

Committee for Risk Assessment
RAC

Annex 3
Response to comments document (RCOM)
to the Opinion proposing harmonised classification and
labelling at EU level of

methyl methacrylate methyl
2-methylprop-2-enoate methyl
2-methylpropenoate

EC Number: 201-297-1
CAS Number: 80-62-6

CLH-O-0000006852-69-01/F

Adopted
18 March 2021

**ANNEX 3 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON METHYL METHACRYLATE;
METHYL 2-METHYLPROP-2-ENOATE; METHYL 2-METHYLPROPENOATE**

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: methyl methacrylate; methyl 2-methylprop-2-enoate; methyl 2-methylpropenoate

EC number: 201-297-1

CAS number: 80-62-6

Dossier submitter: France

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2019	Netherlands		MemberState	1
Comment received				
<p>The DS proposes an Annex VI entry for methyl methacrylate (CAS nr. 80-62-6) as Resp Sens Cat. 1 H334 without subcategory. The DS bases its conclusion on human case studies and epidemiological data obtained from several databases registering occupational disease and public literature. The DS considers the available information too limited for subcategorisation in Cat. 1A or Cat. 1B, since it is largely unknown at what exposure levels humans are sensitised, and the frequency of disease as reported in the public literature and databases may be affected by underreporting.</p> <p>The NL-CA agrees with the DS on the proposed classification as Resp. Sens Cat. 1 H334 without subcategory. The NL-CA considers the available data not sufficient for classification as Resp. Sens Cat. 1A, since there is too limited information available on the concentrations at which sensitisation of the airways occur. We furthermore agree with the DS that it is difficult to distinguish between the clinical symptoms following from the irritant properties of methyl methacrylate and the sensitisation potential of the substance. Nevertheless, the human data in the CLH dossier illustrate several cases of asthma with late reaction in specific inhalation challenge (SIC), pointing to respiratory sensitisation. Please also consider in this respect the publication by Walters et al. (2017). This study supports the association between occupational asthma and exposure to acrylates (among which eight cases occupational asthma caused by predominantly methyl methacrylate reported to the UK SHIELD surveillance scheme between 1989 and 2014).</p> <p>Among the case studies in the CLH report are also several cases of nail salon workers with occupational asthma due to workplace exposure to methyl methacrylate. A recent publication by DeKoven et al. (2017) reports an increasing trend in the incidences of allergic contact dermatitis in this category of professionals visiting their clinic, reflective of</p>				

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<p>a more general trend in nail salon workers due to occupational (meth)acrylate exposure. This trend is of concern also with regard to potential new cases of work-related respiratory sensitisation among nail technicians.</p> <p>DeKoven, S., DeKoven, J., & Holness, D. L. (2017). (Meth) acrylate occupational contact dermatitis in nail salon workers: a case series. <i>Journal of cutaneous medicine and surgery</i>, 21(4), 340-344.</p> <p>Walters, G. I., Robertson, A. S., Moore, V. C., & Burge, P. S. (2017). Occupational asthma caused by acrylic compounds from SHIELD surveillance (1989–2014). <i>Occupational Medicine</i>, 67(4), 282-289.</p>
Dossier Submitter's Response
Thanks for your support and the additional data provided.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2019	Germany		MemberState	2
Comment received				
<p>The CLH proposal for the classification of methyl methacrylate (CAS Nr. 80-62-6) in Resp Sens. 1, H334 is supported. The data presented show that MMA induces asthma in humans, so a classification is justified. Since the human data did not contain a description of the level of exposure, a subcategorization is not possible.</p> <p>However, the dossier could provide more detail on how to ensure that the allergic reaction is specific to the exposure with MMA and did not result from another component of the cement used in dentistry, medicine and nail design.</p>				
Dossier Submitter's Response				
Thanks for your support. Regarding the specific exposure to MMA, the cases, as explained in the dossier, came mainly from a French specific database in which occupational doctor reported cases. The cases with a high attributability have been included. Because of the medical confidentiality it is not possible to include all the details in the CLH dossier..				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2019	Germany	Evonik Röhm GmbH	Company-Manufacturer	3
Comment received				
<p>This CLH proposal lacks fundamental scientific standards of ECHA and EUCOM's SCHEER. The weight-of-evidence (WoE) approach of the CLH proposal is thus not balanced and not scientifically justified.</p> <p>A lack of fundamental understanding was also observed for endpoint specific aspects on respiratory sensitization: Neither obligatory evidence for a biphasic mode of action nor a valid determination of "causation" of the development of asthma in relationship to Methyl Methacrylate (MMA) exposure nor a clear differentiation distinguish between respiratory irritation effects (for which this substance is already classified) against the claimed respiratory sensitization effects was provided in sufficient detail.</p>				

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Our alternative WoE approach, following the aforementioned standards and based on a broader database, demonstrates clearly a lack of confidence in the CLH proposal that MMA is a causative agent for occupational asthma. Instead, all available evidence reviewed in the literature of sufficient strength confirm that MMA has the potential to aggravate asthmatic symptoms in pre-existing asthmatics.

We thus do not agree to the CLH proposal and, instead, we propose that the current Annex VI entry remains unchanged.

A detailed comment is attached.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2019-07-05_MMA_CLH_comment_final_with_coverletter.pdf

Dossier Submitter's Response

We note your disagreement with proposal. Nevertheless we consider that there is, as explained in details in the dossier, a clear evidence that MMA is a respiratory sensitizer as reported in several cases, by different occupational practitioner, in several countries, for various field of exposure as described in the dossier.

The asthma linked to an occupational exposure to methyl methacrylate is recognised in France by the the French National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS) since 1987. Additionally all the cases reported in the dossier especially from the RNV3P (The National Network for the Monitoring and Prevention of Occupational Diseases) were reported by specialized occupational practitioner who clearly linked an occupational exposure to MMA with different kind of asthma. Moreover the cases with a high attributibility only were included.

It was reported in different publications the clear link between exposure to MMA and asthma as described in the dossier and not only in France like in the publication by Walters *et al.* (2017) as indicated in the comment number 1 : "This study supports the association between occupational asthma and exposure to acrylates (among which eight cases occupational asthma caused by predominantly methyl methacrylate reported to the UK SHIELD surveillance scheme between 1989 and 2014)".

Therefore based on all the cases reported there is a clear evidence that an exposure to methyl methacrylate can lead to a respiratory sensitization.

Walters, G. I., Robertson, A. S., Moore, V. C., & Burge, P. S. (2017). Occupational asthma caused by acrylic compounds from SHIELD surveillance (1989–2014). *Occupational Medicine*, 67(4), 282–289.

RAC's response

Thank you for your comment. RAC agrees that evidence for a biphasic mode of action was not included in the CLH report. However, in addition to the above mentioned Walters *et al.* (2017), which has been included in the RAC opinion, a new study has been published recently, giving such kind of evidence (*Suojalehto et al. in J Allergy Clin Immunol Pract. 2019 Oct 31. doi: 10.1016/j.jaip.2019.10.017. [Epub ahead of print]*). The data from this publication, supplemented with additional information received directly from the authors, has been included and taken into account in the RAC opinion. Briefly, this was a multicentre cohort study evaluating the characteristics of acrylate-induced occupational asthma, and also included subjects that were verified to have predominantly been exposed to methyl methacrylate. The occupational asthma diagnoses in this study were confirmed by placebo-controlled specific inhalation challenges (SIC). The SIC is widely considered a reference standard in the diagnosis of occupational asthma when performed adequately.

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RAC also acknowledges that the causation between occupational exposure to methyl methacrylate and asthma development is not very well described in the CLH report. In the case of low molecular weight molecules, which do not cause IgE-mediated responses, demonstration of causality is always more difficult than in the case of allergens resulting in clear IgE-mediated responses. However, RAC is of the opinion that the placebo-controlled positive responses in the SIC tests (Suojalehto *et al.* 2019) strongly argue for methyl methacrylate specific sensitisation. Furthermore, the additional data in the RAC opinion showing also negative SIC responses to methyl methacrylate in asthmatic patients, show that the effects of methyl methacrylate are not merely due to its respiratory irritant effect in asthmatics. RAC also views it important to note that a negative result in a skin prick test should not be interpreted as a negative result for respiratory sensitisation by methyl methacrylate, as it is known to systematically produce negative results in this test (like other low molecular weight agents, such as diisocyanates). Also according to the CLP Guidance, "immunological mechanisms do not have to be demonstrated" in order to classify a substance as respiratory sensitiser.

The RAC opinion document also includes some further information related to other comments presented in the attachment.

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2019	Finland		MemberState	4
Comment received				
Based on the available human data from case reports and epidemiological studies, MMA induces asthma. At present, there are no appropriate animal models for the testing of respiratory sensitisation. However, the evidence in humans indicate that exposure to the substance can lead to specific respiratory hypersensitivity. The data are not sufficient for sub-categorisation. The results meet the criteria for classification as Resp. Sens. 1; H334. FI CA supports the proposed classification of Resp. Sens. 1; H334 for methyl methacrylate.				
Dossier Submitter's Response				
Thanks for your support.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS

1. 2019-07-05_MMA_CLH_comment_final_with_coverletter.pdf [Please refer to comment No. 3]