's Response

Thank you for your comment.

The assessment of human exposure was not included in the CLH report because we had no adequate data available to allow a reliable evaluation of the exposure to the specific substance. There is lack of data on the products containing the substance. Therefore, it is not possible to know the concentration/ dose exposed to. The same goes for information of repeated exposure and the number of exposures. In our view, only assumptions can be made as there is no reported information of the exact exposure. We would be careful to base an evaluation on assumptions and to use that data to conclude on the classification.

Regarding the LLNA we agree the test concentrations were high. In the pre-test 2 animals were treated with 50 and 100% test substance. On day 4 the mouse treated with the undiluted test substance showed transiently a slightly reduced spontaneous activity. An erythema of the ear skin was observed in both animals (50%: score 1 on days 3-6; 100%: score 1 on day 2, 3 and 6 and score 2 on days 4-5). Furthermore, scabby ears were observed on day 5 in the animal treated with 100% test substance. Increase in ear thickness on day 6 was 6% and 3% in mouse treated with 50 and 100 % test substance respectively. No relevant change in body weights was observed. According to the study authors "*The highest concentration tested was the highest level that could be achieved whilst avoiding systemic toxicity and excessive local skin irritation as confirmed in the pre-test*". Thus, doses of 25, 50 and 100% were selected for the main test. According to the OECD TG 429 "*Excessive local skin irritation is indicated by an erythema score ≥3 and/or an increase in ear thickness of ≥25% on any day of measurement*". No excessive local skin irritation was observed in pre-test animals as erythema scores were 1-2 (<3) and increase in ear thickness was not more than 6% (<25%). We note the substance has self-classification as Skin Irrit. 2, however, according to data on registration dossier the substance is not a skin irritant. OECD TG 429 states also that "*The highest dose selected for the main LLNA study will be the next lower dose in the pre-screen concentration series that does not induce systemic toxicity and/or excessive local skin irritation"*. It is unclear

why the concentration of 100% was selected for the main test. In the main test all treated animals showed an erythema of the ear skin (25%: score 1 on days 3-4; 50%: score 2 on days 3-5; 100%: score 1 on days 2 and 6) but there was no excessive skin irritation. The unspecific clinical symptoms: reduced spontaneous activity, ruffled fur and hunched posture were observed in all treated animals on day 3 (25%: 1h after the third application; 50% and 100%: 1h before and 1h after the third application). Furthermore, the animals in mid and high dose groups showed eyelid closure and abnormal walk. A loss in body weight or mortality was not observed in any of the test substance treated animals during the study period. According to the authors, it cannot be confirmed whether these symptoms were signs of systemic toxicity or mere reactions to the irritant nature of the test substance. However, the study was considered valid by the authors. In the registration dossier the study is reliable without restrictions with klimisch score 1. It can not be concluded, if the effects observed in LLNA, were reactions to the irritant nature of the substance. Without any more detailed information on the clinical signs and taking into account that there was no relevant body weight loss, it is difficult to conclude on systemic toxicity either. Nevertheless, we note that slight clinical signs were observed in the study and they might indicate systemic toxicity.
RAC's response
Thank you for comment. RAC agrees with the opinion of Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2021	France		MemberState	7
Comment received				
Based on results of the LLNA, criteria for Skin Sens. 1B are fulfilled. In contrast, GMT assays are negative. Based on human data and according to CLP guidance document, there is a high frequency of occurrence of skin sensitisation based on the available studies on selected patients (in general > 2%) and considering the number of published cases (> 100). Assessment of exposure data is lacking from the CLH report (refer to table 3.3 of CLP guidance). If no adequate exposure data is available and based on the high frequency of occurrence of skin sensitisation based on human data, a subcategorisation as Skin Sens. 1A cannot be excluded. In this context, subcategorisation may be not possible. Thus, it should be discussed at the RAC level if classification as Skin Sens. 1 instead of 1B as proposed is more appropriate.				
Dossier Submitter's Response				
Thank you for your comment. The assessment of human exposure is not included in the CLH report as there is no adequate data available. Proposed sub-categorization as 1B is based on LLNA. In this case, our view is that insufficient human exposure data would not overtake animal data. However, we agree it is the RAC to consider the most appropriate classification.				
RAC's response				
Thank you for comment. RAC agrees with the opinion of Dossier Submitter.				

PUBLIC ATTACHMENTS
1. 2021-18-01_Comment on CLH Dossier 1,4-BDDMA_public.pdf [Please refer to comment No. 4]
2. DE-CA-Comments_Tetramethylene dimethacrylate.pdf [Please refer to comment No. 5]

CONFIDENTIAL ATTACHMENTS
1. 2021-18-01_Comment on CLH dossier on 1,4-BDDMA.pdf [Please refer to comment No. 4]