SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2-hydroxyethyl methacrylate

EC No 212-782-2

CAS No 868-77-9

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. It should be noted that only the human health was evaluated.

Further information on registered substances here:

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

DISCLAIMER

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

2-hydroxyethyl methacrylate (or HEMA) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected CMR
- Sensitiser
- 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.

This data gap was also acknowledged by the registrants in 2016. Therefore, in February 2019, the evaluating MSCA recommended ECHA to perform a comprehensive CCH for this substance. 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 ethylene glycol, judged 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 e-MSCA considers that the current EU harmonized classification of HEMA should be updated with the following classifications:

- Resp. Sens. 1 – H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.
- STOT SE 3 –H335: May cause respiratory irritation

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

Not applicable.

4.1.3. Restriction

Not applicable.

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 HEMA 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 at the earliest	France

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

2-hydroxyethyl methacrylate (HEMA) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected CMR
- Sensitiser
- 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	HEMA has already a harmonised classification as: - Skin Irrit. 2 – H 315 - Eye Irrit. 2 – H 319 Regarding respiratory irritation, a C&L proposal should be initiated in order to add the following classification: - STOT SE 3 – H335
Skin / respiratory sensitisation	Regarding the skin sensitisation HEMA has already a harmonised classification as: Skin Sens. 1 – H317. No further action is needed regarding the classification nevertheless a RMOA will be prepared and further RMM may be proposed. Regarding respiratory sensitisation, the initial concern was confirmed. It was concluded that a C&L proposal should be initiated in order to add the following classification: Resp. Sens. Cat. 1 – H334 An update of the CSR by registrants is strongly recommended to take into account the sensitisation 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 ethylene glycol acceptable with medium confidence.

	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 is needed 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 ethylene glycol acceptable with medium confidence. Thus, no further data has been required. 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 HEMA 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. Uncertainties remain regarding the uses of the substance as such and the uses of polymer and the approach is not aligned between registrants. A limit of 0.1% of residual (unreacted) monomer in polymer is proposed by the lead registrant 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. Some registrants advise against the use of liquid mixture containing unreacted monomer intended to come into contact with skin and nails. Regarding the consumer uses, since HEMA 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. One option could be to restrict the use on nails to professionals as some other cosmetic ingredients but then the question of risk of sensitisation among them remains. Regarding the wide dispersive uses since the substance is widely used, appropriate RMM will be identified in a further RMOA. 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, 2-hydroxyethyl methacrylate 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 2-hydroxyethyl methacrylate, 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 HEMA 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 concern under the scope of substance evaluation. It was therefore agreed with the registrants that they would 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.

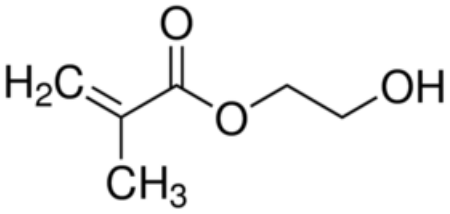
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	2-hydroxyethyl methacrylate
EC number:	212-782-2
CAS number:	868-77-9
Index number in Annex VI of the CLP Regulation:	607-124-00-X
Molecular formula:	$C_6H_{10}O_3$
Molecular weight range:	130.1418 $g.mol^{-1}$
Synonyms:	1,2-Ethanediol mono(2-methylpropenoate), Glycol methacrylate

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

Structural formula:



Based on compositions submitted by the registrants, the substance is considered a monoconstituent 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 their 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:*** - 99 °C at 101.3 kPa *Melting point was determined in accordance with the test method OECD Guideline 102.*
Boiling point	***Value used for SEV:*** 213 °C at 101.3 kPa *Boiling point was determined in accordance with the test method OECD Guideline 103.*
Relative density	***Value used for SEV:*** 1.07 at 20 °C *Data comes from peer-reviewed handbook.*
Granulometry	Not relevant. HEMA is a liquid.
Vapour pressure	***Value used for SEV:*** 0.08 hPa at 20 °C *Vapour pressure was determined according to the test procedure OECD Guideline 104.*
Water solubility	***Value used for SEV:*** > 100 g/L at 25 °C
Partition coefficient n-octanol/water (Log Kow)	***Value used for SEV:*** Log Kow (Pow): 0.42 at 25 °C *Partition coefficient was determined according to the test procedure OECD Guideline 117/EU Method A.8 (HPLC method).*
Surface tension	*Based on the chemical structure 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:*** 106 °C at 1013 hPa

	Flash point was determined in accordance with the test method A.9 (closed-cup method).
Autoflammability / self-ignition temperature	***Value used for SEV:*** 375 °C at 1024 hPa *Auto-ignition temperature was determined according to test procedure EU test method A.15.*
Flammability	***Value used for SEV****:* Non flammable *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 *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 *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: 6.36 mm²/s (static) 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 11 registrants for this substance. New registration dossiers have been submitted since then, and in January 2019, there were 38 active registrants and 3 inactive registrants.

7.5.2. Overview of uses

Information on uses, as available in the disseminated registration dossier in January 2019 (corresponding to 38 active registrations and 3 inactive registrations):

Table 7

USES	**Use(s)**
Uses as intermediate	Yes
Formulation	Production of formulations, re-packing: - ERC 2, 3 - PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 10, 14, 15, 19, 28 - PC 1, 39 - Substance supplied to that use as such and in a mixture
Uses at industrial sites	Manufacture: - ERC 1 - PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 15 Manufacture and use as intermediate, in production of formulations and end use as monomer, intermediate or formulation: - ERC 1, 4, 5, 6a, 6b, 6c, 6d, 7 - PROC 1, 2, 3, 4, 5, 6, 7, 8a, 8b, 9, 10, 12, 13, 14, 15, 17, 18, 19, 21, 22, 23, 24 - PC 15, 39 or unspecified PC - SU 2a, 2b, 5, 6a, 6b, 7, 12, 13, 14, 15, 16, 17, 18, 19, 20, 23 or unspecified SU - Substance supplied to that use as such and in a mixture Use as monomer in formulations: - ERC 5 - PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 10, 12, 13, 14, 15, 19 - PC 1, 39 or unspecified SU - Substance supplied to that use as such and in a mixture End-use as monomer in polymerisation: - ERC 6c - PROC 1, 2, 3, 4, 5, 7, 8a, 8b, 9, 14, 15, 19, 28 - Substance supplied to that use as such and in a mixture - PC 32, 39 or unspecified PC - SU 9, 20 - Substance supplied to that use as such and in a mixture Use as a polymer - ERC 6c - PROC 1, 3, 8a, 8b, 9, 14, 15 - Subsequent service-life is relevant

	Use at industrial site: - ERC 5, 7 - PROC 8a, 8b, 9 - PC 1 - SU 16 - Substance supplied to that use in a mixture Industrial use in adhesives/sealants - ERC 5 - PROC 2, 5, 8a, 8b, 9, 10, 13 - Substance supplied to that use in a mixture
Uses by professional workers	Professional end-use in formulations - ERC 8a, 8b, 8c, 8d, 8e, 8f - PROC 2, 3, 4, 5, 6, 8a, 8b, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 23, 24 - PC 1, 39 or unspecified PC - SU 19, 22 or unspecified SU - Substance supplied to that use as such and in a mixture Professional use in dental/orthodontic products - ERC 8c - PROC 10, 0 (mixing and/or application of dental/orthodontic materials) - Substance supplied to that use in a mixture Professional use in adhesives/sealants - ERC 8c - PROC 5, 8a, 8b, 9, 10, 13 - Substance supplied to that use in a mixture
Consumer Uses	Consumer end-use in formulations - ERC 8b, 8c, 8e, 8f - PC 1, 2, 3, 7, 8, 9a, 9b, 9c, 14, 15, 18, 19, 20, 21, 23, 24, 26, 29, 30, 31, 32, 33, 34, 35, 37, 39 - Substance supplied to that use as such and in a mixture
Article service life	Articles used by consumers: - ERC 10a, 11a - AC 1, 2, 3, 5, 6, 8, 10, 11, 13 - Subsequent service-life is relevant
Uses advised against	Mixtures containing unreacted liquid monomer intended to come into contact with skin or nails - PC 0: Other: Applications where liquid monomer is intended to come into contact with skin or nails. - PC 1, 39

- **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 2a: Mining, (without offshore industries)
  - SU 2b: Offshore industries
  - 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 9: Manufacture of fine chemicals
  - 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 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 precisely 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 HEMA. Therefore, all uses currently declared in registration dossiers, and which are disseminated, have been considered by the evaluating MSCA as possible uses of HEMA. 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)

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
607-124-00-X	2-hydroxyethyl methacrylate	212-782-2	868-77-9	Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1	H315 H319 H317		D

7.6.2. Self-classification

- In the registration(s):

Same as the current harmonized classification.

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:
  - Skin Sens. 1B – H317
  - Aquatic Chronic 4 – H413

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

Read-across approach

In order to fulfil all toxicological endpoints (in particular, subchronic toxicity, carcinogenicity and reproductive/developmental toxicity endpoints), the registrants proposed a read-across approach based on the metabolites of HEMA. In particular, when evaluating the substance in 2014, data on methyl methacrylate (MMA) was used in the registration dossier. Additional data on ethylene glycol (EG) were included in the registration dossier dated in 2017.

Based on the information in hand, the evaluating MSCA considered that the rationale for the read-across was not sufficiently justified. Indeed HEMA 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/ethylene glycol and HEMA is acceptable with medium confidence despite some remaining uncertainties. Therefore, it seemed not reasonable to request new information for the inhalation route for HEMA, 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 9 Studies on absorption, metabolism, distribution and elimination

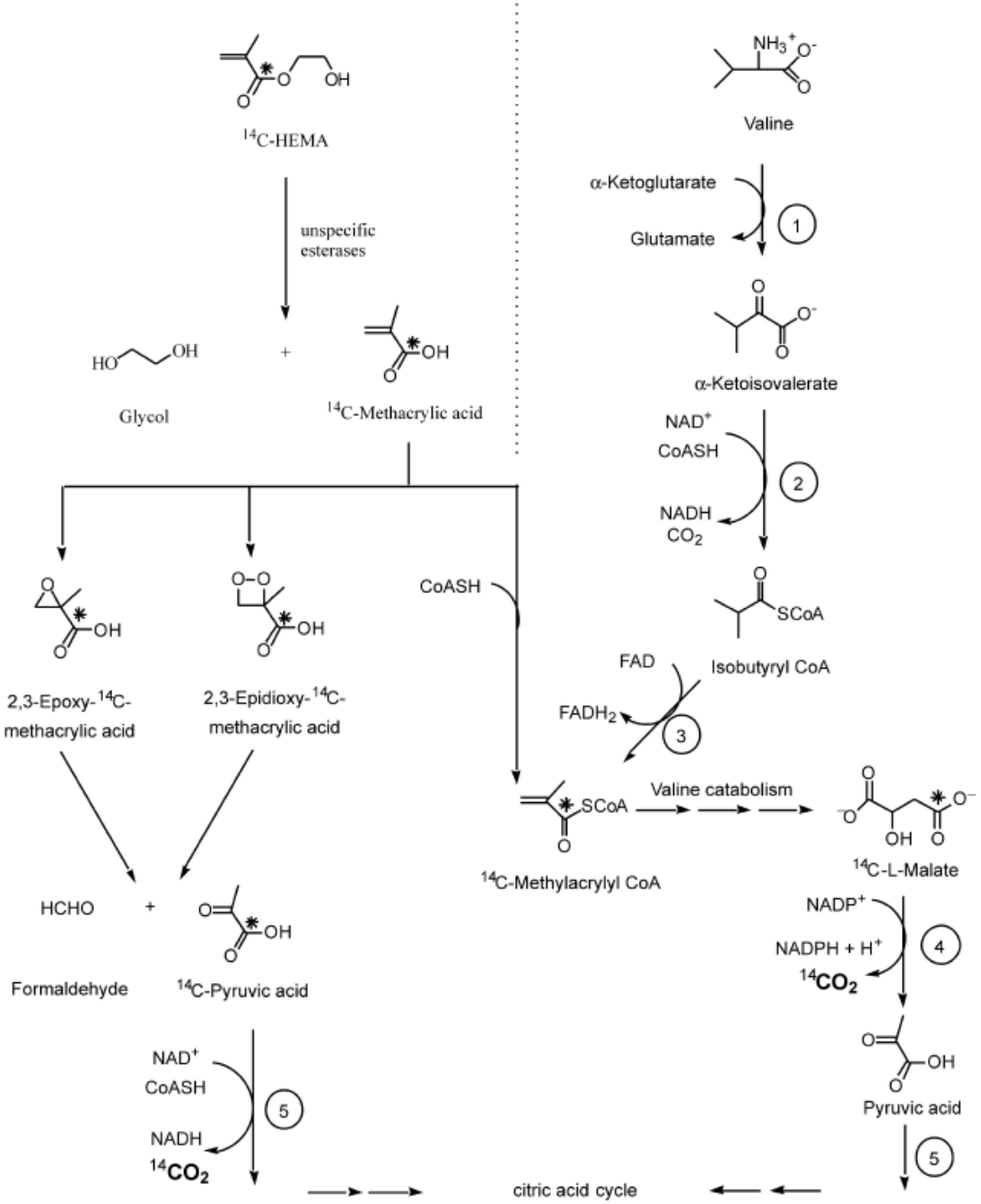
Method	Results	Remarks	Reference
In vivo studies			
Guinea pig (Dunkin-Hartley Pirbright White) male Gavage (gastric tube) and subcutaneous injection Exposure regimen: single exposure Doses/conc.: 0.02 mmol/kg HEMA, labelled with a tracer dose of radioactive ^{14}C-HEMA (0.3 kBq/g) Urine, faeces, and exhaled carbon dioxide were collected for 24 h after administration. Guinea pigs were killed 24 h after the beginning of the experiment and various organs removed and 14C radioactivity measured.	Radioactivity was principally found in exhaled air > urine > faeces after oral and subcutaneous routes in guinea pigs. The sum of ^{14}C activity in the organs was about 8%, with clearance from most tissues essentially complete within one day. Two metabolism pathways were described, both beginning by the enzymatic hydrolysis of HEMA to methacrylic acid and glycol.	2 (reliable with restrictions) key study experimental result Test material (EC name): 2-hydroxyethyl methacrylate	Reichl, F.X., *et al* (2002)

Method	Results	Remarks	Reference
Mouse (ICR) male Subcutaneous injection and oral gastric tube Exposure regime: single exposure Doses/conc.: 20 µmol/kg bw HEMA dissolved in 0.9% NaCl solution - Volume: 10 µL/g bw The clearance of ^{14}C-HEMA and ^{14}C content were determined by measuring the ^{14}C activity in organs, wall and content of organs, blood, urine, feces and exhaled air.	Radioactivity was principally found in exhaled air > faeces > urine after oral and subcutaneous routes in mice. Sum of amounts in organs were about 1% after 24 hours. Same metabolite pathway as described in Reich, 2002. The total ^{14}C recovery was about 96%.	2 (reliable with restrictions) key study experimental result Test material (EC name): 2-hydroxyethyl methacrylate	Durner, J. (2009)
In vivo study two male rats (F344/DuCrj) received HEMA via intravenous administration at the dose of 5 mg/kg bw. Blood samples were collected at 5, 10, 30, 60 and 180 minutes. Analyzed by GC/MS-MS	Estimated half-life = 1 min (0.84 and 1.06 min for each animal, respectively) Very few information available on the study	4 (not reliable) Test material (EC name): 2-hydroxyethyl methacrylate	Study report#3, 2017
In vitro studies			
in vitro study Measurement of the detoxication of HEMA mediated by N-acetylcysteine (NAC) in mouse 3T3 fibroblast cells in culture. The intracellular HEMA concentration able to cause toxic effects on 3T3-fibroblasts was determined and the decrease in intracellular and extracellular HEMA levels in the presence of NAC.	HEMA reduced 3T3 cell vitality *in vitro*. Concentration inside the cells was 15-20 times lower than that added to the culture medium. Concentration of HEMA decreased with the adding of NAC. NAC-HEMA adducts were detected.	2 (reliable with restrictions) supporting study experimental result Test material (EC name): 2-hydroxyethyl methacrylate	Nocca, G. (2010)
In vitro study Determination of *in vitro*	Half-life of HEMA in rat liver microsomes (phase I) = 4.62 min and in whole rat blood	2 (reliable with restrictions) supporting study	Study report#2 (2013)

Method	Results	Remarks	Reference
hydrolysis rates in rat liver and whole rat blood.	(phase II) = 99 min.	experimental result Test material (EC name): 2-hydroxyethyl methacrylate	
in vitro study Two methods of *in vitro* enzyme degradation and a method for the separation of the degradative products by high performance thin layer chromatography were used. Extracts were examined for decomposition products resulting from enzyme activity. Enzymatic hydrolysis: Hydroxyethyl methacrylate was hydrolyzed with nonspecific porcine liver esterase and analyzed by ion chromatography to establish the sensitivity of the enzyme simulator. The hydrolytic reactions were under enzyme-limited conditions to ease direct sampling for ion chromatographic analysis.	HEMA hydrolyzed more than 80 % in a 1-day period. The half-life for esterase hydrolysis of HEMA was 9.3 hours.	4 (not assignable) Supporting study experimental result Test material (EC name): 2-hydroxyethyl methacrylate	Bean T.A. (1994)
QSPR model			
QSPR model Dermal absorption estimation Calculation using the principles defined in the Potts and Guy prediction model.	Relative dermal absorption high; predicted flux: 151.3 µg/cm2/h	Test material (EC name): 2-hydroxyethyl methacrylate	Study report#4, 2013

Reichl *et al.* (2002) investigated the metabolism and toxicokinetics of HEMA (no further specification) in guinea pigs at a dose of 0.02 mmol/kg (equivalent to 2.6 mg/kg) administered by either oral or subcutaneous routes. After 24 hours, radioactivity was mainly found in exhaled air (about 68% after subcutaneous application and 75% after oral administration). Urinary levels ranging from 10 to 17% were noted with either route of administration. In the faeces, radioactivity was found between 1% (subcutaneous) to 3%

(oral). The sum of ^{14}C activity in the organs was about 8%. Clearance from most tissues following gastric and intradermal administration was essentially complete within one day. Two metabolic pathways were described, both beginning by the enzymatic hydrolysis of HEMA to methacrylic acid and glycol.



Similarly, Durner *et al.* (2009) measured the absorption, distribution and toxicokinetics of HEMA (20 µmol/kg bw) in mice following oral and subcutaneous injection routes. In the first experiment, the distribution and clearance of HEMA were determined by measuring the ^{14}C activity at different time intervals (5 min, 15 min, 30 min, 1h, 12h, and 24h). After oral application, radioactivity was found to be 62% of the applied ^{14}C-HEMA dose in organs 5 min after application, with highest contents found in the stomach and in the wall of stomach (19.8% and 10.5%, respectively) followed by liver (5.1%), blood (3.3%), brain and lung (0.2%). After 24 hours, the elimination was nearly complete with a sum of 0.5%

in the organs (amounts only detected in liver, large intestine and bone). The half-life period was lower than 10 minutes. After subcutaneous application, 43% of the applied dose were found in organs 5 min after application, with highest contents in muscle (18.4%) followed by blood (5.7%), skin (5.6%), injection area (3.7%) and liver (2.7%). After 24 hours, the elimination was nearly complete with a sum of <1 % in the organs (amounts only detected in liver, skin, kidney and muscle). The half-life period was lower than 10 minutes. In a separate experiment, each mouse was kept in a closed chamber with controlled airflow to determine excretion of HEMA in exhaled CO_2. Urine and feces were collected at 0.5, 1, 2, 6, 12 and 24 h after the beginning of the experiment. Organs were also analyzed 24 hours after the application. After oral administration, mice excreted about 7% of the applied dose via urine (mainly within the first 6 hours) and about 23% via feces within 24 h. Exhaled CO_2 was equivalent to about 62% of the applied dose within 24 h, with 59% of the applied dose excreted within 1 h. Amount in organs was estimated at about 1% at 24 hours. The total ^{14}C recovery was about 95%. After subcutaneous application, mice excreted about 14% of the applied dose via urine (mainly within the first 6 hours) and about 12% via feces within 24 h. Exhaled CO_2 was about 67% of the injected dose within 24 h. The total ^{14}C recovery was about 96%. In conclusion, HEMA was rapidly absorbed and widely distributed after oral and subcutaneous routes. A similar metabolism pathway as described in Reichl et al (2002) publication was proposed.

In an *in vitro* assay, HEMA (no further specification) was hydrolyzed by nonspecific porcine liver esterase (more than 80 % in a 1-day period). The half-life for esterase hydrolysis of HEMA was 9.3 hours (Bean et al, 1994). In a further *in vitro* study in rat microsomes and rat whole blood, the half-life of HEMA was 4.62 min and 99 min respectively (Study report#2, 2013).

Nocca *et al.* (2010) measured the detoxication of HEMA mediated by N-acetylcysteine (NAC) in mouse 3T3 fibroblast cells in culture. HEMA reduced 3T3 cell vitality in a dose- and time-dependent manner over an applied dose-range up to 8 mM. The concentration of HEMA inside the cells was 15–20 times lower than that added to the culture medium for cell treatment (1.2-1.6 mM). In the presence of 10 mmol/L NAC, both intracellular and extracellular HEMA concentrations greatly decreased in conjunction with cytotoxicity. NAC–HEMA adducts were detected both in the presence and absence of cells.

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

Regarding dermal absorption, a value of 112 µg/cm^2/event was estimated by the Danish QSAR toolbox. This value is consistent with the result found in study report#4 (2013) predicting a flux of 151.3 µg/cm^2/h (high dermal absorption) using a QSPR model.

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity

The oral LD_{50} of HEMA in rats was determined to be 5564 mg/kg (Study report#5, 1977a).

In a study of low reliability, the dermal LD_{50} of HEMA was higher than 3000 mg/kg bw in rabbits (Kirk-Othmer, 1984).

No acute toxicity study was available for HEMA after inhalation.

Based on these results, there is no need to classify HEMA for acute toxicity.

Corrosion/ Irritation

HEMA has an EU harmonized classification as Skin Irrit. 2 – H315. HEMA was not found to be irritating to the skin of rabbits in a study available in the registration dossier (mean primary dermal irritation index of 0.167 at 24 and 72h) (Study report#6 (1977b)).

HEMA is irritating to eyes in rabbits (Study report#7, 1978). The scores obtained in the study (cornea = 1.2; iris score = 0.8; conjunctivae score = 2.1; chemosis score = 1.33; fully reversible within 6 days) are in accordance with the current harmonized classification of the substance as Eye Irrit. 2 – H319.

HEMA is hydrolyzed to methacrylic acid (MAA), a substance known to cause respiratory tract lesions (SIDS, 2001). In particular, methacrylic acid has an existing harmonised entry for STOT SE 3; H335 if concentration is ≥ 1 %. No irritation was reported in rats exposed to atmosphere saturated with HEMA (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 HEMA can be hydrolyzed 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 HEMA as STOT SE 3 – H335 according to CLP Regulation.

7.9.3. Sensitisation

Skin sensitisation

Results of several dermal sensitization assays in experimental animals and in human case studies have been reported for HEMA. The SIDS Initial Assessment Report (2001) for HEMA concluded that:
"Animal studies suggest HEMA is a weak skin sensitizer in guinea pigs giving variable (mixed) results depending on the protocol. Positive reactions were shown only with injection of Freund's adjuvant but not by topical application alone. Whether or not this chemical induces skin sensitization in humans is equivocal; mixed results are reported in the literature on dental clients. Based on human patch test results, HEMA has sensitizing properties and HEMA has potential for cross-reaction with other (meth)acrylates."

HEMA was found not to be sensitizing to skin in the Buehler assay in guinea pigs (Study report#8, 1982). However, the validity of this study is questionable due to the lack of positive control and lack of sensitivity of this test (Buehler 3 inductions). In contrast, several Magnusson and Kligman assays showed positive results (Clemmensen, 1984 &1985; Katsuno, 1995 &1996). Other experimental studies are available but were judged as not reliable or not assignable due to insufficient level of details or significant methodological deficiencies (Sandberg, 2006, Rao, 1981, Lehé, 2003; Rustemeyer, 1998, Parker, 1983; Study Report#1, 1981; van der Walle, 1982).

Human case reports of skin sensitization with HEMA have been published. Among them, numerous positive patch tests with different concentrations of HEMA were observed in persons who had developed reactions after exposure to HEMA or with products supposed to contain methacrylates (e.g. dental composite resin products, prosthesis, photoprepolymers) (Kanerva, 1988, 1989, 1991 & 1993; Pedersen, 1983; Malten, 1979; Romaguera, 1989; Hayakawa, 1989; Estlander, 1990; Wahlberg, 1983; Peters, 1986; Marren, 1991; Conde-Salazar, 1988; Wallenhammer, 2000; Tucker, 1999; Lovell, 1985; Geukens, 2001; Peiler, 2000; Ranchoff, 1985; Lindström, 2002; SCCS, 2018). Cross sensitization between methacrylates is also possible (Kanerva, 1991; Estlander, 1990).

Skin sensitizing property of HEMA was also assessed by the SCCS (2018). The SCCS concluded that HEMA can be considered as an allergen with weak to moderate potency

based on animal studies. In addition, it was noted that human studies indicate that this substance can be considered as an allergen of concern.

In conclusion, HEMA is a skin sensitizer, which is consistent with its current harmonized classification as Skin Sens. 1 – H317.

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 FR-MSCA, the RIVM has run different SAR models (Derek, Jarvis, CatSAR, Enoch, MultiCase) with acrylates, including HEMA. No prediction could be obtained from Derek, CatSAR and Multicase. Enoch gave positive results for respiratory sensitization, whereas HEMA is negative according to Jarvis. According to the RIVM, Derek gives the most reliable prediction of a substance being a respiratory sensitizer and MultiCase the most reliable prediction for respiratory non-sensitization. Therefore, since no prediction can be obtained with these two models, no conclusion can be reached for the potential respiratory sensitization properties of HEMA 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, two publications in which HEMA was cited are described below.

Lindström *et al.* (2002) reports the case of a female dentist working in general dentistry for 22 years who developed occupational dermatitis and had eye and respiratory symptoms. These symptoms were found to be work-related since they disappeared during weekends and holidays. Inhalation challenge tests were performed in a 6 m^3 chamber with a primer and adhesive both containing HEMA. The adhesive and primer induced cough, rhino conjunctivitis and decrease in FEV1 (forced expiratory volume in one second). Patch test was positive with 1% HEMA and induced itching, swelling and soreness of the eyelids. Therefore, it can be considered as a clear sensitizing reaction to HEMA.

Sauni *et al.* (2008) reports two cases of occupational asthma caused by sculptured nails containing methacrylates. HEMA was detected in the bonding agent, the sealing resin, the sculpture resin and the gel nails. Bronchial provocation tests were performed in an 8 m^3 chamber with their own products (they attached the plastic nail with a glue and then filed and sculptured the nails). A 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 HEMA. These cases were mainly observed in dental professionals and nail technicians.

Although HEMA was only cited in few 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 HEMA 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 summarized in the following table:

Table 10. Studies on repeated dose toxicity after oral administration

Method	Results	Remarks	Reference
rat (Crj: CD(SD)) male/female subchronic (oral: gavage) 0 (vehicle), 30, 100, 300, 1000 mg/kg/day Vehicle: water Exposure: Males, 49 days; Females, from 14 days before mating to day 3 of lactation (Once daily) OECD Guideline 422 (1996) (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)	NOAEL: 100 mg/kg bw/day (nominal) (male): increased BUN value and increased relative kidney weight NOAEL: 300 mg/kg bw/day (nominal) (female): clinical signs, decreased body weight and food consumption, increased kidney weight and histopathological findings.	2 (reliable with restrictions) key study experimental result **Test material (EC name): 2-hydroxyethyl methacrylate**	Nihon Bioresearch, Inc. (1997)

Oral route

Effects of HEMA (purity of 97.6%) have been evaluated in a combined repeat-dose developmental/reproductive toxicity screening test in Sprague-Dawley rats (Nihon Bioresearch, Inc. (1997)).

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 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).

At the highest dose, i.e. 1000 mg/kg bw/day, one male and six females died. Significant decreased body weight was observed in both sexes at this dose. This was associated with a statistically significant decrease in food consumption. Clinical symptoms of intoxication observed at 1000 mg/kg included salivation in both sexes and decrease in locomotor activity, adoption of a prone position, soil fur, hypothermia, bradypnea and lacrimation in females only.

No haematological changes were reported. Male rats in 30, 300 mg/kg and 1000 mg/kg dose groups had statistical elevated levels of BUN (blood urea nitrogen).
Liver weight was increased in males only, but it was not correlated with histopathological changes. Relative kidney weight was increased in males from 100 mg/kg bw/day and at 1000 mg/kg bw/day in females. Absolute kidney weight was also increased at 100 and 1000 mg/kg bw/day in females.

Histopathological changes in male rats were mainly confined to kidney with slight to moderate grade severity in 1000 mg/kg group animals: basophilic tubules (4 animals versus 3 in control), renal tubule dilatation (3 rats versus 0 in control), collecting duct dilatation (2 rats versus 0 in control), unilateral cyst (1 rat versus 0 in control), diffuse mineralization (1 rat versus 0 in control) and neutrophilic cellular infiltration (1 rat versus 0 in control). Only renal tubule dilatation was statistically increased. Haemorrhage of thymus was observed in one rat at 1000 mg/kg bw/day (versus 0 in control). At 300 mg/kg, minimal focal renal tubule degeneration was found in one male rat (versus 0 in control). At 100 mg/kg, hyaline droplet in proximal tubule was found in one male rat (versus 0 in control).
Histopathological changes in female rats were only found at 1000 mg/kg bw/day and included mild unilateral neutrophilic cellular infiltration into the medulla and papilla in one rat and an elevated incidence of malacia of the medulla oblongata in one rat.
The NOAEL for males is set at 100 mg/kg bw/day, based on the increased of relative kidney weight and elevated BUN observed at 300 mg/kg bw/day. These effects can be considered precursor indicators of histopathological renal effects observed at the dose just above. The elevated BUN observed at 30 mg/kg bw/day was not considered treatment-related since no statistical increase was found at 100 mg/kg bw/day. The increase of kidney weight in males at 100 mg/kg bw/day was not considered in the choice of the NOAEL since this was not found in females at this same dose and there was no histopathological correlate at 100 and 300 mg/kg bw/day.

The NOAEL for females is set at 300 mg/kg bw/day based on mortality, clinical signs, decreased body weight, increased kidney weight and histopathological findings observed at 1000 mg/kg bw/day.
Other repeated-dose toxicity studies of low reliability performed with HEMA are also available.

In a second oral toxicity study, rats were orally exposed to HEMA (unspecified purity) at 0.5, 2.5 or 12.5 mg/kg bw/day for 4 months (Vyshemirskaya, 1987; only abstract in Russian). The reported NOAEL was set at 0.5 mg/kg bw/day. Effects included decreased body weight and pathological changes in liver, spleen, heart and stomach. A dose of 2.5 mg/kg bw/day in pregnant rats induced embryo mortality and a dose of 12.5 mg/kg bw/day led to mutagenic effects on spermatozoa. The level of details available is not sufficient to adequately assess the relevance of these results.

In a third study, HEMA was orally administered to male and female rats for 21 days at the unique dose of 2000 mg/kg bw/day (Study report#9, 1966). One female died. General clinical signs including salivation, piloerection, and incoordination were reported at the end of the second week of dosing and persisted during all the treatment. Animals recovered within the 7-day post-exposure period. Some rats presented hepatocellular fatty vacuolation. Screening tests showed some impairment of clotting in some animals.

Inhalation route

One study of low quality was available (Gage, 1970). Only minor interference in clotting function was found in rats exposed to an atmosphere saturated with HEMA (no further specification) at 0.5 mg/L for 3 weeks. This study was judged as not reliable because there is no information on an analytical verification of the concentration tested, only one

concentration was tested with no control group, a low number of animals was used and the level of details was very limited.

Dermal route

No adequate repeated-dose toxicity study by dermal route is available with HEMA.

In a 7-day dermal study, HEMA (no further specification) caused insignificant irritation to the dermis of rabbits (Manabe, 1990). This study was considered as not reliable due to the too low level of details available and since only histopathological examination of skin was performed.

In another not reliable study, no evidence of clinical evidence of cerebellar damage in female rats exposed to 47 daily applications of HEMA (Study report#9, 1966).

Conclusion

Regarding repeated-dose toxicity study with HEMA, 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. Furthermore, a full histopathological evaluation comparable as that recommended in the OECD 408 guideline (repeated dose 90 day oral toxicity study) was not performed.

In order to complete this endpoint, data available on methyl methacrylate (MMA) were also provided. However, the read-across was not considered as acceptable since MMA and HEMA 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 HEMA do not meet the requirements for the respective tonnage band. However, they proposed to perform this subchronic toxicity study by oral route.

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 related 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 ethylene glycol (EG) in addition to data on MMA and HEMA to complete this endpoint. EG was tested by the NTP in a 13-week dietary study in mice (NTP, 1993). Chemical-related kidney and liver lesions (nephropathy and centrilobular hepatocalluclar hyaline degeneration) were seen from 25,000 ppm (equivalent to about 3750 mg/kg bw/day using OECD conversion[2]) with a NOAEL of 12,500 ppm (equivalent to about 1875 mg/kg bw/day). Comparison of this NOAEL with the one from the OECD 422 study performed with HEMA suggests a higher toxicity of the parent molecule (with some limitations due to difference of the route of exposure: gavage versus

[2] ENV/JM/MONO(2002)19

diet and species used: rat versus mouse). Despite the new data provided on ethylene 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 according Annex IX of REACH, section 8.6.2. ECHA checked the compliance with the standard information requirements under REACH for this endpoint and judged the dossier as compliant with medium confidence at the currently registered tonnage levels, based on a read-across with methacrylic acid and ethylene glycol. 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 various strains of bacteria (*S. typhimurium* TA 97a, 98, 100, 102, 1535, 1537, 1538; *E. Coli* WP2 uvrA) exposed to HEMA with and without metabolic activation (Study Report#11, 1997; Schweikl *et al.* (1994; 1998); Waegemaekers, 1984; Heil, 1996). An occasional increase in the number of revertants over the control level was observed with *S. typhimurium* strain TA 100 with metabolic activation in an Ames assay performed with HEMA (no further specification). This result cannot be scientifically assessed due to insufficient level of details available (Study report#1, 1981).

Mammalian cell assays

- **Gene mutations**

HEMA (no further specification) was evaluated for its ability to cause forward mutation at the hprt locus in Chinese hamster lung fibroblast V79 cells in culture (Schweikl, 1998). Cells were exposed for 24 hours without metabolic activation or for 4 hours with S9. In the absence of metabolic activation, concentrations of HEMA of 2.5 and 5 mM did not increase the mutant frequency; plating efficiencies were 84-113% of control. Results with metabolic activation were not presented in the publication. However, it is not expected that HEMA induced gene mutations in the presence of metabolic activation in mammalian cells. Indeed, HEMA does not induce mutations in several Ames tests and according to Johannsen review (2007) on the mutagenicity of acrylates and methacrylates, these substances (with few exceptions) are non mutagenic in point mutation tests. Therefore, the results appeared consistent within each of several types of tests across the functional spectrum of acrylates and metacrylates, with no apparent differences in response related to a specific structure.

- **Chromosomal aberrations**

HEMA has been evaluated for its ability to induce chromosomal aberrations in mammalian cells in culture. Kusakabe *et al.* (2002) evaluated the clastogenic potential of HEMA along with a large number of other substances in Chinese hamster lung cells in culture, exposed to concentrations up to 1.3 mg/ml. HEMA was reported to induce structural chromosome aberrations following 6-hour exposure of cells but only in the presence of S9 at 1.3 mg/ml. Continuous exposure of cells for 24 or 48 hours without S9 also caused an elevated incidence of chromosome aberrations (from 0.16 mg/ml for the 48-hour exposure and from 0.65 mg/ml for the 24-hour exposure). Polyploidy was reported after both short-term treatment and 48-hour continuous treatment exposures. However, no dose-dependency was observed for polyploidy in the short-term treatment with metabolic activation. These effects were found at exposure levels without cytotoxicity or at concentrations which caused <50% cell death (no toxicity up to 0.65 mg/ml).

Lee *et al.* (2006) evaluated the induction of micronuclei and DNA fragmentation by HEMA (no further specification). In this study, HEMA at 3-5 mM was added to V79-4 cells, and

the cultures were incubated for 24 hours. Treatment was stopped by replacing the exposure medium with fresh culture medium and the cell cultures were reincubated for 24 hours. Micronuclei were analyzed microscopically in three parallel cultures (slides) of 1000 cells/slide per concentration of resin monomer. All concentrations of HEMA increased micronuclei incidence, with a cell survival exceeding 60%. After exposure of RPC-C2A cells to HEMA at 14 mM for 24 hours, DNA fragmentation and apoptosis were observed. GSH depletion is suggested to be a primary cause of apoptosis induced by HEMA. N-acetylcystein (NAC), an antioxidant agent, inhibited the induction of micronuclei by more than 50% at 4-5 mM HEMA and decreased HEMA-induced DNA fragmentation and apoptosis in RPC-C2A cells in culture. According to author, this result supports the hypothesis of the role of oxidative stress in mutagenicity of HEMA.

Induction of micronucleus in V79 cells exposed to HEMA (no further specification) was reported with and without metabolic activation by Schweikl *et al.* (2001). However, the level of details on protocol is limited to adequately assess these results. The same authors in 2007 also reported the induction of micronuclei in V79 cells in culture exposed to 6 mmol/L of HEMA (no further specification) for 24 hours. No increase of micronucleus was observed at concentrations of 2 and 4 mmol/L. At 8 mmol/L of HEMA, no micronuclei were identified due to severe cytotoxicity. Furthermore, V79 cells accumulated in the G2 phase of the cell cycle. N-acetylcysteine inhibited the effect of HEMA on both the induction of micronuclei and the cell cycle, suggesting that the observed effects were at least partly mediated by oxidative stress.

Urcan *et al.* (2010) reported that 1 – 11 mM of HEMA (no further specification) applied to human gingival fibroblast cells *in vitro* for 6 hours caused double strand DNA breaks (DSB). This is a non-guideline study using γ-H2AX immunofluorescence as a direct marker for DSBs.

- **DNA damage**

Pawlowska *et al.* (2010) reported that HEMA (no further specification) was able to damage DNA in lymphocytes in culture, exposed for 1 hour, using the Comet assay system. HEMA at concentrations up to 10 mM did not affect the viability of the cells. However, HEMA induced concentration dependent DNA damages in lymphocytes in the alkaline and pH12.1 versions of this test. The increase of the percentage of tail DNA was over 100% for the highest HEMA concentration (10 mM, $p < 0.01$). No changes in the percent tail DNA in the neutral version of this test were observed, which indicates that the chemical did not introduce DNA-strand breaks in lymphocytes. The inability of HEMA to induce DNA double-strand breaks was confirmed by pulsed-field gel electrophoresis. The results indicated that HEMA induced mainly alkali-labile sites in DNA. Authors suggest that ROS (reactive oxygen species), including free radicals, may play an important role in the DNA-damaging effects induced by HEMA (presence of oxidative modifications to DNA bases).

Enhanced migration of DNA was also observed in an alkaline Comet assay performed with HEMA (no further specification) at concentrations > 10^{-6} M, with cell vitality at 84% (Kleinsasser, 2004). This study was performed in human lymphocytes exposed to HEMA for 1 hour without metabolic activation with concentrations ranged from 10^{-8} to 2.5×10^{-2} M. The DNA migration was assessed using the Olive Tail Moment (OTM) method (relative amount of DNA in the tail of the comet x median migration distance). Positive control was hydrogen peroxide.

***In vivo* studies**

HEMA has been evaluated for its ability to cause chromosomal aberrations *in vivo* in a micronucleus assay in rats (Study report#10, 2001). HEMA was administered by oral gavage twice per day to groups of 5 male rats at doses of 500, 1000 and 2000 mg/kg. In this study, no animals died and there were no clinical symptoms of intoxication. A

significant increase in the incidence of PCEs (polychromatic erythrocytes) at 1000 mg/kg bw was noted. According to Durner (2009), regarding the toxicokinetics and distribution of 2-hydroxyethyl methacrylate in mice, HEMA was found in bone after gastric administration (0.2% and 0.1%, 5 and 24 hours after administration, respectively). Therefore, it is expected that HEMA reaches the bone marrow of rodents after oral administration. There was no increase in the number of micronucleated PCEs at any HEMA dose level. Cyclophosphamide, used as positive treatment, did cause an increase in micronucleated PCEs.

Arossi *et al.* (2009) reported that HEMA (no further specification) was not active in a test of mutagenicity in Drosophila melanogaster *in vivo*. The Somatic Mutation and Recombination Test (SMART) can detect mitotic recombination and a various set of mutational events such as point mutations, deletions and certain types of chromosome aberrations. SMART detects the loss of heterozygosity of marker genes expressed phenotypically on the fly's wings. HEMA, at concentrations ranging from 0.675 to 2.5 %, had no statistically significant effect on total spot frequencies – suggesting no genotoxic action in the SMART assay. However, it should be noted that no harmonized EU guideline is available for this assay.

Therefore, it can be concluded that HEMA does not induce gene mutations. While HEMA causes chromosomal aberrations in mammalian cells in culture, probably at least partially *via* an oxidative mode of action, it is not clastogenic *in vivo*.

7.9.6. Carcinogenicity

No carcinogenic study with HEMA 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 study on fertility is summarized in the following table:

Table 11. Studies on fertility

Method	Results	Remarks	Reference
rat (Crj: CD(SD)) male/female oral: gavage 0 (vehicle), 30, 100, 300, 1000 mg/kg/day Vehicle: water Exposure: Exposure period: Males, 49 days (from 14 days before mating); Females, from 14 days	NOAEL (parent male) = 100 mg/kg bw/day, based on the increased of relative kidney weight and elevated BUN NOAEL (parent female) = 300 mg/kg bw/day based on mortality, clinical signs, decreased body weight, increased	2 (reliable with restrictions) key study experimental result **Test material (EC name): 2-hydroxyethyl methacrylate**	Nihon Bioresearch, Inc. (1997)

Method	Results	Remarks	Reference
before mating to day 3 of lactation Equivalent or similar to OECD Combined Repeated Dose and Reproductive / Developmental Toxicity Screening Test (OECD 422 guideline (1996))	kidney weight and histopathological findings NOAEL (reproductive toxicity): >= 1000 mg/kg bw/day (male/female) (no effect) NOAEL (development): >= 1000 mg/kg bw/day (male/female) (no effect)		

Animal data

There is neither an EOGRTS nor prenatal developmental toxicity study available with HEMA. Instead, one combined repeat-dose developmental/reproductive toxicity screening test on the substance is available to cover both fertility and developmental endpoints (Ministry of Health and Welfare of Japan, 1997). 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 systemic effects in male parents is set at 100 mg/kg bw/day, based on the increase of relative kidney weight and elevated BUN observed at 300 mg/kg bw/day. The NOAEL for systemic effects in female parents is set at 300 mg/kg bw/day based on mortality, clinical signs, decreased body weight, increased kidney weight and histopathological findings observed at 1000 mg/kg bw/day (further details in section 7.9.4).

Concerning the reproductive toxicity part of the study, only 7 females were mated at the highest dose, due to the death of 5 animals. Among these seven females, only 5 became pregnant, which is lower than what is recommended in the OECD guideline (at least 8 pregnant females per group is the minimum acceptable number of pregnant females per group). There were no effects of the test substance on the estrus frequency, number of conceiving days, fertility index, length of gestation, number of corpora lutea or gestation index. Copulation index[3] was slightly reduced at the highest dose (91.7%, 100%, 100%, 100%, and 71.4%). There were no effects of the test substance 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 or necropsy findings. The NOAEL for reproductive and developmental toxicity is ≥ 1000 mg/kg bw/day.

Human data

[3] number of pairs with successful copulation / number of pairs × 100

A study conducted among dental workers women was compared to a group of workers occupationally unexposed to dental restorative materials in Finland (Lindbohm, 2007). Information on pregnancies was obtained from national registers and outpatient units of hospitals. Data on occupational exposure were obtained using postal questionnaires. The final study population included 222 cases of miscarriage and 498 controls (births). Non-significant associations between exposure to HEMA and the risk of miscarriage among the dental personnel were found. There was no clear indication of a dose-response relationship.

Conclusion

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 of Annex IX of REACH, Section 8.7.2 nor the existing OECD TG 443, as a standard requirement of Annex X of REACH, 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 behavior, 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. Moreover, the number of pregnant females obtained in this test is very low, limiting even more the sensitivity of this screening test. Finally, 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, data on methyl methacrylate was provided by the registrants. No concern for toxicity on reproduction is raised from a 2-generation study (Conclusion document for MMA, Anses, 2018). When performing the substance evaluation, the read-across between MMA and HEMA 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 HEMA 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 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 HEMA do not meet the requirements for the respective tonnage band.

After exchanges with ECHA and registrants, it was finally considered that these requests are rather related to a non-compliance with REACH Annexes than really 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 still not been done, neither in the IUCLID dossier nor in the updated CSR. Instead, in the latest version of the

CSR (2017), the registrants added data on ethylene glycol (EG) and concluded that it is unlikely that HEMA is a reproductive/developmental toxicant considering the absence of this type of effect reported in the OECD TG 422 study performed with HEMA and supported by data available on MMA and EG. However, this approach was still considered as not 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 ethylene 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 HEMA 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

2-hydroxyethyl methacrylate (HEMA) is well absorbed and rapidly metabolized into methacrylic acid (MAA) and ethylene glycol (EG).

HEMA has a low acute toxicity.

According to CLP Regulation, HEMA is currently classified as Skin Irrit. 2; Eye Irrit. 2 and Skin Sens. 1.

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

Although HEMA was only cited in 3 cases of occupational asthma, several human cases were reported with methacrylate 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, HEMA has also the potential to induce skin sensitisation. Thus, a C&L process should be foreseen to introduce a harmonised classification and classify HEMA as Resp. Sens. 1.

Only a combined repeat-dose developmental/reproductive toxicity screening test on HEMA is available to cover repeated toxicity, reproductive toxicity and developmental toxicity endpoints. Based on this study, HEMA induced effects on the kidney leading to a NOAEL of 100 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.

HEMA is clastogenic *in vitro* but not *in vivo*. There is no carcinogenicity data available with the substance.

Data on methyl methacrylate, as a representative of methacrylic toxicity, and on ethylene glycol were included by the registrants to justify a read-across approach and not perform any additional tests with HEMA. 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 (repeated-dose toxicity and toxicity on reproduction and development), it judged the read-across with methacrylic acid and ethylene 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 HEMA. 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 (11 registrants at the start, and in January 2019, 38 active and 3 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, the evaluating MSCA cannot distinguish with certainty which ones correspond to the uses of HEMA and which ones correspond to the uses of polymer made from HEMA. 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 route to potential residual monomer.

The evaluating MSCA took into account the information that all 38 registrants provided as of January 2019. Considering the vapour pressure of HEMA (8 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 HEMA, exposure by inhalation cannot be excluded for HEMA.

Regarding the consumer uses since HEMA 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

According to CLP Regulation, HEMA is an eye and skin irritant and a skin sensitiser. In addition, it should be considered as a respiratory irritant and sensitiser, even if there is no harmonised classification for this endpoint. Therefore, appropriate personal protective equipments should be worn to avoid skin and respiratory contact. The evaluating MSCA considers that a CLH report should be initiated to classify the substance as STOT SE 3 and Resp. Sens. 1 in order to make mandatory the wearing of adequate protective equipment when handling the substance to prevent respiratory local effects. 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. Some

even advise against uses as PC 1 and PC 39. However, some other registrants still support such uses (PC 1: adhesives, PC 39: cosmetics and also 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. The 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 HEMA to produce polymers:

Polymers are exempted from registration and evaluation according to Article 2(9) of the REACH Regulation. For HEMA, 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 did not 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 this is not explicitly specified by each registrant 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. This has been confirmed by the Board of Appeal (BoA) 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.

A migration study has been provided by the lead registrant to support the hypothesis. 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 HEMA and it is therefore difficult to extrapolate directly the results of the migration study to HEMA:
    - Molecular weight: 130.142 g/mol (slightly lower than the highest molecular weight of tested acrylate (142.2 g/mol))
    - Boiling point: 213°C (higher than the highest boiling point of tested acrylate (160°C))
    - Solubility in water: 100 g/L (much higher than the highest solubility of tested acrylate (49.4 g/L))
    - Log Kow: 0.42 (lower than 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 HEMA.

Therefore, this study does not support the registrant's approach not to 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, HEMA is 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 concerning 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.

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.

Arossi, G.A., Lehmann, M., Dihl, R.R., Reguly, M.L.and de Andrade, H.H.R. 2009: Induced DNA Damage by Dental Resin Monomers in Somatic Cells, Basic and Clinical Pharmacology and Toxicology 106, 124-129.

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

Clemmensen S. 1985: Sensitizing potential of 2-hydroxyethyl-methacrylate, Contact Dermatitis 12(4): 203-208.

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

Bean T.A., Zhuang W.C., Tong P.Y., Eick J.D., Yourtee D.M. 1994: Effect of esterase on methacrylates and methacrylate polymers in an enzyme simulator for biodurability and biocompatibility testing, Journal of Biomedical Materials Research 28: 59 - 63.

Durner, J., H. Kreppel, J. Kaspel, H. Schweikl, R. Hickel, and F. Reichl 2009: The Toxicokinetics and Distribution of 2-Hydroxyethyl methacrylate in Mice, Biomaterials 30, 2066-2071.

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.

Geukens S, Goossens A. 2001. Occupational contact allergy to (meth)acrylates. Contact Dermatitis 44(3): 153-159

Hayakawa R., Takeuchi Y., Kojima S. 1989. Occupational Allergic Contact Dermatitis due to 2-Hydroxy-Ethyl-Methacrylate; Hifu|31(7): 17-23

Heil J, Reifferscheid G, Waldmann P, Leyhausen G, Geurtsen W. 1996. Genotoxicity of dental materials. Mutation Research 368; 181-194

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

Johannsen FR, Vogt B, Waite M, Deskin R. 2008. Mutagenicity assessment of acrylate and methacrylate compounds and implications for regulatory toxicology requirements. Regul Toxicol Pharmacol. 2008 Apr;50(3):322-35.

Jones O. 2002. Using physiologically based pharmacokinetic modelling to predict the pharmacokinetics and toxicity of methacrylate esters. A Thesis submitted to Univ. of Manchester for the degree of Doctor of Philosophy. Owner company; Univ. of Manchester

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.

Katsuno K, Manabe A, Itoh K, Hisamitsu H, Wakumoto S, Nakayama S, Yoshida T. 1995. A delayed hypersensitivity reaction to dentine primer in the guinea pig. Journal of Dentistry vol 23 no 5: 295-299

Katsuno K, Manabe A, Itoh K, Nakamura Y, Wakumoto S, Hisamitsu H, Yoshida T. 1996. Contact dermatitis caused by 2-HEMA and GM dentin primer solutions applied to guinea pigs and humans. Dental materials Journal. 15(1): 22-30

Kirk-Othmer - Encyclopedia of chemical technology, 3th ed. Vol. 15. New York: John Wiley and sons; 1981: 398-415.

KleinsasserNH, Wallner BC, Harréus UA, Kleinjung T, Folwaczny M, Hickel R, Kehe K, Reichl FX. 2004. Genotoxicity and cytotoxicity of dental materials in human lymphocytes as assessed by the single cell Microgen electrophoresis (comet assay). Journal of Dentistry. 32:229-234

Lee DH, Lim BS, Lee YK, Ahn SJ, Yang HC. 2006. Involvement of oxidative stress in mutagenicity and apoptosis caused by dental resin monomers in cell cultures. Dental Materials 22: 1986-1092

Lehé CL , Jacobs JJ, Elliott GR, Das PK. 2003. A two-centre evaluation of the human organotypic skin explant culture model for screening contact allergens. Altern Lab Anim. 31(6): 553-61

Lindbohm, M-L, Ylostalo, P., Sallmen, M. et al 2007: Occupational exposure in dentistry and miscarriage (publication), Occupational Environ. Med. 64: 127-133.

Lindström M, Alanko K, Keskinen H, Kanerva. L. 2002. Dentist's occupational asthma, rhinoconjunctivitis, and allergic contact dermatitis from methacrylates. Allergy 2002: 57: 543–545

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.

Malten K.E., Bende W.J.M. 1979. 2-Hydroxy-ethyl-methacrylate and|di- and tetraethylene glycol dimethacrylate: Contact sensitizers in a photoprepolymer printing plate procedure. Contact Dermatitis 5: 214-220

Manabe A., Hasegawa T., Chigira H., Itoh K., Wakumoto S., Nakayama S., Tachikawa T. 1990. Morphological Changes of Rabbit Skin by Application of Dentin Primer; Dent. Mater. J. 9(2):147-152

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. Nihon Bioresearch, Inc. 1997. Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test of 2. Hydroxyethyl methacrylate by Oral Administration in Rats, Toxicity Testing Reports of Environmental Chemicals 5: 525 - 552.

Nocca, G., D'Anto, V., Desiderio, C., Rossetti, D.V., Valletta, R., Baquala, A.M., Schweikl, H., Lupi, A., Rengo, S. and Spagnuolo, G. 2010: N-acetyl cysteine directed detoxification of 2-hydroxyethyl methacrylate by adduct formation, Biomaterials 31: 2508-2516.

NTP. 1993. Toxicology and carcinogenesis studies of ethylene glycol (CAS No. 107-21-1) in B6C3F1 mlice (feed studies). Technical report series No. 413

NTP. 2004. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. NTP CERHR MON. 2004 Jan;(11):1-III36.

Parker D., Turk J.L. 1983. Contact sensitvity to acrylate compounds in guinea pigs; Contact Dermatitis 9: 55-60

Pawlowska E, Poplawski T, Ksiazek D, Szczepanska J, Blasiak J. 2010. Genotoxicity and cytotoxicity of 2-hydroxyethyl methacrylate. Mutation Research 296: 122-129

Pedersen N.B., Senning A., Nielsen A.O. 1983. Different sensitising acrylic monomers in Napp printing plate; Contact Dermatitis 9: 459-464

Peiler D, Rustemeyer T, Pflug B, Frosch PJ. 2000. Allergic Contact Dermatitis in Dental Laboratory Technicans. Dermatol. Beruf Umwelt 48(2): 48-54

Peters K., Andersen K.E. 1986. Allergic hand dermatitis from 2-hydroxyethyl-acrylate in contact lenses; Contact Dermatitis 15: 188-189

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.

Ranchoff R.E., Taylor J.S. 1985. Contact dermatitis to anaerobic|sealants; J. Am. Acad. Dermatol. 13: 1015-1020

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

Reichl, F.X., et al 2002: Toxicokinetic of HEMA in guinea pigs, Journal of Dentistry 30: 353–358.

Rustemeyer T, de Groot J, von Blomberg BME, Frosch PJ, Scheper RJ. 1998. Cross-Reactivity Patterns of Contact-Sensitizing Methacrylates. TOXICOLOGY AND APPLIED PHARMACOLOGY 148, 83–90.

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

Sandberg, E. and Dahlgrean, U.I. 2006: Application of HEMA on intact mouse skin- effects on the immune system, Contact Dermatitis 54, 186-191.

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

SCCS. 2018. Opinion on the safety of cosmetic ingredients HEMA and Di-HEMA trimethylhexyl dicarbamate. Submission I (sensitization only). SCCS/1592/17. Adopted on 21-22 June 2018.

Schweikl H., Schmalz G., Bey B. 1994: Mutagenicity of dentin bonding agents, Journal of Biomedical Materials Research Vol. 28: 1061 - 1067.

Schweikl H., Schmalz G., Rackebrandt K. 1998: The mutagenic activity of unpolymerized resin monomers in Salmonella typhimurium and V79 cells, Mutation Research 415: 119 - 130.

Schweikl H, Hartmann A, Hiller KA, Spagnuolo G, Bolay C, Brockhoff G, Schmalz G. 2007. Inhibition of TEGDMA and HEMA-induced genotoxicity and cell cycle arrest by N-acetylcysteine. Dental materials 23: 688–695

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

OECD SIDS. 2001. 2-hydroxyethyl methacrylate. CAS N°: 868-77-9.

OECD SIDS. 2004. Methanol.

OECD SIDS. 2004. Ethylene glycol, Diethylene glycol, Triethylene glycol, Tetraethylene glycol, Pentaethylene glycol (Ethylene Glycols Category)

Study report#1. 1981. Initial Submission: Irritation and Mutagenicity tests of Hydroxyethyl methacrylate and related studies with cover letter.

Study report#2. 2013: Methacrylate Esters: In Vitro Metabolism in Rat Blood and Liver Microsomes.

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

Study report#4. 2013: Higher Methacrylates: In Silico Prediction of Dermal Absorption (study report).

Study report#5. 1977a. Akute Toxizitätsprüfung von "2-Hydroxyäthyl-methacrylat" nach oraler Applikation an der Ratte, unpublished report.

Study report#6. 1977b: Prüfung von "2-Hydroxyäthylmethacrylat" auf primäre Hautreizwirkung beim Kaninchen.

Study report#7. 1978. Prüfung von "2-Hydroxyäthylmethacrylat" im Augenreiztest am Kaninchen, unpublished report.

Study report#8. 1982. 2-Hydroxyethylmethacrylat (HEMA) Delayed Contact Hypersensitivity modified by E.V. Buehler.

Study report#9. 1966. Hydroxypropyl methacrylate - Toxicological properties; unpublished report.

Study report#10. 2001. Micronucleus Test of HEMA using Rats, unpublished study.

Study report#11. 1997. Toxicity Testing Reports of Environmental Chemicals 5: 525 – 552.

Tucker SC, Beck HM. 1999. A 15-year study of patch testing to (meth)acrylates. Contact Dermatitis 40: 278-279

Urcan, E., Scherthan, H., Styllou, M., Haertel, U., Hickel, R., and Reichl, F-X. 2010. Induction of DNA double-strand breaks in primary gingival fibroblasts by exposure to dental resin composites. Biomaterials 31: 2010-2014

van der Walle B, Bensink T. 1982. Cross reaction pattern of 26 acrylic monomers on guinea pig skin. Contact Dermatitis. 1982 Nov;8(6):376-82.

Vyshemirskaya L.D., Doloshitskii S.L., Romaniv R.V. 1987. Investigation of thresholds and delayed effects of ethylene glycol monomethacrylate; Gig. Sanit. 11: 81 - 82 (russian)

Waegemaekers THJM, Bensink MPM. 1984. Non-mutagenicity of 27 aliphatic acrylate esters in the Salmonella-microsome test. Mutation Research 137: 95-102

Wahlberg J.E. 1983. Contact sensitivity to NAPP printing plates|secondary to a relapsing hand dermatitis; Contact Dermatitis 9(3): 239

Wallenhammer LM, Ortengren U, Andreasson H, Barregard L, Bjokner B, Karlsson S, Wrangsjo K, Meding B. 2000. Contact Allergy and hand eczema in Swedish dentists, Contact Dermatitis 43(4): 192-199

7.15. Annex I: Read-across assessment

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 HEMA 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 HEMA registration is deficient in some data requirements, namely subchronic, reproductive and prenatal developmental data to complete the assessment.

However, in the latest version of the CSR (2017), the registrants included data on ethylene glycol to justify that no further toxicological data on HEMA 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	HEMA	HEMA → MAA + EG	Methacrylic acid (MAA)	Ethylene glycol (EG)*
Source	MMA	MMA → MAA + methanol	Methacrylic acid (MAA)	Methanol

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

Read-across assessment

- **Structure similarity:**

MMA and HEMA are 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 HEMA 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 and HEMA are 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. Indeed, MMA was less soluble in water and more volatile than HEMA (see table below).

- **Toxicological profile:**

HEMA and MMA were both hydrolyzed into methacrylic acid and respective alcohols (ethylene glycol (EG) for HEMA and methanol for MMA).

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

Toxicological profile of MMA and HEMA 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, 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.

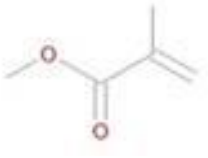
Based on these data, a difference of toxicity is observed between the substances, with potential different target organs. The reported systemic effects are consistent with their metabolization into methanol (MMA) or ethylene glycol (for HEMA). Therefore, this is not in favor of a read-across between MMA and HEMA. In particular, methanol induced neurotoxicity and hepatic toxicity (SIDS, 2004; INRS, 2018) originating from MMA whereas ethylene glycol induced renal toxicity (SIDS, 2004) originating from HEMA. However, some quantitative differences can be noted between the parent molecule and the alcohol formed. For example, the NOAEL reported with EG (NOAEL = 1875 mg/kg bw/day from a 13-week dietary study in mice, from NTP, 1993) is higher than that reported for HEMA (100 mg/kg bw/day), suggesting a higher toxicity of the parent molecule (with some limitations due to difference on the route of exposure: gavage versus diet and species used: rat versus mouse).

A similar genotoxicity profile, characterized by a clastogenicity *in vitro* was observed with MMA and HEMA. Neither the parental, 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 test with HEMA. Embryo-mortality and mutagenic effects on spermatozoa after administration to pregnant rats was noted at doses > 2000 mg/kg bw/day in a study with very limited reporting (Vyshemirskaya, 1987). Regarding the uncommon metabolites, some effects on fertility and/or development were reported with EG (SIDS, 2004; NTP, 2004). 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.

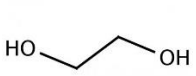
In conclusion, based on the arguments presented above, the read-across first identified as not sufficiently robust to allow predicting properties from MMA/EG to HEMA for subchronic toxicity, carcinogenicity and toxicity on reproduction and development endpoints, is accepted with medium confidence in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

Comparison of MMA and HEMA profiles:

	MMA (data issued from Anses, 2018)	HEMA
Chemical structure		
Current EU harmonized classification	Skin Irrit. Cat 2 - H315 Skin Sens. Cat 1 - H317 STOT SE 3 – H335	Skin Irrit. Cat 2 - H315 Eye Irrit. Cat 1 -H319 Skin Sens. Cat 1 - H317
Water solubility	15.3 g/L (20°C)	> 100 g/L (20°C)
Log Pow	1.38 (20°C)	0.42 (25°C)
Vapour pressure	37.8 hPa	0.08 hPa
Acute toxicity	LD_{50} (oral) > 7900 mg/kg bw LD_{50} (dermal) > 5000 mg/kg bw LC_{50} (inhalation) = 29.8 mg/L	LD_{50} (oral) > 5000 mg/kg bw LD_{50} (dermal) > 3000 mg/kg bw No data for inhalation route
Local toxicity	Skin and respiratory irritation No eye irritation Skin and respiratory sensitisation	Skin and eye irritation Respiratory irritation potential Skin sensitization Respiratory sensitisation potential
Repeated dose toxicity (oral)	21-day-study (rats): NOAEL = 200 mg/kg bw/day (locomotor activity and learning ability were impaired, and foot shock induced aggressive behaviour) 5 month-study (rats): 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). Repeated-dose toxicity study (rats) of limited quality: NOAEL < 100 mg/kg bw/day (effects on the liver, stomach and kidney) 2 year-study (rat): NOAEL = 124 mg/kg/d (highest tested dose - transitory decreased bw and fluid consumption at this dose).	OECD 422 (rat): NOAEL = 100 mg/kg bw/day (effect on kidney at 300 mg/kg bw/day)
Repeated dose toxicity (dermal)	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. Respiratory irritation identified as the most sensitive effect observed in experimental studies (from short-term to chronic term).	No reliable study by inhalation route.
Genotoxicity	*in vitro* : clastogenic effect *in vivo*: negative result (no proof of bone marrow exposure)	*in vitro* : clastogenic effect *in vivo*: negative result
Carcinogenicity	Lack of carcinogenicity of MMA in experimental animals but inadequate evidence in humans	No data
Toxicity on reproduction and development	OECD 416 (rats, oral route): NOAEL reproduction and development = 400 mg/kg bw/day (no effect) NOAEL parental = 50 mg/kg bw/day (decreased food consumption at 150 mg/kg bw/day)	OECD 422 (rats, oral route): NOAEL reproduction and development ≥ 1000 mg/kg bw/day (no effect) NOAEL parental = 100 mg/kg bw/day (effect on kidney at 300 mg/kg bw/day)
	No developmental effect in prenatal developmental studies by oral and inhalation routes	No developmental toxicity study
Other	Number of findings may indicate an effect on the nervous system at high doses.	

Comparison of EG and HEMA profiles for specific toxicity:

	Ethylene glycol	HEMA
Chemical structure		
Current EU harmonized classification	Acute Tox. 4* - H302	Skin Irrit. Cat 2 - H315 Eye Irrit. Cat 1 -H319 Skin Sens. Cat 1 - H317
Repeated dose toxicity (oral)	13-week dietary study in mice (NTP, 1993) Target organs: kidney and liver NOAEL = 1875 mg/kg bw/day	OECD 422 study in rats by gavage Target organ: kidney NOAEL = 100 mg/kg bw/day
Toxicity on reproduction and development	« No evidence of adverse reproductive effects in mice exposed to 2826 mg/kg bw/day in drinking water or in rats exposed	OECD 422 (rats, oral route): NOAEL reproduction and development ≥ 1000 mg/kg bw/day (no effect)

	to 1000 mg/kg bw/ day in feed" (NTP, 2004).	NOAEL parental = 100 mg/kg bw/day (effect on kidney at 300 mg/kg bw/day)
	Developmental toxicity in rodents after oral exposure to high doses: fetal deaths, skeletal malformations, external malformations and reduced body weight (≥ 500 mg/kg bw/day in mice and ≥ 1000 mg/kg bw/day in rats) (NTP, 2004).	No developmental toxicity study. 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 (Vyshemirskaya, 1987)