Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2-hydroxyethyl methacrylate; [HEMA]

EC Number: 212-782-2
CAS Number: 868-77-9

CLH-O-0000007378-64-01/F

Adopted

30 November 2023

30 November 2023

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted on **30 November 2023** by **consensus** an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **2-hydroxyethyl methacrylate; [HEMA]**

EC Number: **212-782-2**

CAS Number: **868-77-9**

Rapporteur, appointed by RAC: **Anna Biró**

Administrative information on the opinion

France has submitted on **30 January 2023** a CLH dossier containing a proposal together with the justification and background information documented in a CLH report.

The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **13 March 2023**.

Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **12 May 2023**.

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The following table provides a summary of the Current Annex VI entry, Dossier submitter proposal, RAC opinion and potential Annex VI entry if agreed by the Commission.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-124-00-X	2-hydroxyethyl methacrylate; [HEMA]	212-782-2	868-77-9	Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1	H315 H319 H317	GHS07 Wng	H315 H319 H317			Note D
Dossier submitters proposal	607-124-00-X	2-hydroxyethyl methacrylate; [HEMA]	212-782-2	868-77-9	**Add** STOT SE 3 Resp. Sens. 1	**Add** H335 H334	**Add** GHS08 **Modify** Dgr	**Add** H335 H335			
RAC opinion	607-124-00-X	2-hydroxyethyl methacrylate; [HEMA]	212-782-2	868-77-9	**Add** STOT SE 3	**Add** H335	**Add** GHS08 **Retain** Wng	**Add** H335 H335		STOT SE 3, H335: C ≥ 10 %	
Resulting Annex VI entry if agreed by COM	607-124-00-X	2-hydroxyethyl methacrylate; [HEMA]	212-782-2	868-77-9	STOT SE 3 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1	H335 H315 H319 H317	GHS07 GHS08 Wng	H335 H315 H319 H317		STOT SE 3, H335: C ≥ 10 %	Note D

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

2-hydroxyethyl methacrylate (HEMA) is used in the following products: adhesive and sealants, non-metal surface treatments products and cosmetics and personal care products.

HEMA is a clear colourless liquid at 20 °C and 101.3 kPa, with a boiling point of 213 °C at 101.3 kPa and vapour pressure of 0.08 hPa at 20 °C. The water solubility is > 100 g/L at 25 °C.

It has an existing harmonised classification as Skin Irrit. 2 (H315), Eye Irrit. 2 (H319) and Skin Sens. 1 (H317). The dossier submitter (DS) proposed to add STOT SE 3 (H335) and Resp. Sens. 1 (H334).

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

As there is no specific data on respiratory irritation for HEMA, the DS performed a read-across assessment. The source substances for the read-across are methacrylic acid (MAA), and short linear chain, volatile methacrylates that are hydrolysed by esterases into a common metabolite: MAA + an alcohol or a glycol. Methyl methacrylate is metabolised into MAA + methanol, ethyl methacrylate (EMA) into MAA + ethanol, butyl methacrylate (BMA) into MAA + butanol. All source substances have a harmonised classification as irritant for the respiratory tract (STOT SE 3; H335). The target substance, HEMA is metabolised into MAA + ethylene glycol.

All considered substances are short methacrylates, with a linear length chain ≤ 4 carbons. Molecular weights range from 86 g/mol (MAA) to 142 g/mol (BMA). MMA, EMA and BMA are highly volatile, with vapour pressure > 1 hPa. HEMA has a lower vapour pressure (8 Pa) but volatility is still expected. Indeed, inhalative exposure is confirmed at occupational settings where air levels of HEMA were measured. Marquardt *et al.* (2009) found maximum concentration for HEMA at 45 µg/m^3 during filling therapies in four dental practices in Germany. The median 8-hour time-weighted averages were 2.5 µg/m^3 (dentists) and 2.9 µg/m^3 (dental nurses), and the maximum short-term exposure levels were 79 µg/m^3 in 5 public dental clinics and at the faculty of Odontology at Goteborg University (Hagberg *et al*., 2005).

The DS presented comparative kinetics: a series of *in vitro* and *in vivo* studies with a series of methacrylates were used to develop PBPK models that accurately predict the metabolism and fate of these monomers (Jones, 2002; cited in MMA disseminated REACH dossier).

Table: *Rate constants for ester hydrolysis by rat-liver microsomes and predicted systemic fate kinetics following i.v. administration (adapted from Jones (2002), cited in the disseminated dossier of MMA) (Table 14 in CLH dossier)*

Ester	Rat liver microsomes (100 mg mL^{-1})		CL (%LBF)	$T_{50\%}$ (min)	C_{max} (MAA) (mg L^{-1})	T_{max} (MAA) (min)
	V_{max} (nmol $min^{-1}mg^{-1}$)	K_m (mM)				
MMA	445.8	164.3	98.8%	4.4	14.7	1.7
EMA	699.2	106.2	99.5%	4.5	12.0	1.8
i-BMA	832.9	127.4	99.5%	11.6	7.4	1.6
n-BMA	875.7	77.3	99.7%	7.8	7.9	1.8

CL(%LBF) – Clearance as percentage removed from liver blood flow i.e. first pass clearance; $T_{50\%}$ - time taken for 50% of parent ester to have been eliminated from the body; C_{max} – maximum concentration of MAA in circulating blood; T_{max} – time in minutes to peak MAA concentration in blood.

The DS presented two studies on the hydrolysis of HEMA showing similar behaviour to the substances above. The estimated half-life of HEMA in rat liver microsomes was 4.62 min, and the half-life of HEMA in rats via intravenous administration was estimated around 1 minute.

Table: *Data on hydrolysis of HEMA (Table 15 in the CLH dossier)*

Method	Results	Reference
Determination of *in vitro* hydrolysis rates in rat liver and whole rat blood. PBPK modelling from *in vitro* Km and Vmax values to simulate *in vivo* blood concentrations.	Half-life of HEMA in rat liver microsomes (phase I) = 4.62 min and in whole rat blood (phase II) = 99 min. Vmax (*in vitro*) = 111 nmol/min/mg Km (*in vitro*) = 889 µM PBPK modelling: Vmax (*in vivo*) = 39 mg/h/g liver Km (*in vivo*) = 116 mg/L	Anonymous, 2013
Two male rats (F344/DuCrj) HEMA via intravenous administration at the dose of 5 mg/kg bw. Blood samples were collected at 5, 10, 30, 60 and 180 minutes and analysed by GC/MS-MS	HEMA not quantifiable by 60 minutes ((LOQ) of 45 ng/mL) Estimated half-life about 1 min	Anonymous, 2017 ECHA website, 2021

The DS stated that based on the *in vitro* and *in vivo* studies, there is a high level of confidence that these substances would have similar toxicokinetic behaviour and that the same processes would occur in humans.

All the substances in the read-across have irritative properties. They are classified for skin irritation/eye irritation in Category 2, with the exception of MAA, which is corrosive to the skin (Skin Corr. 1A). Methacrylic acid, MMA, EMA and BMA are classified as respiratory irritants.

Table: *Hazard properties of target and source substances relevant for the read-across*

Substances	**Harmonised classification**	**Respiratory irritation hazard**
HEMA	Skin Irrit. 2; H315 Eye irrit. 2; H319 Skin Sens. 1; H317	No adequate data
MAA	Acute Tox. 4*; H302 Acute Tox. 4*; H312 Skin Corr. 1A; H314 STOT SE 3; H335; C ≥ 1%	90-day inhalation study in rats and mice reported rhinitis of the anterior regions of the turbinates (EU RAR, 2002)
MMA	Flam. Liq. 2; H225 Skin Irrit. 2; H315 Skin Sens. 1; H317 STOT SE 3; H335	Degeneration of the olfactory epithelium after 6h exposure to 200 ppm in rats (disseminated REACH dossier, ECHA website, 2022) Reversible irritation reactions after short-term peak exposures to humans at concentration levels exceeding 100 ppm (Anses, 2018)
EMA	Flam. Liq. 2; H225 Skin Irrit. 2; H315 Eye Irrit. 2; H319 Skin Sens. 1; H317 STOT SE 3; H335	Degeneration of the olfactory epithelium after a 6 h exposure to 200 ppm in rats (disseminated REACH dossier, ECHA website, 2022)
BMA	Flam. Liq. 3; H226 Skin Irrit. 2; H315 Eye Irrit. 2; H319 Skin Sens. 1; H317 STOT SE 3; H335	Respiratory irritation at concentration > 300 ppm) (disseminated REACH dossier, ECHA website, 2022)

The mode of action by which olfactory lesions are formed is considered to be due to hydrolysis by carboxylesterases of the parent ester to MAA, an irritant and corrosive substance to the olfactory epithelium. Local formation of MAA is expected as there are high levels of non-specific esterases in the Bowman's glands of the nasal olfactory tissues. Local effects are not anticipated from the corresponding alcohol/glycol. Therefore, even if there is no data on HEMA itself regarding respiratory irritation, there is no reason that the mode of action of short length methacrylates does not occur.

Based on toxicokinetic considerations and data available for other analogous methacrylates, the DS concluded that HEMA fulfils CLP criteria for STOT SE 3; H335.

Comments received during consultation

There were two comments, one from a Member State Competent Authority (MSCA) and one from an Industry representative (IND).

The MSCA supported the DS's proposal to classify HEMA as STOT SE 3; H335 based on the read-across, the common hydrolysis product MAA, the physico-chemical properties (molecular weight: 130.14 g/mol; vapour pressure: 0.08 hPa at 20°C) and the skin/eye irritating potential of HEMA.

IND did not agree with the CLH proposal for STOT SE (respiratory irritation). They considered that although MAA is the primary metabolite of HEMA after ester hydrolysis by carboxyl esterases, hydrolysis in the respiratory tract requires the uptake of the substance via the respiratory air, for which the substance must have a sufficiently high vapour pressure. In their view, HEMA is a substance of very low volatility, and even combined exposure from MAA as impurity and as metabolite cannot reach relevant local levels in the human respiratory tract. In their comments, IND agreed with the irritating properties of MAA in the nasal mucosa, but pointed out that the carboxylesterase capacity in the olfactory epithelium responsible for the intracellular ester cleavage to MAA is much lower in humans than in rats (~13-fold). They recognised that MAA, the common acid metabolite of HEMA and other methacrylate esters, is of concern to human health due to its corrosive properties. In their weight of evidence analysis based on a 90-day inhalation study on MAA, where local effects were observed at 350 ppm, and taking into account that local effects were seen at 200 ppm with MMA in an acute toxicity study, 100 ppm was considered as NOAEC for MAA. They concluded 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.

Assessment and comparison with the classification criteria

In the absence of adequate data on HEMA for this hazard property, read-across assessment was carried out by the DS.

***Table**: List of target and source substances considered in the read-across, their water solubility and vapour pressure (source: ECHA dissemination site) and biotransformation products (modified from Table 13 of the CLH dossier).*

	Parent substance	**Water solubility**	**Vapour pressure**	**Biotransformation**	**Common compounds**	**Non-common compounds**
Target	HEMA	>100 g/L at 25°C	0.08 hPa at 20°C	MAA + ethylene glycol	MAA	Ethylene glycol
Source	MAA	98 g/L at 20°C	0.97 hPa at 20°C	NA	MAA	NA
	MMA	15.3 g/L at 20°C	37 hPa at 20 °C	MAA + methanol	MAA	Methanol
	EMA	4.69 g/L at 20 °C	20 hPa at 20 °C	MAA + ethanol	MAA	Ethanol
	BMA	0.36 g/L at 25°C	2.12 hPa at 20°C	MAA + butanol	MAA	Butanol

Read-across assessment to HEMA from other short-chain methacrylates is considered appropriate as these substances have a common functional group and a common hydrolysis product: MAA. All source substances are short methacrylates, with linear length chain ≤ 4 carbons, and they are small with molecular weights ranging from 86 g/mol (MAA) to 142.2

g/mol (BMA). MMA, EMA and BMA are highly volatile with vapour pressure > 1 hPa. HEMA has a lower vapour pressure (8 Pa) but some volatility is still expected. Indeed, inhalative exposure is confirmed at occupational settings where air levels of HEMA were measured. All the substances in the read-across have irritative properties. They are classified for skin irritation/eye irritation in Category 2, while MAA is corrosive to the skin (Skin Corr. 1A). The source substances (MAA, MMA, EMA and BMA) have a harmonised classification as irritant for the respiratory tract (STOT SE 3; H335).

The DS presented comparative kinetic data: from a series of *in vitro* and *in vivo* studies with a series of methacrylates (MMA, EMA, i-BMA and n-BMA), PBPK models were developed that accurately predict the metabolism and fate of these monomers. The DS presented an *in vitro* study on the hydrolysis of HEMA in which the estimated half-life of HEMA in rat liver microsomes (phase I) was 4.62 min, and in whole rat blood (phase II) it was 99 min. However, in an *in vivo* pharmacokinetic study, the half-life of HEMA in rats via intravenous administration was estimated around 1 minute. RAC considers this latter *in vivo* study to carry more weight.

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 liver, blood, gastrointestinal tract, nasal epithelium and skin. Carboxylesterases at the first site of contact, the nasal mucosa and upper respiratory tissues, are responsible for the production of MAA. Overall, it can be assumed that the morphology of the respiratory and olfactory mucosa are largely similar in rats and humans and only minor differences exist with regards to the distribution of carboxylesterases in nasal tissues of these species. In addition, it was demonstrated that carboxylases in the nasal olfactory epithelium of humans metabolise MMA to MAA, although to a lower extent than in rats. Thus, RAC agrees with the DS's view that the metabolic pathway of HEMA (being metabolised to MAA) is likely to occur in humans.

The IND comment considered that acute inhalation of 100 ppm MAA is a "borderline concentration" that may exert irritative properties. The "borderline concentration" may be interpreted from the evidence of an acute inhalation study showing respiratory irritation at 200 ppm MAA (Jones, 2002). As there are no data on lower concentrations, IND proposed that 100 ppm might be assumed to be close to the NOAEC.

RAC notes, however, that there is a reliable short-term repeated dose inhalation toxicity study with MMA in rats available[1], focussing on the irritation effects in the (upper and lower) respiratory tract including the time-course and recovery of these irritation effects. As MMA is instantly metabolised to MAA, the outcome of this study is considered very relevant when determining the existence of a potential "borderline concentration" for MAA (and thus, for other methacrylates as well). The results of the study demonstrate that MMA exposure led to the damage of the olfactory epithelium at concentrations of 110 ppm and 400 ppm, respectively. Beginning at day 1 of exposure, there was degeneration/necrosis of the olfactory epithelium of minimal severity at 110 ppm and of mainly moderate severity at 400 ppm. Seeing necrotic effects due to the irritative properties of the substance and/or its metabolite MAA at a dose as low as 110 ppm, questions the existence of a "borderline concentration" for irritative effects, but most definitely questions the proposed NOAEC of 100 ppm for irritative effects of MAA. Moreover, RAC questions whether quantitative data on external vapour concentrations of the main metabolite, at which no adverse effects on the nasal mucosa were seen or assumed, are sufficiently predictive for the on-site intracellular situation where MAA is produced following aerosol inhalation to HEMA.

[1] https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15528/7/6/3/?documentUUID=6706baaa-455a-4723-ba59-5d31ec11df51

RAC notes that HEMA is a substance of rather low volatility, but besides vapour inhalation, the potential for irritative effects of HEMA following inhalation to aerosols also have to be considered (HEMA is a liquid). In comparison to the half-lives of the source methacrylates, the shorter half-live of HEMA and, in addition, the higher water solubility (see Table 4) of HEMA compared to the other methacrylates listed for read-across, raise the concern that acute irritancy of HEMA, (particularly aerosolised HEMA), could be even stronger than the irritative potency of the other methacrylates. RAC also notes, that should the source substances to the read-across be classified as STOT SE 1 or 2 in the future, a revision for HEMA should also be considered for the same.

Conclusion

There is no specific data related to respiratory irritation for HEMA. Read-across assessment to HEMA from other short-chain methacrylates (MAA, MMA, EMA and BMA) is considered appropriate, based on the common functional group and a common hydrolysis product. All substances (including HEMA) are classified for skin irritation/eye irritation in Category 2, while methacrylic acid is corrosive to the skin (Skin Corr. 1A). The source substances for the read-across have a harmonised classification as irritant for the respiratory tract (STOT SE 3; H335). Rapid hydrolysis of HEMA is likely to occur in human respiratory epithelium to methacrylic acid, a corrosive substance.

Therefore, based on this information, **RAC concludes that classification of HEMA for respiratory tract irritation (STOT SE 3; H335) is warranted**.

SCL setting

The setting of generic/specific concentration limits (i.e., GCL/SCL) was not discussed by the DS. The CLP guidance (2017) states in this regard: "*Classification in STOT SE Category 3 for respiratory tract irritation and narcotic effects does not take potency into account and consequently does not have any guidance values. A* ***pragmatic default GCL of 20% is suggested****, although a lower or higher SCL may be used where it can be justified. Therefore,* ***an SCL can be determined on a case-by-case basis for substances classified as STOT SE Category 3 and expert judgement shall be exercised***." Hence, although there is the possibility to derive an SCL for STOT SE 3 substances, no specifics on how to derive an SCL for respiratory tract irritation are given.

RAC notes that for MMA, EMA and BMA, the harmonised classification is to be applied by using the GCL for STOT SE 3 substances, i.e., 20%. These harmonised classifications were taken over from previous legislations and were not re-evaluated under CLP. Thus, the underlying database for deciding on the use of the GCL instead of an SCL is not known. For dodecyl methacrylate, a slightly longer methacrylate, an SCL of 10% was agreed upon; however, again the underlying database for SCL derivation in unknown, as it was decided upon before CLP came into force. For MAA, the common metabolite of HEMA and the other short methacrylates used for read-across, which is considered the cause of the irritation in the respiratory tract, a much lower SCL of 1% is to be applied according to its entry in CLP Annex VI. No data on SCL derivation for MAA is available.

In the absence of adequate data on HEMA for SCL derivation, data from the read-across source substances has to be taken into account when considering applying an SCL. In a reliable short-term repeated dose inhalation toxicity study in rats, a LOAEC of 110 ppm (= 450 mg/m³) for local effects on nasal mucosa was determined after a single 6 hours exposure to MMA vapour[2].

[2] https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/15528/7/6/3/?documentUUID=6706baaa-455a-4723-ba59-5d31ec11df51

Similarly low LOAECs for local effects in the nose were derived based on supporting repeated dose inhalation toxicity studies with MAA and MMA, respectively. After ≥ 5 days of MAA vapour exposure[3] (mice), a local LOAEC of 100 ppm (= 352 mg/m³; NOAEC of 20 ppm = 69 mg/m³) was determined. After ≥ 90 days of MMA vapour exposure[4] (rats), a local LOAEC of 100 ppm (= 400 mg/m³; NOAEC of 25 ppm = 102 mg/m³) was reported.

It is anticipated that both substances, HEMA and MMA, are instantly and completely metabolised to MAA. Thus, for derivation of effective doses of HEMA eliciting respiratory tract irritation, it is assumed that 100% of HEMA (MW = 130.14 g/mol) and MMA, respectively, is rapidly hydrolysed to MAA.

Based on these assumptions, a local LOAEC of 590 mg/m³ for HEMA can be derived when using the LOAEC of 110 ppm for MMA after a single 6 hours exposure. A similar local LOAEC (i.e., 530 mg/m³) can be derived for HEMA when considering the LOAECs of 100 ppm after repeated MAA and MMA exposure, respectively. Based on these calculated LOAECs for HEMA, effective doses of rounded 0.00005% (w/w) can be estimated. As these low effective doses, however, bear no relation to the much higher (generic) concentration limits assigned to much more severe effects (e.g., lethality as in Acute Tox. 1 (LC_{50} of < 0.05 mg/L) and carcinogens of the category 1A/B have a GCL of 0.1%; reproductive toxicants have a GCL of 0.3%), these effective doses are considered as inappropriate to be used as SCL values in the case at hand.

Considering that the low LOAECs calculated for HEMA are all way below the guidance value (GV) for STOT SE 1 substances (i.e., below 10 mg/L/4h according to Table 3.8.2 of CLP), RAC considers using the equation for SCL calculation for STOT SE 1 substances given in the CLP guidance document (Equation A, below) also in this case of respiratory tract irritation. To account for the less severe nature of STOT SE 3 (H335), in comparison to STOT SE 1, RAC further addresses the differences between the GCL for STOT SE 1 substances (i.e., 10%) and the GCL for STOT SE 3 substances (i.e., 20%) in the equation for SCL derivation for STOT SE 3 (H335) (

A)

$$SCLCat.1 = \frac{ED}{GV1} \times 100\%$$

B)

$$SCLCat.3 = \frac{ED}{GV1} \times 100\% \div \frac{GCL\ STOT\ SE\ 1\ (= 10\ \%)}{GCL\ STOT\ SE\ 3\ (= 20\ \%)}$$

B, below).

A)

$$SCLCat.1 = \frac{ED}{GV1} \times 100\%$$

B)

$$SCLCat.3 = \frac{ED}{GV1} \times 100\% \div \frac{GCL\ STOT\ SE\ 1\ (= 10\ \%)}{GCL\ STOT\ SE\ 3\ (= 20\ \%)}$$

[3] https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15411/7/6/3/?documentUUID=3056b501-a039-4ca8-adb3-c4683898fe9d

[4] https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/15528/7/6/3/?documentUUID=c6482d19-7d01-4130-befa-0e80a23869ae

Equation: A) Equation for SCL derivation for STOT SE 1 substances according to the CLP guidance. B) RAC derived an equation for the SCL derivation for STOT SE 3 substances with a LOAEC below the GV for STOT SE 1 (i.e., 10 mg/L/4h) based on the equation given in A) and considering the differences between the GCL for STOT SE 1 substances (i.e., 10%) and STOT SE 3 substances (i.e., 20%). This approach further accounts for the less severe nature of effects warranting STOT SE 3 classification in comparison to effects that warrant classification for STOT SE 1.

Calculating an SCL for HEMA based on the equation as derived above (Equation B) and using the LOAEC for HEMA (i.e., 590 mg/m³) calculated using the LOAEC of 110 ppm MMA after a single 6 hours exposure, results in an SCL of 11.8%. When considering the slightly lower LOAECs of the repeated dose inhalation toxicity studies with MAA in mice and MMA in rats (i.e., 100 ppm), an SCL of 10.6% can be inferred.

RAC preferred taking a pragmatic approach leading to an SCL of 10%. An SCL of 10% is further supported by the calculations described in detail above and considering that the CLP guidance states that for STOT SE 1 and 2 substances, the calculated resulting SCL has to be rounded down to the nearest preferred value.

Therefore, **RAC concludes** that **an SCL for STOT SE 3; H335, of 10% is appropriate for HEMA.** RAC notes that this SCL is one order of magnitude higher than the SCL assigned to MAA (1%) and equal to the SCL that is assigned to DMA.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

(Q)SAR assessment using several different models on acrylates, including HEMA, gave varying (positive and negative) results with respect to the respiratory sensitising properties of HEMA. The DS concluded that the models are not reliable to predict respiratory sensitisation.

According to the DS, there are 19 cases of patients who developed asthma from occupational exposure to methacrylates and where HEMA is cited as the possible causative agent. These cases originate from 4 publications: Piirila *et al*. (1998); Lindstrom *et al*. (2002); Sauni *et al.* (2008); Moulin *et al*. (2009), and from the Finnish Institute of Occupational Health (FIOH) database. The cases were verified by Specific Inhalation Challenge (SIC) tests. There are also three cases of allergic conjunctivitis and one case of laryngitis reported in the literature, although the causal relationship between these symptoms and HEMA specifically is difficult to reach since these patients were exposed to various methacrylates.

The DS stated that 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 is not yet implemented in the 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 under-reported since reporting is based on spontaneous and voluntary activity. On the other hand, it is known that methacrylates cross-react and that acrylates are often used as mixtures. In such cases, it can be difficult to establish in clinical studies which compound had specifically induced the sensitisation, or whether it was due to mixed exposure.

Several cases of respiratory sensitisation related to (meth)acrylate exposure are reported in

the literature, although in these publications HEMA is not specifically identified or occurs together with other methacrylates (e.g. Savonius, 1993 [case reports]; Lindstrom, *et al*. 2002 [case reports]; Piirila, 2002 [retrospective study]; Jaakkola, 2007 [cross-sectional study]; Walters, 2017 [retrospective review]; Suojalehto, 2020 [retrospective study]).

The DS pointed out that MMA has been recently classified as Resp. Sens. 1 by RAC (2020). They considered that the respiratory sensitising properties of MMA can be attributed to the formation of methacrylic acid during rapid hydrolysis, consequently, respiratory sensitisation is suspected for potentially all methacrylates that have this hydrolysis product in common. Since HEMA also rapidly degrades into methacrylic acid, the substance is expected to have respiratory sensitising properties.

The intrinsic skin sensitising property of the molecule is clearly established in humans since HEMA has a harmonised classification as Skin Sens. 1. Thus, HEMA can also have the intrinsic potential to induce respiratory sensitisation. Although the mechanism of respiratory hypersensitivity by methacrylates remains unclear, "immunological mechanisms do not have to be demonstrated" according to CLP. HEMA is volatile (molecular weight of 130 g/mol and vapour pressure of 8 Pa) and it was found in air measurements made in occupational settings, confirming that the substance can reach the respiratory tract where it can cause hypersensitivity.

Overall, taking into account the human cases of occupational asthma reported in the literature and in the national occupational disease databases, along with data on methacrylates and physicochemical/toxicokinetic considerations, the DS proposes Resp. Sens. 1; H334 classification for HEMA. The human data do not allow subcategorisation since there isn't adequate information on the level of exposure or the frequency of occurrence in the case reports.

Comments received during consultation

There were two comments, one from an MSCA and one from IND.

The MSCA posed two questions:

a) In the CLH report, there are eight patients with occupational asthma verified with positive SICs to HEMA-containing products at FIOH during 2000-2018. Is the strength of evidence for these eight positive SIC cases considered to be as strong as for the six positive SIC cases related to MMA (EC 201-297-1)?

The DS considered the strength of evidence of the HEMA cases at least similar to the MMA cases. The data are issued from the same institute (FIOH) using the same methodology, and more cases of occupational asthma are available with HEMA than with MMA.

b) The DS assumed that the metabolite MAA (EC 201-204-4) is the underlying cause for the development of respiratory sensitisation after exposure to MMA. Since HEMA is quickly hydrolysed to MAA, the DS concluded that HEMA can be expected to cause respiratory sensitisation as well, although MAA has no harmonised classification for respiratory sensitisation but "only" a specific concentration limit for STOT SE 3; H335 with C ≥ 1%.

The DS answered that there are numerous publications reporting cases of respiratory sensitisation induced by methacrylates. This suggests a common mechanism of action, and one hypothesis is that respiratory sensitisation is driven by the common metabolite. Harmonised classification of MAA was set under Directive 67/548/EC (DSD). There is no information on whether respiratory sensitisation was assessed or not. No data is provided for this hazard in the disseminated REACH dossier on ECHA website. In the RAR (2002) on MAA, the part related to sensitisation only covers dermal sensitisation with the conclusion that MAA is not a skin

sensitising substance. It is unknown if there was no data on respiratory sensitisation or if this endpoint was not assessed.

IND did not agree with the CLH proposal for Respiratory Sensitisation (Cat. 1, H334). According to IND, the proposal is based upon clinical evidence in individuals exposed to complex mixtures (including other sensitizers and irritants) in the workplace and in SIC tests, thus precluding a causal relationship between possible exposure to HEMA and the development of occupational asthma to be drawn with sufficient confidence. According to IND, information on the chemical composition of these complex mixtures used in the SIC is incomplete, in some cases incorrectly reported and referenced, or selectively used to emphasise involvement of HEMA. IND emphasized a much more complex composition 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, 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. IND provided a detailed table on all the cases in the CLH proposal, with additional information on the composition of the products (based on available safety data sheets (SDS)) used in the SIC tests, compared to what the CLH report mentioned.

According to IND, in the clinical cases where bronchial hyperreactivity data was reported, non-specific bronchial hyperresponsiveness (NSBHR) was observed for the majority of cases. For those cases where bronchial hyperreactivity data were not reported, NSHBR cannot be excluded with confidence. Guidance on the Application of CLP Criteria (CLP guidance, ECHA, 2017) paragraph 3.4.2.1.3.2 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*." Therefore, NSBHR cannot be excluded with sufficient confidence for any of the clinical case studies cited and thus, a specific, intrinsic hazard of causing respiratory sensitisation by the substance HEMA has not been demonstrated.

Furthermore, IND stated that 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 by the European Respiratory Society (ERS) Task Force on best practices for the conduct of SIC tests (Vandenplas *et al*., 2014; 2016). They noted that almost all reported asthma cases originated from one clinical centre, where, according to them, SIC tests were performed typically with 10-20-fold excess of test item and thus not in accordance with accepted clinical guidelines.

IND opposed the hypothetical mode of action, i.e. hydrolysis to a common metabolite (MAA) as not evidenced by data since no published literature can be found to support such a hypothesis.

IND provided a weight of evidence assessment, concluding that there is insufficient evidence to implicate HEMA as a cause of respiratory sensitisation or occupational asthma. They also cited a publication: Pemberton *et al*. (2023) "*Challenges in the classification of chemical respiratory allergens based on human data: Case studies of 2-hydroxyethylmethacrylate (HEMA) and 2-hydroxypropylmethacrylate (HPMA)*".

Assessment and comparison with the classification criteria

Non human data

QSAR modelling

In 2014 following a request by France, the RIVM ran different SAR models (Derek, Jarvis, CatSAR, Enoch, MultiCase) with acrylates, including HEMA. No prediction could be obtained

from Derek, CatSAR and MultiCase. Enoch gave positive results for respiratory sensitisation, whereas Jarvis was negative for HEMA. According to the RIVM, Derek gives the most reliable prediction of a substance being a respiratory sensitiser and MultiCase the most reliable prediction for respiratory non-sensitisation. Therefore, considering the profile of HEMA obtained with these two models, no reliable conclusion can be reached for the potential respiratory sensitisation properties of HEMA based on these SAR models. In October 2021, DK QSAR Toolbox was run and pointed rather to a negative potential for respiratory sensitisation (Leadscope). In July 2021, the QSAR Toolbox (profiler: respiratory sensitisation v1.1) indicated a structural alert for respiratory sensitisation. A Michael addition mechanism has been suggested to be responsible for the ability of these types of chemicals to react with proteins in the lung. However, the dataset from which the profiler was developed contained a single chemical with this alert, which was reported as a respiratory sensitiser in humans. The DS noted that according to the REACH Guidance R.7a, (Q)SAR models are known not to be predictive for this endpoint since there is no assay available. Therefore, RAC concludes that no reliable conclusion can be reached based on these modelling data for the potential of HEMA to induce respiratory sensitisation.

Experimental data

In vitro: Jeppsson *et al*. (2010) investigated the chemical structures of adducts formed after reaction of human haemoglobin with 3 acrylates, including MMA and HEMA. The results showed that MMA and HEMA bound to all the cysteines in both chains, Cys104 in the α-chain and Cys93 and 112 in the β-chain. This is consistent with the first key event to induce sensitisation.

In vivo: one inhalation study of low quality is available (Gage, 1970). Only minor interference in clotting function was found in rats exposed to an atmosphere saturated with HEMA (no further specification) at 0.5 mg/L for 3 weeks. This study was judged not reliable because only one concentration was tested with no control group, no information was provided on an analytical verification of the concentration tested, a low number of animals were used and the level of details was very limited.

Human data

Case reports of occupational asthma in the literature

Piirila *et al.* (1998) investigated the cases of acrylates-induced respiratory hypersensitivity in dental personnel diagnosed in Finland in 1992-1997. Among the 12 cases identified, 9 cases of occupational asthma were verified according to the challenge tests with dental acrylate compounds (acrylates, methacrylates and epoxy acrylates), including 6 cases for which the causative product contains HEMA.

***Table**: Details of the Piirila et al. cases (Table 10 of the CLH dossier)*

Patient	**No. 2**	**No. 3**	**No. 7**	**No. 9**	**No. 11**	**No. 12**
	48 year-old male dentist	61 year-old female dentist	53 year-old female dental nurse	61 year-old female dentist	34 year-old female dental nurse	49 year-old female dental nurse
Atopy own history	No	No	No	No	Yes	No
Duration of exposure to acrylics (years)	22	24	22	25	10	28
Duration of symptoms (years)	3	22	5	10	9	1
Spirometry	Normal	Normal	Normal	Slight obstruction	Normal	Slight obstruction
Histamine	> 1.6 mg	> 1.6 mg	> 1.6 mg	0.15 mg	0.79 mg	> 1.6 mg

challenge (PD_{15})				Moderate hyperresponsiveness	Slight hyperresponsiveness	
Prick test positivity	No	No	No	No	No	No
Causative product	Rely-A-Bond paste Scotchbond a	Scotchbond multipurpose p+a	Scotchbond multipurpose a	Scotchbond multipurpose p+a	Scotchbond multipurpose p+a	Scotchbond multipurpose p+a
Challenge dose (drops)	1d+12d	20d+20d	4d	10d+10d	20d+20d	20d+20d
Ingredient	Bis-GMA HEMA	Mm1*	Bis-GMA HEMA	Mm1*	Mm1*	Mm1*
Max FEV1/PEF reduction	- / 16% Immediate reaction	20%/20%** Late reaction	5/18% Immediate reaction	20%/16%** Late reaction	13%/17% Late reaction	24%/13%** Late reaction
Occupational effect in PEF	Yes**	Yes	Yes**	Yes	Yes**	Yes

** Mm1, methacrylate mixture: primer (p) containing HEMA 40% and adhesive (a) containing 62% Bis-GMA (bisphenol-A-diglycidyl-ether methacrylate) and HEMA 37% FEV1: forced expiratory volume in 1 second, PEF: peak expiratory flow*

*** major diagnostic criteria for asthma*

Overall, skin prick tests were generally negative. Late reactions occurred in 4 patients and immediate reactions in 2 patients. In all cases, the causative products were methacrylate compounds that contained at least 37% of HEMA declared, in addition to Bis-GMA with other unspecified substances. In three patients, occupational asthma was diagnosed based on the inhalation provocation tests (forced expiratory volume in 1 second (FEV1) reduction ≥ 20%) combined with the patients' history of exposure and symptoms. Allergic rhinitis, laryngitis, pharyngitis or conjunctivitis were also diagnosed following tests in a provocation chamber. All patients diagnosed to have asthma showed a work-related effect of peak respiratory flow (PEF) recordings. In one patient with asthma, PEF monitoring was not performed. In the case of patient 2, simultaneous FEV1 measurement during the maximal PEF reduction is missing. In his case, the findings supporting the diagnosis of asthma were the suggestions of a positive challenge test reaction, the patient history, and the PEF workplace monitoring with about 20% variation during working days and < 10% during days off.

Regarding HEMA, one case was particularly detailed in the publication (patient No 12 in the table above). This patient is a 49 year-old woman who had worked as a dental nurse since the early 1970s. In the beginning of 1996, she felt slight rhinitis symptoms, and in April 1996 the symptoms of dyspnoea appeared when she was handling acrylate compounds. In spirometry, slight partially variable central obstruction was found. No bronchial hyperreactivity was found in histamine challenge test. PEF monitoring showed increased (> 20%) variation during working days. In the first bronchial challenge test with Scotchbond primer and adhesive (containing HEMA and Bis-GMA (Bisphenol-A-diglycidyl-ether methacrylate), 10 drops of both), there was no significant reduction in PEF or FEV1 (maximally –11%/– 9%). In the second challenge test with 20 drops of both substances, a maximal reduction of FEV1 by 24% was measured 6h after the challenge test. On the day after the challenge test, the lung functions had returned to pre-challenge level. In the control challenge test no reduction of PEF or FEV1 was found.

The CLH dossier did not specify the components of the materials used in the SIC tests apart from Bis-GMA and HEMA. RAC has tried to rectify this.

	Patient 5	**Patient 6**	**Patient 7**	**Patient 8**
	dentist	dental hygienist	dental hygienist	hairdresser
Acrylates and their percentage concentration in the products at work (SIC material in bold) From CLH report	**Scotch Bond Multipurpose:** HEMA 30-40%; Bis-GMA 60-70%	No SDS available from the patient, but **Scotch Bond adhesive** is known to have contained 30-40% HEMA at the time of the investigations	**Scotchbond Primer + adhesive** No SDS available from the patient, but Scotch Bond adhesive is known to have contained 30-40% HEMA at the time of the investigations	**LCN Sculpture** -gel nail material contained 6.7% HPMA in chemical analysis; **LCN Bonder** contained 7.5% HPMA in chemical analysis; SDS of **LCN (probably Sealant):** HEMA 15-20%; polyetherolyol tetraacrylate 20-25%; HPMA 5-10%
SIC acrylate containing agent From RCOM	ScotchBond Multipurpose Adhesive (HEMA)	ScotchBond Adhesive (HEMA)	Scotchbond Primer + Adhesive (HEMA)	Newly made gel nails containing HEMA and HPMA
SIC physical form	liquid	liquid	liquid	solid
SIC control agent	in-house control solution	in-house control solution	in-house control solution	lactose powder
SIC method of delivery	evaporation from a small cup	evaporation from a small cup	evaporation from a small cup	grinding structure nails
SIC amount used in one challenge	40 drops	20 drops	20 + 20 drops	5 nails
SIC cumulative duration of acrylate challenge/ challenges (minutes)	30	30	30	20
Clinical data				
Asthma (physician-based diagnosis) prior to occupational exposure	Patient's consent not obtained	no	no	no
Atopy (defined by at least one positive skin test to a battery of local common aeroallergens		no	no	yes
Prick test		Not performed	Not performed	Not performed
Monitoring PEF (peak expiratory flow) at work		Not performed	uncertain	uncertain
Maximum fall in FEV1 during the first 60 minutes after the end of challenge exposure (% from pre-challenge value)		17	10	16
Maximum fall in FEV1 recorded between the 60th minute and the end of the follow-up (% from pre-challenge value)		31	24	19
Pattern of reaction		dual	late	dual

The materials/mixtures used in the SIC tests are poorly described, and may contain other methacrylates classified as skin sensitisers or respiratory irritants.

Scotch Bond Universal adhesive (patient 1) has 2 substances mentioned: Bis-GMA 60-70%, and HEMA 30-40%. In reality, it was probably a much more complex mixture, with a much lower % of HEMA, as according to the SDS (2015) it contains: 15-25% Bis-GMA, 10-15% HEMA, 5-15% decamethylene dimethacrylate (self-classified as Skin Sens. 1 and STOT SE 3 (H335), 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). The additional information in the RCOM is even more vague, mentioning that no SDS was filed for the patient, and the material used in the SIC test was "*most likely*" Scotchbond Universal Adhesive.

Scotch Bond Universal Primer (SIC test of patient 2): no information.

One step dental restorative (SIC test of patient 3):

biphenylmethacrylate 15-40%, 2-HEMA 8-30%, Bis-GMA 7-13%, all bond primer part A: glycidyl methacrylate 1-5%, all bond primer part B: biphenylmethacrylate 8-30%. In this mixture glycidyl methacrylate (1-5%) is classified as Skin Sens. 1 and STOT SE 3 (H335).

Scotch Bond dental adhesive (SIC test patient 4): is described as HEMA 35-40%, "Light-hardened polymer" 10-15%, but it is not clear which Scotchbond adhesive was used.

Scotch Bond Multipurpose adhesive (patient 5): has 2 substances mentioned: HEMA 30-40% and Bis-GMA 60-70%.

Scotch Bond adhesive (SIC test patient 6): No SDS available from the patient, the only information in the CLH report on the SIC product tested was "Scotch Bond adhesive is known to have contained 30-40% HEMA at the time of the investigations". There is no information on which Scotchbond adhesive was used, and what other substances it contained.

Scotchbond Primer + adhesive (SIC test patient 7): No SDS available from the patient, the only information in the CLH report on the SIC product tested was "Scotch Bond adhesive is known to have contained 30-40% HEMA at the time of the investigations". There is no information on which Scotchbond products were used, and what other substances they contained.

Patient 8: LCN Sculpture gel nail material contained 6.7% HPMA in chemical analysis, LCN Bonder contained 7.5% HPMA in chemical analysis, SDS of LCN (probably Sealant): HEMA 15-20%, polyetherolyol tetraacrylate 20-25%, HPMA 5-10%. The materials used contained not only HEMA, but also HPMA, which is volatile, is self-classified as Skin Sens. 1/1B and has a CLH dossier running parallel to HEMA. The test was performed by grinding newly hardened nails, producing dust. The HEMA content of the hardened material was very low in the chemical analysis, probably < 0.01%. The composition of the SIC test products was complex and incompletely described; the role of HEMA as causative agent in the occupational asthma uncertain.

Other human data

The CLH report also elaborates on several other cases of respiratory sensitisation related to (meth)acrylates exposure reported in the literature, but in these publications, HEMA is not specifically identified or occurs with other methacrylates.

The CLH dossier also describes some case reports of other hypersensitivity reactions:

Estlander *et al*. (1996) reported 2 cases of patients (a dental laboratory assistant and a hearing aid worker) who had developed symptoms of conjunctivitis in addition to allergic contact dermatitis, neither had nasal or chest symptoms. Both were exposed to chemically curable and light-curable methacrylates. According to the authors, the association between their conjunctivitis and allergy to methacrylates was supported by different observations: positive

patch tests with different methacrylates (including HEMA: patch test results: 3+ and 2+, respectively for patients 1 and 2), simultaneous appearance of their eye symptoms and allergic contact dermatitis, high exposure to methacrylates, disappearance of the eye symptoms during holidays; and opthalmologist's findings of follicular conjunctivitis with some papillae, eosinophilia and lymphocytosis in conjunctival scrapings corresponding to allergic contact conjunctivitis. Nevertheless, HEMA was not cited as component in the acrylate compounds used at work, while MMA was, and patch tests were positive not only to HEMA, but also to MMA and HPMA.

Sala *et al.* (1996) reported 20 patients with occupational laryngitis diagnosed during 1990-1993 in Finland. Skin prick test and provocation tests were performed. For one patient (49 year-old woman, dentist), the causative agents identified were Scotchbond (containing 40-60% Bis-GMA and 40-50% HEMA) and Scotchprep (containing 30-65% HEMA). Prick test was negative and specific IgE not measured.

Lindström *et al.* (2002) reported delayed allergic conjunctivitis after a patch test with HEMA (the same patient as mentioned in the "case reports of occupational asthma" section).

Comparison with the criteria

According to CLP, *"Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience. […] The evidence referred to above could be:[…] 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."*

No formally recognised and validated animal or *in vitro* tests currently exist for respiratory sensitisation; therefore, the identification of substances as respiratory sensitisers can only be derived from human observations in exposed populations. The data available for HEMA and included in the CLH dossier consisted of reports on 19 diagnosed occupational asthma cases where HEMA is cited as the possible causative agent. These cases originate from 4 publications: Piirila *et al.* (1998); Lindstrom *et al*. (2002); Sauni *et al*. (2008); Moulin *et al*. (2009), and from the Finnish Institute of Occupational Health (FIOH) database.

As reported in the previous paragraph, the material used in the mentioned studies was often poorly described increasing the uncertainties regarding the relevance of the provided data for HEMA classification.

The SIC tests were carried out with mixtures/products with which the patients were exposed at the workplace, and the materials used in the SIC tests were inadequately described. The materials/products are complex mixtures of chemicals, but in many cases only the HEMA and/or Bis-GMA content were given in the description of the tests, ignoring other actual or possible constituents. This lack of information increases the uncertainties regarding the provided data.

Specific Inhalation Challenge tests have been devised to diagnose sensitiser-induced occupational asthma and are not designed to identify individual substances (contained in the complex mixtures/products) that may cause respiratory sensitisation.

RAC notes that, although the data raises concern for HEMA potentially being able to elicit respiratory sensitisation, it is overall insufficient to support classification for respiratory sensitisation according to CLP criteria.

Due to the insufficient data on the materials of the SIC tests, it can not be determined with sufficient confidence that it was HEMA that caused the respiratory sensitisation experienced in the specific inhalation challenges. Therefore, **RAC concludes that no classification for HEMA for respiratory sensitisation is warranted due to inconclusive data.**

Additional references

Kanerva L, Henriks-Eckerman M-L, Jolanki R, Estlander T. Plastics/acrylics: material data safety sheets need to be improved. Clinics Dermatol 1997,15:533–46.

Henricks-Eckerman M-L, Kanerva L. Product analysis of acrylic resins compared to information given in material safety data sheets. Contact Dermatitis 1997, 36:164–5.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter, and additional information (if applicable).

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).