Committee for Risk Assessment

RAC

Annex 2

Background document

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

methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate

EC Number: 201-297-1
CAS Number: 80-62-6

CLH-O-0000006852-69-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

18 March 2021

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

methyl methacrylate; methyl 2-methylprop-2-enoate; methyl 2-methylpropenoate

EC Number: **201-297-1**

CAS Number: **80-62-6**

Index Number: **607-035-00-6**

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ANNEX 2 - BACKGROUND DOCUMENT TO RAC OPINION ON METHYL METHACRYLATE

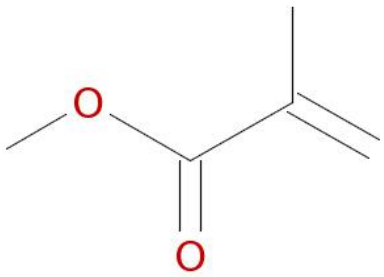
CONTENTS

ANNEX 2 - BACKGROUND DOCUMENT TO RAC OPINION ON METHYL METHACRYLATE

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)	methyl methacrylate; methyl 2-methylprop-2-enoate; methyl 2-methylpropenoate
Other names (usual name, trade name, abbreviation)	2-Propenoic acid, 2-methyl-, methyl ester
ISO common name (if available and appropriate)	na
EC number (if available and appropriate)	201-297-1
EC name (if available and appropriate)	methyl methacrylate
CAS number (if available)	80-62-6
Other identity code (if available)	na
Molecular formula	C5H8O2
Structural formula	
SMILES notation (if available)	na
Molecular weight or molecular weight range	100.1158
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	na
Description of the manufacturing process and identity of the source (for UVCB substances only)	na
Degree of purity (%) (if relevant for the entry in Annex VI)	99.0 – 100%

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)**
Methyl methacrylate EC no.: 201-297-1	≥ 99.0 - ≤ 100%	Flam. Liq. 2, H225 Skin. Irrit. 2 – H315 Skin Sens. 1 – H317 STOT SE 3 – H335	

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

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Confidential	-	-	-	-

There are a number of process impurities identified in the substance. These have been taken into account and are not considered to impact on the classification proposed in this dossier.

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

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Confidential	-	-	-	-	-

There are a number of additives identified in the substance. These have been taken into account and are not considered to impact on the classification proposed in this dossier.

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	607-035-00-6	methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate	201-297-1	80-62-6	Flam. Liq. 2 Skin Irrit. 2 Skin Sens. 1 STOT SE 3	H225 H315 H317 H335	GHS02 GHS07 Dgr	H225 H315 H317 H335			Note D
Dossier submitters proposal	607-035-00-6	methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate	201-297-1	80-62-6	**Add** Resp. Sens. 1	H334	GHS08 Dgr	H334			
Resulting Annex VI entry if agreed by RAC and COM	607-035-00-6	methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate	201-297-1	80-62-6	Flam. Liq. 2 Skin Irrit. 2 Skin Sens. 1 STOT SE 3 Resp. Sens. 1	H225 H315 H317 H335 H334	GHS02 GHS08 Dgr	H225 H315 H317 H335 H334			Note D

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

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier Existing harmonised classification: Flam. Liq. 2 – H225	No
Flammable solids	Hazard class not assessed in this dossier	No
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 assessed in this dossier	No
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 assessed in this dossier	No
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 Existing harmonised classification : Skin Irrit. 2 - H315	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Classification proposed: Resp. Sens. 1 – H334	Yes
Skin sensitisation	Hazard class not assessed in this dossier Existing harmonised classification: Skin Sens. 1 – H317	No
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	Hazard class not assessed in this dossier Existing harmonised classification: STOT SE 3 – H335	No
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

Hazard class	Reason for no classification	Within the scope of public consultation
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance was classified under Directive 67/548/EEC. The classification was translated into CLP regulation (CLP00): Flam. Liq. 2 – H225; Skin Irrit. 2 – H315; Skin Sens. 1 – H317; STOT SE 3 – H335.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[A.] There is no requirement for justification that action is needed at Community level (respiratory sensitization).

5 IDENTIFIED USES

The substance has several uses[1] which include adhesive and sealants, as a monomer for polymerisation or intermediate in synthesis of other chemicals, manufacturing of acrylic sheets, in the manufacture of resins.

Consumers may be exposed via adhesives and sealants, machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners.

6 DATA SOURCES

- REACH registration dossiers
- Literature
- French National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P) database[2]

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Information relative to the physicochemical properties come from the REACH registration dossier.

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Colourless liquid at 20°C and 101.3 kPa Odour: pungent	GESTIS (2005) (Registration dossier, IUCLID 6)	Visual inspection, purity not given
Melting/freezing point	-48 °C	Weast (1988) (Registration dossier, IUCLID 6)	Reliable handbook value, purity not given
Boiling point	100.36 °C at 1013.25 hPa	BASF (1986) (Registration dossier,	Measured value, purity: 99.9 %

[1] https://echa.europa.eu/brief-profile/-/briefprofile/100.001.180

[2] https://www.anses.fr/en/content/rnv3p-national-network-monitoring-and-prevention-occupational-diseases

Property	Value	Reference	Comment (e.g. measured or estimated)
		IUCLID 6)	
Relative density	0.94 g/cm³ at 20 °C	Weast (1988) (Registration dossier, IUCLID 6)	Reliable handbook value, purity not given
Vapour pressure	37 hPa at 20 °C	BASF (1986) (Registration dossier, IUCLID 6)	Measured value, purity: 99.9 %
Surface tension	Not surface active	Study report (1996) Registration dossier, IUCLID 6	Based on chemical structure, no surface activity is to be expected.
Water solubility	15.3 g/L at 20 °C	Jones (2002) (Registration dossier, IUCLID 6)	Measured value, purity: 99 %
Partition coefficient n-octanol/water	Log Pow = 1.38 at 20°C and pH7	Tanii H, Hashimoto K (1982) (Registration dossier, IUCLID 6)	Measured value, purity not given
Flash point	10 °C at 1013 hPa	BASF (1968) (Registration dossier, IUCLID 6)	Measured value, purity not given
Flammability	Flammable liquid	-	Flammability is derived from flash point and boiling point: **Flam. Liq. 2, H225** The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.
Explosive properties	No explosive properties	Registration dossier, IUCLID 6	Statement. There are no chemical groups associated with explosive properties present in the molecule.
Self-ignition temperature	435 °C at 1013.25 hPa	Bauer (1990) (Registration dossier, IUCLID 6)	Reliable handbook value, purity not given
Oxidising properties	No oxidising properties	Registration dossier, IUCLID 6	Statement. Not required since the substance is highly flammable, furthermore the substance does not contain chemical structures associated with oxidising properties.
Stability in organic solvents and identity of relevant degradation products	Not applicable	Registration dossier, IUCLID 6	The substance does not contain any ionic, dissociable structures.
Dissociation constant	Not applicable	Registration dossier, IUCLID 6	The substance does not contain any ionic, dissociable structures.
Viscosity	0.53 mPa s (dynamic) at 20°C	Elvers et al. (1990) (Registration dossier, IUCLID 6)	Reliable handbook value, purity not given

8 EVALUATION OF PHYSICAL HAZARDS

Current harmonised EU classification: **Flam. Liq. 2, H225**.

Physical hazards are not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies in animals

Method	Results	Remarks	Reference
Inhalation exposure of female Fisher F344 rats (*in vivo* and *in vitro*), Syrian hamsters and humans (in vitro) Effects of bis-(p-nitrophenyl)phosphate, an inhibitor of carboxylesterase enzymes, were studied in rats after single inhalative exposure to methyl methacrylate. Additionally, the distribution of the carboxylesterases in nasal tissues has been investigated and the metabolism of methyl methacrylate to methacrylic acid has been compared in rat, hamster and human nasal tissue fractions *in vitro*.	The methacrylic acid is the main metabolite for MMA	2 (reliable with restrictions) key study Non Guideline GLP compliance not specified	Mainwaring G, Foster JR, Lund V, Green T (2001)
rat (Fischer 344) male exposure of isolated URT Exposure regime: 1 hour Doses/conc.: Measured: 0.090, 0.437, 2.262 mg methyl methacrylate/L; nominal ca. 0.10, 0.41 and 2.05 mg MMA/L (corresponding to 25, 100 and 500 ppm) The current study was designed to provide inhalation dosimetric data for the methyl methacrylate vapor as well as for its carboxylesterase metabolite, methacrylic acid. Deposition of methyl methacrylate vapors in the surgically isolated upper respiratory tract (URT) of urethane anaesthetised rats was studied after inhalation of methyl methacrylate.	Details on metabolites: bis-nitrophenylphosphate (BNPP) a carboxylesterase inhibitor significantly reduced URT MMA deposition suggesting that MMA is metabolized in nasal tissue and such metabolism enhances the efficiency of nasal extraction. The data suggest that MMA deposits with 10-20% efficiency in normally breathing rats.	2 (reliable with restrictions) key study Not GLP compliant	Anonymous (1992) Morris JB, Frederick CB (1995)
Exposure of rats by inhalation route to 100 ppm MMA for 1, 2, 3 and 4 hours	concentrations of methyl methacrylate were found to be about 11 mg/100 ml in blood, about 21 µg/g in lungs and about 25 µg/g in brain (independent of	2 (reliable with restrictions) Not GLP compliant	Raje *et al.*, 1985

Method	Results	Remarks	Reference
	the exposure time) at the end of exposure		
Infusion of MMA (33 mg/kg.min for 3 min) in rabbits and dogs	MMA diseappared very rapidly from the blood of the experimental animals. Half-life was less than 30s in rabbits and 41s in dogs.	2 (reliable with restrictions) Not GLP compliant	Paulet *et al*., 1979

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

There are extensive data available for methyl methacrylate, which have been reviewed, inter alia, in the EU RAR (2002).

After inhalation exposure, methyl methacrylate is rapidly absorbed and distributed. The substance is mainly transformed into CO_2 and then exhaled.

Absorption: Methyl methacrylate is rapidly absorbed by inhalation and oral route. *In vitro* skin absorption studies in human skin indicate that methyl methacrylate can be absorbed through human skin, absorption being enhanced under occluded conditions. However, only a very small amount of the applied dose (0.56%) penetrated the skin under unoccluded conditions (presumably due to evaporation of the ester from the skin surface). After inhalation exposure to rats, 10 to 20% of the substance is deposited in the upper respiratory tract where it is metabolized (by non-specific esterases) to the methacrylic acid (MAA).

Distribution: Methyl methacrylate concentration in serum rapidly decrease. After an exposure to 800 mg/kg by gavage in rats, the peak concentration is reached after 10 to 15 minutes and decrease is done in 50 minutes. The *in vitro* half-life in human blood is 10 to 40 mn.

The radio-labelled MMA is distributed after i.v. administration in rats to blood, heart, lungs liver, kidneys and salivary glands. The substance is also detected in seminal vesicles (EU RAR, 2002).

Metabolism Methyl methacrylate is rapidly metabolized, mainly in the liver. Toxicokinetics seem to be similar in man and experimental animal. Three metabolic pathways exist:

- The main one is the oxidative pathway which leads to CO_2. Indeed after oral or parenteral administration, methyl methacrylate is further metabolised by physiological pathways with the majority of the administered dose being exhaled as CO_2.
- The second one involves the carboxylesterases. As described to OECD SIAR (2004), short chain alkyl-methacrylate esters, like MMA, are initially hydrolysed by non-specific carboxylesterases to methacrylic acid and the structurally corresponding alcohol in several tissues, which is the methanol for methyl methacrylate. Activities of local tissue esterases of the nasal epithelial cells appear to be lower in man than in rodents (Mainwaring *et al*., 2001; Anonymous, 1992 and Morris, 1995). Methacrylic acid and the corresponding alcohol are subsequently cleared predominantly via the liver (valine pathway and the TCA (TriCarboxylic Acid) cycle, respectively). The carboxylesterases are a group of non-specific enzymes that are widely distributed throughout the body and are known to show high activity within many tissues and organs, including the 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, alkyl-methacrylate esters are the tissues at the primary point of exposure, namely the nasal epithelia and the skin, and systemically, the liver and blood.
- And finally methacrylate esters can conjugate with glutathione (GSH) *in vitro*, although they show a low reactivity, since the addition of a nucleophile at the double bond is hindered by the alpha-methyl side-group. Hence, ester hydrolysis by carboxylesterases is considered to be the major metabolic pathway for alkyl-methacrylate esters, with GSH conjugation only playing a minor role in their metabolism, and then possibly only when very high tissue concentrations are achieved, meaning when the oxidative route is saturated.

In workers exposed to methyl methacrylate (0.4 to 112 ppm during 8h) there is a linear correlation between the concentrations of methanol in blood, serum and urine and the amount of MMA in air. Nevertheless only 1.5% of inhaled MMA is excreted as methanol in urine. The elimination via exhaled CO_2 occurs 60 seconds after MMA to be detected in the blood (Mizunuma *et al*., 1993)

Elimination: As summarized in the EU RAR (2002), after i.p. administration of 14C-methyl methacrylate to rats within 24 hours 80% of the radiolabel was exhaled as $14CO_2$, 7-14% was excreted in the urine and approximately 3% was retained in tissues at this time (Crout *et al*., 1982). Clearance of 14C- methyl methacrylate from blood was determined in beagle dogs after simulated hip arthroplasty and after subsequent i.v. administration of 25, 50 or 75 mg/kg bw. Following hiparthroplasty, venous blood concentrations reached a maximum after 3 min and decreased over the next 16 min. Only 0.5% of the total amount of implanted monomer was detected in the venous circulation and no radioactivity could be detected in the arterial blood. After i.v. administration of 25 or 50 mg/kg bw maximum arterial levels were found at 30 s, but were below the limit of detection after 3 min (McLaughlin *et al*., 1973).

MMA and the other methacrylate esters are readily absorbed by all routes and rapidly hydrolyzed by carboxylesterases to methacrylic acid and the respective alcohol, in this case methanol. However, the rate of absorption decreases with increasing ester chain length. Clearance of the parent ester from the body is in the order of minutes. The primary metabolite, MAA, is subsequently rapidly cleared from blood and, as indicated by studies with MMA, this metabolism is by standard physiological pathways, with the majority of the administered dose being exhaled as CO_2.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Hazard class not assessed in this dossier

10.2 Acute toxicity - dermal route

Hazard class not assessed in this dossier

10.3 Acute toxicity - inhalation route

Hazard class not assessed in this dossier

10.4 Skin corrosion/irritation

Hazard class not assessed in this dossier. The substance is currently classified as Skin Irrit. 2 – H315 according to CLP Regulation.

10.5 Serious eye damage/eye irritation

Hazard class not assessed in this dossier.

10.6 Respiratory sensitisation

Table 9: Summary table of human data on respiratory sensitisation from RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Case report #1	MMA	Woman (26-year old) working as nail technician.	Occupational disease: allergic occupational asthma. Needed an professional reconversion. High level of attributability	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Case report #2	MMA	Woman (30-year old) working as nail technician.	Occupational disease: occupational allergic asthma High level of attributability	RNV3P database
Case report #3	MMA	Man (44-year old) working as dental technician.	Occupational disease: occupational asthma High level of attributability	RNV3P database
Case report #4	MMA	Man (58-year old) working in public administration	Occupational disease: predominantly allergic asthma due to an exposure to MMA. Pleural plaques observed following a scanner examination High level of attributability	RNV3P database
Case report #5	MMA	Man (35-year old) working as dental technician	Occupational disease: severe occupational asthma because of MMA exposure High level of attributability	RNV3P database
Case report #6	MMA	Man (57-year old) working as dental technician.	Occupational disease: Allergic occupational asthma High level of attributability	RNV3P database
Case report #7	MMA	Man (48-year old) working in car industry	Occupational disease: predominantly allergic asthma and rhinitis proved using functional respiratory investigations. High level of attributability	RNV3P database
Case report #8	MMA	Man (29-year old) exposed to UV inks composed of MMA	Occupational disease: asthma High level of attributability	RNV3P database
Case report #9	MMA	Woman (51-year old) working as dental assistant.	Occupational disease: asthma High level of attributability	RNV3P database
Case report #10	MMA	Man (27-year old) working as road painter.	Occupational disease: Increase in the frequency of asthma crisis following exposure to special paints designed for roads and which contain MMA High level of attributability	RNV3P database
Case report #11	MMA	Man (43-year old) working as dental technician.	Occupational disease: occupational asthma for 30 years with FEV1 (Forced expiratory volume in one second) of 1.6L. No silicosis but respiratory function worsening with a major post tabacco emphysema High level of attributability	RNV3P database
Case report #12	MMA	Woman (31-year old) working as nail technician.	Occupational disease: occupational asthma High level of attributability	RNV3P database
Case report #13	MMA	Woman (38-year old) formely working as nail	Occupational disease: typical occupational asthma with sequelae from	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		manufacturer.	her previous job. Forced to change her job. High level of attributability	
Case report #14	MMA	Man (54-year old) working as silkscreen designer.	Occupational disease: predominantly allergic asthma due to an exposure to MMA. High level of attributability	RNV3P database
Case report #15	MMA	Woman (53-year old) working as moulder technician in a beach umbrella factory.	Occupational disease: predominantly allergic asthma due to an exposure to resins. High level of attributability	RNV3P database
Case report #16	MMA	Man (36-year old) working as dental technician.	Occupational disease: predominantly allergic occupational asthma due to resins handling. High level of attributability	RNV3P database
Case report #17	MMA	Man (50-year old) working as dental technician.	Occupational disease: non allergic occupational asthma High level of attributability	RNV3P database
Case report #18	MMA	Man (39-year old) working as construction electrician.	Occupational disease: asthma. High level of attributability	RNV3P database
Case report #19	MMA	Woman (23-year old) working as a professional nail prothesist.	Occupational disease: allergic rhinitis. Asthma due to an exposure to MMA. high level of attributability	RNV3P database
Case report #20	MMA	Woman (40-year old) working as a professional nail prothesist.	Occupational disease: occupational asthma. High level of attributability	RNV3P database
Case report #21	MMA	Woman (44-year old) working as dental technician.	Occupational disease: asthma and eczema following an exposure to MMA. High level of attributability	RNV3P database
Case report #22	MMA	Man (58-year old) working as dental technician.	Occupational disease: asthma following an exposure to MMA. High level of attributability	RNV3P database
Case report #23	MMA	Woman (22-year old) working as nail technician.	Occupational disease: occupational asthma Moderate level of attributability	RNV3P database
Case report #24	MMA	Man (25-year old) working as dental technician	Occupational disease: occupational asthma because of MMA exposure Moderate level of attributability	RNV3P database
Case report #25	MMA	Woman (50-year old) working as dental technician	Occupational disease: asthma Moderate level of attributability	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Case report #26	MMA	Man (62-year old) working as carpenter	Occupational disease: asthma which led to disability Moderate level of attributability	RNV3P database
Case report #27	MMA	Man (30-year old) working in furniture industry exposed to MMA	Occupational disease: asthma. Breathing difficulties due to occupational exposure. Moderate level of attributability	RNV3P database
Case report #28	MMA	Man (51-year old) working as machine operator in polystyrene industry.	Occupational disease: respiratory symptoms, asthma. Moderate level of attributability	RNV3P database
Case report #29	MMA	Woman (46-year old) working as machine operator in polystyrene industry.	Occupational disease: asthma Moderate level of attributability	RNV3P database
Case report #30	MMA	Men (49-year old) packer in polystyrene industry.	Occupational disease: asthma Moderate level of attributability	RNV3P database
Case report #31	MMA	Man (32-year old) working in manufacturing medical instruments industry.	Occupational disease: asthma following exposure to powders containing MMA Moderate level of attributability	RNV3P database
Case report #32	MMA	Man (57-year old) working as painter-decorator on glass or ceramic.	Occupational disease: predominantly allergic asthma. Moderate level of attributability	RNV3P database
Case report #33	MMA	Woman (45-year old) working as dental technician.	Occupational disease: asthma aggravated by MMA and dust. Moderate level of attributability	RNV3P database
Case report #34	MMA	Man (63-year old) working as house painter.	Occupational disease: asthma. Moderate level of attributability	RNV3P database
Case report #35	MMA	Man (38-year old) working as house painter.	Occupational disease: asthma, rhinitis because of MMA handling. If still exposed to MMA, will need to change his job Moderate level of attributability	RNV3P database
Case report #36	MMA	Man (48-year old) working as dental technician.	Occupational disease: possible occupational asthma. Moderate level of attributability	RNV3P database
Case report #37	MMA	Man (49-year old) working as dental technician.	Occupational disease: asthma. Moderate level of attributability	RNV3P database
Case report #38	MMA	Woman (23-year old) working as nail	Occupational disease: asthma and rhinitis.	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		technician.	Moderate level of attributability	
Case report #39	MMA	Woman (39-year old) working as nail technician.	Occupational disease: asthma High level of attributability	RNV3P database
Case report #40	MMA	Woman (31-year old)	Occupational disease: asthma Moderate level of attributability	RNV3P database
Case report #41	MMA	Woman (29-year old) working as dental technician.	Occupational disease: asthma High level of attributability	RNV3P database
Case report #42	MMA	Woman (50-year old) working in automotive industry	Occupational disease: asthma High level of attributability	RNV3P database
Case report #43	MMA	Man (48-year old) working in furniture industry	Occupational disease: asthma proved by a very positive reversibility test High level of attributability	RNV3P database
23 actual cases : Cases #44-66	MMA	61% men working in various sectors	Occupational disease: asthma reported by chest physicians No information on attributability	SWORD database
Case #67	MMA	Man working in the manufacture of medical devices	Occupational disease: asthma Reported by occupational physicians No information on attributability	OPRA database
Case #68	MMA	Dentist has worked with dental primers, adhesives and fillers; prosthetic methacrylate liquid and powder during 15 years before asthma symptoms	Occupational disease: asthma with a late reaction in specific inhalation challenges (SIC) after 1-8 hour after exposure. No information on attributability	FIOH database
Case #69	MMA	Dentist working with prosthetic material. Has worked during 5 years before asthma symptoms	Occupational disease: asthma with a late reaction in specific inhalation challenges (SIC) meaning after 1-8 hour after exposure. No information on attributability	FIOH database
Case #70	MMA	Dental technician working with prosthetic material. Has worked for 23 years before asthma symptoms	Occupational disease: asthma with dual reaction in specific inhalation challenges (SIC) meaning both early and late reactions No information on attributability	FIOH database
Case #71	MMA	Production worker working with 2-component lamination resin. Has worked during 1 years before asthma symptoms	Occupational disease: asthma with an early reaction in specific inhalation challenges (SIC) meaning within 1 hour after exposure. No information on attributability	FIOH database

Table 10: Summary table of other human data on respiratory sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Cohort study 8 + 32 workers with less or more than 10-year exposure to MMA	MMA	Investigation of the lung function parameters in 40 workers exposed to MMA in 2 different factories.	Increased incidence of chronic cough and mild airway obstruction were observed, not related with smoking habits.	Marez *et al.*, 1993
Personal communication Survey of 211 male workers	MMA	Medical examination of workers in acrylic sheet production exposed to methyl methacrylate Present exposures to MMA varied between < 3 and 40 ppm (8 h TWA, calculated as geometrical means of personal sampling measurements according to TRGS 402). Past exposures were between 10-70 ppm MMA (8 h TWA). Occasional short-term peak concentrations of 100-680 ppm MMA had also been recorded.	In the exposed group, no case of MMA exposure related skin **or respiratory sensitization was observed**. Observation of irritation of the eyes and the upper respiratory tract was limited to acute and reversible reactions after short-term peak exposures at concentration levels exceeding 100 ppm (ca. 410 mg/m3). There were no indications for clinical symptoms of a work related rhinopathy or any substance related abnormalities in the exposed group.	Röhm GmbH, 1994
Case report	Methyl methacrylate	A 56 year old female theatre sister, with at least 7-year of experience of working with bone cements consisting of poly-MMA and MMA liquid, developed respiratory symptoms characterised by a persistent cough, wheeziness and breathlessness. These symptoms were associated with periods at work and resolved on rest days or on leave. Despite smoking 10-20 cigarettes per day, her pulmonary function tests were normal when she was not working.	Controlled exposure to the cements and MMA, under simulated working conditions, resulted in delayed asthmatic reaction occurring 6 h after exposure with a maximum fall in FEV1 of 25 % 13 h after the challenge. A controlled exposure, in which the poly-MMA based cement was mixed with water, was reported not to produce a fall in FEV1 but due to the colour and odour of MMA it was not possible to perform the challenge under blind conditions.	Pickering *et al.* (1986)
Case reports	MMA	3 cases of respiratory sensitization	Case 1 (W, 48-year old) exposed during the use of a glue during plate engraving and have developed respiratory distress at work, strain, sneezing, rhinorrhoea and stuffiness. Challenge to the	Savonius *et al.* (1993a and b)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			implicated glue caused a maximal 24% fall in Peak Exploratory Flow (PEF) values and her symptoms persisted even after a change to a cyanoacrylate glue. Case 2 (M, 32 year old) involved in the assembly of hearing devices, showed a small maximal 15% decrease in PEF values following the grinding of "a piece of methacrylate" in an exposure chamber. Case 3 (W, 46-y old) who had worked for about 20 years as a dental technician. She developed paraesthesia on the unular side of both hands but not dermatitis. She subsequently experienced a feeling of tickling in her throat, yawning, cough, tiredness and chest tightness; the symptoms subsided on sick leave and vacations but recurred within a week at work. Simulated occupational exposed to "methacrylate powder and methacrylate liquid" for 30 minutes resulted in a maximal fall of 26% in PEF value. Skin prick test to "methacrylate" was negative. Although this case report appears to show an association between occupational exposure to "methacrylate liquid" and the respiratory symptoms observed, it is not possible from the data provided to conclude that the symptoms resulted from exposure to MMA	
Case report	MMA	Worked-related asthma in a plumber	Case of a 48-year-old man with no history of atopy who worked as a professional plumber for over 30 years and had consulted for progressive dyspnea and dry cough during the last 3 years. His symptoms were triggered at work and persisted outside work. The patient had never had skin lesions and never used protective clothing, gloves, or a mask at work. He has been on sick leave for 24 months with persistent symptoms and no treatment. After performing a SIC for MMA the asthma reaction following an exposure to the substance was confirmed.	Uriarte et al. (2013)
Case report	MMA	Work-related asthma in an orthopaedic surgeon	An orthopaedic surgeon with no history of lung disease developed cough and dyspnoea. The patient was diagnosed with asthma by spirometry and bronchial provocation test with methacholine. A clear correlation between symptoms and work was established meriting a referral to a	Roth *et al.* (2017)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			centre for occupational health. The patient was diagnosed with work-related disease, which was recognized by the industrial injury board. The cause was methyl methacrylate, a known airway irritant, which is an important component of bone cement. Previously, no cases of work-related asthma in orthopaedic surgeons have been reported	
Case report	MMA	Work-related hypersensitivity pneumonitis in dental technicians	Study reports 2 cases of dental technicians with a diagnosis of hypersensitivity pneumonitis due to an a inhalation exposure to MMA : - 24-year old female with an exposure during 6 months as dental technician that led to severe dyspnoea and hypoxemia. Had to quit her job. - 20-year old female hospitalised for acute respiratory distress. Had also hypoxemia. Effects due to an occupational exposure as dental technician student.	Scherpereel *et al.* (2004)

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

Methyl methacrylate is used in the industry because of its good properties in polymerization process. Therefore, it is used widely in paints, adhesive glues, coating. In addition, it is used in nail sculpture, bone or dental cement.

MMA is not only a skin irritant but it also has the potential to induce skin sensitization and allergic contact dermatitis.

There are no data available for animals regarding respiratory sensitization, since no assay exists to assess this type of effects. Based on the available data, on case-reports and epidemiological studies, MMA is associated with occupational asthma. Indeed, in literature, several cases of asthma have been identified.

In a cohort study by Marez *et al.* (1993), it was found that an increased incidence of chronic cough and mild airway obstruction is linked with an occupational exposure to MMA.

In a report by Rohm GmbH (1994) a medical examination was performed for workers exposed to MMA during the production of acrylic sheets. The report concluded that in the group of exposed mal workers no case of skin or respiratory sensitisation was observed. The only observations were irritation of the eyes and the upper respiratory tract, but these reactions were reversible.

In a case report by Pickering *et al.* (1986), it was reported that a 56-year-old female theatre sister, with at least 7-years of experience in working with bone cements consisting of poly-MMA and MMA liquid, developed respiratory symptoms characterised by a persistent cough, wheeziness and breathlessness. These symptoms were associated with periods at work and resolved on rest days or on leave. Despite smoking 10-20 cigarettes per day, her pulmonary function tests were normal when she was not working. A controlled exposure to the cements and methyl methacrylate, under simulated working conditions, resulted in delayed asthmatic reaction occurring 6 h after exposure with a maximum fall in FEV1 of 25 %, 13 h after the

challenge. A controlled exposure, in which the poly-MMA based cement was mixed with water, was reported not to produce a fall in FEV1. It could be due to the fact that because of the colour and odour of methyl methacrylate it was not possible to perform the challenge under blind conditions.

In two other publications, 3 cases of respiratory sensitization due to an exposure to methyl methacrylate were reported. In the case 1, a woman (48-year old) was exposed during the use of a glue during plate engraving and she have developed respiratory distress at work with strain, sneezing, rhinorrhoea and stuffiness. Challenge to the implicated glue caused a maximal 24% fall in Peak Exploratory Flow (PEF) values and her symptoms persisted even after she changed to the use of a cyanoacrylate glue. Her symptoms persisted and she had to quit her job. The second case was a man (32 year oldworking in an earplugs factory, showed a small maximal 15% decrease in PEF values following the grinding of "a piece of methacrylate" in an exposure chamber. The third case is a woman (46-y old) who had worked for about 20 years as a dental technician. She developed paraesthesia on the unular side of both hands but not dermatitis. She subsequently experienced a feeling of tickling in her throat, yawning, cough, tiredness and chest tightness; the symptoms subsided on sick leave and vacations but recurred within a week at work. Simulated occupational exposed to "methacrylate powder and methacrylate liquid" for 30 minutes resulted in a maximal fall of 26% in PEF value. Skin prick test to "methacrylate" was negative. Although this case report appears to show an association between occupational exposure to "methacrylate liquid" and the respiratory symptoms observed, it is not possible from the data provided to firmly conclude that the symptoms resulted from exposure to methyl methacrylate (Savonius *et al*.; 1993a and b).

Uriarte *et al.* (2013) reported a case of a 48-year-old man with no history of atopy who worked as a professional plumber for over 30 years and had consulted for progressive dyspnea and dry cough during the last 3 years. His symptoms were triggered at work and persisted outside work. The patient had never had skin lesions and never used protective clothing, gloves, or a mask at work. He has been on sick leave for 24 months with persistent symptoms and no treatment. After performing a SIC for MMA the asthma reaction following an exposure to the substance was confirmed.

In a case report by Roth *et al.* (2017), an orthopaedic surgeon with no history of lung disease developed cough and dyspnoea. The patient was diagnosed with asthma by spirometry and bronchial provocation test with methacholine. A clear correlation between symptoms and work was established meriting a referral to a centre for occupational health. The patient was diagnosed with work-related disease, which was recognized by the industrial injury board. The effects were caused by his occupational exposure to methyl methacrylate, which is an important component of bone cement.

Finally Scherpereel *et al.* reported in 2004 two cases of hypersensitivity pneumonitis in dental technicians following an inhalation exposure to MMA. First, a 24-year old female has been exposed to MMA during 6 months as dental technician that led to severe dyspnoea and hypoxemia. She had to quit her job. The second case is a 20-year old female hospitalised for acute respiratory distress. She also showed hypoxemia. The effects were due to an occupational exposure as dental technician student.

Additionnally this substance is listed in France in the table #82 of occupational disease for respiratory sensitization. This occupational asthma is often associated with rhinitis and hypersensitivity pneumonitis.

In France, the national network for the monitoring and prevention of occupational disease (RNV3P) created in 2001, collects every year more than 8000 new occupational health reports throughout France. Their methology has been reviewed by the EU-OSHA in 2017 in a review which analysed all the existing monitoring systems and methodologies to identify work-related diseases across the world. This French non-compensation –based system primarly designed for data collection and statistics can also be used for the detection of new/emerging work-related diseases.

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. This network's goal is to record the data from consultations in a national database (patient demographics data, diseases, exposures, job sectors and professions). After investigation, the expert physicians from the CCPPs establish a possible link between the occupational exposure(s) and the pathology which motivated the

consultation (this causal link is recorded in the data base) with a level of attributability (low, moderate or high). The level of attributability which link an occuptational exposure and a disease is the analysis to determine if, for a specific patient, the substance to which he/she is exposed to during work is responsible for the detected pathology. In the RNV3P database 4 levels of attributability exist:

- 0 = No causal link
- 1 = Low: low or questionable link
- 2 = Moderate: Possible link or direct but not essential
- 3 = High: High, direct and essential link

The French RNV3P is a good example of dissemination and the exchange of information at a national level, which can be used to initiate preventive actions. Upon detecting a signal, this system provides an internal alert to clinicians in the RNV3P network, conducts a search for similar cases outside the network and widely diffuses the information via ANSES to authorities, so that necessary actions can be taken. In addition, all cases of suspected new/emerging WRDs are collected in the corresponding web-based information system (database), with coded variables that enable periodical data mining.

From this database, a research was performed in order to sort out the cases of asthma related to an exposure to methyl methacrylate with a high or moderate level of attributability. Forty-three cases were found between 2001 and 2017 and have been specifically related to an exposure to methyl methacrylate with a high or intermediate level of attributability. Indeed, occupational asthma is clearly observed and in some cases is predominantly allergic in professionals working in printing sector (UV inks), plastics (polystyrene), dental, optical (eyewear), construction (resins, paints), nails. However, no exposure level has been mentioned for these cases.

The cases that are reported in this French database are related to occupational exposure only. Therefore all the cases reported there are not all the existing cases in France but probably only a small partof them. However all these cases allow us to highlight the fact that there is a concern related to a respiratory sensitization following at least an occupational exposure to methyl methacrylate.

Different European countries were contacted by France in December 2018 in order to obtain additional human cases related to respiratory sensitization after MMA exposure. Other cases were reported as following:

In Belgium, for the last 5 years, 736 claims for compensation of an occupational asthma have been received by the Fedris (Belgian fund of occupational diseases), of which 2 cases were related to Methacrylate. Of the 2 cases only 1 case was accepted as occupational disease by Fedris.

In Netherlands, 3 cases of occupational asthma (a plasterer in 2013 and a dental technician in 2005 and in 2017) were reported to the Netherlands Center for Occupational Diseases (NCOD) due to exposure to acrylates (not specified as MMA) in the past years..

There have been 23 actual (78 estimated[3]) cases of occupational asthma attributed to methyl methacrylate reported to the UK Health and Occupation Research Network (THOR[4]) by the chest physicians to the Surveillance of Work-Related and Occupational Respiratory Disease (SWORD) between 1989 and 2017. It has to be noted that:

· 61% of the cases were reported in males;

· Mean age (all cases) 43 years (age range 18-77 years);

· The industry sectors reported for the cases were as follows: 11/23 (48%) Health and social care; 8/23 (35%) manufacturing; and 1 case reported in each of the following industries, education, construction, other

[3] Estimated cases = (cases reported on a monthly basis) + cases reported by sample reporters during a single randomly allocated month per year x 12) therefore cells based on a small number of actual cases may exhibit appreciable random fluctuation

[4] http://research.bmh.manchester.ac.uk/epidemiology/COEH/

service activities, other business activities.

One other case of occupational asthma attributed to methyl methacrylate was reported to THOR by occupational physicians in the Occupational Physicians Reporting Activity (OPRA) between 1996 and 2017. The case was reported in a male working in the manufacture of medical devices.

In Sweden, the Swedish Work Environment Authority (SWEA) received, during the period 2008-2018, a couple of reports of respiratory complaints possibly caused by methyl methacrylate.

Regarding Finland, a relatively large proportion of suspected occupational asthma cases due to chemicals is investigated at the Finnish Institute of Occupational Health (FIOH), where also specific inhalation challenges (SIC) with workplace agents are performed. The cases are referred to FIOH for confirmation of the diagnosis from all over Finland. During 1997-2018, four cases of occupational asthma to MMA were diagnosed at FIOH. Of these, one case had an early reaction (asthma reaction within 1 hour after exposure), two cases had late (meaning after 1-8 hour after exposure) SIC and one with both early and late reaction

In a publication by Vandenplas *et al.* (2014), it is explained that a task force has been formed by the European Respiratory Society in 2011, and their methodology and the use of the Specific inhalation challenge (SIC) in order to identify and score an occupational asthma. It is mentioned that this challenge is especially useful where it can be performed efficiently ; the highest level of diagnostic confidence is required ; the patients is no longer exposed at work ; there is need to identify a particular agent and there is an unrecognised causal agent. The main objective of this Task Force was to harmonise occupational SIC testing in Europe and to provide guidance to physicians who wish to develop SIC testing in new centres.

Therefore cases of occupational asthma could be found in different countries among Europe. The industry sectors in which the cases were reported are quite always the same, demonstrating a coherence inside Europe.

In a review by Leggat and Kedjarune (2003) the various toxicities of methyl methacrylate in dentistry are listed including the respiratory toxicity. In this review several measures are listed to reduce the exposure to methyl methycralate in the dental workplace.

Several SAR models were runned by RIVM (following a request by FR-MSCA) in 2014 and DK QSAR Toolbox was also runned in 2018 but unconclusive results were found. Additionnaly, as mentioned in the 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.

In addition, there is no test to robustly demonstrate a respiratory sensitization because small molecules which have a low molecular weight are not acting via a IgE-dependent mechanism. There is no suitable assay to identify this kind of respiratory sensitizer, contrary to larger molecules for which the dosage of IgE could be sufficient to conclude on the mechanism of a respiratory sensitization.

As the methyl methacrylate is also a respiratory irritant, it may be difficult to distinguish the mechanism which lead to asthma. Indeed, the difference between an irritating mechanism and sensitization is quite hard to define since:

- clinical symptoms (asthma, hypersensitivity pneumonitis, associated with rhinitis…) for both affection are similar,

- there is no information on exposure doses for clinical cases in order to show if sensitizing effects may appear at lower doses than irritating doses. But latency between the first exposure and the occurrence of the symptoms is more in favour of a sensitization.

In conclusion, several human cases of clear respiratory sensitization, identifying the exposure to methyl methacrylate to be responsible for an occupational asthma, were reported in the literature, in the French RNV3P database or in other European network related to the surveillance of occupational diseases like in

United Kingdom or Sweden. These data clearly relate the exposure to this substance to an occupational asthma.

10.6.2 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

There is evidence from human data that MMA induces asthma.

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

There is no appropriate animal test with MMA to conclude on respiratory sensitization. However, experimental data show that MMA is a skin sensitizer. These data may be indicative of the potential of MMA to cause respiratory sensitization in humans.

In conclusion, a substance should be classified as a respiratory sensitiser when there is evidence in humans that the substance can lead to specific respiratory hypersensitivity. As the methyl methacrylate is a respiratory irritant, it may be difficult to distinguish the mechanism which lead to asthma. However, according to CLP, "*the condition will have the clinical character of an allergic reaction*", that is the case for methyl methacrylate and "*immunological mechanisms do not have to be demonstrated*". Therefore the conclusion of the review by Borak *et al*., 2011 stating that the MMA is not a respiratory sensitizer since it is not possible to distinguish the effects form an irritation is not considered as relevant. Consequently a classification of methyl methacrylate as Resp Sens. Cat. 1 H334 is considered as justified.

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.

10.6.3 Conclusion on classification and labelling for respiratory sensitisation

Methyl methacrylate should be classified as Resp Sens. Cat. 1 H334 according to CLP Regulation.

RAC evaluation of respiratory sensitisation
Summary of the Dossier Submitter's proposal Respiratory sensitisation was the only endpoint assessed by the dossier submitter (DS) France for harmonised classification and labelling (CLH). The DS proposed to classify

methyl methacrylate (MMA) as Resp. Sens. 1; H334.

As part of this weight of evidence assessment, the DS also briefly summarised the animal and human data for skin sensitisation, for which MMA has an existing classification as Skin Sens 1; H317.

In order to distinguish between potential irritative and sensitising properties of MMA after inhalation, the DS also presented data on respiratory irritation. MMA has been reported to have a strong, readily detectable smell at concentrations between 32 and 65 ppm, and irritation has been observed at concentrations exceeding 100 ppm, being "very definite" at concentrations between 170 to 248 ppm. In addition to skin sensitisation, MMA has existing harmonised classifications as STOT SE 3; H335 and Skin Irrit. 2; H315. Data on toxicokinetics was also presented by the DS in the CLH dossier.

There are no validated experimental animal assays with which to assess respiratory sensitisation. Therefore, the data available for this endpoint and included in the CLH dossier consisted of reports on diagnosed occupational asthma cases and epidemiological studies on human respiratory sensitisation. The case reports were both from the scientific literature and extracted from national occupational disease databases.

National Occupational databases

Forty-three case reports on respiratory sensitisation were extracted by the DS from the French National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P) database (n=43; 2001-2017). For these cases, the causal link between occupational asthma and MMA exposure had been determined as a "high level of attributability", meaning a high, direct and essential link, or "Moderate level of attributability", meaning a possible link or direct but not essential link. There were an additional 23 case reports extracted from the UK Surveillance of Work Related and Occupational Respiratory Disease (SWORD) database (1989-2017), where occupational asthma had been reported by chest physicians. There was one case report in the Occupational Physicians Reporting Activity (OPRA) database, reported by an occupational physician (1996–2017). Four additional methyl methacrylate specific case reports were extracted from the Finnish Institute of Occupational Health's (FIOH) database (1997–2018). This database includes the Finnish occupational asthma cases, all of which are confirmed at FIOH. These four asthma diagnoses were confirmed by a positive response in the specific inhalation challenge (SIC), which RAC notes is widely considered a reference standard in the diagnosis of occupational asthma when performed adequately (Suojalehto *et al.,* 2019; Vandenplas *et al*., 2014). Two of these SIC-responses were reported as late reactions (meaning after 1-8 h of exposure), one was a dual reaction (meaning both early and late reactions) and one was an early reaction (meaning within 1 h of exposure).

These case reports from European databases cover workers of both sexes representing different ages and who are involved in a number of occupational sectors – mainly nail technicians, dental technicians, car industry workers, polystyrene industry workers and painters. More detailed information on the extracted cases is provided in Annex 1.

Reports of National Authorities

In addition to the aforementioned case reports, National Authorities reported the following:

- One case was accepted within the last five years by the Belgian Fund of Occupational Diseases (Fedris) for compensation of an MMA-induced occupational asthma.

- Three cases of occupational asthma were reported to the Netherlands Centre for Occupational Diseases (NCOD) due to exposure to acrylates between 2005 and 2017.
- The Swedish Work Environment Authority (SWEA) received a small number of reports of respiratory complaints during 2008–2018.

However, in the Dutch and Swedish cases, methyl methacrylate was not specified as the causative agent.

Scientific literature

From the scientific literature, one cohort study (Marez *et al*., 1993) was included, reporting increased incidence of chronic cough and mild airway obstruction linked with an occupational exposure to MMA (not related to smoking habits). There are several case reports published in the literature (Pickering *et al*., 1986; Savonius *et al*., 1993a,b; Uriarte *et al*., 2013; Roth *et al*., 2017; Scherpereel *et al*., 2004), which described asthmatic reactions and respiratory sensitisation. However, it was not possible to conclude that the symptoms of all the subjects resulted specifically from exposure to methyl methacrylate.

Other evidence

In a survey by Röhm GmbH in 1994 (described by the DS as a personal communication), 211 male workers in acrylic sheet production and exposed to methyl methacrylate were included in a medical examination. No cases of MMA-related skin or respiratory sensitisation were observed. Reversible irritation of the eyes and the upper respiratory tract were observed.

Following a request by the DS, several SAR models and the DK QSAR Toolbox were run by RIVM, but the results were inconclusive. The DS mentioned that in the ECHA Guidance on Information Requirements and Chemical Safety Assessment, it is stated that QSAR models are known not to be predictive, as there are no validated test methods available to assess this type of endpoint.

Conclusion of the DS

The DS viewed the evidence that MMA is a skin sensitiser (current harmonised classification Skin Sens. 1; H317) as indicative of its potential to cause respiratory sensitisation in humans. In addition, MMA is readily absorbed via all routes of exposure, including the inhalation route, although it is rapidly metabolised and excreted. The DS considered that there is evidence from human data that MMA induces asthma, and that it should therefore be classified as a respiratory sensitiser. The DS acknowledged that methyl methacrylate is a (respiratory) irritant (current harmonised classification STOT SE 3; H335 and Skin Irrit. 2; H315), and therefore it may be difficult to distinguish the mechanism that leads to asthma. They mentioned that according to CLP however, *"the condition will have the clinical character of an allergic reaction"*, and that is the case here, and further noted that *"immunological mechanisms do not have to be demonstrated".* Sub-categorisation was not proposed by the DS, as there is no adequate information on the level of exposure mentioned in the case reports and the frequency of this pathology.

Comments received during consultation

Four comments were received during the consultation, three from Member State Competent Authorities (MSCAs) and one from a Company-Manufacturer. All three MSCAs

supported classification as Resp. Sens. 1 without sub-categorisation. One MSCA also gave information on two publications, of which Walters *et al*. (2017) supports the association between occupational asthma and exposure to acrylates, and DeKoven *et al*. (2017) who reported an increasing trend in the incidence of allergic contact dermatitis in nail salon workers. They pointed out that this reflects a more general trend in nail salon workers due to occupational (meth)acrylate exposure and was considered by them to be of concern also with regard to potential new cases of work-related respiratory sensitisation among nail technicians.

A Company-Manufacturer disagreed with the proposed classification and instead was of the view that the current Annex VI entry should remain unchanged. They argued that the weight-of-evidence approach in the CLH proposal was not balanced and not scientifically justified. In a detailed report, they presented their argumentation for not classifying MMA as a respiratory sensitiser. This was based on three main arguments: 1) obligatory evidence for a biphasic mode of action was not included, 2) a valid "causation" of the development of asthma in relationship to MMA exposure was not determined, and 3) a clear differentiation distinguishing between respiratory irritant effects (for which this substance is already classified) against the claimed respiratory sensitisation effects was not provided in sufficient detail.

They provided an alternative assessment, in their view following the scientific standards of ECHA [Guidance], the European Commission's Scientific Committee Health and Environment Emerging Risk (SCHEER) and based on a broader database than that presented in the CLH report. They concluded that, there is a lack of confidence in the CLH proposal that MMA is a causative agent for occupational asthma and were of the view that instead, all available evidence reviewed in the literature of sufficient strength confirmed that MMA only has the potential to aggravate asthmatic symptoms in pre-existing asthmatics.

They also pointed out literature that had been missing from the CLH proposal:

- EU Risk assessment (ECB, 2002), which concluded that there was "*no convincing evidence that MMA is a respiratory sensitiser in humans"* and viewed that "*possible non-specific asthmatic responses due to respiratory tract irritation cannot be excluded and labelling with R37 is sufficient for the protection of humans"*.
- SCOEL (2006), which similarly concluded that "*MMA is clearly a sensory irritant towards the respiratory tract and in the majority of these cases "asthmatic" respiratory responses have been attributed to exposure to transiently high concentrations of MMA that may have resulted in respiratory irritation in individuals with normal airway responsiveness, or perhaps in some cases with pre-existing, generally hyperreactive airways."* And that *"overall, there is no convincing evidence that methyl methacrylate is a significant inducer of asthma in humans".*
- A review by Borak *et al.* (2011), which also concluded that "*the weight of evidence, both experimental and observational, argues that MMA is not a respiratory sensitizer*".
- Pickering *et al*. (1993), based on which risk assessment reports by the EU and OECD concluded: "*From these studies there is no convincing evidence that MMA is acting as a respiratory sensitizer, however, there is clear evidence of acute respiratory irritation, at high exposure levels"*.

- Several scientific papers (listed in the public attachment to their comment) that the Company-Manufacturer considered of low reliability.

The DS noted in their reply as follows (with some typos corrected): "*The asthma linked to an occupational exposure to methyl methacrylate is recognised in France by the French National Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS) since 1987*. *Additionally, all the cases reported in the dossier especially from the RNV3P (The National Network for the Monitoring and Prevention of Occupational Diseases) were reported by specialized occupational practitioners who clearly linked an occupational exposure to MMA with different kinds of asthma. Moreover, only the cases with a high attributability were included*".

RAC accepts that evidence for a biphasic mode of action was not included in the CLH report. However, for the development of the RAC opinion, two additional publications were considered:

1. Walters *et al*. (2017), which supports an association between occupational asthma and exposure to predominantly methyl methacrylate in eight cases reported to the UK SHIELD surveillance scheme between 1989 and 2014.

2. A recent study by Suojalehto *et al*. (2020), supplemented with additional information received directly from the authors, providing further evidence of occupational asthma in six subjects verified to have predominantly been exposed to methyl methacrylate (see "Further discussion" below). The occupational asthma diagnoses in Suojalehto *et al*. (2020) were confirmed by placebo-controlled SICs.

It should also be noted that in the case of low molecular weight substances, which do not cause IgE-mediated responses, demonstration of causality is always more difficult than in the case of allergens resulting in clear IgE-mediated responses.

More detailed responses to the Company-Manufacturer's comment are given in the response to comments (RCOM) document annexed to this opinion.

An additional *ad hoc* consultation was held in February 2020 on the Suojalehto *et al.* 2020 publication (for further details, see "Discussion of additional data" below). In this consultation, two further MSCAs supported the classification proposal. In addition, several Company-Manufacturers, Company-Downstream users, Industry or trade associations and Company-Importers disagreed with the proposal. Their main concerns were related to 1) lack of data available to assign causality to specific substances, 2) uncertainty of potential co-exposure and irritating peak exposures, and 3) lack of trust in the original WoE approach of the classification proposal. In addition, several comments concerned the lack of methyl methacrylate-induced asthma cases in selected companies or use sectors.

Concerning the data available to assign causality to specific substances, potential co-exposure and peak exposures causing irritation, RAC considers the publication by Suojalehto *et al.* (2020), with the additional information received from the authors, to provide relevant evidence. RAC agrees that the original classification proposal had shortcomings. However, the Committee considers that the detailed comments received also in the original public consultation have been appropriately taken into account. Subsequently, additional key elements were identified and evaluated by RAC to form the current RAC opinion.

RAC notes that case reports on methyl methacrylate-induced occupational asthma, for example in the European occupational diseases databases, particularly concern nail

beauticians and dental and medical prosthesis technicians. It should be noted that specific exposure conditions, not applicable to all uses, may play a role. Therefore, lack of MMA-induced asthma cases in the particular use scenarios of specific companies or sectors does not demonstrate a lack of intrinsic respiratory sensitising potential by MMA. Even if occupational asthma induced by methyl methacrylate is mostly seen in a special group of users, such as in the dental or cosmetic sector, it indicates an intrinsic property to induce respiratory sensitisation, which must be considered relevant for classification. In addition, it is quite possible that MMA-induced occupational asthma cases are underdiagnosed and underreported.

More detailed responses to all concerns raised in the *ad hoc* consultation are provided in the targeted consultation response to comments document.

Discussion of additional data

After the original public consultation, during the development of its opinion, RAC was made aware of a new publication (Suojalehto *et al*., 2020). In addition, supplementary data and information, which had not been included in this publication, were received from the authors in response to ECHA's information request D(2021)0116 (Annex 5).

In this study, acrylate exposure was clearly connected with occupational asthma by the authors. The characteristics of acrylate induced occupational asthma were evaluated in a large series of cases (n=55 for acrylates), and were compared with the characteristics of occupational asthma induced by other low molecular weight (LMW) agents (n=418 for other LMW agents, of these n=125 for isocyanates). The study examined an international, multicentre retrospective cohort of subjects with occupational asthma ascertained by positive, placebo controlled SICs (between January 2006 and December 2015). The subjects' jobs and exposures, clinical and functional characteristics, and markers of airway inflammation were analysed. The SICs aimed to recreate an exposure comparable to that at the subjects' workplace. The aim of the placebo test was to expose the subjects with a similarly irritant, non-sensitising agent to rule out asthmatic responses due to irritation. The methodology of SIC conformed with international recommendations (Vandenplas *et al*., 2014).

In the SICs, the exposures were kept well below known respiratory irritant concentrations and relevant OELs, but MMA concentrations were not measured in any of the SICs included in Suojalehto *et al.* (2020). However, 3/6 of the MMA-cases in this publication were diagnosed at the Finnish Institute of Occupational Health, where a stable SIC protocol for two-component MMA-based methacrylate products has been used since 2000, and detailed information on the exposure levels in SICs exist (Annex 5: response from Suojalehto *et al.* to ECHA request D(2021)0116). Data of five MMA measurements during 2007-2020 were available from very similar SICs, using the same kind of products, the same chamber and having similar conditions such as humidity, temperature and ventilation. In these SICs, the measured concentrations were 0.56, 3.6, 5.1, 5.6 and 13 mg/m^3 (time-weighted averages; TWAs). The highest value was reported by the authors to be an outlier, which might be due to contamination in the sensitive analysis. According to the authors, it is extremely unlikely that any of the three Finnish MMA cases in Suojalehto *et al.* (2020) were exposed to more than the highest measured level (13 mg/m^3) during the SIC. Due to similar products and SIC protocols, it is likely that the exposure levels in two further MMA cases, diagnosed in other units, were comparable to those from which the measured concentration data were available. In the third case, which was diagnosed in other units, the patient ground a recently hardened prosthesis during the SIC. Air measurements in similar SICs at FIOH have produced about 1/10 of

the MMA concentration measured during mixing of liquid and powder. Most international 8 h OELs for MMA range from 100 to 410 mg/m^3 (GESTIS International limit values database), being around 200 mg/m^3 in many European countries. Exceptions to the aforementioned are Finland (42 mg/m^3), Latvia (10 mg/m^3) and Japan (8.3 mg/m^3), based on information in GESTIS.

As mentioned, the measurement data available for the SICs were average levels, and therefore the presence of MMA-peaks could not be excluded. However, RAC considers it unlikely that peaks would have been of paramount importance in the cases described in Suojalehto *et al*. (2020). The SICs were placebo-controlled, and data is available also on negative responses in similar SICs performed with MMA on asthmatics, described in more detail further below (p. 11). Of the 55 subjects with ascertained acrylate occupational asthma in Suojalehto *et al.* (2020), six had been predominantly exposed to MMA and tested positive specifically for this substance (Annex 5: response from Suojalehto *et al*. to ECHA request D(2021)0116; "predominantly" meaning that the main component of the products used was MMA, as opposed to mixed-exposures with other (meth)acrylates). In the Finnish cases (n=3), experts were able to verify from the original product information that they were two-component, self-curing methacrylate products containing MMA as their main ingredient. Based on the product information provided by the other centres (n=3), they were also able to conclude that these patients had used two-component MMA products to make prostheses.

Three of these six subjects had a delayed reaction in the SIC, two had a bi-phasic reaction (meaning both early and delayed), and one had an early reaction. While irritant effects cannot always be ruled out in early reactions, late and bi-phasic reactions in adequately performed SICs are considered by experts a hallmark of an immunological response. Two of these six subjects were dentists, three were dental and medical prosthesis technicians, and one was a nail beautician using MMA for acrylic nails.

As supporting data to the above, the table below presents 55 acrylate occupational asthma subjects, of which 24 had asthma considered by the authors to be ascertained as methacrylate induced. Of these, 20/24 had either late or bi-phasic positive SIC reactions. Apart from the six subjects that had specifically used MMA, most of these 24 were occupationally exposed to mixtures of methacrylates.

The study also showed that acrylates may induce occupational asthma through different immunologic mechanisms than other LMW agents, as asthma induced by acrylates had differing phenotypic characteristics, and in fact showed some characteristics that have previously been linked to occupational asthma caused by high molecular weight agents. However, the mechanism for acrylate induced asthma is still unknown, but it is seen by experts as clearly immunological. This view is supported also by this study.

In addition, an "asthma hazard index" was generated using the most recent iteration of a QSAR model by Jarvis *et al*. (2015). The index ranged from 0 to 1, 1 flagging the highest probability that the compound has respiratory sensitisation potential, based on its chemical structure (not its volatility). Using this model, the asthma index for MMA was 1, implying that the QSAR interprets its chemical structure as having the features required to cause asthma by sensitisation. The model's external statistics suggested that applying a cut-off point of 0.39 enables discrimination of respiratory sensitisers from controls with a sensitivity of 90% and a specificity of 96%.

***Table**: Supplementary data to (Suojalehto et al., 2020), received from the authors*.

Table 2. Functional characteristics of subjects with occupational asthma caused by cyanoacrylates, methacrylates and plain acrylates

	Cyanoacrylates (n=28)	Methacrylates (n=24)	Acrylates (n=3)	P-value
Baseline spirometry:				
FVC, % pred[a]	95.8 (87.0-102.1)	97.0 (89.8-111.2)	92.0 (86.0-93.5)	0.300
FEV_1, % pred [a]	92.0 (83.0-99.1)	96.0 (83.8-102.8)	90.0 (76.5-93.0)	0.440
FEV_1 <80%	5 (17.9)	3 (12.5)	1 (33.3)	0.480
FEV_1/FVC [a]	81.3 (76.5-85.5)	80.5 (75.8-84.0)	79.0 (70.5-85.5)	0.810
Airflow obstruction[b]	2 (7.1)	0	1 (33.3)	0.080
Baseline level of NSBH:	(n=25)	(n=20)	(n=3)	0.510
Absent	8 (32.0)	8 (40.0)	0	
Mild	10 (40.0)	8 (40.0)	3 (100.0)	
Moderate-to-severe	7 (28.0)	4 (20.0)	0	
Post-challenge change in NSBH[c]	(n=15)	(n=6)	(n=3)	
Pre/post-SIC NSBH ratio[a]	2.0 (1.0-3.9)	1.5 (0.6-2.0)	3.6 (2.1-3.8)	0.710
Pattern of bronchial response to SIC	(n=27)	(n=24)	(n=3)	
Isolated early	6 (22.2)	4 (16.7)	2 (66.7)	0.160
Isolated late	15 (55.6)	8 (33.3)	1 (33.3)	0.320
Both early and late components	6 (22.2)	12 (50.0)	0	0.070

Data are presented as n (% of available data) unless otherwise specified. Values in boldface are statistically significant. FEV_1: forced expiratory volume in one-second; FVC: forced vital capacity; NSBH: nonspecific bronchial hyperresponsiveness; SIC: specific inhalation challenge.

[a] Median value with interquartile range (IQR) within parentheses;

[b] Airflow obstruction defined by a FEV_1 <80% predicted value and a FEV_1/FVC ratio <70%;

[c] See ref (24) for the threshold values used for grading the level of NSBH.

Walters *et al*. (2017) described a series of occupational asthma cases caused by acrylic compounds, extracted from a UK-based regional surveillance scheme between 1989 and 2014. This study included 20 affected patients whose occupational asthma diagnoses were confirmed by OASYS (Occupational Asthma SYStem) analysis of serial peak flow measurements. Furthermore, three positive SIC tests were included. These cases were not included in Suojalehto *et al*. (2020; see Annex 5: response from Suojalehto *et al*. to ECHA request D(2021)0116).

Of these 20 patients in Walters *et al.* (2017), methyl methacrylate was reported as the predominant causative agent for eight patients. For six of these eight, MMA was reported as the only causative agent, but for the other two patients a mixture of MMA and cyanoacrylate was reported. Two of these diagnoses had been confirmed also with SIC, but the SIC methodology was not described. In both of these cases, MMA was mentioned as the only causative agent; the occupations of these patients were plastic moulder (prosthetic limbs) and orthopaedic theatre nurse. However, one of these patients (plastic moulder) had also been occupationally exposed to methylene diphenyl diisocyanate (MDI), to which he also reacted positively in the SIC.

Regarding the differentiation between irritating and sensitising effects of MMA, it is important to note that also negative responses (i.e. no asthmatic response) in the SIC are seen in asthmatics tested for MMA. Although not related to the cases in Suojalehto *et al.* (2020), the authors also provided information on negative responses in SIC in patients tested for MMA (Annex 5: response from Suojalehto *et al.* to ECHA request D(2021)0116). At the Finnish Institute of Occupational Health, during 2013-2019, seven patients were tested due to occupational asthma suspicion possibly related to MMA exposure with negative SIC results. Five of them already had an asthma diagnosis. Altogether 16 challenges (12 challenges to patients with existing asthma diagnosis) were performed with negative results with products containing only or predominantly MMA. In 11/16 of these cases, the product tested contained > 90-95% MMA or MMA and non-sensitising solvents. In 3/16 cases, the exposure was to a mixture of 50-100% MMA and ≤ 10% TMDMA. In 1/16 cases, a mixture of 50-70% MMA and < 10% triethyleneglycol dimethacrylate was used, and in 1/16 cases a mixture of 50-70% MMA and other methacrylates was used. In all of these cases, the SIC aimed to recreate an exposure comparable to that at the patient's workplace. RAC considers this information to demonstrate that it is not plausible that MMA induces reactions in asthmatics purely due to irritation.

Assessment and comparison with the classification criteria

No animal data are available regarding respiratory sensitisation due to lack of appropriate tests for this hazard class. The DS provided information on a number of published human occupational studies including one epidemiological cohort study on workers occupationally exposed to MMA (Marez *et al*., 1993), one survey with medical examination of workers involved in acrylic sheet production (Röhm GmbH, 1994) and six case studies of exposure of single workers exposed to MMA in differing applications (Pickering *et al*., 1986; Savonius *et al.*, 1993a and 1993b; Scherpereel *et al.,* 2004; Uriarte *et al*., 2013; Roth *et al*., 2017).

All of them gave indications of a positive correlation between MMA exposure and occupational asthma and/or deterioration of lung functions and related lung disease

symptoms, with the exception to the survey on workers involved in acrylic sheet production (Röhm GmbH, 1994). In this latter survey, 211 male workers were exposed to MMA concentrations that varied from 3 to 40 ppm (personal sampling measurements performed at the time of the study, according to TRGS 402 and calculated as 8 hours TWA geometrical mean concentration). It was reported that previously 8 h TWA concentrations had been between 10 and 70 ppm. No cases of MMA exposure related to skin or respiratory sensitisation were observed. Observation of irritation of the eyes and the upper respiratory tract was limited to acute and reversible reactions after short-term peak exposures at concentration levels exceeding 100 ppm (410 mg/m^3). No clinical symptoms of lung diseases were reported.

Marez *et al*. (1993) investigated a cohort of 40 workers in two factories with either less or more than 10 years exposure to MMA and compared it with a control group of 45 workers which had not been exposed to MMA. The study included a questionnaire, spirography and an evaluation of the occupational air concentration of MMA by passive samplers (mean air concentration detected: 18.5-21.6 ppm). Examination of the lung function parameters showed an increased incidence of chronic cough (20% in the exposed group compared with 1% in controls) and mild airway obstruction, neither of which were attributed to smoking. Spirometic values at the beginning of the work shift were similar in both groups, but a mild airway obstruction appeared during the work shift for the exposed group. The study did not give any clear indication of occupational asthma symptoms.

The case study by Pickering *et al.* (1986) reported on a 56 year old female working as a nurse in a hospital operating theatre with at least 7 years of experience in working with bone cements consisting of poly(methyl methacrylate) and methyl methacrylate liquid. The patient developed respiratory symptoms characterised by a persistent cough, wheeziness and breathlessness. These symptoms were associated with periods at work and resolved on rest days or on leave. A controlled exposure to the cements and MMA, under simulated working conditions, resulted in a delayed asthmatic reaction occurring 6 h after exposure with a maximum fall in forced expiratory volume in 1 second (FEV1) of 25% 13 h after the challenge.

Savonius *et al.* (1993a and 1993b) described three cases reportedly of respiratory sensitisation due to exposure to MMA. A 48 year old woman involved in plate engraving was exposed during the use of a glue and had developed respiratory distress at work with strain, sneezing, rhinorrhoea and stuffiness. Challenge to the implicated glue caused a maximal 24% fall in Peak Exploratory Flow (PEF) values and her symptoms persisted even after she changed to using cyanoacrylate glue. Her symptoms persisted and she had to quit her job. The second case was a 32 year old man involved in the assembly of hearing devices showing a small maximal 15% decrease in PEF values following the grinding of "a piece of methacrylate" in an exposure chamber. The third case was a 46 year old woman who had worked for about 20 years as a dental technician. She experienced a feeling of tickling in her throat, yawning, cough, tiredness and chest tightness; the symptoms subsided on sick leave and vacations but recurred within a week after returning to work. Simulated occupational exposures to "methacrylate powder and methacrylate liquid" for 30 minutes resulted in a maximum reduction of 26% in the PEF value. A skin prick test to "methacrylate" was negative. The authors of the study concluded that it is not possible to firmly conclude that the symptoms resulted from exposure to methyl methacrylate.

Scherpereel *et al. (*2004) reported on two cases of hypersensitivity pneumonitis in dental technicians following an inhalation exposure to MMA. Firstly, a 24 year old female dental

technician exposed to MMA for 6 months developed severe dyspnoea and hypoxemia and had to quit her job. The second case was a 20 year old woman – a student dental technician hospitalised for acute respiratory distress. She also showed hypoxemia.

Uriarte *et al.* (2013) reported a case of a 48 years old man with no history of atopy who worked as a professional plumber for over 30 years and had sought medical advice for progressive dyspnoea and dry cough during the last 3 years. His symptoms were triggered at work and persisted outside work. After performing a SIC for methyl methacrylate, the asthma reaction following an exposure to the substance was confirmed.

Roth *et al.* (2017) reported a case of an orthopaedic surgeon with no history of lung disease, who developed cough and dyspnoea. The effects were attributed to his occupational exposure to MMA, which is an important component of bone cement. The patient was diagnosed with asthma by spirometry and a bronchial provocation test with methacholine. The patient was diagnosed with work related disease, which was recognized by the industrial injury board.

According to the industry, the asthmas attributed to bone cement may also have been caused by gentamicin, an antibiotic medicine present in bone cement that has a self-classification as Resp. Sens. 1, H334. There is, however, no information available on the data this self-classification is based on, and RAC was not able to identify literature related to respiratory sensitisation by gentamicin. Gentamicin is also administered via inhalation as a medication, including long-term treatment in cystic fibrosis patients. Systemic gentamicin treatment can in rare cases cause an anaphylactic shock in patients. It is also a known skin sensitiser. The only study found related to gentamicin and asthma concluded: "Substantial obstructive reactions may occur in some asthmatic subjects after inhalation of gentamicin. The reactions appear to be non-immunological in nature and may be due to an irritant effect of the drug vehicle" (Dally *et al*., 1978). Overall, in the light of the information available, RAC does not consider gentamicin as a likely cause for asthmas induced by bone cements.

In addition, there are several case reports on respiratory sensitisation from European occupational disease databases. For most of them, there is minimal contextual information available, and RAC could not evaluate them. For the four case reports extracted from the Finnish Institute of Occupational Health database, it was reported that the asthma diagnoses were based on a positive response in the SIC. In two of these cases, the reactions were late (meaning that they occurred after 1-8 h of exposure), one was a dual reaction (meaning both early and late reactions) and one was an early reaction (meaning within 1 h of exposure). In particular, the late and dual reactions strongly argue for an immunological response rather than one due to respiratory irritation. Three of these four Finnish Institute of Occupational Health cases were also included in Suojalehto *et al.* (2020).

In the study reported by Suojalehto *et al.* (2020), acrylates were clearly linked with occupational asthma using placebo-controlled SIC exposures. Of the 55 subjects in whom acrylate related occupational asthma was ascertained, 24 tested positive for methacrylates and six tested positive specifically for methyl methacrylate. Five of these six subjects presented a delayed or bi-phasic (meaning early and delayed) reaction in the placebo-controlled SICs, considered by experts to strongly indicate an immunological response. One subject presented an early reaction. It should be noted that even though irritant effects cannot always be ruled out in early reactions, this does not mean that they are necessarily due to them in adequately performed SICs. In addition to a placebo-

control exposure, also measurement of pulmonary function can be used to distinguish sensitisation and irritation also in early reactions in SIC. Moreover, an increase in inflammatory markers supports the diagnosis. In the SICs reported by Suojalehto *et al.* (2020), placebo exposures were conducted for the subjects. The aim of the placebo test is to expose the subject with a similarly irritant, non-sensitising agent. If the subjects' positive reactions would have been due to respiratory irritation, they should also have had a positive reaction in the placebo exposure.

Importantly, negative responses in the SIC are also seen in asthmatics tested for MMA, as described above. This clearly indicates that it is not plausible that methyl methacrylate purely induces reactions in asthmatics due to its respiratory irritant properties.

RAC notes that the relatively low number of MMA related occupational asthma cases reported in the scientific literature or occupational disease databases should not be seen as evidence of low prevalence. As none of the acrylates are classified for respiratory sensitisation, most occupational physicians are unlikely to suspect the acrylates or more specifically methyl methacrylate as a causative agent in a patient's asthma. Therefore, RAC considers it possible that MMA occupational asthma cases are underdiagnosed and are therefore also under-reported.

RAC is of the opinion that the existing cases reviewed here, already reliably attributed to methyl methacrylate, clearly demonstrate its potential to induce respiratory sensitisation.

On the other hand, it is known that methacrylates cross-react, and as 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. However, as presented earlier, six individual cases could be identified in the cohort of Suojalehto *et al*. (2020), where the predominant occupational exposure was known to be specifically to MMA (based on careful expert judgment of the ingredients of the products used), and those patients had a positive reaction to MMA in the SIC. These subjects had occupations as dentists, dental and medical prosthesis technicians, and nail beauticians. It should be noted that dental and medical prosthesis technicians and nail beauticians continue to use liquid-powder mixtures, of which the liquid is typically 100% MMA. Also the independent dataset by Walters *et al*. (2017) gives support that MMA has potential to induce respiratory sensitisation in humans. Due to uncertainty regarding the diagnostic methodology used, RAC considers Walters *et al*. (2017) as supporting information.

Finally, RAC would like to note that a negative result in a skin prick test should not be interpreted as a negative result for respiratory sensitisation by MMA. It is well known that methyl methacrylate and other low molecular weight agents (such as diisocyanates) tend to systematically produce negative results in the skin prick test (Suojalehto *et al*., 2020). Nevertheless, MMA is a known skin sensitiser and has an existing harmonised classification as Skin Sens. 1; H317. Although this is not proof of its respiratory sensitising potential, the intrinsic skin sensitising property of the molecule is established. In addition, MMA is volatile (vapour pressure 37 hPa at 20 °C), meaning that exposure by inhalation is relevant.

The CLP criteria for classification of a substance as the respiratory sensitiser are the following:

Table 3.4.1

Hazard category and sub-categories for respiratory sensitisers

Category	Criteria
Category 1	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 (b) if there are positive results from an appropriate animal test.
Sub-category 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 (1). Severity of reaction may also be considered.
Sub-category 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 (1). Severity of reaction may also be considered.
(1) At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.	

On human evidence, the regulation states: "*Evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.*"

And furthermore: "*The evidence referred to above could be:*
(a) *clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include: (i) in vivo immunological test (e.g. skin prick test); (ii) in vitro immunological test (e.g. serological analysis); (iii) studies that indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects; (iv) chemical structure related to substances known to cause respiratory hypersensitivity;*
(b) *data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.*"

Moreover, it is stated that "*The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own*."

RAC considers that the epidemiological cohort study (Marez *et al.*,1993) as well as the

survey of workers (Röhm GmbH, 1994) exposed to MMA do not provide conclusive evidence either for classification or for non-classification of the substance as a respiratory sensitiser. For example, the information on Röhm (1994) is minimal and based only on a personal communication from one company, without any information on the health questionnaire used, results or description of exposure scenarios and possible risk management measures (e.g. the use of RPEs).

A number of published single case studies as well as information extracted from occupational diseases databases (RNV3P, SWORD, FIOH) provide *ca*. 70 cases in total, covering the period from 1989 to 2017 in at least three different countries and showing similarities with respect to areas of occupation (particularly nail beauticians and dental and medical prosthesis technicians), raise a concern of MMA induced respiratory sensitisation. However, RAC notes that overall, due to medical confidentiality, there was minimal information available for these case reports, and therefore it is not possible to assess them, including whether the patient was indeed sensitised specifically to methyl methacrylate and the reliability of the occupational asthma diagnosis. Most of the published case studies are also lacking in this respect. **Therefore, the opinion of RAC does not rely on these cases.**

RAC considers that the recent cohort study by Suojalehto *et al*. (2020) provides reliable human data showing the potential of MMA to induce respiratory sensitisation, although the number of cases that could be attributed specifically to it was low (n=6). This was a clinical study and not designed for classification purposes. However, RAC considers that it employed the state-of-the art methodology available for diagnostics of occupational asthma due to respiratory sensitisation. Therefore, and considering the CLP criteria, RAC is of the opinion that the study is valid for the purpose of classification. Also the study by Walters *et al*. (2017) supports the conclusion that MMA has respiratory sensitising potential. According to the authors of Suojalehto *et al.* (2020), the patients in these two studies did not overlap. Although the specific link between methyl methacrylate exposure and specific reaction in SIC could be verified in only the cases in Suojalehto *et al*. (2020), it cannot be concluded that such a link does not exist in the rest of the reported cases, where details were lacking.

RAC acknowledges the fact that methyl methacrylate is a respiratory irritant that can provoke asthmatic reactions due to its irritant effects and has an existing harmonised classification as STOT SE 3; H335. Moreover, with the currently available information, it is not possible to identify the mechanism leading to asthma. RAC takes into account that there are no immunological tests available to robustly demonstrate respiratory sensitisation caused by methyl methacrylate, because low molecular weight molecules do not act via an IgE dependent mechanism. According to CLP provisions, "*immunological mechanisms do not have to be demonstrated*" in order to classify a substance as respiratory sensitiser.

In addition, the difference between an irritating mechanism and sensitisation can be difficult to define with respect to clinical symptoms. However, generally a latency between the first exposure and the occurrence of the symptoms indicates more in favour of a sensitisation. Also, the positive reactions in the placebo controlled SICs strongly argue for a mechanism based on respiratory sensitisation (Suojalehto *et al*., 2020).

The prevalence of asthma cases in the MMA exposed population is unknown. As a consequence, sub-categorisation into Resp. Sens. 1A or 1B is not possible. It should also be noted that overall, it is possible that MMA induced occupational asthma cases are

underdiagnosed and underreported. As MMA is not classified as a respiratory sensitiser, physicians are generally unlikely to suspect it as a causative agent behind (occupational) asthma cases). It is also possible that particular exposure conditions, not applicable to all uses, play a role. Finally, according to the CLP, the results of positive specific bronchial challenge tests are considered to provide sufficient evidence for classification on their own.

In conclusion, RAC agrees with the classification proposed by the DS as **Resp. Sens. 1; H334** based on evidence in humans for methyl methacrylate. The available data do not allow for sub-categorisation.

10.7 Skin sensitisation

Data are only presented as a weight of evidence for supporting the evidence that MMA has sensitizing properties. It is considered that the existing harmonised classification for methyl methacrylate: Skin Sens. 1 – H317 does not need to be reconsidered for Public Consultation or assessed by RAC.

Table 11: 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
Similar to OECD TG 429 LLNA Positive control : 2,4 - Dinitrochlorobenzene (DNCB)	Young adult CBA/Ca mice	MMA	Doses of 0, 10, 30, 50, 75, and 100% (neat) MMA in acetone or acetone/oil (4:1 v/v) DNCB (acetone/olive oil): 0.036 % (w/v) Exposed on the dorsum of both ears daily for 3 consecutive days	Positive. MMA is sensitising	Registration dossier (2006)

Table 12: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Observations	Reference
case report in occupational population 175 dental technicians or students, with and without previous handling experience with MMA containing dental materials, were patch tested with MMA (2%).	MMA	No positive reactions were observed.	Marx H., et al. (1982)
case report in occupational population 4913 patients suspected of occupational contact dermatitis examined during the years January 1, 2001 to December 31, 2002. All patients were patch-tested with a screening series of 65 allergens. The patch-tests were done with the standardized technique using Finn	MMA	Of the 4900 individuals tested for methyl methacrylate at a patch test concentration of 2% (w/w), 1.4% showed a positive reaction.	Pratt MD, et al. (2004)

Type of data/report	Test substance	Observations	Reference
Chambers on Scanpor tape. Patch testing was performed on the back with an occlusion time of 2 days and assessment at 2 and 3 days and again after 7 days. 4900 patients were patch-tested with methyl methacrylate (in petrolatum (2%)).			
Study type: case report Type of population: patients with dermatitis with previous contact with (meth)acrylate (acrylic glues) Subjects: Review of test files from 1994 to 2006 at the Finnish Institute of Occupational Health for allergic reactions to acrylic monomers in 32 patients working in dental professions.	MMA	32 patients with a history of exposure to (meth)acrylates were identified. They had allergic reactions to acrylic monomers: 15 dental nurses, 9 dentists, and 8 dental techinicans. 36 acrylic monomers were analysed in patch test reactivity. The dentists and dental nurses were most commonly exposed to 2-hydroxyethyl methacrylate (2-HEMA), triethyleneglycol dimethacrylate (TREGDMA), and 2,2-bis[4-(2-hydroxy- 3-methacryloxypropoxy) phenyl]propane (bis-GMA. The dental technicians were mainly exposed and sensitized to MMA and ethyleneglycol dimethacrylate (EGDMA). Of the 32 cases (occupationally exposed and sensitised to acrylic monomers), 8 showed a positive reaction to MMA (25%).	Aalto-Korte K, Alanko K, Kuuliala O, Jolanki R (2007)
Study type: case report Type of population: patients with dermatitis with previous contact with (meth)acrylate (acrylic glues) Subjects: A retrospective appraisal of 473 patch test records from September 1994 to August 2006 at the Finnish Institute of Occupational Health was made. 39 (meth)acrylates were tested. Ten patients were tested at a patch test concentration of 2% MMA in pet.(w/w).	MMA	473 patients with a history of exposure to (meth)acrylates were identified. For methyl methacrylate, 10 individuals were tested at a patch test concentration of 2% in pet.(w/w). Of these 10 (occupationally exposed and sensitised to acrylic glues) individuals, 4 showed a positive reaction to MMA.	Aalto-Korte K, et al. (2008)
Study type: case report Type of population: 23 (meth)acrylate-exposed persons were tested, no further details Subjects: Among 1619 patients suspected of occupational contact dermatitis examined during the years 1990-1994, sensitivity to acrylates was diagnosed in 9 persons (4 dental technicians, 4 dentists, 1 textile printer). Additional tests with (meth)acrylate series (Chemotechnique Diagnostics AB) were performed on 23 patients (methyl methacrylate was tested in pet. 2 %). Patients with a history of exposure to (meth)acrylates had been tested with a	MMA	Of the 23 individuals tested for methyl methacrylate at a patch test concentration of 2% (w/w), 4 (17%) showed a positive reaction. Comparison of patch results in dental technicians and dentists indicated that dentists were sensitive to a greater no of (meth)acrylate (acrylate and methacrylate) allergens and also to certain or other allergens (metals and rubber additives). Dental technicians were sensitive almost exclusively to methacrylates, while the textile printer only to acrylates.	Kiec-Swierczynska M. (1996)

Type of data/report	Test substance	Observations	Reference
commercially available kit. Patch testing was performed on the back with an occlusion time of 2 days and assessment at 2 and 3 days.			
Study type: case report Type of population: patients with dermatitis, (suspected of (meth) acrylate allergy; no further details)	MMA	Among the examined patients, a positive patch-test reaction against methyl methacrylate (test concentration: 2 % in pet.) was found in 0.8 % (9 patients) of the tested patients. 4 of the 9 patients were dental technicians.	Schnuch Dr. A (1997)
Study type: case report Type of population: dental technicans with dermatitis, (details on exposure to methyl methacrylate not reported)	MMA	A group of 72 dental technicans handling preparations containing acrylic monomers, including MMA were surveyed in clinics of the IVDK since 1989 to 1994 in epicutaneous tests. 9 dental technicans showed a positive reaction towards MMA. No further details concerning the compositions of the preparations is given in the article.	Schnuch A., Geier J. (1994)
Study type: case report Type of population: occupational Subjects: Among 3120 patients suspected of occupational contact dermatitis examined during the years July 1, 1994 to June 30, 1996. All patients were patch-tested with a screening series of 49 allergens (Chemotechnique Diagnostics (Malmö, Sweden)). The patch-tests were done with the standardized technique using Finn Chambers on Scanpor tape. Patch testing was performed on the back with an occlusion time of 2 days and assessment at 2 and 3 days and again after 7 days. 3080 patients were patch-tested with methyl methacrylate (in petrolatum (2%)).	MMA	Of the 3080 individuals tested for methyl methacrylate at a patch test concentration of 2% (w/w) from July 1, 1994 to June 30, 1996, 1.2% showed a positive reaction.	Marks JG, et al. (1998)
Study type: case report Type of population: patients with dermatitis, (suspected of (meth) acrylate allergy; no further details)	MMA	Among the examined patients, a positive patch-test reaction against methyl methacrylate (test concentration: 2 % in pet.) was found in 1.2 % (51 patients) of the tested patients. 37 of the 51 patients with a positive patch-test reaction have had contact to methyl methacrylate. For the other patients it is not known if they have had contact to methyl methacrylate or not.	Schnuch Dr. A (1995)
Study type: study with volunteers Type of population: Patch test with volunteers to assess the potential for	MMA	After 2 d, one case of erythema was observed, at day 10 no skin reaction were observed in the 27 volunteers who returned.	Cavelier C., et al. (1981)

Type of data/report	Test substance	Observations	Reference
skin sensitisation in humans. Subjects: Undiluted test substance A 48 h occlusive patch test with undiluted MMA, containing 1% hydroquinone, was conducted with 30 volunteers. A challenge was performed with 20 persons at day 19. 20% test substance Forty five volunteers were patch tested with 20% MMA in olive oil (stabiliser content 1%) for 48 to 72 h (Finn Chamber). No skin reactions were observed after 2, 10, 20 and 30 d. Challenge application on day 30.		On day 19, 20 of the volunteers were challenged using the same procedure at a different part of the back. In 2 cases, a positive skin reaction (irritation) was seen after 48 h. A third case of a positive reaction was observed 10 d after the second application. In this case, lymphocyte infiltration of the skin area was observed. Two of the volunteers with skin reactions were subsequently tested with hydroquinone 1% in petrolatum, and did not show any reaction. No skin reaction in the 45 volunteers on days 2, 10, 20 and 30. Due to the unusually high stabiliser content in the test material (1% hydroquinone) the relevance of the findings is unclear.	
Study type: case report Type of population: patients with dermatitis with previous contact with (meth)acrylate (no further details) Subjects: A retrospective appraisal of approximately 14,000 patch test records from January 1983 to March 1998 at the Hope Hospital, U. of Manchester, UK was made. Patients with a history of exposure to (meth)acrylates had been tested with a commercially available kit and, when possible, to the product to which they were exposed. Patch testing was performed on the back with an occlusion time of 2 days and assessment at 2 and 4 days.	MMA	440 patients with a history of exposure to (meth)acrylates were identified. 30 (meth)acrylates were tested in 83 to 352 of these individuals. For Methyl methacrylate, 352 individuals were tested at a patch test concentration of 2% (w/w). Of these, 17 (4.8%) showed a positive reaction. In addition, 47 of the positive responders were sensitized at work and were categorized by occupation. Dentistry (17%) and printing/lithography (17%) were considered by the authors to show the greatest incidence. Other occupations cited were gearbox testers testing acrylate sealed gear-boxes (3 of 4 in the same plant) and gas workers using adhesives (8.5%). Patients sensitized to artificial fingernails developed dermatitis of the finger tip and approximately 50% of these patients also had ectopic facial involvement.	Tucker SC, Beck HM (1999)
Study type: case report Type of population: patients with dermatitis with previous contact with (meth)acrylates (detal products, adhesives); ((meth)acrylate allergy suspected, no further details)	MMA	Among 82 patients suspected of occupational sensitisation to acrylates from either exposure to dental materials or anaerobic sealants, 11 were identified as having been sensitised to acrylates over a 5 year period. One patient (1.2%) reacted positively in a patch test with MMA (5% in petrolatum).	Guerra L., et al. (1993)
Study type: case report Type of population: occupational Subjects: 3549 patients suspected of occupational contact dermatitis examined during the years July 1, 1992 to June 30, 1994. All patients were patch-tested with a screening series of 52 allergens (Chemotechnique Diagnostics (Malmö, Sweden)). The	MMA	Of the 3472 individuals tested for methyl methacrylate at a patch test concentration of 2% (w/w) from July 1, 1992 to June 30, 1994, 1.1% showed a positive reaction.	Marks JG, et al. (1995)

Type of data/report	Test substance	Observations	Reference
patch-tests were done with the standardized technique using Finn Chambers on Scanpor tape. Patch testing was performed on the back with an occlusion time of 2 days and assessment at 2 and 3 days and again after 7 days. 3472 patients were patch-tested with methyl methacrylate (in petrolatum (2%)).			
Study type: case report Type of population: mainly occupational: Of the 66 patients, 57 were occupational cases, 1 resulted from using artificial nails, 1 from dental products and 7 had an unknown source of sensitization	MMA	Among 66 patients with contact allergy to acrylic monomers 43 (65 %) patients showed a positive patch test reaction to at least one (meth)acrylate. 18 (27 %) positive reaction to methyl methacrylate. Multiple sensitization to various acrylates and methacrylates were found. So it is impossible to distinguish between concomitant sensitization and cross-reactivity.	Aalto-Korte K, et al. (2010)
Study type: case report Type of population: patients with dermatitis with previous contact with (meth)acrylate (no further details)	MMA	48 patients (17.5 %) had an allergic reaction to at least 1 (meth)acrylate. The (meth)acrylates most often provoking an allergic patch test reaction were 2-Hydroxyethyl acrylate (2-HEA, 12.1 %), 2-Hydroxypropyl methacrylate (2-HPMA, 12.0 %), 2-Hydroxyethyl methacrylate (2-HEMA, 11.4 %) and Methylmethacrylate (MMA, 20/271 patients; 7.4 %).	Kanerva Lasse, et al. (1997) Kanerva L (1999)
Study type: case report Type of population: dental technicans with dermatitis, (details re. exposure to methyl methacrylate not reported)	MMA	Among 93 dental technicans examined, allergic contact dermatitis was diagnosed in 50 %, irritant contact dermatitis in 29 % and atopic hand dermatitis in 15 % of the patients. 2 % showed a mixture of irritative and allergic contact dermatitis. 17 patient reacted to Methyl methacrylate In 26 patients, multiple sensitization to various methacrylates were found. So it is impossible to distinguish between concomitant sensitization and cross-reactivity.	Peiler D, et al. (1996)
Study type: Study with volunteers to assess the potential for skin irritation and skin sensitisation in humans. Details on study design: Twenty female volunteers without reported previous contact to MMA were patch tested with 5% MMA in liquid paraffin or olive oil (purity, stabiliser content not indicated) continuously for 48 h.	MMA	Eighteen of 20 volunteers responded with skin reactions varying from erythema to delayed eczematous dermatitis. A distinct differentiation between sensitisation and irritation reactions was not made by the author. In a follow-up patch test of the same subjects with small plates of heat cured acrylic resin containing 5.2% to 6.4% of residual MMA monomer no skin reactions were observed.	Nyquist G. (1958)

Type of data/report	Test substance	Observations	Reference
Study type: human - skin sensitization, case reports Details on study design: 22 patients (19 women and 3 men) classified with the burning mouth syndrome (BMS) were patch tested with a standard routine series and a standardized denture-dental ((meth)acrylate and metal) series.	MMA	Twenty of the 22 patients wore a complete or partial denture. None of the 22 patients showed a positive reaction to the tested methacrylates including methyl methacrylate.	Dutrée-Meulenberg R.O.G.M., et al. (1992)

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

There are a great number of reliable studies available to assess the skin sensitising potential of methyl methacrylate. The variety of used test methods is large, providing positive and negative results in almost equal proportions. Among them, Anonymous, (2006) is considered as a key study. They conducted a LLNA comparable to OECD guideline 429 using concentrations from 10 to 100% dissolved in either acetone or acetone/olive oil (4:1 v/v administered daily for three days to four CBA/ca mice per treatment. Five days after the initiation, animals received 3H labelled thymidine five hours before sacrifice. The EC3 value for methyl methacrylate were 60% (w/v) in acetone and 90% (w/v) in acetone/olive oil (4:1); the EC3 value of the 2,4 -Dinitrochlorobenzene as positive control was 0.036%, leading to the assessment that methyl methacrylate has to be considered as weak skin sensitiser.

Numerous reports of skin sensitisation exist mainly, from occupational environments (dentistry, printing/lithography, gear boxes testers and gas workers using adhesives and wearing artificial fingernails). Incidence of positive reaction occurred at an incidence between 0.8 to 17% in selected workers.

10.8 Germ cell mutagenicity

Hazard class not assessed in this dossier

10.9 Carcinogenicity

Hazard class not assessed in this dossier

10.10 Reproductive toxicity

Hazard class not assessed in this dossier

10.11 Specific target organ toxicity-single exposure

Data are presented just in order to discriminate potential irritative and sensitizing properties of MMA after inhalation. No change of the current EU harmonized classification is proposed in this CLH report.

This endpoint is not in the scope of public consultation.

Table 13: Summary table of human data on STOT SE

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference

Letter of Chief Industrial Hygienist of the Occupational Health Section of the Labour Department of the State of Connecticut	MMA	Letter which include some observations regarding exposure to MMA at workplace	Strong, easily detectable smell in areas with concentrations between 32 and 65 ppm, very definite irritation in areas with 170 to 248 ppm and unbearable discomfort in an area with a spot concentration of 2300 ppm. The author and his team concluded that 100 ppm could be tolerated continuously without discomfort.	Coleman, 1963
Personal communication Survey of 211 male workers	MMA	Medical examination of workers in acrylic sheet production exposed to methyl methacrylate Present exposures to MMA varied between < 3 and 40 ppm (8 h TWA, calculated as geometrical means of personal sampling measurements according to TRGS 402). Past exposures were between 10-70 ppm MMA (8 h TWA). Occasional short-term peak concentrations of 100-680 ppm MMA had also been recorded.	In the exposed group no case of MMA exposure related skin or respiratory sensitization was observed. Observation of irritation of the eyes and the upper respiratory tract was limited to acute and reversible reactions after short term peak exposures at concentration levels exceeding 100 ppm (ca. 410 mg/m^3). There were no indications for clinical symptoms of a work related rhinopathy or any substance related abnormalities in the exposed group.	Roehm, 1994
Case report	MMA	Man (50-year old) working as dental technician.	Occupational disease: non allergic occupational asthma High level of attributability	RNV3P database

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

In a letter from the chief industrial Hygienist of the occupational health section of the labour department of the state of Connecticut to the Chairman of ACGIH regarding work place experience of MMA, the author and the members of his team noted a strong, easily detectable smell in areas with concentrations between 32 and 65 ppm, very definite irritation in areas with 170 to 248 ppm and unbearable discomfort in an area with a spot concentration of 2300 ppm. The author and his team concluded that 100 ppm could be tolerated continuously without discomfort. Therefore it can be concluded that a respiratory irritation occurs in humans at concentrations exceeding 100 ppm.

Reversible irritation reactions have been observed in human studies after short-term peak exposures at concentration levels exceeding 100 ppm (Coleman, 1963, Roehm 1994).

No damage to olfactory function was reported in a cross-sectional smell test in workers exposed to MMA up to 50 ppm during the past 6 years and up to 100 ppm the time before (mean duration of exposure 9.6 years) (Muttray *et al.*, 1997). No effects were seen after single exposures to 50 ppm in a study with human volunteers investigating changes in cytokine levels indicative of subclinical, irritating effects (Muttray *et al.*, 2007).

Additionally a case of non allergic asthma was reported in the French RNV3P database in a man working as a dental technician.

Methyl methacrylate is currently EU classified as STOT SE3 – H335. The current harmonized classification does not need to be reconsidered.

10.12 Specific target organ toxicity-repeated exposure

Hazard class not assessed in this dossier

10.13 Aspiration hazard

Hazard class not assessed in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Hazard class not assessed in this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Hazard class not assessed in this dossier

13 ADDITIONAL LABELLING

14 REFERENCES

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15 ANNEXES

[Please add ANNEX I to the CLH report and potential other annexes.]