Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

methacrylic acid, monoester with propane-1,2-diol [HPMA]

EC Number: 248-666-3
CAS Number: 27813-02-1

CLH-O-0000007381-77-01/F

Adopted

30 November 2023

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON METHACRYLIC ACID, MONOESTER WITH PROPANE-1,2-DIOL [HPMA]

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: methacrylic acid, monoester with propane-1,2-diol [HPMA]
EC number: 248-666-3
CAS number: 27813-02-1
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2023	Germany	Higher Methacrylates REACH Task Force	Industry or trade association	1
Comment received				
We are concerned about the quality of the CLH proposal in connection with a number of formal deficiencies highlighted in Section 1 of the attached response document, namely that the dossier lacks transparency, is highly selective in the information contained therein, contains significant information unrelated to the substance itself and contains multiple, scientifically unsupported statements which taken together highlights what can be considered a significant bias in the authors assessment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-05-12_HPMA response_final.pdf				
Dossier Submitter's Response				
In your attached document, you state that not all information presented in the registration dossier submitted in 2022 is included in the CLH report. You refer to hazard classes other than those covered in the CLH report. We would like to remind you that it is not mandatory to open all hazard classes in a CLH report for a substance covered by Reach Regulation. Regarding the endpoints covered in this CLH report - Skin Sens, Resp. Sens, Eye Irrit and STOT RE - the only information that is present in the updated registration dossier but not in the CLH report, is related to the *in vitro* studies for Skin Sensitisation. Even if we indeed regret that this information is lacking in the CLH report, this is now taken into account in these RCOM (see response to comment below). These data do not change our conclusions since relevant and valid data exist in humans that overcome the *in vitro*				

findings. In contrast, we note that several publications detailed in the CLH report are not present in the updated registration dossier.

You note that "*the guidance on preparation of CLH dossiers clearly prescribes that all information that is considered accurate, reliable and relevant for the proposal should be provided in the CLH report*". We consider that the CLH report is compliant with these criteria. Most of the studies detailed in the CLH report are issued from publications, and thus are peer-reviewed by the editors. Regarding surveillance data, see response to comment 2.

In your attachment, you refer to the recent Judgement of the General Court of the European Union (Cases T-279/20 and T-288/20) where intrinsic hazard was interpreted as in its literal sense as referring to the '*properties which a substance has in and of itself'*. This case refers to TiO_2 and its property to induce lung cancer. The appellant claimed that the lung cancer is a consequence of lung overload rather than TiO_2 itself. The case therefore refers to the concept of direct toxicity or secondary toxicity. It is not related to the issue pointed here by you. Moreover, it should be noted that European Commission and France appealed this Decision in 2023 which suspends this judgement. This argumentation is therefore considered out of the scope of our proposal.

See also responses to other comments below, for specific endpoints.

RAC's response

Noted.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2023	Germany	Higher Methacrylates REACH Task Force	Industry or trade association	2

Comment received

We do not agree with the CLH proposal for Respiratory Sensitisation (Cat 1, H334) for the reasons presented in Section 2 of the attached response document; the proposal is scientifically not justified based on a weight of evidence assessment of all available data (Appendix I, therein).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-05-12_HPMA response_final.pdf

Dossier Submitter's Response

QSAR:

Regarding your comment on QSAR estimation for Respiratory sensitisation, we agree that these models are not adequately predictive. This is already noted in the CLH report.

Volatility:

Based on the vapour pressure of HPMA of 11 Pa at 20 °C, the substance can not be considered as a substance with low volatility. Indeed, a substance with a vapour pressure between 5 and 1000 Pa is considered as a moderate volatility substance (https://www.inrs.fr/publications/bdd/solvants/aide-en-ligne.html). Moreover, a definition of a low volatility substance can be retrieved in Reach guidance R7a: *"[…] low volatility*

substances, which are defined as having vapour pressures < 1x10^{-5} kPa for indoor uses, and < 1x10^{-4} kPa for outdoor uses".).

With a boiling point of 213°C, HPMA also fullfills the criteria of a VOC (volatile organic compound) according to the definition of US EPA (a VOC is any organic compound having an initial boiling point less than or equal to 250° C measured at a standard atmospheric pressure of 101.3 kPa; cf. https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds)

Moreover, the volatility of the substance can also be supported by the exposure data you provided in your attachment (with detection and quantification of HPMA in the air).

Mechanism of action and use of read-across:

You note that "*hydrolysis to a common metabolite is not evidenced by established science since no published literature can be found to support such a hypothesis*". Toxicokinetics data are available showing that HPMA is quickly metabolised into methacrylic acid, as other methacrylates such as MMA (see CLH report section 9 on toxicokinetics and section 10.9.1 with details on read-across assessment).

You state that the hypothesised mode of action of methacrylates to cause respiratory allergy through metabolism to the common acid metabolite (MA) and its retained acryl group is not established according to REACH guidance such as the RAAF. First, we remind you that RAAF is not mandatory for preparation of CLH dossier since it was elaborated in the context of Reach Regulation and not CLP Regulation.

For Respiratory sensitisation, data are available with HPMA. So, a read-across with other methacrylates is not formally proposed in the CLH report. Instead, data on methacrylates, and in particular MMA (see recent opinion of RAC for MMA), are used as supportive evidence. Asthma is reported for different methacrylates. So one hypothesis is that this hazard could be linked to the hydrolysis into methacrylic acid. This hypothesis is also raised in the GMT 201 by ECHA (2021: https://echa.europa.eu/fr/assessment-regulatory-needs/-/dislist/details/0b0236e1855700f8).

However, we recognise that there is no available data on methacrylic acid regarding respiratory sensitisation, and thus, we cannot distinguish if this hazard is due to the formation of this metabolite or to the parent itself.

This is the reason why this argumentation has not been developed further for this endpoint in our proposal. It is still relevant to consider the analogue approach between HPMA and MMA. Please find below the RAAF assessment elements (AE) to be considered for this endpoint:

- AE A.1 Identity and characterisation of the source substance: data are already addressed in table 18 of the CLH report.
- AE A.2 Link of structural similarities and differences with the proposed prediction: HPMA and MMA are both short methacrylates, with linear length chain ≤ 4 carbons. Both substances are volatile. Both substances are quickly metabolised into methacrylic acid within minutes order. Cases of asthma are reported with both substances.
- AE A.3 Reliability and adequacy of the source study: MMA has been classified as Resp. Sens by the RAC.

- AE A.4 Bias that influences the prediction: Cases of respiratory sensitisation related to (meth)acrylates exposure are reported in the literature. This point to a common mechanism of action (either due to similar structure of parent substance or due to common metabolite). There are more data with MMA regarding respiratory sensitisation (justifying the classification as Resp. Sens according to RAC opinion).

Regarding your comment on mechanistic considerations of immunological involvement: it should be noted that according to CLP guidance (2017): "*immunological mechanisms do not have to be demonstrated*".

MMA classification:

You bring to our attention that "*developments discussed at CARACAL throughout the year 2022 indicate that this RAC Opinion was premature due to incomplete provision of case details from clinical institutes in Europe. At the CARACAL 48 meeting held in March 2023, the Commission has proposed, on the basis of new evidence, that RAC be given the opportunity to re-evaluate their earlier decision*". We recognise that further scientific discussions will take place at the RAC level. At the time being, the RAC opinion has concluded that MMA should be classified as Resp. Sens. 1. Until new evaluation, this conclusion is still relevant.

Test material:

In your attachment, you state that "*the proposed classification of HPMA as a respiratory sensitiser is based entirely on evidence pertaining to exposure to mixtures containing at most minor fractions of HPMA or in some cases not containing HPMA at all*".

The evidence of respiratory sensitisation for HPMA comes from human data. Humans are generally exposed to mixtures and not only to one single substance. This is a consistent limitation of human data (and not specific to this case). The fact that products used contain different substances, in general different methacrylates, is clearly indicated in the CLH report. We recognise that complete composition of the tested products is not fully known. Safety data sheets are considered as the principle data source of chemicals' harmful effects – clinicians are dependent on these data as producers are generally not willing to disclose the entire composition. When available, the concentration of HPMA is above the generic concentration limit as sat up in tables 3.4.5 and 3.4.6 of the CLP. Considering these limits, concentration ranging from 1 to 10% (non exhaustive interval of concentrations used) is not considered as a "*minor fraction*".

You indicate that the tested products are complex mixtures, including other sensitisers and irritant substances (they contain in general different methacrylates). We agree that all the products contained other methacrylates in addition to HPMA. Their effects cannot be excluded. However, as the other methacrylates listed in the SDS's were poorly volatile, FIOH believes that they had a minor role in the patients' respiratory exposure and occupational asthma.

In addition, the substances that you cite are only skin sensitisers but not to respiratory sensitisers. We support the fact that skin sensitisation is an important alert for respiratory sensitisation (some molecular key events are in common) but that these two hazards are not always concomittant. Thus, this consideration is not sufficient to dismiss the relevance of the reported cases.

You consider that that there is no sufficient evidence that HPMA is the causative agent despite:

- the results of the SIC tests,

- the presence of HPMA in the products,
- the volatility of the substance,
- the expert judgment of the physicians on the imputability.

Instead you propose that asthma can be due to other factors based on general statement on complex workplace atmospheres. Even if we cannot rule out the potential presence of confundant factors, the weight of evidence points to HPMA as a causative agent of the cases reported in the CLH report. The limits highlighted have been considered in the CLH report.

Exposure data

In your attachment, you provide exposure information in industry sectors. We remind you that exposure considerations are not part of CLP Regulation. Instead measurement of HPMA at occupational setting can give information on the presence of the substance in the air (and thus its volatility). However, we remind you that these information should be reported in the registration dossier if not done in your recent update.

You also refer to HPMA's exposure in sectors where no cases of asthma are reported. This cannot be used as a proof of lack of hazard. This may be due, for example, to the lack of reporting by the personals to their physician, the lack of diagnosis, the lack of publications on this topic, the use of adequate PPE….

The relevance of human data in the CLP regulation:

According to CLP regulation (Title II, chapter 1, article 5), the different sources of data include " *epidemiological data and experience on the effects on humans, such as occupational data and data from accident database*". In addition, with the pressure to diminish animal testing, and considering that neither animal models nor *in vitro* nor *in silico* models are relevant for this endpoint, it should be recognised that **only human data** (with their known limitations) can serve to identify this hazard.

Occupational surveillance data:

Regarding methodology of these surveillance systems, please find details in a publication by the EU-OSHA [https://osha.europa.eu/en/publications/methodologies-identify-work-related-diseases-review-sentinel-and-alert-approaches]. These alert and sentinel systems allow "*the early identification of work-related diseases and are useful to complement the official figures of occupational diseases and to set-up evidence-based prevention"* and "*to detect emerging work-related diseases".* Due to confidential issues, case-by-case reports have not been generally published, also considering that it is not the primary goal of these alert and sentinel systems.

FIOH

Regarding FIOH data, you state in the attachment that "*It should be noted that since these cases have not been reported in full in any publication or communication, no assessment can be made of the clinical history of the patients, the materials tested, the methods employed in the Specific Inhalation Challenge (SIC) tests or exposure measurements during testing as required by CLP guidance*".

The cases reported in the CLH report are included in a European multicenter case series of 55 patients with occupational asthma due to various acrylates published by Suojalehto et al. 2019. Thus, information on the method is also available from this publication. In particular, you state that the SIC testing was not conducted according to guideline. However, according to Suojalehto et al. 2019, "*the methodology of SIC conformed with*

international recommendations in terms of safety precautions, "placebo" challenge, and duration of functional monitoring". Regarding your reference to Vandenplas et al. 2014, FIOH representatives had an essential role in writing this article, especially as regards technical methods in SIC. So, the presented guidelines are followed in the cases presented in the CLH report. They were also the responsible compilers of the SIC Handbook that is a supplement in Vandenplas et al. 2014 article (the latest version Suojalehto et al. 2019, Specific challenge testing for occupational asthma: revised handbook, doi: 10.1183/13993003.01026-2019), and they have presented FIOH methods there. Regarding exposure (air) measurements, in general, they are an ideal but by no means required or generally available in SIC, as stated in the article by Vandenplas et al 2014: "*In practice, appropriate techniques for measuring the wide variety of agents causing occupational asthma are seldom available*."

This methodology was previously reviewed by the RAC. Indeed, in its opinion on MMA, RAC considered that the FIOH employed the state-of-the art methodology available for diagnostics of occupational asthma due to respiratory sensitisation. Therefore, the classification was agreed based on data from Suojalehto et al. 2019.

Moreover, details are also present in the EU-OSHA review. As noted in page 123 of this review, cases are reported by physicians and evaluation and analysis are made based on experts judgment and literature.

Overall, **the methodology followed by the FIOH is considered as robust**. Details present in the CLH report regarding exposure (including tested materials) and clinical data (including clinical history) are considered adequate for proper independent assessment.

Additional information on the cases:

	Patient 1	Patient 2	Patient 3
SIC acrylate containing agent	Newly made gel nails contaning HEMA and HPMA	Loctite 620; Loctite 290	Loctite 603 (HPMA 2-5 %)
SIC physical form	solid	viscous liquid	liquid
SIC control agent	lactose powder	saline spraying 1 ml	in-house control solution
SIC method of delivery	grinding structure nails	evaporating, heated 100°C	spreading on a cardboard
SIC amount used in one challenge	5 nails	2ml; 2ml	1 ml
SIC cumulative duration of acrylate challenge/ challenges (minutes)	20	30	30

UK SWORD:
We recognise that independent interpretation of this case is complicated by the lack of details. Please find below additional information on the sources of information and selection of cases:

Sources of information: Overview of work-related respiratory sensitisation attributed to 2-hydroxyethyl methacrylate (HEMA) or methacrylic acid monoester with propane-1,2-diol (HPMA) reported by chest physicians to the Surveillance of Work-Related and Occupational Respiratory Disease (SWORD 1989-2020), by occupational physicians to the Occupational Physicians Reporting Activity (OPRA 1996-2020), and by general

practitioners to The Health and Occupation Research network in General Practice (THOR-GP 2005-2020).

Selection of cases: All cases of work-related respiratory sensitisation whereby the suspected agent has been reported as HEMA or HPMA (substance code 951.9).

Please note that methodogy of this system is also summarised in the links below: https://osha.europa.eu/en/publications/methodologies-identify-work-related-diseases-review-sentinel-and-alert-approaches.

https://sites.manchester.ac.uk/thor/thor-uk-reporting-schemes/sword/

Even if there is no details, the cases reported in this system are assessed by chest physicians.

Concerning the disparity about the number of reported cases between FIOH and SWORD, the explanation can be due to the fact that the reporting is voluntary-based for SWORD in contrast to FIOH (reporting mechanism: obligatory).

Overall, data in humans are central part of hazard assessment within CLP Regulation. This is particularly the case for respiratory sensitization for which no validated experimental protocol is currently available. In that way, classification of this hazard class is based on human data. However, this hazard (considered of high priority) can be underestimated since human data are rarely published. Having that in mind, data from surveillance systems represent a very useful source of data. We recognize that these data can be associated with some uncertainties, in particular due to confidentiality issues. In contrast, we have to note that these data are collected by expert physicians who made the diagnosis and who assessed the link between the pathology and occupational exposure. This ensures confidence in the quality in the extracted data. Finally, it should be highlighted that these data reflect real situations that cannot be ignored.

RAC's response

RAC has taken note of the Industry's comments and the DS' response. In the opinion, RAC concludes that the overall evidence from human data on HPMA and supporting data from MMA is insufficient for the classification for respiratory sensitisation, as data are considered inconclusive.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2023	Germany		MemberState	3

Comment received

The assessment of the proposal for Resp. Sens. 1 is quite complex. Therefore, we would highly appreciate if the dossier submitter could respond to the following issues which emerged during our review of the proposal:

a) In the CLH report it is stated on page 15:

„Altogether, there were three patients with occupational asthma verified with positive SICs to HPMA containing products at FIOH during 2000-2018."

Is the strength of evidence for these three positive SIC cases considered to be as strong as for the six positive SIC cases related to MMA (methyl methacrylate, EC 201-297-1) or are they considered less convincing for the purpose of establishing a causal relationship

between exposure to HPMA and development of asthma within the meaning of the CLP Regulation? (In 2021, RAC agreed on the proposal Resp. Sens. 1 for MMA in its opinion and mainly based its conclusion on data related to individual cases with positive placebo-controlled SICs after exposure to MMA.)

b) The dossier submitter assumes that the metabolite methacrylic acid (EC 201-204-4) is the underlying cause for the development of respiratory sensitisation after exposure to MMA. Since HPMA is quickly hydrolysed to methacrylic acid, the dossier submitter concludes that, from a metabolic point of view, HPMA can be expected to cause respiratory sensitisation as well.
Interestingly, methacrylic acid has no harmonised classification for respiratory sensitisation but „only" a specific concentration limit for STOT SE 3 – H335 with C ≥ 1%.
We would appreciate if the dossier submitter could explain in more detail why methacrylic acid should be considered the underlying cause for respiratory sensitisation despite discrepancies between this assumption and the substance's harmonised classification („old" data? controlled exposure conditions?).

Dossier Submitter's Response

a) We consider that the strength of evidence of the HPMA cases is similar to the MMA cases. Indeed, the data are issued from the same institute (FIOH) using the same methodology. These data represent the basis of the MMA classification as Resp. Sens agreed by the RAC.

Please find below further details on the approach followed by the FIOH in response to our consultation to obtain information on occupational respiratory disease related to HPMA:
"*We recently published a European multicenter case series of 55 patients with occupational asthma due to various acrylates (Suojalehto et al. 2019), of which 27 were from the Finnish Institute of Occupational Health (FIOH). For the current purpose, we extracted the FIOH cases in which we have concluded HEMA and/or HPMA to be the main causative agent of asthma. During the 2000's, we have performed specific inhalation challenges (SIC) with products containing HEMA and/or HPMA to approximately 150 patients with suspicion of occupational asthma and/or rhinitis*".

In its opinion on MMA, RAC considered that the FIOH employed the state-of-the art methodology available for diagnostics of occupational asthma due to respiratory sensitisation. Some details on the methodology followed by the FIOH is described by the EU-OSHA [https://osha.europa.eu/en/publications/methodologies-identify-work-related-diseases-review-sentinel-and-alert-approaches]

We acknowledge that the number of cases is lower than for MMA. However, the number of cases is not a criteria for classification as Resp. Sens. In addition to the cases reported by the FIOH, the strength of evidence is reinforced by other cases reported in the literature with HPMA and by the scientifical knowledge on other methacrylates (in particular MMA) with regard to respiratory sensitisation.

See also response to comment 2.

b) There are numerous publications (e.g. references in the CLH report of HPMA) that report cases of respiratory sensitisation induced by methacrylates. This suggests a common mechanism of action. That's why one hypothesis is that this property is driven by the common metabolite. This hypothesis is also raised in the GMT 201 by ECHA (2021: https://echa.europa.eu/fr/assessment-regulatory-needs/-/dislist/details/0b0236e1855700f8).

Harmonised classification of methacrylic acid (MA) was set under Directive 67/548/EC. Thus, we have no information if Resp. Sens endpoint was assessed or not. No data is provided for this endpoint in the disseminated dossier in ECHA website. In the RAR (2002) on MA, the part related to sensitisation only covers dermal sensitisation with the conclusion that MA is not a skin sensitising substance. It is unknown if there was no data on respiratory sensitisation or if this endpoint was not assessed.

However, we recognise that there is no available data on methacrylic acid regarding respiratory sensitisation, and thus, we cannot distinguish if this hazard is due to the formation of this metabolite or to the parent itself. Analogue approach can be considered between HPMA and MMA (see response to comment 2).

RAC's response

RAC highlights in its opinion document that a robust link between HPMA as the solely-responsible agent and the observed cases of respiratory sensitisation in humans is lacking.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2023	Germany	Higher Methacrylate REACH Task Force	Industry or trade association	4

Comment received

The attached publication Pemberton et al. (2023) (Regulatory Toxicology and Pharmacology 141 (2023) 105404) "Challenges in the classification of chemical respiratory allergens based on human data: Case studies of 2-hydroxyethylmethacrylate (HEMA) and 2-hydroxypropylmethacrylate (HPMA)" and electronic appendix has been published online in the second half of the public comment period so that, very likely, the majority of stakeholders was not in the position to review its content in the context of the CLH proposal in that comment period. The article addresses relevant, and partially new aspects in the regulatory assessment of those clinical cases potentially related to HPMA that were also considered as relevant by the dossier submitter of the CLH proposal, plus additional cases. In brief, the authors concluded that none of the performed bronchial challenge tests were performed according to guidelines, and thus a formal weight of evidence assessment should be performed. None of the discussed cases provide sufficient evidence that HPMA is the causal agent for the observed respiratory effects.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Pemberton_2023_Challenges in the classification of chemical respiratory allergens_w_appendix.pdf

Dossier Submitter's Response

This paper written by some of the registrants analysed published data already described in the CLH report and thus raised similar issues discussed in comments above. Please see response to comment 2.

It was noted in this publication that "*The important conclusion that can be drawn from these analyses is that clinical studies, while providing an essential element of the diagnosis and management of occupational asthma, are usually not suited to the reliable identification of specific chemicals as respiratory allergens*".

So, authors concluded that the substance should not be classified for this endpoint. They refer to a system of classification proposed by Sadekar et al. 2021. This system of

classification has been developed by interested stakeholders but not discussed by international recognised organisms. It cannot replace the CLP criteria.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2023	Germany	Higher Methacrylates REACH Task Force	Industry or trade association	5
Comment received				
We agree with the CLH proposal for Eye Irritation (Cat 2, H319) as justified based on all available data. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-05-12_HPMA response_final.pdf				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2023	Germany		MemberState	6
Comment received				
DE CA supports the dossier submitter's proposal to classify HPMA as Eye Irrit. 2 – H319. In an in-vivo eye irritation study (Anonymous 1978), corneal opacity, conjunctival redness and conjunctival chemosis were observed after instillation of undiluted HPMA to the eyes of rabbits. All effects disappeared on day 4 of the study. Since the mean score (24, 48, and 72 hours) for corneal opacity reached „1" in 5/6 rabbits, classification for eye irritation in category 2 is warranted according to chapter 3.3.2.3.2.2 of the CLP Guidance (version 5.0).				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2023	Germany	Higher Methacrylates REACH Task Force	Industry or trade association	7
Comment received				
We do not agree with the CLH proposal for Skin Sensitisation (Cat 1, H317) based on the assessment in Appendix III of the attached response document; Category 1B is justified based on the assessment of all available data.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-05-12_HPMA response_final.pdf

Dossier Submitter's Response

Human data:

We thank you for tables 6 and 7 present in your attachment that summarize human data and can complete the CLH report. Based on the data presented in this table, we understand that you agree with the fact that there is a high frequency of occurrence of skin sensitisation as defined in table 3.2 of CLP guidance (> 100 cases and frequency of occurrence generally clearly above 2% in selected patients) (also reflected in your table 10).

Even if you claim that human diagnostic patch tests have several limitations, these studies are part of criteria for CLP Regulation. Regarding your reference to OECD guidance 497, the aim of this document is to define an integrated testing strategy based on *in vitro* / in silico assays and not call into question the relevance of human data for classification purpose.

In page 119 of your attached document, you consider that the total number of people working as dental technician can be used as suitable reference for cases reported by the IVDK database. On this basis, you consider that the response value would be 0.15%. We cannot agree with this approach that is not in line with CLP guidance and is clearly under-estimated (it cannot be excluded that some sensitised dental technicians do not consult occupational physician for diagnostic purpose).

Regarding exposure data, you conclude to relatively high exposure, that is consistent with our assessment (total score = 6).

In summary, you conclude to high frequency of occurrence of skin sensitisation and relatively high exposure, as also set in the CLH report. Based on the table 3.4 of the CLP guidance, this leads to classification as Skin Sens. Cat 1.

Defined approaches – *chemico / in vitro* studies

According to table 8, we note that at least one test was positive for each key event for HPMA (in particular with DPRA, keratinocyte activation assay and U937 cell line activation test). Positive results are mainly reported by Kolle (2013) and Nukada (2013).

You consider that the reporting of these results is often insufficient to allow sub-categorisation. In contrast, you conclude that HPMA should be classified as Skin Sens. 1B based on these studies considering the integrated approach set in the OECD guideline 497.

In section 7.5 of your attached document, you claim that key event 1 is unconclusive due to positive and negative results and that key events 2 and 3 are negative. In contrast, in table 8, positive results are noted with keratinocyte activation assay and U-Sens (with the statement "*no assessment of potency*").

Overall, you consider that a subcategorization toward 1B is warranted "*based on the non-human data that partially do not support classification at all (in-chemico, in-vitro, valid animal data) and that partially support classification as low-to-moderate potent sensitiser (defined approaches acc. OECD 497)*".

In vitro / in silico data can not be used to dismiss the evidence from human data (even if available from diagnostic studies and not HRIPT or HMT), in particular, considering the large dataset available for this substance, with results consistent among publications. Thus, based on human data and considering the CLP guidance, classification as Skin Sens. 1 is warranted.
RAC's response
RAC agrees with the DS' argumentation.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2023	Germany		MemberState	8
Comment received				
DE CA supports the dossier submitter's proposal to classify HPMA as Skin Sens. 1 – H317. Evidence for a skin sensitising potential of HPMA is provided by a number of case reports and clinical studies. The assignment to Category 1 (i.e. no sub-categorisation) seems appropriate taking into account the frequency of occurrence of skin sensitisation caused by HPMA and considerations related to the exposure to HPMA.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2023	Germany	Higher Methacrylates REACH Task Force	Industry or trade association	9
Comment received				
We do not agree with the CLH proposal for Respiratory Irritation (STOT-SE Cat 3, Resp. Tract, H335) for the reasons presented in Section 3 of the attached response document; the proposal is scientifically not justified based on a weight of evidence assessment of all available data (Appendix II, therein) ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-05-12_HPMA response_final.pdf				
Dossier Submitter's Response				
According to your attachment, one of the main argumentation against the proposed classification is based on the volatility of the substance. Based on the vapour pressure of HMPA of 11 Pa at 20 °C, the substance can not be considered as a substance with low volatility. Indeed, a substance with a vapour pressure between 5 and 1000 Pa is considered as a moderate volatility substance (https://www.inrs.fr/publications/bdd/solvants/aide-en-ligne.html). Moreover, a definition of a low volatility substance can be retrieved in Reach guidance R7a: *"[…] low volatility substances, which are defined as having vapour pressures < 1x10^{-5} kPa for indoor uses, and < 1x10^{-4} kPa for outdoor uses".*).				

With a boiling point of 213°C, HMPA also fullfills the criteria of a VOC (volatile organic compound) according to the definition of US EPA (a VOC is any organic compound having an initial boiling point less than or equal to 250° C measured at a standard atmospheric pressure of 101.3 kPa; cf. https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds)

Moreover, the volatility of the substance can also be supported by the exposure data you provided in your attachment (with detection and quantification of HPMA in the air).

Finally, the value of pressure vapour cannot be used as a stand alone argument to refute the proposed argumentation. For example, methacrylic acid has a similar pressure vapour (9.7 Pa) and is classified STOT SE 3 – H335 if concentration is above 1%.

You indicate that methacrylic acid is an impurity of HPMA at concentration below 1%. We agree that HPMA cannot be classified STOT SE 3 only based on the presence of this impurity. The proposed classification is based on a read across assessment with others volatile short methacrylates having a common breakdown product (methacrylic acid), all are classified as irritant for the respiratory tract.

In your assessment, you estimate the quantity of methacrylic acid needed to induce respiratory irritation. You conclude on a local NOAEL of 100 ppm from a 90-d study with methacrylic acid. However, EU RAR (2002) concluded to a much lower NOAEL : "*Due to the toxicity on the nasal epithelia in rats of all dose tested and in mice of the mid and high doses, the LOAEC was 20 ppm in rats (0.0714 mg/l) and NOAEC was 20 ppm in mice (0.0714 mg/l) for local effects on the respiratory tract*", based on another 90-day study (CIIT, 1984).

Regarding HPMA, you stated that *"no local respiratory effects have been reported in rat exposed to maximum technically achievable concentrations of HPMA in a poorly described, older subacute inhalation study".* Based on methodological deviations, it cannot be used to reach a conclusion of no respiratory effect. In addition, there is no relevant repeated dose toxicity study by inhalation available for HPMA despite the concern raised in our conclusion document (Anses, 2021) regarding respiratory irritation. https://echa.europa.eu/documents/10162/9f5b3eb0-0b0b-dffe-f494-abae562547fd. Thus, there is no relevant quantitative information with HPMA regarding local effect on respiratory tract to be compared with methacrylic acid.

Concerning your statement about interspecies difference regarding carboxyesterase activity in the olfactory epithelium, Lewis et al. 1994 compared localisation of carboxyesterase in rats, dogs and humans. They concluded that the distribution of carboxyesterase is very similar in healthy nasal mucosae accross the 3 species studies. *Lewis JL, et al. 1994. Comparative localization of carboxylesterase in F344 rat, Beagle dog, and human nasal tissue. The anatomical record. 239:55-64.*

Thus, your conclusion that « *it is implausible that relevant local concentrations in humans can be reached, even in combination with the few MAA molecules coming from the impurity*" is not sufficiently robust to rule out the hazard.

Finally, you state that "*In 1996, the EU Commission Working Group on the Classification and Labelling of Dangerous Substances discussed an appropriate harmonised classification of HPMA according to the earlier DSD 67/548/EEC. In the meeting dated April 17-19, 1996 it was decided not to classify HPMA with R37/ Irritating to the respiratory system*". However, you clearly mention that the reasons for non classification

are not documented and you assume that the low vapour pressure plays a significant role in the discussion. We are not aware of these discussions. Without any scientifical documentation, this cannot be used to call into question the classification proposed within CLP framework.
RAC's response
RAC has taken note of the comment. RAC considers the read across from the source substances as plausible, as all substances generate the same relevant metabolite, which is known for its corrosive properties at the olfactory mucosa. RAC further takes potential aerosol exposure into account as well.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2023	Germany		MemberState	10
Comment received				
DE CA supports the dossier submitter's proposal to classify HPMA as STOT SE 3 – H335. Due to missing substance-specific data the proposal is based on a read-across approach, performed with the volatile short-chain methacrylates MMA (methyl methacrylate, EC 201-297-1), EMA (ethyl methacrylate, EC 202-597-5), BMA (butyl methacrylate, EC 202-615-1) and methacrylic acid (EC 201-204-4) as source substances. MMA, EMA and BMA already have an harmonised classification for STOT SE 3 – H335. Methacrylic acid has a specific concentration limit for STOT SE 3 – H335 with C ≥ 1% and is also harmonised classified for Skin Corr. 1A. HPMA and the above mentioned source substances have in common that they are quickly metabolised by esterases to the main metabolite methacrylic acid which is a corrosive substance. Taking this intrinsic property into account, it is reasonable to assume that respiratory irritation is caused by this metabolite and that this effect will also occur when HPMA reaches the respiratory tract. Consideration of the physico-chemical properties (molecular weight: 144.17 g/mol; vapour pressure: 0.11 hPa at 20°C) and eye irritating potential of HPMA further supports this assumption.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. 2023-05-12_HPMA response_final.pdf [Please refer to comment No. 1, 2, 5, 7, 9]
2. Pemberton_2023_Challenges in the classification of chemical respiratory allergens_w_appendix.pdf [Please refer to comment No. 4]