CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

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

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

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

Index Number: **NA**

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Version number: V2 **Date: September 2022**

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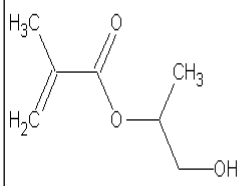
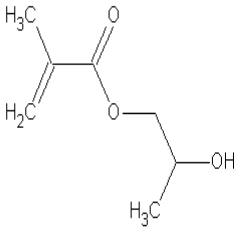
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Methacrylic acid, monoester with propane-1,2-diol
Other names (usual name, trade name, abbreviation)	Hydroxypropyl methacrylate
EC number (if available and appropriate)	248-666-3
EC name (if available and appropriate)	
CAS number (if available)	27813-02-1
Other identity code (if available)	
Molecular formula	$C_7H_{12}O_3$
Structural formula	Mixture of:  Minor compound  Major compound
Molecular weight or molecular weight range	144.1684 $g.mol^{-1}$
Degree of purity (%) (if relevant for the entry in Annex VI)	> 80%

During the Substance Evaluation under Reach Regulation, clarifications have been required by France to lead registrants regarding the identity and composition of the registered substance. The response was the following:

This is a recurrent problem caused by the changes in the way substances were described over time and differences in the way substances are described under different legal systems. I am copying text regarding the isomer composition dating back to the time of the Japanese OECD evaluation. It is still valid: (xx)... produces HPMA by addition of propylene oxide to methacrylic acid. This reaction produces a mixture of two isomers, the main isomer 2-Propenoic acid, 2-methyl-, 2-hydroxypropyl ester (CAS no. 923-26-2) which is present to approx. 70-80 % and the minor isomer, 2-Propenoic acid, 2-methyl-, 2-hydroxy-1-methylethyl ester (CAS no. 4664-49-7) which is present to approx. 20-30 %. Separation of the isomers is technically and economically not viable and has never been undertaken. All tests performed on behalf of our company have been performed with the commercial product (isomer mixture).

Prior to 1990, our company used the CAS no. 923-26-2 describing that product (the isomer mixture). In consequence, the other isomer (CAS no. 4664-49-7) was treated as a process-related impurity. At that point, the decision was taken that the CAS no. 27813-02-1 for the isomer mixture describes our product more appropriately. Since that time we use the CAS no. 27813-02-1 for HPMA.

To our knowledge, no other production process for HPMA is in use at present (or in the past) (note added: anywhere in the world). Hence, all HPMA batches in use commercially or for testing are expected to be very similar in isomer composition.

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**
Methacrylic acid, monoester with propane-1,2-diol [HPMA] EC n°248-666-3 CAS n°27813-02-1	> 80% w/w	None	Skin Sens.1 – H317 Skin Sens.1B – H317 Skin Irrit. 2 – H315 Eye Irrit. 2 – H319 STOT SE 3 – H335 Muta 2 – H341
Corresponding to a mixture of:			
2-Hydroxypropyl methacrylate *EC no.: 213-090-3* *CAS no.: 923-26-2*	*70-90% w/w*	*Skin Sens.1 – H317* *Skin Irrit. 2 – H315*	*Same as harmonised classification*
2-Hydroxy-1-methylethyl methacrylate *EC no.: 225-109-2* *CAS no.: 4664-49-7*	*10-30% w/w*	*None*	*None*

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

See confidential annex.

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

See confidential Annex.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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 harmonized classification										
Dossier submitters proposal	tbd	methacrylic acid, monoester with propane-1,2-diol [HPMA]	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 H335			
Resulting Annex VI entry if agreed by RAC and COM	tbd	methacrylic acid, monoester with propane-1,2-diol [HPMA]	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			

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not applicable (liquid)	-
Oxidising gases	Hazard class not applicable (liquid)	-
Gases under pressure	Hazard class not applicable (liquid)	-
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not applicable (liquid)	-
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not applicable (liquid)	-
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not applicable (liquid)	-
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Harmonised classification proposed: Eye Irrit 2 – H319	Yes
Respiratory sensitisation	Harmonised classification proposed: Resp. Sens. 1 – H334	Yes
Skin sensitisation	Harmonised classification proposed: Skin Sens. 1 – H317	Yes
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	Harmonised classification proposed: STOT SE – H335	Yes
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance has no harmonised classification.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

For Respiratory sensitisation: There is no requirement for justification that action is needed at Community level.

Justification that action is needed at Community level is required for Eye irritation, Skin sensitisation and STOT SE:

Differences in self-classification

- Eye irritation: 1198/1272 registrants notified the substance as Eye Irrit 2. No classification is notified by the others registrants.
- Skin Sens: 1204/1272 registrants notified the substance as Skin Sens. 1, 25/1272 as Skin Sens 1B. No classification is notified by the others registrants.
- STOT SE 3: 3/1272 registrants notified the substance as STOT SE 3 – H335. No classification is notified by the others registrants.

Further detail on need of action at Community level

According to the French conclusion document on Substance Evaluation for methacrylic acid, monoester with propane-1,2-diol [HPMA] (ANSES, 2021):
"Based on the available data assessed in this substance evaluation, the evaluating MSCA considers that HPMA should be classified according to CLP Regulation as: - Eye Irrit. 2 – H319: Causes serious eye irritation - STOT SE 3 – H335: May cause respiratory irritation - Skin Sens. 1 – H317: May cause an allergic skin reaction - Resp. Sens. 1 – H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled."

5 IDENTIFIED USES

According to ECHA website (2021), the substance is registered under REACH Regulation and is manufactured in and / or imported to the European Economic area at ≥ 10 000 to ≤ 100 000 tonnes per annum. HPMA is used in the following products: adhesive and sealants, polymers and cosmetics and personal care products.

Information on uses, as available in the disseminated registration dossier in December 2018 (Anses, 2021), is detailed in the table below.

Table 7: Summary of uses of HPMA (Anses, 2021)

USES	
	Use(s)
Uses as intermediate	Yes
Formulation	Formulation of products: - ERC 2, 3 - PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 10, 14, 15, 19, 28 - PC 1
Uses at industrial sites	Manufacture: - ERC 1, 4, 5, 6a, 6b, 6c, 6d, 7 - PROC 1, 2, 3, 4, 5, 6, 7, 8a, 8b, 9, 10, 11, 12, 13, 14, 15, 17, 18, 19, 21, 22, 23, 24 Industrial end-uses (as intermediate, as monomer or in formulations[1]):

[1] Some registrants distinguished intermediate/monomer use from formulation use, but some did not; therefore for the purpose of summarising the "uses at industrial sites", descriptors for industrial uses have been pooled.

	- ERC 1, 4, 5, 6a, 6b, 6c, 6d, 7 - PROC 1, 2, 3, 4, 5, 6, 7, 8a, 8b, 9, 10, 12, 13, 14, 15, 17, 18, 19, 21, 22, 23, 24, 28 - SU 0, 2a, 2b, 3, 5, 6a, 6b, 7, 8, 9, 12, 13, 14, 15, 16, 17, 18, 19, 20, 23 - PC 1, 15 - Substance supplied to that use as such and in a mixture
Uses by professional workers	Professional end use in formulations: - ERC 8a, 8b, 8c, 8d, 8e, 8f - PROC 2, 3, 4, 5, 6, 8a, 8b, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 23, 24 - SU 0, 7, 11, 12, 17, 19, 22, 23 - PC 1 - Substance supplied to that use as such and in a mixture Some registrants declared that the subsequent service life to this use is relevant.
Consumer Uses	Consumer end use in formulations: - ERC 8b, 8c, 8e, 8f, 10a, 11a - PC 1, 2, 3, 7, 8, 9a, 9b, 9c, 14, 15, 18, 19, 20, 21, 23, 24, 26, 29, 30, 31, 32, 33, 34, 35, 37, 39 - Substance supplied to that use in a mixture Some registrants declared that the subsequent service life to this use is relevant.
Article service life	Articles used by workers: - ERC 10a, 11a - AC 2, 7, 8, 10, 13 - PROC 21 Articles used by consumers: - ERC 10a, 11a - AC 1, 2, 3, 5, 6, 7, 8, 10, 11, 13
Uses advised against	Mixtures containing unreacted liquid monomer intended to come into contact with skin or nails - PC 0: Other: Applications where liquid monomer is intended to come into contact with skin or nails.

Indications from registrants suggest that the uses reported in the various registration dossiers may refer to the use of the monomer and/or the use of the polymers.

However, it has not been possible to distinguish for each use and for each registrant which scenario correspond to monomer and/or polymers (and/or even pre-polymers), to have a clear and reliable overview of the uses of HPMA.

6 DATA SOURCES

Data were obtained from registration dossier and from literature searches performed in September 2021. Key words used included: hpma, hydroxypropyl methacrylate, dermatitis, allergy, allergic, asthma, sensitisation, sensitization.

HPMA was subjected to Substance Evaluation under Reach Regulation. A conclusion document prepared by FR-MSCA is publicly available (ANSES, 2021).

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Physical state at 20°C and	Clear colorless liquid at	Röhm GmbH & Co.	Visual inspection, purity not

Property	Value	Reference	Comment (e.g. measured or estimated)
101,3 kPa	20 °C and 101.3 kPa	KG (2000) (Registration dossier, IUCLID 6)	given
Melting/freezing point	- 90 °C at 101.3 kPa	Rohm GmbH Analytical Services (2007) (Registration dossier, IUCLID 6)	Measured value (method OECD Guideline 102), 99.08% purity
Boiling point	209 °C at 1025 hPa	Rohm GmbH Analytical Services (2007) (Registration dossier, IUCLID 6)	Measured value (method OECD Guideline 103), 99.08% purity
Relative density	1.03 at 20 °C	Ullmann's Encyclopedia of Industrial Chemistry (1978) (Registration dossier, IUCLID 6)	Measured value (no method reported), purity not given
Vapour pressure	0.11 hPa at 20 °C	AQura GmbH (2006) (Registration dossier, IUCLID 6)	Measured value (method OECD Guideline 104), 99.05% purity
Surface tension	/	(Registration dossier, IUCLID 6)	Statement Based on the chemical structure of the substance no surface activity is predicted.
Water solubility	130 g/L at 25 °C	METI, Japan (1995) (Registration dossier, IUCLID 6)	Measured value (method OECD Guideline 105), purity not given
Partition coefficient n-octanol/water	Log Kow (Pow): 0.97 at 20 °C	Tanii, H.; Hashimoto, K. (1982) (Registration dossier, IUCLID 6)	Measured value (method OECD Guideline 107), purity not given
Flash point	111 °C at 1013 hPa	Ugilor (1971) (Registration dossier, IUCLID 6)	Measured value (method ASTM D92-52), purity not given
Flammability	Non flammable	(Registration dossier, IUCLID 6)	Statement Flash-point is higher than 60°C.
Explosive properties	Non explosive	(Registration dossier, IUCLID 6)	Statement There are no chemical groups associated with explosive properties present in the molecule.
Autoflammability / Self-ignition temperature	355 °C at 1020 hPa	AQura GmbH (2006) (Registration dossier, IUCLID 6)	Measured value (EU test method A.15), 98.86% purity
Oxidising properties	Non oxidizing	(Registration dossier, IUCLID 6)	Statement Based on the chemical structure

Property	Value	Reference	Comment (e.g. measured or estimated)
			the substance is incapable of reacting exothermically with combustible materials.
Viscosity	8.88 mm²/s (static) at 20 °C	Evonik Rohm GmbH (2008) (Registration dossier, IUCLID 6)	Measured value (method OECD Guideline 114), 98.1% purity

8 EVALUATION OF PHYSICAL HAZARDS

Methacrylic acid, monoester with propane-1,2-diol [HPMA] has no physical properties warranting classification under CLP.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 9: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
in vitro study (enzymatic hydrolysis assay) **Test material: HPMA** Identification and measurement of monomers and methacrylic acid were performed by high-pressure liquid chromatography.	HPMA was hydrolysed to methacrylic acid and 1, 2-propanediol by an unspecific esterase *in vitro.*	2 (reliable with restrictions) key study experimental result	Munksgaard *et al.* (1990)
In vivo pharmacokinetic study 2 male F344/DuCrl rats received HPMA via intravenous administration at the dose of 5 mg/kg bw. Blood samples were collected at 5, 10, 30, 60 and 180 minutes. **Test material: HPMA** No guideline, not GLP	HPMA was not quantifiable by 60 minutes ((LOQ) of 48.8 ng/mL) and the estimated half-life was less than or near 1 minute.	2 (reliable with restrictions) key study experimental result	Anonymous. 2017

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Following the REACH guidance document 7c, the physicochemical 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.

Based on its structure, HPMA is expected to be hydrolysed by esterases into methacrylic acid 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. The methacrylic acid is the main metabolite, the parent being almost completely metabolised.

In an *in vitro* enzymatic hydrolysis assay, HPMA was suspended with porcine liver esterase. The substance was hydrolysed to methacrylic acid 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 registration dossier, an *in vivo* pharmacokinetic study was performed in 2017. In this study, 2 male rats received HPMA 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 by 60 minutes and the estimated half-life was less than or near 1 minute (Anonymous. 2017).

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).

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity

Not assessed in this dossier.

10.2 Skin corrosion/irritation

HPMA was not found to be irritating to the skin of rabbits (mean primary dermal irritation index = 0 at 24 and 72h) (Anonymous. 1977).

This endpoint was not assessed in regards to CLP criteria; data are only presented in this dossier in the light of classification proposal for eye irritation and skin sensitisation.

10.3 Serious eye damage/eye irritation

Table 10: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results** **- Observations and time point of onset** **- Mean scores/animal** **- Reversibility**	**Reference**
In vivo eye irritation study Draize method GLP: no	Rabbit New Zealand White 6 animals (no information on sex)	HPMA	0.1 mL undiluted substance No washing	Observation at 24, 48, 72 hours and 4, 5, 7 days Mean scores (24, 48, 72h): Cornea opacity = 0.8 (1, 1, 1, 1, 0, 1) Iritis = 0 (0, 0, 0, 0, 0, 0) Conjunctival redness = 1 (1.3, 2, 1, 1, 0.3, 1) Conjunctiva chemosis = 0.1 (0, 0, 0, 0.3, 0, 0.3) Reversibility on day 4.	Anonymous, 1978

10.3.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

Based on a study in rabbits exposed to HPMA undiluted (Anonymous. 1978), the mean scores for the 6 animals (24, 48, 42 hours) are 0.8 for cornea opacity (5 animals with a score of 1; 1 with a score of 0); 0 for iris; 1 for conjunctiva redness (1.3, 2, 1, 1, 0.3, 1); 0.1 for conjunctiva chemosis (0, 0, 0, 0.3, 0, 0.3). The effects were reversible on day 4.

The fact that HPMA degrades into methacrylic acid which has an harmonised classification as Skin Corr. 1A supports the irritative properties of HPMA, due to the effect of the parent molecule and/or its metabolites when they are in contact with eye.

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.

10.3.2 Comparison with the CLP criteria

According to 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 based on the Draize test in rabbits.

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.

Even if the threshold scores are not reached when considering all the 6 animals, there are at least 4 out of 6 animals with corneal opacity = 1 (5 observed/6 animals tested). Therefore, criteria for classification as Eye. Irrit. 2 are fulfilled.

10.3.3 Conclusion on classification and labelling for serious eye damage/eye irritation

HPMA should be classified as Eye Irrit. 2 – H319 according to CLP Regulation.

10.4 Respiratory sensitisation

Table 11: Summary table of human data on respiratory sensitisation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Case report	Methacrylates, including HPMA	1 case report in Finland. Occupational exposure Spirometry, histamine challenge test, skin prick tests, patch tests, inhalation challenge tests, measurement of IgE.	47 year-old female dentist with symptoms of asthma, rhinoconjunctivitis and allergic contact dermatitis Spirometry normal and no significant response in the bronchodilatation test. Histamine challenge test showed moderate bronchial hyperreactivity. Total serum IgE and eosinophils in the peripheral blood were normal. Negative skin prick tests for different substances, including acrylates (but not HPMA). Inhalation challenge tests with the placebo (negative) and with dental liquid methacrylates (cough, rhinoconjunctivitis and decrease in FEV1). Simulating challenge test with the products	Lindstrom *et al.,* 2002

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			(containing methacrylates) used by the dentist in her work: reduction of FEV1 and dyspnea. Patch test positive to various acrylates, including HPMA at 2% in petroleum (++) Case of occupational asthma, rhinoconjunctivitis and allergic contact dermatitis caused by dental acrylate compounds.	
Case report	Methacrylates, including HPMA	2 case reports in Finland (FIOH) Occupational exposure Sculptured nails. Spirometry, histamine challenge test, measurement of exhaled nitric oxide, peak expiratory flow (PEF) measurements at home and at the workplace, skin prick tests (SPT) (only for patient 1 with different substances but not with HPMA), bronchial provocation tests, lung function measurements, clinical symptoms and lung auscultation. In addition, only for patient 2: acetone-soluble acrylates and methacrylates in gel nail materials and in gel nails were identified by gas chromatography-mass spectrometry (GC-MS) and quantified by liquid chromatography with ultraviolet (UV) detection at 210 nm	**Patient 1**: 30-year-old female who had worked for 6 years as a manicurist and a nail technician. Her main job was to apply sculptured nails and artificial tips to nails. Diagnosis of allergic contact dermatitis (ACD) with positive patch test with HEMA and EGDMA. Rhinitis, wheezing, dyspnea. At FIOH: SPT negative. X-rays of the thorax and nasal sinuses normal. Spirometry showed mild peripheral obstruction without bronchodilatation effect. Exhaled NO normal. Mild bronchial hyperresponsiveness. Significant variation of PEF measurements at home and at workplace (from 360 to 580 L/min with a maximal diurnal variation of 26% and frequent bronchodilating effects up to 43%). Dual asthmatic reaction in the active bronchial challenge test. Diagnosis of occupational asthma due to methacrylates. **Patient 2**: 27-year-old woman who had worked for 5 years both as a hairdresser and as a nail technician preparing artificial gel nails. Allergy to animal epithelia and to common pollens. Rhinitis, loss of voice and recurrent sinusitis. At FIOH: Moderate bronchial hyperresponsiveness and exhaled NO value increased. Diagnosis of occupational asthma due to methacrylates. In the workplace PEF follow-up, there were no significant diurnal variations, but the patient did not prepare nails during the follow-up. Dual asthmatic reaction in the active bronchial challenge test. 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. The main methacrylate was HEMA (8%) in the bonding agent and BIS-GMA (42%) in the sculpture resin. The sculpture resin also contained 7% of HPMA. The identification of the main methacrylates in the sealing resin could not be confirmed. Hardened gel nails contained no detectable amounts of HEMA or aliphatic dimethacrylates.	Sauni *et al*., 2008
Case report	Methacrylates, including HPMA	1 case report in Italy A 38-year-old woman, who was working as a nail art operator, came to observation because of facial dermatitis and multiple episodes of asthma that occurred in the previous two months. Nail art	Case of a nail art operator who developed occupational allergy to acrylates, manifested by simultaneous presence of asthma and dermatitis: Mild airflow obstruction and mild bronchial hyperresponsiveness. Patch test positive to acrylates including HPMA (2% in pet.) 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	Vaccaro *et al.,* 2014

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		Occupational exposure Spirometry, bronchial provocation test and reversibility test	composition	

10.4.1 Short summary and overall relevance of the provided information on respiratory sensitisation

Non human data

Some animal and non-animal test methods for the identification of respiratory sensitisers have been described in the literature, but these are not formely accepted yet.

Theorically, the mechanistic pathway of respiratory sensitisation includes four molecular key events, the first one being the covalent binding to proteins to form haptens (AOP39 under development). This molecular event is shared in principle with skin sensitisers. HPMA being a skin sensitiser (see below section 10.5), it can also have, in principle, the intrinsic potential to induce respiratory sensitisation.

- **QSAR modelisation**

In 2014, following a request by France (in the framework of Substance evaluation process under Reach Regulation), the RIVM (Rijksinstituut voor Volksgezondheid en Milieu) has run different SAR models (Derek, Jarvis, CatSAR, Enoch, MultiCase) with different acrylates including HPMA. Enoch, MultiCase and Jarvis gave positive results for respiratory sensitisation whereas HPMA was negative according to Derek and CatSAR. According to the RIVM, Derek gave the most reliable prediction of a substance being a respiratory sensitiser and MultiCase the most reliable prediction for respiratory non-sensitisation. Therefore, considering the profile of HPMA obtained with these two models, no reliable conclusion can be reached for the potential respiratory sensitisation properties of HPMA based on these SAR models.

DK QSAR Toolbox was run in January 2019 and pointed rather to a negative potential for respiratory sensitisation. The results are presented in the table below:

Table 12: DK QSAR Toolbox: endpoint related to respiratory sensitisation in humans

	Battery	CASE Ultra	Leadscope	SciQSAR
Respiratory Sensitisation in Humans	NEG_IN	POS_OUT	NEG_IN	NEG_IN

Finally, dossier submitter runs the OECD QSAR Toolbox in July 2021 (profiler: respiratory sensitisation v1.1): structural alert for respiratory sensitisation was noted. A Michael addition mechanism has been suggested to be responsible for the ability of these types of chemicals to react with proteins in the lung. However, the dataset from which the profiler was developed contained a single chemical containing this alert, which has been reported as being a respiratory sensitiser in humans.

Nevertheless, as mentioned in the Reach guidance R. 7 3.9.2, the SAR models are known to not be predictive for this endpoint since there is no assay available to assess this type of effects. Therefore, it is difficult to identify a substance as respiratory sensitiser based on such data.

- **Experimental data**

Only one study of low quality is available by inhalation for HPMA (Gage, 1970). No adverse effect was found in rats exposed to an atmosphere saturated with HPMA (no further specification) at 0.5 mg/L for 3 weeks. This study was judged not reliable because there is no information on an analytical verification of the concentration tested, only one concentration was tested and the level of details was very limited (ANSES, 2021).

Human data

- Case reports of asthma

Only few number of publications related to cases of occupational asthma and where HPMA is cited are available (Lindstrom, 2022; Sauni, 2008, Vaccaro, 2014). In general, HPMA cannot be clearly identified as the causative agent. Indeed, in the publications below, provocations were not performed with HPMA alone. Instead, the patients were tested with products containing various methacrylates (and possibly methacrylates as contaminants or impurities not declared in the safety datasheet).

Lindstrom *et al.* (Lindstrom, 2002) reported the case of occupational asthma and rhinoconjunctivitis in a dentist. Spirometry was normal and there was no significant response in the bronchodilatation test. The histamine challenge test showed moderate bronchial hyper-reactivity (15% reduction in the forced expiratory volume in 1 second (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. Inhalation challenge tests with a placebo (Coca solution) and dental liquid methacrylates were performed in a 6 m^3 challenge chamber according to international guidelines. The products used by the dentist in her work were used in the work simulating challenge tests (Scotchbond primer containing 40% of HEMA and adhesive containing 62% of BIS-GMA and HEMA 37%). The placebo (Coca solution) challenge test was negative. In the first inhalation challenge test with methacrylates, the adhesive induced cough, rhinoconjunctivitis and a 10% decrease in FEV1 after 45 min. In the second test, with both the adhesive and the primer, an "early late"[2] 23% FEV1 reduction was recorded, at a maximum at 3 hours, as well as increased symptoms with dyspnea. Patch test was positive for several methacrylates, including HPMA. In addition, patch testing induced 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. Concerning the identification of the causal agent for asthma, it is noted that 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. The positive patch-test reaction with HPMA can represent cross reactivity, although concomitant sensitisation may also occur. Indeed, 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 safety datasheet). 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.

Sauni *et al.* (Sauni, 2008) reported two cases of occupational asthma caused by sculptured nails containing methacrylates in Finland. Patient 1 was a 30-year-old female who had worked for 6 years as a manicurist and a nail technician. Her main job was to apply sculptured nails and artificial tips to nails. The patient 2 was a 27-year-old woman who had worked for 5 years both as a hairdresser and as a nail technician preparing artificial gel nails. Both developed respiratory symptoms, including rhinitis, sinusitis, dyspnea. 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. Bronchial provocation tests were performed in an 8 m^3 chamber with their own products (they attached the plastic nail with a glue and then filed and sculptured the nails). A portable, pocketsize spirometer recorded the lung function measurements (FEV1, PEF); a drop of 20% in PEF or FEV1 was regarded as significant. 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 causing a

[2] There is no definition of this term in the publication.

similar decrease in FEV1 or PEF after the first post-challenge hour; and a dual reaction as a combination of the afore-mentioned. For both patients, mild / moderate bronchial hyperresponsiveness 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. Occupational asthma due to exposure to sculptured nails containing methacrylates was diagnosed in both patients. 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. Several methacrylates were identified in the gel nail materials, with HPMA present at 7% in the sculpture resin, HEMA (8%) in the bonding agent and BIS-GMA (42%) in the sculpture resin. The identification of the main methacrylates in the sealing resin could not be confirmed. To ascertain what exact component is causing the asthmatic reactions, provocations with all individual substances contained in the products ought to be undertaken. This was not done here.

Vaccaro *et al.* (Vaccaro, 2014) reported a case of a 38-year-old woman, who was working as a nail art operator since she was 36, and presented facial dermatitis and multiple episodes of asthma that occurred in the previous 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 showed 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 ERS/ ATS, showed a 14% increase of FEV1 15 min after administration of a short acting beta agonist (salbutamol). The results of patch test were positive to methacrylates, including HPMA. 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 respiratory reactions observed can neither be claimed nor excluded. Authors diagnosed airborne ACD (allergic contact dermatitis) and asthma caused by acrylates.

- Case reports of other hypersensitivity reactions

According to CLP guidance document: "*hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered*".

One case of allergic conjunctivitis, associated with occupational asthma, is reported by Linstrom *et al.* (Linstrom, 2002). Description of the case is detailed above.

- National occupational disease databases

In France, the national network for the monitoring and prevention of occupational diseases (RNV3P) created in 2001, collects every year more than 8000 new occupational health reports throughout France. The French RNV3P network is composed of the 30 Occupational disease consultation centres (CCPP) in mainland France and a number of occupational health services (SSTs) associated with the network. The goal of this network is to record the data from consultations in a national database (patient demographics data, diseases, exposures, job sectors and professions). From this database, several cases of asthma were reported with (meth)acrylates but none has been specifically related to HPMA. These cases were mainly observed in dental professionals and nail technicians. For example, a retrospective study based on data obtained between 2001-2018 by the RNV3P network reported 169 cases of occupational asthma related to exposure to (meth)acrylates among the 8385 cases identified (corresponding to 2%) (Robin *et al.,* 2022).

Different European countries were contacted by the dossier submitter in February 2021 in order to obtain additional human cases related to respiratory sensitisation after HPMA exposure.

In UK, there has been one case of work-related respiratory sensitisation attributed to HPMA reported by the chest physicians to SWORD (Surveillance of Work-Related and Occupational Respiratory Disease) between 1989 and 2020. Details are provided in the table below.

Table 13: Case of work-related respiratory sensitisation reported to SWORD between 1989-2020 (UK)

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

In Finland, cases from the FIOH (Finnish Institute of Occupational Health), for which HEMA (hydroxyethyl methacrylate) and/or HPMA was concluded to be the main causative agent of asthma, were extracted. During the 2000's, FIOH have performed specific inhalation challenges (SIC[3]) with products containing HEMA and/or HPMA to approximately 150 patients with suspicion of occupational asthma and/or rhinitis. Altogether, there were three patients with occupational asthma verified with positive SICs to HPMA containing products at FIOH during 2000-2018. Based on the exposure data, FIOH believes that these patients had respiratory exposure predominantly to HPMA at work, and they were mainly exposed to HPMA also in the SIC. As all of the products contained other methacrylates in addition to HPMA, their effects cannot be excluded. However, as the other methacrylates listed in the SDS's (safety datasheet) were poorly volatile, FIOH believes that they had a minor role in the patients' respiratory exposure and occupational asthma.

Table 14: Cases 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[4] 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 in the products at work (SIC material in bold)	**LCN Sculpture** - gel nail material contained 6.7 % HPMA in chemical analysis; **LCN Bonder** contained 7.5% HPMA in chemical analysis; SDS of **LCN (probably Sealant)**: HEMA 15-20%, polyether polyol tetraacrylate 20-25%, HPMA 5-10%	**Loctite 620:** HPMA 1-<5%, polyethylene glycol methacrylate (unknown CAS and amount)	**Loctite 603:** "PEGDMA-based methacrylates", total 45-80 % of which 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	yes	no	yes

[3] The SIC aims to recreate an exposure comparable to the patients' work

[4] Volatile organic compound

by at least one positive skin test to a battery of local common aeroallergens			
Prick test	not performed	negative	negative
Monitoring PEF (peak expiratory flow) 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

Data with methacrylates (HPMA not specifically identified or with methacrytates other than HPMA):

Several cases of respiratory sensitisation related to (meth)acrylates exposure are reported in the literature (e.g. Savonius, 1993 [case reports]; Piirila, 2002 [retrospective study]; Lindstrom, 2002 [case reports]; Jaakkola, 2007 [cross-sectional study]; Walters, 2017 [retrospective review]; Suojalehto, 2020 [retrospective study]). Some of them are further summarised:

Piirila *et al.* (2002) studied the causes of respiratory hypersensitivity in dental personnel based on the statistics of the Finnish Register of Occupational Diseases (FROD; 1975–1998) and the patient material of the Finnish Institute of Occupational Health (FIOH; 1990–1998). Twenty-eight cases were related to occupational asthma, including 18 caused by methacrylates. Twenty-eight cases were related to allergic rhinitis, including 6 caused by methacrylates.

A cross-sectional study of 799 female dental assistants from the membership register of the Finnish Association of Dental Hygienists and Assistants was conducted by Jaakkola *et al.* (2007). The use of (meth)acrylates was assessed by questionnaire. Asthma was defined based on affirmative answers to questions: “have you ever had asthma?” and “was it diagnosed by a physician?”. The authors concluded that daily use of methacrylates was related to a significantly increased risk of adult-onset asthma (adjusted OR 2.65, 95% CI 1.14-7.24).

Walters *et al.* performed in 2017 a retrospective review of all cases reported to the SHIELD surveillance scheme for occupation asthma in UK between 1989 and 2014. Twenty patients with occupation asthma caused by sensitisation to acrylic compounds were diagnosed among 1790 total cases of occupational asthma (1%). Occupational asthma was confirmed by OASYS (Occupational Asthma SYStem) analysis of serial PEF measurements in all 20 patients, with positive SIC tests to methyl methacrylate or acrylic co-polymer in 3 patients.

Suojalehto *et al.* (2020) performed a retrospective observational study including subjects with acrylate-induced occupational asthma who were mostly recruited between January 2006 and December 2015 from 20 tertiary centers participating in the European network for the Phenotyping of Occupational Asthma (E-PHOCAS). For 55 subjects, acrylates were clearly linked with occupational asthma using SIC procedure (26 subjects for methacrylates, specifically). A placebo control challenge was also included, using materials without acrylate ingredients, such as glues without acrylates, organic solvents or saline. Skin prick tests with the causal acrylate compounds were performed in 22 subjects and were negative in all cases. In addition, lung function was assessed and markers of airway inflammation included. The authors concluded that: *Work-related rhinitis was more frequent in acrylate-induced than isocyanate-induced occupational asthma and the increase in post-challenge fractional exhaled nitric oxide was greater than in occupational asthma induced*

by other low-molecular-weight agents or isocyanates. In the publication, the identity of the methacrylates responsible of the asthma is not specified. No specific data related to HEMA is described in the publication. However, when contacted, the authors declared that the cases extracted from the FIOH (see above) are included in Suojalehto *et al.* analysis.

Consistent with this, methyl methacrylate (MMA) has been recently classified by the RAC as Resp. Sens. (RAC, 2021). This conclusion has been principally reached based on the results issued from Suojalehto *et al*. (2020). Due to rapid hydrolysis, it is considered that the respiratory sensitising properties of MMA **can be attributed to methacrylic acid formed as a metabolite**. This could be explained as the reactive acrylate group is maintained upon hydrolysis of MMA to methacrylic acid. Consequently, **respiratory sensitisation is suspected for potentially all methacrylates that have this hydrolysis product/metabolite in common. This suspicion is particularly high for those substances that hydrolyse quickly, are of low molecular weight and which are volatile.**

Available data indicate that HPMA is quickly hydrolysed by esterases to methacrylic acid and propylene glycol. The estimated half-life of HPMA was less than or near 1 minute from an *in vivo* pharmacokinetic study in male rats receiving the substance via intravenous administration at the dose of 5 mg/kg bw (Anonymous, 2017). For comparison, *in vitro* half-life of MMA in human blood is 10 to 40 minutes (Anses, 2019).

The metabolic pathway is likely to occur in humans. Indeed, the carboxylesterases are a group of non-specific enzymes that are widely distributed throughout the body and are known to show high activity within many tissues and organs, including the liver, blood, GI tract, nasal epithelium and skin. Those organs and tissues that play an important role and/or contribute substantially to the primary metabolism of the short-chain, volatile, alkylmethacrylate esters are the tissues at the primary point of exposure, namely the nasal epithelia and the skin, and systemically, the liver and blood (Anses, 2019).

Molecular weight of HPMA is 144 g.mol^{-1} and its vapour pressure, 11 Pa. Therefore, the same property as MMA of respiratory sensitisation is expected for HPMA.

The mechanism of respiratory sensitivity by methacrylates is still unclear.

The mechanism of respiratory hypersensitivity by methacrylates remains unclear.

It is generally recognised that the asthmatic reactions induced by methacrylates are probably not mediated by an IgE dependent mechanism. According to Sauni *et al.* (2008), the late or dual asthmatic reactions reported in dental personnel exposed methacrylates, refer usually, but not necessary to reactions other than hypersensitivity type I. Moreover, there is currently no evidence of an increase of IgE or of positive prick tests with these substances (Piirila, 1998; Lindstrom, 2002). This is consistent with the assumption that small molecules with a low molecular weight are not acting via this type of mechanism. However, Suojalehto *et al.* (2020) showed that acrylate-induced occupational asthma has phenotypic characteristics suggesting that acrylates may induce occupational asthma through different immunological mechanisms than other low molecular weight agents. Overall, type I hypersensitivity cannot be entirely excluded in susceptible individuals (Walters, 2017).

According to Torres *et al.* (2005), a type IV mechanism have been suggested based on the results of patch tests performed in patients with contact dermatitis (Eslander, 1996) and a case of rhinoconjunctivitis and asthma (Lindstrom, 2002).

Conclusion

Three publications and FIOH data describe cases of patients who developed asthma and/or other types of hypersensitivity (i.e conjunctivitis) from occupational exposure to methacrylates and where HPMA can be the causative agent. Conclusion on the causal relationship between these symptoms and HPMA specifically is somewhat difficult to reach since these patients are exposed to various methacrylates.

No immunological test is available to robustly demonstrate respiratory sensitisation caused by the substance itself even if this type of test is not a re-requisite according to CLP provisions. In contrast, the intrinsic skin

sensitising property of the molecule is clearly established in humans (see section 10.5 below). Thus, HPMA can also have the intrinsic potential to induce respiratory sensitisation. HPMA has a low molecular weight and is volatile, this supports the fact that the substance is able to reach the respiratory tract where it can cause hypersensitivity.

The relatively low number of HPMA related occupational asthma cases reported in the scientific literature or in occupational disease databases should not be seen as evidence of low prevalence. As currently none of the acrylates have harmonised classification for respiratory sensitisation (classification of MMA not yet implemented in CLP Regulation), most occupational physicians are unlikely to suspect the acrylates or more specifically HPMA as a causative agent in a patient's asthma. Therefore, it is possible that HPMA occupational asthma cases are underdiagnosed and are therefore also under-reported. On the other hand, it is known that methacrylates cross-react, and that acrylates are often used as mixtures. In such cases, it can be difficult to establish in clinical studies, which compound specifically had induced the sensitisation, or whether it was due to mixed exposure.

Several publications identified (meth)acrylates as related to an occurrence of asthma in humans. In particular, methyl methacrylate (MMA) has been recently classified as Resp. Sens. 1 by the RAC (2020). Due to rapid hydrolysis, it is considered that the respiratory sensitising properties of MMA can be attributed to methacrylic acid formed as a metabolite. Consequently, respiratory sensitisation is suspected for potentially all methacrylates that have this hydrolysis product/metabolite in common. Since HPMA also rapidly breaks down into methacrylic acid, the substance is expected to have respiratory sensitising properties.

Overall, taken 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, HPMA should be considered as a respiratory sensitiser.

10.4.2 Comparison with the CLP criteria

According to CLP, "*Substances shall be classified as respiratory sensitisers (Category 1) 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 specific respiratory hypersensitivity; and /or

Three publications and FIOH data describe cases of patients who developed asthma and/or other types of hypersensitivity (i.e conjunctivitis) from occupational exposure to methacrylates and where HPMA can be the causative agent. The fact that HPMA can induce asthma is strongly supported by:

- human data with methacrylates in general, and in particular with MMA which has been classified as Resp. Sens. 1 by the RAC;
- metabolic pathway: HPMA is hydrolysed rapidly into methacrylic acid and propylene glycol;
- physicochemical properties: molecular weight of 144.1684 g.mol^{-1} and vapour pressure of 11 Pa.

(b) if there are positive results from an appropriate animal test".

There is no appropriate animal test with HPMA to conclude on respiratory sensitisation.

Are data sufficient for subcategorization?

- *Subcategory 1A: Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered.*

- *Substance 1B: Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered.*

Human data do not allow proposing a subcategory since there is no adequate information on the level of exposure mentioned in the case reports and the frequency of this pathology.

10.4.3 Conclusion on classification and labelling for respiratory sensitisation

HPMA should be classified as Resp. Sens. 1 – H334 according to CLP Regulation.

10.5 Skin sensitisation

Table 15: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Maguire method derived from the Split adjuvant technique GLP not specified	Guinea pigs males 7/group	HPMA Purity unknown	Topical application of 0.1 mL of test substance 4 times in 10 days. At the time of the third application, 0.2 ml of Freund's adjuvant was injected intradermally at one point adjacent to the insult site. After a 2-week rest period, the guinea pigs were challenged with the test material on one flank and a solvent (if used) on the other flank. The challenge site was evaluated for erythema and/or oedema at 24 and 48 hours. Diglycidyl ether of 2,2-di-(p,p'-hydroxyphenyl)propane as a positive control	**Negative** 0% positive reactions Positive control: at least 70% sensitised guinea pigs	Rao *et al.* 1981
Maximisation assay No GLP	Guinea pigs; sex not given 10/group	HPMA Purity > 95%	Intradermal concentration: 5% in mixture of olive oil and acetone (10:1) Topical induction: 25% in petrolatum after pretreatment with SLS Challenge concentration: 2% in petrolatum No indication of positive control to validate the study	**Negative** 1/10 (10%) animal reacted to HPMA	Bjorkner, 1984
Maximisation assay GLP non specified	Outbred Guinea pig, SSc:AL Females; 12 animals	HPMA Purity unknown	Intradermal concentration: 10% Topical induction: 100% Challenge concentration: 25% No indication of positive control to validate the study	**Negative** 25% positive reactions	Clemmensen *et al.,* 1984
LLNA Interlaboratory study – validation study GLP non specified	Mice CBA/Ca Females, 4/group	HPMA Purity unknown	5.0, 10.0, 25.0, 50.0% 3 consecutive days; study terminated on day 5 Vehicle: acetone olive oil (AOO) or dimethylformamide (DMF) Positive control: not specified	**Negative** SI (T/C ratio): <u>for 5, 10, 25% conc:</u> (HPMA in AOO) Lab A: 1.1, 1.2, 1.3 <u>for 10, 25, 50% conc.:</u> (HPMA in AOO) Lab. B: 0.8, 1.0, 0.9 Lab. C: 1.0, 1.9, 0.8 (HPMA in DMF) Lab. D: 1.4, 0.7, 0.9	Scholes *et al.,* 1992
Maximisation assay GLP non specified	Dunkin Hartley guinea pigs	HPMA Purity unknown	Intradermal concentration: 1% Topical induction: 100%	**Negative** 0% positive reactions	

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
	N=10 for treated groups and N=4 for vehicle group		Challenge concentration: 10% Positive control: not specified		
LLNA Comparison study LLNA/Maximisation assay GLP non specified	Mice CBA/Ca Females, 4/group	HPMA Purity unknown	10.0, 25.0, 50.0% 3 consecutive days; study Vehicle: acetone olive oil (AOO)	**Negative** SI (T/C ratio): 1.1, 1.2, 1.3	Basketter *et al.*, 1992
Maximisation assay Comparison study LLNA/Maximisation assay GLP non specified	Dunkin Hartley guinea pigs Sex not given N=10 for treated groups	HPMA Purity unknown	Intradermal concentration: 1% Topical induction: 100% Challenge concentration: 100%	**Negative** 0% positive reactions	

Table 16: Summary table of human data on skin sensitisation

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 allergic contact dermatitis (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 year-old) with	Patch test positive to HPMA in the 2	Kanerva *et al.*,

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		ACD 2 dental nurses tested with HPMA. Occupational exposure	patients tested. Patient 1: +++ Patient 2: +++	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 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	HPMA: ++ on days 2 and 3 and +++ on day 4. Positive reactions also reported with other acrylates.	Kanerva *et al.,* 1992
Case report	HPMA (1% w/w in pet.)	4 patients (23-32 year-old) 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 year-old) with eczema on the sites where TENS electrodes were applied General population	Patient number 1 not tested with HPMA Patient number 2 positive to HPMA: +/- at 48 h and + at 96 h readings.	Weber-Muller *et al.,* 2004

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			Positive reactions also reported with other acrylates.	
Case report	HPMA	4 women (26-41 year old) 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 year-old): two with periungual eczema and one with face and eyelid dermatitis after contact to acrylates in artificial 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
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	Le *et al.,* 2015

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			(Australia): 57 positive to acrylates with 14 being beauticians and 9/14 positive to HPMA	
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 year-old) and 3 men (28-41 year-old) 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 year-old, with ACD; nail technicians Occupational exposure	All patients reacted to HPMA: + Positive reactions also reported with other acrylates.	DeKoven *et al.,* 2017
Case report	HPMA (2% in pet.)	Patch tests for 4 consumers (females; 35-65 year-old) 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				

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Clinical study on selected patients (1982-1986; Finland) 22 patients tested between 1982-1985 24 patients tested between 1985-1986	HPMA (1 % w/w in pet.) between 1982-1985 HPMA (2% w/w in pet.) between 1985-1986	Routine patch testing with (meth)acrylate series Practically every patient with contact dermatitis was tested at least with the European standard series. Acrylate series were tested in cases where contact allergy to acrylates was suspected.	Observation 1982-1985: 4/22 patients had an allergic occupational contact dermatitis from acrylate: 3/4 positive to HPMA → total frequency: **16%** Positive reactions also reported with other acrylates. Observation 1985-1986: 3/24 patients with active (iatrogenic) sensitisation: 1 positive to HPMA 3/24 with allergic contact dermatitis: 2 positive to HPMA → total frequency: **8.3%** Positive reactions also reported with other acrylates. Publication focusing on sensitisation to patch test acrylate.	Kanerva *et al.,* 1988
Clinical study on selected patients (1974-1988, Finland) Occupational study	HPMA (1% in pet.): 1982-1985 HPMA (2% in pet.) since Sept. 1985	1,622 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. 7 patients diagnosed as having allergic eczema caused by acrylates to which they were exposed in dental restoration work → 3/7 positive to HPMA. 4 patients diagnosed as having allergic eczema due to acrylic compounds developed in exposure other than dental work → 2/4 positive to HPMA. Positive reactions also reported with other acrylates.	Eslander, 1990
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
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
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 those already reported by Kanerva *et al.* 1995b) 1991-195: 14/118 **(11.9%)** Positive reactions also reported with other acrylates.	Kanerva *et al.,* 1997

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
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 reactions 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 (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 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)	Teik-Jin 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 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.	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 23/32 (72%) patients having at least one positive reaction to acrylate. Positive reactions also reported with other acrylates.	Aalto-Korte *et al.,* 2007
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.	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

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		15 patients diagnosed (14 beauticians, 1 client), all women were patch tested with a standard battery of allergens and a battery of acrylates		
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
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: 114 440 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 neither as nail artists nor as cosmetologists, but in whom nail cosmetics/materials were	Uter *et al.,* 2015

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			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 cyanoacrylates	16 patients with positive patch test reaction. 8 with occupational 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.	Muttardi *et al.,* 2016
Retrospective study (2011-2015, Portugal)	HPMA	Review of files of patients with ACD caused by (meth)acrylates related to nail cosmetic products. Total of 11 639 patients. All patients were patch tested with the Portuguese and European baseline series and an extended series of 15–17 (meth)acrylates 230 cases of ACD caused by (meth)acrylates (187 tested with HPMA)	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
		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. 18 228 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
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
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

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)

10.5.1 Short summary and overall relevance of the provided information on skin sensitisation

Experimental studies

HPMA has been evaluated, among other various chemicals, for skin sensitisation potential in LLNA and/or maximisation assays (Clemmensen, 1984; Bjorkner, 1984; Scholes, 1992 [validation studies]; Basketter, 1992 [comparison studies]). In these studies, none or few animals only (< 30%) were sensitised. Negative result was also obtained in an experimental system derived from a split adjuvant method (Rao, 1981). However, it is generally not reported in the publications if a positive control had been included to validate the system.

In contrast, cross-reactions were reported by Clemmensen *et al.* (Clemmensen *et al.*, 1984) in maximisation assays, in particular, when animals were induced with HEMA (2-hydroxyethylmethacrylate) or HEA (2-hydroxyethylacrylate) and challenged with 25% HPMA (5/15 and 8/12 animals sensitised, respectively). Similar observations were reported by Rustemeyer *et al.* (Rustemeyer *et al.,* 1998).

Parker and Turk (Parker and Turk, 1983) investigated the ability of different (meth)acrylate chemicals to evoke contact sensitivity skin reaction in guinea pigs using 5 different sensitisation protocols. The experiments indicated that using a variety of methods, it was not always possible to induce contact sensitivity in guinea pigs with known inducers of contact dermatitis in humans.

Human studies

- Case reports

Several publications reports cases of positive patch tests with HPMA in patients presenting allergy contact dermatitis (ACD) but also for some of them, conjunctivitis or lesions in the nails, lips or external auditory canals (Jordan, 1975; Bjorkner, 1984; Lovell, 1985; Romaguera, 1989; Kanerva, 1989; Kanerva, 1991; Marren, 1991; Kanerva, 1992; Kanerva, 1993; Kanerva, 1995a; Hemmer, 1996; Estlander, 1996; Lindstrom, 2002; Weber-Muller, 2004; Cravo, 2008; Llamas, 2010; Goulding, 2011; Maio, 2012; Kiec-Swierczynska, 2013; Vaccaro, 2014, Le Q, 2015; Alcantara-Nicolas, 2016; Stingeni, 2015; Salazar, 2017; DeKoven, 2017; Gatica-Ortega, 2018; Romita, 2020; Alves, 2020; Rodenas-Herranz, 2020). The patients cited in these publications can be workers occupationally exposed, in particular dental staff with cases reported since 80's and more recently nail salon workers. In parallel, cases of skin sensitisation to HPMA have also been reported in general population, after exposure to prosthesis, acrylic nails, bleaching treatments or electrodes.

- Clinical studies

A large number of diagnostic patch tests is available for HPMA. Currently, HPMA is routinely used in the (meth)acrylate series (in general 2% in petroleum) but the composition of this series had varied among years.

Kanerva *et al* (Kanerva, 1988 and 1995b) underwent clinical studies in selected patients in Finland, with frequency of positive reactions to HPMA between 8 and 16%. Eslander (Eslander, 1990) analysed occupational skin diseases in Finland based on observations made between 1974 and 1988. Positive patch tests to HPMA mainly occurred on dental restoration work and with industrial exposure. Specific investigation of occupational skin diseases in dental laboratory technicians was performed by Rustemeyer *et al.* (Rustemeyer, 1996) who reported positive patch tests to HPMA in 7/27 tested patients (25.9%).

Numerous observational retrospective studies are available, the oldest performed in the 80's and the newest published in 2021 (Kanerva, 1997; Tucker, 1999; Lazarov, 2007; Teik-Jin Goon, 2007; Aalto-Korte, 2007 & 2008 & 2010 & 2021; Roche, 2008; Christoffers, 2012; Ramos, 2014; Uter, 2015; Spencer, 2016; Pestana, 2016; Muttardi, 2016; Raposo, 2017; Gatica-Ortega, 2017; Heratizadeh, 2018; Goncalo, 2018; Fisch, 2019). Most of them were performed in European countries. Patients included had a history of exposure to (meth)acrylates, including dental workers or workers exposed to artificial nails, glue, anaerobic sealants,

paints and lackers but also due to non-occupational exposure (dental or orthopaedic prostheses, consumer of nail products…). All reported high frequency of occurrence of skin sensitisation when patients were patch tested with HPMA (≥2%). The lowest frequency is reported at about 4% (Aalto-Korte, 2021) and the highest at about 80-90% (Aalto-Korte, 2008; Gatica-Ortega, 2017; Goncalo, 2018). However, for some of the retrospective studies, it has to be noted that the "real" frequency of positive reaction to HPMA can be biased because the total number of patients tested with HPMA is not reported (but only the number of positive reactions to HPMA among positive patch tests to (meth)acrylates), the occurrence therefore being possibly overestimated. Among the positive patch tests to the (meth)acrylate series, a high number of the patients reacted to HPMA supporting the fact that this substance is a frequent cause of allergy to (meth)acrylates. Finally, if only publications where the total number of patients tested with HPMA is defined (frequencies in bold in the above table) are considered, the occurrence of skin sensitisation is always clearly higher than 2%.

Many of these studies demonstrated that several patients were allergic to more than one (meth)acrylate suggesting cross-sensitisation. It has also been suggested that multiple acrylate allergy occurs as a result of meth(acrylate) cross-contamination and the presence of various undisclosed acrylate contaminants in products (Muttardi, 2016). For example, chemical analyses carried out at the Finnish Institute of Occupational Health have shown that most acrylate-based industrial products contain numerous other acrylates as impurities, sometimes as much as 46% of the total weight of the product. These additional compounds are not disclosed on material safety data sheets. Therefore, many of the so-called cross reactions could in fact be concomitant reactions (Sasseville, 2012).

Overall, although HPMA is not a skin sensitiser based on experimental data, there are numerous epidemiological studies that confirm its potential to induce eczema or other allergenic reactions in humans. This can also be explained from a chemical point of view for (meth)acrylic acid structures. As observed by 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*".

10.5.2 Comparison with the CLP criteria

The decision logic for classification of substance described in the CLP guidance version 5.0 (July 2017) has been followed:

" *Are there data and/or information to evaluate skin sensitisation?"*

Yes: there are both experimental studies and human data assessing skin sensitisation properties of HPMA.

a) *Is there evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons*

Yes: positive reactions were reported in a substantial number of diagnostic studies on selected patients with incidence > 2%.

b) *Are there positive results from an appropriate animal test or in vitro / in chemico test?*

No: available experimental studies only report no to low frequency of skin reactions (25%).

Are data sufficient for sub-categorisation?

According to CLP, *"Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub-categorisation*

Sub-category 1A*: Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.*

Sub-category 1B*: Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered."*

Non-human and human data have been analysed to determine if they are sufficient for sub-categorisation.

Non-human data:

LLNA and maximisation assays are available with HPMA. Classification criteria according to CLP are the following:

Classification	Assay	Criteria
Subcategory 1A	LLNA	EC3 value ≤ 2%
	Maximisation test	≥ 30 % responding at ≤ 0,1 % intradermal induction dose or ≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose
Subcategory 1B	LLNA	EC3 value > 2%
	Maximisation test	≥ 30 % to < 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose

Stimulation index (SI) < 3 are reported in the LLNA assays, therefore, no EC_3 can be derived.

In Maximisation assays, the frequency of positive reactions was < 30%.

Thus, HPMA does not fulfil criteria for classification as Skin Sensitiser according to the CLP guidance based on experimental data.

Human data:

The frequency of occurrence of skin sensitisation should be considered as a first step to conclude on classification for skin sensitisation:

Table 3.2 Relatively high or low frequency of occurrence of skin sensitisation*

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	≥ 0.4 %	< 0.4 %
2: selected workers with known exposure or dermatitis	≥ 1.0 %	< 1.0 %
Number of published cases	≥ 100 cases	< 100 cases

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

Several human diagnostic patch test studies were performed with methacrylates including HPMA. Taking into account all available studies, the number of published cases is > 100 cases and the frequency of occurrence of skin sensitisation > 2%. It should be 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, when the number of patients tested with HPMA is indicated, the frequencies of skin reactions are clearly higher than 2%.

In addition to the frequency of occurrence of skin sensitisation, the level of exposure to the substance should be considered:

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)

This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 10 000 to < 100 000 tons per annum (ECHA, 2021).

Several uses are notified by the registrants with uses at industrial site or by professional workers and also consumer uses (ANSES, 2021). HPMA is principally used in adhesive and sealants, non-metal treatment products, polymers and cosmetics and personal care products (ECHA, 2021).

More specifically, the maximum use concentration reported for HPMA in nail enhancement products is 25% (CIR, 2005). In addition, HPMA can be used as monomer in acrylic resin coatings for food cans at use levels up to 20% (EFSA, 2012).

When considering the publications related to skin sensitisation induced by HPMA, the main occupational areas subjected to the reported dermatitis are dental and beauty domains. Cases of skin sensitisation to

HPMA have also been reported in general population, after exposure to prosthesis, acrylic nails, bleaching treatments or electrodes.

Overall, according to table 3.3 of the CLP guidance, the following scores can be attributed related to exposure data:

- **Concentration / dose: score = 2**
  - Considering available exposure data, relatively high exposure can be expected.
- **Repeated exposure: score = 2**
  - Considering the products in which HPMA can be included, a repeated exposure ≥ once/daily can be expected.
- **Number of exposure: score = 2**
  - Considering the uses of products containing HPMA, exposure can be more than 100 times.

In conclusion the total score for exposure data is set at 6 which corresponds to a relatively high exposure.

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

Based on this table and considering only human data, HPMA fulfills criteria for classification Skin Sens. 1. Subcategorisation is not possible for HPMA considering both animal and human data.

10.5.3 Conclusion on classification and labelling for skin sensitisation

HPMA should be classified Skin Sens. 1 – H317 according to CLP Regulation.

10.6 Germ cell mutagenicity

Not assessed in this dossier.

10.7 Carcinogenicity

Not assessed in this dossier.

10.8 Reproductive toxicity

Not assessed in this dossier.

10.9 Specific target organ toxicity-single exposure

10.9.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

There is no specific data on respiratory irritation for HPMA. Even more, only one study of low quality is available by inhalation for this substance (Gage, 1970). No adverse effect was found in rats exposed to an atmosphere saturated with HPMA (no further specification) at 0.5 mg/L for 3 weeks. This study was judged not reliable because there is no information on an analytical verification of the concentration tested, only one concentration was tested and the level of details was very limited (ANSES, 2021). However, it is reported in Toxnet website that vapour of hydroxypropyl methacrylate is irritating to nose (U.S. Coast Guard, Department of Transportation. CHRIS - Hazardous Chemical Data. Volume II. Washington, D.C.: U.S. Government Printing Office, 1984-5).

In the absence of adequate data for this hazard property, read-across assessment has been performed. Extrapolation would be relevant for volatile short methacrylates considering that these substances have a common functional group and a common breakdown product. Among them, some analogous substances, listed in the table below, have harmonised classification as irritant for respiratory tract (STOT SE 3 – H335).

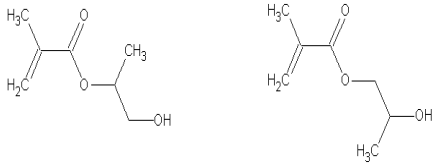
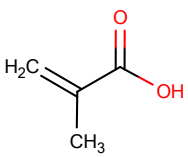
Table 17: List of target and source substances considered in the read-across

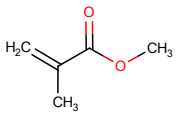
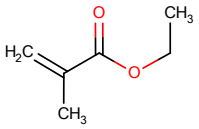
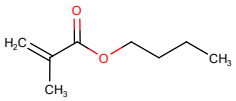
	Parent substance	Biotransformation	Common compounds	Non-common compounds
Target	HPMA	Methacrylic acid + propylene glycol	Methacrylic acid	Propylene glycol
Source	Methacrylic acid	NA	Methacrylic acid	NA
	MMA	Methacrylic acid + methanol	Methacrylic acid	Methanol
	Ethyl methacrylate (EMA)	Methacrylic acid + ethanol	Methacrylic acid	Ethanol
	Butyl methacrylate	Methacrylic acid + butanol	Methacrylic acid	Butanol
	Dodecyl methacrylate	Methacrylic acid + dodecanol	Methacrylic acid	Dodecanol

NA: not applicable

All substances are metabolised by esterases into a common metabolite: methacrylic acid and an alcohol or a glycol.

Table 18: Identity and physicochemical properties of target and source substances relevant for the read-across

	CAS number	EC	Structure	Molecular weight	Vapour pressure
HPMA	27813-02-1	248-666-3		144.17 g/mol	0.11 hPa at 20°C
Methacrylic acid	79-41-4	201-204-4		86.06 g/mol	0.97 hPa at 20°C

MMA (Methyl methacrylate)	80-62-6	201-297-1		110.11 g/mol	37 hPa at 20 °C
EMA (Ethyl methacrylate)	97-63-2	202-597-5		114.14 g/mol	20 hPa at 20 °C
BMA (Butyl methacrylate)	97-88-1	202-615-1		142.2 g/mol	2.12 hPa at 20°C

All considered substances are short methacrylates, with linear length chain ≤ 4 carbons. Molecular weights ranged from 86 g/mol (methacrylic acid) to 144 g/mol (HPMA). MMA, EMA and BMA are highly volatile with vapour pressure > 1 hPa. HPMA has lower vapour pressure but volatility is still expected (11 Pa).

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

Table 19: Rate constants for ester hydrolysis by rat-liver microsomes and predicted systemic fate kinetics following i.v. administration (adapted from Jones (2002), cited in the disseminated dossier of MMA)

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

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

In comparison, similar behaviour has been reported for HPMA in an *in vivo* pharmacokinetic study where the half-life was estimated to be less than or near 1 minute (Anonymous. 2017).

There is a high level of confidence that these substances would have similar toxicokinetic behaviour and that the same processes would occur in humans.

Table 20: Hazard properties of target and source substances relevant for the read-across

Substances	CAS number	Harmonised classification	Skin irritation hazard	Eye irritation hazard	Respiratory irritation hazard

HPMA	27813-02-1	None but contains 70-90% of 2-hydroxypropyl methacrylate (CAS 923-26-2) having a classification as: - Skin Sens 1 – H317 - Skin Irrit. 2 – H315	Not irritating to rabbits' skin (mean primary dermal irritation index = 0)	Irritating to eye (corneal opacity = 1 in 5/6 animals	No adequate data
Methacrylic acid	79-41-4	Acute Tox. 4* - H302 Acute Tox. 4* - H312 Skin Corr. 1A – H314 STOT SE 3 – H335; C ≥ 1%	Skin irritation indicative of corrosivity (i.e. concave eschar) was observed after 4 hours, after 1 hour and after 3 minutes of exposure (EU RAR, 2002)	Severe corneal, iridial and conjunctival irritation persisting through the 7-day observation period. On 7-day: corneal opacity = 4, iris and conjunctival irritation = 3-4 (EU RAR, 2002)	90-day inhalation study in rats and mice reported rhinitis of the anterior regions of the turbinates (EU RAR, 2002)
MMA	80-62-6	Flam. Liq. 2 – H225 Skin Irrit. 2 – H315 Skin Sens. 1 – H317 STOT SE 3 – H335	Contradictory results for skin irritation are observed in animals. Irritation was observed in humans following exposure of volunteers (Anses, 2018)	Study in rabbits: no irritation effects observed on cornea, iris and conjunctivae (redness and chemosis) (Anses, 2018)	Degeneration of the olfactory epithelium after a 6 h exposure to 200 ppm in rats (disseminated dossier. ECHA website, 2022) Reversible irritation reactions after short-term peak exposures to humans at concentration levels exceeding 100 ppm (Anses, 2018)
EMA	97-63-2	Flam. Liq. 2 – H225 Skin Irrit. 2 – H315 Eye Irrit. 2 – H319 Skin Sens. 1 – H317 STOT SE 3 – H335	In one study mean oedema scores were > 2.3 in 2/6 animals. Observation time was too short to demonstrate full reversibility (disseminated dossier. ECHA website, 2022)	In one study: mean erythema scores over a period of 24, 48 and 72 h were 0.33 - 2.66 and mean chemosis scores: 0 - 2.66. No full reversibility at the end of the 72 h observation time (disseminated dossier. ECHA website, 2022)	Degeneration of the olfactory epithelium after a 6 h exposure to 200 ppm in rats (disseminated dossier. ECHA website, 2022)
BMA	97-88-1	Flam. Liq. 3 – H226 Skin Irrit. 2 – H315 Eye Irrit. 2 – H319 Skin Sens. 1 – H317 STOT SE 3 – H335	Considerable variation in the irritation responses between studies. In one study: mean scores for shaved skin over 24 and 72 hours were 2.08 for erythema and 1.83 for oedema (disseminated dossier. ECHA website, 2022)	Slightly irritating to eyes (disseminated dossier. ECHA website, 2022)	Respiratory irritation at concentration > 300 ppm) (disseminated dossier. ECHA website, 2022)

According to the available data and current harmonised classifications, all substances have irritative properties.

The mode of action by which olfactory lesions are formed is considered due to hydrolysis, by carboxylesterases in the olfactory epithelium, of the parent ester to methacrylic acid, a corrosive substance. Indeed, local formation of methacrylic acid is expected as there are high levels of non-specific esterases in the Bowman's glands of the nasal olfactory tissues. Local effects are not anticipated as a result of the localised concentration of the corresponding alcohols / glycol since the alcohols / glycol themselves do not

produce local effects. Therefore, even if there is no data on HPMA itself regarding respiratory irritation, there is no reason that the mode of action of short length methacrylates does not occur.

10.9.2 Comparison with the CLP criteria

According to CLP Regulation, classification as STOT SE 3 includes "*narcotic effects and respiratory tract irritation*".

The criteria for classifying substances as Category 3 for respiratory tract irritation 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. hyperemia, edema, 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 no specific data related to respiratory irritation for HPMA. However, irritating properties of HPMA is supported by the fact that the substance induces eye irritation. So respiratory irritation can also be anticipated if HPMA reaches the respiratory tract. Volatility of the substance is confirmed by its vapour pressure. Moreover, HPMA is quickly hydrolysed by carboxyesterases present in the respiratory tract into methacrylic acid, which is a corrosive substance. Respiratory local effects are thus expected due to the formation of this metabolite (the other metabolite formed, propylene glycol, does not present this property). This assumption is supported by data available from other analogous short length methacrylates.

In conclusion, based on toxicokinetic considerations and data available for other analogous methacrylates, HPMA fulfils CLP criteria for STOT SE 3 – H335.

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10.9.3 Conclusion on classification and labelling for STOT SE

HPMA should be classified as STOT SE 3 – H335 according to CLP Regulation.

10.10 Specific target organ toxicity-repeated exposure

Not assessed in this dossier.

10.11 Aspiration hazard

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this dossier.

13 ADDITIONAL LABELLING

Not assessed in this dossier.

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15 ANNEXES

ANNEX I for study summaries

ANNEX II for confidential data