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12/05/2023

[redacted]
Hazard & Risk Management
Product Stewardship

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Comments on the dossier proposing harmonised classification and labelling of 2-hydroxyethyl methacrylate; [HEMA]

Dear Sir or Madam,

The Higher Methacrylates REACH Task Force (HMRTF), representing BASF SE, Dow Europe GmbH, Evonik Operations GmbH, Mitsubishi Chemical Methacrylates and Röhm GmbH, welcomes the opportunity to submit comments on the CLH report on the proposal for harmonised classification and labelling for 2-hydroxyethyl methacrylate; [HEMA] (EC Number: 212-782-2; CAS Number: 868-77-9), Version number: V2, dated September 2022.

To aid the reader, the comments provided herein are structured such that general comments addressing formal deficiencies of the dossier are detailed initially. Technical comments provided for each hazard endpoint are then listed by citing the relevant section of the CLH dossier with our comments provided thereunder.

General comment

- We are concerned about the quality of the CLH proposal in connection with a number of formal deficiencies highlighted in Section 1 , 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.

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Registered Office is Darmstadt
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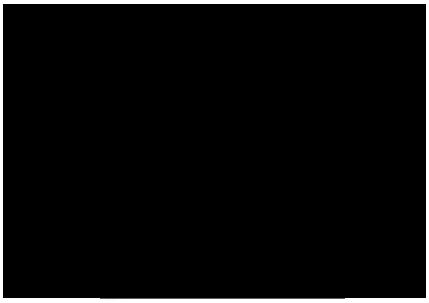
Comments on hazard classes

- We do not agree with the CLH proposal for Respiratory Sensitisation (Cat 1, H334) for the reasons presented in **Section 2**; the proposal is scientifically not justified based on a weight of evidence assessment of all available data (**Appendix II**);
- 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**; the proposal is scientifically not justified based on a weight of evidence assessment of all available data (**Appendix III**);
- We do not agree to the existing harmonised Annex VI classification[1] for Skin Irritation (Cat 2, H315); no classification is justified based on all available data (**Appendix IV)**;
- We agree to the existing harmonised Annex VI classification[1] for Skin Sensitisation (Cat 1, H317) as justified based on all available data (**Section 4**); and
- We agree to the existing harmonised Annex VI classification[1] for Eye Irritation (Cat 2, H319) as justified based on all available data.

Thank you in advance for your careful consideration of our comments.

Sincerely yours,

Director Hazard & Risk Management
Product Stewardship



Toxicologist (certified)
Product Stewardship

[1] Index 607-124-00-X

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Section 1. General comment: Concerns on the quality of the CLH proposal

In our review, we have noted a number of formal deficiencies relating to the overall dossier quality and approach taken.

1. The dossier does not contain all relevant information pertaining to the substance.

According to Part 2 in Annex VI of Regulation (EC) 1272/2008 'For all dossiers any relevant information from registration dossiers shall be considered and other available information may be used'.
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 dossier and that since Member States have access to all registration dossiers via REACH-IT, information contained in the registration dossiers must be considered when preparing the CLH dossier.
As registrants under REACH we have noted that the CLH dossier currently subject to public consultation refers to the registration dossier submitted in January 2019. At the time of listing of HEMA on the Registry of Intentions in 2021, the registration dossier had in fact been updated already in July 2019. Furthermore, in 2022 a subsequent registration dossier update was performed which included but was not limited to relevant information on the hazard classes currently subject to public consultation. The information provided in the updated registration dossier does not appear to have been addressed in the current CLH proposal and therefore does not form part of the current public consultation. Furthermore, since no valid reason is provided for not including this information, we must conclude that it has been overlooked or dismissed without due consideration.

2. Sections of the dossier lack transparency thereby precluding an independent assessment of the information provided.

According to the guidance on preparation of CLH dossiers, Version 2.0 2014, Section 5.4.1.1 'The CLH report should be a 'stand-alone' report since, in accordance with the legal requirements, it will be subject to a public consultation. This means that it should provide sufficient information to make an independent assessment of the physical, health and environmental hazards based on the information presented'.
In the dossier, information is provided from National Occupational Disease Databases. It is mentioned that different European countries were contacted by France in February 2021 in order to obtain additional human cases and that FIOH (Finnish Institute of Occupational Health), provided information on 8 cases over a period of 18 years where HEMA was suspected as being the causative agent of asthma. The report further states that "*Based on the exposure data, they believe that these patients had respiratory exposure predominantly to HEMA at*

work and that they were mainly exposed to HEMA also in the SIC. All of the products contained other methacrylates in addition to HEMA, and their effect cannot be excluded. However, as the other methacrylates listed in the SDS's (safety datasheet) were poorly volatile, they believe that they had a minor role in the patients' respiratory exposure and occupational asthma."

The dossier submitter has provided some limited information on these cases in the report. However, no further details are provided in the ANNEX and as such the cases cannot be independently assessed for relevance to the classification proposal. 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. Therefore, the evidence presented cannot be assessed for reliability and, as such, the available information is not sufficient for classification decision making.

3. Information provided is not consistent with the CLP regulation in that for certain hazard endpoints information on the substance itself is not provided.

In the CLP regulation, a clear distinction is made between classification of substances and classification of mixtures.

According to the CLP regulation Article 2(7), '*substance' means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used'*.

In preparing the dossier the submitter has proposed classification of HEMA as a respiratory sensitiser based entirely on evidence pertaining to exposure to mixtures containing moderate to minor fractions of HEMA. This is contrary to the CLP regulation that stipulates the aim of harmonised classification and labelling is to determine the intrinsic properties of the substances which must lead to their classification as hazardous products, so that the hazards of those substances (and of the mixtures containing them) can be correctly identified and notified. The CLP regulation does not clearly define the term 'intrinsic property' however in a recent Judgement of the General Court of the European Union (Cases T-279/20 and T-288/20) intrinsic hazard was interpreted as in its literal sense as referring to the 'properties which a substance has in and of itself'. That interpretation of the expression 'intrinsic properties' is consistent with the objectives and purpose of harmonised classification and labelling under Regulation No 1272/2008, from which it follows that only the properties specific to a substance must lead to its classification as a hazardous product, so that the hazard associated with such properties can be correctly identified and notified.

By proposing classification of HEMA as a respiratory sensitiser based on clinical evidence involving the testing of complex mixtures, which contained other known skin sensitisers and respiratory irritants, the dossier submitter is failing to provide adequate, reliable and relevant information as required by the regulation. Therefore, any decision on classification cannot be

supported by the information provided in the CLH report and any decision to classify based on the evidence provided would be considered a manifest error of assessment.

4. The dossier contains multiple statements of conjecture and assumptions with little evidence to support such claims.

The dossier presents, on several occasions, statements which have no recognisable scientific basis. Hypothetical modes of action (hMOAs), such as metabolism of the parent ester to methacrylic acid as being a determinant step in the acquisition of respiratory sensitization has no basis for regulatory decision making unless this can be adequately justified. At the time of writing, literature searches reveal no scientific publications exist that refer to such a MOA and there are no documented cases of asthma associated with occupational exposure to methacrylic acid.

Furthermore, the dossier submitter states, '*it is possible that HEMA occupational asthma cases are underdiagnosed and are therefore also under-reported*'. Again, this is not supported by any evidence presented in the dossier and is merely speculation not suitable for decisions on classification. It is pertinent to note that the dossier submitter themselves consider a '*conclusion on the causal relationship between these symptoms and HEMA specifically is somewhat difficult to reach since these patients are exposed to various methacrylates*'. It should be noted that these patients were also exposed to other dermally sensitising substances that were not methacrylates. Furthermore, although it is recognised that skin exposure to known chemical respiratory allergens can cause allergic sensitisation of the respiratory tract, this does not imply that skin sensitisers per se are able to cause respiratory sensitisation. There are many hundred, and possibly thousands, of chemicals that have some potential to cause skin sensitization, but those with a proven ability to cause sensitisation of the respiratory tract are far fewer in number, and probably total no more than 50 in number – and possibly less. Such unsubstantiated statements in the dossier do not add further weight or justification to the classification decision and as such should be considered as purely speculative.

Section 2. Respiratory Sensitisation (Cat 1, H334)

1. Executive summary

HMRTF believe that the evidence presented in the proposal is insufficient for classification of HEMA as a respiratory sensitizer (Cat 1, H334) based on the following main points, and is scientifically not justified based on a weight-of-evidence assessment of all the available data (see Appendix II)

The proposal is based upon clinical evidence in individuals exposed in the workplace and in Specific Inhalation Challenge (SIC) tests made with complex mixtures (including other sensitizers and irritants) thus precluding a causal relationship between possible exposure to HEMA and the development of OA to be drawn with sufficient confidence.

Furthermore, the supporting evidence shows that information on the chemical composition of these complex mixtures used in the SIC is incomplete, or in some cases incorrectly reported and referenced.

The guidance on the application of the CLP criteria under §1.1.3. Hazard classification, states "*chapters R.7a/b/c of the same Guidance provide more detailed information and endpoint-specific guidance*". In this respect, R.7a: Endpoint specific guidance §3.10.12. Human data on respiratory sensitisation states, "*For evaluation purposes, existing human experience data for respiratory sensitisation*" .... that "*substance or preparation studied should be the main, and ideally, the only substance or preparation present which may possess the hazard under investigation*" (emphasis added). The product combinations used in the SIC tests do not contain HEMA as the sole, or main component in these products. Furthermore, where HEMA is present in a product used in a SIC this is in the presence of other known skin sensitising and irritant chemicals preventing the attribution of the observed SIC response to any single substance, not least HEMA. As such, the clinical evidence relied upon does not meet the CLP requirements under §1.1.3. that testing should be conducted with "*the substance as the only or main component*".

Guidance on the Application of CLP Criteria (ECHA 2017) § 3.4.2.1.3.2 in referring to the potential of a substance to cause sensitisation by inhalation in humans, states that "*if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyper reactivity, they should not be considered respiratory sensitisers*." In the clinical cases where bronchial hyper reactivity data was reported, non-specific bronchial hyperresponsiveness (NSBHR) was observed for the majority of cases, where documented, i.e. increased airway hyperreactivity as a result of exposure to a non-specific stimulus. For those cases for which bronchial hyperreactivity data was not reported, NSHBR cannot be excluded with any confidence. Therefore, NSBHR cannot be excluded with sufficient confidence for any of the clinical case studies cited and contradictory to the CLP requirement, a specific, intrinsic hazard of causing respiratory sensitisation by the substance HEMA has not been demonstrated.

SIC testing was not conducted according to guideline, i.e., exposures were not controlled so as to mimic workplace conditions as recommended in the consensus statement made by the

European Respiratory Society (ERS) Task Force on best practices for the conduct of SIC tests (Vandenplas et al., 2014; 2016).
The claim of chemical reactivity of methacrylates and HEMA as Michael addition donors and this property used in QSARs to predict the potential of HEMA to be a respiratory sensitizer has not been validated for any established respiratory sensitiser beyond those substances comprising the learning set for these models and therefore the predictive value of these QSARs has not been established. Furthermore, recent literature indicates that while Michael addition is associated skin sensitisation (Dearden et al., 2015; OECD, 2021) it is not associated with respiratory sensitisers (Ponder et al. 2022).
The read-across proposed, via a hypothesized mode of action, i.e. hydrolysis to a common metabolite is not evidenced by established science since no published literature can be found to support such a hypothesis. Furthermore, this appears to be contradictory to the claim that it is the Michael addition reactivity of the parent ester that is responsible for the allergenicity of these chemicals.

1.1. Introduction

The clinical data in the CLH report comprises four publications (consisting of 14 clinical case studies) and so far unpublished data from FIOH (eight case descriptions) that is at best sparse and of low relevance to HEMA for reasons as discussed in the general comments in **Section 1.** Regarding the case studies, the composition details of the products involved in the workplaces and in SIC, when performed, in these case studies is incomplete. This weakness is exacerbated in the proposal with selective extraction of details to emphasise involvement of HEMA. Further investigation by HMRTF member companies reveals a very different picture with much more complex compositions with a set of other chemicals that could potentially also cause the seen effects: While HEMA was typically present as by-component in the dental and the cosmetic products that were generally tested in product combinations, this was alongside several other contact sensitisers. Therefore, the SIC tests do not meet the CLP criteria as being the main or only substance used in the SIC, so any claim of causality cannot be substantiated - , something acknowledged by the Authors of the CLH proposal themselves (see **2.3 Specific comments on the text of the CLH proposal**).
Of the eight cases reported by FIOH between 2000-2018 with HEMA and claimed as the "possible causative agent", one SIC was conducted with polymer dust not HEMA, while the other seven SIC were conducted with complex mixtures containing irritant and skin sensitising chemicals where HEMA was a co-component and therefore attributability cannot be substantiated.
Overall, the clinical evidence presented in the proposal is at best weak for HEMA.
The proposal further draws upon multiple lines of evidence in a non-formalised weight of evidence argument. Underpinning this approach is a hypothesised mode of action (hMOA) of methacrylates to cause respiratory allergy through metabolism to the common acid metabolite (methacrylic acid) and its retained acryl group. This hMOA is not established according to REACH guidance such as the RAAF, is contradictory to peer reviewed literature

and contradicts the author's own statements in section 10.9 in the CLH proposal (e.g. Table 16, page 29). Contrary to that being claimed, current scientific understanding is that such metabolism of methacrylate esters is a detoxification and not an activation process for sensitisation.

The proposal draws analogy to HPMA, the subject of another CLH proposal so comments on this will not be made in this response. Please refer to the HMRTF comments on HPMA for further details. The proposal also draws analogy to MMA and makes the claim that this is a Resp. Sens. Cat 1. substance agreed at RAC in 2021. 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.

This line of argument is further corroborated with unsubstantiated claims that HEMA induced asthma is generally underdiagnosed and underreported, as explanation for the very low numbers of potential asthma cases. Given the fact that HEMA and other methacrylates are well known weak skin sensitisers with their own standard prick test series, and that one clinical centre alone has performed approx. 150 SIC tests with products containing HPMA/ HEMA in suspected OA patients[2], this claim of under reporting appears highly speculative and merely an attempt to compensate for the weakness of the individual lines of evidence and to justify classification. We also note that the CLH report did not scrutinize the fact that almost all reported asthma cases were originating from one clinical centre where, based on our investigations, SIC tests were performed typically with 10-20-fold excess of test item and thus were not conducted in accordance with accepted clinical guidelines.

Overall, HMRTF considers that the incomplete and in some cases incorrect information and unsubstantiated claims presented in the proposal are insufficient to meet CLP criteria which calls for *"evidence in humans that the substance can lead to specific respiratory hypersensitivity".*

Detailed comments on the proposal are provided below under 3 sub-sections; 2.) Substance identity; 3.) Clinical evidence, and 4.) Grouping and use of read across. Comments are numbered and referenced by page and line number in the proposal to allow attribution. Key information per sub-section were written in bold.

[2] Of those 150 SIC tests, around 140 gave negative results, as can be concluded from information in the CLH proposal, p 15

2. Test material: Comments relating to the substances involved in the cited clinical case studies

2.1. CLP requirements

Classification according to CLP is based on intrinsic hazards. In this context, guidance on the Application of the CLP Criteria state under Annex I: §3.4.2.1.2.1. that in the case of classification for respiratory sensitisation that "*Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience*", and under §3.4.2.1.2.3 (b) that this could include "*data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction*" (emphasis added).
Additionally, CLP criteria under §1.1.3. Hazard classification, state that "*chapters R.7a/b/c of the same Guidance provide more detailed information and endpoint-specific guidance*".
R.7a: Endpoint specific guidance §3.10.12. Human data on respiratory sensitisation states, that "*For evaluation purposes, existing human experience data for respiratory sensitisation*" .... that "*substance or preparation studied (should be the main, and ideally, the only substance or preparation present which may possess the hazard under investigation*" (emphasis added) and that data should contain sufficient information about "*the extent of exposure (magnitude, frequency and duration)*".

2.2. Summary on test material

The clinical case studies relied upon in the CLH proposal are insufficient to reliably identify the causative chemical allergen(s) responsible for acquisition, and/or elicitation of the asthma both in the workplace and in SIC, where performed. This is acknowledged by the Authors of the CLH proposal themselves.
In the case of the workplace environment that can be anticipated for the individuals reported as case studies there is use of, and potential for exposure to, a wide variety of chemical-based products. The case studies include only very limited or no information about the chemical composition of these products and the relative levels of exposure in the workplace. In the case of SIC tests, despite these being "controlled", they were performed with proprietary products that are complex mixtures of chemicals, the composition of which are not fully disclosed and incompletely reported. Where available the data cited in the publications and summarised in the proposal does not confirm that the chemical under proposal is the *"main, and ideally, the only substance or preparation present which may possess the hazard under investigation*". These factors prohibit identification of the causative agent(s) both in the workplace and in SIC tests.

2.3. Specific comments on the text of the CLH proposal

For the majority of the few clinical cases listed, information on the products used in the respective SIC test is available. The common denominator for all such information is that these

products are complex mixtures which compositions are incompletely documented in the report and the underlaying publications. Furthermore, several mixed products were frequently tested together in one SIC so that even at the product level, a causal relationship between effect and HEMA is impossible to identify with sufficient confidence.

Products tested in SIC tests

Comment 1: on Table 9 (pages 13-15), Table 10 (page 17) and Table 11 (pages 21-22), and related text passages between pages 16 and 20.

These tables document the reported product information relied upon in the CLH proposal of cases, as from scientific literature in general (Table 9), from Piirilä et al., 1998 (Table 10) or from the Finnish Institute of Occupational Health, FIOH (Table 11).

HMRTF response: The details on tested products in these tables and text passages are those identified as supporting the classification proposal. In all cases, details are available that inform on aspects that do not support classification and therefore the report appears selective and not balanced in its assessment (see comments 3-11). In the assessment of the CLH proposal all relevant product details should be considered to understand the plausibility of a causal relation between the substance and the observed effect, ideally in a formal weight-of-evidence framework as required under R.7a: Endpoint specific guidance §3.10.12.

For overview reasons, the entirely available information on the respective test products per case is compiled in the **Appendix I-Table 1**; the cases are clustered in this table by industry sector for improved readability. The case numbers in the following text refer to the numbers in that **Appendix I-Table 1**.

Comment 2 on the **ambiguity/ uncertainty about the causative substance raised by the DS itself.**

In various text passages, the report acknowledges the above described uncertainty about the causal relationship on substance level: On page 16, paragraph 4, the report stated that "***HEMA cannot be clearly identified as the causative agent***. *In particular [since prick tests were negative but also] because patients used different products containing various methacrylates (and* ***possibly methacrylates as contaminants or impurities not declared in the safety datasheet****).*" Accordingly, the report partially refers to the term "*causative products*", not causative substances (e.g. page 17, paragraph 1). The report addresses the identified ambiguity on substance level with the statements "*To ascertain what exact component is causing the asthmatic reactions, provocations with all substances contained in the product ought to be undertaken. This was not practicable in this series of clinical challenge tests*" (page 17, paragraph 2), "*To ascertain what exact component is causing the asthmatic reactions, provocations with all individual substances contained in the products ought to be undertaken. This was not done here*" (page 19, paragraph 1), or "*All of the products contained other methacrylates in addition to HEMA, and their effect cannot be excluded*" (page 20, last paragraph). This uncertainty is neither documented nor discussed in the "Conclusions" section on this endpoint (page 25) or the chapter "*10.4.2 Comparison with CLP Criteria*" (pages 25/26).

HMRTF comment: HMRTF fully supports the considerations in the report that HEMA cannot be clearly identified as the causative agent in the SIC tests due to combined product testing in the majority of SIC tests, with many products representing complex mixtures of partially unknown composition. Such uncertainty must be considered when assessing the strength of the causal relationship between effects and exposure, and subsequently, the resulting evidence against criteria to ensure a robust hazard evaluation. Given the complexity and partial uncertainty on the composition of the test items, there is a low level of confidence that this data support the classification of the substance.

Dental cases

Comment 3: on several dental cases that were challenged with Scotchbond™ Multipurpose primer and/ or adhesive products described as follows:

- **Cases 2, 3, 4, 5 and 6** (i.e. patients 3, 7, 9, 11 and 12 in Piirilä et al. 1998) were challenged with Scotchbond™ Multipurpose primer and Multipurpose adhesive; and
- **Case 12** (FIOH patient 5) was challenged only with the Scotchbond™ Multipurpose adhesive. For the primer, HEMA was reported as sole component with 40% HEMA, while main components of the adhesive were reported as being bis-GMA (62%) and HEMA (37%).
- **Case 7** (Lindström et al. 2002) was challenged with an unspecified Scotchbond™ adhesive and a Scotchbond™ primer[3], and the reported bis-GMA and HEMA concentrations indicate the product as being the Scotchbond™ Multipurpose adhesive and primer system.
- No test product information on SDS level is available for **Cases 13 & 14** (FIOH patients 6 and 7) but an assumption was made by the DS that the patient were challenged to Scotchbond™ primer and adhesive (case 13) or only to the adhesive (case 14).

HMRTF response: The review of the reported composition and the available information on the products (see Appendix I-Table 1 for details) basically confirm the reported information that HEMA is neither the sole nor the main component of the SIC test item, especially not in the Multipurpose adhesive. The primer contains also a copolymer that is frequently not reported. Beside bis-GMA as the confirmed main component, a further substance may be part of the adhesive (ethyl 4-dimethylaminobenzoate, EDMAB) <= 0.5% (3M, 2022).

Comment 4: on **Case 8** (i.e. FIOH patient 1) that was challenged with **Scotchbond™ Universal adhesive**. As main components, bis-GMA (60-70%) and HEMA (30-40%) were reported.

HMRTF comment: The supplier SDS reveals a different, much more complex composition of this product, with 15-25% Bis-GMA, 10-15% HEMA, 5-15% decamethylene dimethacrylate, 10-20% 2-propenoic acid 2-methyl reaction products with 1,10 decanediol and phosphorous oxide, 10-15% ethanol, 10-15% water, 7-13% silane treated silica, 1-5% acrylic acid and itaconic acid copolymer, <2% camphorquinone, <2% DMAEMA, 2% dimethylaminobenzoate and <0.5%

[3] Primer tested in one of two SIC tests

2,6-di-tert-butyl-p-cresol (SDS 3M, 2015; see also **Appendix I-Table 1** for details). Despite the inconsistencies in the reported percentages of Bis-GMA and HEMA, both data sources basically confirm that HEMA is neither the sole nor the main component of the SIC test item.

Comment 5: on **Case 1** (i.e. patient 1 in Piirilä) that was challenged with Scotchbond™ "a" and **Rely-a-bond paste**. Scotchbond™ "a" is considered as abbreviation for an adhesive, either "Multipurpose" or "Universal". As components, bis-GMA and HEMA were reported without concentrations.
HMRTF comment: For compositions of Scotchbond™ "adhesive types "Multipurpose" and "Universal", see comments 2 & 3 above. Rely-a-Bond® represents a dental kit to eliminate bonding failures. The kit is composed of the paste, primers and an etchant. The paste has a declared composition according the SDS of other multifunctional methacrylates and Benzoyl Peroxide with at least 60% undeclared components (see **Appendix I-Table 1** for details). Although it is not clear from Piirilä et al. (1998) whether a primer was used in the SIC test, the primer and the etchant must have been used routinely in the workplace for the product to work, see below. HEMA is not present in the paste, and neither the sole nor the main component of the adhesive in this SIC test.

Comment 6: on **Case 9** (i.e. FIOH patient 2) that was challenged with Scotchbond™ **Universal primer**, Scotchbond adhesive and a product reported as "**Silyx restorative**". Following components were reported: 35-40% HEMA, a "Light-hardened polymer" without CAS number 10-15%, and, for the "Silyx restorative", Bis-GMA and TEGDMA 30-80%.
HMRTF comment: Information on the composition of the Universal primer was not identified, so analogy is made to Multipurpose Primer that contains identical levels of HEMA as reported, and also a copolymer (10-20% acrylic and itaconic acid copolymer). For compositions of Scotchbond™ "adhesive types "Multipurpose" and "Universal", see comments 2 & 3 above. Apparently, the Bis-GMA and HEMA concentrations have not been reported. Information on the composition of the "Silyx restorative" was not identified during the public comment period, so the reported information can neither be supported nor amended. Despite these ambiguities on exact composition levels for all three components, it is obvious that HEMA is neither the sole nor the main component of the SIC test items.

Comment 7: on **Case 11** (i.e. FIOH patient 4) that was reported to be challenged with Scotchbond™ dental adhesive with component information on HEMA (35-40%) and again a "Light-hardened polymer" without CAS number (10-15%).
HMRTF comment: The reported information appears inconsistent: information on the composition indicate a challenge test with a primer rather than with an adhesive. In both cases, HEMA is neither the sole nor the main component of the SIC test items. The imprecise reporting lowers the reliability of this case.

Comment 8: on **Case 10** (i.e. FIOH patient 3) was reported to be challenged with a "**One step dental restorative material**" with a very complex composition consisting of at least two primer

parts and including substances that were not named in products of other cases, i.e. biphenylmethacrylate 15-40/ 8-30 % and glycidyl methacrylate 1-5 %. HEMA is reported as component in one of the primer parts in a concentration range of 8-30%.

HMRTF comment: The product composition is weakly described, with the main parts being completely unknown. Furthermore, the product is not sufficiently described for further independent research. Overall, it is obvious that HEMA is neither the sole nor the main component of the SIC test items.

Cosmetic

Comment 9: on two cosmetician cases where the **SIC tests were performed during sculpturing** the artificial nails, described as follows:

- **Case 16** (i.e. patient 2 in Sauni et al. 2008) that was reported to be challenged with a bonding agent (containing 7.5% HEMA) and a sculpture resin, containing 42% bis-GMA and < 0.1% HEMA.
- **Case 19** (i.e. FIOH patient 8) was reported to be challenged with a combination of three gel nail products of the company LCN in one SIC test (see **Appendix I-Table 1** for details). HEMA is neither contained in the LCN sculpture resin nor in the LCN bonding agent while it is contained in the LCN sealant at 15-20%.

HMRTF comment: The FIOH patient, case 19, was challenged during the SIC test while "*grinding of newly hardened nails*" so the SIC was performed with polymer dust and not liquid nail product. In this regard, the authors state that the HEMA content of hardened material was "very low" so the positive SIC response was to polymer dust and not the substance HEMA so a causal link to HEMA cannot be claimed. Furthermore, there are clear indications of comparable dust exposure during the SIC test of Case 16. This case is referenced in the revised Handbook for SIC procedures (Suojalehto et al. 2019) as standard SIC procedure for artificial nail products at FIOH, again as "*grinding the newly prepared nails*". The relevance of nail dust exposure for OA has been described by Vaccaro et al. (2014) where sculptured nail material was identified as most potent skin sensitising agent in patch tests in nail art operator and where the respiratory "*symptoms occurred when she was using a nail drill machine to remove the preexisting nail decorations"*.

For both cases, the product compositions are insufficiently described. Given the publicly known wide variety of product types with their heterogeneous compositions, and the vague description in the paper it is impossible to conclude for case 16 on any relevance of this case to HEMA, other than that it is very likely that the respective (combination of) test item(s) will not contain HEMA as sole or main component.

Regarding case 19, the claim that some components of the three artificial nail products contained HEMA so was the cause of the development of asthma in this case can also not be substantiated. During the public consultation period, HMRTF contacted the manufacturer LCN who confirmed the presence of HEMA in the sculpture (5-10%w/w) along with four other acrylates and other components; the presence of HEMA (10-25%w/w) in the bonder; and no presence of HEMA in the sealant. This clearly indicates inaccuracies in reporting of product composition involved in this publication and that HEMA was not a main component in any of

the products used in the workplace of this individual. Since similar inaccuracies were involved in the reporting of product information for the Sauni case, the use of gel nail materials and cyanoacrylate adhesives in this sector should raise serious doubts as to the level of confidence that can be attributed to claims of causation by any specific chemical.

Comment 10: on **Case 17** (i.e. patient 1 in Moulin et al. 2009) that was reported to be challenged with nail prosthesis material with "new solvents and resins". On the substance level, the publication states that the SIC test was performed with "HEMA without hardener". Comparably, **Case 18** (i.e. patient 2 in Moulin et al. 2009) was reported to be challenged with nail prosthesis material containing HEMA.
HMRTF comment: For both cases, the product compositions are insufficiently and misleadingly described. From information of case 17 it can be concluded that several solvents and resins were part of the composition that are not reported in the publication. It is thus questionable whether HEMA is the sole component of the SIC test items as reported.

Comment 11: on **Case 15** (i.e. patient 1 in Sauni et al. 2008) for which no information is given on the SIC test item.
HMRTF comment: Given the publicly known wide variety of product types with their heterogeneous compositions it is impossible to conclude on any relation of this case to HEMA, other than that it is very likely that the respective (combination of) test item(s) will not contain HEMA as sole or main component.

2.4. HMRTF section summary

2.4.1. Products implicated in reported SIC tests

HMRTF recognises that there is no evidence of asthma specifically linked to HEMA from national occupational health databases of two large European countries (GB, F) over a large time period. In contrast, with the exception of the two cases of Moulin, all clinical cases are contributed by FIOH. This apparent disparity in incidence despite comparable or higher numbers of employees in these sectors remains unexplained. It could reflect a true lower prevalence in these countries, lack of reporting, or a perceived inability to assign causality to a specific substance(s) within the wide range of chemical-based products used in these sectors. To further investigate this there is an urgent need to comprehensively document these FIOH clinical case reports and make them available for independent assessment by stakeholders.
Presently there is insufficient evidence to implicate a single substance(s) in the development of asthma in any of these clinical cases. In no case reported was a comprehensive assessment of exposure in the workplace completed. The apparent attribution to methacrylates and HEMA was made upon the basis of an a priori assumption of causality and the result of SIC conducted with complex mixtures. This is true for cases from both the dental and cosmetic sector.
Several potential cases were identified from the **dental sector**. Dentists and dental nurses/ assistants, were frequently challenged with 2-part dental resins systems, a primer and an adhesive, which are typical product systems in these workplaces. These product systems are

complex mixtures containing multiple reactive chemicals, and impurities, that are irritating and skin sensitising so that responses cannot be ascribed to a single substance with any certainty of a causal link.

The same is true for products used in the **cosmetic sector** where the information level on the product composition of artificial nails is generally even lower than in the dental sector. Moreover, for all five reported cases confounding exposure to either other sensitising substances (cyanoacrylates) or asthmagenic nail dust must be considered as alternative plausible causative agents in a weight of evidence assessment.

Furthermore, sector-overarching research on actual compositions of mixed products containing (meth)acrylic esters revealed that declarations on SDSs consistently do not report all components of the respective mixtures (Henriks-Eckerman & Kanerva, 1997), at least in a time period approx. two decades before. In this work, dental products, glues, paints and lacquers were investigated. This misinformation in (earlier) SDSs hinders the exclusion of co-exposure to other substances that are equally or more likely to be responsible for the observed health effects.

Overall, the available SIC tests do not provide sufficient evidence that HEMA is the causative agent in these studies as required by CLP criteria ("*The evidence referred to above could be: (a) … data from appropriate lung function tests related to exposure to the substance*"[4]). The CLH report acknowledged this weakness at several text passages but missed to reflect it in the concluding chapters. From that perspective alone the conclusion section is incomplete.

2.4.2. Other products and substances of relevance per industry sector

a. The dental and cosmetic sectors have complex workplace atmospheres with confounding chemicals

CLP criteria requiring the investigation of a causal relationship between a specific substance and the observed effects indirectly necessitate the investigation of other substances to that the patients were frequently exposed during work ("*Clinical history shall include both medical and occupational history to determine a relationship between* ***exposure to a specific substance*** *and development of respiratory hypersensitivity."*[5]). Such sector-specific investigation on potential confounding substances is missing in the CLH report.

HMRTF comment: Some industry sectors giving rise to asthma cases potentially related to HEMA, i.e. dental and cosmetic, are well recognised in public literature as workplaces with complex atmosphere. The breathing air frequently contains various hazardous VOCs that can cause respiratory effects including OA (e.g. dental: Lyapina et al., 2016; Piirilä, et al., 2002; Hong et al. 2015, Stoeva 2021; cosmetic: Henriks-Eckerman & Korva, 2012; Ceballos et al., 2019; Heaton et al., 2019; Zhong et al., 2019).

[4] CLP, § 3.4.2.1.2.3.
[5] CLP, § 3.4.2.1.2.4.

Dental sector

In dental laboratories formulations of monomers and methacrylic polymers are used for restorative purposes, e.g. to construct orthodontic components, fillings and inlays. Exposure relevant tasks like mixing, filling and polymerizing with liquid methacrylate esters may take place several times for a short duration or regularly over a longer period, both over the whole shift. During these tasks, workers are generally exposed to a broad cocktail of chemicals (solvents, acrylates/ methacrylates) and dusty materials (see BG ETEMs homepage on dental labs[6]). The last can be grouped to inorganic dusts of plaster, non-precious and precious metals (chrome, nickel, cobalt, gold, palladium etc.) ceramics (amorphous and crystalline silica, quartz, cristobalite etc.) and rare metal oxides (zirconium dioxide, hafnium and yttrium oxides etc.) and organic dusts (PMMA and acrylic polymers). Individual exposure profiles may vary depending on specific tasks or job profiles.

Potentially relevant co-exposure in this sector, namely in the work field of dental nurses and dentists handling composite products, is related to Glutaral or Glutaraldehyde, GA (CAS# 111-30-8). GA is an acknowledged occupational respiratory sensitizer with a vapour pressure of 20 hPa at 20 °C. GA is typically used as disinfectant in the clinical and dental sector and it has been used as a component in primers in some bonding systems with typical concentrations between <1 and 5% (Kanerva et al. 1994) and used for its desensitizing and antimicrobial properties and also for improving physical properties of the bonding systems.

GA can cause late and dual asthmatic responses in SIC tests (Di Stefano et al. 1999) and was identified as significant causal agent for OA in the health care sectors (Walters et al. 2013).

Cosmetic sector

Artificial nails encompass a wide range of product types including Acrylic, Gel, Wraps, etc. that are either formed in place or adhered with cyanoacrylate adhesive or cements. “Acrylic” and “Gel” nails are composed primarily of “acrylic” polymers and are made by reacting together monomers with polymers. While these artificial nails are colloquially called “acrylic” they are actually made predominantly of methacrylic monomers and polymers. True “Acrylic” nails were historically made from methyl methacrylate (MMA) monomer and PMMA polymer but nowadays commonly use ethyl methacrylate monomer in place of MMA and are air dried. “Gel” nails, in contrast use higher methacrylate ester monomers and PMMA polymer and are usually cured with ultraviolet light (UV) or a light emitting diode (LED). In the case of both technologies, when the reaction is completed, traces of residual monomer(s) are likely to remain within the polymer matrix. Beside the exposure to vapours of low molecular weight substances, dust exposure to polymer dust is likely when artificial nails are grinded during sculpturing (see Sauni et 2008, above).

Overall, both described sectors (dental and cosmetic) with asthma cases that are potentially proposed as being linked with HEMA can be commonly described as workplaces with a wide

[6] https://sicheres-dentallabor.bgetem.de/taetigkeiten/arbeiten-mit-gefahrstoffen

variety of inorganic and organic substances that can cause the acquisition or elicitation of OA or other respiratory diseases. It is further acknowledged that in both sectors, industrial hygiene practices (PPE and local extraction ventilation)safety measures are partially or not completely consistently established implemented so that excessive exposure cannot be ruled out, as described in the clinical case described by Vaccaro and coworkers (2014) as example. This significant co-exposure should be considered as a potential confounding factor for the clinical history of these patients. Thus, co-exposure further reduces the already low level of confidence that asthma cases from these sectors support the classification of the substance are due to HEMA.

3. Clinical evidence

3.1. CLP requirements

Guidance on the Application of the CLP Criteria state under Annex I: §3.4.2.1.2.1. that "*Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience*". Further, under Annex I: §3.4.2.1.2.3. states that "*The evidence referred to above could be:*" ... *"(a) clinical history and data from appropriate lung function tests related to exposure to the substance*" ..... and ... "*(b) data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction*". Regarding SIC, the guidance states under Annex I: §3.4.2.1.2.5. that "*The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own*".
Although CLP and related guidance do not define "accepted guidelines for the determination of a specific hypersensitivity reaction" a consensus statement was made by the European Respiratory Society (ERS) Task Force (Vandenplas et al., 2014; 2016) and can act as reference guidance in this context. The consensus statement prescribed best practices for conducting SIC and correspond closely to the data requirements outlined in CLP and REACH guidance.

3.2. Summary on clinical evidence

CLP criteria recognises the primary importance of human experience for classification for respiratory sensitisation since, as the proposal recognises, there is no appropriate animal test to conclude on respiratory sensitisation. The available clinical data potentially related to HEMA include four published papers containing 11 clinical cases[7] and eight cases from FIOH. In all cases where SIC had been conducted the available details demonstrate the studies did not conform to essential key requirements prescribed in the ERS consensus statement and CLP and REACH guidance. Consequently, they cannot be considered as having been conducted according to "*accepted guidelines for the determination of a specific hypersensitivity reaction*".
The ERS statement states "The basic principle of SIC is to deliver the suspected occupational agent <u>in the same conditions as those that prevail in the workplace</u> in terms of its physical characteristics (i.e. gas, fumes, liquid or particles aerosols) and its chemical form (e.g. monomer versus polymer), preferably on the basis of a detailed workplace exposure assessment" (emphasis added) and that "The concentration of the occupational agent in the air during SIC should be based on the estimated level in the workplace but should not exceed relevant occupational exposure limits (OEL). Ideally, the concentration and, when relevant, particle size should be continuously monitored during SIC and the concentration kept below the OEL in order to avoid irritant responses and/or severe asthmatic reactions".

[7] Piirilä et al. 1998: 6 cases; Lindström et al. 2002: 1 case; Sauni et al. 2008: 2 cases, Moulin et al. 2009: 2 cases

In the case of the SIC test data relied upon in the CLH proposal both requirements were not met. From the limited available data, a "*detailed workplace exposure assessment*" appears not to have been done in any case study.

a) **As per the ERS guideline, the quantities of test product used in the SIC tests referenced in the CLH dossier appear to have been increased stepwise until a positive response was obtained. Consequently, exposure levels far in excess of those used in the workplace were used for the SIC tests which, combined with an absence of exposure monitoring, makes it not possible to determine if exposure levels exceeded the OEL and therefore it is not possible to exclude the likelihood of irritant reactions. Indeed, where no SIC response was observed, even when challenged with 10x the quantity typically used in the workplace as seen in the dental case described by Lindström and coworkers (2002), this can be interpreted as clear evidence that the products used were not the cause of the occupational symptoms, and that non-specific irritation not only could not be excluded at the higher exposure levels but was likely. Information from the other published cases from the dental sector in Finland, as described by Piirilä and coworkers (1998; cases #1-6 in Appendix I-Table 1), indicate that SIC tests were typically performed with 20 to 40 drops of test materials. Based on the initial workplace assessment that HMRTF performed and that was confirmed by the manufacturer of the dental products (3M, 2012[8]; 3M, 2023), these amounts used in SIC tests exceeds 10-20 times the standard amounts used in the workplace. In the other seven cases reported from FIOH (cases #8-14 in Appendix I-Table 1), the amount of test item in the respective SIC tests has not been described. However, the SIC tests have all been performed in the same institute, and the standard SIC procedure for dental materials in this institute is using "*2 x 10-20 drops of a dental adhesive*" according to the revised Handbook for SIC procedures (Suojalehto et al. 2019). Thus, there is a strong likelihood that exposure levels far in excess of those used in the workplace have been generated in these SIC tests as well.**

b) **In many SIC the claim that HEMA was the main VOC present was not substantiated by full details on the chemical composition of the product (by the manufacturer's SDS, see chapter 2.3 and Appendix I-Table 1).**

c) **Despite positive responses being observed with complex mixtures, in no clinical case study were further SIC tests conducted with individual chemicals making it impossible to claim specificity of the hypersensitivity reaction to a single substance not alone HPMA.**

The CLH proposal includes a superficial review of selected publications referring to immunological mechanisms involved in contact and respiratory allergy to leave an impression that acrylates induce occupational asthma through a mechanism that may be type 1 and Late Asthmatic Reactions (LAR) in SIC as proposed Vandenplas et al., (2019).

[8] https://www.ultimatedental.com/uploads/3M_ScotchbondUniv_DC.pdf

However, this review is far from comprehensive since LAR have been reported with purely irritant chemicals (Sastre et al., 2011) and elicitation of an LAR in a SIC test cannot be regarded as being convincing or conclusive evidence for an allergic mechanism (Pemberton and Kimber, 2021). Furthermore, the consistent coincidence of non-specific bronchial hyperreactivity (NSBHR) in these patients[9] precludes the attribution of these clinical findings to a substance-specific, intrinsic property of HEMA.
Taken together the use of analytically undetermined, but excessively high exposure levels in SIC combined with the inability of confirming involvement of an immune (substance-specific) mechanism (i.e., based upon the observation of LAR) with any confidence renders the clinical data insufficient to be regarded as reliable evidence that the substance, HEMA, "*can lead to specific hypersensitivity*" (CLP Annex I: §3.4.2.1.2.1).

3.3. Specific comments on the text of the CLH proposal

With reference to the introductory comment 1 above (see chapter 2.3), following additional comments are made:

Comment 12: dentist cases published by **Lindström** et al. (2002), **Piirilä** et al. (1998) and as reported from **FIOH 2000-2018**; see also comments 3-8 above). The CLH proposal, including Annex I, reports information on several aspects of the SIC procedure but did mention the amount of test item used in the SIC tests and how the test material was applied only in two cases. In most detail, the case of the Lindström patient is described, where the amount of test material was described with 20 drops of the adhesive in the first SIC (resulting in a negative response) and 40 drops of both the primer and adhesive in the second SIC with "early/late" response. A moderate non-specific bronchial hyperreactivity (NSBHR) was noted for the Lindström patient. From the patients reported from the Piirilä paper, four responded with late reactions in their SIC test and two with an early response. Information on the amounts of test item during SIC was made available for one SIC test (i.e., in total 20 drops of the adhesive/ primer system were used); while four of six cases had NSBHR, thereof one moderate and three mild. From the cases reported from FIOH, no information on amounts used in the SIC tests or on NSBHR was made available. Four of the patients from FIOH responded with dual reactions in their SIC tests, one patient with a late response, while two patients were not diagnosed by SIC testing.
Neither the amount of product used in the respective SIC tests, nor the frequent appearance of NSBHR, indicating non-specifically increased sensitivity respiratory tract is not mentioned in the CLH proposal, nor is it discussed in the conclusions as a confounding factor.
HMRTF response: The significance of the used amounts of test material have apparently not been considered in the CLH proposal, as this available information from the publications was

[9] NSBHR is known from all patients where such information on the health status is provided, i.e. in 4 of 8 cases; in the other 4 cases, this information is not made available

sporadically reported in the CLH report, and not discussed in the conclusions. The same is true for the observed NSBHR.

HMRTF acknowledges that typical amounts of dental material are one drop of each component according to the manufacturers technical guide[10]. It should thus be noted that, in the case of the Lindström patient as an example, 20 times the quantity of products containing methacrylates that would be encountered in the workplace failed to invoke a clinically significant asthmatic response. While 40 times the quantity routinely used did invoke a significant asthmatic response no exposure measurements were made upon which to exclude the possibility that irritation may have been the cause of the clinical findings, especially as the patient had hypersensitive airways as indicated by the moderate NSBHR. This is particularly relevant as the patient had hypersensitive airways as indicated by the moderate NSBHR and CLP guidance Annex I: §3.4.2.1.3.1. states "*if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyper reactivity, they should not be considered respiratory sensitisers*". For the six cases from Piirilä et al., the used amounts were again 2 to 20 times the typical workplace amounts[11]. Overall, the SIC tests reported by Piirilä et al. and Lindström et al., all performed in one institute in Finland, were not performed "*in the same conditions as those that prevail in the workplace",* and failed to measure VOCs during the SIC. This combined with some patients having moderate NSBHR points to the likely involvement of non-specific irritation which cannot be discounted on the basis of an "early/late" SIC response with a sufficient level of confidence. Therefore, this case does not indicate a substance-specific property of HEMA to cause respiratory sensitisation.

In the other seven cases reported from FIOH (cases #8-14 in **Appendix I-Table 1**), the amount of test item in the respective SIC tests has not been described. However, the SIC tests have all been performed in the same institute, and the standard SIC procedure for dental materials in this institute is using "2 x 10-20 drops of a dental adhesive" according to the revised Handbook for SIC procedures (Suojalehto et al. 2019). Thus, there is a high likelihood that exposure levels far in excess of those used in the workplace have been generated in these SIC tests as well, and that the same deficiencies apply to them as in the published cases of Piirilä et al. and Lindström et al..

Comment 13: cosmetician cases reported by **Sauni** et al. (2008); **Moulin** et al. (2009) and as reported from **FIOH 2000-2018** (see also comments 9-11 above). For both cases published by Sauni and coworkers, the SIC response was reported as a "*Dual asthmatic reaction in the active bronchial challenge test*". Details of the responses were also given in Annex I to the CLH proposal. Also in the Annex I, mild to moderate non-specific bronchial hyperreactivity was noted for both patients but this aspect indicating highly sensitive respiratory tracts has not been reported in the CLH proposal as such, nor discussed in the conclusions as confounding

[10] https://www.ultimatedental.com/uploads/3M_ScotchbondUniv_DC.pdf

[11] 4 drops: case 3/ Piirilä #7, 13 drops : case 1/ Piirilä #2, 20 drops: case 4/ Piirilä #9 and 40 drops: cases 2, 5, 6/ Piirilä #3, 11, 12

factor. For patient 17 (Moulin #1), an early response was reported while no SIC was performed with patient 18. For patient 17, NSBHR was reported. No non-specific challenge test has been performed with patient 18 for which however "*asthmatiform bronchitis and seasonal spring rhinitis in her childhood*" was reported. From the cases reported from FIOH, no information on NSBHR was made available. The patient from FIOH responded with a dual reaction in her SIC test; no information is given on the NSBHR of the respiratory tract.
For none of these cases, amounts of test material used in the respective SIC tests was reported.
HMRTF response As with the case reported by Lindström et al. (2002) the investigators failed to measure VOCs during the SIC test. These patients also had NSBHR predisposing them to reacting to non-specific irritation. As described above, the observation of dual asthmatic responses does not allow for the exclusion of non-specific irritation with sufficient confidence to conclude that the observed responses in the SIC tests are a substance-specific property of HPMA to cause respiratory sensitisation (see comment 12 above).
Regarding the FIOH case #19, the reported information level on this case is extremely low, so that it fails to provide key information that is required in ECHA's guidance document R.7a on existing human experience data for respiratory sensitization[12] (i.e., the "*test protocol used; the substance or preparation studied (should be the main, and ideally, the only substance or preparation present which may possess the hazard under investigation); the extent of exposure (magnitude, frequency and duration); the frequency of effects (versus number of persons exposed); the persistence or absence of health effects (objective description and evaluation); the presence of confounding factors (e.g. pre-existing respiratory health effects, medication; presence of other respiratory sensitizers*)" (emphasis added). From that perspective, the reliability of these cases cannot be established (resulting in a Klimisch rating of 4) on that information level. This deficiency must be considered in a weight of evidence approach. Based upon the currently available information this case report is insufficient to conclude a substance-specific property of HPMA to cause respiratory sensitisation.

Comment 14: on potential underdiagnosis as explanation of the relatively low number of asthma cases potentially related to HEMA ("*The relatively low number of HEMA related occupational asthma cases reported in the scientific literature or in occupational disease databases should not be seen as evidence of low prevalence. As currently none of the acrylates have harmonised classification for respiratory sensitisation (classification of MMA not yet implemented in CLP Regulation), most occupational physicians are unlikely to suspect the acrylates or more specifically HEMA as a causative agent in a patient's asthma. Therefore, it is possible that HEMA occupational asthma cases are underdiagnosed and are therefore also under-reported.*", page 25)
HMRTF response: This line of argument being presented on page 25 of the report could be considered as unsubstantiated conjecture and represents an opinion of the author.
Firstly, none of the identified case reports can be claimed with sufficient confidence as confirmed "*HEMA related occupational asthma cases*", see **Section 2** plus **Appendix I** and

[12] https://echa.europa.eu/documents/10162/17224/information_requirements_r7a_en.pdf

Appendix II for further details. When combined with the absence of asthma cases in national databases in France, Germany (dental sector[13]) and the UK indicate an "incidence" rate that, if taken as a most precautious approach, that is extremely low. Therefore, if exposure to HEMA is as widespread as reported in the CLH proposal then the "prevalence" is negligible. As such, this is inconsistent with the claim that respiratory sensitisation is an inherent hazard property of HEMA and perhaps more consistent with idiosyncratic or irritant induced (as a result of use of excessively high challenge concentrations) responses in hypersensitive individuals.

Secondly, the claim that "most occupational physicians are unlikely to suspect the acrylates or more specifically HEMA as a causative agent in a patient's asthma" is not substantiable as acrylates and methacrylates are well recognised skin sensitisers in the relevant industry sectors, with a dedicated prick test series.

Thirdly, the tertiary centre of FIOH alone performed approx. 150 SIC tests with products containing HPMA/ HEMA in suspected OA patients[14] over two decades. For other tertiary centres in Europe, comparable numbers are unknown, while information from the revised handbook for SIC testing (Suojalehto et al. 2019) indicate that SIC test procedures of methacrylate containing products is established in many other tertiary centres[15], so that a general awareness on this substance group can be assumed and would not have gone undetected.

Thus, this statement appears as undocumented conjecture and should be further substantiated or disregarded in the CLH process.

[13] See **3.8.1.1** or **3.8.2** in **Appendix II**(WoE assessment on Respiratory Sensitisation for HPMA), BG ETEM data

[14] Of those 150 SIC tests, around 140 gave negative results, as can be concluded from information in the CLH proposal, p 15

[15] In total five tertiary centers with established SIC procedures related to (meth)acrylate-related products (excluding cyanoacrylate-related SIC procedures in a few centres more)

4. Grouping and use of read-across

4.1. CLP requirements

Guidance on the Application of the CLP Criteria state under Annex I: §3.4.2.1.3.1. on use of Human data that "*Substances shall be classified as respiratory sensitisers if there is evidence in humans or other sufficient evidence, including read-across that the substance can lead to specific respiratory hypersensitivity*" (emphasis added). Further said guidance under §1.4.3. Read-across, states that "*Extensive guidance on the use of read-across is given in IR&CSA, Chapter R.6.2.2.1*." and this is further outlined in the Read-Across Assessment Framework or RAAF (ECHA, 2017).

4.2. Summary on grouping and use of read-across

The CLH proposal refers to a hypothesised mode of action (hMOA) of methacrylate esters, including Methyl Methacrylate (MMA) and the CLH candidate (HEMA), in which the parent ester is hydrolysed to methacrylic acid, a metabolite that is claimed to be the cause of the respiratory sensitisation common to this group of chemicals. HMRTF is not aware through the CLH proposal or by review of the scientific literature that this hMOA is justified and assessed for reliability according to any of the criteria outlined in the RAAF (ECHA, 2017), any formalised assessment process such as OECD guidance on grouping of chemicals (OECD, 2017) or indeed, any peer reviewed published literature. Furthermore, the reference to and use of analogy to MMA and its claim as being a respiratory sensitiser agreed by RAC is presumptive as it does not reflect recent developments at CARACAL at which the CLH proposal for MMA has not been confirmed.
HMRTF acknowledges that Annex I: §3.4.2.1.1. of the CLP Criteria (Identification of hazard information) recognises the value of information on structural considerations and read across. However, the information provided in the proposal is not sufficiently validated to act as a reliable surrogate for the requirements of Annex I: §3.4.2.1.2.1. of the CLP Criteria that states "*Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience*" (emphasis added).

4.3. Specific comments on the text of the CLH proposal

Grouping & Mode of Action
Comment 15: on various text passages that refer non-specifically to methacrylates as a homogeneous group in the section heading "*Data with methacrylates (HEMA not specifically identified or with other methacrytates)*" (page 23). The comment refers specifically to the text passage on page 23/24 "*Due to rapid hydrolysis, it is considered that the respiratory sensitising properties of MMA can be attributed to methacrylic acid formed as a metabolite. This could be explained as the reactive acrylate group is maintained upon hydrolysis of MMA to methacrylic acid. Consequently, respiratory sensitisation is suspected for potentially all methacrylates that have this hydrolysis product/metabolite in common. This suspicion is particularly high for those*

substances that hydrolyse quickly, are of low molecular weight and which are volatile" (emphasis added).

HMRTF response: Firstly, the term "*HEMA not specifically identified*" implies that HEMA was generally identified as the causative agent for the described effects. Considering all ambiguities and deficiencies detected in the above HMRTF comments and even by the dossier submitter themselves (see comment 2), and also with regard to the comprehensive, formal WoE assessment according to ECHA guidance that identified no relevant evidence to classify HEMA as respiratory sensitiser (see **Appendix II Weight-of-Evidence Assessment Respiratory Sensitisation HEMA**), this implication appears premature, if not suggestive.

The attribution of HEMA's claimed respiratory sensitisation property to rapid hydrolysis to Methacrylic acid (MAA; CAS 79-41-4) is an unfounded, and to the best of our knowledge, unproven hypothesised MOA (hMOA). This hypothesis is not documented in any peer reviewed publication, so must be regarded as new information. Indeed, this hMOA appears to contradict the mechanism of action of these esters claimed in many papers including that of Suojalehto et al. (2020) within which the authors, in referring to the reactive double bond (vinyl group) of the parent ester, state that "*the same reactive vinyl group that allows polymerization has also been proposed as the reactive group responsible for respiratory sensitization potential of methacrylates and plain acrylates*" citing Enoch et al., 2012. Furthermore, the claimed causal "acrylate group" present on MAA appears not to be immunogenic in vivo as the substance is not classified with respect to skin or respiratory sensitisation[16] and according to the studies presented in the REACH registration has been shown to be consistently negative in predictive skin sensitisation studies[17]. Thus, the hydrolysis to MAA and the alcohol (that typically has no structural alert for a sensitising potential) can be understood as detoxification with regards to sensitisation (Borak et al. 2011; Gelbke et al. 2018). As a consequence, this means that methacrylates with very rapid hydrolysis (such as HEMA) have in general a lower sensitisation potential. Given the consistently contradicting evidence in public literature, the absence of a comprehensive read across assessment according to OECD or ECHA's RAAF is considered as a crucial deficiency in the confidence of this hMOA. With its current unvalidated argumentation, this hMOA and its related grouping approach is considered as not reliable.

Comment 16: on mechanistic considerations of immunological involvement for acrylate/methacrylates and cites selected publications that "*Late or dual reactions are generally found in the cases reported above (Piirilä, 1996; Sauni 2008). Even if these modes of reactions refer usually to reactions other than hypersensitivity type I, this mechanism cannot be neither completely excluded. In particular early/immediate reactions were also reported by Piirilä et al. (1996) and Moulin et al. (2009). Thus, type I hypersensitivity cannot be entirely excluded in susceptible individuals (Walters, 2017).*" (page 24).

[16] C&L Inventory (europa.eu)
[17] Registration Dossier - ECHA (europa.eu)

HMRTF response: HMRTF acknowledges this synopsis as being far from comprehensive and balanced as it does not adequately address the scientific literature on this subject and presents a misrepresentation of the state of knowledge. In this regard, Late Asthmatic reactions (LAR) have been reported with purely irritant chemicals (Sastre et al., 2011) and it has been argued recently that the elicitation of LAR in a SIC test cannot be regarded as being convincing or conclusive evidence for an allergic mechanism (Pemberton and Kimber, 2021). Furthermore, the relatively weak reactivity of HEMA and other methacrylate esters as Michael acceptors, which is the most probable mechanism for skin sensitisation (Borak et al. 2011), has turned out to be no relevant mechanism in known respiratory sensitisers (Krutz et al. 2021; Ponder et al. 2022). From this perspective, Michael addition reactivity is a questionable "predictor of respiratory sensitisation". HMRTF is thus of the opinion that the proposal oversimplifies an extremely complex situation. In our view there is substantial information available in peer reviewed literature that needs to be integrated in a weighed manner to ensure a hazard assessment of defensible quality.

Comment 17: on the relation between skin and respiratory sensitisation by intrinsic properties ("*the intrinsic skin sensitising property of the molecule...*" … "*Thus, HEMA can also have the intrinsic potential to induce respiratory sensitisation. The fact that HEMA is volatile and found in air measurements made in occupational settings confirm that the substance can reach the respiratory tract where it can cause hypersensitivity*." on page 25).

HMRTF response: This claim of intrinsic potential to be a respiratory sensitiser as a consequence of being a skin sensitiser could be said to be true for all contact allergens that can be inhaled. However, it is clearly not the case that this "potential" translates to such a hazard for all such substances since only a few contact allergens have to date been implicated as causing respiratory allergy. So, this in itself is not sufficient confirmatory evidence for classification under CLP. HMRTF recognises that CLP Guidance on the Application of the CLP Criteria §1.1.3. Hazard classification, states that "*Classification according to CLP is based on intrinsic hazards, i.e. the basic properties of a substance or mixture as determined in standard tests or by other means designed to identify hazards*". As such, classification is not based upon "*intrinsic potential*".

Furthermore, the claimed relation between respiratory sensitisation and skin sensitisation is not established in CLP. Although some assessment elements can be found in both hazard endpoints, respiratory sensitisation is assessed under CLP independently from skin sensitisation in CLP chapter 3.4.2.1.[18] In this regard, ECHA Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017, page 8, when referring to 3.4 (Respiratory or skin sensitisation) it states that in this update the "Deletion of the relationship between skin and respiratory sensitisation potential". The complex and still ongoing development of an independent AOP for respiratory sensitisation is a further, strong indication that such "hazard read across" is an simplistic approach that is not scientifically justified.

[18] The only reference in this CLP chapter to skin related data is made to skin prick tests, and these are all negative for HEMA related cases, with one exception.

Read across

Comment 18: on various read across statements to MMA as classified respiratory sensitiser (e.g. "*Consistent with these results, methyl methacrylate (MMA) has been recently classified by the RAC as Resp. Sens. (RAC, 2021)*", page 23, or "*In particular, MMA has been recently classified as Resp. Sens. 1 by the RAC (2020). Due to rapid hydrolysis, it is considered that the respiratory sensitising properties of MMA can be attributed to methacrylic acid formed as a metabolite. Consequently, respiratory sensitisation is suspected for potentially all methacrylates that have this hydrolysis product/metabolite in common. Since HEMA also rapidly breaks down into methacrylic acid, the substance is expected to have respiratory sensitising properties*.", page 25).

HMRTF response: HMRTF acknowledges that at the time of compiling the proposal RAC had developed its opinion to classify MMA as Respiratory Sensitiser. However, more recently at CARACAL-48 the EU Commission announced that new information had become available that justified a re-evaluation of MMA by RAC. It is therefore premature to cite this as grounds for concluding that HEMA is also a respiratory sensitiser. In our view, the current status of the RAC opinion development on MMA should be considered in light of the ongoing process.

The read across to MMA is justified superficially on the rapid hydrolysis to the common metabolite MAA. In public literature this process has been consistently described as detoxification (see comment 15). In the absence of a comprehensive read across assessment according to ECHA's RAAF, the read across approach to MMA appears, at best, as not acceptable in its current form.

Comment 19: on the half-life of MMA quoting "*For comparison, in vitro half-life of MMA in human blood is 10 to 40 minutes (Anses, 2019)*" (page 24).

HMRTF response: The reported in vitro half-life of MMA in human blood is inconsistent with published half-life data for MMA, also in the rat, that indicate a much shorter half-life of 4.4 minutes that is more comparable to HPMA (e.g. Gelbke et al. 2018[19]).

[19] https://echa.europa.eu/en/registration-dossier/-/registered-dossier/15528/7/2/1

Section 3. Respiratory Irritation (STOT-SE Cat 3 Respiratory Tract, H335)

1. Executive summary

HEMA is only a weakly irritating substance. Under UN-GHS with its additional hazard subcategory for weak irritants the available data justify a classification for eye irritation of Cat 2B with no classification for skin irritation.

No local respiratory effects have been reported in rats exposed to maximum technically achievable concentrations of HEMA in a poorly described, older subacute inhalation study (Gage 1970).

Respiratory tract irritation depends on the volatility or vapor pressure of a substance. The CLH dossier reports HEMA as "volatile", but does not cite any reference for this declaration with reference to the vapour pressure.

In Chapter R.7.12 of ECHA Guidance R.7c (2017), substances with low volatility are defined to have a vapour pressure of less than 0.5 kPa (or a boiling point above 150°C). As HEMA has an approx. 50 times lower vapour pressure (0.08 hPa at 20°C; boiling point 213°C), HEMA could be considered as a substance of very low volatility.

Furthermore, the concentration (< 0.2%) of the low volatile, corrosive impurity methacrylic acid (MAA) is at least five times below the respective specific concentration limit (SCL) that triggers classification as respiratory irritant.

MAA is also the primary metabolite of HEMA after ester hydrolysis by carboxyl esterases. However, ester hydrolysis in the respiratory tract requires the uptake of the substance via the respiratory air, for which the substance must have a sufficiently high vapor pressure. This is not given for HEMA as very low volatile substance. It can therefore be excluded that even combined exposure from MAA as impurity and as metabolite can reach relevant local levels in the human respiratory tract.

Consequently, criteria for classification of HEMA as respiratory irritant with STOT SE3 H335 are not fulfilled (see Appendix III for the respective Weight-of-Evidence assessment).

Section 4. Skin Sensitisation (Cat 1, H317)

1. Executive summary

HEMA is currently classified as skin sensitization category 1 (Skin Sens. 1, H317, may cause an allergic skin reaction) according to the harmonised classification in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).
This classification is supported by HMRTF and is consistent with the self-classification for that endpoint according to UN GHS as provided in the REACh registration dossier.
Available data from animal tests and observations in humans are not sufficient for sub-categorisation. Evaluation of frequency and exposure from observations in humans according to CLP classification criteria indicate that relatively high frequencies were seen only at relatively high exposures (for detailed information see the endpoint summary for skin sensitization in the REACh registration dossier). This supports the relatively low potency of HEMA for skin sensitization and consequently excludes the assignment of sub-category 1A.

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Appendix I Table 1

Table 1: Composition information on products used during clinical diagnosis (SIC tests)

Case	Industry sector	Product(s)	Composition information in CLH report	Additional composition information with source
1/ Piirilä #2	Dental	Rely-A-Bond paste Scotchbond a	bis-GMA[20] HEMA	Paste: 10-30% Bis-GMA, 5-10% TREGDMA, <1% Benzoyl Peroxide with at least 60% undeclared components (SDS Reliance, 2018a) The kit necessarily consists of a primer (that contains 10-30% Bis-GMA, 5-10% TREGDMA, <1% Benzoyl Peroxide with at least 60% undeclared components (SDS Reliance, 2018a)) and an etchant (~30% phosphoric acid (SDS Paterson dental, 2022)). "Scotchbond a": "a" is considered as postscript for "adhesive". This could be either the Multipurpose Adhesive (see other Piirilä cases, e.g. 2/ Piirilä case #3) or the Universal Adhesive (with 15-25% Bis-GMA, 10-15% HEMA, 5-15% decamethylene dimethacrylate, 10-20% 2-propenoic acid 2-methyl reaction products with 1,10 decanediol and phosphorous oxide, 10-15% ethanol, 10-15% water, 7-13% silane treated silica, 1-5% acrylic acid and itaconic acid copolymer, <2% camphorquinone, <2% DMAEMA, 2% dimethylaminobenzoate and <0.5% 2,6-di-tert-butyl-p-cresol (SDS 3M, 2015))
2/ Piirilä #3	Dental	Scotchbond Multipurpose Primer & Adhesive	Primer: 40% HEMA Adhesive: 62% bis-GMA 37% HEMA	Primer: 40-50% water, 35-45% HEMA and 10-20% acrylic and itaconic acid copolymer (SDS 3M ESPE, 2017) Adhesive: different compositions are available: 3M™ Adper™ Scotchbond™ Multi-Purpose Adhesive (3009/7543) dated 29/11/2020 discloses it contains 30-40% HEMA (3M, 2020). Whereas a SDS dated 10/03/22 discloses it containing BISGMA 55-65%, HEMA 35-45%, ethyl 4-dimethylaminobenzoate (EDMAB) <= 0.5% (SDS 3M, 2022).
3/ Piirilä #7	Dental	Scotchbond Multipurpose	62% bis-GMA 37% HEMA	"a" is considered as postscript for "adhesive"; see case 2/ Piirilä #3 for Scotchbond Multipurpose Adhesive

[20] Bis-GMA: Bisphenol-A-diglycidyl-ether methacrylate, CAS

		a		
4/ Piirilä #9	Dental	Scotchbond Multipurpose Primer & Adhesive	Primer: 40% HEMA Adhesive: 62% bis-GMA 37% HEMA	See case 2/ Piirilä #3
5/ Piirilä #11	Dental	Scotchbond Multipurpose Primer & Adhesive	Primer: 40% HEMA Adhesive: 62% bis-GMA 37% HEMA	See case 2/ Piirilä #3
6/ Piirilä #12	Dental	Scotchbond Multipurpose Primer & Adhesive	Primer: 40% HEMA Adhesive: 62% bis-GMA 37% HEMA	See case 2/ Piirilä #3
7/ Lindström	Dental	SIC 1 (negative): Scotchbond Adhesive	62% bis-GMA 37% HEMA	The adhesive could be either the Multipurpose Adhesive (see e.g. 2/ Piirilä case #3) or the Universal Adhesive (see 1/ Piirilä case #2)
		SIC 2 (positive): Scotchbond Primer & Adhesive	Primer: 40% HEMA Adhesive: 62% bis-GMA 37% HEMA	Primer: see case 2/ Piirilä case #3 Adhesive: could be either the Multipurpose Adhesive (see e.g. 2/ Piirilä case #3) or the Universal Adhesive (see 1/ Piirilä case #2)
8/ FIOH #1	Dental	Scotchbond Universal Adhesive	60-70% bis-GMA 30-40% HEMA	see 1/ Piirilä case #2
9/ FIOH #2	Dental	Scotchbond Universal Primer Scotchbond adhesive	35-40% HEMA "Light-hardened polymer" without CAS number 10-15% Silyx restorative: Bis-GMA, TEGDMA 30-80%	Universal Primer: no information Multipurpose Primer: 40-50% water, 35-45% HEMA and 10-20% acrylic and itaconic acid copolymer (SDS 3M ESPE, 2017) Adhesive: could be either the Multipurpose Adhesive (see e.g. 2/ Piirilä case #3) or the Universal Adhesive (see 1/ Piirilä case #2)
10/ FIOH #3	Dental	One step dental restorative material	biphenylmethacrylate 15-40 %; HEMA 8-30%; Bis-GMA 7-13%; All bond primer part A: glycidyl methacrylate 1-5 %; All bond primer part B: biphenylmethacrylate	

			8-30 %	
11/ FIOH #4	Dental	Scotchbond dental adhesive	HEMA 35-40%; "Light-hardened polymer " 10-15%	Compositions indicates primer rather than an adhesive that typically contain high concentrations of bis-GMA Primer: see case 2/ Piirilä case #3 Adhesive: could be either the Multipurpose Adhesive (see e.g. 2/ Piirilä case #3) or the Universal Adhesive (see 1/ Piirilä case #2)
12/ FIOH #5	Dental	Scotchbond Multipurpose Adhesive	62% bis-GMA 37% HEMA	See case 2/ Piirilä #3
13/ FIOH #6	Dental	No SDS available (Scotchbond adhesive assumed by DS)	30-40 % HEMA (assumed by DS)	Adhesives typically contain high concentrations of bis-GMA, and other components, see case 2/ Piirilä #3
14/ FIOH# 7	Dental	No SDS available (Scotchbond Primer & Adhesive assumed by DS)	30-40 % HEMA (assumed by DS)	Primers typically contain 10-20% acrylic and itaconic acid copolymer. Adhesives typically contain high concentrations of bis-GMA, and other components, see case 2/ Piirilä #3
15/ Sauni #1	Cosmetic	Gel nails material	Not determined	
16/ Sauni #2	Cosmetic	Bonding agent Sculpture resin	Bonding: 7.5% HEMA Resin: 0.03% HEMA 42% bis-GMA	
17/ Moulin #1	Cosmetic	nail prosthesis material with “new solvents and resins”	HEMA “without hardener”	
18/ Moulin #2	Cosmetic	Nail prothesis material	HEMA	
19/ FIOH #8	Cosmetic	Various LCN gel nail products	Sculpture: 6.7 % HPMA Bonder: 7.5% HPMA SDS of probably Sealant: 15-20% HEMA 20-25% Polyetherolyol Tetraacrylate; 5-10% HPMA	

1. Appendix I References

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WEIGHT OF EVIDENCE/ UNCERTAINTY ASSESSSMENT

HEMA
Respiratory sensitisation

For the Higher Methacrylates REACH Task Force,
Knut Kreuzer, Röhm GmbH

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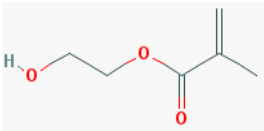
Note

This assessment structure follows that of the ECHA template for WoE / uncertainty evaluation in hazard assessment
(https://www.echa.europa.eu/web/guest/support/guidance-on-reach-and-clpimplementation/
formats)

Chemical Information

Substances	Structure
2-Hydroxyethyl methacrylate, HEMA EC-no. 212-782-2, CAS 868-77-9	

1. Problem Formulation

CLP defines a respiratory sensitiser as “a substance that will lead to hypersensitivity of the airways following inhalation of the substance” (EU, 2008). It is a further CLP requirement to demonstrate “evidence in humans that the substance can lead to specific respiratory hypersensitivity” so that available data must allow for the determination of “causation” of the development of asthma by the "substance” (instead of “provoking” or “aggravating” a pre-existing condition). From this perspective, following question has to be answered:

1. “Is there sufficient evidence that HEMA can cause the development of respiratory sensitisation, or occupational asthma (OA), in subjects that were not previously asthmatic”.

and if so,

2. “is there sufficient evidence for an irritative mechanism?” or “is there sufficient evidence for an immune-based mechanism”?

2. Method

2.1. Background

It is acknowledged that validated or widely accepted non-human test methods (*in vivo*, *in vitro* or *in silico*) does not exist for the predictive identification of chemical respiratory allergens. On human data, also no guidelines, e.g. for bronchial challenge tests or so-called “specific inhalation challenge” tests (SIC), were explicitly mentioned in the CLP text as an a priori information so that a weight of evidence (WoE) approach, as opposed to a strength of evidence, has been taken for the respective assessment of HEMA/HPMA. As part of this WoE assessment, available SIC data will be evaluated against identified scientific best practices including the aforementioned CLP requirement for a test “*with the substance*” in chapter 3.8. Such WoE approaches have been described by many authorities worldwide including the European Food Safety Authority (EFSA, 2008), the EU Scientific Committee on Emerging and Newly-Identified Health Risks (SCENHIR, 2012), European Chemicals Agency (ECHA, 2017d) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) (SCHEER, 2018), to remain in the European region. Just recently, an expert group highlighted the importance of a formal WoE framework “*to increase the consistency, objectivity and transparency in the regulatory assessment of respiratory sensitisers and associated uncertainties*” (Meek et al. 2023). In the context of classification of chemicals, Article 9 of the EU Classification, Labelling and Packaging (CLP) Regulation (EC, 2008) refers to the use of WoE and expert judgement in such cases and provides a template for constructing a WoE assessment (ECHA, 2017e). The structure of this assessment is closely in line with the ECHA template.

2.2. Collection and documentation of all information

Publicly available peer reviewed literature on HEMA published between 1990 and April 2021 has been collected, evaluated for relevance and combined with findings of earlier literature searches. The relevant hazard information has been integrated in the REACh dossier in the respective chapters on Acute Toxicity (inhalation), Skin Sensitisation, Respiratory Sensitisation, and Other Effects/ Human information.
In addition, additional information on unpublished clinicial cases, diagnosed by the Finnish Institute of Occupational Health (FIOH) and reported in a CLH proposal (ANSES 2022, published Mar 2023) has been integrated.

2.3. Documentation of search strategy & documentation/ reporting of evidence

The applied search strategy for the peer reviewed literature including search terms is briefly described in the **Supplementary information 8.1 Literature search documentation** and, in more detail, in the respective IUCLID entries in the chapter "Literature search".

2.4. Assessment of quality of individual evidence

The quality of non-clinical data was assessed in terms of relevance, reliability and adequacy using the standard scoring system based upon the prescriptive method described by Klimisch et al. (1997), thereby following ECHA guidance R.4 (2011). It should be noted that the Klimisch scoring is frequently interpreted as score for reliability only but here all three aspects are considered.
The Klimisch scoring system formed also the basis for the assessment of the quality of clinical data, but it was adapted here according to Lavelle et al. (2012) and Money et al. (2013). The resulting scoring system considers the degree of transparency in the documentation of the methodology, analysis and results, the degree to which potential methodological bias, such as information and selection bias, and on the extent and nature of the scientific data (e.g., whether supporting data are direct or indirect), are consistent with the approach taken by Martin et al. (2018) and recently used in a comparable situation by Pemberton & Kimber (2022, see **Table 2**).
A summary of this quality assessment is given at the end of each LoE.

Table 2: Description of adapted Klimisch categories for clinical studies on OA

Code	Category	Category definitions
1	Reliable without restriction	This includes studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted or specific(national) testing guideline and which address all applicable parameters by ECHA R.7a guidance (section R7.3.10.2 Human data on respiratory sensitisation)*.
2	Reliable with restriction	This includes studies or data from the literature or reports, in which the test parameters documented do not totally comply with generally valid and/or internationally accepted or specific(national) testing guideline, but which are nevertheless well documented and scientifically acceptable and sufficient to address all applicable parameters by ECHA R.7a guidance*.
3	Not reliable	This includes studies or data from the literature/reports in which there are interferences between the measuring system and/or effects observed, or the causal relationship between cannot be established with sufficient confidence, or the study was carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment.
4	Not assignable	This includes studies or data from the literature or reports, which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)

* ECHA R.7a guidance (section R7.3.10.2 Human data on respiratory sensitisation) state that "For evaluation purposes, existing human experience data for respiratory sensitisation should contain sufficient information about:"

- *the test protocol used (study design, controls);*
- *the substance or preparation studied (should be the main, and ideally, the only substance or preparation present which may possess the hazard under investigation);*
- *the extent of exposure (magnitude, frequency and duration);*
- *the frequency of effects (versus number of persons exposed);*
- *the persistence or absence of health effects (objective description and evaluation);*
- *the presence of confounding factors (e.g., pre-existing respiratory health effects, medication; presence of other respiratory sensitisers);*
- *the relevance with respect to the group size, statistics, documentation;*
- *the healthy worker effect.*

2.5. Integration and weighing of evidence (WoE analysis), application of levels of confidence

The strength of the causal relationship for the individual lines of evidence (LoE) against the tested hypothesis was assessed using the scheme of the ECHA template which can be understood as selection of adapted Bradford Hill criteria (see Supplementary information **8.6 Explanations on Integration & Weighing of evidence (WoE analysis)/ Application of Levels of Confidence**).

A level of confidence (Strength of Evidence) was then assigned to individual lines of evidence based upon the score for a) quality (i.e., adequacy and reliability, see chapter 2.4), and b) their score with respect to causation (i.e., adapted BH criteria, see above).
An assessment of the overall level of confidence in the evidence was derived by integrating the weighted level of confidence for each LoE. The use of modified Bradford Hill considerations to assess causality, and an integration of all relevant data into a weight-of-evidence protocol was also postulated recently by Meek et al. (2023).
The strength of the causal relationship, as well as the level of confidence, was expressed in terms of strength i.e., high, medium or low for each element of the criteria.

2.6. Uncertainty analysis

Specific uncertainties per LoE were identified and, where possible, their potential impact on the assessment described in terms of Source, Nature, Magnitude and Impact and again expressed in the above-mentioned terms of strength.

2.7. Conclusions

An overall conclusion was drawn against the tested hypothesis (see chapter 1 of this appendix) based upon the completeness and level of confidence in the available evidence.
The ECHA template also foresees to place optional recommendations in this chapter (e.g., for additional work or research).

3. Assessment of quality of individual evidence

Following lines of evidence were considered as relevant.

3.1. Structural alerts

2HEMA does not belong to the groups of chemicals with known potential for respiratory sensitisation according to ECHA Guidance R7.a, Chapter R.7.3 (ECHA, 2017b; e.g. isocyanates or diamines) or own respective structural alerts (like acid anhydrides or platinum salts) which would justify a respective classification per se.

The C=C double bond of methacrylate esters however makes these chemicals Michael acceptors capable of electrophilic attack of protein and other cellular macromolecules. Here, the reactivity towards Michael addition of HEMA, like many other methacrylate esters, is considered as limited due to the alkyl group on the alpha-carbon. This is in line with QSAR data where the reactivity profiler in the OECD QSAR Toolbox classified HEMA as "slightly reactive", the second lowest potency beyond five potency classes (non-reactive, slightly reactive, moderately reactive, highly reactive and extremely reactive) based on the experimental using glutathione (Cronin, 2012). This reactivity is a considered as a structural alert for sensitization or for mutagenicity/genotoxicity (Borak, 2011; Ehrenberg & Osterman-Golkar, 1983). In a recent study, no known respiratory sensitizer was identified with Michael addition as protein binding mechanism (Krutz et al. 2021). From this perspective, Michael addition reactivity is a questionable "predictor of respiratory sensitisation". Moreover, contraindicating to any reactivity is the rapid hydrolysis of the parent esters yielding metabolites (MAA and relevant alcohol) that do not possess sensitizing properties. Hydrolysis can, therefore, essentially be understood as a detoxification step from the perspective of a general sensitisation MoA (see also chapter 3.4).

LoE summary

HEMA does not own structural alerts that are specifically known for respiratory sensitisation. A general potential for sensitisation, irrespective of the route, can be derived from their properties as weak Michael addition reactants. In a recent study, this reactivity scheme was found as questionable indicator for respiratory sensitisation.

This LoE was thus considered with a low level of relevance, and also a low level of adequacy for the classification assessment, while the available data itself has a high level of reliability. The weak potential for sensitisation is actually existing in the body only for a very short time period before the ester detoxification by rapid hydrolysis.

3.2. QSAR (in silico)

Reflecting the regulatory need to identify asthmagens in absence of commonly approved in vitro or in vivo models, some attempts have been made in the recent past to develop suitable QSAR models. They all suffer from regulatory non-acceptance for the time being (see ECHA 2017b, chapter 7.3.9.1).

OECD Toolbox (2021)

The OECD toolbox provides only information on the inherent structural alert for Michael addition that was mentioned above, so there is insufficient information, e.g. on potency (Röhm, 2021).

Danish National Food Institute (2021)

An online QSAR assessment on the respiratory sensitisation potential in humans is available on the website of the Danish National Food Institute DTU[21] (2021). By CAS number, following information is provided for HEMA.

Substance	Battery	CASE Ultra	Leadscope	SciQSAR
HEMA	NEG_OUT	INC_OUT	NEG_IN	POS_OUT

Table 3: QSAR prediction of Respiratory Sensitisation in Humans (extracts from DTU, 2021)

The "Battery" outcome represents the overall conclusion from the three individual software systems CASE Ultra, Leadscope and SciQSAR. The respective algorithm and description of the systems are described in the Exposure details/ Monomer production (Industrial use)

Part **A - Industrial uses / Röhm**

A campaign of **measurements has been made** to determine workplace exposures vs. HEMA and HPMA (Röhm internal report, BL-WO 20/12/1996). Personal related measurements have been performed during worker's shift for up to 8 hours duration. Standard procedures respectively manufacturing, substance transfers and maintenance have been included. Measurements have been focused on tasks for which exposure was likely (manufacture,

Endpoint	N in training set	Cross validation result (%)[a]	QMRF
Respiratory sensitisation in humans	80	Sens=68.2, Spec=96.3, Conc=86.4	CASE Ultra
		Sens=91.7, Spec=95.5, Conc=93.9	Leadscope
		Sens=80.0, Spec=87.5, Conc=83.8	SciQSAR

Table 4 Model documentation for the endpoint Respiratory Sensitisation in Humans (extract from DTU, 2021; https://qsardb.food.dtu.dk/db/index.html/ model documentation)

sampling, drum filling, maintenance work like opening reactors and tanks, filter exchange).

Measuring conditions

Personal related measurements took place. Workers wore measuring equipment to detect the level of exposure. Small pumps (HFS 513A with transport volume of 20 l/h and limit of

[21] Danish (Q)SAR Database (dtu.dk)

detection ca. 0.07 mg/m³ or 50 l/h and limit of detection ca. 0.02 mg/m³, both by Gilian) transported air to tubes of type NIOSH (by Draeger) filled with absorbing agent (silica gel). Substances were desorbed with methanol. Analytical investigations proceeded by GC.

Results

28 measurements were performed during handling of the substances, for which exposure was likely. Even for exposure-prone tasks the actual exposure to HEMA and HPMA was several orders of magnitude below the expected NOAEC.

HEMA: Under standard manufacturing conditions 14/28 measurements were below the limit of detection. For the rest a 90 percentile of 0.048 ppm (0.26 mg/m³) was determined (max. 0.076 ppm, 0.41 mg/m³). See Table (suppl. Info) 1 and Table (suppl. Info) 2.

HPMA: Under standard manufacturing conditions 2/28 measurements were below the limit of detection. For the rest a 90 percentile of 0.058 ppm (0.35mg/m³) was determined (max. 0.217 ppm, 1.3 mg/m³). See table 4 and 5.

Data

	MW	**Vp**	**Saturation density**
HEMA	130.1 g/mol	0.08 hPa @ 20 °C	79 ppm/427 mg/m³

Table (suppl. Info) 1: Properties HEMA

Date	HEMA mg/m³	HEMA ml/m³ (ppm)	HEMA ml/m³ (ppm) LoD eliminated	Measurement duration (h)	Workplace/activity
19.11.1996	<0.038	<0.007	0.007	2.03	transfer
20.11.1996	<0.017	<0.003	0.003	4.62	production
20.11.1996	<0.022	<0.004	0.004	1.48	transfer
21.11.1996	<0.019	<0.004	0.004	5.98	production
22.11.1996	0.41	0.076	0.076	2.35	transfer
22.11.1996	<0.016	<0.003	0.003	4.15	production
27.11.1996	<0.012	<0.002	0.002	4.78	production
28.11.1996	<0.013	<0.002	0.002	4.48	production
29.11.1996	0.011	0.002	0.002	1.62	transfer
29.11.1996	0.029	0.005	0.005	5.23	production
30.11.1996	0.019	0.004	0.004	0.5	maintenance
30.11.1996	<0.014	<0.003	0.003	1.25	maintenance
01.12.1996	0.019	0.004	0.004	0.75	maintenance
01.12.1996	<0.027	<0.005	0.005	1	maintenance
02.12.1996	0.004	0.001	0.001	2.35	transfer
02.12.1996	0.045	0.008	0.008	5.27	transfer
02.12.1996	0.129	0.024	0.024	0.42	maintenance
02.12.1996	0.311	0.058	0.058	1.13	maintenance
09.12.1996	<0.027	<0.005	0.005	0.85	transfer
12.12.1996	0.032	0.006	0.006	1.83	maintenance
14.12.1996	0.02	0.004	0.004	7.2	production
15.12.1996	0.009	0.002	0.002	5.43	production
16.12.1996	<0.046	<0.009	0.009	1.23	transfer
17.12.1996	0.021	0.004	0.004	1.12	maintenance
17.12.1996	<0.059	<0.011	0.011	0.52	transfer
18.12.1996	0.129	0.024	0.024	2.93	transfer
19.12.1996	<0.035	<0.006	0.006	0.8	transfer
19.12.1996	<0.036	<0.007	0.007	0.88	transfer

Table (suppl. Info) 2: Workplace monitoring data of Röhm for HEMA (transfer = drum and IBC filling, outdoors and indoors with LEV; production = control of batch reaction and distillation, sampling; maintenance = filter exchange, cleaning operations)

Evaluation HEMA (ppm)		Evaluation HEMA (ppm) LOD eliminated	
0.0478	90 % Percentile	0.024	90 % Percentile
0.0045	50 % Percentile	0.0045	50 % Percentile
0.001	Lowest Value	0.001	Lowest Value
0.076	Highest Value	0.076	Highest Value
14	No. of Values	28	No. of Values

Table (suppl. Info) 3: Evaluation HEMA

Part B - Industrial uses / SIDS HEMA

One can found in the report that occupational exposures at production sites may occur by the inhalation route. The exposure concentration was measured at one production site (Japan Industrial Safety and Health Association, JISHA, 2001). Only short-term measurements have been proceeded. For most of the measurements it was found that the limit of detection did not exceed. The level of exposure is observed on a low level, but could be slightly higher than indicated in the Röhm data. The monitored data are shown in Table 6. Highest exposure concentrations can be found during maintenance. For these operations a higher level regarding risk measurements is in place (i.e., respirator).

Operation	Monitoring data (mg/m3)	Number of measurements	Frequency Times/day	Working time hrs/time
Sampling	<2.3	14	1	0.05
Drum filling	<2.3	5	1	0.75
Waste fluid processing	<2.3	2	1	0.05
Analysis work	<2.3	6	1	0.05
Maintenance work	<2.3 – 4.6 3.5 (mean)	3	1	0.25

Table (suppl. Info) 4: Workplace monitoring data for HEMA (JISHA)

[Monitoring method: Air sample was suctioned at the breathing zone of the worker at the suction rate of 0.2 L/min. and adsorbed by activated carbon in a collection tube and analyzed by GC.]

HEMA has a very low vapour pressure (see Table (suppl. Info) 1). In consequence, the saturated vapour density is low, too. Furthermore, risk management measures (e.g. ventilated workplace) are typically in place to lower exposure during handling of substances on industrial scale. For that reason, current workplace concentrations have been determined very low. In conclusion, by practical experience and using protection measurements vapour inhalation does not indicate a significant risk for HEMA.

Battery algorithm and used software of the QSAR of the Danish EPA. The battery outcome is negative for both substances, whereas HPMA is inside the applicability domain, in contrast to HEMA. There are several other inconsistencies in the results of the three systems for the two substances which appears not plausible for such structurally closely related substances. Moreover, the training set for this endpoint is very small with 80 substances (see below; the smallest training set of all endpoints). Thus, this QSAR appears of limited reliability.

Jarvis et al. (2015)

A quantitative structure activity relationship (QSAR) model of Jarvis et al. 2015 can be used to generate an "asthma hazard index" (HI). According to ANSES (2022/2023), the model gave a negative result for HEMA during a RIFM investivation in 2014. The model was also used by Suojalehto et al. (2020) for the identification of potential asthmagens within a broad group of acrylic substances. Here, a positive result was reported, with maximum HI of 1.0 to HEMA that was at the same time misclassified as "highly volatile". In an erratum of the Suojalehto paper in 2021, the assigned volatility was corrected towards "low to moderate volatility" while the HI was not recalculated. It is assumed that the inconsistent output of the model is related to the varying volatility information that was used.

Another reason could be that different versions of the models were used. For that reason, the model has been investigated further. The authors of Suojalehto et al. (2020) describe the HI for a given compound as "the QSAR model's estimate of the probability that the compound has respiratory sensitization potential based on its chemical structure." The QSAR model of Jarvis et al. 2015 is not available for validation nor is its training set of cited positive and negative compounds[22]. The lack of availability for an independent assessment by other scientists prevents any conclusion on the predictive value of this model.

Limitations were identified also for the previous version of the model: Review of the training set of compounds in the earlier Jarvis et al. 2005 model shows a number of sub-grouping of mechanisms of the cited positive compounds. The model was developed to predict potential respiratory asthma not specifically respiratory sensitization. For instance, several of the compounds in the available training set of Jarvis et al 2005 are widely prescribed therapeutic drugs known to sensitize some patients after oral dosing due to the presence of an embedded beta lactam ring. Other compounds show no credible facile reactivity of the parent or any known metabolite (i.e. they are false positives), yet have persisted in various published databases as potential respiratory sensitizers. Still others cause potential respiratory effects due to mechanisms such as mitochondrial toxicity that have no relationship to the chemistry addressed herein.

The lack of transparency and lack of validated acceptance of this model should be recognised and taken into account when this LoE is assessed. Risk and hazard assessment of the compounds should be conducted using a weight-of-evidence approach on a reliable read-across basis based on consideration of sub-mechanisms and route-specific bioavailability.

[22] Status as of Sep 2022

Furthermore, there are apparent anomalies in the predictions made using the QSAR model of Jarvis et al. 2015:

Firstly, “Plain” acrylates are generally known to be more reactive to tissue nucleophiles than methacrylates based on their higher electrophilicity, leading to a higher Michael addition potential and thus to a higher skin sensitization potential. In the used QSAR model, the HI values for “plain” acrylates are however lower than those for methacrylates so that it must be concluded that this QSAR model does not consider electrophilicity as one potential trigger for a sensitization potential which is difficult to reconcile since the grouping argument presented in the publication is the chemical analogy based on the acrylate ion CH2=CHCOO- which is presumably linked to their claimed mode of action.

Secondly, HEMA and another methacrylate ester with even lower volatility[23], received the maximum HI value. It can be concluded from this observation that this QSAR model does not consider at least some physico-chemical parameters relevant to potential for inhalation exposure.

Based on the aforementioned inconsistencies the used QSAR for “asthma hazard index” (HI) is considered as not reliable assessment tool for the probability that a certain compound has respiratory sensitization potential.

Information from the SEV Conclusions for HEMA (ANSES, 2021) and the CLH proposal (ANSES, 2022/23)

In these documents, the FR-MSCA concluded that, based on various SAR models (Derek, Jarvis [see above], CatSAR, Enoch, MultiCase) that were run by RIVM in 2014, no “*reliable conclusion can be reached for the potential respiratory sensitization properties of HEMA based on these SAR models*”. Further, that “*SAR models are known to not be predictive for this endpoint since there is no assay available to assess this type of effects*".

LoE summary

Various QSAR models are available with limited reliability for each model and with limited regulatory acceptance[24]. Moreover, the results are inconsistent to each other. Thus, this LoE is considered with a low level of relevance and also with a low level of adequacy for classification purposes as respiratory sensitiser. In addition, the currently available data has a low level of reliability.

[23] Triethyleneglycol dimethacrylate, TREGDMA (VP of 0.077 Pa at 20°C)

[24] ECHA (2017), chapter R.7.3.9 “A need still remains to develop new (Q)SARs when a robust predictive test method becomes available.”

3.3. Volatility (physico-chemical properties)

A prerequisite for the existence of a relevant hazard is a sufficiently intense exposure to the substance of interest. In Chapter R.7.12 of ECHA Guidance R.7c (2017) on the Interpretation of data regarding respiratory absorption, substances with low volatility are defined to have a vapour pressure of less than 0.5 kPa. As HEMA has an approx. 50 times lower vapour pressure (0.08 hPa at 20°C), HEMA could be considered as a substance of very low volatility.
Saturated vapour concentration at 20°C were calculated with 79 ppm or 427 mg/m³ for HEMA, respectively, on the basis of the aforementioned vapour pressure.
According to the REACH registration for HEMA there are no identified uses that involve the formation of inhalable aerosol.

LoE summary

HEMA is a substance of very low volatility that limits the risk of relevant inhalation exposure. This information is of indirect help for classification purposes, thus this LoE is assessed with a moderate level of relevance. The available physico-chemical data itself is highly reliable but are of low adequacy for classification purposes as respiratory sensitiser.

3.4. ADME

Metabolism/ Toxikokinetics

After oral or inhalation administration, methacrylate esters such as HEMA are expected to be rapidly absorbed and distributed. Short chain alkyl-methacrylate esters are initially hydrolyzed by non-specific carboxylesterases to methacrylic acid (MAA) and the structurally corresponding alcohol in several tissues (see Figure below). MAA is subsequently cleared predominantly via the liver (valine pathway and the TCA (Tricarboxylic Acid) cycle, respectively). The carboxylesterases are a group of non-specific enzymes that are widely distributed throughout the body and are known to show high activity within many tissues and organs, including the olfactory and nasal respiratory tract, liver, blood, GI tract, and skin (Jones, 2002). Those organs and tissues that play an important role and/or contribute substantially to the primary metabolism of the short-chain, volatile, alkyl-methacrylate esters are the tissues at the primary point of exposure, namely the nasal epithelia and the skin, and systemically, the liver and blood. Toxicokinetics seem to be comparable in man and experimental animals.

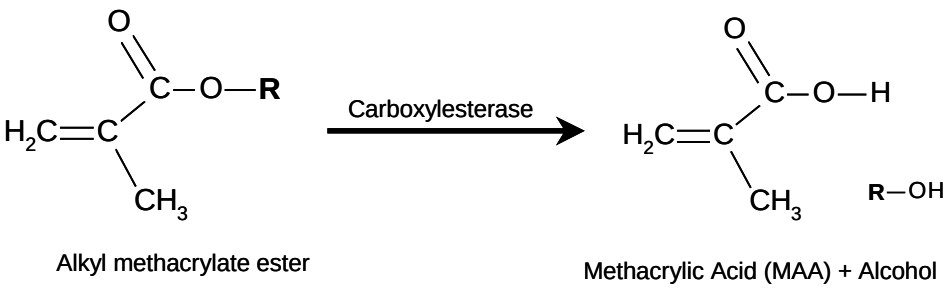


Figure 1: Ester hydrolysis by carboxylesterase

This understanding has been verified experimentally, latest in a non-GLP toxicokinetic study of HEMA in rats via intravenous administration was conducted to evaluate the potential rapid hydrolysis of HEMA in vivo (Dow, 2017). The estimated half-life for HEMA was around one minute (i.e. 0.84 and 1.06 minutes for the two tested animals), indicating that the current study results support the assumption that HEMA was quickly hydrolyzed after intravenous administration in rats.

Ester hydrolysis in the respiratory tract

Tissue specific information on the enzymatic capacity in the respiratory tract of mammals is available from mechanistic studies with other alkyl methacrylic esters, including the methyl ester of MAA, MMA[25]. Gelbke and coworkers (2018) explained in a toxicological assessment of that substance category that "*Former studies have shown that inhalation of MMA predominantly leads to destruction of the olfactory epithelium in the upper respiratory tract of rats. Studies … have demonstrated that this is the consequence of intracellular ester cleavage to MAA, an irritant and corrosive metabolite (Mainwaring et al., 2001) leading to decreased intracellular pH. … whenever ester cleavage to MAA is taking place, this is a detoxification pathway with respect to sensitization*.".

Primary Metabolites – hazard potential

Methacrylic acid (MAA, CAS 79-41-4), the acid metabolite of HEMA, is classified as corrosive upon contact (skin, eyes and respiratory system) depending upon the concentration; harmful when inhaled or ingested, toxic (by skin contact)) again due to its skin corrosive hazard. MAA is not skin sensitizing and, in absence of relevant electrophilicity or protein reactivity (Frederick and Reynolds, 1989; Smith and Hotchkiss,2001), also considered as not respiratory sensitizing.

Ethylene Glycol (EG, CAS 107-21-1), the alcohol metabolite of HEMA, is classified for its systemic toxicity with Acute oral tox. Cat 4 and STOT RE Cat 2 (kidney). EG shows no relevant local toxicity nor is a skin or respiratory sensitizing substance.

Conjugation

The C=C double bond of methacrylate esters makes these chemicals potential Michael acceptors capable of electrophilic attack of protein and other cellular macromolecules. This reactivity also means, however, that methacrylate esters are capable of conjugating with cellular glutathione (GSH). The reactivity towards glutathion of more than 50 methacrylates

[25] Methyl methacrylate, CAS no. 80-62-6

and other chemicals with related structures *has* been estimated with a QSPR model by Cronin (2012). This model predicts that HEMA is slightly reactive towards glutathione (GSH). This is consistent with experimental data by Freidig et al. (1999) who investigated and compared the reactivity with glutathione of a series of acrylate and methacrylate esters.
Methacrylate esters can conjugate with GSH in vitro, although they show a low reactivity, since the addition of a nucleophile at the double bond is hindered by the alpha-methyl side-group. Hence, ester hydrolysis is considered to be the major metabolic pathway for alkyl-methacrylate esters, with GSH conjugation only playing a minor role in their metabolism, and then possibly only when very high tissue concentrations are achieved. With the very low volatility of HEMA then after inhalation exposure this is extremely unlikely to be achieved.
Conclusions
HEMA is readily absorbed by all routes and relatively rapidly hydrolyzed by carboxylesterases at the site of entry and in the liver to MAA and the respective alcohol, EG, which are all not sensitising. Thus the sensitising potential of HEMA is short lived in the body.

LoE summary

HEMA is a subject of rapid enzymatic hydrolysis in the upper respiratory tract with a high level of confidence.
As consequence, the Michael reactivity of the parent ester that is relevant for their weak, general sensitising potential is short lived with again a high level of confidence. This LoE is considered with a moderate level of relevance and a low level of adequacy for classification purposes as respiratory sensitiser. The available set of data is considered moderately reliable.

3.5. Other relevant hazards

3.5.1. Respiratory Irritation

This hazard is briefly considered in this WoE assessment as respiratory irritation can cause comparable symptoms in humans if a substance is highly irritant and sufficiently volatile to reach relevant concentrations in the respiratory tract. Thus, respiratory irritation can be understood as theoretically appearing, alternative, confounding mechanism, or potential uncertainty, as recently discussed for another methacrylate with however much higher volatility ("irritant induced OA"; Pemberton & Kimber, 2022). However, HEMA is not a strong irritant and is likely not sufficiently volatile nor used in aerosol form to create the circumstances of local high concentrations that would be associated with irritant induced OA (see **Appendix III**).

3.5.2. Skin Sensitisation

Based on human data, HEMA is considered as skin sensitiser. Following ECHA's decision scheme for sub-categorisation into relative potency (2017a[26]), for HEMA a classification with Category 1 without subcategorisation is considered as justified as available data from animal tests and observations in humans are not sufficient for sub-categorisation. A clear relation between the potential of a substance for skin sensitisation and for respiratory sensitisation, respectively, is not established in the CLP, although some elements of the respective AOP[27] are likely common. A logic consequence is that respiratory sensitisation is assessed under CLP independently from skin sensitisation in CLP chapter 3.4.2.1. However, a relation between respiratory sensitisation and skin sensitisation is claimed periodically, as for example in the CLH proposal for HEMA (ANSES 2022/2023).

LoE summary

Regarding skin sensitisation, HEMA is considered as skin sensitiser based on human data. This part of the LoE is assessed with a moderate level of relevance (postulated, but not documented link between the two hazards) and a high level of reliability. This classification for skin sensitisation is however not a reliable basis for classification with respect to respiratory sensitisation (low adequacy).
Weak irritation properties have been identified in eye irritation studies. Regarding respiratory irritation however, hydroxyalkyl methacrylates are not considered as respiratory irritants based on these weak irritation properties and also their very low volatility. This part of the LoE is, like the skin sensitisation aspect, considered as inadequate for classification purposes of the substance as respiratory sensitiser. For completeness reasons, this part of the LoE is assessed with a moderate level of relevance for the classification assessment and the available data with a moderate level of reliability.

3.6. In vitro/ ex vivo studies

An Adverse Outcome Pathway (AOP) for respiratory sensitisation to low molecular weight substances is under development at the OECD and the interim status has been published (Sullivan et al. 2017). From the proposed Key Events, only data for Key Event 1 (Covalent binding of substances to proteins) are available for HPMA and a few other alkyl methacrylates. A pre-guideline DPRA test with HEMA, addressing Key Event 1, showed a dominating depletion of cysteine (lysine 13.3%, cysteine 62.4% BASF, 2013). According to ECHA Guidance R.7a (2017b; "*there seems to be a greater selectivity of respiratory sensitisers for lysine*

[26] Section 3.4.2.2.3.1., Table 3.4
[27] The AOP for respiratory is currently under development, as the MoA for this hazard is not fully understood

reactivity than for cysteine, whereas skin sensitisers bind both to cysteine and lysine (Lalko et al., 2013a[28])") this pattern appears contra-indicative for a respiratory sensitiser. Other research indicate that the protein reactivity (for either cysteine or lysine) is not a unifying, general pattern of respiratory sensitisation but associated primarily with chemical structure (Krutz et al. 2021). Irrespective of the inconclusive adequacy of the protein binding pattern, the analogous hydroxyalkyl methacrylate HPMA, as well as other alkyl methacrylates like MMA and nBMA, show a comparable pattern in the DPRA with cysteine depletion generally >30% and lysine depletion generally <10% (e.g. Strickland et al. 2017, Dow, 2020, Wareing et al. 2017), so that a common protein binding pattern for methacrylates can be concluded.
For the other proposed Key Events in the AOP (#2 Cellular danger signals (activation of inflammatory cytokines and chemokines and cytoprotective gene pathways (Th2)); #3 Dendritic cell activation and migration (Th2 skewed); #4: Activation and proliferation of T-cells (Th2), no data is available for HEMA.

LoE summary

For the majority of key events of the proposed AOP for respiratory sensitisation, no data are available. From the available DPRA test with HEMA, there is weak evidence that HEMA is a skin sensitiser but unlikely respiratory sensitiser. This LoE is considered with a high level of relevance, a low level of reliability (in absence of further key event information) and a moderate level of adequacy for classification purposes as resp. sensitiser.

3.7. In vivo/ animal studies

HEMA has been studied in an early series of subacute inhalation rat studies in "nearly saturated vapour" atmospheres (Gage 1970[29]). There was no indication of local effects to the respiratory tracts but the investigation level in this study is considered as insufficient for this assessment.

LoE summary

In absence of relevant data, this LoE is not assessable for its quality levels.

[28] Cited publication – not in reference list below
[29] discussed in more detail in the simplified WoE assessment for respiratory irriation

3.8. Human data

Due to its complexity and heterogeneity, information on human data has been organised by study type, thereby allowing a differentiated assessment of this LoE.
Upfront it should be noted that in the identified public literature and in the information from FIOH to the DS during the preparation of the CLH proposal for HEMA (ANSES 2022/2023), some cases of occupational asthma and related respiratory diseases were described with relation to exposure to HEMA and/ or HPMA and that in all cases, the information in the respective publications are insufficient to provide sufficient information for independent assessment as compiled in ECHA guidance document R.7a (2017). As consequence, the Industry grouped under the HMRTF[30] has contacted all corresponding authors in 2021 to gain more information, however no feedback has been received (by April 2023).
Furthermore, it should be recognised that CLP guidance recognises that positive data from bronchial challenge tests ("specific inhalation challenge" tests, SIC) is sufficient for classification when these tests comply with recognised guidelines. However, CLP or associated guidance does not define what recognises guidelines are. The consensus statement of the European Respiratory Society (ERS; Vandenplas et al., 2014) can serve in this respect and since the available SIC tests fail to meet several key aspects of these guidleines a strength of evidence approach based solely on SIC results cannot be justified. In which case CLP states that a WoE approach should be used. In such a WoE assessment, "*expert judgement is needed … taking relevance, reliability, and adequacy of the information into account*" (ECHA, 2017a; chapter 3.1.2.3.1).

3.8.1. Clinical Case studies

The identified cases below (in total 21) are organised according to the respective industry sector, wherever a sector was identifiable. For overview reasons, all cases are described below briefly while the aforementioned assessment against R.7a criteria is summarised in the LoE summary. In addition, for those cases that where publicly available before the CLH proposal March 2023 (ANSES 2022/2023), the available information per case was assessed against the information requirements in ECHA guidance R.7a and hazard specific critical parameters, like type of diagnosis, likelihood of exposure to HEMA, co-exposure information, pre-existing diseases of relevance and SIC test outcome (see Supplementary information **8.7 Tabulated clinical case assessment (status September 2022)**; this assessment in the Supplementary information does currently not contain the unpublished cases that we became aware of within the CLH proposal in Mar 2023).

[30] Higher Methacrylate REACh Task Force

3.8.1.1. Dental Sector (15 cases)

Piirilä et al., 1998

Piirilä and coworkers investigated 12 cases of potential respiratory hypersensitivity to methacrylate esters in dental personnel of which 7 were claimed to be due to exposure to HEMA. Methacrylate-related skin prick tests (SPT) have been performed with MMA, HEMA, bis-GMA, EGDMA[31] and TREGDMA. The patients described below did dental care, dental fillings and orthodontics. The mean age and working experience of the 6 dental nurses and 6 dentists was 47.3 years and 21.8 years, respectively; mean onset of symptoms was reported with 13.5 years. SIC[32] tests were performed with a placebo (polyol or lactose) and dental methacrylate products in liquid or powder form for 30 min, with a reported number of drops of dental primer and dental adhesive, respectively. If negative, the SIC test was repeated the following day with the double amount of materials.

Case 1

Patient 2 of the publication was a 48-year-old male dentist with a clinical diagnosis of occupational asthma, pharyngitis and laryngitis. He was a non-smoker with familial atopic background, had been exposed to acrylics for 22 years and had symptoms for 3 years. Total IgE was normal with 83 kU/L. SPT was negative for common environmental allergens, latex, and the above mentioned methacrylates. Spirometry and non-specific SIC were normal (no hyperresponsiveness). SIC was slightly positive (no effect in FEV1, 16% in PEV) with an early response after workplace simulation with 1 drop Rely-a-Bond paste and 12 drops of Scotchbond™ adhesive. The composition of the Rely-a-Bond paste is not fully clear but it is unlikely to contain HEMA. A GAC product of this name contains Bis-GMA, Polyethleneglycol dimethacrylate, Quartz, Alumina, Silica and Benzoyl peroxide (GAC International Inc. SDS, 2007[33]), whereas a Reliance product of the same name contains 10-30% Bis-GMA and 50-75% Quartz, last being classified as Respiratory Sensitizer (Reliance Orthodontic Products Inc, 2014). The composition of the Scotchbond™ adhesive was vaguely reported as “containing HEMA and bis-GMA”. An Scotchbond™ adhesive called “Multi-purpose adhesive system” contains 35-45% HEMA, a copolymer of acrylic and Itaconic acid and water, in an SDS issued approx. 10 yrs after the Piirilä cases (3M, 2005); the actual composition of the adhesive composite is thus not fully confirmed but presence of HEMA in the adhesive can be assumed. Diagnosis of occupational asthma was based upon a claimed occupational effect in peak expiratory flow (PEF); the causing agent is not clear.

Case 2

Patient 3 was a 61-year-old female dentist with a clinical diagnosis of occupational asthma. She was a non-smoker with familial atopic background, had been exposed to acrylics for 24 years and had unspecified symptoms for 22 years. Total IgE was elevated at 289 kU/L. SPT

[31] Bis-GMA = bisphenol A-glycidyl methacrylate; EGDMA = Ethyleneglycol Dimethacrylate
[32] Specific inhalation challenge
[33] Not in reference list

was negative for common environmental allergens, latex, and the above mentioned methacrylates. Spirometry and non-specific SIC were normal (no hyperresponsiveness). SIC was positive (20% FEV1 and 20% PEV) delayed after workplace simulation with 20 and 20 drops of Scotchbond™ multipurpose primer and adhesive. Scotchbond™ multipurpose primer was reported to contain 40% HEMA, and the adhesive contained 62% bis-GMA and 37% HEMA (not verified). A more recent product compositions of the multipurpose primer is identically described in the respective SDS as the adhesive mentioned above in case 1 and confirms roughly the concentration of HEMA in the primer (3M, 2017). Diagnosis of occupational asthma was based upon a claimed occupational effect in PEF.

Case 3

Patient 7 was a 53-year-old female dental nurse with a clinical diagnosis of occupational asthma. She was a non-smoker with no atopic background, had been exposed to acrylics for 22 years and had unspecified symptoms for 5 years. Total IgE was normal with 59 kU/L. SPT was negative for common environmental allergens, latex, and the above mentioned methacrylates. Spirometry and non-specific SIC were normal (no hyperresponsiveness). SIC was slightly positive (5% FEV1 and 18% PEV) with an early response after workplace simulation with 4 drops of Scotchbond™ multipurpose adhesive (composition information see case 2). Diagnosis of occupational asthma was based upon a claimed occupational effect in PEF.

Case 4

Patient 9 was a 61-year-old female dentist with a clinical diagnosis of occupational asthma. She was a non-smoker with no atopic background, had been exposed to acrylics for 25 years and had unspecified symptoms for 10 years. Total IgE was normal with 93 kU/L. SPT was negative for common environmental allergens, latex, and the above mentioned methacrylates. Spirometry was indicative of slight obstructive airways disease and a non-specific SIC indicated moderate hyperresponsiveness. SIC was positive (20% FEV1 and 16% PEV) with a late response after workplace simulation with 10 drops of each, Scotchbond™ multipurpose primer and adhesive (compositions see case 2). Diagnosis of occupational asthma was based upon a claimed occupational effect in PEF.

Case 5

Patient 10 was a 41-year-old female dental nurse with a clinical diagnosis of rhinitis. She was a non-smoker with no atopic background, had been exposed to acrylics for 22 years and had unspecified symptoms for 6 years. Total IgE was elevated with 270 kU/L. SPT was negative for common environmental allergens, latex, and the above mentioned methacrylates. Spirometry was indicative of slight obstructive airways disease and a non-specific SIC indicated slight hyperresponsiveness, too. There was no claimed occupational effect in PEF. No change in SIC was reported after workplace simulation with 20 drops of each Scotchbond™ multipurpose primer and adhesive (compositions see case 2). The basis for the diagnosis of occupational asthma was not indicated.

Case 6

Patient 11 was a 34-year-old female dental nurse with a clinical diagnosis of asthma. She was a non-smoker with atopic background (also familiar), had been exposed to acrylics for 10 years and had unspecified symptoms for 9 years. Total IgE was elevated with 260 kU/L. SPT was positive for at least common environmental allergens, latex, and the above mentioned methacrylates. Spirometry was normal whereas a non-specific SIC indicated slight hyperresponsiveness. SIC was positive (13% FEV1 and 17% PEV) with a late response after workplace simulation with 20 drops of each, Scotchbond™ multipurpose primer and adhesive (compositions see case 2). Diagnosis of occupational asthma was based upon a claimed occupational effect in PEF.

Case 7

Patient 12 was a 49-year-old female dental nurse with a clinical diagnosis of asthma. She was a non-smoker with a familiar atopic background, had been exposed to acrylics for 28 years and had unspecified symptoms for 1 year. Total IgE was normal with 43 kU/L. SPT was negative for common environmental allergens, latex, and the above mentioned methacrylates. Spirometry was indicative of slight obstructive airways disease while a non-specific SIC was normal (no hyperresponsiveness). SIC was positive (24% FEV1 and 13% PEV) with a late response after workplace simulation with 20 drops of each, Scotchbond™ multipurpose primer and adhesive (compositions see case 2). Diagnosis of occupational asthma was based upon a claimed occupational effect in PEF.

Lindström et al., 2002

A 47-year-old non-smoking female dentist, being 22 yrs at work, had not had allergic symptoms as a child. She developed symptoms of rhinoconjunctivitis and sneezing for 12 years, cough attacks for 10 years, and shortness of breath for 2 years. Furthermore, she had had hand and face dermatitis for 3 years. The symptoms were work-related and disappeared during weekends and holidays. PEF monitoring at work and at home pointed towards occupational asthma. The histamine challenge test showed moderate bronchial hyper-reactivity. There were no positive reactions in SPTs to common allergens including "acrylates" while the dentist had positive patch tests with various methacrylates (bisGMA, HEMA, HPMA, EGDMA, EMA, MMA) and EA[34] which are components of dental Scotchbond™ products. In the first SIC with the adhesive (containing 62% of BisGMA and 37% of HEMA; 20 drops altogether during 30 min), a borderline weak early response was observed that was considered as negative response (10% decrease in FEV1[35] after 45 min). In the second test, with both the adhesive and the primer (containing 40% HEMA; no further information on other components in the product; 40 drops during 30 min), an early late 23% FEV1 reduction was recorded, at a maximum at 3 h.

In this case, occupational exposure to several components was given so that the acquisition of a sensitisation cannot be assigned to a single substance. Also, the challenge tests were

[34] EMA = Ethyl Methacrylate; EA = Ethyl Acrylate

[35] FEVI = Forced expiratory pressure in 1 sec

done with mixtures of partially unknown composition; HEMA (or HPMA) concentrations during SIC were not measured. The SIC response is not fully consistent as the first SIC actually failed to reach relevant effect strength (set to 15% as trigger for positive SIC response in the consensus statement for SIC tests by Vandenplas et al., 2014).

ANSES, 2022/2023

In the CLH proposal of March 2023, ANSES as DS reported information on seven cases that were initially provided by the Finnish Institute of Occupational Health (FIOH), referring to patients from the dental sector that were diagnosed between 2000 and 2018. The information per case is limited to some information in tabular form (job, limited clinical information of the patients, SIC products with methacrylate concentrations, SIC responses and other clinical diagnosis; assumed exposure during SIC and during work) but it is insufficient to provide sufficient information for independent assessment as compiled in ECHA guidance document R.7a (2017). Relevant, missing information include information on the non-specific bronchial hyperreactivity of the airways, amounts of material used, eventual exposure measurements during SIC and at the workplace and the presence of confounding other substances.

For all cases, a conclusion of FIOH is reported that "*HEMA and/or HPMA (hydroxypropyl metacrylate) to be the main causative agent of asthma*" and that FIOH believe "*that these patients had respiratory exposure predominantly to HEMA at work and that they were mainly exposed to HEMA also in the SIC*". The documented conclusion itself, or the underlying assessment, is not provided in the CLH proposal, so that this conclusion appears unsubstantiated.

From the limited available information, the cases can be briefly described as follows.

Case 1

Patient 1 was a dental hygienist. A PEF (peak expiratory flow) monitoring at work was not performed, so the basis of the diagnosis of OA remains unclear. He was "probably" exposed to HEMA in the SIC test *"together with other methacrylates*", and the test item "*ScotchBond Universal adhesive"* is reported with concentrations of 60-70% Bis-GMA and 30-40% HEMA (see **Appendix I Table 1** for more details on product compositions). The patient had no asthma prior to work and no atopy. He was negative to HEMA in a skin prick test. A SIC was positive with a dual reaction (maximum 18% fall in FEV1 during first 60 min and maximum 25% fall in FEV1 after first 60 min). No further information available.

Case 2

Patient 2 was a dentist. A PEF (peak expiratory flow) monitoring at work was "*uncertain*", so the basis of the diagnosis of OA remains somewhat unclear. He was reported to be exposed to HEMA in the SIC test, but the basis for this information is unclear. It appears that the patient was challenged in the SIC test with a combination of products, whereas one test item "*ScotchBond Universal Primer"* is reported with concentrations of 35-40% HEMA and a polymer, and another test item "*Silyx restorative*" is reported to contain no HEMA. The patient had no asthma prior to work but was atopic. He was negative to HEMA in a skin prick

test. A SIC was positive with a dual reaction (maximum 27% fall in FEV1 during first 60 min and maximum 17% fall in FEV1 after first 60 min). No further information available.

Case 4

Patient 4 was a dental hygienist. A PEF (peak expiratory flow) monitoring at work was not performed, so the basis of the diagnosis of OA remains unclear. He was reported to be exposed to HEMA in the SIC test, but the basis for this information is unclear. The patient was challenged in the SIC test with a "*Scotchbond dental adhesive*" which is reported with concentrations of 35-40% HEMA and a polymer (see **Appendix I Table 1** for more details on product compositions). The patient had no asthma prior to work and no atopy. He was negative to HEMA in a skin prick test. A SIC was positive with a dual reaction (maximum 16% fall in FEV1 during first 60 min and maximum 26% fall in FEV1 after first 60 min). No further information available.

Case 6

Patient 6 was a dental hygienist. A PEF (peak expiratory flow) monitoring at work was not performed, so the basis of the diagnosis of OA remains unclear. He was reported to be exposed to HEMA in the SIC test, but the basis for this information is unclear. The SIC test item was not exactly reported, but was apparently "*ScotchBond adhesive"* with a "known" concentration of 30-40% HEMA (see **Appendix I Table 1** for more details on product compositions). The patient had no asthma prior to work and no atopy. He was not tested in a skin prick test. A SIC was positive with a dual reaction (maximum 17% fall in FEV1 during first 60 min and maximum 31% fall in FEV1 after first 60 min). No further information available.

Case 7

Patient 7 was a dental hygienist. A PEF (peak expiratory flow) monitoring at work was "*uncertain*", so the basis of the diagnosis of OA remains somewhat unclear. He was reported to be exposed to HEMA in the SIC test, but the basis for this information is unclear. It appears that the patient was challenged in the SIC test with a combination of products ("*Scotchbond adhesive & primer*"), whereas one test item is reported with "known" concentrations of 30-40% HEMA. The patient had no asthma prior to work and had no atopy. He was negative to HEMA in a skin prick test. A SIC was positive with a late reaction (maximum 10% fall in FEV1 during first 60 min and maximum 24% fall in FEV1 after first 60 min). No further information available.

Cases 3 & 5

These patients, two dentists, did not agree to contribute to the investigations by sharing their data ("*patient's consent not obtained*"). Thus the information level for these two cases is extremely low and restricted to information on the product (case 5) or product combination (case 3; see **Appendix I Table 1**for more details on product compositions). Thus, these cases cannot be assessed independently.

3.8.1.2. Cosmetic Sector (6 cases)

Moulin et al., 2009

Moulin reported a study on the occurrence of Allergic Contact Dermatitis (ACD) in combination with Occupational Asthma (OA) on workers diagnosed with Contact Dermatitis (CD). Out of eligible 234 subjects in various industry sectors, three patients were identified with ACD and OA of which 2 were claimed to be caused by HEMA.

Case 1

Patient 1 was a 44-year-old female beautician with a clinical diagnosis of ACD and OA. She was a non-smoker and claimed to have no atopic background although she showed intolerance to jewelry, make-up pencils and her daughter had asthma. She experienced cutaneous and unspecified respiratory symptoms 5 months after using a new nail prosthesis method with new solvents during work. She however used artificial nails also for herself (method and material unknown). Total IgE was normal. SPT was negative to the standard series of allergens but she tested positive to HEMA in a SPT. Spirometry was normal, while the non-specific SIC test with methacholine indicated the presence of reactive airways. She reported a pattern of work-related respiratory symptoms although no PEF monitoring was done so that this claimed pattern remains unconfirmed. SIC was reported after challenge with HEMA without hardener and she developed an early 20% drop in PEV1 after 60 minutes with dyspnea.

Case 2

Patient 2 was a 22-year-old female beautician with a clinical diagnosis of ACD and a claimed OA. She was a non-smoker and had asthmatiform bronchitis and seasonal spring rhinitis in her childhood, and her mother was asthmatic. She experienced cutaneous and unspecified respiratory symptoms 5 months after working with nail prostheses, whereas her symptoms improved during weekends and especially holidays. She was reported to be involved in applying nail prosthesis with an activated ultraviolet gel and acrylic liquid, the SDS of which indicated that it contained HEMA (without any further information). Total IgE was normal. SPT was negative to the standard series of allergens but she tested positive to the activated ultraviolet gel and acrylic liquid in SPT. No spirometry, non-specific or specific SIC was made. The diagnosis of OA was made on the basis of positive ACD to HEMA and a claimed work related pattern of respiratory complaints.

In the case of patient 1 she was atopic with ACD to multiple agents. There was also an indication of familial asthma so the bronchial reactivity observed with the nonspecific SIC and the early SIC could be due to irritant provocation of pre-existing sensitive airways by other volatile chemicals. In the case of patient 2 she was clearly atopic and asthmatic and other than the confirmed ACD to HEMA there was no evidence that HEMA caused the asthmatic condition. Moreover, the health effects appear to be related to the use of activated UV gels – a product type that typically contains highly reactive photoinitiators like the acknowledged

skin sensitizer benzoyl peroxide (MPA, 2021)[36,37]. The experience of a work related pattern in respiratory symptoms could equally be related to irritant provocation of pre-existing sensitive airways. Furthermore, the involvement of other chemicals, such as contained in the UV gel (UV cure resins have been implicated in the development of ACD and OA) cannot be excluded. In summary neither case provides strong evidence of a causative association between exposure to HEMA and development of asthma.

Sauni et al., 2008

Case 1

The patient was a 30-year-old female manicurist and nail technician with 6 yrs work experience. Her main job was to apply sculptured nails and artificial tips to nails including sanding the nail plate. She attached the plastic nail with a glue that contained both cyanoacrylate and methacrylates esters as known skin sensitising components; last were reported by the authors as HEMA, bis-GMA, EDGMA, MMA and TEGDMA. The typical procedure was performed on a special downdraft table to reduce exposure.

The patient had smoked for 2 years some years ago. The patient developed hand eczema 3 months after starting to apply artificial nails. Skin patch tests provided an inconsistent picture: while being positive to 2-HEMA and EGDMA in a local hospital, she was negative to methacrylates four year later at the Finnish Institute of Occupational Health (FIOH). She experienced rhinitis, wheezing, and dyspnoea during exercise. In pulmonary examinations at a local central hospital, spirometry was normal but the bronchodilatation test was positive. In the histamine challenge test, there was moderate bronchial hyperresponsiveness, and the patient had typical asthmatic symptoms (dyspnoea and wheezing). Because she had respiratory symptoms when applying artificial nails, her asthma was also suspected to have an occupational origin.

At FIOH, X-Rays of the thorax and nasal sinuses were normal. Spirometry showed mild peripheral obstruction without a bronchodilatation effect. The exhaled NO was normal. In the histamine challenge test, mild bronchial hyperresponsiveness occurred. A significant variation was noted in the PEF measurements at home and at the workplace: the PEF values varying from 360 to 580 L/min with a maximal diurnal variation of 26% and frequent bronchodilating effects up to 43%. The reference SIC test was negative. In the active bronchial challenge test with the product mixtures described below under “Exposure to chemicals”, a dual asthmatic reaction was noted: an immediate significant decrease of 25% in the FEV1, and 4 hr after the start, a delayed significant decrease of 37% in the FEV1. On the basis on the work-related respiratory symptoms and findings in the workplace PEF follow-up, as well as the positive work simulation test, OA due to exposure to sculptured nails containing MAs was diagnosed. Exposure to the highly irritating cyanoacrylate esters was not further described but cannot be excluded as causation for the health effects.

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[36] Methacrylates+Use+in+Nail+Enhancements+6-3-20.pdf (sqspcdn.com)

[37] Datenbank des C&L-Verzeichnisses (europa.eu)

Case 2

The patient was a non-smoking 27-year-old female hairdresser/ nail technician with 5 yrs work experience. The job process and the used products were similar to that of Patient 1. The patient was SPT positive to cat and pollen allergens. She developed rhinitis, loss of voice, and recurrent sinusitis during the first year as nail technician. In pulmonary examinations at a local central hospital, bronchial asthma was diagnosed with no skin symptoms and normal spirometry but significant diurnal PEF variation and recurrent bronchodilating effects, so that this patient was considered atopic. In the histamine challenge test, she showed mild bronchial hyperresponsiveness.

At FIOH, the patient had no respiratory symptoms, while spirometry showed mild peripheral obstruction and in the histamine challenge test, moderate bronchial hyperresponsiveness was noted. Exhaled NO value was increased. No significant diurnal variations were observed in the workplace PEF follow-up, where the patient did not prepare nails. Standard SPTs confirmed earlier findings, whereas methacrylate esters were not tested. Also in this patient, the reference bronchial challenge test was negative while in the active SIC test with the product mixtures described below, a dual asthmatic reaction (immediate decrease of 20% in the PEF and 16% in FEV1 followed by a delayed drop of 27% in the PEF and 19% in FEV1 after 8 hrs. In analogy to Patient 1, OA due to exposure to sculptured nails containing MAs was diagnosed.

Exposure to chemicals

The concentrations of methacrylate esters in the gel nail materials and in the gel nails themselves were determined after the active SIC test of Patient 2 (see **Table 5**) and those can be anticipated for Patient 1 as well. inhalation exposure to those substances at the workplace or during the SIC tests was however not reported. Also, exposure to sanding dust is likely but was neither reported nor quantified.

While for the various gel nail materials different compositions of esters were detected, with maximum concentrations of HEMA (8%) in the bonding agent and of HPMA (7%) in the sculpture resin, their complete compositions remain unclear. Actually, the unknown components account for approx. 90% w/w in the bonding agent, approx. 80% in the sealing resin, and 40% in the sculpture resin. As further skin sensitising components, cyanoacrylates were mentioned by the authors but neither specified nor quantified. Plausibly, hardened (= polymerised) gel nails contained no detectable amounts of methacrylic monomers.

Product	Identified methacrylates	Concentration (%, w/w)	Identification
Bonding agent	HEMA	7.5	GC-MS/LC
	EGDMA	0.8	GC-MS/LC
	TREGDMA	0.2	GC-MS/LC
	Ethyleneglycol acrylate methacrylate	1	GC-MS
	Ethyleneglycol-based dimethacrylates[a]	2	GC-MS
	Ethyleneglycol monomethacrylate	0.5	GC-MS
	MMA	<0.05	GC-MS/LC
Sealing resin	HEMA	<0.01	GC-MS/LC
	MMA	<0.01	GC-MS/LC
	EGDMA	0.1	GC-MS/LC
	Ethyleneglycol-based dimethacrylates[a]	20	GC-MS
Sculpture resin	HEMA	0.03	GC-MS/LC
	MMA	<0.01	GC-MS/LC
	HPMA	6.7	GC-MS/LC
	TREGDMA	≤0.1	GC-MS
	BUDMA	≤0.1	GC-MS
	Ethyleneglycol-based dimethacrylates[a]	12	GC-MS
	Bis-GMA	42	GC-MS/LC
Gel nails	HEMA	<0.01	GC-MS
	Aliphatic dimethacrylates	<0.01	GC-MS

HEMA, hydroxyethyl methacrylate; EGDMA, ethyleneglycol dimethacrylate; TREGDMA, triethyleneglycol dimethacrylate; MMA, methylene methacrylate; HPMA, hydroxypropyl methacrylate; BUDMA, butandiol methacrylate; Bis-GMA, 2,2-bis-(4-(2-hydroxy-3-methacryloxypropoxy)phenyl)-propane; GC-MS, gas chromatography with mass selective detection; LC, liquid chromatography.
[a]Tentatively identified according to the presence of the ions 69 and 113 in the mass spectrum.

Table 5: Concentrations of methacrylate esters in gel nail materials and gel nails (taken from Sauni et al. 2008)

In both cases, respiratory effects were postulated to be linked to dermal exposure to methacrylates contained in artificial nail material. Skin sensitisation to two methacrylates including HEMA was however documented only for Patient 1. For Patient 2, skin sensitisation is rather unlikely in absence of skin symptoms. Further uncertainty on this postulation arises from the missing measurement of respiratory exposure to those methacrylates, or sanding dust as alternative causing agent for these respiratory effects. Moreover, unknown components in the materials including cyanoacrylates could also be potential causal agents for the observed effects. Finally, it is important to understand that these two SIC cases were provenly not guideline-conform as complex mixtures were tested, above all with a dominance of unknown components, and not substances as requested in the aforementioned ERS consensus statement (see chapter 3.8) . As not guideline-conform SIC tests, the results cannot be regarded as clear evidence for the respiratory sensitising hazard potential of HEMA/ HPMA according to CLP criteria.

Moshe et al., 2019

A case study report of a 48-year-old female nail beautician that developed contact dermatitis and coughing and shortness of breath, which was worsen at the start of work, and improved on vacations. She was patch tested positive to HEMA and HPMA. She had unspecific reactive airways (22% decrease in FEV1 with methacholine challenge). A PEF test was reported but no information on the details or outcome was provided. A TLV-TWA was reported as 2 ppm without naming the respective substance. Also occupational levels have not been reported. No further relevant information is available from this conference abstract.

In this case, respiratory effects were only vaguely reported so that this case cannot be assessed further. However, any diagnosis and causative investigation must be evaluated in relation to the unspecific respiratory hypersensitivity of the patient.

ANSES, 2022/2023

For background information on data source and data level, see "Dental sector" above.

From the limited available information, the case can be briefly described as follows.

Case 8

Patient 8 was a hairdresser. A PEF (peak expiratory flow) monitoring at work was "*uncertain*", so the basis of the diagnosis of OA remains somewhat unclear. It was claimed that he was "probably" exposed to HEMA in the SIC test although the HEMA content in the test item, hardened artificial nails was *"very low in the chemical analysis, probably < 0,01%*". As the SIC test was performed during "*grinding of newly hardened nails*", the patient was primarily exposed to dust. Details on the three basic products before hardening are reported but appear not relevant for assessment (see **Appendix I Table 1** for more details on product compositions). The patient had no asthma prior to work but was atopic. He was negative to HEMA in a skin prick test. A SIC was positive with a dual reaction (maximum 16% fall in FEV1 during first 60 min and maximum 19% fall in FEV1 after first 60 min). No further information available.

3.8.1.3. Undefined Sectors (unknown number of cases)

Suojalehto et al., 2020 (unknown case numbers of cases with HEMA)

An international group of investigators published this retrospective, observational study on clinical cases with claimed acrylate-induced Occupational Asthma (OA). Various information was collected for a broad chemical group of acrylates containing "plain acrylates", cyanoacrylates and methacrylates without specific substance details. The diagnostic temporal patterns of bronchial responses to SIC and other characteristics of 55 'acrylate' related cases were statistically compared with 418 cases with "other Low Molecular Weight (LMW) agents" and 125 cases with Isocyanates. The cases cited are from across 20 tertiary centers in Europe participating in the "European Network for the Phenotyping of Occupational Asthma" (E-PHOCAS) and the majority of subjects underwent several diagnostic observations including

SIC (Specific inhalation Challenge) for almost all of the acrylate-related 55 cases, plus FENO (fractional exhaled nitric oxide) and eosinophil counting in blood in about half of those cases. Workplace and 'acrylate' related exposure information, demographic and clinical history data was collected for a broad grouping of acrylates and sub-categorised into "plain acrylates", cyanoacrylates and methacrylates. Whilst representative substances per subgroup were named cases were not identified by specific substance. The diagnostic patterns and other characteristics of the 55 'acrylate' related cases were statistically compared with 418 cases with "other Low Molecular Weight (LMW) agents" and 125 cases with Isocyanates.
The investigators presented groupwise data from tests of the non-specific bronchial hyperreactivity (2/3 of cases with mild to severe hyperreactivity) and temporal patterns of bronchial responses to SIC, being indifferent to other LMW agents or Isocyanates.
The authors concluded that "*Acrylate-induced OA shows specific characteristics, concomitant work-related rhinitis, and exposure related increases in fractional exhaled nitric oxide, suggesting that acrylates may induce asthma through different immunologic mechanisms compared with mechanisms through which other LMW agents may induce asthma. Our findings reinforce the need for a reevaluation of the hazard classification of acrylates, and further investigation of the pathophysiological mechanisms underlying their respiratory sensitizing potential.*"
On request, the corresponding author of this paper provided information on chemical subgroup level, indicating 24 cases related to methacrylates in Feb 2020 (Cullinan, 2020). Six of these 24 cases were assigned to MMA in the course of the CLH process of MMA by the authors. From the remaining 18 cases, ten cases diagnosed at FIOH can be assigned to potential exposure to HEMA and HPMA (see above[38]). For the remaining eight cases, the potential methacrylate ester is unclear.
The information provided in this publication is too limited to consider this source of information as relevant for assessment. Authors have been contacted in 2021 but denied to provide further information.

LoE summary

Dental
Fifteen cases, thereof six dentists, five dental nurses and four dental hygienists, were identified from the dental sector from three source documents (publications: Piirilä et al. 1998 with seven cases plus Lindström et al. 2002; CLH proposal ANSES 2022/2023: seven cases), interestingly all from the same clinical institute in Finland. One reason for this concentration of cases from one single institute is likely that the SIC tests with dental material were, by default, performed at FIOH by using "*2 x 10-20 drops of a dental adhesive*" according to the

[38] Two of ten only relevant for HPMA, thus not discussed in this assessment

revised Handbook for SIC procedures (Suojalehto et al. 2019). Based on the initial workplace assessment that HMRTF performed and that was confirmed by the manufacturer of the dental products (3M, 2012[39]; 3M, 2023), these amounts used in SIC tests exceed 10-20 times the standard amounts used in the dental workplace. This approach apparently conflicts with the principle stated in the ERS consensus statement "*to deliver the suspected occupational agent in the same conditions as those that prevail in the workplace in terms of its physical characteristics (i.e. gas, fumes, liquid or particles aerosols) and its chemical form (e.g. monomer versus polymer), preferably on the basis of a detailed workplace exposure assessment*" (emphasis added). It should be noted that, in the case of Lindström patient as example, 20 times the quantity of products containing methacrylates that would be encountered in the workplace failed to invoke a clinically significant asthmatic response. While 40 times the quantity routinely used did invoke a significant asthmatic response there were no exposure measurements to exclude the possibility that irritation may have been the cause of the clinical findings, especially as the patient had hypersensitive airways as indicated by the moderate NSBHR. Overall, the testing with excess of dental material is understood as critical confounding factor for the interpretation of observed effects.

Of the eight published cases, seven were diagnosed with OA, and rhinitis in the 8th case. Based on the case descriptions, occupational contact to HEMA is considered as likely but not necessarily inhalation exposure. In all cases, there is relevant co-exposure to other substances that are contained in dental products used as primers and adhesives, predominantly bis-GMA but also other methacrylates (MMA, EGDMA, EMA) or ethyl acrylate, in SIC tests as well as at daily work. In addition, co-exposure to inorganic material like quartz, Alumina or silica is known from dental labs. However, co-exposure to known respiratory sensitisers was not mentioned.

Overall, it becomes obvious that all SIC tests were performed with rather complex mixtures, or even combinations of these complex mixtures, which is typical for this sector but this conclusion prohibits a guideline conformity as the ERS consensus statement postulates testing with single substance to establish a clear causal relationship, at least for effects seen in a SIC test. As significantly deriving from the guideline just at this criteria, the SIC results cannot be regarded as clear evidence for the respiratory sensitising hazard potential of HEMA according to CLP criteria.

Furthermore, it is reported in the CLH proposal that FIOH diagnosed approximately 150 patients with suspicion of occupational asthma and/or rhinitis related to HEMA (or HPMA). The vast majority apparently reacted negative in the respective SIC tests, seven of them were tested with amounts of dental product combinations far in excess of occupational levels, and one (from the cosmetic sector, FIOH case 8) was exposed to dust. Thus, only weak evidence that is related to this observed pattern.

[39] https://www.ultimatedental.com/uploads/3M_ScotchbondUniv_DC.pdf

Where reported, the vast majority of patients had a clinical history that indicate immunologic hypersensitivity (atopy – individual or in the family) or respiratory hypersensitivity (unspecific bronchial hyperreactivity; information not available for the FIOH cases). The IgE[40] responses (unspecific indicator for immune-based mechanisms; data only available for the Piirilä patients), were heterogenous with four cases without increase and 3 with increase. SIC tests were performed in 15 cases with the HEMA containing dental primers and/ or adhesives and thus with mixtures, by repeating typical dental handling routines during the SIC. Like the IgE responses, the SIC responses were heterogeneous, with a borderline EAR and one negative test. A second SIC with the Lindstrom case was positive but the response pattern was unclear ("early late"). Regarding the R.7a requirements, the majority of information was not available to assess the cases (see Supplementary information **8.7 Tabulated clinical case assessment** for publicly available cases) .

Cosmetic

Five cases were identified from the cosmetic sector within three publications (Moulin et al. 2009, Sauni et al. 2002 with 2 cases each plus Mosche et al. 2019. In all cases, OA was diagnosed. Based on the case descriptions of Moulin et al., occupational inhalation exposure to HEMA is considered as likely in one case (in absence of analytic confirmation) and as unknown in the other case, but in no case to HPMA. For the cases of Sauni and Mosche, dermal exposure was reported to HEMA and HPMA but inhalation exposure is considered as questionable. There is relevant co-exposure to other substances but the publications suffer from substantial descriptions. Case #2 of Moulin was co-exposed to unspecified UV cure resins; Sauni described dermal exposure to various crosslinking methacrylates but not on inhalation exposure, while for the 1st case of Moulin and the Mosche case no information on coexposure was reported. inhalation exposure to dust as potential respiratory sensitising agent is documented for the two cases of Sauni. All patients had a clinical history that indicate immunologic hypersensitivity (atopy – individual or in the family; or dermal intolerances) or respiratory hypersensitivity (unspecific bronchial hyperreactivity or asthma). IgE responses were only reported for the two Moulin cases showing both no effect. SIC tests were performed in 3 cases with the with sector specific product mixtures of incomplete declaration, by repeating typical handling routines during the SIC. As for the dental cases above, testing with rather complex mixtures in this sector prohibits a guideline conformity also of these SIC tests, and thus CLP criteria are not fulfilled to regard these tests as clear evidence for the respiratory sensitising hazard potential of HEMA/ HPMA.

In all cases SIC tests, patients responded positive while the response pattern was again heterogeneous, with 2 dual responses, and one EAR. Regarding the R.7a requirements, the majority of information was again not available to assess the cases (see Supplementary information**Tabulated clinical case assessment** for publicly available cases).

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[40] Immune globuline E

This branch of the human LoE is considered to be highly relevant for the classification assessment (as per CLP guidance on use of human data). However, the currently available set of data has a low level of reliability (by failing to provide the majority of R.7a information and failing the CLP criteria for guideline-compliant bronchial challenge (SIC) tests), reducing the strength of this evidence and rendering it unsuitable for classification purposes.

3.8.2. National health surveillance databases

France/ RNV3P

In France, the national network for the monitoring and prevention of occupational disease (RNV3P) collects every year a few thousands of new occupational health reports throughout France since 2001. This national database is "*primarly designed for data collection and statistics can also be used for the detection of new/emerging work-related diseases*" (ANSES, 2019), i.e. not for chemical regulation purposes.

From this database, ANSES stated in its SEV conclusion for HEMA (2021) and the recent CLH proposal (2022/2023) that "*several cases of asthma were reported with acrylates or methacrylates but none has been specifically related to HEMA. These cases were mainly observed in dental professionals and nail technicians*." In 2021, RAC assessed the reliability of RNV3P cases as too weak for classification purposes due to the minimal level of information and thus disregarded provided information in a CLH process for another methacrylate, MMA (ECHA, 2021). Correspondingly, eventual existing asthma cases with claimed relation to HEMA are assumed to be irrelevant for this assessment if no additional case information will be provided.

Germany – dental/ BG ETEM

The BG ETEM[41] investigated occupational diseases between 2015 and 2019 for dental technicians in Germany (BG ETEM, 2021). Here, this Workers Compensation Funds identified no asthma case with relation to HEMA beyond those approximately 45,000 – 50,000 workers that are expected to have frequent contact to methacrylates.

LoE summary

Only very limited information is available from national health surveillance databases. As a note, this is not surprising as the content of national health surveillance databases is, by purpose, not publically available.

On sector overarching, national level, extremely vague information from one European country is currently available (France/ RNV3P). RAC concluded that even with an improved

[41] Berufsgenossenschaft Energie Textil Elektro Medienerzeugnisse (Workers Compensation Funds for the vast majority of dental technicians in Germany)

information level, the information level from the French database is too weak for classification purposes and thus should be disregarded in a CLH process. Thus, this vague information from the French database is disregarded.
Sector specific information from another European country (Germany/ BG ETEM) is available for a five year period. No potential OA cases are known in this relevant Industry sector with relation specifically to HEMA beyond a relative high number of frequently exposed workers. In other words, data from the likely largest national dental sector in the EU contradicts to the hypothesis that HEMA can cause OA.
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This branch of the human LoE is considered with a high level of relevance (in line with CLP texts that overweigh human data), and a correspondingly high level of adequacy for classification purposes as respiratory sensitiser. However, the available information are of different reliability (RNV3P: low reliability by failing to provide the any R.7a information; ETEM: high reliability with regards to R.7a requirements) requiring a careful further assessment of this LoE.

3.8.3. Exposure

For the assessment of the strength of this line of evidence, exposure information was structured by industry sectors below.
A sector-overarching research on actual compositions of mixed products containing (meth)acrylic esters revealed that declarations on SDSs consistently do not report all components of the respective mixtures (Henriks-Eckerman & Kanerva, 1997), at least in a time period approx. two decades before. In this work, dental products, glues, paints and lacquers were investigated. This misinformation in (earlier) SDSs hinders the exclusion of co-exposure to other substances that are equally or more likely to be responsible for the observed health effects as required by CLP criteria ("*Clinical history shall include both medical and occupational history to determine a relationship between* ***exposure to a specific substance*** *and development of respiratory hypersensitivity.*"[42]).

Exposure in sectors WITH asthma cases suspected to be linked to exposure to HEMA
Dentistry (Professional use)
In dental laboratories formulations of monomers and methacrylic polymers are used for restorative purposes, e.g. to construct orthodontic components, fillings and inlays. Exposure relevant tasks like mixing, filling and polymerizing with liquid methacrylate esters may take place several times for a short duration or regularly over a longer period, both over the whole shift. During these tasks, workers are generally exposed to a broad cocktail of chemicals (solvents, acrylates/ methacrylates) and dusty materials (see BG ETEMs homepage on dental

[42] CLP, § 3.4.2.1.2.4.

labs[43]). Last can be grouped to anorganic dusts of plaster, non-precious and precious metals (chrome, nickel, cobalt, gold, palladium etc.) ceramics (amorphous and crystalline silica, quartz, cristobalite etc.) and rare metal oxides (zirconium dioxide, hafnium and yttrium oxides etc.) and organic dusts (PMMA). Individual exposure profiles may vary depending on specific tasks or job profiles.

In a study of dental clinics, levels for HEMA were reported as being low (0.003 mg/m³) in the breathing zone of dental nurses working on composite resin restorations (CRRs) in sampling periods of 15-30 min, with a maximum concentration of 0.033 mg/m³ with peaks being 3-5 times higher (Henriks-Eckerman et al., 2001). Typical CRR materials are reported to consist of a resin matrix and filling particles. The resin system typically consists of bis-GMA, UDMA[44], TEGDMA, HEMA or other short chain oligomers, according to the authors.

In another study in five public dental clinics, 8hr TWA levels of HEMA were low (median 0.003 mg/m³, maximum 0.015 mg/m³,) while short-term, task specific exposure levels showed a significant higher variability with somewhat more pronounced maximum levels (median 0.001 mg/m³, maximum 0.079 mg/m³, Hagberg et al., 2005). As components of the bonding agent, the authors named "HEMA (20–40%), or TEGDMA, and sometimes also methylmethacrylate (MMA)" without providing a complete component list.

Similar findings were also reported during dental filling treatments with maximum concentrations of 0,045 mg/m3 for HEMA being reported (Marquardt et al., 2009). Beside HEMA, MMA, EGDMA, and TEGDMA were identified in the air of dental practices during short-term sampling of 15 min using the solid phase microextraction method.

Nilsen and coworkers (2019) studied the inhalation exposure to certain organic substances in resin-based dental materials in the breathing zone of dental students. Here, HEMA, as 20-40% component in the used primer and bonding agent, respectively, was identified, but it was not quantifiable by GC-MS.

Other publications investigating the workplace atmosphere in the dental sector had a different focus. For example, Hong et al. (2015) identified in total 68 volatile organic substances (VOCs) in various sampling sites within a dental clinic in Taiwan. MMA was the only named representative of methacrylic esters; maximum concentrations were up to 11.5 mg/m3. Other quantified substances were methylene chloride, chloroform, chloromethyl benzene, benzene, acetone, isobutene, n-butane, toluene, propane, 1,2,4,-trichlorobezene, formaldehyde and styrene (full list of 68 VOCs not reported).

Potentially relevant co-exposure in this sector, namely in the work field of dental nurses and dentists handling composite products, is related to Glutaral or Glutaraldehyde, GA (CAS# 111-30-8). GA is an acknowledged occupational respiratory sensitizer[45] with a vapour pressure of 20 hPa at 20 °C[46]. GA is typically used as disinfectant in the clinical and dental sector and it has been used as a component in primers in some bonding systems with typical

[43] https://sicheres-dentallabor.bgetem.de/taetigkeiten/arbeiten-mit-gefahrstoffen
[44] uretanedimethacrylate
[45] Annex VI classification, Index 605-022-00-X
[46] Registration Dossier - ECHA (europa.eu)

concentrations between <1 and 5% (see below **Figure 2: "Table 1" from Kanerva et al.** 1994, citing Johnson et al. 1991 as Ref. 10) and used for its desensitizing[47] and antimicrobial

TABLE 1

Components of some dentin bonding systems (from Ref. 10)

System/Manufacturer	Components
1. Clearfil Photo-Bond/ J. Morita, USA, Inc.	**Etchant:** 40% phosphoric acid, colloidal silica **Catalyst:** BIS-GMA, 10-MDP, HEMA, camphoroquinone, benzoyl peroxide **Universal:** aromatic sodium sulfinate, tertiary aromatic amine in ethanol
2. Gluma/Miles Inc., Dental Products	**Cleanser:** 16% EDTA **Primer:** 35% 2-HEMA, 5% glutaraldehyde in water **Sealer:** BIS-GMA resin
3. Prisma Universal Bond-3/Caulk/Dentsply	**Primer:** 30% 2-HEMA + 6% PENTA in ethanol **Adhesive:** 5% PENTA, 55% urethane resin, 39% polymerizable monomers (TREGDMA, 2-HEMA, etc.). < 1% glutaraldehyde, < 1% photoinitiators
4. Scotchbond 2/3M	**Primer:** 2.5% maleic acid, 58.5% 2-HEMA in water **Adhesive:** 62.5% BIS-GMA, 37 5% 2-HEMA, Photoinitiators
5. Syntac/Ivoclar North-America, Inc.	**Primer:** 25% TREGDMA + 4% maleic acid in acetone and water **Adhesive:** 35% PEGDMA, 5% glutaraldehyde in water **Resin:** (Heliobond) 60% BIS-GMA 40% TEG-DMA
6. XR-Bond/Kerr Manufacturing Co.	**Primer:** 3.75% phosphonated dimethacrylate ester, 50 % ethanol, 46% water, camphoroquinone **Resin:** 10% phosphonated dimethacrylate ester, UDMA, aliphatic dimethacrylate, camphoroquinone

Abbreviations of (meth)acrylates, see Table 3.
MDP, a phosphate resin (10 methacryloyloxy decyl dihydrogen phosphate); PENTA, phosphonated penta-acrylate ester; UDMA, urethane dimethacrylate A.

properties and also for improving physical properties of the bonding systems.

Figure 2: *"Table 1"* from Kanerva et al. 1994

GA can cause late and dual asthmatic responses in SIC tests (Di Stefano et al. 1999) and was identified as significant causal agent for OA in the health care sectors (Walters et al. 2013).

Cosmetics (Manicure/ artificial nails; unsupported professional use)

Artificial nails are composed primarily of "acrylic" polymers and are made by reacting together monomers with polymers. While these artificial nails are colloquially called "acrylic" they are actually made predominantly of methacrylic materials (monomers, like EMA, and polymers, mainly PMMA). When the reaction is completed, traces of the monomer are likely to remain within the polymer matrix. It should be noted that various application types of artificial nails exist, mainly "acrylic nails" and "gel nails", with type-specific monomer compositions and handling tasks, and that this variety can explain a certain inconsistency in exposure information. Furthermore, it should be noted that the use of methacrylate monomers is not supported from a regulatory perspective to avoid the risk of skin

[47] In terms of reduction of post-operative sensitivity of dental patients

sensitization caused by unreacted monomer[48], but that this lack of support by manufacturers has not effectively impacted the downstream use in nail salons for various reasons.

An exposure study was performed by Henriks-Eckerman and coworkers (2012) to obtain information about inhalation exposure levels of various methacrylate esters and nail dust during application by the gel nail method. According to the authors, there was technical ventilation in the salons and sometimes downdraft tables were in place. Different tasks like nail sculpturing and finishing and decoration have been investigated. Mean levels of around 0.01 mg/m^3 were found in the breathing zones for HEMA during these tasks (see Figure 3, "Table I" from the Henriks-Eckerman publication below for details). Corresponding maximum levels were 0.03 mg/m^3 for HEMA. Total VOC levels in the breathing zone were around 2 orders of magnitude higher (i.e. mean 2 mg/m^3, with peaks up to 4 mg/m^3 during nail

TABLE I. Concentrations of Methacrylates in Workplace Air During Sculpturing of Artificial Nails in Three Nail Salons Using the Gel Nail Technique

Measurement Site (Sampling Time)	No. Measurements	Methacrylate Detected	Air Concentrations (μg/m^3)		
			Mean	SD[A]	Actual Concentrations
Ambient air (1 hr 57 min, 2 hr 16 min, and 5 hr)	3	Methacrylic acid	10	8.5	<1, 12, 17
		Methyl methacrylate	11	12	<1, 7, 24
		Ethyl methacrylate	31	20	12, 30, 52
		2-HEMA	3.8	3.8	<1, 3, 8
		HPMA	5.7	2.5	3, 6, 8
		TVOC[B]	1200	426	760, 1300, 1600
In the breathing zone of the worker during nail sculpturing (30 min–1 hr)	6	Methacrylic acid	62	73	9, 10, 17, 26, 140, 170
		Methyl methacrylate	43	65	<1, <1, 7, 31, 46, 170
		Ethyl methacrylate	108	109	15, 15, 58, 70, 216, 272
		2-HEMA	11	11	<1, <1, 6, 12, 21, 27
		HPMA	30	8.0	20, 24, 26, 33, 36, 41
		TVOC[B]	2130	1076	1200, 1400, 1500, 1800, 3000, 3900
In the breathing zone of the worker during finishing and decoration (15–45 min)	5	Methacrylic acid	20	14	8, 10, 11, 34, 35
		Methyl methacrylate	13	15	<1, <1, 5, 28, 29
		Ethyl methacrylate	61	83	15, 17, 32,33, 210
		2-HEMA	7.4	7.1	<1, <1, 7, 13, 16
		HPMA	32	10	19, 28, 31, 36, 46
		TVOC[B]	1780	713	920, 1200, 1900, 2300, 2600
Close to the worker's hand during nail sculpturing (0.5–1 hr)	5	Methacrylic acid	60	69	7, 8, 17, 120, 150
		Methyl methacrylate	18	22	<1, <1, 6 ,38, 47
		Ethyl methacrylate	32	21	14, 15, 23, 46, 62
		2-HEMA	10	13	<1, <1, <1, 22, 27
		HPMA	26	7.4	13, 26, 28, 29, 32
		TVOC[B]	1800	604	1200, 1200, 1800, 2300, 2500

[A]SD = standard deviation.
[B]Total volatile organic compounds, determined with toluene as external standard. Areas of all compounds that eluted between the retention times of hexane and hexadecane on a nonpolar column were included in the TVOC calculations.

Figure 3: Table 1 Concentrations of Methacrylates in workplace Air

sculpturing). Exposure by dust occurred in the range of 0.6-3.8 mg/m³ during removing the old nail sculpture by filing.

[48] In Europe, this use is not supported by manufacturers for methacrylate esters for the risk of skin sensitization and thus a formal "use advice against" this use is integrated in the respective REACH dossiers

Mean and peak concentrations of nail dust (approximately to be understood as inhalable PMMA particles) in the breathing zone of workers were determined with a real-time aerosol spectrometer. Mean concentrations were 0.6 mg/m^3 (when using a down draft table), or 2.3 mg/m^3, and 3.8 mg/m^3 (with separate table dust extractors in use). The respective peak concentrations were 13.7, 16.5, and 45.3 mg/m^3. The gravimetrically determined concentrations of total dust were below the quantification limits of 1.0 mg/m^3 and 3.3 mg/m^3 in all salons. Overall, the thoracic and alveolic fractions were about 40% and 10% of the inhalable fraction, respectively.
In other exposure studies in nail salons, HEMA was not detected or not measured. However, for co-exposure assessment, it should be noted that

- Partially extremely high levels of MMA, EMA and iBMA were measured in intermittent time periods in an older study (up to 81.2 mg/m3, 63.5 mg/m3 and 36.6 mg/m3, respectively; Froines et al. 1986);
- Total VOC concentrations were in the same range as the Hendriks-Eckerman study (Cebellos et al., 2019) or partially extremely higher (up to 48.4 mg/m3; Zhong et al. 2019);
- In total 20 solvents and other volatiles of partially critical hazard profile were identified that are not methacrylate esters, including Formaldehyde, 1-Butyl Alcohol, Acetone, Methyl acetate, Butyl Acetate, Ethyl Acetate, n-propyl acetate, Isopropyl acetate, Ethyl Alcohol, Isopropyl alcohol, Styrene, Benzene, Toluene, Ethyl benzene, o-Xylene, m,p-Xylene, p-Isopropyltoluene, d-Limonene, Carbon tetrachloride, N-heptane (Heaton et al., 2019; Cebellos et al., 2019; Zhong et al., 2019; Hiipakka & Samini, 1987); respective exposure levels are listed in Identified solvents and other volatiles in nail ;
- Respirable nail dust concentrations were determined on TWA basis as 0.9 mg/m^3 by Hiipakka & Samini (1987)

Exposure in sectors with exposure to HEMA WITHOUT asthma cases

Monomer production (Industrial use)

In a production plant of HEMA, personal related measurements have been performed during worker's shift for up to 8 hours duration. Standard procedures respectively manufacturing, substance transfers and maintenance have been included.
Under standard manufacturing conditions 14/28 measurements were below the limit of detection (LoD) for HEMA. For the other 14 measurements, a 90 percentile of 0.26 mg/m^3 and a maximum level of 0.41 mg/m^3 was determined (Röhm, 1996; see Supplementary information **8.2 Exposure details/ Monomer production (Industrial use)** Part A for more details).
In the OECD SIDS Report on HEMA (2001), short-term exposure data were provided by the Japan Industrial Safety and Health Association (JISHA, 2001). For most of the 30 measurements the LoD was not exceeded. However, the LoD was reported inadequately high with 2.3 mg/m^3 when compared with other industrial exposure levels (see above) so that the used analytical method appears not sensitive enough to provide a detailed picture. Highest

exposure concentrations can be found during maintenance with 3.5 mg/m^3 mean and 4.6 mg/m^3 maximum level (see Supplementary information **8.2 Exposure details/ Monomer production (Industrial use)**, Part B for some more details).

Other sectors

No measured exposure data are available for other sectors in which HEMA are known or likely to be used but should be listed here for completeness reasons.

Sectors with known use of these substances are:

- Contact lens manufacturing (HEMA; indoor industrial use)
- Metal impregnation (HEMA; indoor industrial use)
- Concrete additives, sealing of walls (HEMA; indoor/outdoor professional use)
- Synthesis of functional monomers, i.e. urethane methacrylates (HEMA; indoor industrial use)

Sectors with likely use of these substances are:

- Photopolymer plates and photoresists
- Textile coating / fiber bonding

LoE summary

This LoE branch should be assessed in two aspects: relevant co-exposure to other substances that can cause comparable health effects, and exposure to HEMA. Both aspects are important in relation to the CLP requirements to assess the evidence for a causal relationship between exposure to a specific substance and the induction/ development, and/or the elicitation/ aggravation of asthmatic symptoms/ respiratory hyperreactivity.

Co-Exposure

Sector-typical co-exposure scenarios can be identified from the synopsis of all publications, while the information from each publication is rather fragmented, depending on the focus of the research. Sectors WITH OA cases potentially linked with HEMA have the common feature that HEMA is present at workplaces in mixtures so that an exposure to a single substance neither appears in the occupational setting nor in documented diagnostic SIC tests. Thus, it is impossible to establish a clear causal relationship between exposure to a single substance and asthmatic symptoms which significantly weakens the evidence from proving substance specificity (an CLP criteria).

In the dental sector, workers are generally exposed to a broad cocktail of chemicals (solvents, disinfectants, acrylates/ methacrylates) and dusty materials either of plaster, metals, ceramics or organic dusts. Individual exposure profiles may vary depending on specific tasks or job profiles so that it almost impossible to conclude on individual co-exposure scenarios with the rather short job descriptions that are typically available. A critical chemical has been identified with GA as acknowledged respiratory sensitiser. GA is used on one hand as disinfectant which is likely relevant for many job profiles. On the other hand, GA has been

used in complex bonding systems as component in some primer products. It has also to be acknowledged for the assessment of the individual cases and the question on acquisition and/or elicitation of OA that SIC tests are typically done with only one (of many) activities and thus cannot cover the whole complexity of workplace co-exposure.

While HEMA is reported in various dental products in the publications, it is a key component in primers with 40% while in adhesives, other substances are dominating in the product compositions.

In the cosmetic sector, the exposure to dusty materials is restricted to PMMA dusts while exposure to volatiles is again very complex, with 20 or more different solvents in the nail salon air. Here, HEMA appears to be used as by-component with minor concentrations in such nail products. From this sector, also information about the total VOC is available, with mean values between 1.8 and 7.8 mg/m^3 per publication.

In the monomer production, workers are frequently exposed to other methacrylate esters during work shifts, e.g. to MMA.

Exposure levels to HEMA

The overall highest exposure levels were measured in the monomer production, interestingly a sector without reported OA cases, with levels up to 0.41 mg/m^3 HEMA. Other measured exposure levels were approx. one or two magnitudes lower: In the dental sector, HEMA was detected at levels of 0.001 to 0.045 mg/m^3. In the cosmetic nail sector, HEMA was detected at levels of around 0.01 mg/m^3, thereby representing an inferior proportion of the total VOC concentration. The observation that sectors with the highest exposure levels are apparently free from reported OA cases while other sectors with significantly lower exposure levels to HEMA and higher risk of critical co-exposure conflicts with a plausible biological gradient of exposure to HEMA. From this conflict it can inferred that the aspect “biological gradient”, a criteria of Bradford Hill for the establishment of causal relationship between exposure and the observed effects, is clearly contradictory to such a causal relationship.

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This branch of the human LoE is considered with high levels of relevance (in line with CLP texts that overweigh human data) and adequacy for classification purposes as respiratory sensitiser. The available information is considered moderately reliable (discount due to incomplete identification & quantification of co-exposition).

3.8.4. Prevalence

It is acknowledged that prevalence should be considered under CLP aspects[49]. However, for HEMA currently no reliable, comprehensive information is available and thus, this aspect will not be considered further in this work.

[49] chapter 3.4.2.1.2.2.: “When considering the human evidence, it is necessary for a decision on classification to take into account, in addition to the evidence from the cases: a) the size of the population exposed”

3.9. Comparable Hazard profiles of analogous substances

HEMA forms a small category with HPMA (EC 248-666-3, CAS 27813-02-1) under aspects of ECHA`s RAAF guidance (2017); it is one of the two hydroxyalkyl methacrylates under REACH, so there is no other direct analogous substance. HEMA is also subject of an analogous CLH proposal; a comprehensive WoE assessment of all available data however results in the conclusion that this classification proposal is not justified[50].

The category of lower alkyl methacrylates, under REACh separately assessed apart from HEMA, consists of rapidly hydrolysing esters with the identical methacrylic moiety. These substances are known as skin sensitisers in humans, in animal models and in vitro with a clear tendency for a weak potency (e.g. Kimber & Pemberton, 2014; Kimber 2021) and they are also known as weak irritant for skin, eyes and, where a high vapour pressure is given, for the respiratory tract (Gelbke et al. 2017).

None of these substances is classified for respiratory sensitization so far.

For MMA however, a CLH process is ongoing in the EU to investigate whether a classification as respiratory sensitizer is justified under CLP requirements. A structured WoE assessment, following ECHA requirements analogously to this work, and as recently recommended by an expert group for the assessment of respiratory sensitisation (Meek et al. 2023), has not taken place so far on EU's authority level, and a rather superficial assessment on low quality data came to the opinion that there is sufficient evidence to classify MMA based on positive SIC tests that have however have not been published in detail (ECHA, 2021). Developments discussed at CARACAL throughout the year 2022 indicate that this RAC Opinion was premature due to incomplete, and partially wrong 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.

More reliable, comprehensive WoE evaluations and reviews on MMA came to a different conclusion of insufficient evidence for classification (Pemberton & Kimber 2022; Borak et al. 2011). Thus, the most comprehensive assessments of analogous substances consistently support the understanding that classification of HEMA is not justified. Vice versa, the read-across to MMA as justification for classification for HEMA, as done in the CLH proposal, is considered unsound.

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This LoE is considered with a moderate to high level of relevance (moderate analogy to the lower alkyl methacrylates; high for HEMA) and a moderate level of adequacy for classification purposes as respiratory sensitiser. Considering that the majority of assessments, but not all, are of high quality, the reliability of the available data is moderate, thereby reducing the strength of this evidence somewhat.

[50] See response of HMRTF to the CLH proposal of HPMA; response planned for submission during the public comment period until May 12, 2023

3.10. Earlier assessments

The only identified assessments of HEMA for respiratory sensitisation have been done by Sedekar et al. (2022) and Scientific Committee on Consumer Safety (SCCS) in its opinion on the safety of cosmetic ingredients HEMA and Di-HEMA Trimethylhexyl Dicarbamate (2018[51]). Sedekar and coworkers evaluated the human evidence in public literature for 97 potential respiratory sensitisers, including HEMA (and the aforementioned MMA). Categories of compelling, reasonable, inadequate, or questionable evidence in humans from occupational exposures were defined in a structured approach. For HEMA (and MMA), the human evidence was considered as inadequate, on a however relatively weak data base. In its opinion the SCCS concluded "*Respiratory problems have been reported among professional users of nail-styling products, but the causative chemicals are often not identified. For 'methacrylates' the evidence for respiratory allergy was denoted as limited or contradictory in one review (Baur 2013) and absent in an updated version (Baur and Bakehe, 2014)".*

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This LoE is generally considered with a moderate level of relevance and a high level of adequacy for classification purposes as resp. sensitiser. The reliability of the available assessments is considered as moderate (correct but not fully comprehensive).

[51] Opinion on the safety of cosmetic ingredients HEMA and Di-HEMA Trimethylhexyl Dicarbamate - Submission I (Sensitisation only) (europa.eu)

4. Integration & Weighing of evidence (WoE analysis)/ Application of Levels of Confidence

4.1. Overview

Results of the assessments for quality, causality, confidence and uncertainties per LoE are summarised in a semiquantitative way in Table 6 for overview reasons. With exception of a) the quality assessment which is discussed in the respective subchapters of chapter 3; and b) not applicable aspects , the respective ratings are explained below the table. A detailed uncertainty analysis is available in chapter 5.

Line of Evidence[1]		Overall quality asessment[2]	Consistency & Specificity[3]	Biological Plausibility	Temporality	Confidence/ Strength of Evidence	Remaining Uncertainty[6]
Structural alerts (low)		Rv **-** Rb **+** Ad **-**	Con **+** Sp **-**	**-/O**	n.a.	**O**	**+**
QSAR (low)		Rv **-** Rb **-** Ad **-**	Con **-** Sp **-**	n.a.	n.a.	**-**	**+**
Phys-Chem. Properties (low)		Rv **O** Rb **+** Ad **-**	Con **+** Sp n.a.	**-**	n.a.	**-***	**O**
ADME (low)		Rv **O** Rb **O** Ad **-**	Con **+** Sp **-**	**+**	n.a.	**-**	**O**
Other relevant hazards[4] (low)		Rv **O** Rb **O/+** Ad **-**	Con **+** Sp n.a./-	n.a/ **O**	n.a./**+**	**-**	**+**
In vitro/ ex vivo (moderate)		Rv **+** Rb **-** Ad **O**	Con **O** Sp **O**	**O**	n.a.	**-**	**+**
In vivo (low)		n.a.	n.a.	n.a.	n.a.	**-**	**+**
Human data (high)	Clin. Cases	Rv **+** Rb **-** Ad **+**	Con **-** Sp **-**	**-**	**+**	**-**	**+**
	NHSD[5]	Rv **+** Rb **-/+** Ad **+**	Con **+** Sp **-**	n.a.	n.a.	**-***	**+**
	Exposure	Rv **+** Rb **O** Ad **+**	Con **+** Sp **-**	**-**	n.a.	**-***	**+**
	Total	Rv **+** Rb **O** Ad **+**	Con **O** Sp **-**	**-**	+	**-***	**+**

Analogous substances (moderate)	Rv **O** Rb **O** Ad **O**	Con **O** Sp n.a.	**O**	**+**	**-***	**+**
Earlier assessments (high)	Rv **O** Rb **O** Ad **+**	Con n.a. Sp n.a.	**+**	n.a.	**-***	**+**
Conclusion from overall confidence	WoE does not allow the conclusion with sufficient evidence that the substance is a respiratory sensitiser					

Table 6: WoE analysis table; + = high; O = moderate; - = low;* = contradicting to hypothesis; n.a. = not applicable

[1] *in brackets: relative weigh for the hazard assessment (widely identical to the respective adequacy level)*
[2] *taken from the respective LoE summaries; Rv = Relevance, Rb = Reliability; Ad = Adequacy of data*
[3] *Con = Consistency, Sp = Specificity*
[4] *assessments for Resp. Irritation/ Skin Sensitisation separately given where necessary*
[5] *National health surveillance databases*
[6] *in terms of magnitude of the uncertainty, see also chapter 5*

4.2. WoE analysis per LoE

Structural alerts

First of all, the development of a specific AOP for respiratory sensitisation (see chapter 3.6) indicates that also hazard-specific structural alerts are theoretically plausible. However, both substances do not contain such structural moieties that are known for the time being.

It should be understood that this LoE is not fully investigated for this particular hazard so far, leading to a low specificity rating, and, vice versa, a rather high uncertainty rating. The widely accepted status of methacrylates including HEMA as Michael acceptors is considered as high consistency in the WoE analysis. A respiratory sensitising mechanism is possible but not indicated, and as no known respiratory sensitisers are known that act as Michael acceptors, a weak to moderate biological plausibility is considered. Taking the quality and causality aspects together, there is a moderate confidence for this LoE (supporting the hypothesis).

QSAR

The results of the various QSAR models are inconsistent to each other. As stated above for structural alerts, a low specificity rating appears justified considering that this LoE is under development for this particular hazard. A high level of uncertainty is concluded for this LoE stemming from the mainly unknown algorithms and applicability domains of the various QSAR models.

Physico-chemical properties

HEMA is a substance of very low volatility that limits the risk of relevant inhalation exposure, especially as no indoor spray applications are known. Thus, it is not plausible that these substances causes inhalation effects and the high confidence in this assessment is expressed as low confidence level against the tested hypothesis. Some uncertainty is coming from the risk that these substances could be very potential respiratory sensitisers that cause effects at very low concentrations.

ADME

HEMA is a subject of rapid enzymatic hydrolysis in the upper respiratory tract. Such rapid hydrolysis lowers the risk for – route-unspecific - sensitisation in the contact tissue coming only from the intact ester. Irrespective of its high biological plausibility it is so far not fully understood how effective this metabolic step prohibits immunologic processes in humans, so the confidence uncertainty is considered as moderate. The assessment of the confidence level of this LoE is based on the confidence level of the "structural alerts" (moderate level) but adds a weakening aspect that results in a low confidence level.

Other relevant hazards

It appears questionable for HEMA whether respiratory effects were caused by an alternative, irritative mechanism, considering consistent phys-chem data. An extensive assessment on Respiratory Irritation has been performed and supports this understanding. However, it is acknowledged that SIC tests with dental workers have been performed with excess of product amounts, while exposure levels have not been determined. Thus, exposure up to irritating levels during SIC cannot be excluded in such SIC tests. Overall, there is a relatively low likelihood for a confounding, irritative mechanism from HEMA itself. Under formal WoE criteria, this assessment appears with a proper level of consistency; specificity and biological plausibility appear not assessable.

Regarding Skin Sensitisation, the aforementioned limitations on the specificity for the transfer from known skin sensitisation properties to respiratory sensitisation (see "structural alerts" and "QSAR"), are also relevant for this LoE aspect and are considered also as uncertainty below. In this LoE aspect, a temporality of effects (following exposure) is seen as given. Overall, the fact that HEMA is a known skin sensitiser does not add substantial confidence to the tested hypothesis.

In vitro/ ex vivo

The hazard specific AOP guidance has the potential to be considered in the future with a relative high weigh, but in its current draft status it is considered with a moderate weigh within the WoE assessment. For this AOP, only few information is available which are however consistent with analogous substances. For this LoE this moderately ambiguous situation is reflected in moderate ratings for consistency, specificity and plausibility. As the outcome speaks against the hypothesis, the uncertainty level of this LoE is considered as high and, consequently, the confidence level as low.

In vivo

In absence of any data and of approved animal models, this LoE is, at best, theoretically assessable for its potential causal relationships, but this is resigned for overview reasons. The level of confidence is thus low and, vice versa, the uncertainty level high.

Human data

The reported clinical cases suffer from a consistent picture in terms of medical diagnosis that would allow to conclude on a typical mode of action for these substances (e.g. heterogeneous IgE and SIC pattern). On substance level, the specificity is rated low as only mixed exposure was investigated, in the occupational setting as well as in the SIC tests. Moreover, confounding effects of co-exposure to the asthmagen and volatile GA (used as disinfectant as well as component in some primers) have to be considered as significant uncertainty. Frequently, non-specific bronchial hyperreactivity has been observed in SIC tests that questions the substance specificity of the observed effects. Given the very low vapour pressure of the substances, and as consequence the partially unknown respiratory exposure in general, a low biological plausibility is assigned. Temporality of effects appears as only causal aspect that supports the tested hypothesis. Overall, a low level of confidence and a high level of uncertainty is considered for this LoE branch.

The very few information from NHSDs show a high consistency for the absence of OA cases related to HEMA. In line with above statements, specificity is rated as low here. Overall, a low level of confidence and a high level of uncertainty is considered for this LoE branch.

The few exposure information shows a high consistency for relevant co-exposure. The specificity is considered as low as OA cases are limited to defined sectors while in other sectors with exposure to HEMA, such cases are missing. The biological plausibility is considered as low for the same reason. Overall, a low level of confidence and a high level of uncertainty is considered for this LoE branch.

For the complete human LoE (the LoE with the highest predefined weigh) it has to be considered that the aspect of consistency supports the tested hypothesis, as caused by the used assessment scheme. However, the respective outcome of the consistency considerations actually speaks again the tested hypothesis (absence of OA cases in the available very few NHSDs, consistently high co-exposure in sectors with OA cases, namely to GA). So, temporality of effects in the few reported cases is the only causal aspect that supports the tested hypothesis while all other aspects do not support the hypothesis.

Analogous substances

Other methacrylate esters are consistently not classified as respiratory sensitisers. In the case of HPMA and MMA with their currently ongoing CLH processes, there is insufficient scientific evidence to do so. The given heterogeneity of assessment outcomes is considered with a moderate consistency. As the outcome of the most comprehensive assessment speaks against the tested hypothesis, the confidence is considered as low and, vice versa, the uncertainty level high.

Earlier assessments

The database for this LoE is very weak with one publication, so that consistency cannot be assessed. The plausibility for the applied approach of this paper is high, but as the outcome

("inadequate human evidence") speaks against the tested hypothesis, the confidence is considered as low and, vice versa, the uncertainty level is high.

Conclusion on strength of confidence

The majority of LoEs actually contradict to the tested hypothesis or account only low confidence to it. The most powerful contradicting argument is the low volatility, accompanied by the rapid, detoxicating metabolism (enzymatic hydrolysis), pointing to a low likelihood for significant inhalation exposure. Further contradictive evidence originates from human data, the LoE with a relative dominant weigh, due to the implausible biological gradient (dose relationship) across the various industry sectors. Beyond all investigated LoE, it is just the very basal LoE for structural alerts that supports the hypothesis with a certain level of confidence to the hypothesis. At best, there is very weak confidence coming from the sum of all LoEs to support the tested hypothesis.

5. Uncertainty analysis

Each LoE is assessed with respect to the level of confidence and their impact on the WoE assessment.

Structural alerts

ECHA guidance R7.a (ECHA, 2017b) recognises that there is still uncertainty regarding the exact mechanisms leading to respiratory sensitisation and that while structural alerts related to respiratory sensitisation have been collected and described in the literature that these are derived from chemical asthmagens, i.e. substances that have been claimed to cause asthma like symptoms with or without immunological mechanisms. HEMA like other methacrylate monomers have in common the acryl meoiety which has been proposed as an alert for contact and respiratory sensitisation. However, recent literature indicates that while Michael addition is is a structural alert for skin sensitisation (Dearden et al., 2015; OECD, 2021) it is not an alert for respiratory sensitisation (Ponder et al. 2022). Therefore, there remains a high level of uncertainty that the structural alert of "Michael additon reactivity" is a reliable predictor of an inherent property to cause either respiratory sensitisation or occupational asthma and an overal low confidence for this LoE.

QSAR

Most QSARs for respiratory sensitisation are based upon structural alerts as described above. In this regard ECHA guidance R7.a (ECHA, 2017b) states that "*a need still remains to develop new (Q)SARs when a robust predictive test method becomes available*". While recent QSARs such as that described by Enoch et al. (2012, 2014) and Jarvis et al. (2015) are based upon a set of mechanism-based structural alerts for low molecular weight organic substances their predictive value is based upon a learning set of chemicals claimed in the literature as causing occupational asthma without formal assessment or consideration of the possible mechanism(s) involved. Consequently there appears to be strong inconsistency and lack of transparency on algorithms/ expert rules (related to the limited knowledge on structural alerts) and applicability domains lead to a high level of uncertainty. Based on these fundamental uncertainties, this LoE should not further assessed.

Physico-chemical properties

When assessed separately from other LoEs, namely that of human exposure, there is a small risk that HEMA could be a very potential respiratory sensitiser that causes effects at very low concentrations. This is consistent with methacrylates generally being regarded as relatively weak Michael addition reactors. This results in a moderate uncertainty level for this LoE.

ADME

Michael addition reactivity of the parent ester and covalent binding to proteins is a key event in the AOP for contact (skin) sensitisation allergy. As such the rapid metabolism of HEMA and

cleavage of the parent ester is widely understood as a detoxificating metabolic step. The rapid hydrolysis of HEMA is counter intuitive to the hypothesis that causes respiratory sensitisation by an immunological mechanism. Recently, it has been proposed that cleavage of the parent ester HEMA to the acid metabolite, MAA, is an activation step for respiratory sensitisation common to all methacrylates (ANSES 2022/2023). As such this proposed MOA is not supported by any evidence and is contrary to the state of knowledge on the allergenicity of methacrylate esters. Overall this LoE has a moderate level of confidence (low uncertainty) and is not supportive of the tested hypothesis.

Other relevant hazards

Asthma-like symptoms in humans can also be caused by irritatant mechanisms i.e. irritant induced asthma or irritant exaccerbated asthma. In the case of irritant exacerbated asthma the mechanism by which the chemical provokes the symptoms is non-specific and not an inherent property of the substance. In the case of Irritant induced asthma the mechanism by which the asthma caused can be considered an inherent property as required by CLP criteria for classification as a respiratory sensitiser. However, only very highly irritant chemicals have been identified as causing irritant induced asthma. HEMA is neither a strong irritant nor sufficiently volatile as to produce high local concentrations in the respiratory tract. Further, the rapid hydrolysis of HEMA would counter indicate an irritant property of the parent ester to the respiratory system. It should be recognised that HEMA is metabolised to the irritant/corrosive primary metabolite, MAA. However, since HEMA has a very low vapour pressure it is unlikely that deposition in the repiratory tract and local tissue concentrations of HEMA, or its metabolite MAA, will be sufficiently high to be regarded as highly irritating or corrosive. This is consistent with the observation of only slight irritation in rats exposed to 350 ppm (1232 mg/m^3) MAA for 6 hours/day, 5 days/week and a NOEL of 100 ppm in a sub-chronic inhalation toxicity. Therefore, any uncertainty relating to this proposed MOA mediated through formation of MAA is of a theoretical nature for HEMA and does not have to be considered further in this assessment.

Regarding Skin Sensitisation, HEMA is a recognised skin sensitiser. Any postulated link between skin sensitisation and respiratory sensitisation is not recognised by ECHA guidance and therefore there is a high level of uncertainty related to this LoE branch.

In vitro/ ex vivo

There are no validated and recognised in vitro/ ex vivo models for respiratory sensitisation and no data exist for HEMA. This LoE does not therefore have to be considered further.

In vivo

There are no data on respiratory sensitisation in animals for HEMA.

Human data

The sectors with reported OA cases have in common significant co-exposure to a broad cocktail of volatile low molecular weight substances and dusts but relatively low levels of HEMA. The co-exposure to other contact sensitisers and Human data on occupational asthma claimed to be caused by HEMA exists. the recognised respiratory sensitiser GA (used as disinfectant as well as component in some dental primers) has to be considered as significant confounding factor. In contrast, other sectors with less complex atmospheres and higher exposure levels of HEMA do not report OA cases. This inconsistency creates a high level of uncertainty as to the causal involvement of HEMA in the observed symptoms both in the workplace and in bronchail challene (SIC) tests.

This is further confounded by all but one clinical case having a clinical history of atopy or unspecific bronchial hyperreactivity reducing the level of confidence in the observed effects both in the workplace and in SIC being specific to HEMA and not non-specific exacerbation of pre-exisitng asthma.

Both aspects address specifically sub-question (1) of the tested hypothesis sectors with reported OA cases can be characterized by significant co-exposure to a broad cocktail of volatile low molecular weight substances and dusts of high molecular weight substances and relatively low levels of HEMA. Especially the co-exposure to the asthmagen and volatile GA (used as disinfectant as well as component in some primers) has to be considered as significant confounding factor. In contrast, other sectors with less complex atmospheres and higher levels of HEMA do not show reported OA cases. This situation creates a high level of uncertainty on the causative involvement of both substances in the observed symptoms.

A second, not less severe aspect of uncertainty is that with exception of one patient, all other cases had a confounding clinical history (like atopy or unspecific bronchial hyperreactivity).

Both uncertainty aspects address specifically sub-question (1) of the tested hypothesis (see chapter 1) and are considered to have a significant impact as the biological plausibility of the hypothesis.

Other available clinical information such as IgE and timings of SIC responses is inconsistent and insufficient to conclude involvement of a substance-specific immune mechanism. Consequently, that there is high uncertainty regarding sub-question (2) of the tested hypothesis.

The absence of cases of OA being reported to National health surveillance databases (NHSD) in two countries point to a low incidence of OA due to HEMA which despite being of low confidence is inconsistent with the higher incidence inferred by the cases identified by FIOH. This inconsistency combined with concerns regarding the composition of products reportedly used in SIC and in the workplace point to this LoE as not supporting the tested hypothesis albeit with a high level of uncertainty.

Analogous substances

Analogy can be drawn to the close structurally related HPMA. While this chemical is also subject to a CLH proposal for respiratory sensitisation the evidence cited in this proposal is

extremely weak (see comments submitted on HPMA) and therefore cannot be relied upon to confer any degree of confidence in classification of HEMA. Analogy could be drawn to MMA but there are significant differences in physical chemical properties e.g. volatility, between these two esters. MMA is also the subject of a CLH proposal and decision by RAC but recently new evidence that calls into question that decision has resulted in it being referred back to RAC for reassessment. It is therefore presumptive to rely upon analogy to MMA to confer any degree of confidence in classification of HEMA. As no other analogous substances have gone through a formal process and classified as respiratory sensitisers it is concluded that this LoE not supportive of the tested hypothesis.

Earlier assessments

Despite their somewhat limited quality of each of the available two assessments, they both concluded consistently that for HEMA the evidence for respiratory sensitisation is limited, or inadequate. It is thus concluded that this LoE not supportive of the tested hypothesis.

Conclusion on uncertainties

For the vast majority of discussed LoEs, the level of respective uncertainties is high. It is further understood that from an overall perspective the strongest uncertainties comes from human data (co-exposure, confounding clinical history and inconsistent immunological pattern) and those speak against the hypothesis.

6. Conclusions

All available information has been systematically assessed for its evidence. This has been done in a structured manner following CLP requirements for the classification of potential respiratory sensitizers (CLP section 3.4.2.1.1.3.) and on the basis of the respective ECHA template for WoE assessments.

For the vast majority of discussed LoEs, the level of respective uncertainties is high. It is further understood that from an overall perspective the strongest uncertainties comes from human data (co-exposure, confounding clinical history and inconsistent immunological pattern) and those speak against the hypothesis that HEMA can cause the development of respiratory sensitisation, or can cause occupational asthma (OA), in subjects that were not previously asthmatic.

As first conclusion it is noted that for none of the investigated Lines of Evidence, there is high quality information that at the same time fulfils relevant Bradford-Hill criteria for causality (in terms of consistency, specificity, biologically plausibility and temporality) and, moreover, has an suitable level of confidence whether for, or against, the tested hypothesis.

According to CLP criteria, human data carry the highest weight in a WoE assessment and have therefore to be evaluated with special attention. The 21 potential clinical cases from the dental and cosmetic sector related to HEMA, respectively, do not fulfil CLP requirements "of reliable and good quality evidence". For example, none of the identified SIC tests have been performed with the singe substance HEMA so that none of these tests can be seen as conform to spirit of the guideline as it relates to distinguishing a substance-specific property to cause respiratory sensitisation. Moreover, patients in the dental sector have been challenged with excess of material so that a basic principle of these challenge tests, to create comparable conditions as in the workplace, have not been fulfilled. Indeed often 10 times the quantity of product used in the workplace failed to elicit an asthmatic response strongly indicating that the product being tested was not the causal agent. Other branches of the human LoE (national health surveillance databases – no cases - despite significant exposure) provide evidence against the tested hypothesis but this is too weak to rely upon. Main sources of uncertainties in this LoE (clinical data) are a) the significant co-exposure in the occupational setting as well in performed SIC tests, including co-exposure to the recognised asthmagen Glutaraldehyde in the dental sector; b) the confounding clinical history of all but one patients (where reported); and c) the inconsistent immunological pattern. In summary, no relevant evidence supporting the hypothesis that HEMA can cause the development of respiratory sensitisation can be derived from the available human data.

Earlier assessments that were also based on human data and that thus have also a relatively high predefined weight in a WoE assessment, came to the same conclusion, albeit on a weaker database.

Other lines of evidences provide either weak evidence for[52] or against[53] the hypothesis that both substances can cause the development of respiratory sensitisation. In addition, all those LoEs are generally afflicted with significant uncertainties so that they are considered as of minor relevance for the WoE assessment. Regarding the possibility the HEMA causes OA through an irritant mechanism, the available evidence in animals and from human experience stongly supports this as being extremely unlikely.

The conclusion drawn from these analyses, with focus on human data, indicate that there is insufficient evidence to implicate HEMA as a cause of respiratory sensitisation or OA. Therefore, there is no basis for classification as respiratory sensitisers under EU CLP, which is widely consistent UN GHS.

[52] Such LoEs were structural alerts, QSAR, ADME, other relevant hazards, in vitro/ ex vivo and in vivo data

[53] Such LoEs were phys-chem properties and analogous substances

7. Appendix II References

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8. Supplementary information

8.1. Literature search documentation

HEMA: The various literature searches are documented in the respective IUCLID entries, with the most recent one with approx. 2000 hits covering the databases BIOSIS, EMBASE, HCAPLUS, MEDLINE; REAXYSFILE and TOXCENTER found in the time period between Jan 2010 and 2021-04-27 (following up to an earlier search) and following descriptors

RN **868-77-9**
CN 2-Propenoic acid, 2-methyl-, 2-hydroxyethyl ester (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Methacrylic acid, 2-hydroxyethyl ester (6CI, 8CI)
CN Methacrylic acid, ester with glycol (7CI)
OTHER NAMES:
CN β-Hydroxyethyl methacrylate
CN 2-(Methacryloyloxy)ethanol
CN 2-HEMA
CN 2-Hydroxyethyl 2-methylprop-2-enoate
CN 2-Hydroxyethyl methacrylate
CN Acryester HISS
CN Acryester HO
CN Acryester HOMA
CN Acryl Ester HO
CN Bisomer HEMA
CN Bisomer SR
CN Blemmer E
CN EB 109
CN EB 109 (monomer)
CN EM 321
CN Ethylene glycol methacrylate
CN Ethylene glycol monomethacrylate
CN GE 610
CN Glycol methacrylate
CN Glycol monomethacrylate
CN HEMA
CN HEMA 90
CN JB 4 Plus
CN Kayarad 2-HEMA
CN Light Ester HO
CN Light Ester HO 250
CN Light Ester HO 250M
CN Light Ester HO 250N
CN M 0085
CN Mhoromer BM 903
CN Mhoromer BM 905
CN Monomer MG 1
CN NSC 24180
CN Rocryl 400
CN Visiomer HEMA 97
CN Visiomer HEMA 98
DR 51026-91-6, 58308-22-8, 60974-06-3, 61497-49-2, 112813-65-7, 123991-13-9, 132051-71-9, 141668-69-1, 151638-45-8, 155280-45-8, 173306-28-0, 201463-85-6, 203300-24-7, 203497-53-4, 211862-46-3, 212555-08-3, 219840-96-7, 225107-31-3, 282528-79-4, 473256-73-4, 1136534-55-8,

1151978-80-1, 1184921-46-7, 1206159-39-8, 1260379-87-0, 1418001-98-5, 1449201-78-8, 2231343-05-6, 2242757-54-4

8.2. Exposure details/ Monomer production (Industrial use)

Part A - Industrial uses / Röhm

A campaign of measurements has been made to determine workplace exposures vs. HEMA and HPMA (Röhm internal report, BL-WO 20/12/1996). Personal related measurements have been performed during worker's shift for up to 8 hours duration. Standard procedures respectively manufacturing, substance transfers and maintenance have been included. Measurements have been focused on tasks for which exposure was likely (manufacture, sampling, drum filling, maintenance work like opening reactors and tanks, filter exchange).

Measuring conditions

Personal related measurements took place. Workers wore measuring equipment to detect the level of exposure. Small pumps (HFS 513A with transport volume of 20 l/h and limit of detection ca. 0.07 mg/m³ or 50 l/h and limit of detection ca. 0.02 mg/m³, both by Gilian) transported air to tubes of type NIOSH (by Draeger) filled with absorbing agent (silica gel). Substances were desorbed with methanol. Analytical investigations proceeded by GC.

Results

28 measurements were performed during handling of the substances, for which exposure was likely. Even for exposure-prone tasks the actual exposure to HEMA and HPMA was several orders of magnitude below the expected NOAEC.

HEMA: Under standard manufacturing conditions 14/28 measurements were below the limit of detection. For the rest a 90 percentile of 0.048 ppm (0.26 mg/m³) was determined (max. 0.076 ppm, 0.41 mg/m³). See Table (suppl. Info) 1 and Table (suppl. Info) 2.

HPMA: Under standard manufacturing conditions 2/28 measurements were below the limit of detection. For the rest a 90 percentile of 0.058 ppm (0.35mg/m³) was determined (max. 0.217 ppm, 1.3 mg/m³). See table 4 and 5.

Data

	MW	Vp	Saturation density
HEMA	130.1 g/mol	0.08 hPa @ 20 °C	79 ppm/427 mg/m³

Table (suppl. Info) 1: Properties HEMA

Date	HEMA mg/m³	HEMA ml/m³ (ppm)	HEMA ml/m³ (ppm) LoD eliminated	Measurement duration (h)	Workplace/activity
19.11.1996	<0.038	<0.007	0.007	2.03	transfer
20.11.1996	<0.017	<0.003	0.003	4.62	production
20.11.1996	<0.022	<0.004	0.004	1.48	transfer
21.11.1996	<0.019	<0.004	0.004	5.98	production
22.11.1996	0.41	0.076	0.076	2.35	transfer
22.11.1996	<0.016	<0.003	0.003	4.15	production
27.11.1996	<0.012	<0.002	0.002	4.78	production
28.11.1996	<0.013	<0.002	0.002	4.48	production
29.11.1996	0.011	0.002	0.002	1.62	transfer
29.11.1996	0.029	0.005	0.005	5.23	production
30.11.1996	0.019	0.004	0.004	0.5	maintenance
30.11.1996	<0.014	<0.003	0.003	1.25	maintenance
01.12.1996	0.019	0.004	0.004	0.75	maintenance
01.12.1996	<0.027	<0.005	0.005	1	maintenance
02.12.1996	0.004	0.001	0.001	2.35	transfer
02.12.1996	0.045	0.008	0.008	5.27	transfer
02.12.1996	0.129	0.024	0.024	0.42	maintenance
02.12.1996	0.311	0.058	0.058	1.13	maintenance
09.12.1996	<0.027	<0.005	0.005	0.85	transfer
12.12.1996	0.032	0.006	0.006	1.83	maintenance
14.12.1996	0.02	0.004	0.004	7.2	production
15.12.1996	0.009	0.002	0.002	5.43	production
16.12.1996	<0.046	<0.009	0.009	1.23	transfer
17.12.1996	0.021	0.004	0.004	1.12	maintenance
17.12.1996	<0.059	<0.011	0.011	0.52	transfer
18.12.1996	0.129	0.024	0.024	2.93	transfer
19.12.1996	<0.035	<0.006	0.006	0.8	transfer
19.12.1996	<0.036	<0.007	0.007	0.88	transfer

Table (suppl. Info) 2: Workplace monitoring data of Röhm for HEMA (transfer = drum and IBC filling, outdoors and indoors with LEV; production = control of batch reaction and distillation, sampling; maintenance = filter exchange, cleaning operations)

Evaluation HEMA (ppm)		Evaluation HEMA (ppm) LOD eliminated	
0.0478	90 % Percentile	0.024	90 % Percentile
0.0045	50 % Percentile	0.0045	50 % Percentile
0.001	Lowest Value	0.001	Lowest Value
0.076	Highest Value	0.076	Highest Value
14	No. of Values	28	No. of Values

Table (suppl. Info) 3: Evaluation HEMA

Part B - Industrial uses / SIDS HEMA

One can found in the report that occupational exposures at production sites may occur by the inhalation route. The exposure concentration was measured at one production site (Japan Industrial Safety and Health Association, JISHA, 2001). Only short-term measurements have been proceeded. For most of the measurements it was found that the limit of detection did not exceed. The level of exposure is observed on a low level, but could be slightly higher than indicated in the Röhm data. The monitored data are shown in Table 6. Highest exposure concentrations can be found during maintenance. For these operations a higher level regarding risk measurements is in place (i.e., respirator).

Operation	Monitoring data (mg/m^3)	Number of measurements	Frequency Times/day	Working time hrs/time
Sampling	<2.3	14	1	0.05
Drum filling	<2.3	5	1	0.75
Waste fluid processing	<2.3	2	1	0.05
Analysis work	<2.3	6	1	0.05
Maintenance work	<2.3 – 4.6 3.5 (mean)	3	1	0.25

Table (suppl. Info) 4: Workplace monitoring data for HEMA (JISHA)

[Monitoring method: Air sample was suctioned at the breathing zone of the worker at the suction rate of 0.2 L/min. and adsorbed by activated carbon in a collection tube and analyzed by GC.]

HEMA has a very low vapour pressure (see Table (suppl. Info) 1). In consequence, the saturated vapour density is low, too. Furthermore, risk management measures (e.g. ventilated workplace) are typically in place to lower exposure during handling of substances on industrial scale. For that reason, current workplace concentrations have been determined very low. In conclusion, by practical experience and using protection measurements vapour inhalation does not indicate a significant risk for HEMA.

8.3. Battery algorithm and used software of the QSAR of the Danish EPA

Copied from the User Manual (2018), Danish QSAR Database (dtu.dk)

Battery algorithm

"*Some of the models are made in two or three of the following independent systems: CASE Ultra (CU), Leadscope Predictive Data Miner (LS) and SciQSAR (SQ). The systems are described in Appendix 5 (here: see "software systems", see below). Based on predictions from each of the applied systems, a battery prediction is made using a so-called battery algorithm. The battery approach can give more reliable predictions and can also expand the applicability domain, which was shown in a previous pilot project including 32 different models and the three systems mentioned above (not published).*"

For a given effect, QSAR predictions are made in each of the independent QSAR model systems and combined into a battery prediction by using the criteria shown in **Table (suppl. Info) 5**. The first column shows the total number of predictions (positive/negative) in domain. The next two columns show the number of positive and negative predictions, respectively. The final battery prediction based on the individual predictions is shown in the fourth column.

8.4. Information requirements on human data for respiratory sensitisation

https://echa.europa.eu/documents/10162/17224/information_requirements_r7a_en.pdf

ECHA guidance document R.7a (2017b) ("Endpoint specific guidance" Version 6.0; July 2017 https://echa.europa.eu/documents/10162/17224/information_requirements_r7a_en.pdf) requests following information:

- the test protocol used (study design, controls);
- the substance or preparation studied (should be the main, and ideally, the only substance or preparation present which may possess the hazard under investigation);
- the extent of exposure (magnitude, frequency and duration);
- the frequency of effects (versus number of persons exposed);
- the persistence or absence of health effects (objective description and evaluation);
- the presence of confounding factors (e.g. pre-existing respiratory health effects, medication; presence of other respiratory sensitizers);
- the relevance with respect to the group size, statistics, documentation;

- the healthy worker effects.

Total POS/NEG in domain	POS in domain	NEG in domain	Battery prediction[a]	Remarks
3	3	0	POS_IN	
3	0	3	NEG_IN	
3	2	1	POS_IN	
3	1	2	INC_OUT or (see remark) NEG_IN	EXCEPT when CU and LS are both NEG_IN, in this case the battery call is NEG_IN
2	2	0	POS_IN	
2	1	1	INC_OUT	
2	0	2	NEG_IN	
1	1	0	POS_OUT	
1	0	1	NEG_OUT	
0	0	0	INC_OUT	If minimum one prediction (out of domain)
0	0	0	-	None predicted

[a] POS, positive; NEG, negative; INC, inconclusive; IN, inside applicability domain; OUT, outside applicability domain. [b] Less weight is put on an SQ POS compared to LS or CU POS in cases where LS and CU agree on a NEG in AD prediction, because SQ in many cases has lower specificity than LS and CU.

Table (suppl. Info) 5: QSAR prediction

Software systems

"Case Ultra

CASE Ultra is a fragment-based statistical model system. The methodology involves breaking down the structures of the training set into all possible fragments from 2 to 10 heavy (non-hydrogen) atoms in length. The fragment generation procedure produces simple linear chains of varying lengths and branched fragments as well as complex substructures generated by combining the simple fragments. A structural fragment is considered as a positive alert if it has a statistical significant association with chemicals in the active category. It is considered a deactivating alert if it has a statistically significant relation with the inactive category. Once final lists of positive and deactivating alerts are identified, CASE Ultra attempts to build local (Q)SARs for each alert in order to explain the variation in activity within the training set chemicals covered by that alert. The program calculates multiple molecular descriptors from the chemical structure such as molecular orbital energies and two-dimensional distance descriptors. A stepwise regression method is used to build the local (Q)SARs based on these molecular descriptors. For each step a new descriptor (modulator) is added if the addition is statistically significant and increases the cross-validated R2 (the internal performance) of the model. The number of descriptors in each local model is never allowed to exceed one fifth of the number of training set chemicals covered by that alert. If the final regression model for the alert does not satisfy certain criteria (R2 ≥ 0.6 and Q2 ≥ 0.5) it is rejected. Therefore, not all alerts will necessarily have a local (Q)SAR. The collection of positive and deactivating alerts

with or without a local (Q)SAR constitutes a global (Q)SAR model for a particular endpoint and can be used for predicting the activity of a test chemical.

Leadscope

Leadscope Predictive Data Miner is a software program for systematic sub-structural analysis of a chemical using predefined structural features stored in a template library, training set-dependent generated structural features (scaffolds) and calculated molecular descriptors. The feature library contains approximately 27,000 pre-defined structural features such as functional groups, heterocycles and pharmacophores. The training set-dependent structural features (scaffold generation) can be added to the pre-defined structural features from the library and be included in the descriptor selection process. The program also calculates a number of physico-chemical descriptors such as logP, molecular weight and the number of hydrogen bond acceptors and donors. Leadscope has a default automatic descriptor selection procedure. This procedure selects the top 30% of the descriptors (structural features and molecular descriptors) according to X2-test for a binary variable or the top and bottom 15% descriptors according to t-test for a continuous variable. After selection of descriptors the program performs partial least squares (PLS) regression for a continuous response variable, or partial logistic regression (PLR) for a binary response variable, to build a predictive model.

SciQSAR

The SciQSAR software provides over 400 built-in molecular descriptors such as connectivity indices, electrotopological (atom E and HE-state) indices, and other descriptors. Furthermore, the program provides a variety of statistical tools that can be used to build predictive models for binary and continuous data. SciQSAR uses discriminant analysis for binary data and includes the capability to perform parametric and nonparametric discriminant analyses. For continuous data, regression analysis is used to build the predictive model, and a number of different regression methods are available such as regression on principal components (PCR) and partial least squares regression (PLS).”

8.5. Identified solvents and other volatiles in nail salons

Table (suppl. Info) 6: List of identified solvents

Source	Activity	Formaldehyde	1-Butyl Alcohol	Acetone	Butyl Acetate	Ethyl Acetate	Ethyl Alcohol	Isopropyl acetate	Isopropyl alcohol	Methyl acetate	n-propyl acetate	Styrene	Benzene	Toluene	Ethyl benzene	o-Xylene	m,p-Xylene	p-Isopropy-ltoluene	d-Limonene	Carbon tetra-	N-heptane
Heaton 2019	Nail polishing	0.12-0.22 ppm	2.23-13.38 ppm	0.67-4.74 ppm	161-330 ppm	314-440 ppm	4.06-10.04 ppm	4.50-18.93 ppm	60.7-77.0 ppm	0.02-0.04 pp	29.5-91.1 pp	no									
Cebellos 2019	all	no	no	no	no	760 µg/m3	no	no	no	no	no	0.17µg/m3	0.46 µg/m3	39 µg/m3	0.32 µg/m3	0.33 µg/m3	0.79 µg/m3	1.2 µg/m3	9.3 µg/m3	0.76 µg/m3	
Zhong 2019	"nail services" - personal air	n/a	no	no	630 µg/m3	1900 µg/m3	no	29 µg/m3	no	no	62 µg/m3	no	4 µg/m3	110 µg/m3	no	no	no	no	28 µg/m3	no	84 µg/m3
	"nail services" - area air	10 µg/m3	no	no	320 µg/m3	1260 µg/m3	no	17 µg/m3	no	no	43 µg/m3	no	3 µg/m3	93 µg/m3	no	no	no	no	16 µg/m3	no	70 µg/m3
Hiipaka 1987	not described	no	no	no	2000 µg/m3	no	no	no	39000µg/m3	no	no	no	no	3000 µg/m3	no	no	no	no	no	no	no

8.6. Explanations on Integration & Weighing of evidence (WoE analysis)/ Application of Levels of Confidence

Following explanations are given in the used ECHA template[54]; modifications are marked in blue.
"The elements of consistency/specificity and likelihood are usually considered necessary for any WoE integration step although the degree of elaboration might differ depending on the problem formulation. They are based on the Bradford Hill considerations as used within the WHO/IPCS MoA framework but can be generalised to fit any hazard assessment. Elements such as temporality (see further below) are often more relevant for complex toxicological endpoints.

Type of Evidence	*Consistency & Specificity*	*Likelihood/ Biological Plausibility*	*Temporality*	*Confidence / Strength of Evidence*	*Remaining Uncertainty*
Conclusion from overall confidence					

Consistency & Specificity

Refers only to the evidence available. For different types of evidence consistency and specificity can be addressed to document:

- if the evidence available for the specific case (e.g. chemical assessment) is consistent with the remaining evidence (e.g. information from a structurally similar chemical substance indicated fertility effects and is consistent with the substance experimental data on fertility parameters and an alert from a QSAR profiler),
- or for example if all the evidence points to the same direction (positive effects only or negative effects only).

*Other examples of defining consistency and specificity from the WHO/IPCS MoA framework are available at WHO/IPCS Mode of Action Analysis Framework Templates (**Formats and templates - ECHA (europa.eu)**)*

[54] https://echa.europa.eu/documents/10162/17169198/template_for_weight_of_evidence_en.docx/eb183c2e-c360-cbce-7a58-ad2d1270e5bd

Likelihood / Biological Plausibility

Refers only to other broader knowledge: Does the hypothesis make sense based on broader knowledge (e.g. biology, established mode of action)?

Temporality

Needed on a case by case basis (mostly relevant in Mode of action analysis when data allows such analysis). Is there a logical order in the occurrence of an effect on the basis of the evidence available?

Levels of Confidence /Strength of Evidence

Confidence levels/strength of evidence can be assigned to individual evidence and to the overall evidence assessment. Confidence levels are derived taking into account the outcome of the weighing of the evidence (both individually and collectively) using the metrics/criteria specified in the corresponding steps of the WoE approach (such as adequacy, relevance, reliability for individual evidence assessment, and consistency/specificity, plausibility/likelihood, temporality for WoE analysis). Confidence levels can be usually expressed as high, medium or low. The confidence levels for each line of evidence should feed to the judgement of the overall confidence level that take into account all the evidence in an integrated and weighed mode. For each line of evidence confidence levels can have as underlying documentation:

1. Qualitative elements (e.g. Likelihood/ Biological plausibility)
2. Semi (quantitative) elements (e.g. temporality)

Level of confidence of each line of evidence is derived by combining the quality assessment elements of each line of evidence (relevance, adequacy, reliability) with the consistency and plausibility elements.

Conclusion from Overall confidence: *The elements of completeness and adequacy for purpose (as described in ECHA Guidance IR/CSA R.4) could be reflected e.g. in the conclusion from the overall confidence part.*

Further information on tools/methodologies for derivation of confidence levels are available in the background document.

Remaining Uncertainty: *Depending on the case, the remaining uncertainty can be recorded in this section as a result of the levels of confidence for each line of evidence (e.g. high confidence would mean low uncertainty). However the uncertainty components can be further elaboration in Section 5 below if considered necessary, or as part of the conclusions and further needs*."

8.7. Tabulated clinical case assessment (status September 2022)

Table (suppl. Info) 7: dental sector

Authors	Study case #	Profession sector	R.7a: Protocol used (study design, controls)	R.7a: Substance or preparation studied (should be	R.7a: Exposure (magnitude, frequency and duration)	R.7a: frequency of effects (versus number of persons	R.7a: Persistence or absence of health effects (objective	R.7a: Confounding factors (e.g. pre-existing respiratory	R.7a: Relevance with respect to the group size,	R.7a: Healthy worker effect	diagnosis of OA	clear evidence of HEMA exposure	clear evidence of HPMA exposure	relevant co-expossure	relevant co-expossure to known resp sens	pre-existing diseases	test data indicating immune-based mechanisms	SIC testing with HEMA/HPMA?	was it positive?	Standard SPT
Piirilä P, Kanerva L, Keskinen H, Estlander T, Hytönen M,Tuppurainen M, Nordman H (1998)	2	dental/ dentist	yes	no	limited (not on product or substance level)	n/a	yes	yes (familial atopy, Quartz)	n/a	n/a	yes	likely (occup & SIC)	no	yes (occup & SIC; Rely-a-Bond paste contains Bis-GMA,	yes (occup & SIC; at least Bis-GMA and Quartz, last '= resp sens	familial atopy	no (IgE normal)	yes (mixed expo via Rely-a-bond paste)	weakly pos, early	SPT negative
	3	dental/ nurse	yes	no	limited (not on product or substance level)	n/a	yes	yes (familial atopy)	n/a	n/a	yes	yes (occup & SIC)	no	yes (occup & SIC; Scotchbond adhesive contains 62% Bis-	not known	familial atopy	yes (IgE elevated)	yes (mixed expo via Scotchbond products)	pos,late	SPT negative
	7	dental/ nurse	yes	no	limited (not on product or substance level)	n/a	yes	no	n/a	n/a	yes	yes (occup & SIC)	no	yes (occup & SIC; Scotchbond adhesive contains 62% Bis-	not known	no	no (IgE normal)	yes (mixed expo via Scotchbond product)	pos, early	SPT negative
	9	dental/ dentist	yes	no	limited (not on product or substance level)	n/a	yes	yes (moderate BHR)	n/a	n/a	yes	yes (occup & SIC)	no	yes (occup & SIC; Scotchbond adhesive contains 62% Bis-	not known	moderate bronchial hyper-reactivity, slight airways	no (IgE normal)	yes (mixed expo via Scotchbond products)	pos,late	SPT negative
	10	dental/ nurse	yes	no	limited (not on product or substance level)	n/a	yes	yes (slight airways obstruction)	n/a	n/a	no (Rhinitis)	yes (occup & SIC)	no	yes (occup & SIC; Scotchbond adhesive contains 62% Bis-	not known	slight airways obstruction	yes (IgE elevated)	yes (mixed expo via Scotchbond products)	no	SPT negative
	11	dental/ nurse	yes	no	limited (not on product or substance level)	n/a	yes	yes (atopy, slight BHR)	n/a	n/a	yes	yes (occup & SIC)	no	yes (occup & SIC; Scotchbond adhesive contains 62% Bis-	not known	atopy, SPT pos to common allergens, slight bronchial	yes (IgE elevated)	yes (mixed expo via Scotchbond products)	pos, late	SPT positive
	12	dental/ nurse	yes	no	limited (not on product or substance level)	n/a	yes	yes (familial atopy, slight airways obstruction)	n/a	n/a	yes	yes (occup & SIC)	no	yes (occup & SIC; Scotchbond adhesive contains 62% Bis-	not known	familial atopy, slight airways obstruction	no (IgE normal)	yes (mixed expo via Scotchbond products)		SPT negative
Lindstrom, M.; Alanko, K. [Reprint author]; Keskinen, H.; Kanerva, L. (2002)	1	dental/ dentist	yes	no	no	n/a	yes	yes (moderate BHR)	n/a	n/a	yes	yes (occup & SIC)	no	yes (MMA, EMA, EGDMA, EA in Scotchbond ; others in	not known	moderate bronchial hyper-reactivity	no	yes (mixed expo via Scotchbond)	one weakly pos (early); one pos ("early late")	SPT negative

Table (suppl. Info) 8: cosmetic sector

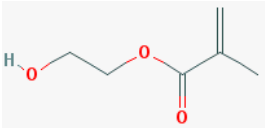
Authors	Study case #	Profession sector	R.7a: Protocol used (study design, controls)	R.7a: Substance or preparation studied (should be	R.7a: Exposure (magnitude, frequency and duration)	R.7a: frequency of effects (versus number of persons	R.7a: Persistence or absence of health effects (objective	R.7a: Confounding factors (e.g. pre-existing respiratory	R.7a: Relevance with respect to the group size,	R.7a: Healthy worker effect	diagnosis of OA	clear evidence of HEMA exposure	clear evidence of HPMA exposure	relevant co-exposure	relevant co-exposure to known resp sens	pre-existing diseases	test data indicating immune-based mechanisms	SIC testing with HEMA/HPMA?	was it positive?	Standard SPT
Moulin P et al. (2009)	1	beautician	limited	no (Test item not fully clear)	no	n/a	yes	yes (familial atopy, BHR)	n/a	n/a	yes	yes (SIC); unclear (occup)	no	unspecifically to other airborne substances	not known	familial atopy, dermal intolerances, reactive airways	no (IgE normal)	yes (HEMA "without hardener")	pos (early)	SPT neg but HEMA pos
	2	beautician	n/a	no	no	n/a	yes	yes (familial asthma)	n/a	n/a	yes	likely (occup)	no	UV cure resins	not known	familial asthma	no (IgE normal)	no	n/a	negative (pos for activated ultraviolet gel and acrylic
Sauni, Riitta; Kauppi, Paula; Alanko, Kristiina; Henriks-Eckerman, Maj-Len; Tuppurainen, Matti; Hannu, Timo	1	nail technici	yes	no	no	n/a	yes	yes (mild-moderate BHR, dust exposure)	n/a	n/a	yes	dermal yes (bonding agent component); inhalative questionabl	dermal yes (scculpture resin component); inhalative questionabl	various Methacrylates (HEMA; HPMA, EGDMA, TREGDMA,	dust (from sanding)	yes (mild-moderate BHR, smoker in the past)	no information	yes (mixed expo as component)	yes (dual)	SPT unknown(pos to HEMA & EGDMA
	2	nail technician/ hairdresser	yes	no	no	n/a	unknown	yes (moderate BHR, atopy, dust exposure)	n/a	n/a	yes	dermal yes (bonding agent component); inhalative questionabl	dermal yes (scculpture resin component); inhalative questionabl	various Methacrylates (HEMA; HPMA, EGDMA, TREGDMA,	dust (from sanding)	yes (moderate BHR, atopy)	no information	yes (mixed expo as component)	yes (dual)	SPT pos to animals and pollens
Moshe, Shlomo (correspondence); Krakov, Ayala Moshe, Shlomo (correspondence); Krakov, Ayala	2	cosmetic/ nail	n/a	no	no	n/a	yes	yes (BHR)	n/a	n/a	yes	dermal yes; inhalative questionabl e	dermal yes; inhalative questionabl e	no information	no information	yes (BHR)	no information	no	n/a	Patch test positive to HEMA &HPMA

Appendix III Weight-of-Evidence Assessment Respiratory Irritation HEMA

HAZARD
ASSESSSMENT
HEMA
Irritation of the respiratory tract
(STOT-SE 3, H335)

For the Higher Methacrylates REACH Task Force,
Knut Kreuzer, Röhm GmbH

Chemical Information

Substances	Structure
2-Hydroxyethyl methacrylate, HEMA EC no. 212-782-2, CAS no. 868-77-9 Relevant impurity: ≤ 0.2% Methacrylic acid, CAS no. 79-41-4	

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1. Problem Formulation

A simplified Weight-of-Evidence assessment has been performed for HEMA, following a respective ECHA template. Following Considering the CLP definition for respiratory irritants[55] (EU, 2008), the following hypothesis has been investigated for HEMA:
HEMA can cause specific, non-lethal toxic effects on the human respiratory tract occurring after a single exposure.

2. Assessment of individual evidences

Following lines of evidence (LoEs) were considered as relevant. LoEs without any data are not listed.

2.1. Physico-chemical properties

Vapour pressure/ volatility
A prerequisite for the existence of a relevant risk is a sufficiently intense exposure to the substance of interest. Following ECHA Guidance R.7c (2017), Table R.7.12-2 on the interpretation of data regarding respiratory absorption, HEMA with a vapour pressure (VP) of 0.08 hPa at 20°C C and a boiling point (BP) of 213 °C has to be considered as substance of very low volatility ("low volatility" is defined by the Guidance already by a VP of <5 hPa (BP > 150 °C), a VP level approx. 50 times more than the VP of HEMA). Thus, inhalation exposure to vapours of HEMA can be estimated as limited.
Furthermore, limit values of volatility of substances are also defined in "Council Directive 1999/13/EC of 11 March 1999 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain activities and installations" with a vapour pressure of > 0.01 kPa (> 0.1 hPa) at 20 °C. The vapor pressure of HEMA is slightly below this limit value of low volatility. It should be kept in mind, that limit values are usually chosen conservatively. STOT SE3 H335 is a hazard for respiratory irritation by single exposure, where usually higher substance concentrations are required which can only be received by a higher vapour pressure. For that reason, single exposure of substances at the limit value for volatile organic compounds of 0.1 hPa does not apply to cause respiratory irritation.
Saturated vapour concentration at 20°C was calculated at 79 ppm or 427 mg/m³ for HEMA on the basis of the aforementioned vapour pressures (Röhm 2005).

[55] „Specific target organ toxicity – single exposure means specific, non-lethal toxic effects on target organs occurring after a single exposure to a substance or mixture."

LoE summary

HEMA is a substance of very low volatility that limits the risk of relevant inhalation exposure. This information is a relevant criterion for classification purposes from a risk perspective, thus this LoE is assessed with a high level of relevance, a high level of reliability and a moderate level of adequacy for classification purposes as resp. irritant.

2.2. ADME

Metabolism/ Toxikokinetics

After oral or inhalation administration, methacrylate esters such as HEMA, are expected to be rapidly absorbed and distributed. Short chain alkyl-methacrylate esters are initially hydrolysed by non-specific carboxylesterases to methacrylic acid (MAA) and the structurally corresponding alcohol (see Figure below). in several tissues MAA is subsequently cleared predominantly via the liver (valine pathway and the TCA (Tricarboxylic Acid) cycle). The carboxylesterases are a group of non-specific enzymes that are widely distributed throughout the body and are known to show high activity within many tissues and organs, including the olfactory and nasal respiratory tract (Jones, 2002). Those organs and tissues that play an important role and/or contribute substantially to the primary metabolism of the short-chain, volatile, alkyl-methacrylate esters are the tissues at the primary point of exposure, namely the nasal epithelia and the skin, and systemically, the liver and blood.

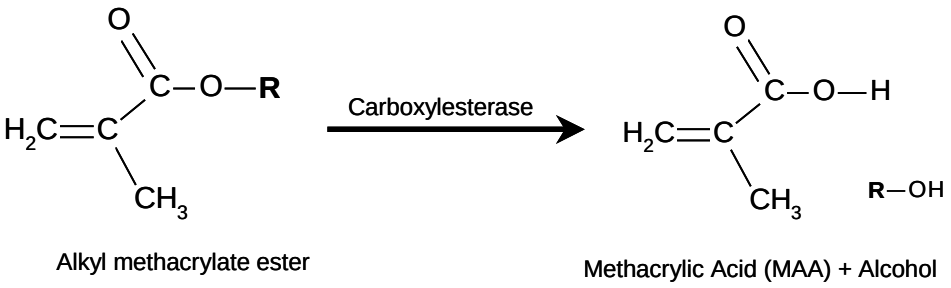

Figure 4 Alkyl methacrylate ester hydrolysis by carboxylesterase

This understanding has been verified in a non-GLP toxicokinetic study with HEMA in rats via intravenous administration. The study was conducted to evaluate the hydrolysis rate of HEMA in vivo (Dow, 2017). The estimated half-live for HEMA was around one minute (i.e. 0.84 and 1.06 minutes for the two tested animals), indicating that the current study results support the assumption that HEMA was rapidly hydrolysed after intravenous administration in rats. Toxicokinetics is considered to be similar in man and experimental animals.

Ester hydrolysis in the respiratory tract

Tissue specific information on the enzymatic capacity in the respiratory tract of mammals is available from mechanistic studies with other alkyl methacrylic esters, including the methyl

ester of MAA, MMA[56]. Gelbke and coworkers (2018) explained in a toxicological assessment the category of lower alkyl methacrylate esters that "*Former studies have shown that inhalation of MMA predominantly leads to destruction of the olfactory epithelium in the upper respiratory tract of rats. Studies … have demonstrated that this is the consequence of intracellular ester cleavage to MAA, an irritant and corrosive metabolite (Mainwaring et al., 2001) leading to decreased intracellular pH. Under the assumption that ester cleavage and intracellular MAA drive local toxicity in the upper respiratory tract and by taking into account the distribution of carboxylesterases and the airflow pattern, the modelling by Andersen and Sarangapani (1999) and Andersen et al. (2002) showed that humans are less sensitive than rats. In summarizing the available PBPK data on MMA, SCOEL (2005) concluded that human nasal olfactory epithelium will be at least 3 times less sensitive than that of rats to the toxicity of MMA. This difference in sensitivity stems from species differences in carboxylesterase activity and distribution of MMA to the olfactory epithelium. Carboxylesterases are heavily localized in the sustentacular cells and Bowman's glands of the rat olfactory region but are more generally distributed in human olfactory epithelium. For the olfactory epithelium the maximum rate of metabolism in humans is about 13-fold lower than that in rats and for respiratory tissue at least 6-fold lower (Mainwaring et al., 2001)*.".

Primary Metabolites – hazard potential

Methacrylic acid (MAA, CAS 79-41-4), the common acid metabolite of HEMA and other methacrylate esters, is of concern to human health due to its corrosive properties. It is classified as a hazardous substance (i.e. irritating to corrosive upon contact (skin, eyes and respiratory system) depending on the concentration; harmful when inhaled or ingested, toxic (by skin contact)). In a repeated dose inhalation study, local effects were observed after 90 d of inhalation exposure at 350 ppm, so that the local NOAEL for effects on the respiratory tract has been determined as 100 ppm in this study (BASF, 2008[57]). This study is considered as most relevant for the identification of locally irritating concentrations of MAA in the respiratory tract. The repeated dosing may be understood as additional safety factor for the assessment of a single exposure hazard. On the other hand, local effects are typically concentration-triggered hazards so that repeated exposure likely is of lower relevance here.

In addition to that, data from the widely analogous methacrylate esters, MMA[58] and n-BMA[59], can be used to define relevant local concentrations of MAA. Both substances also show a comparable rapid hydrolysis to MAA (and the respective alcohol) within minutes but have a significantly higher volatility compared to HEMA. In an acute inhalation study in rats, using special histopathology techniques to study the nasal tissues, n-BMA did not produce lesions

[56] Methyl methacrylate, CAS no. 80-62-6

[57] not in reference list; see chapter "Repeated Dose Toxicity" in the REACH dossier

[58] Vapour pressure 37 hPa @ 20°C

[59] n-Butyl methacrylate, CAS no. 97-88-1; vapour pressure 2.1 hPa @ 20 °C

in the olfactory region of the nasal cavity following exposure at 200 ppm for 6 hrs (Jones, 2002). In the same acute study, MMA caused local effects at 200 ppm. Degenerative changes in the olfactory epithelium were observed after chronic exposure for two years to MMA at 100 ppm but not at the next lower dose of 25 ppm (Rohm & Haas, 1979). The outcome of both studies provides confidence in the conclusion that local MAA concentrations of around 100 ppm can be seen as internal borderline concentrations to cause irritative effects in the respiratory tract of rats after single exposure.

MAA, a substance with a somewhat higher vapour pressure of 0.97 hPa than HEMA and classified as respiratory irritant in concentrations ≥ 1.0% according to CLP Annex VI, is also a typical impurity in the composition of the registered substance, with concentrations up to 0.2% (w/w).

Ethylene Glycol (EG, CAS 107-21-1), the alcohol metabolite of HEMA, is classified for its systemic toxicity with Acute tox. 4 (oral) and STOT RE 2 (kidney) (oral). EG shows no relevant local toxicity nor is a skin or respiratory sensitizing substance.

LoE summary

HEMA is readily absorbed from various routes of exposure and is rapidly hydrolysed by carboxylesterases to MAA and the respective alcohol, EG. There is high confidence that clearance from the body of the parent ester is in the order of minutes. The primary acid metabolite, MAA, is a corrosive substance which can cause local effects in contact with tissues in a concentration-depended manner, so that the hydrolysis can be understood as toxification step from an irritation/corrosion MoA. Local effects (irritation) resulting from the hydrolysis of the ester to MAA were observed following inhalation exposure of other methacrylate esters and this has been shown to be due to the localised concentration of non-specific esterases in the respiratory tract, specifically in the olfactory epithelium. Here, the human nasal olfactory epithelium appears significantly less sensitive to this mechanism of intracellular acidification than that of rats. For example, SCOEL estimated the human sensitivity at least 3 times less than that of rats.

MAA is also a typical impurity in HEMA. Its concentration of up to 0.2% is however significantly below the SCL[60] of MAA for H335/ Respiratory Irritation of 1.0%. The vapor pressure of MAA is with 0.97 hPa slightly higher than HEMA but also within the range of low vapour pressure. The concentration of MAA, seen solely from the perspective as impurity, does thus not represent a concern for human health. Moreover, this concentration does not justify a classification of HEMA as respiratory irritant.

[60] Specific Concentration Level as defined per CLP, Annex VI for STOT-SE 3, H335.

As a consequence of the low impurity level of MAA and also due to the lower sensitivity of the human respiratory tract it appears unlikely that irritation or corrosion by MAA is a relevant mode of action for HEMA in humans, particularly since the vapour pressure of these esters is relatively low so that toxic, local MAA levels cannot be reached in the respective tissues.
This LoE is considered with a moderate level of relevance, a moderate level of reliability and a moderate level of adequacy for classification purposes as respiratory irritant.

2.3. Other relevant hazards: skin & eye irritation

HEMA is a weak irritant to the eyes:
HEMA is classified as skin and eye irritant, Category 2 with H315 and H319, respectively, according to Annex VI of CLP. Available animal data however do not confirm the classification for skin irritation.

LoE summary

HEMA is a weak irritant to the eyes, so that a limited, but general irritating potential is given. Omitting aspects of low vapour pressures, this LoE is assessed with a moderate level of relevance, a moderate level of reliability and a low level of adequacy for classification purposes as respiratory irritant.

2.4. In vivo/ animal studies

HEMA has been studied in an early series of subacute rat inhalation studies in "nearly saturated vapour" atmospheres (Gage 1970). Due to the general description of the study methods and the narrow reporting of the outcome, this source is considered of limited reliability. Repeated exposure to HEMA (15 exposures within 3 weeks for á 6 hrs to approx. 0.5 mg/L or 90 ppm[61]) caused no nose irritation, no treatment-related changes in the lungs and other investigated organs (at least liver, kidneys, spleen and adrenals; further organs on occasion) but "erratic body weight gain" in the four female rats (not in males). A histopathological investigation of the potentially most sensitive tissue of the upper respiratory tract (URT), the olfactory epithelium, has not been performed.

[61] Indirectly measured; roughly comparable to the calculated vapour saturations in chapter 2.1

LoE summary

There is no indication of local effects of the respiratory tract after repeated exposure to saturated atmospheres of HEMA. Some uncertainty stems from the fact that the potentially most sensitive URT tissue has not been thoroughly investigated in this older study. This LoE is assessed with a high level of relevance, a moderate level of reliability and a high level of adequacy for classification purposes as respiratory irritant.

2.5. Human data & exposure

Some clinical cases of respiratory symptoms with potential or claimed causal relationship to HEMA exposure have been identified in the public literature, with focus on the diagnosis of occupational asthma ("OA"). It is acknowledged that this diagnosis can include also irritant-induced types of OA following the differentiation of the World Allergy Organisation[62] so that these cases are theoretically of relevance for this WoE assessment.
However, those cases have been assessed already in detail in a separate WoE assessment for respiratory sensitisation (see **Appendix II** Weight-of-Evidence Assessment Respiratory Sensitisation HEMA). In that assessment, it is described, that these human data lack of many details that are required by ECHA guidance R7.a (section R7.3.10.2; ECHA, 2017) and also fail in documenting evidence for a causal relationship between exposure to the chemicals and appearance of symptoms that these cases are disregarded here.
For orientation, however, it should be mentioned that those cases were observed in the dental and the cosmetic sector, where HEMA is used as component in complex product mixtures and where the work atmospheres can be characterised as complex mixtures of volatile substances and/or dusts of various origins so that a causal relationship of effects to a single substance is almost impossible to establish with a sufficient confidence level. Moreover, in all but one case, a confounding pre-existing health status (like non-specific bronchial hyperreactivity) was observed, where reported.
In the industrial monomer production, a sector with significant lower co-exposure and no documentation of potential OA cases, the highest exposure levels to HEMA (maximum level of 0.41 mg/m³ or 0.08 ppm) was measured (Röhm, 1996).
Indoor spray applications that could reach highest theoretical concentrations of these low volatile substances, are not known for HEMA.

[62] https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/diagnosis-of-occupational-asthma

LoE summary

Some clinical cases of respiratory symptoms with potential or claimed causal relationship to HEMA exposure have been identified in the dental and cosmetic sector but were considered as not reliable in the separate WoE analysis on respiratory sensitisation. The maximum identified exposure levels were found in the range of 0.1 ppm for HEMA. This levels is about three magnitudes lower than the calculated saturated vapour pressure (see chapter **2.1**).
This LoE is considered with a high level of relevance (human = “target organism”), a low level of reliability for the clinical cases but a high level of reliability for the exposure data and a high level of adequacy for classification purposes as respiratory irritant.

3. Weight of evidence analysis including uncertainty analysis

HEMA is understood as eye irritant of weak potency so that an inherent irritative potential is given for this substance.
Saturated atmospheres of HEMA, did not cause signs of nose irritation or local effects in the lung in subacute repeated dose studies in rats. However, this potential has not been thoroughly investigated in the URT in animals in that older study, so there remains rather weak uncertainty whether low exposure levels of weak eye irritants can cause irritation specifically in the URT.
Beside the irritative potential of HEMA as parent ester, also the corrosive potential of MAA as impurity and also as primary metabolite has to be considered. MAA is formed – equimolar to the respective parent ester - in various first contact organs, including the respiratory tract of rodents and humans, due to rapid hydrolysis within the order of a few minutes. In a repeated dose study, 350 ppm MAA were identified as lowest concentration that caused irritation in the respiratory tract of rats, with 100 ppm as NOAEL for such local effects. This NOAEL is almost identical with the maximum achievable vapour concentration of HEMA (79 ppm). Moreover, this NOAEL is approx. 3 magnitudes higher than the maximum measured exposure levels of HEMA (0.08 ppm) in the industrial monomer production. An additional safety margin stems from interspecies differences between rat and human respiratory tissue: the last is considered at least 3 times less sensitive than that of rats and thus 3 times less vulnerable to the corrosive metabolite. The impurity level is at least 5 times below the SCL for MAA triggering such classification.
There remains no uncertainty that the metabolite MAA cannot reach a relevant local concentration in the human respiratory tract.

4. Conclusions

There is, at best, questionable evidence for the tested hypothesis that HEMA can cause specific effects on the human respiratory tract after a single exposure based on following considerations

- The substance has a very low vapour pressure;
- It is only a low potent irritant, just reaching criteria of eye irritation Cat 2B under UN-GHS, but no classifiable effects on skin irritation;
- No local effects have been observed in a subacute inhalation study in rats exposed to maximum technically achievable concentrations of HEMA;
- The concentration of the low volatile, corrosive impurity MAA is at least five times below the respective SCL that triggers classification as respiratory irritant;
- MAA, as primary metabolite of methacrylic acid esters, can theoretically cause irritative effects in the respiratory tract of rats in atmospheres saturated with one of the substances. However, it is implausible that relevant local concentrations in

humans can be reached, even in combination with the few MAA molecules coming from the impurity.

Therefore, there is no basis for classification of HEMA as respiratory irritant under EU CLP.

5. Appendix III References

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Andersen ME, Sarangapani R (1999). Clearance concepts applied to the metabolism of inhaled vapors in tissues lining the nasal cavity. Inhal. Toxicol. 11, 873–897.

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ECHA (2017). Guidance on Information Requirements and Chemical Safety Assessment; Chapter R.7a: Endpoint specific guidance; Version 6.0

EU (2008). Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008

Gelbke H-P et al. (2017). Toxicological assessment of lower alkyl methacrylate esters by a category approach. Regulatory Toxicology and Pharmacology, 92:104-127. doi: 10.1016/j.yrtph.2017.11.013

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Appendix IV Hazard Assessment Skin Irritation HEMA

Skin Irritation of Hydroxyethyl methacrylate

1. Non-human information

1.1. Studies on skin irritation

HEMA has been evaluated in skin irritation studies in experimental animals.
In the key study the skin irritation potential of HEMA has been evaluated in a test in rabbits according to "Appraisal of the safety of chemicals in food, drugs and cosmetics by the Staff of the Division of Parmacology, FDA, 1959 in food, drugs and cosmetics" (Sterner, Stiglic, 1977). This study was assigned a Klimisch rating of 2, reliable with restriction. Undiluted HEMA was applied with occlusion to the scarified and non-scarified skin of six rabbits for 24 hr. 2/6 animals had erythema scores of 1 after 24 hrs (one animal died not treatment related within 24 hrs.). After 72 hours none of the remaining five animals showed erythema. 0/6 animals showed edema after 24 and 72 hrs. HEMA was found to be not irritating to the rabbit skin acc. CLP and GHS classification criteria. Other available studies were reviewed and judged to be not reliable or not assignable.
In a supporting study HEMA (impurity ca. 1 % methacrylic acid) was tested in a skin irritation test in 6 New Zealand White rabbits. Animals were treated under occlusive conditions for 24 hours and observed for 72 hrs after start of exposure. Non abraded animals were reevaluated under EU regulation 1272/2008 and GHS criteria. Mean irritation scores for erythema after 24 and 72 hrs were 0 in 5/6 animals , in one animal 0.5 which was fully reversible within 72 hours. Mean irritation scores for edema after 24 and 72 hrs were 0 in 6/6 animals In this study HEMA is not irritating to skin acc. CLP and GHS criteria.
Additional studies are available which are not reported sufficiently and/or which use test material with unspecified or up to 5 % methacrylic acid. In these tests HEMA was qualitatively reported to be not irritating or slightly irritating.
The results of studies on skin irritation are summarised in the following table:

Table 7 HEMA Study records

Method	Results	Remarks
rabbit [common species] (New Zealand White [rabbit]) Coverage: occlusive (shaved, shaved and scarified) according to guideline Appraisal of the safety of chemicals in foods, drugs and cosmetics (1959) Method: Appraisal of the safety of chemicals in foods, drugs and	GHS criteria not met erythema score animal #1 0.5 of max. 4 (Time point: mean 24+72 h) Reversibility: fully reversible within: 72 h (occlusive, exposure time 24 h, observation time 72 h, intact skin,	2 (reliable with restrictions) key study experimental study Test material 2-Hydroxyethyl methacrylate CAS 868-77-9, Standard material ca. 98.9 %, Form: liquid

cosmetics by the Staff of the Division of Pharmacology, FDA, Hautgiftigkeit nach Draize (1959)	reevaluated acc. GHS (overall mean).) animal #2 1 of max. 4 (Time point: 24 h) (before end of test, animal died, not treatment related) animal #3, #4, #5, #6 0 of max. 4 (Time point: mean 24+72 h) (occlusive, exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. GHS (overall mean).) edema score animal #1, #2,#3, #4, #5, #6 0 of max. 4 (Time point: 24+72 h) (occlusive, exposure time 24 h, observation time 72 h, intact skin, reevaluated acc. GHS (overall mean).)	Methacrylic acid: 0,071 bis 0,91 % (company data in the years of the report) Reference Sterner, Stiglic (1977)
rabbit [common species] (New Zealand White [rabbit]) Coverage: occlusive (clipped and abraded skin and only clipped skin - and intact skin) equivalent or similar to guideline Reactions were scored according to the scale shown in the following table i.e Draize J.H (1959) Association of Food & Drug Officials of the USA, Austin, Texas, "The Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics".	GHS criteria not met erythema score animal #4 0.5 of max. 4 (Time point: 24h/72h) Reversibility: fully reversible within: 72 h animal #1, #2,#3, #5, #6 0 of max. 4 (Time point: 24h/72h) edema score animal #1, #2,#3, #4, #5, #6 0 of max. 4 (Time point: 24h/72h)	2 (reliable with restrictions) supporting study experimental study Test material 2-Hydroxyethyl methacrylate CAS 868-77-9, Standard material ca. 98.9 %, Methacrylic acid ca. 1% Reference Safepharm (1983)