Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

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

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

CLH-O-0000007381-77-01/F

Adopted

30 November 2023

30 November 2023

CLH-O-0000007381-77-01/F

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

EC Number: **248-666-3**

CAS Number: **27813-02-1**

Rapporteur, appointed by RAC: **Agnes Schulte, Frauke Hoffmann (advisor)**

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	No current Annex VI entry										
Dossier submitters proposal	TBD	methacrylic acid, monoester with propane-1,2-diol [HMPA]	248-666-3	27813-02-1	STOT SE 3 Eye Irrit. 2 Resp. Sens. 1 Skin Sens. 1	H335 H319 H334 H317	GHS08 GHS07 Dgr	H335 H319 H334 H317			
RAC opinion	TBD	methacrylic acid, monoester with propane-1,2-diol [HMPA]	248-666-3	27813-02-1	STOT SE 3 Eye Irrit. 2 Skin Sens. 1	H335 H319 H317	GHS08 GHS07 Wng	H335 H319 H317		STOT SE 3, H335: C ≥ 10 %	D
Resulting Annex VI entry if agreed by COM	TBD	methacrylic acid, monoester with propane-1,2-diol [HMPA]	248-666-3	27813-02-1	STOT SE 3 Eye Irrit. 2 Skin Sens. 1	H335 H319 H317	GHS08 GHS07 Wng	H335 H319 H317		STOT SE 3, H335: C ≥ 10 %	D

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

According to ECHA website, methacrylic acid, monoester with propane-1,2-diol (HPMA) (EC Number: 248-666-3; CAS Number: 27813-02-1) is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area, at ≥ 10000 to ≤ 100000 tonnes per annum.

HPMA is used by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

Consumers and professional workers can be exposed to the substance by using products such as adhesives and sealants. The widespread uses by professional workers further include the use of polymers products and cosmetics and personal care products. This substance is used in the following areas: printing and recorded media reproduction, building & construction work and municipal supply (e.g., electricity, steam, gas, water) and sewage treatment. HPMA is used for the manufacture of chemicals, rubber products, plastic products and machinery and vehicles.

At industrial sites, the substance is used in adhesives and sealants as well, but is further used in non-metal-surface treatment products in the area of printing and recorded media reproduction and municipal supply (e.g., electricity, steam, gas, water) and sewage treatment.

The dossier submitter (DS) proposed to classify HPMA as STOT SE 3 (H335), Eye Irrit. 2 (H319), Resp. Sens. 1 (H334) and Skin Sens. 1 (H317).

Currently, the substance has no harmonised classification, and numerous diverging self-classifications, including Eye Dam. 1 (H318), Eye Irrit. 2 (H319), Skin Irrit. 2 (H315), Skin Sens. 1/1B (H317), STOT SE 3 (H335; respiratory system), Muta. 2 (H341), Carc. 2 (H351), see classification and labelling (C&L) inventory. Other C&L notifiers proposed no classification for the substance. The registrants self-classified HPMA as Eye Irrit. 2 (H319), and Skin Sens. 1 (H317, according to the ECHA dissemination site.

Substance ID and physicochemical properties

HPMA is a multi-constituent substance (figure below) and contains several impurities and additives as listed in the two tables below. The main component, 2-hydroxypropyl methacrylate (2-HPMA; 70 – 90%) has harmonised classifications for Skin Sens. 1 (H317), and Skin Irrit. 2 (H315). The minor component, 2-hydroxy-1-methylethyl methacrylate (HMEMA; 10 – 30%) has no harmonised and no self-classifications.

HPMA is a clear colourless liquid at 20 °C and 101.3 kPa with a boiling point of 209 °C at 1025 hPa and a vapour pressure of 0.11 hPa at 20 °C. The water solubility is 130 g/L at 25 °C. In Table 8 of the CLH dossier, a summary of all physico-chemical properties of HPMA can be found.

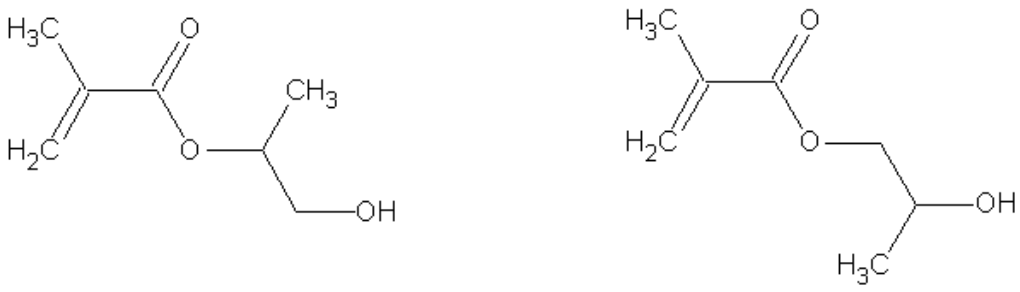

Figure: Molecular structure of HPMA, which is a mixture of 2-HPMA (right) and HMEMA (left).

***Table**: Impurities (non-confidential information) if relevant for the classification of the substance*

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
2-Propenoic acid, 2-methyl-, 2-(2-hydroxymethylethoxy) methylethyl ester EC n° - CAS n° 105760-11-0	≤ 5% w/w	/	/	/
2-Propenoic acid, 2-methyl-, 1-methyl-1,2-ethanediyl ester EC n° - CAS n° 7559-82-2	≤ 1% w/w	None	Skin Sens. 1B – H317 STOT SE 3 – H335	No
Methacrylic acid EC n° 201-204-4 CAS n° 79-41-4	≤ 1% w/w	Acute Tox. 4*- H302 Acute Tox. 4* - H312 Skin Corr. 1A – H314 (SCL: STOT SE 3; H335; C ≥ 1%)	Acute Tox. 4 – H302 Acute Tox. 4 – H312 Acute Tox. 3 – H311 Skin Corr. 1A – H314 Eye Dam. 1 – H318 STOT SE 3 – H335 STOT RE 1 – H372 Muta. 2 – H341 Carc. 1B – H350	No
Water EC n° 231-791-2 CAS n° 7732-18-55	≤ 1% w/w	None	None	No

***Table**: Additives (non-confidential information) if relevant for the classification of the substance*

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
4-Methoxyphenol EC n° 205-769-8 CAS n° 150-76-5	Stabiliser	≤ 0.05% w/w	Acute Tox. 4* - H302 Eye Irrit. 2 – H319 Skin Sens. 1 – H317	Acute Tox. 4 - H302 Eye Irrit. 2 – H319 Skin Sens. 1 – H317 Repr. 2 – H361 Aquatic Chronic 3 – H412 Aquatic Chronic 2 – H411	No

Toxicokinetic

Absorption/distribution

Following the REACH guidance document R.7c, the physico-chemical properties of HPMA (molecular weight of ~144 g/mol, log Pow of 0.97 and water solubility of 130 g/L) are favourable to absorption. According to Danish QSAR database, an absorption from gastrointestinal tract is estimated at 50%. The dermal absorption is estimated at 0.0806 mg/cm²/event.

Metabolism/Excretion

Based on its structure, HPMA is expected to be hydrolysed by esterases into methacrylic acid (MAA) and propylene glycol. OASIS TIMES (ver. 2.29.1.88) was run by ECHA to calculate metabolism as simulation of *in vitro* rat S9, and as rat *in vivo*. TIMES predicts with high probability the phase I hydrolysis of HPMA. MAA is suggested as the main metabolite and the parent compound is anticipated to be metabolised quickly and almost completely.

In an *in vitro* enzymatic hydrolysis assay, HPMA polymer powder (purity not reported) was suspended with porcine liver esterase. The substance was hydrolysed to MAA and 1,2-propanediol (propylene glycol) at pH 6.5 and 37°C catalysed by an unspecific esterase (Munksgaard *et al*., 1990). This is consistent with the general metabolism of methacrylate esters in mammals.

According to the disseminated REACH registration dossier, an *in vivo* pharmacokinetic study was performed in 2017. In this study, 2 male rats received HPMA (purity not reported) via intravenous administration at the dose of 5 mg/kg bw. Blood samples were collected at 5, 10, 30, 60 and 180 minutes. HPMA was not quantifiable 60 minutes after exposure and the estimated half-life was less than or near 1 minute (Anonymous, 2017), supporting the hypothesis of quick hydrolysis.

According to the Danish QSAR database, the substance is not expected to be a substrate of CYP2C9 and 2D6. The log brain/blood partition coefficient is considered to be medium (-0.2573).

Note D

Due to its use for polymerisation and the structural similarity with other short-chain methacrylates (2-hydroxyethyl methacrylate (HEMA), methyl methacrylate (MMA), ethyl methacrylate (EMA), butyl methacrylate (BMA)) that also contain 'Note D' in their entry in CLP Annex VI, it can be assumed that HPMA might also be capable of spontaneous polymerisation or decomposition.

Thus, RAC considers that 'Note D' should be assigned to the CLP Annex VI entry for HPMA.

HUMAN HEALTH HAZARD EVALUATION

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

Summary of the Dossier Submitter's proposal

In the absence of specific data on respiratory irritation (except a 3-week inhalation study of low quality (Gage, 1970)) the DS performed a read-across assessment based on other short-chain methacrylates sharing a common functional group and a common breakdown product, i.e., MAA (see detailed assessment below). Based on this approach the DS came to the conclusion that HPMA warrants classification for STOT SE 3 (H335).

Irritancy of HPMA vapour on the nose was reported in the Toxnet website (U.S. Coast Guard, Department of Transportation. CHRIS - Hazardous Chemical Data. Volume II. Washington, D.C.: U.S. Government Printing Office, 1984-5) (no further details given in the CLH dossier). This information was used as supporting data for classification of HPMA for STOT SE 3 (H335).

Comments received during consultation

Industry associations (IND) provided a comment, in which they did not agree with the proposal to classify HPMA for STOT SE (respiratory irritation). To their view, HPMA with a vapour pressure of 0.11 hPa (11 Pa) at 20°C and a boiling point of 209°C has to be considered as substance of very low volatility.

In their comment, 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). It was recognised that MAA, the common acidic metabolite of HPMA and other methacrylate esters, is of concern to human health due to its corrosive properties. IND weight of evidence analysis included a 90-day inhalation study on MAA where local effects have been observed at 350 ppm (1232 mg/m³, BASF, 2008, see REACH registration dossier[1], no effects at 100 ppm (352 mg/m³)), local effects seen at 200 ppm MMA, but absent at 200 ppm n-BMA, in acute 6h toxicity studies (Jones, 2002) (no data on lower concentrations in the Jones paper). 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.

A Member State Competent Authority (MSCA) supported the proposed classification of HPMA for STOT SE 3 (H335). In their view, the assumption that HPMA has irritating properties to the respiratory tract is considered reasonable based on the fact that HPMA and short-chain volatile methacrylates (MMA, EMA, and BMA), used as source substances, they all quickly metabolise to MAA which is the common metabolite. Physico-chemical properties (molecular weight: 144.17 g/mol; vapour pressure: 0.11 hPa at 20°C) and eye irritating potential of HPMA were considered to support this assumption.

Assessment and comparison with the classification criteria

In the absence of adequate data on HPMA for this hazard property, read-across assessment has been suggested by the DS. Extrapolation is considered relevant for short methacrylates taking into account that these substances have a common functional group and a common metabolite product (i.e., MAA); read-across substances and their metabolites are listed in the table below. Among them, some analogous substances have harmonised classification as irritant for the respiratory tract (STOT SE 3, H335) (see table below).

RAC agrees with the DS that based on the limited reporting and weaknesses, the study of Gage (1970) cannot be used as a reliable source of information. In this publication, the effects of repeated exposures of 4 male and 4 female rats to HPMA (15 exposures within 3 weeks for 6h to approximately 0.5 mg/L or 90 ppm) were reported. As no data on analytical concentrations are available, there is no information on the "effective" vapour concentration in the exposure chambers. The animal behaviour was recorded during the exposure period. Lungs and few other organs were taken for microscopical examination. No data on histopathology of the tissues of the

[1] https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15411/7/6/3

respiratory tract or other organs are available. The only results on HPMA reported are the following: erratic weight gain (F): autopsy, organs normal. The limited information on the study design leaves open whether a gross examination of the nasal cavity was conducted. In the same study, nose and eye irritation observed after 6 hours of exposure on 5 consecutive days to saturated concentrations (1300 ppm) of MMA were reported, while no irritation was seen after 20 days of daily 6 hours exposure to MMA. As the same study design was applied, it is assumed that clinical signs (no details given) were interpreted as nose and eye irritation caused by MMA.

RAC notes that HPMA has rather low volatility. While vapour inhalation may be of lesser concern for respiratory irritation, the HPMA potential for irritative effects following carboxylesterase-mediated cleavage to MAA at the first site of contact in the (upper) respiratory tract following inhalation to aerosols are to be considered (HPMA is a liquid).

Read-across assessment to HPMA from other short-chain methacrylates is considered appropriate as these substances have a common functional group and a common breakdown product, MAA. All substances listed in the table below are metabolised by esterases into a common metabolite, MAA, and an alcohol or a glycol.

All substances considered for read-across are short methacrylates, with linear length chain ≤ 4 carbons (except for dodecyl methacrylate (DMA)). All substances are small with molecular weights ranging from 86 g/mol (MAA) to 144 g/mol (HPMA). Water solubility of HPMA is higher compared to the solubility of the other methacrylates. MMA, EMA and BMA are highly volatile with vapour pressure 1 hPa or higher, whereas DMA shows a low vapour pressure. HPMA has lower vapour pressure (11 Pa), but some volatility is still expected. In fact, inhalation exposure was confirmed at occupational settings where air levels of HPMA were measured.

The DS highlighted that some of the substances listed in the table below have harmonised classification as irritant for the respiratory tract (STOT SE 3, H335), including MMA, EMA and BMA. For MAA no harmonised classification as STOT SE 3 (H335) is listed in Annex VI of CLP, but a specific concentration limit for STOT SE 3, i.e., "STOT SE 3, H335: C ≥ 1%" is present in Annex VI. RAC notes that the harmonised classification for MAA was taken over from previous legislations and no updated assessments have been performed under CLP so far. RAC highlights that although DMA has a very low vapour pressure (much lower than the vapour pressure of HPMA), and thus has to be considered of low volatility, the substance has a harmonised classification for STOT SE 3 (H335), as well. In 2017, RAC[2] assessed this classification that stems from prior legislations and confirmed the existing STOT SE 3 (H335) classification, as "*no information was made available to RAC regarding the basis for this classification*", which is why "*no assessment of the potential for respiratory tract irritation of dodecyl methacrylate or an assessment of read across to other shorter- or longer- chain methacrylates could be made by RAC*". RAC further stated that "*exposure to the aerosol form cannot be excluded based on the physico-chemical properties of dodecyl methacrylate*" and subsequently concluded on maintaining the CLP Entry.

[2] https://echa.europa.eu/documents/10162/50add813-66ff-ae5f-4a89-2ca7a739a515

***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 17 of the CLH dossier)*

	Parent substance	**Water solubility**	**Vapour pressure**	**Biotransformation**	**Common compounds**	**Non-common compounds**
Target	HPMA	130 g/L at 25°C	0.11 hPa at 20°C	MAA + propylene glycol	MAA	Propylene 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
	DMA	< 1 µg/L at 25°C	Ca. 0.06 Pa at 20°C	MAA + dodecanol	MAA	Dodecanol*

NA: not applicable. *considered by the DS, not further used in their argumentation, not a short-chain methacrylate

Some comparative kinetic data are presented in the table below (table 18 of the CLH dossier). A series of *in vitro* and *in vivo* studies with various methacrylates were used to develop PBPK models that accurately predict the metabolism and fate of these monomers (Jones (2002), cited in the disseminated dossier of MMA, see table below).

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

Ester	**Rat liver microsomes (100 mg/mL)**		**CL (%LBF)**	**$T_{50\%}$ (min)**	**C_{max} (MAA) (mg/L)**	**T_{max} (MAA) (min)**
	V_{max} (nmol/min.mg)	**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.

A behaviour, similar to that observed for the methacrylates listed in the table above, has been reported for HPMA in an *in vivo* pharmacokinetic study where the half-life of the substance was estimated to be less than or near 1 minute (Anonymous, 2017).

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, e.g. the nasal mucosa and upper respiratory tissues, are responsible for the production of MAA (See Supplementary Information in the Appendix).

Overall, it can be assumed that the morphology of the respiratory and olfactory mucosa are largely similar in rats, dogs and humans and only minor differences exist with regards to the distribution of carboxylesterases in nasal tissues of these species. In addition, it was suggested that carboxylesterases in the nasal olfactory epithelium of humans metabolise MMA to MAA, although potentially to a lower extent than in rats. Overall, RAC agrees with the DS' view that the metabolic pathway of HPMA (being metabolised to MAA) is likely to occur in humans and considers the proposed read-across approach as plausible and acceptable.

IND concluded that acute inhalation of 100 ppm MAA is considered as a "borderline concentration" that may exert irritative properties. In the comment it was stated that the "borderline concentration" may be interpreted as 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, the commenter 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[3], 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. Supporting data come from repeated dose inhalation toxicity studies, in which a LOAEC of 100 ppm was determined for local effects in the nose after ≥ 5 days of MAA vapour exposure (mice; NOAEC of 20 ppm) and ≥ 90 days of MMA vapour exposure (rats; NOAEC of 25 ppm; no earlier time points analysed)[4,5]. Seeing necrotic effects due to the irritative properties of the substance and/or its metabolite MAA at a dose as low as 100 ppm MAA/MMA after repeated exposure and 110 ppm after single exposure to MMA, may question 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 HPMA.

In addition, RAC highlights that classification for respiratory irritation is based on the irritative property of the substance to cause clinical or (reversible) morphological signs of irritation after single exposure – irrespective of the test substance concentration. The CLP criteria on STOT SE 3, hence, do not consider any concentration limits below which classification is warranted, but rather include all substances that elicit respiratory irritant effects, primarily in humans. Animal data, if available, may be included in the weight of evidence evaluation.
The local concentration of MAA resulting from intracellular cleavage from exposure to HPMA aerosol is unknown. HPMA is assumed to be hydrolysed almost completely and within minutes to MAA independently of whether it is inhaled as vapour, aerosol or a mixture of both. Thus,

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

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

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

particularly with regard to aerosol exposure the concentration of HPMA will be equivalent to the local concentration of MAA. In comparison to the half-lives of the source methacrylates, the shorter half-live of HPMA and, in addition, the higher (water) solubility of HPMA compared to the other methacrylates listed for read-across, raise the concern that the acute irritancy of HPMA, particularly aerosolised HPMA, could even be stronger than the irritative potency of the other methycrylates.

In conclusion, the read-across from MAA released from other short-chain methacrylates is considered more relevant than the assessment based on vapour effects of MAA alone.

Supporting evidence comes from irritation properties on eyes and skin, either from HPMA itself or from its cleavage products. In line with many self-classifications, classification as Eye Irrit. 2 (H319) was proposed for HPMA. Although HPMA itself is not irritative to skin, its cleavage product MAA has a harmonised classification as Skin Corr. 1A (which covers also the potential for eye corrosivity). Table 20 of the CLH dossier gives an overview on the irritation properties of HPMA and the methacrylates used as source substances. Eye irritation was seen for MAA, MMA, EMA and BMA, the latter two have a harmonised classification for Eye Irrit. 2. In addition, it is to note that MMA, BMA and EMA have a harmonised classification for Skin Irrit. 2 (H315).

There are also data available indicative of irritating properties of the HPMA metabolite propylene glycol[6], albeit RAC concluded that the overall evidence was not sufficient for classification for STOT SE 3 (H335) (RAC, 2016).

Comparison with the criteria

According to CLP Regulation, section 3.8.1, classification as STOT SE 3 includes narcotic effects and respiratory tract irritation[7].

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6 https://echa.europa.eu/documents/10162/c02bcec3-641b-6770-a361-99776015680e

7 The criteria for classifying substances as Category 3 for respiratory tract irritation (Annex I, section 3.8.2.2.1) are:

(a) respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data;

(b) subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (such as electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids);

(c) the symptoms observed in humans shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of 'irritation' shall be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory irritation;

(d) there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g., hyperaemia, oedema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation;

(e) this special classification would occur only when more severe organ effects including in the respiratory system are not observed.

There is neither human nor animal data available related to HPMA inducing respiratory irritation. However, irritating properties of HPMA are generally supported by the fact that the substance induces eye irritation. In addition, the HPMA metabolite MAA – which is quickly formed after inhalation exposure due to carboxylesterase hydrolysis within the (upper and lower) respiratory tract – is corrosive to the skin and has irritating properties on the respiratory tract, as indicated by its harmonised classification for Skin Corr. 1A, and STOT SE 3 (H335, with a concentration limit of ≥ 1%). In addition, inhalation exposure to other short methacrylates (read-across supported by RAC as detailed above) was previously demonstrated to result in respiratory tract irritation. Accordingly, the source substances MMA, EMA, BMA and DMA have harmonised classifications for STOT SE 3 (H335) as well. The assessment for the source substances was mainly based on animal data and in some cases limited additional human data (e.g., for MMA).

Based on the read-across from the source substances MAA, MMA, EMA and BMA, RAC concludes that respiratory irritation can also be anticipated for HPMA, when the substance, as vapour or aerosol, reaches the respiratory tract.

Thus, RAC concludes that respiratory local effects have to be expected after inhalation of HPMA vapours or aerosols, due to local formation of the metabolite MAA, particularly in the upper respiratory tract.

In conclusion, based on physico-chemical properties, toxicokinetic considerations and data available for other analogous methacrylates used in a read-across approach, **RAC concludes that classification for STOT SE in category 3 (H335) is warranted for HPMA.**

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 as follows: "*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*" (emphasis added). Hence, although there is the possibility to derive an SCL for STOT SE 3 substances, no specific detail on how to derive an SCL for respiratory tract irritation are given in the guidance document.

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 DMA, 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 HPMA 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 CLP Annex VI Entry. No data on SCL derivation for MAA is available.

In the absence of adequate data on HPMA 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 one 6 hours exposure to MMA vapour[8]. 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[9] (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[10] (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, HPMA and MMA, are instantly and completely metabolised to MAA. Thus, for derivation of effective doses of HPMA eliciting respiratory tract irritation, it is assumed that 100% of HPMA (and MMA), respectively, is rapidly hydrolysed to MAA.
Furthermore, for HPMA, which is a mixture of the 2 compounds 2-HPMA and HMEMA (see figure above), for practical reasons only the major component 2-HPMA is considered (molecular weight of 2-HPMA: 144.2 g/mol) when deriving the SCL.
Based on these assumptions, a local LOAEC of 650 mg/m³ for HPMA can be derived when using the LOAEC of 110 ppm for MMA after a single 6 hours exposure. A similar local LOAEC (i.e., 590 mg/m³) can be derived for HPMA when considering the LOAECs of 100 ppm after repeated MAA and MMA exposure, respectively. Based on these calculated LOAECs for HPMA, effective doses of rounded 0.00006% (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); 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 this case.

Considering that the low LOAECs calculated for HPMA are all way below the guidance value (GV) for STOT SE 1 substances (i.e., below 10 mg/L/4h according to CLP Table 3.8.2), RAC considers using the equation for SCL calculation for STOT SE 1 substances given in the CLP guidance (see equations 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)

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

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

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

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

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

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 HPMA based on the equation as derived above and using the LOAEC for HPMA (i.e., 650 mg/m³) calculated using the LOAEC of 110 ppm MMA after a single 6 hour exposure, results in an SCL of 13%. 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 11.8% can be inferred.

RAC preferred taking a pragmatic approach using an SCL of 10% (as used for DMA and other STOT SE 1 substances). An SCL of 10% is supported by the calculations described in detail above and the consideration that the CLP guidance states that for STOT SE 1 and 2 substances, the calculated resulting SCL has to be rounded to the nearest preferred value.

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

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

Based on a pre-GLP *in vivo* study in rabbits exposed to undiluted HPMA (Anonymous, 1978), showing reversible corneal opacity with a severity ≥ 1 at 24, 48 and 72h after application in 5 of the 6 animals tested, the DS concluded that HPMA warrants classification for Eye Irrit. 2 (H319).

The DS noted that further assays are available in the REACH registration dossier. However, they were considered to be associated with major deficiencies (e.g. individual scores not available, no clear information on tested substance, recovery not adequately assessed) and therefore should not be used for classification purposes.

In addition, the DS stated that HPMA was not found to be irritating to the skin of rabbits (mean primary dermal irritation index = 0 at 24 and 72h) (Anonymous, 1977). However, this hazard class was not assessed in the CLH dossier and this information was only provided for the assessment of the endpoints eye irritation and skin sensitisation.

Comments received during consultation

Two comments were received during the consultation, one from IND and one from MSCA, both supporting the classification of HPMA for Eye Irrit. 2 (H319).

Assessment and comparison with the classification criteria

One relevant and reliable but pre-GLP *in vivo* study was presented in the CLH dossier. In the study, 6 New Zealand White rabbits were tested in a Draize study design. 0.1 mL of the undiluted/unchanged substance was applied in one eye, while the other eye served as negative control. According to the ECHA dissemination site, the purity of the substance was not specified in the study report. The test substance was not washed/removed. Grading of effects was performed at 24, 48, 72 hours and 4, 5 and 7 days after application. The mean scores for the 6 animals (24, 48, 72 hours) were as follow: cornea opacity 1, 1, 1, 1, 1, 0; 0 for iris (all animals); conjunctiva redness 1.3, 2, 1, 1, 0.3, 1; conjunctiva chemosis 0, 0, 0, 0.3, 0, 0.3. The effects were reversible on day 4.

The DS noted that "*other assays are available in the registration dossier. However, they are associated with major deficiencies (individual scores not available, no clear information on tested substance, HPMA not tested unchanged, recovery not adequately assessed). Therefore, these studies cannot be used for classification purpose*". Details on the studies or references were not provided in the dossier.

Although HPMA itself was not found to be irritating to the skin of rabbits (mean primary dermal irritation index = 0 at 24 and 72h, Anonymous, 1977), the harmonised classification of MAA as Skin Corr. 1A supports the general irritative properties of HPMA, as the substance is quickly metabolised to MAA by esterase cleavage. The hazard class Skin Irrit. was not assessed by the DS.

Comparison with the CLP criteria

In the case of 6 rabbits, the following applies:

"a. Classification for serious eye damage – Category 1 if:

i. at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

ii. at least 4 out of 6 rabbits show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis."

Criteria for classification as Eye. Dam. 1 are not fulfilled in the available *in vivo* Draize test in rabbits, classification in Cat. 1 is therefore not warranted.

"b. Classification for eye irritation – Category 2 if at least 4 out of 6 rabbits show a mean score per animal of:

i. ≥ 1 for corneal opacity and/or

ii. ≥ 1 for iritis and/or

iii. ≥ 2 conjunctival erythema (redness) and/or

iv. ≥ 2 conjunctival oedema (swelling) (chemosis)

and which fully reverses within an observation period of normally 21 days."

The mean score for cornea opacity (24h, 48h and 72h) in 5 of the 6 animals was 1, thus fulfilling the classification criteria for classification in Cat. 2.

Thus, RAC concludes that classification as **Eye Irritation Cat. 2 (H319) is warranted** in accordance with the DS proposal.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

(Q)SAR assessment by implementing several different models on different acrylates including HPMA gave varying (positive and negative) results with respect to the respiratory sensitising properties of HPMA. Therefore, the DS indicated that no reliable conclusion can be reached for HPMA based on these SAR models.

With respect to animal data, only one unreliable repeated dose inhalation toxicity study is available for HPMA (Gage, 1970). In this study, no indications for respiratory sensitising effects of HPMA were reported.

Only few publications related to cases of occupational asthma in which HPMA is specifically cited are available (Lindström *et al.*, 2022; Sauni *et al.*, 2008; Vaccaro *et al.*, 2014). In these studies, HPMA cannot be clearly identified as the agent causing respiratory sensitisation, as provocations were not performed with HPMA alone, but rather with products containing various methacrylates (and possibly methacrylates as contaminants or impurities not declared in the safety datasheet (SDS)).

Regarding information from national occupational disease databases, there has been one case of work-related respiratory sensitisation attributed to HPMA reported in a gas mains layer in the UK in 1993 (Surveillance of Work-Related and Occupational Respiratory Disease). The Finnish Institute of Occupational Health (FIOH) reported on three patients with occupational asthma verified with positive Specific Inhalation Challenge (SIC) tests to HPMA containing products during 2000-2018. Based on the exposure data, FIOH derived that these patients had respiratory exposure predominantly to HPMA at work, and they were mainly exposed to HPMA also in the SIC tests. However, as all of the products contained other methacrylates in addition to HPMA, their effects cannot be excluded. In the database of the French national network for the monitoring and prevention of occupational diseases (RNV3P), several cases of asthma were reported with (meth)acrylates, but none of these cases could specifically be assigned to effects due to exposure to HPMA.

Human data on cases of respiratory sensitisation related to (meth)acrylates exposure in general are also reported in the CLH dossier. In these studies, HPMA could not specifically be identified or it was focussed on methacrylates other than HPMA.

The DS noted that HPMA being a skin sensitiser (see section on skin sensitisation with a proposed classification for Skin Sens. 1) in principle supports the intrinsic potential of the substance to also induce respiratory sensitisation.

In addition, the DS referred to the recent adopted RAC opinion on the classification of MMA as Resp. Sens. 1. Based on its recently adopted RAC opinion and the data available on HPMA toxicokinetics, the DS concluded that respiratory sensitisation has to be suspected for potentially all methacrylates that are hydrolysed to MAA by carboxylesterases. The DS further stated that "*this suspicion is particularly high for those substances that hydrolyse quickly, are of low molecular weight and which are volatile*".

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/toxicokinetics considerations, the DS concluded that HPMA should be considered as a respiratory sensitiser and accordingly be classified for Resp. Sens. 1 (H334) without sub-categorisation.

Comments received during consultation

IND submitted a comment, in which it was argued that the evidence presented in the CLH proposal is insufficient for classification of HPMA as a respiratory sensitiser. The IND questioned whether, based upon clinical evidence in three individuals exposed in the workplace and in SIC tests made with complex mixtures (including other sensitisers and irritants, and not conducted according to guideline), a causal relationship between exposure to HPMA and the development of occupational asthma can be drawn with sufficient confidence. Furthermore, it was noted that the supporting evidence showed that information on the chemical composition of these complex mixtures used in the SIC tests is incomplete, or in some cases incorrectly reported and referenced. In addition, IND noted that in the clinical cases where bronchial hyper-reactivity data were reported, non-specific bronchial hyper-responsiveness (NSBHR) was observed for every case, i.e., increased airway hyper-reactivity as a result of exposure to a non-specific stimulus. The

potentially supporting data, i.e., data referring to the hypothesised mode of action, i.e., hydrolysis to a common metabolite that is inducing respiratory sensitisation, is not evidenced by established science since no published literature can be found to support such a hypothesis.

One MSCA also commented on this hazard class and concluded that "the assessment of the proposal for Resp. Sens. 1 is quite complex". The commenter asked the DS for clarification of the following issues:

a) Whether the mentioned positive SIC tests to HPMA containing products at FIOH during 2000-2018 are considered as strong as the six positive SIC cases related to MMA or as less convincing for the purpose of establishing a causal relationship between exposure to HPMA and development of asthma.
b) Regarding the assumption that the formed MAA is the underlying cause for the development of respiratory sensitisation after exposure to methacrylates, it was questioned why MAA itself has no harmonised classification for respiratory sensitisation.

Assessment and comparison with the classification criteria

Non-human data

QSAR modelling

(Q)SAR assessment by implementing several different models on different acrylates including HPMA gave varying (positive and negative) results with respect to HPMA respiratory sensitising properties. In 2014, Enoch, MultiCase and Jarvis gave positive results for respiratory sensitisation whereas HPMA was negative according to Derek and CatSAR. The most reliable prediction of a substance being a respiratory sensitiser was reported for Derek according to RIVM, while MultiCase gave the most reliable prediction for respiratory non-sensitisation. DK QSAR Toolbox modelling results from 2019 pointed toward to a negative potential of HPMA for respiratory sensitisation. OECD QSAR Toolbox modelling from 2021 (profiler: respiratory sensitisation v1.1) yielded a structural alert for respiratory sensitisation. More specifically, a Michael addition mechanism was suggested to be responsible for the ability of these types of chemicals to react with proteins in the lung. However, it was noted that the dataset from which the profiler was developed contained only one single chemical, which has been reported as being a respiratory sensitiser in humans. In addition, the DS highlighted that according to the REACH Guidance R.7a (section R.7.3.9.1), (Q)SAR models are known to not be predictive for this endpoint since there is no assay available to assess this type of effects reliably. Therefore, RAC in line with the DS concludes that no reliable conclusion can be reached for the potential of HPMA to induce respiratory sensitisation based on these model results.

Experimental data

Only one unreliable repeated dose inhalation toxicity study was available for HPMA (Gage, 1970). In this study, no indications for respiratory sensitising effects of HPMA were reported, as no relevant adverse effects were found in rats exposed to an atmosphere saturated with HPMA (no further specification) at 0.5 mg/L for 3 weeks. Information on analytical HPMA concentrations tested were not given. In addition, only one concentration was tested and the level of reported details was very limited, in general.

Human data

Case reports of asthma in the scientific literature

Only few publications related to cases of occupational asthma are available, in which HPMA is specifically cited (Lindström *et al.*, 2022; Sauni *et al.*, 2008, Vaccaro *et al.*, 2014).

Lindström *et al.* (2022) reported a single case of occupational asthma and rhinoconjunctivitis in one dentist. The patient had been exposed to methacrylates for nearly 20 years and developed respiratory symptoms after about 10 years of exposure. Spirometry was normal and there was no significant response in the bronchodilatation test. The histamine challenge test showed moderate bronchial hyperreactivity (15% reduction in the forced expiratory volume in 1 minute (FEV1): PD15 = 0.255 mg). There were no positive reactions in skin prick test with common environmental allergens, natural rubber latex, chloramine-T or acrylates (HPMA not tested). The total serum IgE was normal (35 kU/l). The eosinophils in the peripheral blood were normal. The placebo (Coca solution) challenge test was negative. In the first inhalation challenge test with methacrylates, the Scotchbond adhesive (containing 62% of bis-GMA and 2-hydroxyethylmethacrylate (HEMA) 37% (no HPMA) – 20 drops altogether during 30 min) induced cough, rhinoconjunctivitis and a 10% decrease in FEV1 after 45 min. In the second test, with both the adhesive and the primer (Scotchbond primer containing 40% of HEMA (no HPMA) – 40 drops during 30 min), an "early late" 23% FEV1 reduction was recorded, with a maximum at 3 hours, as well as increased symptoms with dyspnoea. In line with the DS, RAC notes that concerning the identification of the causal agent for asthma, the bronchial provocation tests were stopped when one positive test had been recorded although the patient had been exposed to many other methacrylates at work.

Subsequent patch testing with a methacrylate series showed allergic reactions to several methacrylates, including HPMA (2% in petrolatum). In addition, patch testing with HPMA was reported to induce itching, swelling and soreness of the eyelids, maximal during the 3-day patch test reading. An optometrist's consultation indicated that the symptoms were in accordance to delayed allergic conjunctivitis. RAC notes that HPMA is a skin sensitiser (see section on skin sensitisation below). Thus, the positive patch test in the study described above is to be expected, although cross-reactivity cannot be excluded. In addition, specifics regarding the observed potential delayed allergic conjunctivitis are not reported and the relevance of this eye effect for classification as respiratory sensitiser is not clear, as no data on a potential inhalation exposure to HPMA during patch testing are available.

Overall, there is no information on which Scotchbond product was used, and whether the product contained HPMA at all. Although RAC can follow the conclusion of the DS that "*even if HPMA is not declared as a component of the tested products in the inhalation challenge tests, it is well known that the dental products may contain various methacrylates (and possibly methacrylates as contaminants or impurities not declared in the SDS). In the absence of a complete identification of the composition of the tested products in the publication, it cannot be excluded that HPMA is present in the products used by the dentist*", RAC does not consider this evidence sufficient for HPMA being a respiratory sensitiser.

RAC concludes, on the contrary, that as HPMA was not declared as a compound in the Scotchbond products tested in the inhalation challenge test, the results of this study are to be considered insufficient to clearly demonstrate any involvement of HPMA in causing respiratory irritation. Overall, RAC concludes that this study cannot be used as supporting evidence for classification of HPMA as respiratory sensitiser.

In another study (Sauni *et al.*, 2008), two cases of occupational asthma caused by sculptured nails containing methacrylates are reported in Finland. Patient 1 was a 30 year-old woman who had worked for 6 years as manicurist and nail technician. Her main job was to apply sculptured nails and artificial tips to nails. Patient 2 was a 27 year-old woman who had worked for 5 years both as hairdresser and as nail technician preparing artificial gel nails. Both developed respiratory symptoms, including rhinitis, sinusitis, dyspnoea. Various examinations were performed, including spirometry, histamine challenge test, measurements of exhaled nitric oxide, peak expiratory flow (PEF) measurements at home and at the workplace, clinical symptoms and lung auscultation. In the active challenge test, the patients simulated their work in the challenge

chamber using their own products containing methacrylates, i.e., they attached the plastic nail with a glue, and then filed and sculptured the nails. During the active challenge test, which took 30 min, three sculptured nails were produced. An asthmatic reaction was defined as follows: an immediate reaction causing a decrease of 20% in the FEV1 or PEF during the first post-challenge hour; a delayed reaction was defined as causing a similar decrease in FEV1 or PEF after the first post-challenge hour; and a dual reaction was defined as a combination of the aforementioned reactions. For both patients, mild/moderate bronchial hyper-responsiveness (15th percentile lung density (PD15) = 0.649 mg and 0.154 mg, respectively) was reported in the histamine challenge test. Variations were noted in the PEF measurements at home and at the workplace. Dual asthmatic reaction was noted in the active bronchial challenge test. Patient 1 presented an immediate significant decrease of 25% in the FEV1, and 4h after the start, a delayed significant decrease of 37% in the FEV1. Patient 2 presented an immediate significant decrease of 20% in the PEF (and a drop of 16% in FEV1) 35 min after the start and after 8h, a delayed significant drop of 27% in the PEF (19% in FEV1). The concentrations of methacrylates in the gel nail materials and in the gel nails themselves were determined after the active challenge test of patient 2 only. The main methacrylate was HEMA (7.5%) in the bonding agent and bis-GMA (42%) in the sculpture resin. The sculpture resin contained 6.7% HPMA. The identification of the main methacrylates in the sealing resin could not be confirmed. Ethylene glycol-based dimethacrylates were tentatively identified in the sealing resin (20%) and in the sculpture resin (12%). To ascertain what exact component was causing the asthmatic reactions, provocations with all individual substances contained in the products ought to be undertaken, but this was not done here.

From the CLH dossier and the original publication, the process in the SIC test was partly sculpturing the nails: "*the method that both of our patients used, several layers of acrylic gel are applied on the nail plate, and every layer needs separate polymerization for some minutes by UV light*" and partly filing the nails. This means that the patients were exposed to the acrylic gel, and also dust from filing. The sculpture resin contained 6.7% of HPMA, which is a skin sensitiser (see section on skin sensitisation below) and one of the constituents of the bonding agent was HEMA (7.5%), which has a harmonised classification for Skin Sens. 1, and is assessed for harmonised classification for respiratory sensitisitisation in parallel to this dossier. The identification of the main methacrylates in the sealing resin could not be confirmed. Ethylene glycol-based dimethacrylates were tentatively identified in the sealing resin (20%) and in the sculpture resin (12%). Hardened gel nails contained no detectable amounts of HPMA, HEMA or aliphatic dimethacrylates. While for the various gel nail materials different compositions of esters were detected, their complete compositions remain unclear. The unknown components account for approximately 90% w/w in the bonding agent, approximately 80% in the sealing resin, and 40% in the sculpture resin. Further skin sensitising components, i.e., cyanoacrylates in the products of patient 1, were mentioned by the authors, but neither specified nor quantified. Thus, it cannot be excluded that there are also unidentified methacrylates contained in the products to which the patients were exposed to during the challenge test. Overall RAC notes that there are uncertainties regarding HPMA being the cause of the observed respiratory effects, as measurement of respiratory exposure to HPMA and other methacrylates, or sanding dust as alternative causing agent for these respiratory effects are lacking. RAC further notes that the provocation SIC tests were not performed according to validated guidelines, as complex mixtures were tested, including unknown components. Provocation tests with the individual substances contained in the products were not performed with any of the two patients.

Overall, RAC is of the opinion that the results of this study cannot be considered clear evidence of HPMA being the responsible agent causing respiratory sensitisation according to CLP criteria.

In a third study (Vaccaro *et al.*, 2014), one case of a 38 year-old woman is reported, who has been working as a nail art operator for 2 years and presented facial dermatitis and multiple

episodes of asthma that occurred in the prior two months. Remission of asthma and improvement of dermatitis were observed on the days when the subject did not work. In addition, the patient reported that self-measurement of PEF with a portable device resulted in lower values at the workplace (65–70% of the predicted values) than at home (> 75% of the predicted values). Spirometry showed mild airflow obstruction: FEV1, forced vital capacity (FVC), and FEV1/FVC ratio were respectively equal to 73%, 89%, and 77% of the predicted values. The results were worse when spirometry was performed at the workplace: FEV1, FVC and FEV1/FVC were 64%, 78% and 69%, respectively. The bronchial provocation test performed according to the guidelines of ATS/ERS (American Thoracic Society/European Respiratory Society) revealed mild bronchial hyper-responsiveness: a 20% FEV1 decrease from the baseline with a 2 mg/mL provocative concentration of methacholine. The reversibility test, performed according to the guidelines of ATS/ERS, showed a 14% increase of FEV1 15 min after administration of a short acting beta agonist (salbutamol). The results of patch tests were positive to methacrylates, including HPMA, MAA, MMA, EMA, and others. The manufacturer confirmed that some of the acrylates which the patient was allergic to were present in the products used, but did not want to reveal the exact composition. Thus, the link between HPMA and the respiratory reactions observed can neither be claimed nor excluded. In addition, the presence of additional compounds in the products, including other irritative and/or sensitising substances cannot be excluded. Authors diagnosed airborne allergic contact dermatitis (ACD) and asthma caused by acrylates, however, the woman denied SIC testing. RAC notes that without accurate SIC testing, an involvement of methacrylates in general, and HPMA in particular, in inducing respiratory sensitisation cannot be confirmed and that there are major uncertainties regarding HPMA being the cause of the observed respiratory effects.

RAC notes that in the publication, it is stated that "*the workplace inspection revealed that the protective mask, worn incorrectly, allowed inhalation of unfiltered air, and that dermatitis was localized in the areas not covered by the mask. We also performed the second patch test with the material obtained using the drill machine on the pre-existing nail decorations, with positive results (+++) at D2 and D4; the same test was negative in ten subjects not allergic to acrylates.[…] Her asthma remarkably improved following the therapy […] and the correct use of a mask*". This additional information further adds to the uncertainty whether methacrylates, and specifically HPMA, are/is responsible for the observed respiratory effects. It may also be that the effects were caused by artificial nail dust.

On the whole, RAC is of the opinion that the results of this study cannot be considered clear evidence of HPMA eliciting respiratory sensitisation according to CLP criteria.

Overall, RAC considers the provided case studies do not clearly show that HPMA causes respiratory sensitisation in humans and, thus, they are considered insufficient for classification of HPMA as respiratory sensitiser according to CLP.

National occupational disease databases

In the database of the French national network for the monitoring and prevention of occupational diseases (RNV3P), several cases of asthma were reported with (meth)acrylates, but none of these cases could specifically assigned to effects due to exposure to HPMA.

In the UK, there has been one case of work-related respiratory sensitisation attributed to HPMA, which was reported by the chest physicians to SWORD (Surveillance of Work-Related and Occupational Respiratory Disease) between 1989 and 2020 (i.e., in 1993). The affected male worker was a gas mains layer, but further information is not provided in the CLH dossier (see table below). RAC notes that particularly no information regarding the exposure situation, exposure levels of HPMA or whether there might have been co-exposure to other acrylates is

available. In addition, it is not clear whether a (reliable) inhalation challenge test with HPMA was performed at all.

***Table**: Information on a case of work-related respiratory sensitisation reported to SWORD between 1989-2020 in the UK*

Year	Diagnosis	Sex	Occupation	Industry	Agent
1993	Asthma / sensitisation / irritation	M	Gas mains layer	Unknown	Hydroxypropyl methacrylate

The Finnish Institute of Occupational Health (FIOH) reported on three (of approximately 150) patients with occupational asthma verified with positive SIC tests to HPMA containing products during 2000-2018. Based on the exposure data, FIOH concluded that these patients had respiratory exposure predominantly to HPMA at work, and they were mainly exposed to HPMA also in the SIC tests. In the CLH dossier it is further reported that, as the other methacrylates listed in the SDS's were poorly volatile, the FIOH hypothesised that they had a minor role in the patients' respiratory exposure and occupational asthma. Details of the studies are shown in the table below.

RAC notes that as all of the products used in SIC tests contained other methacrylates in addition to HPMA a rather high concentration (i.e., the similarly volatile HEMA (up to 15-20%), polyether polyol tetraacrylate (up to 20-25%), polyethylene glycol methacrylate (unknown amount), PEGDMA-based methacrylates with a total amount of 45-80% of which 2-5% can be assigned to HPMA). Thus, it cannot be excluded that the other compounds contained in the products, but not HPMA, are responsible for the respiratory effects seen in the patients. Furthermore, RAC notes that with the three patients, it is not entirely clear whether HPMA was the compound eliciting the positive SIC test, as exposure levels of HPMA (and other compounds, including other methacrylates) were not measured during the SIC test. RAC additionally notes that the other methacrylates the workers were exposed to, particularly HEMA, which is of similar volatility compared to HPMA and has a harmonised classification for Skin Sens. 1, H315. Therefore, the conclusion of the FIOH and the DS that (only) HPMA is causing respiratory sensitisation due to its high volatility cannot be supported.

It is further highlighted that with regards to the Finnish data, the identical argumentation was used by the DS for classifying HEMA as Resp. Sens. 1.

Table: Details on cases reports of work-related respiratory sensitisation reported by the FIOH between 2000-2018 with HPMA as possible causative agent (Finland).

	Patient 1	**Patient 2**	**Patient 3**
Exposure data			
Exposure to HPMA in positive SIC	Probably yes: SIC done during grinding newly hardened nails. HEMA/HPMA content of the hardened material has been very low in the chemical analysis probably < 0.01%	Yes; the main VOC[11] component as measured in in the SIC was HPMA	Yes, HPMA in the SIC product but occupational exposure also to other methacrylates
Job	Hairdresser	Assembler	Mechanic
Acrylates and their percentage concentration	**LCN Sculpture** - gel nail material contained 6.7% HPMA in chemical	**Loctite 620:** HPMA 1-<5%, polyethylene glycol methacrylate	**Loctite 603:** "PEGDMA-based methacrylates", total 45-80% of which

[11] Volatile organic compound

in the products at work (SIC material in bold)	analysis; **LCN Bonder** contained 7.5% HPMA in chemical analysis; SDS of **LCN (probably Sealant**): HEMA 15-20%, polyether polyol tetraacrylate 20-25%, HPMA 5-10%	(unknown CAS and amount)	HPMA 2-5%; Loctite 577 and 542: "PGDMA-based methacrylates" with no further information.
Clinical data			
Asthma (physician-based diagnosis) prior to occupational exposure	No	No	No
Atopy Is the patient atopic as defined by at least one positive skin test to a battery of local common aeroallergens	Yes	No	Yes
Prick test	Not performed	Negative	Negative
Monitoring PEF at work	Uncertain	Positive	Not performed
Maximum fall in FEV1 during the first 60 minutes after the end of challenge exposure (% from pre-challenge value)	16	14	1
Maximum fall in FEV1 recorded between the 60th minute and the end of the follow-up (% from pre-challenge value)	19	27	23
Pattern of reaction	Dual	Late	Late

In the IND comment received during the consultation, it was stated that regarding patient 1 of the cases reported by FIOH "*the manufacturer LCN confirmed the presence of HPMA in the sculpture (5-10%w/w) along with four other acrylates and other components; the presence of HEMA (10-25%w/w), but not HPMA, in the bonder; and neither presence of HEMA nor HPMA in the sealant (Wilde, 2023)*". This information further increases the uncertainties regarding the provided data in general, but specifically regarding the relevance of the case reported for patient 1, as HPMA was not even a main component in the composition of the tested products. Moreover, patient 1 was only exposed to dust of hardened nails (HPMA concentration in hardened nails < 0.1%) and not to a liquid mixture. In addition, it is not known, whether protective masks were worn during work and SIC test, respectively. No measurement of respiratory exposure to HPMA and/or other relevant substances was performed/reported. Thus, the relevance of this case for classification of HPMA is questionable.

With respect to patient 2, the product the assembler was exposed to the thread sealing Loctite620 and which, thus, was used for SIC testing. According to its SDS, Loctite620 also contains other skin sensitisers and respiratory irritants at considerable concentrations (e.g., 10-20% N,N-(m-phenylene)dimaleimide, which has a harmonised classification as Skin Sens. 1A; up to 3% cumene hydroperoxide, which has an SCL of 10% for STOT SE 3 (H335) according to its Annex VI entry; up to 1% maleic acid, which has a harmonised classification for STOT SE 3 (H335)). With respect to the SIC test performed with patient 2, it is mentioned that HPMA was "*confirmed as main volatile organic compound (VOC)*" measured during testing; however, details on time points of measurements or exposure levels of HPMA and other relevant components are missing, hampering a detailed assessment of the involvement of HPMA in the observed respiratory effects.

Regarding patient 3, the products (glues) Loctite577 and Loctite542 to which the mechanic was exposed to during work do not and never did contain HPMA according to their SDS[12], as commented by the IND. These glues instead contain other known skin sensitising and respiratory irritating substances at considerable concentrations (up to 20%). The third product mentioned here is Loctite603. According to its SDS, this product includes HPMA at a concentration of 5% up to < 10%, but also contains other methacrylates that are self-classified as STOT SE 3 (H335), Skin Sens. 1 and/or Eye/Skin Irrit. 2. The latter methacrylates are contained at considerably higher concentrations in the product (e.g., 25 – 50% 4-t-butylcyclohexyl methacrylate; 10 – 20% 1-methyltrimethylene dimethacrylate and others at < 10%) than HPMA (up to < 10%). In addition, it is not clarified in the CLH dossier which of the products (or a mixture of all) was used for SIC testing. As no measurements of respiratory exposure to HPMA and/or other relevant substances was performed/reported, it is not entirely clear whether HPMA was the only/the main component tested in the SIC or whether HPMA was tested at all, overall questioning the relevance of this case for classification of HPMA.

Other human data

Human data on cases of respiratory sensitisation related to (meth)acrylates exposure in general are also reported in the dossier. RAC highlights that none of these studies provide evidence that HPMA specifically can induce respiratory sensitisation, as HPMA was not tested alone in a relevant test design or may have been tested together with other (meth)acrylates, but was not mentioned specifically.

See Supplementary information in the Appendix for further information for consideration.

Conclusion

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*."

As explained in detail above, RAC notes – in line with the DS – that in the case reports of asthma found in the scientific literature and described above, provocations were – if performed at all – not performed with HPMA alone. Instead, the patients were mainly tested in non-guideline tests with products containing various methacrylates and possibly also contaminants or other compounds that were not declared in the SDS or measured at the workplace. In some cases, the tested products did not even contain HPMA (or at least the presence of HPMA in the products was not decaled). Thus, RAC concludes that although data raises concern for HPMA potentially being able to elicit respiratory sensitisation, the available data is overall insufficient to support classification of HPMA as respiratory sensitiser according to the CLP criteria.

In addition, few case studies were found in national occupational disease databases and are mentioned above, where only limited data are available. In the cases reported in the Finnish database, several SIC tests were carried out to diagnose occupational asthma. The SIC tests were always performed with mixtures/products to which the patients were exposed at the workplace, which in most cases included but were not limited to HPMA. The materials used in the SIC tests were generally inadequately described. The materials/products tested were reported to be complex chemical mixtures, and in all cases also contained other (meth)acrylates in addition

[12] https://docs.rs-online.com/c968/0900766b812fd111.pdf, https://docs.rs-online.com/7fa6/0900766b8001f128.pdf, https://docs.rs-online.com/a0ba/0900766b80162f5e.pdf, https://docs.rs-online.com/1b00/0900766b8001f546.pdf (last accessed on 20 October 2023).

to HPMA. RAC further notes that the presence of additional actual or possible constituents is not reported, although in some cases these account for up to > 90% of the product. This lack of information increases the uncertainties regarding the provided data.

Furthermore, it is noted that SIC tests are generally designed 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. .

Thus, overall RAC concludes that due to the insufficient information on the materials used in the SIC tests in the reported cases of respiratory sensitisation from national occupational disease databases, , it cannot be determined with sufficient confidence that the respiratory sensitisation experienced in the specific inhalation challenges was actually caused by HPMA.

Therefore, RAC considers these data from national occupational disease databases as inconclusive and thus insufficient to support classification of HPMA as respiratory sensitiser according to CLP criteria.

Taken together, based on the argumentation detailed above, **RAC concludes on no classification for HPMA as a respiratory sensitiser due to inconclusive data.**

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Based on the available animal data, the DS concluded that HPMA does not fulfil the criteria for classification as skin sensitiser according to the CLP Regulation. However, several human diagnostic patch test studies with methacrylates (including HPMA) are available, showing an overall frequency of occurrence of skin sensitisation of > 2% when considering all available studies (i.e., > 100 published cases).

The DS noted that for some retrospective studies, only the number of positive reactions to HPMA among positive patch tests to (meth)acrylates was reported leading to an overestimation of the "real" frequency of occurrence of skin sensitisation in these cases. However, in cases where the number of patients tested with HPMA is reported, the frequency of skin reactions indicating sensitisation are clearly higher than 2%, which depicts the threshold value for high frequency of occurrence according to the CLP guidance.

The DS further stated that as the tonnage band at which the substance is registered under REACH is high (≥ 10000 to < 100000 tons per annum), frequent exposure of humans can be expected. Moreover, as the substance is used in adhesive and sealants, non-metal treatment products, polymers and cosmetics and personal care products, professional workers but also consumers are expected to be exposed.

In addition, the maximum concentration of HPMA may be high in articles and products, e.g., HPMA concentrations in nail enhancement products can be as high as 25% (CIR, 2005), HPMA can be used as monomer in acrylic resin coatings for food cans at levels up to 20% (EFSA, 2012).

According to the DS, the total score for HPMA in reference to Table 3.3 of the CLP guidance is 6 (concentration/dose score of 2, repeated exposure score of 2 and no. of exposure score 2), corresponding to a relatively high exposure.

Table 3.3 Relatively high or low exposure *

Exposure data	Relatively low exposure (weighting)	Relatively high exposure (weighting)
Concentration / dose	< 1.0% < 500µg/cm^2 (score 0)	≥ 1.0% ≥ 500µg/cm^2 (score 2)
Repeated exposure	< once/daily (score 1)	≥ once/daily (score 2)
Number of exposures (irrespective of concentration of sensitizer)	<100 exposures (score 0)	≥100 exposures (score 2)

The DS concluded according to Table 3.4 of the CLP guidance that based on human data alone, HPMA fulfils the criteria for classification as Skin Sens. 1. The DS further did not propose sub-categorisation considering both, animal and human data.

Table 3.4 Sub-categorisation decision table

	Relatively low frequency of occurrence of skin sensitisation	Relatively high frequency of occurrence of skin sensitisation
Relatively high exposure (score 5-6)	Sub-category 1B	Category 1 or case by case evaluation
Relatively low exposure (score 1-4)	Category 1 or case by case evaluation	Sub-category 1A

Comments received during consultation

One MSCA agreed with the proposed classification as Skin Sens. 1.

On the other hand, IND did not agree with the proposed classification and indicated that classification of HPMA as Skin Sens. 1B may rather be justified. In the comment it is referred to the hydrolysis of HPMA to MAA and propylene glycol by carboxylesterase enzymes in the stratum corneum, which is considered a detoxification process reducing the sensitisation potential of HPMA. This reduction in sensitisation potential is proposed to be due to the fact that MAA is not electrophilic or protein reactive as shown *in vivo* (Borak *et al*. 2011) and propylene glycol has no skin sensitising potential.

The IND provided an assessment, in which the OECD "Defined Approach" was partially followed:

1) Available *in chemico* and *in vitro* studies covering all three key events (KE1-3) were taken into account, which however yielded inconsistent results and further often lacked sufficient reporting necessary for a reliable conclusion on skin sensitisation hazard and potency, as well as sub-categorisation.
2) Nevertheless, the commenter cited the outcome of the evaluation of two expert groups using an integrated testing strategy, i.e. "the integrated testing strategy (ITSv1) for UN GHS potency categorisation based on *in chemico* (KE1) and *in vitro* (KE3) data, and *in silico* (Derek Nexus) predictions, with a DIP developed with expert group (EG DASS) input" and "a modification of the integrated testing strategy (ITSv2) for UN GHS potency categorisation based on *in chemico* (KE1) and *in vitro* (KE3) data, and *in silico* (OECD QSAR Toolbox) predictions, with a DIP developed with expert group (EG DASS) input", both supporting with high confidence the classification of HPMA in Cat. 1B according to UN GHS criteria.

3) In line with the conclusion by the DS, the available animal data were reported to not meet the classification criteria for this hazard class.
4) Although IND highlighted the possibility of cross-reactions of different methacrylates (as described in several animal studies), which may lead to an increase of uncertainties of the available human patch test data, it is agreed that based on the available human data HPMA is to be considered a skin sensitiser with high frequency of occurrence and high relatively high exposure, meaning that sub-categorisation is not possible. Nevertheless, as relatively high local concentrations are required for the elicitation of dermal effects in humans by HPMA, IND considered the substance not of high potency, in spite of the high number of positive patch test results reported.

In conclusion and integrating all the above listed information, IND were of the opinion that HPMA warrants classification as Skin Sens. 1B: the skin sensitisation potential of HPMA is clearly documented by human data, which however does not allow robust sub-categorisation beyond the exclusion of a high potency. However, based on the non-human data that partially do not support classification at all (*in chemico*, *in vitro*, valid animal data) or partially support classification as low-to-moderate potent sensitiser (defined approaches according to OECD TG 497[13]), IND considered warranted the sub-categorisation towards Cat. 1B for HPMA.

Assessment and comparison with the classification criteria

Animal data

The available animal studies testing the skin sensitising potential of HPMA were all considered negative, as none or only few animals were sensitised.

The studies included four Guinea Pig Maximisation Tests (GPMT, all non-GLP or GLP not specified). In two of the four studies, HPMA with unknown purity elicited 0% of positive reactions at an intradermal concentration of 1% and a challenge concentration of 10% and 100%, respectively (Scholes *et al*., 1992; Basketter *et al.*, 1992). In one Maximisation test, HPMA (with unknown purity) at an intradermal concentration of 10% (and challenge concentration of 15%) yielded 25% positive reactions (3/12) and was thus concluded negative for classification (Clemmensen *et al.*, 1984). In the fourth Maximisation test, an intradermal HPMA concentration of 5% or a topical induction concentration of 25% (after pre-treatment with sodium lauryl sulphate) and a challenge concentration of 2% resulted in a positive reaction (10%) in one animal (Bjorkner, 1984). Two LLNA-studies testing HPMA concentrations up to 50% were also negative (stimulation index < 2) (Scholes *et al.*, 1992; Basketter *et al*., 1992). In none of these studies was it indicated whether a positive control was concomitantly tested and/or the tested positive control was valid. In addition, a study using the Maguire method derived from the Split adjuvant technique is available. In that study none of the tested Guinea pigs showed positive reactions, while 70% of the animals of the (valid) positive control were sensitised (Rao *et al*., 1981).

In the study by Clemmensen *et al.* (1984), besides HPMA, also other (meth)acrylates were tested in maximisation assays. Cross-reactions were noted, in particular when animals were induced with HEMA or 2-hydroxyethylacrylate (HEA) and challenged with 25% HPMA (5/15 and 8/12 animals sensitised, respectively). Of 12 animals treated with 2-hydroxypropyl acrylate (HPA), 3 animals also reacted positive to 25% HPMA (Clemmensen *et al.*, 1984). Similar observations were reported by Rustemeyer *et al*. (1998), who tested the sensitisation potential of three to

[13] https://www.oecd-ilibrary.org/docserver/b92879a4-en.pdf?expires=1699024843&id=id&accname=oid018224&checksum=84275EDF07B2C8C099769FAF9237C80B

four methacrylates (MMA, EGDMA, HEMA and HPMA) in a modified FCA test design and the cross-reactivity of the substances at day 28 in a randomized rotary distribution. All four tested methacrylates were obvious sensitisers, and MMA and EGDMA were found to be most potent when tested with the modified FCAT method. Regarding cross-reactivity, MMA sensitised animals showed only infrequent and weak cross-reactivity with HPMA (5/15; median strength of 0.0) and higher cross-reactivity with HEMA (most potent with EGDMA). HEMA sensitisation caused generally strong cross-reactions with all other methacrylates: MMA (7/7; 0.6), HPMA (8/11; 0.9), and EGDMA (7/7; 1.1). Sensitisation with HPMA similarly resulted in strong or intermediate cross-reactivity to EGDMA (11/11; 1.0), HEMA (15/15; 0.7) and MMA (78/11; 0.3). Björkner (1984) also tested for cross-reactivity of HPMA with other (meth)acrylates in a GPMT and found that the one animal sensitised to HPMA also reacted to HEMA with the same response as to HPMA, but not HPA and HEA.

Human data

Besides the animal data, a large number of case reports and clinical studies, including diagnostic patch tests and observational retrospective studies, are available (see table in Supplementary information in the Appendix).

Numerous case reports can be found in the scientific literature, in which single individuals are reported to show signs of contact allergy dermatitis towards HPMA. In some cases, also signs of conjunctivitis or lesions in the nails, lips or external auditory canals were reported after repeated contact to the substance. Most case reports refer to affected workers occupationally exposed to various (meth)acrylates, in particular dental staff with cases reported since 80's and more recently nail salon workers. However, several cases of skin sensitisation to HPMA have also been reported in the general population, e.g., after exposure to prosthesis, acrylic nails, bleaching treatments or electrodes.

Besides the case reports, also numerous clinical studies, i.e., human diagnostic patch test (HDPT) data in selected dermatitis patients, and additional retrospective studies are available. RAC notes that data from studies on the general population or unselected clinical patients are not available. Furthermore, human predictive patch tests (HPPT) data are also not available for HPMA.

HPMA was usually tested as part of (meth)acrylate patch test series and its established test concentration was 2% in petrolatum. The patients were pre-selected strongly based on presumed contact with (meth)acrylic compounds (e.g., women with artificial nails) or special occupational groups (e.g., dentists, dental workers, nail artists). The frequency of positive reactions was generally high (> 50% and up to 90% in individual studies, but generally ≥ 2%), but depended on the selection of patient groups. Patients with suspected exposure related to cosmetic nail products (occupational and general population) had the highest incidences of positive reactions to HPMA.

RAC notes that HDPT data has limitations, as only elicitation of sensitisation, but not the induction is tested and prior exposure to the test substance or cross-reacting sensitisers, as frequently seen with (meth)acrylates, is usually not quantifiable. Nevertheless, such data are suitable for classification purposes according to CLP as highlighted in the CLP guidance (section 3.4.2.2.3.1).

RAC further notes that in some of the clinical reports, particularly in some of the retrospective studies, the number of patients specifically exposed to HPMA in patch-tests and/or the number of patients positively tested to HPMA cannot be verified as these numbers are not always reported (but only the number of positive reactions to HPMA among positive patch tests to (meth)acrylates in general). As the DS, RAC considers that this might lead to a possible overestimation of the occurrence of sensitisation to HPMA. In addition, cross-sensitisation may have affected the outcome of the studies leading to a higher number of sensitised patients. Nevertheless, in the various available studies, in which the total number of patients specifically tested with HMPA and

the resulting numbers of positive reactions are reported, the frequency of occurrence is consistently considerably above 2% (i.e., up to 50% in individual HDPT studies and up to 95% in individual retrospective studies), which – according to Table 3.2 of the CLP guidance – corresponds to a relatively high frequency of occurrence of skin sensitisation among selected dermatitis patients.

During the consultation, additional cross-sectional patch test (and/or prick test) studies on risk occupations were provided, which are designed to mimic a workplace study (Eslander, 1984; Rustemeyer *et al.*, 1996; Peiler *et al.*, 1996; Schnuch *et al.*, 1998; Peiler *et al.,* 2000; Heratizadeh *et al.*, 2018; Schubert *et al.,* 2021). In most of these studies the percentages of positive (sensitising) reactions to HPMA ranged between 12.7% and 28.5%. According to Table 3.2 of the CLP guidance, the threshold for a high frequency of occurrence of sensitisation in selected workers with known exposure or dermatitis is ≥ 1%. Thus, in accordance with the results of the patch tests in selected dermatitis patients, the occurrence of skin sensitisation reported in the cited cross-sectional studies is of high frequency.

Overall and although some of the individual human studies may be of limited power, the vast human evidence consistently points towards HPMA eliciting skin sensitisation in humans with a relatively high frequency of occurrence.

In the CLH dossier, no *in chemico/in vitro* data is presented. In the consultation, however, one commenter provided data on all three key events for sensitisation (KE1-3), which is listed in the following table.

Table: Summary of all *in chemico/in vitro* data provided during the consultation

Key Event	Assay	Result	rating of potency in report (quantitive results)	Reference
KE1	Direct Peptide Reactivity Assay (DPRA)	2 x positive	moderate reactivity weak positive (mean peptide depletion 33.0 and 22)	Kolle S. (2013) Nukada (2013)
	Amino Acid Derivative Reactivity Assay (ADRA)	1 x positive 2 x negative	?	Fujita (2013) Fujita (2019) Yamamoto (2015)
KE2	Keratinocyte Activation Assay – LuSens	positive	No assessment of potency	Kolle S. (2013)
KE3	U937 cell line activation test (U-SENS)*	positive	No assessment of potency	Kolle S. (2013)
	human Cell Line Activation Test (h-CLAT)	negative	?	Ashikaga (2008, 2010) Nukada (2011)
	Interleukin-8 Reporter Gene Assay (IL-8 Luc Assay)	negative	?	Takahashi (2011)

*Former MUSST: Dendritic Cell Line Activation Assay Myeloid U937 Skin Sensitisation Test

It was stated in the comment that all studies listed above had been performed before the respective OECD test guidelines were fully validated and are, in addition, non-GLP studies. RAC notes that the results of these studies are very inconsistent: in some cases, positive and negative

results were obtained for the same key event or even using the identical assay. Moreover, the reporting of the results in the publications were stated to be of rather low detail. Thus, according to the "2 out of 3" Defined Approach (OECD TG 497), the available *in chemico/ in vitro* data is insufficient in order to allow for a robust conclusion on skin sensitisation hazard.

The commenter, on the other hand, highlighted that respective expert groups assessed the skin sensitising potency of HPMA together with further 195 chemicals in a comprehensive data set when developing the Guideline (GL) on Hazard Assessment Skin Sensitisation Appendix III – 4 Defined Approaches (DAs) for skin sensitisation (Series on Testing and Assessment No. 336). The outcome of the evaluation of the expert groups was published in Annex 2 to the Supporting document of to the GL on the DAs for skin sensitisation and resulted in Category 1B with high confidence for the "*integrated testing strategy for UN GHS potency categorisation based on in chemico (KE1) and in vitro (KE3) data, and in silico (Derek Nexus) predictions*" (ITSV1) and "*a modification of the integrated testing strategy for UN GHS potency categorisation based on in chemico (KE1) and in vitro (KE3) data, and in silico (OECD QSAR Toolbox) predictions, with a DIP developed with expert group (EG DASS) input*" (ITSV2) (OECD TG 497, Annex 2, 2021). RAC notes that both cited ITS DAs are based on three information sources only: two *in chemico/in vitro* assays (DPRA; OECD TG 442C (OECD, 2015) and h-CLAT; OECD TG 442E (OECD, 2018)) and one *in silico* tool (prediction from Derek Nexus (= ITSv1) or OECD QSAR Toolbox (= ITSv2)). Human and animal data, on the other hand, are not taken into account. In turn, the reliability and applicability of the non-animal method (NAM) DAs (i.e., accuracy, specificity, and sensitivity) were assessed based on a direct comparison of the *in chemico/in vitro* data to the available human reference data (mostly HPPTs, but also HDPTs) and animal reference studies, respectively. The balanced accuracy and thus, predictability of ITSv1 and ITSv2 into correct UN GHS sub-categories was ≤ 81% when compared to LLNA data (n = 153) and ≤ 80% when compared to human reference data (n = 60). In addition, RAC notes that the ITSv1 and ITSv2 DA approaches were performed with the main component of HMPA, i.e., 2-HPMA (70 – 90% of HMPA), but not with the multi-component substance. Moreover, the second component of HPMA, i.e., 2-hydroxy-1-methylethyl methacrylate (10 - 30%) was not tested at all in the DA approaches.

With respect to the mode of action, the DS stated according to Stingeni *et al.* (2015), *"the carbonyl group (in the form of free acid or an alkyl ester) bound to a vinyl group, which is immediately adjacent (α–β position). Such a structure, which is common to many known allergens, is strongly polarized. The oxygen atom takes a part of the electron cloud from the adjacent carbon atom; this causes accumulation of negative charges around the oxygen and of positive charges around the carbon atom bound to it. This structure is very reactive, as it can easily react with proteins and other molecules to produce addition products. Moreover, the space geometry of substituents can favour or depress the electronic polarization or shield the electron cloud".*

Conclusion

The available animal data points towards a very low skin sensitising potential of HPMA, that would not warrant classification according to CLP (See classification criteria in Supplementary information in the Appendix) as only few animals (< 30%) were sensitised in the GPMTs at a rather high intradermal inductions dose of 10% and the stimulation index in the available LLNA tests were too low (< 2) to calculate an EC3 value.

However, the available human data consist of case studies and HDPTs in selected dermatitis patients and from these studies, there is vast evidence that HPMA has the potential to cause skin sensitisation in humans. In order to account for the above-mentioned limitations of such diagnostic patch test data, the CLP guidance describes principles in order to inform on potency and sub-categorisation. Initially it needs to be determined whether the frequency of occurrence of skin sensitisation in the studies is to be considered high or low to moderate. As described in

detail above, in the vast majority of the available studies **the percentage of sensitised individuals was considerably above the threshold values depicting a high frequency of occurrence in selected dermatitis patients (i.e., ≥ 2%) and selected workers with known exposure or dermatitis (i.e., ≥ 1%),** respectively (table 3.2, CLP guidance, see below). Although some uncertainties remain with respect to the number of positive reactions due to cross-reactivity to other (meth)acrylates; it cannot be excluded that the positive results are in fact due to HPMA exposure in these cases, particularly as the tests were performed with the substance itself and not with mixtures additionally containing other (meth)acrylates.

***Table**: Table 3.2 of the CLP guidance (ECHA, 2017)*

Human diagnostic patch test data	High frequency	Low/moderate frequency
General population studies	≥ 0.2 %	< 0.2 %
Dermatitis patients (unselected, consecutive)	≥ 1.0 %	< 1.0 %
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0 %	< 2.0 %
Work place studies: 1: all or randomly selected workers 2: selected workers with known exposure or dermatitis	 ≥ 0.4 % ≥ 1.0 %	 < 0.4 % < 1.0 %
Number of published cases	≥ 100 cases	< 100 cases

* Only one or two types of information may be sufficient for sub-categorisation.

In a second step, the exposure index is to be calculated according to Table 3.3 of the CLP guidance (below): scores have to be assigned with respect to the concentrations/doses of the substance in the products (i.e. < 1% or < 500µg/cm² for low exposure and ≥ 1% or ≥ 500 µg/cm² for high exposure), the repetition of the exposure (less than once a day and ≥ once daily), and the total number of exposure irrespective of the concentration of the sensitiser (< 100 exposures or ≥ 100 exposures). An additive exposure index of 1-4 equates to low exposure, whereas 5-6 reflects high exposure.

***Table**: Table 3.3 of the CLP Guidance (ECHA, 2017)*

Exposure data	Relatively low exposure (weighting)	Relatively high exposure (weighting)
Concentration / dose	< 1.0% < 500µg/cm² (score 0)	≥ 1.0% ≥ 500µg/cm² (score 2)
Repeated exposure	< once/daily (score 1)	≥ once/daily (score 2)
Number of exposures (irrespective of concentration of sensitizer)	<100 exposures (score 0)	≥100 exposures (score 2)

When estimating HPMA exposure, it is known that HPMA is used at rather high concentrations at industrial site or by professional workers and also consumers. Thus, relatively high exposure is expected with concentrations > 1% (score 2). In nail enhancement products, for example, the maximum use concentration reported for HPMA is 25% (CIR, 2005), while in acrylic resin coatings for food cans HPMA as monomer can be found at use levels up to 20% (EFSA, 2012). Regarding

the repetition of exposure, no specific information is available for HPMA, but it may be assumed that repeated exposures exceed once/daily (score 2) considering the products in which HPMA is included (e.g., adhesive and sealants, non-metal treatment products, polymers and cosmetics and personal care products (ECHA, 2021)).

Moreover, it may be anticipated that the total number of exposures exceeds 100 times (score 2). In total, these assumptions would lead to a score of 6 for HPMA exposure, which depicts a relatively high exposure according to Table 3.3 of the CLP guidance. However, RAC notes that specific information on exposure to HPMA is not available and the derived high exposure must be considered with care.

According to Table 3.4 of the CLP guidance, a relatively high frequency of occurrence of skin sensitisation and a relatively high exposure result in classification of the substance as Skin Sens. 1 without sub-categorisation

***Table**: Table 3.4 of the CLP guidance (ECHA, 2017)*

	Relatively low frequency of occurrence of skin sensitisation	Relatively high frequency of occurrence of skin sensitisation
Relatively high exposure (score 5-6)	Sub-category 1B	Category 1 or case by case evaluation
Relatively low exposure (score 1-4)	Category 1 or case by case evaluation	Sub-category 1A

Considering the animal data in addition to the human data, sub-categorisation does not seem supported for HPMA.

RAC notes that human data are only available on selected dermatitis patients or selected workers with dermatitis, which limits the relevance of the data for potency determination and, thus, increases the uncertainties regarding HPMA being a high potency sensitiser. Exposure to HPMA is assumed to be high according to Table 3.3 of the CLP guidance, nevertheless specific data corroborating this assumption are not available except for use data on the substance indicating that high concentrations of the substance are used in products, which are generally used rather frequently. This lack of robust information further hampers a conclusive assessment on the sub-categorisation of HPMA. Thus, when taking into account both, animal and human data, classification of HMPA as skin sensitiser Cat. 1 is considered supported, but sub-categorisation is not considered applicable. In addition, the conflicting and very inconsistent *in chemico/in vitro* data provided during the consultation are considered insufficient to conclude on a sub-categorisation for HPMA as well.

Hence, overall RAC concludes that HPMA **warrants classification as Skin Sens. 1,** without sub-categorisation.

The setting of generic/specific concentration limits (i.e., GCL/SCL) was not discussed by the DS. RAC notes that for MMA, EMA and BMA, the harmonised classification is to be applied by using the GCL for skin sensitisers Cat. 1, i.e., 1% (Table 3.4.5 of the CLP Regulation). MAA, the common metabolite of HPMA and the other short methacrylate, is not classified for the hazard class skin sensitisation.

As neither the available animal and *in vitro/in chemico* studies with HPMA, nor the human data on HPMA can be considered sufficiently robust for SCL setting, **RAC considers that a GCL of 1% is warranted for HPMA.**

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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 (when applicable).

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

Appendix

Supplemental information - In depth analyses by RAC

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

As cited by IND's comment, Jones (2002, referring to Thornton-Manning & Dahl, 1997, p. 234 in his thesis) mentioned that concentrations of carboxylesterases tend to be higher in the cells of the olfactory epithelium and the Bowman's gland of the rat than in humans. To RAC's view this conclusion cannot be taken from the studies cited in this review publication (Thornton-Manning & Dahl, 1997; the relevant citation: Lewis *et al.,* 1994). However, Mainwaring *et al.* (2001) demonstrated that the carboxylesterases are heavily localised in the sustentacular cells and Bowman's glands of the rat olfactory region. Based on the microscopical staining intensity at the comparable localisations lower amounts of carboxylesterases were concluded by the authors for the human olfactory region. RAC notes that the robustness of this conclusion is questionable, only one specimen was documented, and it is unknown whether factors having effects on staining intensity were considered (i.e., section thickness, the use of similar immunohistochemistry methods, impact of sampling after death on enzyme activity versus fresh samples from rats). The maximum rates (Vmax) of metabolism of MMA vapour to MAA in rat olfactory tissue S9-fractions were higher compared to those in human olfactory tissue S9-fractions (~13-fold) (Mainwaring *et al.*, 2001), suggesting that rats in fact may be more sensitive towards methacrylates' irritative properties in the nasal olfactory tissue, as they may have a greater capacity to produce the toxic metabolite. RAC notes, however, that in this study olfactory tissue of only one human individual was used for species comparison limiting the general validity of this finding. On the other hand, Lewis *et al.* (1994) determined similar carboxylesterase activity in rats, dogs and human nasal tissues. While carboxylesterase was similarly distributed in dogs and human respiratory mucosa in the surface epithelial cells and submucosal glands (of the respiratory mucosa), rats did not show esterases in the submucosal glands of the respiratory mucosa. It is to note that distribution of carboxylesterase in the sustentacular cells and Bowmans' gland of the olfactory mucosa are almost identical in rats and dogs, whereas no human tissue of the olfactory mucosa was examined (Lewis *et al.*, 1994).

Human olfactory epithelium is similar in organisation and cell morphology to that of most vertebrate species. The epithelium has a pseudostratified columnar organization and consists of olfactory neurons, supporting and basal cells (Morrison and Constanzo, 1992).

RAC evaluation of respiratory sensitisation

Further information for consideration

The DS noted that HPMA – being a skin sensitiser (see section on skin sensitisation below) – can also have the intrinsic potential to induce respiratory sensitisation. RAC agrees that in principle the potential to induce skin sensitisation may support the intrinsic potential of the substance to also induce respiratory sensitisation. However, RAC clarifies that this assumption cannot be considered evidence for the substance eliciting sensitisation in the respiratory tract, as also other factors may play a role. Based on its vapour pressure, volatility of the substance is considered limited, but exposure to aerosols cannot be excluded. Nevertheless, RAC highlights that CLP is hazard-based. Therefore, exposure is not further considered here.

In addition, the DS referred to the recent adopted RAC opinion on the classification of MMA as respiratory sensitiser. Based on this recently adopted RAC opinion and the data available on HPMA toxicokinetics, the DS concluded that respiratory sensitisation has to be suspected for potentially all methacrylates that are hydrolysed to MAA by carboxylesterases. The DS further states that "*this suspicion is particularly high for those substances that hydrolyse quickly, are of low molecular weight and which are volatile*". RAC agrees that there is a valid concern regarding short chain methacrylates (including HPMA) eliciting respiratory sensitisation in general. In addition, it is agreed that the RAC Opinion on the classification of MMA as Resp. Sens. 1 was adopted in March 2021, but RAC notes that the available data base and, thus, the assessment for classification differed from the available data for HPMA.

RAC evaluation of skin sensitisation

***Table**: Summary human data on skin sensitisation. Frequencies reported in bold in the table are those that can be directly compared to CLP criteria (number of positive reactions / total number of patch tests with HPMA)*

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Case reports				
Case report	HPMA (5% in olive oil)	5 subjects with ACD to one or more acrylate compounds. Patch test performed to examine cross-reaction.	2/5 of the patients were further tested with HPMA: both show positive reactions	Jordan *et al.,* 1975
Case report	HPMA (2% in petrolatum (pet.))	52 year-old man employed for 10 years in an ink laboratory, formulating inks and varnishes for UV cure, developed a dermatitis on his hands	Tests using the different acrylates showed positive reaction only for HPMA	Bjorkner, 1984
Case report	HPMA Purity > 90% Patch test: HPMA (2% pet.)	39 year-old man with erythematous papular eruption working as a maintenance fitter in a company involved in the manufacture of HPMA Occupational exposure	Positive to HPMA among other acrylates	Lovell *et al.,* 1985
Case report	HPMA (2% w/w in pet.)	51 year-old male patient with dermatitis when using a new-varnished lower-leg prosthesis General population	Positive patch test to HPMA among other acrylates.	Romaguera *et al.,* 1989
Case report	HPMA (2% w/w in pet.)	6 dental nurses and 1 dentist with ACD due to dental composite resin products; all women Occupational exposure	All patients were allergic to their composite resin products 5 patients tested with HPMA: 3/5 with positive reactions	Kanerva *et al.,* 1989
Case report	HPMA (2%)	6 patients (36-49 years of age) with ACD 2 dental nurses tested with HPMA Occupational exposure	Patch test positive to HPMA in the 2 patients tested. Patient 1: +++ Patient 2: +++	Kanerva *et al.,* 1991
Case report	HPMA (2% w/w in pet.)	35 year-old woman with eczema after undergoing TENS (transcutaneous electrical nerve stimulation) General population	Positive patch test to HPMA among other methacrylates	Marren *et al.,* 1991
Case report	HPMA (2%)	45 year-old orthodontist with work-related cough	HPMA: ++ on days 2 and 3 and +++ on day	Kanerva *et*

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		suspected to be caused by acrylics Patient experienced itching on day 13 after patch test performed with methacrylate series. Patient was retested 2.5 months later Occupational exposure	4 Positive reactions also reported with other acrylates	*al.,* 1992
Case report	HPMA (1% w/w in pet.)	4 patients (23-32 years of age) who developed ACD from working with dental protheses Occupational exposure	3 patients tested with HPMA: all with positive reactions Positive reactions also reported with other acrylates	Kanerva *et al.,* 1993
Case report	HPMA (2%)	38 year-old woman with ACD working in the production of car rear-view mirrors and using acrylate adhesive Occupational exposure	Positive patch test to HPMA (although not present in the adhesive: cross-allergy suggested by the authors)	Kanerva *et al.,* 1995a
Case report	HPMA (0.2 and 0.6% in pet.)	5 women with photobonded acrylic nails presenting a pruritic and painful perionychial and subonychial dermatitis for several months General population	Results with HPMA: Patient 1: reaction +++ (0.6%); ++ (0.2%) Patients 2 and 3: reaction ++ (0.6%); + (0.2%) Patients 4 and 5: reaction + (0.6% and 0.2%) Positive reactions also reported with other acrylates.	Hemmer *et al.,* 1996
Case report	HPMA	2 patients with ACD and conjunctivitis (one dental laboratory assistant and hearing aid worker) Occupational exposure	Results with HPMA: Patient 1: reaction +++ Patient 2: reaction ++ Positive reactions also reported with other acrylates	Eslander *et al.,* 1996
Case report	HPMA (2% in pet.)	47 year-old female dentist with symptoms of asthma, rhinoconjunctivitis and ACD Occupational exposure	Reaction to HPMA: ++ Positive reactions also reported with other acrylates	Lindstrom *et al.,* 2002
Case report	HPMA (2% vaseline)	2 men (50-54 years of age) with eczema on the	Patient number 1 not tested with HPMA	Weber-Muller *et al.,* 2004

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		sites where TENS electrodes were applied General population	Patient number 2 positive to HPMA: +/- at 48 h and + at 96 h readings Positive reactions also reported with other acrylates	
Case report	HPMA	4 women (26-41 years of age) with ACD from photobonded acrylic gel nails Occupational exposure and general population	Results with HPMA: Patient 1: ++ Patient 2: +++ Patient 3: ++ Patient 4: negative Positive reactions also reported with other acrylates	Cravo *et al.,* 2008
Case report	HPMA (2% pet.)	42 year-old woman with itchy erythematous papules and scaling where she applied the TENS electrodes General population	Reaction with HPMA: ++ on day 2 and day 4 readings Positive reactions also reported with other acrylates	Llamas *et al.,* 2010
Case report	HPMA (2% pet.)	55 year-old woman with marked symmetrical lip and gingival oedema and erythema after undertaking a series of home dental bleaching treatments General population	Reaction with HPMA: ++ on days 1 and 4 Positive reactions also reported with other acrylates	Goulding *et al.,* 2011
Case report	HPMA	3 women (35-50 years of age): two with periungual eczema and one with face and eyelid dermatitis after contact to acrylates in artifiial sculptured nails. 2 customers and 1 technical nail	Positive reaction with HPMA in all three patients Positive reactions also reported with other acrylates	Maio *et al.,* 2012
Case report	HPMA	32 year-old woman with skin lesions of the ears and external auditory canals, hand eczema and bullous lesions on fingers when working as manicurist and with reappearance of lesions when working as dental nurse Occupational exposure	Reaction with HPMA: +++ on day 2 and 4 Positive reactions also reported with other acrylates	Kiec-Swierczynska *et al.,* 2013

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Case report	HPMA (2% pet.)	38 year-old woman working as a nail art operator with facial dermatitis and multiple episodes of asthma Occupational exposure	Positive patch test to HPMA (reaction ++) Positive reactions also reported with other acrylates	Vaccaro *et al.,* 2014
Case report	HPMA (2% in pet.)	64 year-old non-atopic man with multiple, itchy, eczematous patches on the anterior aspect of his chest, corresponding to the sites of contact with disposable pre-gelled F2060® electrodes General population	Results for HPMA: Day 2: +++ Day 4: +++ Positive reactions also reported with other acrylates.	Stingeni *et al.,* 2015
Case report	HPMA	4 cases of ACD to acrylates found in Shellac nail products (3 beauticians and 1 consumer)	2/4 patients reacted to HPMA (++ and + respectively) Positive reactions also reported with other acrylates Additional information: 1320 patients tested between 1993-2013 (Australia): 57 positive to acrylates with 14 being beauticians and 9/14 positive to HPMA	Le *et al.,* 2015
Case report	HPMA	40 year-old non-atopic male, working as a flamenco guitarist and formerly as a construction worker, with a 1 year history of lesions on the fingers. Use acrylic materials in order to strengthen his nails for guitar playing General population	Results for HPMA: Day 2: ++ Day 4: ++ Positive reactions also reported with other acrylates	Alcantara-Nicolas *et al.,* 2016
Case report	HPMA (2%)	1 woman (33 years of age) and 3 men (28-41 years of age) working with varnishes and presenting eczema/skin lesions Occupational exposure	2/4 patients reacted to HPMA Patient 3: ++ Patient 4: + Positive reactions also reported with other acrylates	Conde-Salazar *et al.,* 2017
Case report	HPMA	6 women, (38-58 years of age), with ACD; nail technicians	All patients reacted to HPMA: + Positive reactions also reported with other	DeKoven *et al.,* 2017

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		Occupational exposure	acrylates	
Case report	HPMA (2% in pet.)	Patch tests for 4 consumers (females; 35-65 years of age) with dermatitis; long-lasting nail polish kits for home use General population	Patch test for HPMA: Patient 1: +++ Patient 2: + Patient 3: - Patient 4: ++ Positive reactions also reported with other acrylates	Gatica-Ortega *et al.,* 2018
Case report	HPMA (2% in pet.)	10 year-old girl with eczema on the dorsal aspect of the thumb and vesicular and bullous lesions on her fingertips, associated with itching and burning. Lesions appeared 10 days after she applied her mother's gel nail polish General population	Patch test for HPMA: ++ Positive reactions also reported with other acrylates	Romita *et al.,* 2020
Case report	HPMA	11 year-old girl with eczema (fingers) Frequent manipulation and "playing" with the mother's professional products, in particular those used for nail aesthetics General population	Patch test for HPMA: ++ Positive reactions also reported with other acrylates	Alves *et al.,* 2020
Case report	HPMA (2% in pet.)	57 year-old man who developed a pruritic rash on the scalp, with erythematous, squamous, and erosive lesions 4 weeks after using a capillary prosthesis fixed by a liquid glue General population	Patch test with HPMA: ++/++ (day 2 and 4, respectively) Positive reactions also reported with other acrylates	Rodenas-Herranz *et al.,* 2020
Clinical studies				
Clinical study on selected patients	HPMA (2% in petrolatum)	45 patients with shoe dermatitis were patch tested. It is unknown whether the shoes the patient had used contained any hydroxypropyl methacrylate	1/45 (2%) patients was positive to HPMA	Grimalt, 1975
Clinical study on selected patients (1982-1986;	HPMA (1% w/w in pet.) between 1982-1985	Routine patch testing with (meth)acrylate series Practically every patient with contact dermatitis	Observation 1982-1985: 4/22 patients had an allergic occupational contact dermatitis from	Kanerva *et al.,* 1988

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Finland) 22 patients tested between 1982-1985 24 patients tested between 1985-1986	HPMA (2% w/w in pet.) between 1985-1986	was tested at least with the European standard series. Acrylate series were tested in cases where contact allergy to acrylates was suspected	acrylate (18.2%): 3/4 positive to HPMA **(13.6%)** Positive reactions also reported with other acrylates and acrylate mixtures (e.g., dental screening series of Chemotechnique) Observation 1985-1986: 3/24 patients with active (iatrogenic) sensitisation (12.5%) --> 1 positive to HPMA **(4.1%)** 3/24 with allergic contact dermatitis: 2 positive to HPMA **(8.3%)** Positive reactions also reported with other acrylates Publication focusing on sensitisation to patch test acrylate	
Clinical study on selected patients	HPMA (5%)	A list of 16 patients with skin and nail reactions to acrylics from 1978 to 1987 was retrieved by computer. There were 13 females and three males in the age of 22 – 62 years. More than one half of the cases were seen since 1985	Positive reactions to HPMA in 3 of 6 (50%) of patients	Taylor, 1989

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Clinical study on selected patients (1974-1988, Finland) Occupational study	HPMA (1% in pet.): 1982-1985 HPMA (2% in pet.) since Sept. 1985	1622 patients diagnosed as having an occupational skin disease and divided in different groups	Selected patients from the study on active sensitisation to acrylates: 3/22 diagnosed as having allergic eczema developed in dental prosthetic work → all positive to HPMA (13.6%) 7 patients diagnosed as having allergic eczema caused by acrylates to which they were exposed in dental restoration work → 3/7 positive to HPMA (42.8%) 4 patients diagnosed as having allergic eczema due to acrylic compounds developed in exposure other than dental work → 2/4 positive to HPMA (50%) Positive reactions also reported with other acrylates	Eslander, 1990
Clinical study in selected patients (1987-1992 Italy)	HPMA (2% in petrolatum)	82 patients suspected of occupational sensitisation to acrylic compounds were patch tested with the standard series and an extensive acrylate series	No positive reaction to HPMA monomer (0%)	Guerra *et al.* 1993
Clinical study in selected patients (anamnestic data on acrylate exposure)	HPMA (2%)	124 patients patch tested with the (meth)acrylate series during a period of 52 months All patients had anamnestic data on acrylate exposure	Positive patch test with HPMA: 15/124 **(12.1%)** Positive reactions also reported with other acrylates	Kanerva *et al.,* 1995b
Retrospective study on selected patients (1990-1994, Poland)	HPMA 2% in petrolatum (Chemotechnique's test substance)	A retrospective study on 23 patients patch tested with (meth)acrylate series at the Nofer Institute of Occupational Medicine, Lodz (PL) in 1990-1994	Positive reactions to the test substance in 2/23 (8.7%) patients. Both patients were dentists	Kiec-Swierczynska, 1996
Clinical study on selected patients (1993-1994, Germany)	HPMA (2% in pet.)	Occupational study 7 laboratories inspected 55 dental technicians: 27 patch tested with HPMA	7/27 positive to HPMA **(25.9%)** Positive reactions also reported with other acrylates	Rustemeyer *et al.,* 1996

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Retrospective study (1985-1995, Finland)	HPMA (2%)	Statistics on 10 years of patch testing with 30 (meth)acrylates were compiled 275 patients were patch tested with a history of exposure to (meth)acrylates (meth)acrylate series of Chemotechnique Diagnostics	Positive patch test to HPMA: 1985-1995: 29/242 **(12%)** 1985-1990: 15/124 (12.1%) (these results seem to be identical to those reported by Kanerva *et al.* 1995b) 1991-195: 14/118 **(11.9%)** Positive reactions also reported with other acrylates	Kanerva *et al.,* 1997
Clinical study in selected patients (reporting period not mentioned, reporting date: 1997-04-16, Germany)	HPMA (purity and concentration not reported)	564 patients tested in German dermatological clinics for possible contact allergy to Hydroxyethyl methacrylate	29/564 **(4.8%)** patients tested positive to HPMA. 19 of these 29 patients were dental technicians	Schnuch, 1997
Retrospective study (1983-1998; UK)	HPMA (2% in pet.)	440 patients with a history of exposure to acrylates were identified Chemotechnique series	67/440 showed at least 1 relevant reaction to (meth)acrylates. 47 were sensitised at work Results with HPMA: positive patch test in 26/330 patients **(7.9%)**	Tucker *et al.,* 1999
Retrospective study (1990-2000, Poland)	HPMA 2% in petrolatum	A retrospective study on 79 dentists and 46 dental nurses patch tested with the European standard set, dental screening and with other allergens at the Nofer Institute of Occupational Medicine, Lodz (PL) in 1990-2000. 20 dentists were tested with the (meth)acrylate series	Among 20 acrylate-sensitive dentists, 10 (50%) reacted to HPMA Acrylates caused allergy only in dentists	Kiec-Swierczynska, 2002
Clinical study on selected patients	HPMA 2% and 5% in petrolatum	56 patients' charts were available for review out of 75 patients with at least one allergic reaction to meth/acrylates	In total 21/56 (37.5%) reacted to HPMA 25 patients had skin symptoms from nail products (17/25 reacted to HPMA)	Sood and Taylor,2003
Clinical study	HPMA 2% in	27 patients (26 women	In a series of patients	Constandt,

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
on selected patients	petrolatum	and 1 man), all in contact with artificial nails were tested. 16 professional beauticians / 11 customers. 12 patients were tested with various substances, 9 with the complete Chemotechnique (Malmö, Sweden) printing series (24 acrylic compounds), 7 with ethyl cyanoacrylate, 5 with a small series of 5 acrylics (MMA, 2-HEMA, EGDMA, BIS-GMA, UEDMA; and 1 with 2-HEMA	known to be exposed to artificial nails 6/11 (> 54%) subjects patch tested with HPMA were positive	2005
Retrospective study (2001-2004, Israel)	HPMA (2% in pet.)	Patients with suspected ACD from artificial nails. Study conducted on 55 female patients European standard series, methacrylate artificial nail (MAAN) series and additional allergens in personal cosmetics, including nail lacquer and ethyl cyanoacrylate	HPMA: positive patch test in 17 patients **(30.9%)** 9 occupational cases; 8 non-occupational cases	Lazarov, 2007
Retrospective study (1995-2004, Sweden)	HPMA (2% in pet.)	90 patients with dermatitis suspected to be caused by acrylates/methacrylates. Acrylate and nail acrylics series	24/90 patients with positive patch tests to acrylate/methacrylate allergens (21 patch tested with HPMA) Only results for these patients presented in the publication Results with HPMA: positive patch test in 8/21 patients **(38%)** Positive reactions also reported with other acrylates (except patient no. 7: + on day 3/4 and not read on day 7)	Goon *et al.,* 2007
Retrospective study (1994-2006, Finland)	HPMA (2% in pet.)	Review of the test files at the FIOH from 1994 to 2006 for allergic reactions to acrylic monomers in dental personnel 55 dentists, 192 dental nurses and 11 dental technicians Allergens provided by	Only those with allergic reaction (+/++/+++) to at least 1 acrylic monomer in the Methacrylate Series were analysed: 9 dentists, 15 dental nurses and 8 dental technicians HPMA was positive in	Aalto-Korte *et al.,* 2007

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		Chemotechnique, but several Trolab's preparations and in-house test substances have also been used. The composition of the series varied during the study period, and different test substances were tested on a different number of patients	23/32 (72%) patients having at least one positive reaction to acrylate Positive reactions also reported with other acrylates	
Retrospective study (1994-2006, Finland)	HPMA (2% in pet.)	Screen of patch test files at the FIOH from 1994 to 2006 for allergic reactions in the 'Methacrylate series': 473 patients The files of 10 patients presenting occupational exposure to acrylic glues were analysed	Patch test to HPMA: +/++/+++: 9/10 (90%) ?+: 0/10 Positive reactions also reported with other acrylates	Aalto-Korte *et al.,* 2008
Retrospective study (Spain)	HPMA	Patients diagnosed with allergic contact dermatitis due to acrylates used in sculpting artificial nails over the last 26 years in the Hospital General Universitario, Valencia 15 patients diagnosed (14 beauticians, 1 client), all women were patch tested with a standard battery of allergens and a battery of acrylates	HPMA: 5/15 **(33.3%)** positive patch tests Three patients - 2 beauticians and 1 client - presented allergic asthma due to acrylates	Roche, 2008 Article in Spanish, only abstract available
Retrospective study (1994-2009, Finland)	HPMA (2%)	Review of the patch test files for the years 1994–2009 at the FIOH for allergic reactions to acrylic monomers 66 patients with contact allergy to some acrylic monomers (meth)acrylate series with composition varying over the years	57/66 occupational cases (dental workers, glue-derived cases, artificial nail-derived cases) Number of patients reacting positively to HPMA: 42/66 (64%) Positive reactions also reported with other acrylates	Aalto-Korte *et al.,* 2010
Retrospective study (1993-2012, Netherlands)	HPMA (2% in pet.)	Patch test database was screened for positive reactions to (meth)acrylates between 1993 and 2012 151 were tested with the (meth)acrylate series	24/151 had positive reaction to at least one acrylate Only detailed results for these 24 cases provided in the publication. Positive reaction to HPMA in 11 patients **(7.3%)**	Christoffers *et al.,* 2012

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Retrospective study (1993-2010, Australia)	HPMA (2% in petrolatum)	Retrospective review of the clinical assessments including patch testing of hairdressers and trainee hairdressers attending an occupational dermatology clinic	6/164 **(2%)** patients reacted positive to HPMA	Lyons, 2013
Retrospective study (2006-2013, Portugal)	HPMA (2% in pet.)	Review of files of patients with suspected ACD caused by (meth)acrylates 2263 patch tested patients, 122 underwent aimed testing with an extended (meth)acrylate series (Chemothechnique) because of oral lesions related to dental prostheses, problems associated with orthopaedic prostheses, exposure to acrylic gel by nail beauty technicians or users, and occupational contact with dentistry products by dentists and dental prosthetics technicians	37/122 positive reactions to at least one (meth)acrylate. Most reacting to multiple (meth)acrylates Among the 37 patients: 29 (78.4%) with positive reactions to HPMA Total: **23.7%** positive (29/122) 67.6% occupational cases: beauty technicians working with artificial nails being the most affected group	Ramos *et al.,* 2014
Retrospective study (2004-2013; Germany)	HPMA (2%)	Data of all patients' patch tested between 2004 and 2013 in the IVDK (Information Network of Departments of Dermatology considered: 114440 consultations.	89 patients both worked as nail artists/cosmetologists and suspected nail cosmetics as the cause of dermatitis. Among these, 47.1% reacted to at least one (meth)acrylate Results with HPMA: Patients in whom nail care/ sculpturing material was considered to be causative and who worked either as nail artists or as cosmetologists: positive reactions in 26/75 **(34.7%)** patients Patients who worked as nail artists or cosmetologists, but in whom nail materials were not explicitly mentioned as culprit products: positive reactions in 16/70 patients **(22.8%)** Patients who worked	Uter *et al.,* 2015

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			neither as nail artists nor as cosmetologists, but in whom nail cosmetics/materials were documented as culprit product: positive reactions in 36/166 **(21.7%)** Remaining patients: positive reactions in 218/8112 patients **(2.7%)** Cross-reactivity between HPMA and other acrylates reported	
Retrospective study (2002-2015, UK)	HPMA (2% in pet.)	Patients with suspected contact allergy and allergic contact disease to (meth)acrylates who were patch tested Database of 6502 patients with 475 tested to an extended series of 28 (meth)acrylates (Chemotechnique)	Results positive in 52 cases (at least 1 positive reaction). Occupational sources in 24 patients HPMA: among these 52 cases, positive patch test in 29 patients (55.8%) Total: 29/475 positive **(6.1%)** Cross-reactivity between HPMA and other acrylates reported.	Spencer *et al.,* 2016
Retrospective study (2012-2014, Portugal)	HPMA (2% in vaseline)	Evaluation of the main occupations diagnosed as occupational ACD. 941 patch tested patients The European and GPEDC (Grupo Português de Estudo das Dermatites de Contacto) Portuguese baseline series was applied to all the patients as well as supplemental series of allergens based on patient's exposure or other data	169 positive patch tests related to occupational exposure Results with HPMA: among the 169 positive patch tests, positive reactions in 26/169 patients (15.4%) Number of patients tested with HPMA over the 941 patients not provided in the publication Positive reactions also reported with other acrylates Causes: nail aesthetics, dental prosthesis	Pestana *et al.,* 2016
Retrospective study (2012-2015, UK)	HPMA (2% in pet.)	241 consecutive patients patch tested with meth(acrylates) and	16 patients with positive patch test reaction. 8 with occupational	Muttardi *et al.,* 2016

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		cyanoacrylates	acrylate exposure Only detailed results for these 16 patients presented in the publication Among these patients, positive reactions to HPMA in 1 patient (6.25%) Number of patients tested with HPMA over the 241 patients not provided in the publication.	
Patch test data, selected patients	HPMA (2% in petrolatum) Chemotechnique Diagnostics (Vellinge, Sweden)	In 2015, 768 dermatitis patients (250 males and 518 females) were patch tested with the Swedish baseline patch test series (with acrylic acid and methacrylic acid temporarily included) because of suspected allergic contact dermatitis. Among the 768 patients patch tested with the baseline series, 50 patients were additionally tested with series containing acrylates/methacrylates (including HEMA and HPMA). Patch testing with acrylic acid and methacrylic acid did not result in any positive or irritant reactions in 768 dermatitis patients. 26 contact allergic reactions to acrylates/methacrylates were seen in 7/50 patients without any simultaneous reactions to acrylic acid and/or methacrylic acid	7/50 showed at least one positive reaction to acrylates/methacrylates. 5/50 patients which underwent aimed testing to a series of 10 methacrylates reacted positive to HPMA Only n=6 tested for HPMA with 5/6 showing positive patch test reactions (83.3%)	Bruze, 2017
Retrospective study (2011-2015, Portugal)	HPMA	Review of files of patients with ACD caused by (meth)acrylates related to nail cosmetic products. Total of 11639 patients. All patients were patch tested with the Portuguese and European baseline series and an extended series of 15–17 (meth)acrylates	Positive patch test to HPMA in 120/187 patients (64.1%)	Raposo *et al.*, 2017

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		230 cases of ACD caused by (meth)acrylates (187 tested with HPMA) Consumers (24.4%) or occupationally exposed (23.9%) or both (51.7%)		
Retrospective study (2013-2016, Spain)	HPMA (2% in pet.)	Review of files of patients with ACD caused by (meth)acrylates in long-lasting nail polish diagnosed in four dermatology departments 2353 patients were patch tested; 43 diagnosed with ACD caused by (meth)acrylates The (meth)acrylate allergens (AllergEaze® or Chemotechnique) 93% with occupational cause	Positive patch test for HPMA: 41/43 (95.3%) Number of patients tested with HPMA over the 2353 patients not provided in the publication	Gatica-Ortega *et al.,* 2017
Retrospective study (2001-2015, Germany)	HPMA (2% in pet.)	188 dental technicians with occupational contact dermatitis tested with HPMA DKG baseline series; 'dental technicians' and 'dental metals' series	Results for HPMA: 137: negative 11: ?+ (5.8%) 24 : + (12.8%) 16: ++ (8.5%) 0: +++ 0: irritant Total: **21.3%** positive	Heratizadeh *et al.,* 2018
Retrospective study (2013-2015, 9 European countries)	HPMA (2% in pet.)	11 European Environmental Contact Dermatitis Research Group (EECDRG) clinics collected information on cases of ACD caused by nail acrylates 18228 studied patients All patients had been patch tested with the European baseline series, and, prompted by their history, also with the acrylate series used in the respective centres 136 had ACD caused by nail acrylates	43.4% as consumers and 56.6% occupationally exposed. Results with HPMA: positive reactions in 99/119 patients (83.2%) 87.5% of the patients had two or more positive reactions to acrylates, mostly associated with HEMA and/or HPMA	Goncalo *et al.,* 2018

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Retrospective study (2007-2016, Sweden)	HPMA (2% in pet.)	Nail technicians investigated for dermatitis. In addition to the Swedish baseline series, the patients were tested with an acrylate series, the composition of which varied during the study period	Contact allergy in 16/28 patients. All classified as occupational and clinically relevant 9/16 (56%) positive to HPMA Total number of patients tested with HPMA not provided in the publication	Fisch *et al.*, 2019
Clinical study on selected patients	HPMA (Purity and concentration not reported)	12 patients (below 18 years old) with diabetes mellitus type 1 and presented a cutaneous reaction under their glucose sensor or insulin infusion set, suspected to be ACD. All patients were using Freestyle Libre	Patch test with HPMA was positive in 1/12 patients **(8.3%)**	Hermann, 2019
Retrospective study on selected patients (2008-1017; Spain)	HPMA (2% in petrolatum)	A retrospective study on patients suspected of nail manicure-related sensitisation to (meth)acrylates at dermatology departments of 3 hospitals. A total of 208 patients were tested with (meth)acrylates	66 patients reacted positively to at least one (meth)acrylate and the sensitisation was due to nail products. In this group, there was a positive reaction to HPMA in 58/208 patients (28%)	Marrero-Alemán *et al.*, 2019
Clinical study on selected patients	HPMA (2% in petrolatum)	Patients with a history of (meth)acrylate exposure, or who tested positive to 2-HEMA, were selectively tested with a short series of eight (meth)acrylate allergens. In total 5920 patients were consecutively patch tested with the baseline series (including HEMA), of whom 669 were then tested with the (meth)acrylate series. Strong bias by 2-step selection of patients. 94% of all patients with a positive reaction to (meth)acrylates were female	61 of the 669 **(9.1%)** selected patients tested to the short (meth)acrylate series tested positive to HPMA	Rolls *et al.*, 2019
Clinical study on selected patients (January – March 2018; Italy)	HPMA (2% in petrolatum)	Additional patch tests with (meth)acrylate series were performed in 30 patients positive to acrylic acid or 2-hydroxyethyl methacrylate or with a history of (meth)acrylate allergy. These patients	Positive reactions to HPMA were observed in 3/30 **(10%)** patients. In 2/3 patients cross-reaction was suspected	Hansel *et al.*, 2020

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		were selected during a prospective study on screening contact allergy to acrylic acid on 436 patch-tested patients in 3 patch test clinics.		
Clinical study on selected patients	HPMA (2% in pet)	A total of 15 patients with suspected ACD to FreeStyle Libre were patch tested with the Swedish baseline series and a new medical device series	None of the patients reacted positive to HPMA or any other methacrylate tested **(0%)**	Ulriksdotter, 2020
Clinical study on selected patients (Spain)	HPMA (2% in pet)	A series of 30 patients with contact dermatitis from glucose sensors were reported by eight participating centres	2/30 were tested positive for HPMA **(6.7%)** (one of them being a nail technician)	Gatica-Ortega (2021)
Retrospective study (2010-2019, Finland)	HPMA (2%)	426 patients were tested with at least one acrylate series: 395 with "Acrylate series A" (which included HPMA)	A total of 55 patients tested positive to some acrylic compound. Positive reaction to HPMA in 16 patients **(4%)**	Aalto-Korte, 2021

Classification criteria are provided in Part 3.4.2.2.2 of the CLP Guidance:

Substances are classified as Category 1 skin sensitisers where data are not sufficient for sub-categorisation in accordance with the following criteria:

a) *if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or*
b) *if there are positive results from an appropriate animal test (Annex I, Table 3.4.2 of the CLP Regulation).*

Substances are classified as Sub-category 1A skin sensitisers where there is evidence of a high frequency of occurrence in humans and/or a high potency in animals and the substance can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.

Such evidence includes:

Human data

- *positive responses at ≤ 500 µg/cm2 (HRIPT, HMT – induction threshold);*
- *diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;*
- *other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.*

Animal data

- *GPMT: ≥30% responding at ≤ 0.1% intradermal induction dose or ≥60% responding at >0.1% to ≤1% intradermal induction dose.*
- *Buehler assay: ≥ 15% responding at ≤ 0,2% topical induction dose or ≥ 60% responding at > 0.2% to ≤ 20% topical induction dose*
- *LLNA: EC3 value ≤ 2%*

Substances are classified as Sub-category 1B skin sensitisers where there is evidence of a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals and the substance can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered.

With respect to human data such evidence includes:

Human data

- *positive responses at > 500 µg/cm^2 (HRIPT, HMT – induction threshold);*
- *diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;*
- *other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.*

Animal data

- *GPMT: ≥ 30% to < 60% responding at > 0.1%to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose.*
- *Buehler assay: ≥ 15% to < 60% responding at > 0,2% to ≤ 20% topical induction dose or ≥ 15% responding at > 20% topical induction dose*
- *LLNA: EC3 value > 2%*