# 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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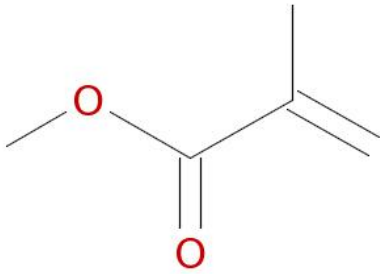
# CONTENTS

# 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<br>EC no.: 201-297-1 | ≥ 99.0 - ≤ 100% | Flam. Liq. 2, H225<br>Skin. Irrit. 2 – H315<br>Skin Sens. 1 – H317<br>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<br>methyl 2-methylprop-2-enoate<br>methyl 2-methylpropenoate | 201-297-1 | 80-62-6 | Flam. Liq. 2<br>Skin Irrit. 2<br>Skin Sens. 1<br>STOT SE 3 | H225<br>H315<br>H317<br>H335 | GHS02<br>GHS07<br>Dgr | H225<br>H315<br>H317<br>H335 | | | Note D |
| Dossier submitters proposal | 607-035-00-6 | methyl methacrylate<br>methyl 2-methylprop-2-enoate<br>methyl 2-methylpropenoate | 201-297-1 | 80-62-6 | **Add**<br>Resp. Sens. 1 | H334 | GHS08<br>Dgr | H334 | | | |
| Resulting Annex VI entry if agreed by RAC and COM | 607-035-00-6 | methyl methacrylate<br>methyl 2-methylprop-2-enoate<br>methyl 2-methylpropenoate | 201-297-1 | 80-62-6 | Flam. Liq. 2<br>Skin Irrit. 2<br>Skin Sens. 1<br>STOT SE 3<br>Resp. Sens. 1 | H225<br>H315<br>H317<br>H335<br>H334 | GHS02<br>GHS08<br>Dgr | H225<br>H315<br>H317<br>H335<br>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<br>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<br>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<br>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<br>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 |
| **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<br>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, IUCLID 6) | Measured value, purity: 99.9 % |
| **Relative density** | 0.94 g/cm³ at 20 °C | Weast (1988) (Registration dossier, IUCLID 6) | Reliable handbook value, purity not given |

[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) |
|---|---|---|---|
| **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:<br>**Flam. Liq. 2, H225**<br>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.<br>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.<br>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)<br><br>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)<br>key study<br><br>Non Guideline<br>GLP compliance not specified | Mainwaring G, Foster JR, Lund V, Green T (2001) |
| rat (Fischer 344) male<br><br>exposure of isolated URT<br><br>Exposure regime: 1 hour<br><br>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)<br><br>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.<br><br>The data suggest that MMA deposits with 10-20% efficiency in normally breathing rats. | 2 (reliable with restrictions)<br><br>key study<br><br>Not GLP compliant | Anonymous (1992)<br><br>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 the exposure time) at the end of exposure | 2 (reliable with restrictions)<br><br>Not GLP compliant | Raje *et al.*, 1985 |
| Infusion of MMA (33 mg/kg.min | MMA diseappared very rapidly | 2 (reliable with | Paulet *et al*., 1979 |

| Method | Results | Remarks | Reference |
|---|---|---|---|
| for 3 min) in rabbits and dogs | from the blood of the experimental animals. Half-life was less than 30s in rabbits and 41s in dogs. | restrictions)<br><br>Not GLP compliant | |

## 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.<br>High level of attributability | RNV3P database |
| Case report #2 | MMA | Woman (30-year old) working as nail | Occupational disease: occupational allergic asthma | RNV3P database |

| Type of data/report | Test substance | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | technician. | High level of attributability | |
| Case report #3 | MMA | Man (44-year old) working as dental technician. | Occupational disease: occupational asthma<br>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<br>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<br>High level of attributability | RNV3P database |
| Case report #6 | MMA | Man (57-year old) working as dental technician. | Occupational disease: Allergic occupational asthma<br>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.<br>High level of attributability | RNV3P database |
| Case report #8 | MMA | Man (29-year old) exposed to UV inks composed of MMA | Occupational disease: asthma<br>High level of attributability | RNV3P database |
| Case report #9 | MMA | Woman (51-year old) working as dental assistant. | Occupational disease: asthma<br>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<br>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<br>High level of attributability | RNV3P database |
| Case report #12 | MMA | Woman (31-year old) working as nail technician. | Occupational disease: occupational asthma<br>High level of attributability | RNV3P database |
| Case report #13 | MMA | Woman (38-year old) formely working as nail manufacturer. | Occupational disease: typical occupational asthma with sequelae from her previous job. Forced to change her job. | RNV3P database |

| Type of data/report | Test substance | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | | 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.<br>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.<br>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.<br>High level of attributability | RNV3P database |
| Case report #17 | MMA | Man (50-year old) working as dental technician. | Occupational disease: non allergic occupational asthma<br>High level of attributability | RNV3P database |
| Case report #18 | MMA | Man (39-year old) working as construction electrician. | Occupational disease: asthma.<br>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.<br>high level of attributability | RNV3P database |
| Case report #20 | MMA | Woman (40-year old) working as a professional nail prothesist. | Occupational disease: occupational asthma.<br>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.<br>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.<br>High level of attributability | RNV3P database |
| Case report #23 | MMA | Woman (22-year old) working as nail technician. | Occupational disease: occupational asthma<br>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<br>Moderate level of attributability | RNV3P database |
| Case report #25 | MMA | Woman (50-year old) working as dental technician | Occupational disease: asthma<br>Moderate level of attributability | RNV3P database |
| Case report #26 | MMA | Man (62-year old) working as carpenter | Occupational disease: asthma which led to disability | RNV3P database |

| Type of data/report | Test substance | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | | Moderate level of attributability | |
| Case report #27 | MMA | Man (30-year old) working in furniture industry exposed to MMA | Occupational disease: asthma. Breathing difficulties due to occupational exposure.<br>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.<br>Moderate level of attributability | RNV3P database |
| Case report #29 | MMA | Woman (46-year old) working as machine operator in polystyrene industry. | Occupational disease: asthma<br>Moderate level of attributability | RNV3P database |
| Case report #30 | MMA | Men (49-year old) packer in polystyrene industry. | Occupational disease: asthma<br>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<br>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.<br>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.<br>Moderate level of attributability | RNV3P database |
| Case report #34 | MMA | Man (63-year old) working as house painter. | Occupational disease: asthma.<br>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<br>Moderate level of attributability | RNV3P database |
| Case report #36 | MMA | Man (48-year old) working as dental technician. | Occupational disease: possible occupational asthma.<br>Moderate level of attributability | RNV3P database |
| Case report #37 | MMA | Man (49-year old) working as dental technician. | Occupational disease: asthma.<br>Moderate level of attributability | RNV3P database |
| Case report #38 | MMA | Woman (23-year old) working as nail technician. | Occupational disease: asthma and rhinitis.<br>Moderate level of attributability | RNV3P database |
| Case report #39 | MMA | Woman (39-year old) working as nail | Occupational disease: asthma<br>High level of attributability | RNV3P database |

| Type of data/report | Test substance | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | technician. | | |
| Case report #40 | MMA | Woman (31-year old) | Occupational disease: asthma<br>Moderate level of attributability | RNV3P database |
| Case report #41 | MMA | Woman (29-year old) working as dental technician. | Occupational disease: asthma<br>High level of attributability | RNV3P database |
| Case report #42 | MMA | Woman (50-year old) working in automotive industry | Occupational disease: asthma<br>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<br>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<br>No information on attributability | SWORD database |
| Case #67 | MMA | Man working in the manufacture of medical devices | Occupational disease: asthma<br>Reported by occupational physicians<br>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.<br>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.<br>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<br>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.<br>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<br>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<br>Survey of 211 male workers | MMA | Medical examination of workers in acrylic sheet production exposed to methyl methacrylate<br>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**.<br>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 implicated glue caused a maximal 24% | Savonius *et al.* (1993a and b) |

| Type of data/report | Test substance | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | | fall in Peak Exploratory Flow (PEF) values and her symptoms persisted even after a change to a cyanoacrylate glue.<br><br>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.<br><br>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.<br><br>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 centre for occupational health. The patient was diagnosed with work-related | Roth *et al.* (2017) |

| Type of data/report | Test substance | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | | 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 :<br>- 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.<br>- 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 service activities, other business activities.

One other case of occupational asthma attributed to methyl methacrylate was reported to THOR by

[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/

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.

## 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<br>LLNA<br>Positive control : 2,4 | 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) | Positive.<br>MMA is sensitising | Registration dossier (2006) |

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|---|---|---|---|---|---|
| - Dinitrochlorobenzene (DNCB) | | | Exposed on the dorsum of both ears daily for 3 consecutive days | | |

**Table 12: Summary table of human data on skin sensitisation**

| Type of data/report | Test substance | Observations | Reference |
|---|---|---|---|
| case report in occupational population<br><br>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<br><br>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 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.<br><br>4900 patients were patch-tested with methyl methacrylate (in petrolatum (2%)). | 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) |
| Study type: case report<br><br>Type of population: patients with dermatitis with previous contact with (meth)acrylate (acrylic glues)<br><br>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<br><br>Type of population: patients with dermatitis with previous contact with | MMA | 473 patients with a history of exposure to (meth)acrylates were identified.<br><br>For methyl methacrylate, 10 individuals were | Aalto-Korte K, et al. (2008) |

| Type of data/report | Test substance | Observations | Reference |
|---|---|---|---|
| (meth)acrylate (acrylic glues)<br><br>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). | | 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. | |
| Study type: case report<br><br>Type of population: 23 (meth)acrylate-exposed persons were tested, no further details<br><br>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 %).<br><br>Patients with a history of exposure to (meth)acrylates had been tested with a commercially available kit. Patch testing was performed on the back with an occlusion time of 2 days and assessment at 2 and 3 days. | MMA | Of the 23 individuals tested for methyl methacrylate at a patch test concentration of 2% (w/w), 4 (17%) showed a positive reaction.<br><br>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) |
| Study type: case report<br><br>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<br><br>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<br><br>Type of population: occupational<br><br>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 | 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) |

| Type of data/report | Test substance | Observations | Reference |
|---|---|---|---|
| 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.<br><br>3080 patients were patch-tested with methyl methacrylate (in petrolatum (2%)). | | | |
| Study type: case report<br><br>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.<br><br>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<br><br>Type of population: Patch test with volunteers to assess the potential for skin sensitisation in humans.<br><br>Subjects: Undiluted test substance<br><br>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.<br><br>20% test substance<br><br>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. | MMA | After 2 d, one case of erythema was observed, at day 10 no skin reaction were observed in the 27 volunteers who returned.<br><br>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.<br><br>No skin reaction in the 45 volunteers on days 2, 10, 20 and 30.<br><br>Due to the unusually high stabiliser content in the test material (1% hydroquinone) the relevance of the findings is unclear. | Cavelier C., et al. (1981) |
| Study type: case report<br><br>Type of population: patients with dermatitis with previous contact with (meth)acrylate (no further details)<br><br>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 | 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.<br><br>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 | Tucker SC, Beck HM (1999) |

| Type of data/report | Test substance | Observations | Reference |
|---|---|---|---|
| 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. | | 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. | |
| Study type: case report<br><br>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<br><br>Type of population: occupational<br><br>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 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.<br><br>3472 patients were patch-tested with methyl methacrylate (in petrolatum (2%)). | 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) |
| Study type: case report<br><br>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.<br><br>18 (27 %) positive reaction to methyl methacrylate.<br><br>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) |

| Type of data/report | Test substance | Observations | Reference |
|---|---|---|---|
| Study type: case report<br><br>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.<br><br>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)<br><br>Kanerva L (1999) |
| Study type: case report<br><br>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.<br><br>17 patient reacted to Methyl methacrylate<br><br>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.<br><br>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.<br><br>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) |
| Study type: human - skin sensitization, case reports<br><br>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<br>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<br>Survey of 211 male workers | MMA | Medical examination of workers in acrylic sheet production exposed to methyl methacrylate<br>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<br>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

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# 15 ANNEXES

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