# SUBSTANCE EVALUATION CONCLUSION

# as required by REACH Article 48

# and

# EVALUATION REPORT

**for**

# methacrylic acid, monoester with propane-1,2-diol

## EC No 248-666-3

## CAS No 27813-02-1

**Evaluating Member State(s):** FRANCE

Dated: January 2021

# Evaluating Member State Competent Authority

**French Agency for Food, Environmental and Occupational Health & Safety (ANSES)**
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## Year of evaluation in CoRAP: 2014

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

**Further information on registered substances here:**

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States.

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# Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

# Contents

# Part A. Conclusion

## 1. CONCERN(S) SUBJECT TO EVALUATION

Methacrylic acid, monoester with propane-1,2-diol (or HPMA) was originally selected for substance evaluation in order to clarify concerns about:

- suspected CMR
- sensitizer
- consumer use
- high (aggregated) tonnage
- high RCR
- wide dispersive use

## 2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

**Compliance check (CCH):**
During the substance evaluation, it was concluded that the mammalian toxicology data requirements related to subchronic toxicity, reproductive and developmental toxicity do not meet the requirements for the respective tonnage band and therefore a potential non-compliance with the REACH Annexes was identified, at least for these endpoints. The registrants also acknowledged this data gaps in 2016. Therefore, in February 2019, the evaluating MSCA recommended ECHA to perform a comprehensive CCH for this substance. The same year, ECHA has checked the compliance with the standard information requirements under REACH for the above endpoints and, based on a read-across (judged as acceptable with medium confidence) with methacrylic acid and propylene glycol, considered the dossier compliant at the currently registered tonnage levels.

## 3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

**Table 1**

| CONCLUSION OF SUBSTANCE EVALUATION | |
|---|---|
| **Conclusions** | **Tick box** |
| Need for follow-up regulatory action at EU level | X |
| Harmonised Classification and Labelling | X |
| Identification as SVHC (authorisation) | |
| Restrictions | |
| Other EU-wide measures | |
| No need for regulatory follow-up action at EU level | |

# 4. FOLLOW-UP AT EU LEVEL

## 4.1. Need for follow-up regulatory action at EU level

### 4.1.1. Harmonised Classification and Labelling

Based on the available data assessed in this substance evaluation, the evaluating MSCA considers that HPMA should be classified according to CLP Regulation as:

- Eye Irrit. 2 – H319: Causes serious eye irritation
- STOT SE 3 – H335: May cause respiratory irritation
- Skin Sens. 1 – H317: May cause an allergic skin reaction
- Resp. Sens. 1 – H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.

### 4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable

### 4.1.3. Restriction

This option may be applicable depending on the outcome of the future RMOA.

### 4.1.4. Other EU-wide regulatory risk management measures

A RMOA could be envisaged in order to analyse the relevant RMM to properly manage the risks related to skin and respiratory sensitisation for workers (especially for uses that may generate aerosols) and consumers (for all consumer uses, and for uses advised against). Uses of sensitizing substances by consumers is an issue not only for HPMA but also for other substances belonging to the same category of substances. Several options for the possible RMM are still open like OELs, a restriction…

# 5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

## 5.1. No need for regulatory follow-up at EU level

Not applicable

## 5.2. Other actions

Not applicable.

# 6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

**Table 2**

| FOLLOW-UP |
|---|

| Follow-up action | Date for intention | Actor |
|---|---|---|
| Annex VI CLH dossier | 2021 at the earliest | France |
| RMOA (sensitisation) | 2022 | France |

# Part B. Substance evaluation

## 7. EVALUATION REPORT

### 7.1. Overview of the substance evaluation performed

Methacrylic acid, monoester with propane-1,2-diol (or HPMA) was originally selected for substance evaluation in order to clarify concerns about:

- suspected CMR
- sensitizer
- consumer use
- high (aggregated) tonnage
- high RCR
- wide dispersive use

**Table 3**

| EVALUATED ENDPOINTS | |
|---|---|
| **Endpoint evaluated** | **Outcome/conclusion** |
| Acute toxicity | Based on the information available, no concern was raised. No further action needed. |
| Corrosion / irritation | Based on the information available, it was concluded that for skin irritation, no further action is needed.<br>A C&L process needs to be initiated to classify HPMA as Eye Irrit. 2 – H319 and STOT SE 3. |
| Skin / respiratory sensitisation | Based on the information available, the initial concern was confirmed. Therefore a proposal for a harmonised classification needs to be initiated to classify the substance as:<br>Skin Sens. 1 – H317<br>Resp. Sens. 1 – H334<br><br>Additionally a RMOA will be prepared and further RMM may be proposed.<br><br>An update of the CSR by registrants is strongly recommended to take into account the sensitization in the chemical risk assessment and communicate adequate risk management measures to downstream users. |
| Repeated-dose toxicity | Based on the information available, the evaluating MSCA identified a data gap and therefore recommended in 2019 ECHA to perform a CCH regarding subchronic toxicity by inhalation route. The same year, ECHA judged the read-across with methacrylic acid and propylene glycol acceptable with medium confidence.<br><br>For concerns related to inhalation exposure (irritation and sensitisation), follow-up regulatory measures (e.g. planned RMOA and classification) are considered by the evaluating MSCA as the most efficient actions to implement adequate risk management measures. |

| | |
|---|---|
| Genotoxicity | Based on the information available the initial concern was clarified. No further action is needed. |
| Carcinogenicity | No data were available. Nevertheless it was concluded that no further action at this time based on the absence of concern identified which could trigger such a study. |
| Toxicity to reproduction | Based on the information available, evaluating MSCA identified a data gap and therefore recommended in 2019 ECHA to perform a CCH for toxicity to reproduction (fertility and development). The same year, ECHA judged the read-across with methacrylic acid and propylene glycol acceptable with medium confidence. Thus, no further data has been required.<br>It was agreed to accept this read-across in order to be able to rapidly implement further RMM despite the remaining uncertainties related to the possible effects of HPMA on reproduction and development. These future risk mitigation measures will allow to reduce the exposure and would therefore indirectly protect from possible other effects. |
| Human exposure | Based on the available information, workers exposure by inhalation route cannot be excluded.<br><br>Uncertainties remain regarding the uses of the substance as such and the uses of polymer and the approach is not aligned between registrants. The lead registrant proposes a limit of 0.1% of residual (unreacted) monomer in polymer but the data are insufficient to conclude if this limit is sufficiently safe. Moreover, the evaluating MSCA has no possibility to surveil if this limit is implemented/respected by all registrants and downstream users.<br><br>Some registrants advise against the use of liquid mixture containing unreacted monomer intended to come into contact with skin and nails.<br><br>Regarding the consumer uses, since HPMA is an eye irritant and respiratory sensitizer, exposure to the substance should be limited. Some registrants advise against the use of mixtures containing unreacted liquid monomer intended to come into contact with skin or nails, because the substance is sensitising. One option could be to restrict the use on nails to professionals as some other cosmetic ingredients but then the question of risk of sensitization among them remains.<br><br>Regarding the wide dispersive uses since the substance is widely used, appropriate RMM will be identified in a further RMOA.<br><br>Regarding the high RCR appropriate RMM will be identified in a further RMOA. |

## 7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, methacrylic acid, monoester with propane-1,2-diol was included in the Community Rolling Action Plan (CoRAP) for evaluation in 2014. The French Competent Authority (Ministry of Environment) appointed the French Agency for Food, Environmental and occupational Health & safety (ANSES) to carry out the evaluation. The substance evaluation started on 26 March 2014.

The evaluation was targeted on human health hazards and human health exposure therefore during the evaluation of the methacrylic acid, monoester with propane-1,2-diol all endpoints related to human health were assessed including exposure. No endpoint related to environment was assessed.

The evaluation started in 2014 and was based on the registration dossiers and the open literature available. Additionally, the French national network for monitoring and prevention of occupational disease (RNV3P) was consulted on possible occupational exposure to HPMA causing respiratory sensitisation.

Initially, based on the evaluation of the available data, the evaluating MSCA concluded that there was a need to request further information to clarify the concerns related to repeated-dose toxicity, fertility/development toxicity and exposure. Therefore, pursuant to Article 46(1) of the REACH Regulation a draft decision was prepared to request further information. The draft decision was submitted to ECHA on 6 March 2015.

Nevertheless, after a discussion with ECHA and the Registrants it was decided that the concerns were rather due to data gaps than a real concern. It was therefore agreed with the registrants that they will submit testing proposals to fulfil these data gaps. However, these testing proposals have never been submitted. Therefore, in 2019, the evaluating MSCA recommended ECHA to perform a Compliance check. This same year, ECHA has checked the compliance with the standard information requirements under REACH and, based on a read-across with methacrylic acid and ethylene glycol, judged the dossier compliant at the currently registered tonnage levels.

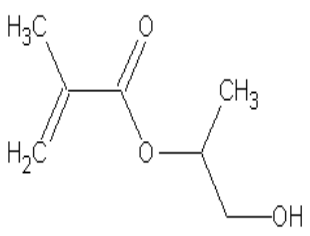
## 7.3. Identity of the substance

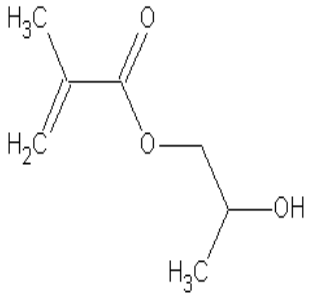
**Table 4**

| SUBSTANCE IDENTITY | |
|---|---|
| **Public name:** | Methacrylic acid, monoester with propane-1,2-diol |
| **EC number:** | 248-666-3 |
| **CAS number:** | 27813-02-1 |
| **Index number in Annex VI of the CLP Regulation:** | None |
| **Molecular formula:** | $C_7H_{12}O_3$ |
| **Molecular weight range:** | 144.1684 $g.mol^{-1}$ |
| **Synonyms:** | Hydroxypropyl methacrylate |

Type of substance ☐ Mono-constituent ☒ Multi-constituent ☐ UVCB

**Structural formula:**



The substance is considered as a multi-constituent based on the compositions submitted by the registrants according to REACH guidance for identification and naming of substances.

Registrants provided analytical information (UV/VIS, IR, NMR and GC chromatograms) to confirm the compositions and the structure of the registered substances.

## 7.4. Physico-chemical properties

**Table 5**

| OVERVIEW OF PHYSICOCHEMICAL PROPERTIES | |
|---|---|
| **Property** | **Value** |
| Physical state at 20°C and 101.3 kPa | ***Value used for SEV:*** clear colourless liquid at 20 °C and 101.3 kPa |
| Melting / freezing point | ***Value used for SEV:*** - 90 °C at 101.3 kPa<br><br>*Melting point was determined in accordance with the test method OECD Guideline 102 (EU test method A.1; differential scanning calorimetry).* |
| Boiling point | ***Value used for SEV:*** 209 °C at 1025 hPa<br><br>*Boiling point was determined in accordance with the test method OECD Guideline 103.* |
| Relative density | ***Value used for SEV:*** 1.03 at 20 °C |
| Granulometry | Not relevant. HPMA is a liquid. |
| Vapour pressure | ***Value used for SEV:*** 0.11 hPa at 20 °C<br><br>*Vapour* pressure *was determined according to the test procedure OECD Guideline 104 (EU test method A.4; dynamic method).* |
| Water solubility | ***Value used for SEV:*** 130 g/L at 25 °C<br><br>*Water solubility was determined according to the test procedure OECD Guideline 105.* |
| Partition coefficient n-octanol/water (Log Kow) | ***Value used for SEV:*** Log Kow (Pow): 0.97 at 20 °C<br><br>*Partition coefficient was determined according to the test procedure OECD Guideline 107 (EU test method A.8; shake-flask method).* |
| Surface tension | *Based on the chemical structure of the substance no surface activity is predicted. According to REACH legislation, Annex VII, 7.13, column 2, the study does not need to be conducted.* |
| Flash point | ***Value used for SEV:*** 111 °C at 1013 hPa<br><br>*Flash point was determined in accordance with the test method ASTM D92-52 (closed cup method).* |

| | |
|---|---|
| Autoflammability / self-ignition temperature | ***Value used for SEV:*** 355 °C at 1020 hPa<br><br>*Auto-ignition temperature was determined according to test procedure EU test method A.15 (*DIN 51794). |
| Flammability | ***Value used for SEV****:* Non flammable<br><br>*Based on the flash-point, which is higher than 60°C, the substance is not a flammable liquid.* |
| Explosive properties | ***Value used for SEV:*** Non explosive<br><br>*There are no chemical groups associated with explosive properties present in the molecule, thus according to REACH legislation, Annex VII, 7.11, column 2, the study does not need to be conducted.* |
| Oxidising properties | ***Value used for SEV:*** Non oxidizing<br><br>*Based on the chemical structure the substance is incapable of reacting exothermically with combustible materials. According to REACH legislation, Annex VII, 7.13, column 2, the study does not need to be conducted.* |
| Stability in organic solvents and identity of relevant degradation products | *In accordance with Column 2 of Annex IX a test on the stability in organic solvents is not necessary because this stability is not considered critical.* |
| Dissociation constant | *In accordance with column 2 of REACH annex IX, dissociation constant testing does not need to be conducted, as there are no dissociable groups.* |
| Viscosity | ***Value used for SEV:*** viscosity at 20°C: 8.88 mm²/s (static)<br><br>Viscosity *was determined according to the test procedure OECD Guideline 114 (capillary method).* |

## 7.5. Manufacture and uses

### 7.5.1. Quantities

**Table 6**

| AGGREGATED TONNAGE (PER YEAR) | | | | |
|---|---|---|---|---|
| ☐ 1 – 10 t | ☐ 10 – 100 t | ☐ 100 – 1000 t | ☐ 1000- 10,000 t | ☒ 10,000-50,000 t |
| ☒ 50,000 – 100,000 t | ☐ 100,000 – 500,000 t | ☐ 500,000 – 1000,000 t | ☐ > 1000,000 t | ☐ Confidential |

When the substance evaluation started (March 2014), there were 10 registrants for this substance. New registration dossiers have been submitted since then, and in December 2018, there were 24 active registrants and 2 inactive registrants.

### 7.5.2. Overview of uses

Information on uses, as available in the disseminated registration dossier in December 2018 (corresponding to 24 active registrations and 2 inactive registrations):

**Table 7**

| USES | Use(s) |
|---|---|
| **Uses as intermediate** | Yes |
| **Formulation** | Formulation of products:<br>- ERC 2, 3<br>- PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 10, 14, 15, 19, 28<br>- PC 1 |
| **Uses at industrial sites** | Manufacture:<br>- ERC 1, 4, 5, 6a, 6b, 6c, 6d, 7<br>- PROC 1, 2, 3, 4, 5, 6, 7, 8a, 8b, 9, 10, 11, 12, 13, 14, 15, 17, 18, 19, 21, 22, 23, 24<br><br>Industrial end-uses (as intermediate, as monomer or in formulations[2]):<br>- ERC 1, 4, 5, 6a, 6b, 6c, 6d, 7<br>- PROC 1, 2, 3, 4, 5, 6, 7, 8a, 8b, 9, 10, 12, 13, 14, 15, 17, 18, 19, 21, 22, 23, 24, 28<br>- SU 0, 2a, 2b, 3, 5, 6a, 6b, 7, 8, 9, 12, 13, 14, 15, 16, 17, 18, 19, 20, 23<br>- PC 1, 15<br>- Substance supplied to that use as such and in a mixture |
| **Uses by professional workers** | Professional end use in formulations:<br>- ERC 8a, 8b, 8c, 8d, 8e, 8f<br>- PROC 2, 3, 4, 5, 6, 8a, 8b, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 23, 24<br>- SU 0, 7, 11, 12, 17, 19, 22, 23<br>- PC 1<br>- Substance supplied to that use as such and in a mixture<br>Some registrants declared that the subsequent service life to this use is relevant. |
| **Consumer Uses** | Consumer end use in formulations:<br>- ERC 8b, 8c, 8e, 8f, 10a, 11a<br>- PC 1, 2, 3, 7, 8, 9a, 9b, 9c, 14, 15, 18, 19, 20, 21, 23, 24, 26, 29, 30, 31, 32, 33, 34, 35, 37, 39<br>- Substance supplied to that use in a mixture<br>Some registrants declared that the subsequent service life to this use is relevant. |
| **Article service life** | Articles used by workers:<br>- ERC 10a, 11a<br>- AC 2, 7, 8, 10, 13<br>- PROC 21<br>Articles used by consumers: |

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

| | |
|---|---|
| | - ERC 10a, 11a<br>- AC 1, 2, 3, 5, 6, 7, 8, 10, 11, 13 |
| **Uses advised against** | Mixtures containing unreacted liquid monomer intended to come into contact with skin or nails<br>- PC 0: Other: Applications where liquid monomer is intended to come into contact with skin or nails. |

- **Environmental release categories:**
  - ERC 1: Manufacture of the substance
  - ERC 2: Formulation into mixture
  - ERC 3: Formulation into solid matrix
  - ERC 4: Use of non-reactive processing aid at industrial site (no inclusion into or onto article)
  - ERC 5: Use at industrial site leading to inclusion into/onto article
  - ERC 6a: Use of intermediate
  - ERC 6b: Use of reactive processing aid at industrial site (no inclusion into or onto article)
  - ERC 6c: Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)
  - ERC 6d: Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article)
  - ERC 7: Use of functional fluid at industrial site
  - ERC 8a: Widespread use of non-reactive processing aid (no inclusion into or onto article, indoor)
  - ERC 8b: Widespread use of reactive processing aid (no inclusion into or onto article, indoor)
  - ERC 8c: Widespread use leading to inclusion into/onto article (indoor)
  - ERC 8d: Widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor)
  - ERC 8e: Widespread use of reactive processing aid (no inclusion into or onto article, outdoor)
  - ERC 8f: Widespread use leading to inclusion into/onto article (outdoor)
  - ERC 10a: Widespread use of articles with low release (outdoor)
  - ERC 11a: Widespread use of articles with low release (indoor)

- **Process categories:**
  - PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
  - PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
  - PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition
  - PROC 4: Chemical production where opportunity for exposure arises
  - PROC 5: Mixing or blending in batch processes
  - PROC 6: Calendering operations
  - PROC 7: Industrial spraying
  - PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
  - PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities
  - PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
  - PROC 10: Roller application or brushing
  - PROC 11: Non industrial spraying
  - PROC 12:Use of blowing agents in manufacture of foam
  - PROC 13: Treatment of articles by dipping and pouring
  - PROC 14: Tabletting, compression, extrusion, pelletisation, granulation
  - PROC 15: Use as laboratory reagent
  - PROC 17: Lubrication at high energy conditions in metal working operations
  - PROC 18: General greasing /lubrication at high kinetic energy conditions

- PROC 19: Manual activities involving hand contact
- PROC 21: Low energy manipulation and handling of substances bound in/on materials or articles
- PROC 22: Manufacturing and processing of minerals and/or metals at
- substantially elevated temperature"
- PROC 23: Open processing and transfer operations at substantially elevated temperature
- PROC 24: High (mechanical) energy work-up of substances bound in/on materials and/or articles
- PROC 28: Manual maintenance (cleaning and repair) of machinery

- **Sectors of end-use:**
  - SU 0: Other
  - SU 2a: Mining, (without offshore industries)
  - SU 2b: Offshore industries
  - SU 3: Industrial uses: Uses of substances as such or in mixture at industrial sites (obsolete)
  - SU 5: Manufacture of textiles, leather, fur
  - SU 6a: Manufacture of wood and wood products
  - SU 6b: Manufacture of pulp, paper and paper products
  - SU 7: Printing and reproduction of recorded media
  - SU 8: Manufacture of bulk, large scale chemicals (including petroleum products)
  - SU 9: Manufacture of fine chemicals
  - SU 11: Manufacture of rubber products
  - SU 12: Manufacture of plastics products, including compounding and conversion
  - SU 13: Manufacture of other non-metallic mineral products, e.g. plasters, cement
  - SU 14: Manufacture of basic metals, including alloys
  - SU 15: Manufacture of fabricated metal products, except machinery and equipment
  - SU 16:Manufacture of computer, electronic and optical products, electrical equipment
  - SU 17: General manufacturing, e.g. machinery, equipment, vehicles, other transport equipment
  - SU 18: Manufacture of furniture
  - SU 19: Building and construction work
  - SU 20: Health services
  - SU 22: Professional uses: Public domain (administration, education, entertainment, services, craftsmen) (obsolete)
  - SU 23: Electricity, steam, gas water supply and sewage treatment

- **Product categories:**
  - PC 1: Adhesives, sealants
  - PC 2: Adsorbents
  - PC 3: Air care products
  - PC 7: Base metals and alloys
  - PC 8: Biocidal products (e.g. disinfectants, pest control)
  - PC 9a: Coatings and paints, thinners, paint removes
  - PC 9b: Fillers, putties, plasters, modelling clay
  - PC 9c: Finger paints
  - PC 14: Metal surface treatment products
  - PC 15: Non-metal-surface treatment products
  - PC 18: Ink and toners
  - PC 19: Intermediate
  - PC 20: Products such as pH-regulators, flocculants, precipitants, neutralisation agents
  - PC 21: Laboratory chemicals
  - PC 23: Leather treatment products
  - PC 24: Lubricants, greases, release products
  - PC 26: Paper and board treatment products
  - PC 29: Pharmaceuticals
  - PC 30: Photo-chemicals
  - PC 31: Polishes and wax blends
  - PC 32: Polymer preparations and compounds
  - PC 33: Semiconductors
  - PC 34: Textile dyes, and impregnating products

  - PC 35: Washing and cleaning products
  - PC 37: Water treatment chemicals
  - PC 39: Cosmetics, personal care products

- **Article categories:**
  - AC 1: Vehicles
  - AC 2: Machinery, mechanical appliances, electrical/electronic articles
  - AC 3: Electrical batteries and accumulators
  - AC 5: Fabrics, textiles and apparel
  - AC 6: Leather articles
  - AC 7: Metal articles
  - AC 8: Paper articles
  - AC 10: Rubber articles
  - AC 11: Wood articles
  - AC 13: Plastic articles

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

However, it has not been possible to distinguish for each use and for each registrant which scenario correspond to monomer and/or polymers (and/or even pre-polymers), to have a clear and reliable overview of the uses of HPMA. Therefore, all uses currently declared in registration dossiers, and which are disseminated, have been considered by the evaluating MSCA as possible uses of HPMA. Regulatory assessment (prioritisation, evaluation, regulatory risk management measures) is conducted based on the available information, and it is the responsibility of registrants to ensure that the registered uses are up-to-date and reliable.

## 7.6. Classification and Labelling

### 7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonized classification is available for the CAS number 27813-02-1. An EU harmonized classification is nevertheless available for 2-hydroxypropyl methacrylate (CAS number: 923-26-2; index number: 607-125-00-5) which is one of the constituents of the substance:

- Eye Irrit. Cat 2 - H319 : Causes serious eye irritation
- Skin Sens. Cat 1 - H317 : May cause an allergic skin reaction

### 7.6.2. Self-classification

- In the registration(s)*:*

- Eye Irrit. 2 – H319
- Skin Sens. 1 – H317

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

- Skin Irrit. 2 – H315: Causes skin irritation
- Muta 2 – H341: suspected of causing genetic defects
- STOT SE 3 – H335: May cause respiratory irritation

## 7.7. Environmental fate properties

Not evaluated

## 7.8. Environmental hazard assessment

Not evaluated.

## 7.9. Human Health hazard assessment

**Characterisation of HPMA in the toxicological assays:**

In the registration dossier, the material tested is not always clearly identified. Indeed for some endpoints, CAS number 923-26-2 corresponding to propenoic acid, 2-methyl-, 2-hydroxypropylester isomer was reported and for other endpoints, it was the CAS number 27813-02-1 corresponding to mixture of 20-30% of propenoic acid, 2-methyl-, 2-hydroxy-1-methylethylester (CAS 4664-49-7) and 70-80% of propenoic acid, 2-methyl-, 2-hydroxypropylester.

A clarification has been requested from the registrants and it was explained that all tests had been performed with the commercial product (isomer mixture).

**Read-across approach**

In order to fulfil all toxicological endpoints (and in particular, subchronic toxicity, carcinogenicity and reproductive/developmental toxicity endpoints), the registrants proposed in their dossier a read-across approach based on the metabolism of HPMA. In particular, when evaluating the substance in 2014, data on methyl methacrylate (MMA) was used in the registration dossier. After exchanges between the evaluating MSCA and the registrants, additional data on propylene glycol (PG) were included in the registration dossier in 2017.

Based on the information in hand, the evaluating MSCA considered that the rationale for the read-across was not sufficiently justified. Indeed HPMA is a small molecule with very reactive functions such as primary alcohol, ester group and double bound. Therefore, even the smallest change in chemical structure can have an impact on the reactivity and the toxicity of the molecule. In addition there are some differences in physicochemical properties and in toxicity between the source and target substances (see Annex I for further details). Having that in mind, the evaluating MSCA requested ECHA to perform a CCH.

Considering data available in 2019, ECHA performed a CCH and concluded that the data is reliable and that the read-across proposed between MMA / propylene glycol and HPMA is acceptable with medium confidence despite some remaining uncertainties. Therefore, it seemed not reasonable to request new information for the inhalation route for HPMA, but rather first consider if other regulatory options are available, within a RMOA or classification dossier (in particular concerns identified for local effect). Indeed, for systemic toxicity by oral route, ECHA recognized that some uncertainties exist but there is high confidence in the reliability of the data.

It was agreed by the evaluating MSCA that this approach is the most efficient one, since it allows to implement risk management measures (e.g. RMOA and classification).

### 7.9.1. Toxicokinetics

The results of studies on absorption, metabolism, distribution and elimination are summarised in the following table:

**Table 8. Studies on absorption, metabolism, distribution and elimination**

| Method | Results | Remarks | Reference |
|---|---|---|---|
| *in vitro* study (enzymatic hydrolysis assay)<br>Identification and measurement of monomers and methacrylic acid were performed by high-pressure liquid chromatography. | HPMA was hydrolysed to methacrylic acid and 1, 2-propanediol by an unspecific esterase *in vitro.* | 2 (reliable with restrictions)<br>key study<br>experimental result<br>**Test material (EC name): methacrylic acid, monoester with propane-1,2-diol** | Munksgaard E.C., Freund M. (1990) |
| *In vivo* pharmacokinetic study<br>2 male F344/DuCrl rats received HPMA via intravenous administration at the dose of 5 mg/kg bw. Blood samples were collected at 5, 10, 30, 60 and 180 minutes.<br>No guideline, not GLP | HPMA was not quantifiable by 60 minutes ((LOQ) of 48.8 ng/mL) and the estimated half-life was less than or near 1 minute. | 2 (reliable with restrictions)<br>key study<br>experimental result<br>**Test material (EC name): HPMA** | Study report#3, 2017 |

Following the REACH guidance document 7c, the physicochemical properties of HPMA (molecular weight of ~144 g/mol, log Pow of 0.97 and water solubility of 130 g/L) are favourable to absorption. According to Danish QSAR database, an absorption from gastrointestinal tract is estimated at 50%. The dermal absorption is estimated at 0.0806 mg/cm$^2$/event.

In an *in vitro* enzymatic hydrolysis assay, HPMA was suspended with porcine liver esterase. The substance was hydrolysed to methacrylic acid and 1, 2-propanediol (propylene glycol) at pH 6.5 and 37°C catalysed by an unspecific esterase (Munksgaard and Freund, 1990). This is consistent with the general metabolism of methacrylate esters in mammals.

An *in vivo* pharmacokinetic study was performed where 2 male rats received HPMA via intravenous administration at the dose of 5 mg/kg bw. Blood samples were collected at 5, 10, 30, 60 and 180 minutes. HPMA was not quantifiable by 60 minutes and the estimated half-life was less than or near 1 minute (Study report#3, 2017).

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

### 7.9.2. Acute toxicity and Corrosion/Irritation

**Acute toxicity**

The oral $LD_{50}$ of HPMA in rats was determined to be > 2000 mg/kg (Study report#8, 1996); Study Report#7, 1992).

The dermal $LD_{50}$ in rabbits was determined to be > 5000 mg/kg (Study Report#7, 1992).

No data was available for inhalation route.

Based on the $LD_{50}$ values, there is no need to classify HPMA for acute toxicity.

**Corrosion/irritation**

HPMA was not found to be irritating to the skin of rabbits (mean primary dermal irritation index = 0 at 24 and 72h) (Study Report#4, 1977).

Based on a study in rabbits (Study Report#5, 1978), HPMA should be classified as irritating to eyes Category 2 – H319 (cornea score = 0.8; iris score = 0; conjunctiva redness score = 1; conjunctiva chemosis score = 0.1; reversible on day 4).

In this context, a C&L proposal should be initiated for this endpoint.

It is expected that HPMA is hydrolysed to methacrylic acid, a substance known to cause respiratory tract lesions (OECD SIDS, 2001). Furthermore, it is reported in Toxnet website that vapour of HPMA is irritating to nose (U.S. Coast Guard, Department of Transportation, 1984-5). Finally, methacrylic acid has an existing harmonised classification of STOT SE 3; H335 if concentration is ≥ 1 %. No irritation was reported in rats exposed to atmosphere saturated with HPMA (no further specification) at 0.5 mg/L in a repeated dose study of low reliability by inhalation (Gage, 1970). In the absence of adequate data, the potential for respiratory irritation effects cannot be ruled out taking into account that HPMA can hydrolyse at site of contact and induce effects via methacrylic acid (the plausibility of such breakdown at olfactory epithelium is also suggested by the Registrants).

In this context, a C&L proposal would be initiated to classify HPMA as STOT SE 3 – H335 according to CLP Regulation.

### 7.9.3. Sensitisation

**Skin sensitisation**

HPMA has been evaluated for skin sensitization potential in tests in experimental animals, including LLNA assay (Scholes, 1992), Maximisation tests (Basketter, 1992; Clemmensen, 1984; Bjoerkner, 1984) and a split adjuvant test (Rao, 1981). In these studies, none or few animals only (< 30%) were sensitized. However, there is no information if a positive control was included in these studies.

Several publications reports cases of positive patch tests with HPMA in patients presenting contact dermatitis (Bjoerkner, 1984; Estlander, 1990; Conde-Salazar, 1988; Jordan, 1975; Kanerva, 1993; Kanerva, 1991; Romaguera, 1990; Lovell, 1985; Kanerva, 1988; Marren, 1991; Kanerva, 1989). Cross reaction between methacrylates is possible.

Based on human data, HPMA should be considered to have skin sensitization potential and classified Skin Sens. 1 – H317.

In this context, a C&L proposal would be initiated for this endpoint. A sub-categorization may be determined when the Annex VI CLH proposal will be drafted.

**Respiratory sensitisation**

Some animal and non-animal test methods for the identification of respiratory sensitizers have been described in the literature, but these are not widely accepted yet, nor close to the point where they could enter into a formal validation. Therefore, it is difficult to identify the substance with such a property based on experimental and modelling data.

In 2014, following a request by e-MSCA, the RIVM has run different SAR models (Derek, Jarvis, CatSAR, Enoch, MultiCase) with acrylates including HPMA. Enoch, MultiCase and Jarvis gave positive results for respiratory sensitization whereas HPMA was negative according to Derek and CatSAR. According to the RIVM, Derek gave the most reliable prediction of a substance being a respiratory sensitizer and MultiCase the most reliable prediction for respiratory non-sensitization. Therefore, considering the profile of HPMA obtained with these two models, no reliable conclusion can be reached for the potential respiratory sensitization properties of HPMA based on SAR models.

Methacrylates are known to cause respiratory hypersensitivity and asthma, but the mechanism mediating these effects is not known and IgE-mediated reactions from methacrylates have not been reported. Several cases of respiratory sensitization from methacrylates were reported in the literature; among them, HPMA was cited in only one publication described below.

Sauni *et al.* (2008) reports two cases of occupational asthma caused by sculptured nails containing methacrylates. HPMA was detected in the sculpture resin (6.7% w/w). Bronchial provocation tests were performed in an $8m^3$ chamber with their own products (they attached the plastic nail with a glue and then filed and sculptured the nails). A dual asthmatic reaction was noted.

In the French national network for the monitoring and prevention of occupational diseases (RNV3P) collects every year more than 8000 new occupational health reports throughout France. The French RNV3P network is composed of the 30 Occupational disease consultation centres (CCPP) in mainland France and a number of occupational health services (SSTs) associated with the network. The goal of this network is to record the data from consultations in a national database (patient demographics data, diseases, exposures, job sectors and professions). From this database, several cases of asthma were reported with acrylates or methacrylates but none has been specifically related to HPMA. These cases were mainly observed in dental professionals and nail technicians.

Although HPMA was only cited in two cases of occupational asthma, several human cases were reported with methacrylates compounds (no clear identification of the causal substance), which are an important aetiological factor in this disease. In particular, based on human data, methyl methacrylate has just been classified in October 2020 by the RAC as Resp. Sens. A C&L proposal would be initiated to classify HPMA as Resp. Sens. Cat. 1, H334 according to CLP Regulation.

### 7.9.4. Repeated dose toxicity

The results of studies on repeated dose toxicity after oral administration are summarised in the following table:

**Table 9. Studies on repeated dose toxicity after oral administration**

| Method | Results | Remarks | Reference |
|---|---|---|---|
| rat (Crj: CD(SD)) male/female<br><br>subchronic (oral: gavage) | NOAEL: 300 mg/kg bw/day (nominal) (male/female) based on hematological | 2 (reliable with restrictions) | Ministry of Health and Welfare: |

| Method | Results | Remarks | Reference |
|---|---|---|---|
| 0 (vehicle), 30, 100, 300 and 1000 mg/kg/ day (nominal in water)<br><br>Vehicle: water<br><br>Exposure:<br><br>Males: 49 days<br><br>Females: from 14 days before mating to day 3 of lactation (daily)<br><br>OECD Guideline 422 (1996)(Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) | changes and liver toxicity (males only), mortality and clinical signs (both sexes). | key study<br><br>experimental result<br><br>**Test material (EC name): methacrylic acid, monoester with propane-1,2-diol** | Japan (1996a) |

**Oral route**

Effects of HPMA (purity = 98%) have been evaluated in a combined repeat-dose developmental/reproductive toxicity screening test in Sprague-Dawley rats (Ministry of Health and Welfare: Japan (1996a)).

In the study, male rats (12/group) were given daily gavage doses of 0 (vehicle), 30, 100, 300 or 1000 mg/kg bw/day for 49 days including pre-mating, mating and post-mating intervals. Females (12/group) were administered the same doses for two weeks prior to mating, during mating and gestation until day 3 of lactation (approximately 54 days depending upon time to conception). This study followed the OECD test guideline 422 set in 1996. However, it should be noted that this guideline was updated in 2016 to include, in particular, endocrine parameters and to extend the duration of treatment until post-natal day 13 (which is thus not the case in the present study).

Two males and one female died at the 1000 mg/kg dose level. Clinical symptoms of intoxication observed at 1000 mg/kg included: salivation, decrease in locomotor activity and ptosis for both sexes. Liver weight was increased in males only at 1000 mg/kg bw/day, and associated with a slight vacuolar degeneration of periportal hepatocytes in 8 animals. Also in males, a significant decrease in hematocrit with tendencies for decrease in RBC (red blood cells) and hemoglobin was observed at 1000 mg/kg bw/day only. The NOAEL was considered to be 300 mg/kg bw/day for both males and females.

Another study is available but judged as not reliable due to the limited level of details (Study Report#6, 1966). Haematological findings (mild iron-deficiency anaemia) and "some testicular tubular degeneration" were noted in rats exposed to 2000 mg/kg bw as a 50% aqueous suspension for 21 days.

**Inhalation route**

One study of low quality was available (Gage, 1970). No adverse effect was found in rats exposed to an atmosphere saturated with HPMA (no further specification) at 0.5 mg/L for 3 weeks. This study was judged not reliable because there is no information on an analytical

verification of the concentration tested, only one concentration was tested and the level of details was very limited.

**Dermal route**

No local or systemic effect was reported in rats after 1-week dermal application of HPMA, undiluted (Study Report#6, 1966). The study was judged as not reliable due to the limited level of details and the low number of animals tested.

**Conclusion**

Regarding repeated-dose toxicity study with HPMA, the only study judged as reliable is a combined repeat-dose developmental/reproductive toxicity screening test by oral route. In this study, animals were exposed for a duration shorter than 60 days. A full histopathological evaluation comparable as that recommended in the OECD test guideline 408 (repeated dose 90 day oral toxicity study) was not performed.

In order to complete this endpoint, data performed with methyl methacrylate (MMA) were also provided. However, the read-across was not considered as acceptable since MMA and HPMA are both small molecules with very reactive functions. Therefore, even the smallest change in chemical structure can have an impact on the reactivity and the toxicity of the molecule. In addition, there are some differences in physicochemical properties and toxicity, with different target organs identified (see Annex I for further details).

Therefore, the evaluating MSCA decided to draft a decision requiring a subchronic toxicity study. It was proposed that, considering the uses identified in the registration dossiers, the physico-chemical properties of the substance and the respiratory irritating properties of methacrylic acid, a metabolite of the substance, this study should be performed by inhalation route.

During the commenting period, the registrants acknowledged that the mammalian toxicology data requirements for HPMA do not meet the requirements for the respective tonnage band. However, they proposed to perform this subchronic toxicity study by oral route with HEMA (2-hydroxyethyl methacrylate; CAS number 868-77-9) to cover HPMA toxicity.

After exchanges with ECHA and registrants, it was finally agreed that this request is rather related to a non-compliance with REACH Annex IX (section 8.6.2) than really linked to an identified concern. Therefore, the registrants agreed in November 2016 to submit a testing proposal in an update version of their dossier. However, at the time being, it has not been done neither in the IUCLID dossier nor in the updated CSR. Instead, the CSR was updated in 2017 with the inclusion of data on propylene glycol (PG) in addition to data on MMA and HPMA data to complete this endpoint. Although PG and HPMA induced hematological changes, the NOAELs reported for PG (NOAELs above 1000 mg/kg bw/day in rats reported in ATSDR, 1997 and INRS, 2010) were higher than that identified from the OECD 422 study with HPMA (300 mg/kg bw/day), suggesting a higher toxicity of HPMA. In addition, liver was also identified as a target organ for HPMA but not for PG. Furthermore, even if the relevance of these results is questionable considering the level of details available, "some testicular tubular degeneration" was observed with HPMA at 2000 mg/kg bw as a 50% aqueous suspension after an exposure for 21 days (Study Report#6, 1966). In contrast, no effect on fertility was reported with PG (INRS, 2010). Therefore, despite the new data provided on propylene glycol, the approach of the registrant was still considered by the evaluating MSCA as leading to too much uncertainties. Therefore, in 2019, the evaluating MSCA recommended ECHA to perform a CCH regarding Reach Annex IX of REACH, section 8.6.2.

The same year, ECHA checked the compliance of the information provided with the standard information requirements under REACH for this endpoint and considered that the

read-across with methacrylic acid and propylene glycol acceptable with medium confidence. Since it would allow to implement RMM more rapidly the evaluating MSCA considers the approach as acceptable. For local effects after inhalation, further RMM should be implemented.

### 7.9.5. Mutagenicity

**Bacterial assays**

No genotoxic effect was observed in different strains of bacteria (*S. typhimurium* TA 98, 100, 1535, 1537, 1538; *E. Coli* WP2 uvrA) exposed to HPMA with and without metabolic activation (Hatano, 1996).

**Mammalian cell assays**

- **Gene mutation**

Possible gene mutation with HPMA was evaluated in an *in vitro* Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) gene mutation assay (Study report#2, 2010). The genotoxic potential of the test material was assessed in the absence and presence of metabolic activation (S9) system. The concentrations ranged from 45.1 to 1442 µg/ml in the absence and presence of S9. Low to moderate cytotoxicity was found: in the presence of S9, RCS (relative cell survival) values ranged from 74.7 to 113.8% and without metabolic activation between 52.9 and 88.4%. HPMA was non-mutagenic in this study either with or without metabolic activation.

- **Chromosomal aberrations**

HPMA has been evaluated for the ability to induce chromosomal aberrations in mammalian cells in culture. Kusakabe *et al.* (2002) evaluated the clastogenic potential of HPMA along with a large number of other substances in Chinese hamster lung cells in culture, exposed to concentrations up to 1.4 mg/ml. HPMA was reported to induce structural chromosome aberrations following 6 hr exposure of cells in the presence of S9 from 0.35 mg/ml. Continuous exposure of cells for 24 hours or for 48 hours without S9 also caused an elevated incidence of chromosome aberrations for HPMA (from 0.35 mg/ml). Polyploidy was reported after both short-term treatment and 48-hour continuous treatment exposures for HPMA. These effects were found at exposure levels which caused <50% cell death.

***In vivo* studies:**

HPMA was tested *in vivo* using a micronucleus assay in mice (Study report #1, 1989). HPMA was administered by gavage once to 6 male and female mice at 2000 mg/kg bw. The dose was established based on preliminary assays where 2 male and female mice per group were exposed to 2000, 3000, 4000 and 5000 mg/kg bw. At all doses, animals expressed toxic reactions including reduction of spontaneous activity, abdominal position, eyelid closure and apathy. Deaths were reported in one male and one female at 5000 mg/kg bw and 4000 mg/kg bw and in one female at 3000 mg/kg bw. Cyclophosphamide (40 mg/kg once) was used as a positive control. Sampling of the bone marrow was done 24, 48 and 72 hours after treatment. In the main study, animals expressed toxic reactions (not further described) and one male died. No cytotoxicity on bone marrow was observed since PCE/NCE was not altered. Therefore, there is a doubt if the substance reached the bone marrow. There was no increase in the number of micronucleated PCEs. The positive control was valid since cyclophosphamide treatment caused an increase in micronucleated PCEs.

The results above were confirmed from additional information available in the literature (EFSA Journal 2012; 10(6):2745)[3]. The toxicity of HPMA was tested in three *in vitro* tests with and without metabolic activation and in a combined *in vivo* micronucleus and comet assay in rats. HPMA was clastogenic and induced polyploidy in cultured mammalian cells, both in presence and absence of an exogenous metabolic activation. Evidence for a clastogenic potential was also obtained in the mouse lymphoma tk+/- assay with increased frequency of small colonies without metabolic activation. Gene mutation assays in bacteria provided negative results. In a combined *in vivo* micronucleus and comet assay, male Sprague Dawley rats were exposed by the oral route to 2000 mg/kg bw of HPMA. HPMA did not induce biologically relevant increases in number of micronucleated polychromatic erythrocytes in bone marrow, where the bioavailability of the substance was demonstrated by a reduced ratio of polychromatic to normochromatic erythrocytes, and did not induce DNA damage measured by Comet assay in liver at the site of first contact (stomach). It is concluded that the genotoxicity activity of HPMA observed *in vitro* is not expressed *in vivo* and that HPMA does not raise concern for genotoxicity.

In conclusion, HPMA is not mutagenic in bacterial and mammalian cells in culture. Additionally, while HPMA causes chromosomal aberrations in mammalian cells in culture, it is not clastogenic *in vivo*.

### 7.9.6. Carcinogenicity

No carcinogenic study with HPMA is available. Data on methyl methacrylate was provided in order to fulfil this endpoint.

The substance is not classified as germ cell mutagen. In addition, there is no evidence of hyperplasia and/or preneoplastic lesions in the combined repeat-dose developmental/reproductive toxicity screening test. However, the duration of this study is probably too short to identify potential pre-neoplastic lesions.

In the absence of identified concern, no further action is needed.

### 7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

The results of the available study on fertility is summarised in the following table:

**Table 10: Studies on fertility**

| Method | Results | Remarks | Reference |
|---|---|---|---|
| rat (Crj: CD(SD)) male/female<br><br>oral: gavage<br><br>0 (vehicle), 30, 100, 300 and 1000 mg/kg/day (nominal in water)<br><br>Vehicle: water | NOAEL (parents): 300 mg/kg (males and females) (based on mortality, clinical signs, haematological changes and liver toxicity)<br><br>NOAEL (reproductive): 1000 mg/kg bw/day | 2 (reliable with restrictions)<br><br>key study<br><br>experimental result<br><br>**Test material (EC name): methacrylic** | Ministry of Health and Welfare: Japan (1996c) |

[3] Scientific opinion on the safety evaluation of the substance, methacrylic acid, 2-hydroxypropyl ester, CAS No 27813-02-1, for use in food contact materials – EFSA panel on food contact materials, enzymes, flavourings and processing aids (CEF)

| Method | Results | Remarks | Reference |
|---|---|---|---|
| Exposure:<br><br>Males 49 days (daily) (from 14 days before mating)<br><br>Females, from 14 days before mating to day 3 of lactation<br><br>OECD Combined Repeated Dose and Reproductive / Developmental Toxicity Screening Test (Precursor Protocol of GL 422) | (male/female). (no effects)<br><br>NOAEL (development): 1000 mg/kg bw/day (male/female). (no effects) | **acid, monoester with propane-1,2-diol** | |

There is neither an EOGRTS nor prenatal developmental toxicity study available with HPMA. Instead, there is only one combined repeat-dose developmental/reproductive toxicity screening test on HPMA (purity of 98%) available in the registration dossier to cover both fertility and developmental endpoints (Ministry of Health and Welfare of Japan, 1996). This study followed the OECD test guideline 422 set in 1996. However, it should be noted that this guideline was updated in 2016 to include, in particular, endocrine parameters and to extend the duration of treatment until post-natal day 13 (which is thus not the case in the present study).

In the study, male rats (12/group) were given daily gavage doses of 0 (vehicle), 30, 100, 300 or 1000 mg/kg for 49 days including pre-mating, mating and post-mating intervals. Females (12/group) were administered the same doses for two weeks prior to mating, during mating and gestation up until day 3 of lactation (approximately 54 days depending upon time to conception).

The NOAEL for parental effect was considered to be 300 mg/kg for both males and females, based on mortality, clinical signs, haematological changes and liver toxicity observed at 1000 mg/kg.

Concerning the reproductive toxicity part of the study, no effects was observed on the oestrus frequency, copulation index, number of days to conception, fertility index, length of gestation, number of corpora lutea and gestation index. There was also no effect on the number of live pups born, birth index, number of dead pups, number of pups born, delivery index, live birth index, sex ratio, viability index, external anomalies, body weight and necropsy. The NOAEL for reproductive and developmental effects was ≥ 1000 mg/kg bw/day.

It is noted that an OECD TG 422 study is not an alternative/does not replace the existing OECD TG 414, as a standard requirement set in Annex IX, Section 8.7.2 nor the existing OECD TG 443, as a standard requirement set in Annex X, Section 8.7.3. Indeed, this study is designed to generate limited information concerning the effects of a test chemical on male and female reproductive performance (such as gonadal function, mating behaviour, conception, development of the conceptus and parturition) and offers only limited means to detect postnatal manifestations of prenatal exposure, or effects that may be induced following a postnatal exposure. In addition, the available study followed the OECD test guideline from 1996 and, thus, endocrine disruptor relevant endpoints were not included and developmental toxicity was assessed until sacrifice on post-natal day 4 only.

In order to fulfil this endpoint, the registrants provided data on methyl methacrylate. No concern for toxicity on reproduction was raised for this compound from a 2-generation

study (Conclusion document for Methyl methacrylate, Anses, 2018). When performing the substance evaluation, the read-across between MMA and HPMA was first not considered as acceptable by the evaluating MSCA (see Annex I for further details).

In this context, the evaluating MSCA decided to draft a decision requesting:

- An extended one-generation reproductive toxicity study in rats, via the most appropriate exposure route (test method: OECD TG 443), without the extension of cohort 1B to mate the F1 animals to produce the F2 generation, but including the cohorts 2 and 3 to assess developmental neurotoxicity (DNT) and immunotoxicity (DIT).

During the commenting period, the registrants acknowledged that the mammalian toxicology data requirements for HPMA do not meet the requirements for the respective tonnage band. Thus, they agreed to perform this assay with some adaptations compared to the initial request. They proposed to perform the EOGRTS by oral route with HEMA (instead of HPMA) combined with a subchronic toxicity study and without DNT and DIT cohorts.

- A prenatal developmental toxicity study in rats or rabbits, via the most appropriate exposure route (test method: OECD TG 414).

During the commenting period, the registrants acknowledged that the so far presented reproductive toxicity related mammalian data for HPMA do not meet the requirements for the respective tonnage band. Thus, they agreed to perform this assay with some adaptations compared to the initial request. Indeed, they proposed to perform the study in rats by oral route with HEMA instead of HPMA.

After exchanges with ECHA and registrants, it was has finally considered that these requests are rather related to a non-compliance with REACH Annexes than related to an identified concern. Therefore, the registrants agreed in November 2016 to submit a testing proposal in an update of their dossier. However, at this time, it has not been done yet neither in the IUCLID dossier nor in the updated CSR. Instead, in the latest version of the CSR (2017), the registrants added data on propylene glycol (PG) and concluded that it is unlikely that HPMA is a reproductive/developmental toxicant considering the absence of this type of effect reported in the OECD 422 study performed with HPMA and supported by data available on MMA and PG for which there is no evidence of selective toxicity to the reproductive system and to development of the organisms. However, this approach was still considered as non acceptable (see section 7.9.4 and Annex I for further details) by the evaluating MSCA who recommended, in 2019, ECHA to perform a CCH for these endpoints.

The same year, ECHA has checked the compliance with the standard information requirements under REACH for the endpoints related to reproductive/developmental toxicity and judged the dossier compliant at the currently registered tonnage levels, based on the read-across with methacrylic acid and propylene glycol. It was agreed to accept this read-across in order to be able to rapidly implement further RMM despite the remaining uncertainties related to the possible effects of HPMA on reproduction and development. These future risk mitigation measures implemented due to the local effects of HPMA will allow to reduce the exposure and would therefore indirectly protect from possible other systemic effects.

### 7.9.8. Hazard assessment of physico-chemical properties

Not relevant.

### 7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

No robust risk characterisation for systemic toxicity has been performed at this time.

### 7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Based on available data, it is expected that HPMA is quickly hydrolysed into methacrylic acid and propylene glycol (PG).

HPMA has a low acute toxicity. The substance is not irritant to skin but irritant to eye.

In the absence of adequate data, the potential for respiratory irritation effects cannot be ruled out taking into account that HPMA can hydrolyse at site of contact and induce effects via methacrylic acid (classified as STOT SE 3; H335 if concentration is ≥ 1 %). Thus, a C&L process should be foreseen to introduce a harmonised classification and classify HPMA as STOT SE 3.

HPMA is sensitizing to skin based on human data and should be classified Skin Sens. 1 – H317.

Although HPMA was only cited in two cases of occupational asthma, several human cases were reported with methacrylates compounds (no clear identification of the causal substance), which is an important aetiological factor in this disease. In particular, based on human data, methyl methacrylate has just been classified in October 2020 by the RAC as Resp. Sens. Moreover, HPMA has also the potential to induce skin sensitisation. Thus, a C&L process should be foreseen to introduce a harmonised classification and classify HPMA as Resp. Sens. 1.

Only a combined repeat-dose developmental/reproductive toxicity screening test on HPMA is available to cover repeated toxicity, reproductive toxicity and developmental toxicity endpoints. Based on this study it was shown that HPMA induced effects on the liver and hematological changes leading to a NOAEL of 300 mg/kg bw/day. There is no effect reported on fertility and development in this study up to the highest tested dose of 1000 mg/kg bw/day. However, this study is only a screening test and cannot provide similar level of data as a study carried out according to OECD TG 413, 443 or 416.

HPMA is clastogenic *in vitro* but not *in vivo*. There is no carcinogenicity data available with HPMA.

Data on MMA, as a representative of the common metabolite methacrylic acid, and on propylene glycol were included by the registrants to justify a read-across approach and not perform additional study with HPMA. This read-across was first judged as not acceptable by evaluating MSCA based on the information available. Therefore, in 2019, evaluating MSCA recommended ECHA to perform a CCH for subchronic toxicity, reproductive toxicity and developmental toxicity endpoints. When ECHA checked the compliance with the standard information requirements under REACH for the above endpoints and it judged the read-across with methacrylic acid and propylene glycol propylene glycol acceptable with moderate confidence despite some remaining uncertainties. Instead, further RMM can be rapidly implemented such as a proposal of classification and a RMOA regarding local effects of HPMA. With the help of these RMM the exposure to the substance will decrease and relevant populations will this way be indirectly protected from the systemic effects not directly targeted.

## 7.10. Assessment of endocrine disrupting (ED) properties

### 7.10.1. Endocrine disruption – Environment

Not evaluated.

### 7.10.2. Endocrine disruption - Human health

No relevant information available.

### 7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

Not applicable.

## 7.11. PBT and vPvB assessment

Not evaluated.

## 7.12. Exposure assessment

### 7.12.1. Human health

*Relevance of inhalation route of exposure:*

Between the start of the substance evaluation and the time of drafting of this report, many additional registrants joined the joint submission (10 registrants at the start, and now (December 2018) 24 active and 2 inactive registrants). All these new registrants have to be taken into account in the conclusions to address the uses of the substance and exposure resulting from these uses.

During the course of the substance evaluation, the registrants that were initially contacted recognized that the registration dossier failed to properly address inhalation route/exposure but judged that inhalation was not a relevant route, based on measured exposure to the substance during its manufacture. Workplace measurements were provided but the report lacks contextual and analytical information (details of workers activities, presence (or not) of ventilation, limits of detection and quantification) and there is a low number of data points for similarly exposed groups of workers. Extrapolation of the findings from the "manufacture" exposure scenarios to all the others scenarios may not be relevant as the processes are likely different. Overall, the measurements do not prove that inhalation is not relevant.

Some registrants decided to remove all scenarios related to polymer uses but some did not. The approach is not harmonised throughout the different registration dossiers, which is confusing for both MSCA and downstream users. Among all the declared uses, evaluating MSCA cannot distinguish with certainty which ones correspond to the uses of HPMA and which ones correspond to the uses of polymer made from HPMA. In addition, even in the cases where a registrant specified that a certain use was a polymer use, he did not demonstrate the absence of exposure by inhalation to potential residual monomer.

The evaluating MSCA took into account the information that all 26 registrants provided as of December 2018. Considering the vapour pressure of HPMA (11 Pa at 20°C), workplace measurements which do not support an absence of exposure by inhalation, and the presence of PROC 7, 10 & 11 as well as high-energy (agitation/temperature) processes

which may imply aerosol formation and/or volatilisation of HPMA, exposure by inhalation cannot be excluded for HPMA.

Regarding the consumer uses since HPMA is an eye irritant and respiratory sensitiser, exposure to the substance should be limited. Some registrants advise against the use of mixtures containing unreacted liquid monomer intended to come into contact with skin or nails, because the substance is sensitising (see section 7.13).

Regarding the wide dispersive uses since the substance is widely used, appropriate RMM will be identified in a further RMOA.

## 7.13. Risk characterisation

Not specifically assessed during the evaluation of the substance.

Some issues raised during the evaluation are discussed below.

*Sensitisation*

HPMA is an eye and respiratory irritant and a skin and respiratory sensitiser even if there is no current harmonised classification for these endpoints. Therefore, appropriate personal protective equipments should be worn to avoid skin and respiratory contact. Evaluating MSCA considers that a CLH report should be initiated to classify the substance in order to make mandatory the wearing of adequate protective equipment when handling the substance. Furthermore, the eMSCA notes that the current chemical safety assessment does not take into account the sensitising and respiratory irritating effects. As the conditions of safe use communicated to the supply chain should be aligned with the CSR, and since the CSR is inadequate, it is likely that no risk management measures are communicated to downstream users to protect workers and consumers from sensitisation. By application of Article 14 and Annex I (5 and 6) of the REACH regulation, the CSR shall be updated to account for skin and respiratory sensitisation and respiratory irritation.

Some registrants advise against the use of mixtures containing unreacted liquid monomer intended to come into contact with skin or nails, because the substance is sensitising. However, some other registrants still support such uses (for example: PC 9b: modelling clay; PC 9c: finger paints; nail care). The consequences of these provisions and of the discrepancies between dossiers for the same substance are not known. The appropriate regulatory option to address such discrepancies is not known. Evaluating MSCA proposes to address the regulatory management options for these uses advised against in a RMOA.

A RMOA could be envisaged in order to analyse RMM to manage the risks related to skin and respiratory sensitisation for workers (especially for uses that may generate aerosols) and consumers (for all consumer uses, and for uses advised against).

*Use of HPMA to produce polymers:*

Polymers are exempted from registration and evaluation according to Article 2(9) of the REACH Regulation. For HPMA, based on the information currently available in the registration dossiers and directly provided by one registrant the evaluating MSCA observes that:

- Some registrants specified that they didn’t include (or removed) all exposure scenarios corresponding to the uses of polymers, in view of the exemption to register. Some others seem to have kept the polymer scenarios.
- It is not possible for FR-MSCA to distinguish with certainty which scenario correspond to the use of monomer or of polymer, because each registrant does not explicitly specify this and they may have had different approaches.

The evaluating MSCA is of the opinion that residual (unreacted) monomer in polymers and/or monomer emitted from polymers (as a degradation product of polymers during service life) are in the scope of the registration of the monomer. Hence describing the uses of the polymers is relevant under REACH. The Board of Appeal (BoA) has confirmed this for Case A-006-2016, since the BoA concluded that requesting information on monomer in polymers as unreacted impurity after polymerisation, or as a degradation product of the polymers, is in agreement with Article 46, Article 2(9) and the general objectives of REACH. However, the way to do so in practice is not resolved. The BoA concluded that information on monomer in polymers can be requested under substance evaluation only from registrants who also produce polymers. However, the evaluating MSCA notes that, based on registration dossiers, it is not possible to know with certainty which registrants are also producers of polymers.

*Maximal amount of residual monomer in polymers:*

To justify not including exposure scenarios for polymers, some registrants indicated that the maximal amount of residual monomer in polymer should be kept below 0.1%.

However, it has not been possible for the evaluating MSCA, based on the available information, to conclude if this limit is implemented/respected by all registrants and downstream users, and if it is sufficient to ensure safe use.

The lead registrant to support the hypothesis has provided a migration study. The data were obtained on other acrylates used to produce rigid polymer and liquid polymer (coatings). Sweat and saliva simulants were used as well as water, fatty food simulant and dry food simulant, at 3 temperatures (20, 40 and 60°C). However, the evaluating MSCA identifies the following limitations:

- Several samples show a migrated amount higher than 0.1% (up to 0.9%) thus it does not support the registrant's claim of a maximal migrated amount of 0.1% from polymers.
- The characteristics and physico-chemical properties of the tested acrylates are different from the ones of HPMA and it is therefore difficult to extrapolate directly the results of the migration study to HPMA:
    - Molecular weight: 144.168 g/mol (similar to the highest molecular weight of tested acrylate (142.2 g/mol))
    - Boiling point: 209°C (higher than the highest boiling point of tested acrylate (160°C))
    - Solubility in water: 130 g/L (much higher than the highest solubility of tested acrylate (49.4 g/L))
    - Log Kow: 0.97 (similar to the lowest log Kow of tested acrylates (1.32-0.80))
- For liquid polymer, only the dried (cured) coatings were tested but not the polymer in its liquid state. However, exposure to the liquid polymer is also possible.
- As the uses of the polymers are not known, it is not possible to determine if the testing conditions reflect the uses of HPMA.

Therefore, this study does not support the registrant's approach to not include exposure scenarios for polymers.

The evaluating MSCA notes that the data to support a maximal amount of residual monomer in polymers should be available, because it is needed for the purpose of compliance with CLP/classification of the polymers. Indeed, HPMA is self-classified Skin Sens 1 which means that a safety data sheet (SDS) and a special labelling is required for mixture containing more than 0.1% of monomer.

*Regulatory options to address polymers under REACH:*

How MSCA can conduct an assessment in the framework of REACH with regards to residual (unreacted) monomer in polymers and/or monomer emitted from polymers (as a degradation product of polymers during service life) is not solved. Case A-006-2016 of the Board of Appeal (BoA) made it clear that requesting information on monomer in polymers as unreacted impurity after polymerisation, or as a degradation product of the polymers, is in agreement with Article 46, Article 2(9) and the general objectives of REACH. The way to do so is not resolved. The BoA concluded that information on monomer in polymers can be requested under SEV only from registrants who also produce polymers. However, based on registration dossiers, it is not possible for MSCA to know with certainty which registrants are also producers of polymers.

Having this said, the evaluating MSCA notes that Article 1 of REACH specifies that registrants and downstream users are responsible for ensuring a high level of protection of human health and the environment, and therefore they should be able to demonstrate that any risk due to residual monomer in polymers, or monomer emitted as a degradation product of polymers, is fully controlled all along the life cycle of the polymers. MSCAs should be able to identify situations were such demonstration fails or is not sufficiently reliable.

The regulatory or non regulatory ways to clarify the uncertainties related to these issues are not yet identified.

Questions related to polymers under REACH are currently in the scope of Action 16 of the second REACH Review.

Regarding the high RCR, identified as an initial concern for the substance, appropriate RMM will be identified in a further RMOA.

## 7.14. References

Anses. 2018. Substance Evaluation conclusion as required by REACH Article 48 and Evaluation report for methyl methacrylate. EC No. 201-297-1; CAS No. 80-62-6. Evaluating Member State: France. 17 December 2018.

ATSDR. 1997. Toxicological profile for propylene glycol. September 1997.

Basketter DA, Scholes EW. 1992. Comparison of the local lymph node assay with the guinea-pig maximization test for the determination of a range of contact allergens. Fd. Chem. Toxic. 30: 65-69

Bjoerkner B. 1984. Contact Allergy to 2-Hydroxypropyl Methacrylate (2-HPMA) in an Ultraviolet Curable Ink; Acta Derm. Venerol (Stockh) 64(3): 264-267 (1984)

Clemmensen. 1984. Cross-reaction patterns in guinea pigs|sensitized to acrylic monomers. Drug and Chemical Toxicology 7(6): 527-540

Conde-Salazar L., Guimaraens D., Romero L.V. 1988. Occupational allergic contact dermatitis from anaerobic acrylic sealants; Contact Dermatitis 18: 129-132

EFSA. 2012. Scientific opinion on the safety evaluation of the substance, methacrylic acid, 2-hydroxypropyl ester, CAS No 27813-02-1, for use in food contact materials – EFSA panel on food contact materials, enzymes, flavourings and processing aids (CEF). EFSA Journal 2012;10(6):2745.

Estlander T. 1990. Occupational skin disease in Finland. Observation made during 1974-1988 at the Institute of Occupational Health, Helsiki; Acta Dermatol-Venereologica 155: 1-85

Gage J.C. 1970: The subacute Inhalation Toxicity of 109 Industrial Chemicals. Brit. J. Industr. Med. 27: 1-18.

INRS. 2010. Propylene-glycol. Fiche toxicologique n°226.

INRS. 2018. Methanol. Fiche toxicologique n°5.

Jordan W.P. 1975. Cross-sensitization patterns in acrylate|allergies; Contact Dermatitis 1: 13-15

Kanerva L., Estlander T., Jolanki R. 1988. Sensitization to patch test acrylates; Contact Dermatitis 18: 10-15

Kanerva L., Estlander T., Jolanki R. 1989. Allergic contact dermatitis from dental composite resins due to aromatic|epoxy acrylates and aliphatic acrylates; Contact Dermatitis. 20: 201-211

Kanerva L., Turjanmaa K., Estlander T., Jolanki R. 1991. Occupational Allergic Contact Dermatitis Caused by 2-Hydroxyethyl Methacrylate (2-HEMA) in a New Dentin Adhesive; American Journal of Contact Dermatitis Vol. 2(1): 24 - 30

Kanerva L., Estlander T., Jolanki R., Tarvainen K. 1993. Occupational allergic contact dermatitis caused by |exposure to acrylates during work with dental |prostheses; Contact Dermatitis 28: 268-275

Kusakabe H, Yamakage K, Wakuri S, Sasaki K, Nakagawa Y, Watanabe M, Hayashi M, Sofuni T, Ono H, Tanaka N. 2002: Relevance of chemical structure and cytotoxicity to the induction of chromosome aberrations based on the testing results of 98 high production volume industrial chemicals. Mutation Research. 517 (1-2): 187-198.

Lovell C.R., Rycroft R.J.G., Williams D.M.J., Hamlin J.W. 1985. Contact dermatitis from the irritancy (immediate and delayed) and allergenicity of hydroxypropyl acrylate;Contact Dermatitis 12: 117-118.

Marren P., De Berker D., Powell S. 1991. Methacrylate sensitivity and transcutaneous electrical nerve stimulation (TENS); Contact Dermatitis 25: 190 - 191

Ministry of Health and Welfare of Japan. 1996: Toxicity Testing Reports of Environmental Chemicals 4: 561 – 586.

Munksgaard E.C., Freund M. 1990: Enzymatic hydrolysis of (di)methacrylates and their polymers (publication), Scand. J. Dent. Res. 98: 261-267.

RAC. 2014. Opinion for proposing harmonized classification and labelling at EU level of methanol. EC number: 200-659-6; CAS numer: 67-56-1. Adopted 12 September 2014.

Rao K.S., Betso J.E., Olson K.J. 1981. A collection of guinea pig sensitization test results--Grouped by chemical class; Drug and Chemical Toxicology 4(4): 331-351

Read-Across Assessment Framework (RAAF), ECHA Guidance, Reference: ECHA-17-R-01-EN Cat. number: ED-02-17-140-EN-N ISBN: 978-92-9495-758-0 DoI: 10.2823/619212.

Romaguera C., Vilaplana J., Grimalt F., Ferrando J. 1990. Contact|Sensitivity to Met(Acrylates) in a Limb Prosthesis; American|Journal of Contact Dermatitis 1(3): 183-185

Sauni R, Kauppi P, Alanko K. Henriks-Eckerman ML, Tuppurainen M, Hannu T. 2008. Occupational Asthma Caused by Sculptured Nails Containing Methacrylates. AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 51:968–974

Scholes, E.W., et al 1992: The Local Lymph Node Assay: Results of a Final Inter-laboratory Validation under Field Conditions. JOURNAL OF APPLIED TOXICOLOGY, VOL. 12(3), 217-222.

OECD SIDS. 2001. Methacrylic acid. CAS N°: 79-41-4

OECD SIDS. 2004. Methanol.

Study report#1 (1989). Micronucleus assay in the bone marrow cells of|the mouse with Hydroxypropylmethacrylate.

Study report #2. 2010: Evaluation of Hydroxypropyl Methacrylate in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay.

Study report#3. 2017. Hydroxyethyl Methacrylate and Hydroxypropyl Methacrylate: In Vivo Hydrolysis of Methacrylates.

Study Report#4. 1977. Prüfung von "2-Hydroxypropylmethacrylat" auf primäre Hautreizwirkung beim Kaninchen.

Study Report#5. 1978. Prüfung von "2-Hydroxypropylmethacrylat" im Augenreiztest am Kaninchen.

Study Report#6. 1966. Hydroxypropyl methacrylate - Toxicological properties.

Study Report#7. 1992. TSCA 8e Initial Submission: Acute oral toxicity study with 2-Hydroxypropyl methacrylate in rats with cover letter; Microfiche No.: OTS0544834 (secondary source).

Study Report#8. 1996. Toxicity Testing Reports of Environmental Chemicals 4: 561 - 586. Ministry of Health and Welfare, Japan.

U.S. Coast Guard, Department of Transportation. CHRIS - Hazardous Chemical Data. Volume II. Washington, D.C.: U.S. Government Printing Office, 1984-5

## 7.15. Annex I: Read-across approach

This Annex presents the original work performed by the evaluating Member state during its evaluation, despite the fact that the read-across was at the end accepted with medium confidence, since it could still be useful information.

**Read-across rationale**

In the registration dossier available at the time of Substance Evaluation, a read-across from MMA to HPMA for repeated-dose toxicity, carcinogenicity and reproductive/ developmental toxicity endpoints was proposed, based on expected similar toxicokinetics for all methacrylates.

At the end of Substance Evaluation, a draft decision requesting a subchronic study, an EOGRTS and a prenatal developmental toxicity study was sent to the registrants. The registrants acknowledged that the HPMA registration is deficient in some data requirements, namely subchronic, reproductive and prenatal developmental data to complete the assessment. Based on a read-across argumentation, they proposed to perform the additional data with HEMA.

However, in the latest version of the CSR (2017), the registrants included data on propylene glycol to justify that no further toxicological data on HPMA is needed.

The scenario is consistent with the scenario 1 (analogue approach for which the read-across hypothesis is based on (bio)transformation to common compound) of the Read-across Assessment Framework (ECHA Guidance on RAAF, 2017).

| | **Parent substances** | **(Bio)transformation** | **Common compound** | **Non-common compound** |
|---|---|---|---|---|
| **Target** | HPMA | HPMA → MAA + PG | Methacrylic acid (MAA) | Polyethylene glycol (PG)* |
| **Source** | MMA | MMA → MAA + methanol | Methacrylic acid (MAA) | Methanol |
| **Source** | HEMA | HPMA → MAA + EG | Methacrylic acid (MAA) | Ethylene glycol (EG) |

* Data on PG was included in the latest version of the CSR to complete the read-across.

**Read-across assessment**

- **Structure similarity:**

MMA, HPMA and HEMA are all small molecules with very reactive functions. In this context, even the smallest change in chemical structure can have an impact on the reactivity and the toxicity of the molecule. In particular, MMA contains a carboxylic acid function while HPMA presents primary alcohol on the ester chain. This will induce different steric hindrance, polarity and metabolites. Therefore, a read-across cannot be assumed based on structure similarity.

- **Physicochemical properties:**

Physico-chemical information, such as water solubility, log Pow and vapour pressure, can give some indications on the bioavailability and activity profile of a substance.

Based on the available information, MMA, HEMA and HPMA are all soluble in water (> 10 g/L), have a log Pow between -1 and 4 and are volatile (vapour pressure > 1 Pa). However, there are some quantitative differences in particular between HEMA/HPMA and MMA. Indeed, MMA was less soluble in water and more volatile than HEMA and HPMA (see table below).

- **Toxicological profile:**

HEMA, HPMA and MMA were all hydrolyzed into methacrylic acid and respective alcohols (ethylene glycol (EG) for HEMA, propylene glycol (PG) for HPMA and methanol for MMA).

A similar acute toxicological profile was observed with MMA, HEMA and HPMA. Indeed, they have a low acute systemic toxicity and have the potential to induce irritation and sensitisation. Some differences were nevertheless found: HPMA and HEMA are eye irritant while MMA is not.

Toxicological profile of MMA, HEMA and HPMA after repeated exposures can be compared based on available studies performed by oral route.

For MMA, repeated-dose toxicity studies point to some effects on liver, stomach and kidney as well as neurotoxicity. A NOAEL < 100 mg/kg bw/day was identified from the available dataset, as a conservative approach. Respiratory irritation was also observed in repeated toxicity studies with MMA by inhalation (Anses, 2018).

For HEMA and HPMA, only one combined repeat-dose developmental/reproductive toxicity screening test was available. HEMA induced an increase of relative kidney weight and elevated BUN at 300 mg/kg bw/day; histopathological findings in kidney were observed at 1000 mg/kg bw/day. HPMA induced mortality, clinical signs, haematological changes and liver toxicity at 1000 mg/kg bw/day.

Based on these data, a difference of toxicity is observed between the 3 substances, with potential different target organs. This observation suggests that the systemic toxicity of these substances is rather related to the alcohol formed. Therefore, this is not in favour of a read-across between MMA, HEMA and HPMA. Indeed, the reported systemic effects are consistent with their metabolization into methanol (for MMA), ethylene glycol (for HEMA) or propylene glycol (for HPMA). In particular, methanol induced neurotoxicity and hepatic toxicity (SIDS, 2004; INRS, 2018) like MMA, ethylene glycol induced renal toxicity (OECD, 2004; NTP, 1993) like HEMA and propylene glycol, haematological changes (INRS, 2010) like HPMA. However, some quantitative differences can be noted between the parent molecule and the alcohol formed. For example, although HPMA and propylene glycol induced both hematological changes, the NOAELs reported with PG (> 1000 mg/kg bw/day reported in ATSDR, 1997 and INRS, 2010) are higher than that reported for HPMA (300 mg/kg bw/day), suggesting a higher toxicity of the parent molecule. The same observation can be noted for HEMA (NOAEL = 100 mg/kg bw/day from the OECD 422 study) and EG (NOAEL = 1875 mg/kg bw/day from a 13-week dietary study in mice, from NTP, 1993).

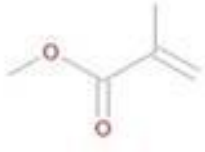
A similar genotoxicity profile, characterized by a clastogenicity *in vitro* was observed with MMA, HPMA and HEMA. Neither the parental molecule, nor their metabolites are considered genotoxic *in vivo*.

No effect on reproduction and development was observed in a 2-generation study with MMA (Anses, 2018) and in combined repeat-dose developmental/reproductive toxicity screening tests with HEMA and HPMA. "Some testicular tubular degeneration" at 2000

mg/kg bw as a 50% aqueous suspension for 21 days was noted with HPMA in a study with very limited reporting (Study report#6, 1966). Regarding the not common metabolites, developmental toxicity was reported with methanol in rodents but the RAC in 2014 concluded that there is not sufficient evidence for classifying methanol for developmental toxicity, mainly due to toxicokinetics differences between humans and rodents. No effect on fertility and/or development was reported with PG (ATSDR, 1997; INRS, 2010). Some developmental effects were reported for EG at high doses (SIDS, 2004; NTP, 2004).

In conclusion, based on the arguments presented above, the read-across first identified as not sufficiently robust to allow predicting properties from MMA/PG to HPMA for subchronic toxicity, carcinogenicity and toxicity on reproduction and development endpoints, is accepted with medium confidence in order to be able to further identify appropriate RMM.

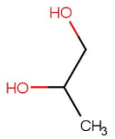
Comparison of MMA, HEMA and HPMA profiles:

| | MMA (data issued from Anses, 2018) | HEMA | HPMA |
|---|---|---|---|
| Chemical structure |  |  |  |
| Current EU harmonized classification | Skin Irrit. Cat 2 - H315<br>Skin Sens. Cat 1 - H317<br>STOT SE 3 – H335 | Skin Irrit. Cat 2 - H315<br>Eye Irrit. Cat 1 -H319<br>Skin Sens. Cat 1 - H317 | No harmonized classification for the racemic.<br>Only classification available for 2-hydroxypropyl methacrylate:<br><br>Eye Irrit. Cat 2 -H319<br>Skin Sens. Cat 1 - H317 |
| Water solubility | 15.3 g/L (20°C) | > 100 g/L (20°C) | 130 g/L (25°C) |
| Log Pow | 1.38 (20°C) | 0.42 (25°C) | 0.97 (20°C) |
| Vapour pressure | 37.8 hPa | 0.08 hPa | 0.11 hPa |
| Acute toxicity | $LD_{50}$ (oral) > 7900 mg/kg bw<br>$LD_{50}$ (dermal) > 5000 mg/kg bw<br>$LC_{50}$ (inhalation) = 29.8 mg/L | $LD_{50}$ (oral) > 5000 mg/kg bw<br>$LD_{50}$ (dermal) > 3000 mg/kg bw<br>No data for inhalation route | $LD_{50}$ (oral) > 2000 mg/kg bw<br>$LD_{50}$ (dermal) > 5000 mg/kg bw<br>No data for inhalation route |
| Local toxicity | Skin and respiratory irritation<br>No eye irritation<br>Skin and respiratory sensitisation | Skin and eye irritation<br>Respiratory irritation potential<br>Skin sensitization<br>Respiratory sensitisation potential | No skin irritation<br>Eye irritation<br>Respiratory irritation potential<br>Skin sensitization<br>Respiratory sensitisation potential |
| Repeated dose toxicity (oral) | <u>21-day-study (rats):</u><br><br>NOAEL = 200 mg/kg bw/day (locomotor activity and learning ability were impaired, and foot shock induced aggressive behaviour)<br><br><u>5 month-study (rats):</u> | OECD 422 (rat):<br><br>NOAEL = 100 mg/kg bw/day (effect on kidney at 300 mg/kg bw/day) | OECD 422 (rat):<br><br>NOAEL = 300 mg/kg bw/day (mortality, clinical signs, effect on liver and hematological changes at 1000 mg/kg bw/day) |

| | | | |
|---|---|---|---|
| | NOAEL ≥ 2000 ppm (= 124.1 mg/kg bw/day in males and 162 mg/kg bw/day in females)(highest tested dose; no biological relevant effect).<br><br><u>Repeated-dose toxicity study (rats) of limited quality:</u><br><br>NOAEL < 100 mg/kg bw/day (effects on the liver, stomach and kidney)<br><br><u>2 year-study (rat):</u><br><br>NOAEL = 124 mg/kg/d (highest tested dose - transitory decreased bw and fluid consumption at this dose). | | |
| Repeated dose toxicity (dermal) | No reliable study by dermal route. | No reliable study by dermal route. | No reliable study by dermal route. |
| Repeated dose toxicity (inhalation) | SCOEL: NOAEC = 50 ppm in humans for respiratory effects.<br><br>Respiratory irritation identified as the most sensitive effect observed in experimental studies (from short-term to chronic term). | No reliable study by inhalation route. | No reliable study by inhalation route. |
| Genotoxicity | *in vitro* : clastogenic effect<br><br>*in vivo*: negative result (no proof of bone marrow exposure) | *in vitro* : clastogenic effect<br><br>*in vivo*: negative result | *in vitro* : clastogenic effect<br><br>*in vivo*: negative result |
| Carcinogenicity | Lack of carcinogenicity of MMA in experimental animals but inadequate evidence in humans | No data | No data |

| | | | |
|---|---|---|---|
| Toxicity on reproduction and development | OECD 416 (rats, oral route):<br><br>NOAEL reproduction and development = 400 mg/kg bw/day (no effect)<br><br>NOAEL parental = 50 mg/kg bw/day (decreased food consumption at 150 mg/kg bw/day) | OECD 422 (rats, oral route):<br><br>NOAEL reproduction and development ≥ 1000 mg/kg bw/day (no effect)<br><br>NOAEL parental = 100 mg/kg bw/day (effect on kidney at 300 mg/kg bw/day) | OECD 422 (oral route):<br><br>NOAEL reproduction and development ≥ 1000 mg/kg bw/day (no effect)<br><br>NOAEL parental = 300 mg/kg bw/day (mortality, clinical signs, effect on liver and hematological changes at 1000 mg/kg bw/day)<br><br>In a study with very limited level of details: "some testicular tubular degeneration" at 2000 mg/kg bw as a 50% aqueous suspension for 21 days |
| | No developmental effect in prenatal developmental studies by oral and inhalation routes | No developmental toxicity study.<br><br>In a study with very limited level of details: Embryo-mortality and mutagenic effects on spermatozoa after administration to pregnant rats at doses > 2000 mg/kg bw/day. | No developmental toxicity study |
| Other | Number of findings may indicate an effect on the nervous system at high doses. | | |

Comparison of PG and HPMA profiles for specific toxicity:

| | PG | HPMA |
|---|---|---|
| Chemical structure |  |  |

| | | |
|---|---|---|
| Current EU harmonized classification | None | No harmonized classification for the racemic.<br>Only classification available for 2-hydroxypropyl methacrylate:<br><br>Eye Irrit. Cat 2 -H319<br>Skin Sens. Cat 1 - H317 |
| Repeated dose toxicity (oral) | Target organ: hematological system<br><br>NOAEL > 1000 mg/kg bw/day (rat, dog) | Target organs: Liver and hematological system<br><br>NOAEL = 300 mg/kg bw/day |
| Toxicity on reproduction and development | NTP continuous breeding study in mice:<br>No effect on fertility and development at doses up to 10 000 mg/kg bw/day | OECD 422 (oral route):<br>NOAEL reproduction and development ≥ 1000 mg/kg bw/day (no effect)<br><br>In a study with very limited level of details: “some testicular tubular degeneration” at 2000 mg/kg bw as a 50% aqueous suspension for 21 days (Study report#6, 1966) |
| | No effect in rat, mouse, rabbit, hamster | No developmental toxicity study |