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(s): France

Dated: 17 December 2018

Evaluating Member State Competent Authority

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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 therefore possible concerns concerning environment could be identified in a further evaluation.

Further information on registered substances here:

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

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

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

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Methyl methacrylate was originally selected for substance evaluation in order to clarify concerns about:
- suspected respiratory sensitizer
- wide dispersive uses
- consumer uses
- high RCR
- exposure of sensitive populations
- high aggregated tonnage

During the evaluation also other concern was identified. The additional concern was:
- Mutagenicity

It should be noted that the human health only was evaluated for the substance, therefore possible concerns concerning environment could be identified in a further evaluation.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

No ongoing process have been identified.

In 2005 the Scientific Committee on Occupational Exposure Limits (SCOEL) published a report for methyl methacrylate in which two Occupational Exposure Limits (OELs) were proposed:

- An 8-hour TWA (Time weighed Average) of 50 ppm

- A STEL (Short-term Exposure Limit) of 100 ppm

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

In the original draft decision, a mutagenicity test was requested (Mammalian Erythrocyte Micronucleus assay in rodent via the most appropriate route (B.12/OECD TG 474)) based on a concern for clastogenic effects identified for the substance. Nevertheless during the discussion at the MSC-47, the request was judged as not proportionate and the concern was not agreed among the MSCAs. Moreover during the introduction of the substance the registrant indicated that they may have new *in vitro* data on the substance which may explain the results obtained in the mutagenicity tests for methyl methacrylate. Therefore, it was decided to conclude this substance evaluation (a termination letter was sent to the registrant) and that the first follow-up should be to prepare a proposal for an update of the harmonized classification, including a proposal for classification for respiratory sensitisation category 1. If the CLH procedure will not result in a harmonized classification which would provide a sufficient level of protection, the substance evaluation of methyl methacrylate may be initiated again to address the remaining concern(s).

4.1.1. Harmonised Classification and Labelling

The substance has a harmonized classification and is therefore currently classified as (CLP Annex VI Index number 607-035-00-6):

- Flam. Liq. 2, H225
- Skin Irrit. 2, H315
- Skin Sens. 1, H317
- STOT SE 3, H335

In addition, the evaluating MSCA considers that the substance should be classified as a respiratory sensitiser. Indeed, several cases of occupational asthma (43) directly related to an occupational exposure to methyl methacrylate (MMA) have been identified by the French Occupational Disease Consultation Centres (CCPPs) between 2001 and the end of 2017 and listed in the French RNV3P database[2]. This national network for the monitoring and prevention of occupational disease created in 2001, collects every year more than 8000 new occupational health reports throughout France.

Additionally, in France, methyl methacrylate is listed in two tables[3] related to occupational diseases:

- The table 82 is specific for methyl methacrylate and lists the afflictions caused by an occupational exposure, which are: rhinitis, asthma, conjunctivitis, eczema and chronic respiratory events.

- The table 65 lists the substances associated with an eczema caused by allergies and includes the methyl methacrylate.

The 43 cases listed in the French RNV3P database are the cases for which an occupational doctor, between 2001 and 2017, directly linked an occupational exposure to methyl

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

[3] http://www.inrs-mp.fr/mp/cgi-bin/mppage.pl?state=1&acc=5&gs=&rgm=2

methacrylate with asthma in France. Based on these cases, which represent only a small part of the possible cases of asthma caused by an occupational exposure to methyl methacrylate, it appeared necessary to classify the substance as a respiratory sensitiser. Additionally according to CLP "*the condition will have the clinical character of an allergic reaction*", which is the case for methyl methacrylate and "*immunological mechanisms do not have to be demonstrated*" to classify the substance as a respiratory sensitizer.

A dossier for harmonised classification and labelling (CLH) was submitted to ECHA in September 2018 in order to update the current harmonised classification for the substance with a proposal covering the respiratory sensitization potential of methyl methacrylate.

Additionally it has not been considered yet whether further regulatory risk management (e.g. SVHC identification) in addition to the CLH proposal would be needed. Depending on the outcome of the CLH proposal this may be further investigated.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not relevant – a follow-up is foreseen at EU level.

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

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Preparation of an Annex VI CLH dossier	September 2018	France MSCA

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Methyl methacrylate was originally selected for substance evaluation in order to clarify concerns about:

- suspected respiratory sensitiser
- wide dispersive uses
- consumer use
- high RCR
- exposure of sensitive population
- high aggregated tonnage

During the evaluation also another concern was identified. The additional concern was:

- Mutagenicity

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Respiratory sensitization	Concern verified, an update of the current harmonised C&L to be proposed for this specific endpoint.
Skin Sensitization	Following evaluation, the eMSCA concluded that the concern is verified. No sub-categorization into 1A or 1B for the current EU harmonized C&L foreseen so far based on the current available dataset.
Mutagenicity	Additional concern identified by eMSCA during evaluation. A Mammalian Erythrocyte Micronucleus assay in rodent (OECD TG 474) was requested in the draft decision sent on 7 May 2015 to the registrants. MSC judged the request non proportionate compared to the concern. Therefore the study was not requested; however this point may be re-opened, depending on the outcome of the CLH proposal.
Carcinogenicity	Based on the available data no further action is proposed neither under CLP nor under another measure or request since no concern has finally been identified.
Other endpoints under human health	All assessed → no further concern identified.
Environment/Ecotoxicity/Environmental exposure	Not assessed. The present evaluation was targeted to human health.

Human health exposure	- wide dispersive uses - consumer use - High RCR - exposure of sensitive population - high aggregated tonnage The evaluating MSCA concluded that these concerns are not verified or may be covered by an eMSCA-proposed harmonised classification providing a sufficient level of protection.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, methyl methacrylate (MMA) was included in the Community Rolling Action plan (CoRAP) for evaluation in 2014. The Competent Authority of France appointed 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 methyl 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 occupational exposure causing respiratory sensitisation.

Based on the evaluation of the available data, the evaluating MSCA concluded that there was a need to request further information to clarify mutagenicity as an additional concern. Pursuant to Article 46(1) of the REACH Regulation, a draft decision to request a "*Mammalian Erythrocyte Micronucleus assay in rodent via the most appropriate route (B.12/OECD TG 474)*" was prepared.

During the discussion at the MSC-47 and after registrant's presentation, this only request in the decision could not be agreed unanimously by the Member State Committee and therefore was deleted from the decision. As there was only one request in the decision no decision was issued. Therefore pursuant to Article 51(6) of the REACH Regulation, the ECHA Member State Committee (Committee) unanimously agreed at its meeting on 28 April 2016 that no further information needs to be requested on Methyl methacrylate regarding its mutagenicity at this stage. The Committee deemed it more appropriate to follow the indication of the evaluating Member State Competent Authority to prepare a proposal for a harmonised classification dossier under Regulation (EC) No 1272/2008 in due course. Furthermore the Registrant(s) had indicated their intension to provide further information, e.g. additional new *in vitro* data on mutagenicity and on skin sensitisation which may impact the overall assessment. It was decided that nevertheless if there will be no harmonised classification which provides a sufficient level of protection, then substance evaluation may be initiated again to address the remaining concern(s) for methyl methacrylate.

The decision-making process was then terminated but the termination of the decision making and conclusion of the substance evaluation process does not imply that methyl methacrylate would not have any potential hazardous properties and, depending on its uses, also potential risks. Therefore, substance evaluation may be initiated again at a later stage to address any remaining concern(s) for methyl methacrylate depending on the outcome of the possible proposal for harmonised classification and other developments.

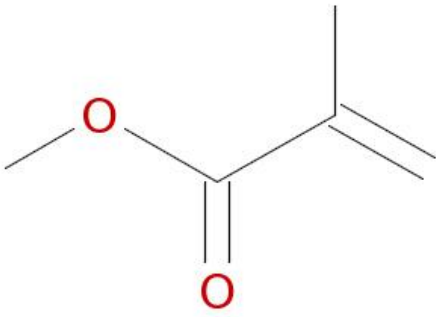
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Methyl methacrylate
EC number:	201-297-1
CAS number:	80-62-6
Index number in Annex VI of the CLP Regulation:	607-035-00-6
Molecular formula:	$C_5H_8O_2$
Molecular weight range:	100.1158
Synonyms:	Methyl 2-methylacrylate 2-Methyl-2-propenoic acid methyl ester methyl 2-methylpropenoate

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

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	liquid at 20°C and 101.3 kPa Colour: colourless Odour: pungent
Vapour pressure	37 hPa at 20 °C

Melting / freezing point	-48 °C
Boiling point	100.36 °C at 1013.25 hPa
Water solubility	15.3 g/L at 20 °C
Partition coefficient n-octanol/water (Log Kow)	LogPow = 1.38
Flammability	Highly flammable. The substance has no pyrophoric properties and does not liberate flammable gases on contact with water. Flammability derived from flash point and boiling point.
Explosive properties	Non explosive. There are no chemical groups associated with explosive properties present in the molecule.
Oxidising properties	No oxidising properties. The substance is highly flammable, but does not contain structures associated with oxidising properties.
Granulometry	According to Annex VII 7.14. Column 2, a study on granulometry does not need to be conducted because the substance is a liquid and is marketed or used in a non-solid or granular form.
Stability in organic solvents and identity of relevant degradation products	The stability of the substance in organic solvents is not considered as critical.
Dissociation constant	The substance does not contain any ionic, dissociable structures.
Relative density	0.94 g/cm³ at 20 °C
Flash point	10 °C (DIN 51 755 / Abel Pensky Closed cup)
Autoflammability / self-ignition temperature	435 °C
Viscosity	0.53 mPa s (dynamic)

Methyl methacrylate is a flammable liquid which fulfils the classification criteria for H225 (Highly flammable liquid and vapour). Based on the chemical structure, methyl methacrylate does not have explosive or oxidising properties, because the structural elements associated with those properties are absent.

Risk for workers or consumers are adequately controlled if normal safe handling practice for highly flammable substances is obeyed.

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 – 1 000,000 t	☐ > 1 000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 7

USES	Use(s)
Uses as intermediate	Refer to Uses at industrial sites
Formulation	Polymers and coating products This substance is used in the following activities or processes at workplace: transfer of chemicals, transfer of substance into small containers, closed batch processing in synthesis or formulation, batch processing in synthesis or formulation with opportunity for exposure, closed processes with no likelihood of exposure, closed, continuous processes with occasional controlled exposure, mixing in open batch processes, hand mixing with intimate contact only with personal protective equipment available and laboratory work. Release to the environment of this substance can occur from industrial use: formulation of mixtures and formulation in materials.
Uses at industrial sites	Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article) Use in adhesive and sealants
Uses by professional workers	End use in formulations Transfer of chemicals, closed batch processing in synthesis or formulation, closed processes with no likelihood of exposure, mixing in open batch processes, transfer of substance into small containers, batch processing in synthesis or formulation with opportunity for exposure, closed, continuous processes with occasional controlled exposure and laboratory work.
Consumer Uses	In adhesives and sealants Machine wash liquids/detergents Automotive care products

	Paints and coatings or adhesives Fragrances and air fresheners
Article service life	This substance is used in the following activities or processes at workplace: production of mixtures or articles by tabletting, compression, extrusion or pelletisation, the low energy manipulation of substances bound in materials or articles, open transfer and processing with minerals/metals at elevated temperature and high energy work-up of substances bound in materials or articles (e.g. hot rolling/forming, grinding, mechanical cutting, drilling or sanding). Other release to the environment of this substance is likely to occur from: outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials), indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment), indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners) and outdoor use. This substance can be found in complex articles, with no release intended: electrical batteries and accumulators, vehicles and machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines). This substance can be found in products with material based on: leather (e.g. gloves, shoes, purses, furniture), plastic (e.g. food packaging and storage, toys, mobile phones), fabrics, textiles and apparel (e.g. clothing, mattress, curtains or carpets, textile toys), paper (e.g. tissues, feminine hygiene products, nappies, books, magazines, wallpaper), rubber (e.g. tyres, shoes, toys), stone, plaster, cement, glass or ceramic (e.g. dishes, pots/pans, food storage containers, construction and isolation material), metal (e.g. cutlery, pots, toys, jewellery) and wood (e.g. floors, furniture, toys).
Uses advised against (workers or consumers)	Mixtures containing unreacted liquid monomer intended to come into contact with skin or nails.

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)**		
607-035-00-6	Methyl methacrylate	201-297-1	80-62-6	Flam. Liq. 2	H225		
				Skin Irrit. 2	H315		D
				Skin Sens. 1	H317		
				STOT SE 3	H335		

A CLH report was submitted by the evaluating MSCA to ECHA in September 2018 in order to update the current harmonized classification and add a classification related to the respiratory sensitization properties of methyl methacrylate.

7.6.2. Self-classification

- In the registration(s)*:*

No deviation from the harmonized classification

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

Skin Sens. 1B; H317

7.7. Environmental fate properties

Since the evaluation was targeted at human health concerns, this part has not been evaluated.

7.8. Environmental hazard assessment

Since the evaluation was targeted at human health concerns, this part has not been evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

There are extensive data available for the methyl methacrylate (MMA) and this has been reviewed in the EU Risk Assessment Report (EU RAR, 2002). Data on methacrylic acid (MAA), the common metabolite for all short chain alkyl-methacrylate esters, has been reviewed in the EU Risk Assessment (2002). Therefore, no additional information is required on this endpoint.

As stated in this report, after oral or inhalation administration, methyl methacrylate is rapidly absorbed and distributed. The substance is mainly transformed into CO2 and then exhaled.

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

Distribution:

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

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

Metabolism:

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

- The main one is the oxidative pathway which leads to CO2. After oral or parenteral administration methyl methacrylate is further metabolised with the majority of the administered dose being exhaled as CO2.
- The second one involves the carboxylesterases. As described to OECD SIAR, short chain alkyl-methacrylate esters, like methyl methacrylate, are initially hydrolysed by non-specific carboxylesterases to methacrylic acid and the structurally corresponding alcohol in several tissues, which is methanol for methyl methacrylate. Activities of local tissue esterases of the nasal epithelial cells appear to be lower in man than in rodents (Mainwaring *et al*., 2001; Morris, 1992 and 1995). Methacrylic acid and the corresponding alcohol are subsequently cleared predominantly via the liver (valine pathway and the TCA (TriCarboxylic Acid) cycle, respectively). The carboxylesterases are a group of non-specific enzymes that are widely distributed throughout the body and are known to show high activity within many tissues and organs, including the liver, blood, GI tract, nasal epithelium and skin. Those organs and tissues that play an important role and/or contribute substantially to the primary metabolism of the short-chain, volatile, alkyl-methacrylate esters are the tissues at the primary point of exposure, namely the nasal epithelia and the skin, and systemically, the liver and blood.
- And finally, methacrylate esters can conjugate with glutathione (GSH) in vitro, although they show a low reactivity, since the addition of a nucleophile at the

double bond is hindered by the alpha-methyl side-group. Hence, ester hydrolysis is considered to be the major metabolic pathway for alkyl-methacrylate esters, with GSH conjugation only playing a minor role in their metabolism when the oxidative route is saturated, i.e. only when very high tissue concentrations occur.

In workers exposed to methyl methacrylate (0.4 to 112 ppm during 8h), there is a linear correlation between the concentrations of methanol in blood, serum and urine and the amount of methyl methacrylate in air. Nevertheless, only 1.5% of inhaled methyl methacrylate is excreted as methanol in urine. The elimination via exhaled CO2 occurs 60 seconds after methyl methacrylate to be detected in the blood (Mizunuma *et al*., 1993).

Elimination:

As summarized in the EU RAR (2002), after i.p. administration of ^{14}C-methyl methacrylate to rats within 24 hours 80% of the radiolabel was exhaled as ^{14}CO2, 7-14% was excreted in the urine and approximately 3% was retained in tissues at this time (Crout *et al*., 1982). Clearance of methyl ^{14}C-methacrylate from blood was determined in beagle dogs after simulated hip arthroplasty and after subsequent i.v. administration of 25, 50 or 75 mg/kg bw. Following hip arthroplasty, venous blood concentrations reached a maximum after 3 min and decreased over the next 16 min. Only 0.5% of the total amount of implanted monomer was detected in the venous circulation and no radioactivity could be detected in the arterial blood. After i.v. administration of 25 or 50 mg/kg bw maximum arterial levels were found at 30 sec, but were below the limit of detection after 3 min (McLaughlin *et al*., 1973).

Conclusion:

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

7.9.2. Acute toxicity and Corrosion/Irritation

No study conducted according to OECD guidelines is available. However, it is possible to conclude on acute toxicity of Methyl methacrylate based on the available data.

Acute toxicity by oral route:
Results from different studies indicate a very low acute toxic potential for methyl methacrylate for the most common test species after oral exposure: the lowest valid LD_{50} values are 7900 mg/kg bw and 9400 mg/kg bw in rats (Spealman *et al*., 1945; Deichmann, 1941).
These studies were performed before GLP and OECD guidelines. Therefore only limited data were available. However, it allows to assess the acute oral toxicity.

Acute toxicity by inhalation route:
The acute toxic potential of methyl methacrylate after inhalation exposure in rats is low (LC_{50} = 29.8 mg/L 4 h exposure; corresponding to 7093 ppm) (Tansy *et al*., 1980b)
The study was performed before GLP and OECD guidelines were established. Therefore only limited data were available. However, it allows to assess the acute inhalation toxicity.

Acute toxicity by dermal route:
There is one valid study available (comparable to OECD guideline 402) in the registration dossier (Study report #11 , 1982a) in which a LD_{50} value in rabbits is reported. The undiluted test substance was applied to the skin of two New Zealand White rabbits per dose for 24 h under occlusive conditions. No mortality, clinical signs (except irritation) or pathological findings were observed and the LD50 was therefore assessed to be >5000 mg/kg bw.

Other routes of exposure:
There are studies available for toxicity using other routes of exposure (i.p.) and using different species which are not considered being relevant for the assessment.
Based on the results available, methyl methacrylate does not need to be classified for its acute toxicity potential according to CLP.

Skin irritation:
Regarding skin or eye irritation numerous *in vivo* studies are available. However, no study conducted according to OECD guidelines is available.
In the studies available, contradictory results for skin irritation are observed in animals. Irritation was observed in humans following exposure of volunteers (Nyquist *et al*;, 1958). Based on data available the evaluating MSCA agrees with the current harmonised CLP classification this substance as Skin Irrit. 2; H315.

Eye irritation - Animal data:
In a first study 0.1 mL of the neat test substance was applied to the eyes of six New Zealand White rabbits and the treated eyes were not washed out. In the relevant reading period between 24 h and 72 h after application there were no irritation effects observed on cornea, iris and conjunctivae (redness and chemosis). The respective mean scores were 0.0 for all parameters. Slight to moderate conjunctivae redness, chemosis and discharge was observed in the readings 1 h to 8 h after application, which were not relevant for classification (Study report#15, 1978).
In addition, slight, transient effects on conjunctive were described in another study, this effect was totally reversible in 48h and no effect was observed at day 7 after exposure (Study report#12, 1982b).

Therefore, methyl methacrylate is not an eye irritant and no classification is needed.

Irritation of the respiratory tract - Human data:

Reversible irritation reactions have been observed after short-term peak exposures to humans at concentration levels exceeding 100 ppm (Coleman, 1963, Roehm 1994). No damage to olfactory function was reported in a cross-sectional smell test in workers exposed to methyl methacrylate up to 50 ppm during the past 6 years and previously to up to 100 ppm (mean duration of exposure 9.6 years) (Muttray *et al*., 1997). No effects were seen after single exposure to 50 ppm in a study with human volunteers investigating changes in cytokine levels indicative of subclinical, irritating effects (Muttray *et al*., 2007).

In conclusion, these results support the existing harmonized classification as irritant to the respiratory tract (STOT single exposure Cat. 3/H335).

7.9.3. Sensitisation

Skin Sensitisation - Animal data:
There are a many reliable studies available to assess the skin sensitising potential of methyl methacrylate. The variety of test methods used is large, providing positive and negative results in almost equal proportions. Among them, the study report #6 (2006) conducted as described in Kimber and Basketter (1992) is considered as a key study. They conducted

a LLNA comparable to OECD guideline 429 using concentrations from 10 to 100% dissolved in either acetone or acetone/olive oil (4:1 v/v administered daily for three days to four CBA/ca mice per treatment). Five days after the initiation, animals received 3H labelled thymidine five hours before sacrifice. The EC3 value for methyl methacrylate were 60% (w/v) in acetone and 90% (w/v) in acetone/olive oil (4:1); the EC3 value of the 2,4 - Dinitrochlorobenzene as positive control was 0.036%, leading to the assessment that methyl methacrylate has to be considered as weak skin sensitiser.
Based on animal data, a subcategory 1B could be proposed for methyl methacrylate.

Skin sensitisation - Human data:
Numerous reports of skin sensitisation exist mainly, from occupational environments (dentistry, printing/lithography, gear boxes testers and gas workers using adhesives and wearing artificial fingernails). Incidence of positive reaction occurred at an incidence between 0.8 to 17% in selected workers.
Based on human data and according to CLP criteria, the evaluating MSCA concludes that only a category 1 without subcategorization can be reached based on the large variability in the frequency of skin sensitisation occurring after a relatively high exposure to MMA.

In conclusion, based on the data available the classification of methyl methacrylate as Skin Sens. Cat. 1 H317 is justified which is consistent with the current EU harmonized classification. According to the evaluating MSCA, the available human data do not allow to propose a subcategorization for the current EU harmonized classification. Animal data could only allow a classification as subcategory 1B. No further action is foreseen for this endpoint neither in the framework of SEv nor proposed harmonised classification.

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

Methyl methacrylate is not only a skin irritant but it also has the potential to induce skin sensitization and allergic contact dermatitis. Based on the available data, on case-reports and epidemiological studies, methyl methacrylate is also associated with occupational asthma. Indeed, in literature, several cases of asthma have been identified.

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

- Same clinical symptoms (asthma, hypersensitivity pneumonitis, associated with rhinitis…) for both properties,

- No information on exposure doses for clinical cases in order to show that effects may appear at lower doses than irritating doses and/or at decreasing doses.

- But latency between the first exposure and the occurrence of the symptoms is more in favour of sensitization.

Unfortunately there is no test available to demonstrate a respiratory sensitization because small molecules like methyl methacrylate which have a low molecular weight are not acting via a IgE-dependent mechanism. Therefore, there is no suitable assay to identify this kind of respiratory sensitizer, contrary to larger molecules for which the measuring the level of IgE could be sufficient to conclude on a respiratory sensitization.

Nevertheless this substance is listed in the table 82[4] of occupational diseases in France which list the affections related to an occupational exposure to methyl methacrylate including occupational asthma. This disease is often associated with rhinitis and hypersensitivity pneumonitis.

In France, the national network for the monitoring and prevention of occupational disease (RNV3P) created in 2001, collects every year more than 8000 new occupational health reports throughout France. Their methodology has been reviewed by the EU-OSHA in 2017 in a review[5] which analysed all the existing monitoring systems and methodologies to identify work-related diseases across the world. This French non-compensation–based system primarily designed for data collection and statistics can also be used for the detection of new/emerging work-related diseases.

The French RNV3P network is composed of the 30 Occupational disease consultation centres (CCPP) in mainland France and a number of occupational health services (SSTs) associated with the network. This network's goal is to record the data from consultations in a national database (patient demographics data, diseases, exposures, job sectors and professions). After investigation, the expert physicians from the CCPPs establish a possible link between the occupational exposure(s) and the pathology which motivated the consultation (this causal link is recorded in the data base) with a level of attributability (low, moderate or high). The level of attributability which link an occupational exposure and a disease is the analysis to determine if, for a specific patient, the substance to which he/she is exposed to during work is responsible for the detected pathology. In the RNV3P database 4 levels of attributability exist:

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

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

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

The cases that are reported in this French database are related to occupational exposure only. Therefore all the cases reported do not represent all the existing cases in France but probably only a small part. However, all these cases allow the evaluating MSCA to highlight

[4] http://www.inrs.fr/publications/bdd/mp/tableau.html?refINRS=RG%2082

[5] European Agency for Safety and Health at Work (EU-OSHA) (2017) Methodologies to identify work-related diseases: Review of sentinel and alert approaches European Risk Observatory Literature Review

the fact that there is a concern related to respiratory sensitization following at least occupational exposure to methyl methacrylate.

In summary, no reliable alert was found from SAR models. However numerous human cases were reported for methyl methacrylate (literature, French RNV3P database) clearly relating the exposure to this substance to at least occupational asthma. Furthermore, considering the exposure potential by inhalation route due to the high vapour pressure of the substance, its respiratory irritating property and its skin sensitizer potential, methyl methacrylate is considered to have a potential for respiratory sensitisation.

No additional data can be requested and the occupational data appear sufficient to regulate: Indeed the evaluating MSCA considers that the CLP criteria to classify the substance as a respiratory sensitizer are met and additionally according to CLP, "*the condition will have the clinical character of an allergic reaction*", is fulfilled for methyl salicylate and "*immunological mechanisms do not have to be demonstrated*". **Therefore the classification of methyl methacrylate as Resp. Sens. Cat. 1, H334 is deemed warranted**.

7.9.4. Repeated dose toxicity

There are several reliable studies (duration up to 2 years) available to assess the potential toxicity of methyl methacrylate after repeated oral and inhalation exposure.

Oral route:

Data available on the effects of methyl methacrylate following an oral exposure are limited. In a first study, twenty-five male and female Wistar rats were administered three doses of methyl methacrylate in the drinking water for two years (Borzelleca *et al*., 1964). Initial doses of 6, 60 or 2000 ppm were partially raised to 7, 70 and 2000 ppm after 5 months.
A special design was employed to reduce the volatilization and measurements were performed which showed that the methyl methacrylate concentrations remained within 15% of the nominal concentration for 72 hours.
Body weight depression was observed at 2000 ppm but did not persist beyond the first few weeks of the study. Significant decrease of water consumption was observed at 2000 ppm, although it regressed at the end of the study.
Individual observations of decreased food consumption were aligned with periods of growth retardation. The only effect observed was an increased kidney/body-weight ratio in female rats exposed to 2,000 ppm methyl methacrylate. This effect has been proposed to be the consequence of reduced food intake and reduced body weight, and in the absence of any histopathology, were considered as not biologically relevant. Therefore the NOAEL is considered to be ≥ 2000 ppm, corresponding to 124.1 mg/kg bw/day and 162 mg/kg bw/day for males and females respectively, on the basis of treatment specific effects on fluid consumption rates and body weight.

Another study, assessing the behavioural and neurochemical changes was provided in the registration dossier. Methyl methacrylate was administered by gavage to 30 rats per group at 100, 200 and 500 mg/kg/d during 21 days (Husain *et al*., 1985). Effects were observed at the highest dose group (500 mg/kg/d). Ten percent of animals died, locomotor activity and learning ability were impaired, and foot shock induced aggressive behaviour. Biogenic amine levels were reported to have been increased in the pons medulla and hippocampus, noradrenaline was increased in the cerebral cortex and the corpus striatum. Dopamine levels were slightly decreased in the corpus striatum and 5-hydroxytryptamine was increased in the midbrain and hypothalamus. A NOAEL of 200 mg/kg/d is therefore proposed for this study.

Others studies of lower reliability were also provided. In these studies, only little information was available.

In the study by Motoc *et al.* (1971) rats were exposed to 100 mg/kg/d of methyl methacrylate by oral route 2 days per week during 10, 20 and 32 weeks. Reported effects were liver dystrophy, inflammatory changes in the stomach, reversibility kidney damage and changes in clinical chemistry data.

Effect on forestomach was more specifically studied in the study by Ghanayem *et al*. (1986). Methyl methacrylate was administered up to 200 mg/kg/d by gavage to 8 rats. No significant increase of mucosal cell proliferation or hyperkeratosis was observed.

Neurotoxic effects were studied in the study by Edwards *et al.* (1975). Methyl methacrylate was administered daily by feed to 4 rats with 2000 mg/kg/d during 5 weeks. No neurotoxic effects and no enhancement of acrylamide neurotoxicity were observed.

Based on this dataset, a NOAEL lower than 100 mg/kg/d is proposed for oral route.

Dermal route:

There is no relevant dermal repeated dose toxicity study available, only one study with a low reliability was provided in the registration dossier (Kanerva *et al*., 1986).
Methyl methacrylate was applied on rat tail skin during 3 h daily (0.78 g was absorbed) during 8 weeks. This caused keratolysis without ulceration in the exposed skin and abnormal muscle responses to stimulation of the rat tail motor nerves by a skin electrode after 4 weeks. The results point out a local neurotoxic reaction caused by absorbed methyl methacrylate. However, the mechanism leading to the toxic effect remains unknown. Myeline figures (sign of degeneration of nerve process) were observed in the dermis.

Inhalation route:

Many studies (more than 40) were provided in the registration dossier for this endpoint, considering the substance as highly volatile compound.
Different species and different duration of exposure were tested.

- *Short term exposure*:

In the first studies, groups of five mice of each sex were exposed to air containing methyl methacrylate at target concentration of 0, 75, 125, 250, 500 and 1000 ppm, 6 hours per day for a total of 9 exposures over 10 days (NTP, 1986). Mice were observed daily and weighed several times. Necropsy was performed on animals that lived until the end of the studies. Five mice of each sex in the control and 1000 ppm groups and 5 males from 125 ppm group and one mouse of each sex in 500 ppm group were examined for histology (lungs, nasal cavity, kidney and nose). No compound related clinical signs, gross pathologic nor microscopic effects were observed. A NOAEC of 1000 ppm for this study is therefore proposed.

In another study, groups of five mice of each sex were exposed to air containing methyl methacrylate at target concentration of 0, 500, 1000, 2000, 3000 or 5000 ppm, 6 hours per day for a total of 10 exposures over 11 days (NTP, 1986). Mice were observed daily and weighed several times. Necropsy was performed on animals that survived until the end of the study. Histopathological examination was performed on one or two male mice from the 500, 1000, 2000 and 3000 ppm groups. Deaths occurred in all exposed groups of male mice. Additionally all animals exposed to 5000 ppm died. The final mean body weights of exposed mice were not concentration related. Dyspnea and redness and swelling of the nasal region were observed and considered as compound related effects. The study

report states that no compound related effects were observed at necropsy. A LOAEC lower than 500 ppm is then proposed for this study. However, this study presents some limitations such as the limited number of observed organs and the fact that only alive animals were examined which could have an impact on the conclusion.

In another study (McLaughlin *et al*., 1979), groups of five rats of each sex were exposed to air containing methyl methacrylate at target concentration of 0, 75, 125, 250, 500 and 1000 ppm, 6 hours per day for a total of 9 exposures over 10 days. Rats were observed daily and weighed several times. Necropsy was performed on animals who lived up to the end of the study (all animals of the study). No histopathological examination was performed. No compound related clinical signs or gross pathologic effects were observed. A NOAEC of 1000 ppm is therefore proposed. It should be noted that this study presents some limitations as mentioned above.

Groups of five rats of each sex were exposed to air containing methyl methacrylate at target concentration of 0, 500, 1000, 2000, 3000 or 5000 ppm, 6 hours per day for a total of 10 exposures over 11 days (NTP, 1986). Rats were observed daily and weighed several times. Necropsy was performed on animals that lived until the end of the study. All rats exposed at 5000 ppm and 2/5 females exposed at 3000 ppm died before the end of the study. Ruffled hair was the only compound related effect reported in animals that lived to the end of the studies. Final body weight exposed at 2000 or 3000 ppm were 10-19% lower than those of controls. However, this study presents some limitations such as the limited number of observed organs, necropsy was realized only on live animals and no histological examination was performed. Based on the available data a NOAEC of 1000 ppm is proposed.

In another study (Study report #8, 1997), Fisher rats were exposed to methyl methacrylate by inhalation at 110 ppm or 400 ppm hours/day, for 1, 2, 5, 10, or 28 consecutive days. No clinical signs and gross pathology effects were reported. However, microscopic findings on olfactory epithelium were observed at 110 (minimal severity) and 400 (moderate severity) ppm. Animals from the 400 ppm group showed minimal degeneration/necrosis of the olfactory epithelium and disorganized/regenerated olfactory epithelium. Four out of five females of this exposure group showed minimal respiratory metaplasia and three of them had adhesions between the septum and turbinate. At 400 ppm, intraluminal inflammatory exudate and submucosal inflammatory cell infiltration were evident in all exposure and recovery groups. After 28 days of exposure, rats of 110 ppm groups did not show any lesions on the nasal cavities. Recovery groups revealed that no lesions persisted in the 110 ppm exposure groups. Minimal disorganization of the olfactory epithelium and minimal inflammatory changes, respiratory metaplasia and adhesions persisted in rats exposed to 400 ppm methyl methacrylate and maintained without treatment on 28 days or 13 weeks of recovery.
Based on these effects a LOAEC of 110 ppm is proposed.
Nevertheless, this study presented the following limitations:
• Only 2 concentrations are tested whereas 3 are recommended in the OECD 412 guideline;
• Some observations seemed to be lacking:

- Tissues assigned for histopathology are limited to nasal cavity, trachea and lung
- No information on details of tissues of nasopharyngeal examined,
- Haematology, clinical chemistry and organs weights are not examined.

To conclude, deaths were observed from concentrations above 500 ppm in mice and above 3000 ppm in rats. Dyspnea and swelling of the nasal region in mice and ruffled hair in rats are also observed.

In this context, **a LOAEC of 500 ppm is proposed for systemic effects**.

In the 28 days study in rats, more details on effects on respiratory tract are proposed. Based on these observations, notably, disorganization of olfactory epithelium and inflammatory change, a **LOAEC of 110 ppm for local effects is proposed**.

Subchronic exposure:
Rats were exposed to methyl methacrylate by inhalation route during 13 weeks at 500, 1000, 2000, 3000 and 5000 ppm (Study report #5, 1980a, NTP (1986)).
All rats exposed to 5000 ppm, 1/10 males and 9/10 females exposed to 3000 ppm, and 1/10 males and 3/10 females exposed to 2000 ppm died.
Final mean body weights were 20% lower than control for males and 25% for females when exposed to 3000 ppm and decreased by 7% and 11% for males and females exposed to 2000 ppm.
Compound related clinical signs observed during the first 2 days included listlessness, serious ocular discharge, nasal discharge and prostration. Inflammation in the nasal cavity associated with necrosis and loss of olfactory epithelium occurred in exposed male (since 3000 ppm) and female (since 2000 ppm).
Other compound-related pathologic effects included follicular atrophy of the spleen in 4/10 males and bone marrow atrophy in 8/10 males in the 5000 ppm group. Extensive cerebellar congestion and haemorrhage in the cerebellar peduncles were found in early-death female in the 3000-5000 ppm groups. Malacia and gliosis of the brain were found in surviving females at 3000 ppm and in female at 5000 ppm which died late in the study. Malacia and gliosis were observed in 5/9 females exposed to 2000 ppm and 1/8 at 1000 ppm.
In this context, a local NOAEC of 500 ppm based on effects in the nose and a systemic NOAEC of 500 ppm for female and 1000 ppm for male are proposed.

Subchronic/Chronic exposure:

In the study by T. (1976), one hundred rats were tested. They were exposed to 0 ppm or 116 ppm of methyl methacrylate 8 hours/day, for 5 days/week. Approximately half of the rats in each group were sacrificed after 3 months; blood and tissue samples were taken. The remainder of the rats were exposed for 6 months. In the 3-month group, a marked absence of visceral and subcutaneous fat deposits was observed. Mean whole body, lung and spleen weights were significantly lower in the exposed group. The only significant haematology effect observed in the treated animals was a significantly elevated mean serum alkaline phosphatase concentration.
In the 6-month group, qualitative observations were not suggestive of any noticeable lack of visceral fat deposits of the exposed group. Difference in the amount of subcutaneous fat was still apparent upon visual inspection. Mean body and popliteal fat pad weights were significantly lower in the exposed group. The haematology effects were that the mean total serum protein, cholesterol, blood urea nitrogen, serum glutamate-oxaloacetate transaminase and calcium/phosphate ratio were lower in the exposed group whereas the mean serum alkaline phosphatase and inorganic phosphate concentration were significantly elevated. A significant decrease in intestinal transit performance was also observed.

In another study by Tansy et al. (1980a), SD rats were exposed to methyl methacrylate by inhalation for 3- and 6-month at 116 ppm 7 hours/day, 5 days/week.
6 of the 14 observed blood chemistry parameters (albumin, glucose, blood urea nitrogen, serum glutamateoxaloacetate transaminase, serum glutamatepyruvate transaminase and albumin-glucose ratio) of the rats exposed to 1000 ppm were significantly decreased. In groups exposed to 116 ppm for 3 and 6 months and 1000 ppm, no animals died, no tumours, growths or other remarkable abnormalities were observed upon gross post-mortem examination.
At the highest dosage, there was lung damage: the visceral pleura adhered to the parietal pleura, in some cases fibrosis was seen, lung oedema was present and the parenchyma showed changes suggestive of emphysema. Histological examination from the upper respiratory tracts of rats exposed to 116 ppm for 6 months revealed evidence of damage

to the tracheal mucosa (area of haemorrhage). In the rat exposed to 116 ppm of methyl methacrylate during 3 months, epithelium was denuded of cilia, and the cellular covering of microvilli was reduced. In both exposure period mild lung damage was observed.
No NOAEC/LOAEC could be derived from these studies.

In the study by Lomax *et al*. (1997), methyl methacrylate was administered by inhalation at 0, 25, 100 and 400 ppm (0.1, 0.41, 1.64 mg/L) to rats Albino F344 6 hours/day, 5 days/week, for up to 104 weeks. It is a re-examination of the nasal tissues from the rats of the R.H. (1979a) study was conducted. The review consisted of microscopic examination of nasal tissue from at least 10% of randomly selected rats from each group, and the slides evaluated included the original study slides plus slides from tissue sections taken deeper into the block.
Decreased body weights; slight increase in the incidence of mild rhinitis in the nasal mucosal lining of the turbinates. The re-examination revealed that rats exposed to 100 or 400 ppm methyl methacrylate had exposure-related and concentration dependent microscopic changes in the olfactory epithelium lining the dorsal meatus in the anterior region of the nasal cavity. The microscopic changes consisted of degeneration/atrophy of the olfactory epithelium and underlying Bowman's glands, hyperplasia of basal (reserve) cells, replacement of olfactory epithelium by ciliated (respiratory-like) epithelium, and inflammation of the mucosa and/or submucosa. The squamous epithelium of the nasal cavity was not affected. The lesions tended to be bilateral in distribution in rats exposed to both 100 and 400 ppm methyl methacrylate. A small nasal polypoid adenoma was observed in one male from both the 100 and 400 ppm exposure groups.

For chronic effects, methyl methacrylate was also tested in mice and rats.

In a NTP study (1986), fifty rats per group and per sex were exposed to vapour of methyl methacrylate through whole body, 6h/day, 5 day/week during 2 years. The doses were 0, 500 and 1000 ppm for males and 0, 250 and 500 ppm for females. The examinations were performed following OECD guidelines. No difference in survival rate between treated and untreated groups was observed. No significant histopathological findings, other than in the respiratory tract was observed.

The primary finding in this study was inflammation of rat nasal cavity as well as olfactory epithelial degeneration at all exposure levels in male and female rats. At 1000 ppm in males, signs of inflammation were also seen in lungs. Mean body weight was reduced in females at 500 ppm (6-11%) and in males (5-10%) at 1000 ppm. These decreases were considered to be due to reduced food consumption due to nasal irritation and damage of olfactory epithelium.

A LOAEC of 250 ppm is proposed for local effects and a NOAEC of 500 ppm for males and 250 ppm for females regarding systemic effects.
In this study, some histological examinations required by OECD guideline were not performed (notably aorta, cervix, coagulating gland, eye, peripheral nerve, skeletal muscle). However, these deviations have no consequence on the reliability of the study.

In the study report #10 (1979) which was reviewed in 1992 (Study report #9 (1992a)), methyl methacrylate vapour was administered to 70 rats/sex/group for six hours per day, five days per week, for 104 weeks at 0, 25, 100 or 400 ppm.
The mortality rates for treated groups were comparable to the control group. No sign of test substance-related toxicity was observed in any of the treated animals. A body weight reduction is observed in females exposed to 400 ppm. Statistical analysis showed numerous significant differences between the treated and the control groups. However, these differences were considered sporadic and were considered in the study report #10 (1979) as a reflection of sampling and biological variability. No consistent dose-related

effect on organ weights was observed. Some effects on nasal mucosa (slight serous exudates, distention of submucosal glands) were observed. Occasionally there was also an accompanying pleocellular infiltrate in the submucosal tissues. Focal areas of squamous metaplasia were observed in seven high-level rats and in two controls. Inflammatory polyps were observed in two high-level males. Overall, the lesions were very mild and although occurring with an increased incidence in treated rats, the total number of rats affected was small and no dose relationship was observed. It was concluded in the study report #10 (1979) concluded that no clear treatment related effect could be established.

However, the study report #9 (1992a) has a different conclusion on 2 points:

- Olfactory epithelium is a target organ in rats exposed to 100 or 400 ppm
- The original diagnosis of inflammatory polyp in the nasal cavity of 2 rats was changed to adenoma.

In this context, a NOAEC of 25 ppm (104 mg/m3) is proposed for local effects and a NOAEC of 400 ppm (1640 mg/m3) is proposed for systemic effects.

In a NTP study (1986), fifty mice were exposed to vapour of methyl methacrylate by whole body, 6h/day, and 5day/week during 2 years. The doses were 0, 500 or 1000 ppm. The examinations were performed according to OECD guideline. No difference in survival between treated and untreated groups was observed. No significant histopathological findings, other than in the respiratory tract was observed.
Histopathological signs of irritation in the upper respiratory tract were present in all dose groups. At the highest dose, in males, inflammatory responses were also seen in the lung. For most of the study the mean body weight of the animals treated at 500 or 1000 ppm was lower than mean body weight in the controls.
To conclude the main effect observed in the study was inflammation of rat nasal cavity as well as olfactory epithelial degeneration at all exposure levels in male and female.
Therefore, a LOAEC of 500 ppm is proposed for local and systemic effects.
In this study, some histological examinations required by OECD guideline were not performed (notably aorta, cervix, coagulating gland, eye, peripheral nerve, skeletal muscle…). But these deviations have no consequence on the reliability of the study.

In another type of study, two experimental groups of male mice received intermittent daily exposures to either 100 or 400 ppm of methyl methacrylate vapour for total exposure times of 160 h for each group. Twenty-four hours after the last exposure, each mouse received an IP dosage of 50 mg/kg sodium pentobarbital. Following injection, the times of the loss and subsequent return of the righting reflex were measured. Sleeping times, determined by the duration to retrieve a righting reflex following intraperitoneal injection of sodium pentobarbital, were significantly decreased with increasing dose ($p < 0.05$). This decrease in sleeping time could be explained by an induction of enzymes capable of metabolizing pentobarbital. However, at approximately 100-fold higher exposure concentrations, acute (14 min) exposures to methyl methacrylate can cause an increase in pentobarbital's induced sleeping time (Lawrence and Autian, 1972), indicating that metabolic rates and processes can vary considerably with different dosing regimens.
The effects observed are essentially:

- Local effect on respiratory tract, leading to a local NOAEC of 25 ppm,
- Decrease of body weight, following decrease of food consumption leading to a systemic NOAEC of 250 ppm. This effect is also observed when methyl methacrylate is administered by another route.

Other studies of lower reliability were also provided. In these studies, effects on neurological and behavioural change, electrocardiogram, heart, blood pressure and liver are reported. However, the low reliability of these studies does not allow deriving NOAEC. These effects are observed in studies of different duration, from several days to several months.

The differences between rodents and humans regarding the physiology of the nasal passages and metabolic rates activity result in the greater susceptibility to inhaled esters of rodents compared to humans. In the EU ESR (2002) these differences were disregarded and rodents were regarded as having a similar sensitivity than humans. Subsequently, in the SCOEL review (SCOEL, 2005) greater emphasis was placed on human data, showing the absence of adverse respiratory effects up to at least 50 ppm and this was considered to be consistent with rodents being at least three times more sensitive than humans based on PBPK considerations (Andersen *et al.* 2002, Mainwaring *et al.* 2001). Consequently, a value of 50 ppm is regarded as being the NOAEC (corresponding to a DNEL) in humans. Control of short-term peak exposures is also needed, in view of the sensory irritancy of methyl methacrylate . There are no data available to clearly define the threshold concentration above which such irritation will occur in humans. However, SCOEL mentioned that it is above 100 ppm.

OTHER ROUTES
Methyl methacrylate was administered daily during 2 years by capsule to 2 male and 2 female dogs. The doses were equivalents to that achieved by dietary concentrations of 0, 10, 100, 1000 - 1500 ppm.
The only significant effect observed is a decrease in body weight gain in the dogs administered methyl methacrylate at a concentration of 1000-1500 ppm. Therefore, a NOAEL of 100 ppm is proposed.
No other study of high reliability is available for others routes. However, studies of reliability 3 were reported for intraperitoneal route.

methyl methacrylate was administered during 4 days to mouse at 60 or 600 mg/kg.
Only one sentence is presented for results: "Decrease in body weight gain and liver to body weight ratio were observed". Therefore, a NOAEL of 60 mg/kg is proposed.

In another study by intraperitoneal route, male rats received methyl methacrylate at 1g/kg for 3 successive days. The only effect reported is a reversible biochemical change in liver and kidney without more information.

To conclude based on the available information, the potential of methyl methacrylate for systemic toxicity after repeated dosing is low. Nevertheless numerous local effects were observed, such as inflammation and degeneration of the olfactory epithelium in the nasal cavity, lung damages, nasal discharge, degeneration/atrophy of the olfactory epithelium and underlying Bowman's glands, hyperplasia of basal (reserve) cells, replacement of olfactory epithelium by ciliated (respiratory-like) epithelium, and inflammation of the mucosa and/or submucosa and even rhinitis. Part of these local effects were considered to be covered by the harmonized classification of methyl methacrylate for the irritation potential on respiratory tract (see section 7.9.2). Moreover, as indicated in the section 7.9.3 a classification of the substance as respiratory sensitizer will be proposed. Therefore, no additional classification is considered as necessary.

7.9.5. Mutagenicity

7.9.5.1 In vitro

Many studies were provided by the registrants to assess *in vitro* genotoxicity of methyl methacrylate. However, only some of them can be considered as reliable.

Gene mutation in bacteria and in mammalian cells and cytogenicity in mammalian cells were examined.

Gene mutation in bacteria

In a first study (Zeiger *et al*., 1987), 4 strains of S. typhimurium (TA1535, TA97, TA98 and TA100) were tested with and without metabolic activation, with 5 doses between 10 – 10000 µg/plate, according to OECD guideline 471.

Increases of the revertant numbers were observed in TA97 with metabolic activation systems following preincubation method. However, the maximum revertant factors were 1.6 in comparison to the vehicle control and the effects were not reproducible; therefore, NTP assessed the results of the single trials as "weak positive". However, an actual international requirement for a positive test result is at least a revertant factor of 2. Additionally, the trials with "weak positive" results produced no clear pattern regarding the used metabolic activation system. Therefore, the general result of the Ames test series is considered as negative despite the fact that the study presented some deviations.

In a second study (Schweikl *et al.,* 1994), methyl methacrylate was tested in Salmonella typhimurium TA 97a, TA 98, TA 100, TA 102 and TA 104 with and without metabolic activation at doses between 0-25 mg/plate. The result was negative.

To conclude, methyl methacrylate was not mutagenic in an Ames test with and without metabolic activation.

Gene mutation in mammalian cells

Four gene mutation assays in mammalian cells of high reliability were available, one in Chinese Hamster Lung Fibroblast V79 and three in mouse lymphoma L5178Y cells.

In the first one, Schweikl *et al.* (1998) tested methyl methacrylate for mutation in Chinese Hamster Lung Fibroblast (V79) with and without metabolic activation. However, only the results without activation were reported with details in the publication. A weak mutagenic response was observed.

In the study performed by the National Toxicology Program (NTP, 1986), methyl methacrylate was tested on mouse lymphoma L5178Y cells with metabolic activation and gave clearly positive results.

In another study (Moore *et al*., 1988), methyl methacrylate was tested on mouse lymphoma L5178Y cells with and without metabolic activation. methyl methacrylate gave positive results with and without metabolic activation, with a majority of small colony at doses non cytotoxic. This suggested a clastogenic mechanism and not a mutagenic effect.

Finally, study report#7 (1981) tested methyl methacrylate in mouse lymphoma L5178Y cells with and without metabolic activation. Without activation, the choice of concentration was not totally appropriate as in the first assay the cytotoxicity was low and in the second assay was too high. With metabolic activation, methyl methacrylate could be considered mutagenic. Information about the size of colonies was not available.

Therefore a mutagenic effect (derived from clastogenicity) was observed in all the good-quality assays performed on mammalian cells.

Cytogenicity in mammalian cells

Three studies to assess clastogenic effects were provided by the registrants:

Anderson *et al*. (1990) studied chromosomal aberrations of methyl methacrylate in two studies on Chinese Hamster Ovary cells with and without metabolic activation. A slight

dose related increase in chromosomal aberrations was observed in the absence of metabolic activation. In the presence of S9, a statistically significant increase was noted at the highest dose. A clear dose related increase on SCE was also reported with and without metabolic activation.

In the NTP study (1986), methyl methacrylate was tested in CHO cells with and without metabolic activation. A dose related increase in the frequency of SCE was observed with and without metabolic activation.

In the last study (Doerr *et al*. 1989), three parameters of clastogenicity effects were observed: the number of metaphases with aberrations, number of binucleates with micronuclei and small colony TK mutant frequency on L5178Y mouse lymphoma cells. The observed effects were considered positive.

Moreover, in the literature, there is a concern that methyl methacrylate may produce genetic damage by inducing mutation. Therefore Yang *et al.* (2003) tested methyl methacrylate for colony forming efficiency, DNA synthesis, and cytogenetic assays in cultured CHO cells. methyl methacrylate was found to decrease colony formation in a dose- and time-dependent manner. methyl methacrylate also inhibited DNA synthesis in a dose-dependent manner. In this study, methyl methacrylate was found to be not only a cytotoxic agent but also a genotoxic agent.

In another study (Cannas *et al.*, 1987), human lymphocytes were used to assess the ability of polymethylmethacrylate to induce micronuclei. The results of the study showed a significant increase in the micronucleus frequency in treated cultures.

Results from all *in vitro* studies showed that methyl methacrylate induces a cytogenetic effect.

7.9.5.2 In vivo

In vivo, two chromosomal aberration assays and one micronucleus assay were provided by the Registrants:

Chromosomal aberration tests were conducted investigating the effect of an inhalation exposure to methyl methacrylate. In both tests acute exposure was for 2 h (sampling 24 h after treatment) and subacute exposure for 5 h/day on 5 consecutive days (sampling 24 h after last treatment).

In the first study by Study report #1 (1976), methyl methacrylate was administered by inhalation (whole body) to Wistar rat at 100, 400, 700 and 1000 ppm. Bone marrow was collected only 24 hours after the single two hours exposure whereas two collections are required in the OECD guideline. It was collected 24 hours after the 5 exposures of 5 hours. Each rat received colchicine intraperitoneally two hours prior to sacrifice to stop dividing cells in metaphase. Fifty cells from each animal were examined for chromatid or chromosome gaps, chromatid breaks, fragments and any other complex abnormalities while 200 cells are required in the OECD guideline. Mitotic index observation was realized on 100 cells while 1000 are required.
For the single exposure study, a significant increase in the percentages of cells with chromosomal aberrations was observed at all doses except at 700 ppm. However, these increases were due to gap-type aberration because when they were excluded, small increase was observed only at 400 ppm. No information on the type of aberration was provided.
For repeated exposure study, an increase in the percentages of cells with chromosomal aberration, when gaps were not considered, was observed only at 100 ppm.
To conclude, methyl methacrylate causes weak, but statistically significant, increases in chromosome damages in rat bone marrow cells at some exposure levels compared to the

negative control values, both after single and repeated exposures. Nevertheless, no consistent dose-response relationship was observed (except after re-analyze for multiple exposures).
This assay presents some deviations mentioned previously (only one collection, only 50 cells examined, 100 cells observed for mitotic index) but also, the choice of the maximal dose (< 2000 mg/kg) which was not justified by general toxicity or toxicity of bone marrow and finally, the metaphase step of the observed cells in first step is doubtful.
Therefore the assay cannot be considered clearly negative and no firm conclusion can be drawn.

In another study by Study report #2 (1979), methyl methacrylate was administered by inhalation (whole body) to Alderley Park rats at 100, 1000 and 9000 ppm for single 2h exposure or repeated 5h exposure during 5 days. The single treatment assay was repeated identically.
The numbers of rats per group in each experiment were: 2-4 rats per group or 5 in the single treatment, and 7 rats per group for the repeated treatment. Bone marrow was collected only 24 hours after the exposure while a second collection is required in the OECD guideline for a single treatment. Fifty cells from each animal were examined for chromatid or chromosome gaps, chromatid breaks, fragments and any other complex abnormalities while 200 cells in metaphase are required in the OECD guideline. No information on the choice of maximal dose was provided.
For the single exposure study, in each experiment the group exposed to methyl methacrylate showed no significant difference from the negative control group. However, when the data from the two single exposure experiments were combined, the groups exposed to methyl methacrylate were significantly different from the controls at 1000 and 9000 ppm, with a dose-response relationship.
For the multiple exposures, only the group exposed to 9000 ppm was significantly different from the negative control. In this experiment there was also evidence of a dose-response relationship at the two highest doses of methyl methacrylate .
When damages other than chromatid or chromosome gaps were considered, there was no statistically significant difference from the negative control in the methyl methacrylate exposed groups but there was a tendency towards an increase in damages with increasing exposure to methyl methacrylate .
Thus the data showed that methyl methacrylate at 9000 ppm caused chromosome damages, statistically significantly from the negative control, after single and repeated exposures. methyl methacrylate induced damages also at 1000 ppm after a single exposure but not after multiple exposures.
Despite the lack of a statistically significant difference between the negative control and the group exposed to multiple exposure of 1000 ppm, there is a tendency towards an increase of damage with increasing methyl methacrylate exposure. As in the first study, some deviations are noted: only one collection, 50 cells examined, the choice of the maximal dose.
In conclusion, both chromosomal aberration assays suffer from severe methodological problems. Therefore, no reliable conclusion can be drawn from these tests.

A micronucleus assay is also available, performed by Hachiya *et al. (*1982*)* in mice. Methyl methacrylate was administered by gavage to 6 animals as a solution in olive oil at 3 single doses: 1130 mg/kg, 2260 mg/kg and 4520 mg/kg, 24 h prior to preparation of the bone marrow. Although two collections are required in the OECD guideline for single exposure, only one collection was done.
A separate group of 5 animals was administered 4 doses of 1130 mg/kg, 96, 72, 48 and 24h prior to preparation. 2000 erythrocytes were evaluated per animal while 4000 are required in the OECD guideline.
No increase in micronucleated polychromatic erythrocytes was observed at any dose, while an induction of micronuclei was seen in the positive control. No toxicity was observed and no information on the decrease of ratio PCE/NCE was provided. In this context, there is no evidence that bone marrow was reached and thus, this study is not considered reliable.

Moreover, the toxicokinetic data do not show that methyl methacrylate reaches the bone marrow.
Finally, this assay was carried out by gavage in olive oil. Since the substance can polymerize quickly, an estimation of absorbed substance would have been interesting. Indeed, if polymerization occurs, the substance can be less absorbed by gastro intestinal route.
Therefore, no conclusion can be drawn from this study.

Based on the available *in vivo* studies, no firm conclusion can be made. **Clastogenic effects leading to a concern for mutagenicity observed *in vitro* cannot be totally ruled out on the basis of the available *in vivo* studies**. In this context, a concern for mutagenicity is identified and needs to be clarified in order to conclude if a classification is needed for the substance and in order to assess the risk based on a DNEL or a DMEL.

Therefore, a new reliable micronucleus assay *in vivo* (OECD 474) via the most appropriate route was required in the draft decision issued at the end of the 12-month of evaluation by France. FR-MSCA mentioned in their request that sufficient exposure of the bone marrow must be ensured to conclude properly on the genotoxic potential of methyl methacrylate . Investigation of levels of the test substance in plasma or in bone marrow was required to prove that the substance reaches the bone marrow.

It was judged necessary to provide this toxicological information in order to clarify the clastogenic concern and to perform an adequate risk assessment (based on DNEL or DMEL).

Therefore, the evaluating Member State proposed in a draft decision that the Registrant(s) provide the following information: *in vivo* Mammalian Erythrocyte Micronucleus assay in rodent via the most appropriate route (OECD TG 474).

Nevertheless during the discussion at the MSC-47 meeting the concern for mutagenicity was not unanimously agreed among the MSCAs. Moreover during the introduction of the substance the registrant indicated that they may have new *in vitro* data on the substance which may explain the results obtained in the mutagenicity tests for methyl methacrylate . Nevertheless these data have never been provided.

Therefore, it was decided to conclude this substance evaluation (a termination letter was sent to the registrant) by preparing a proposal for updating the harmonized classification, including a proposal for classification for respiratory sensitisation category 1. If the CLH procedure will not result in a harmonized classification which would provide a sufficient level of protection, the substance evaluation of methyl methacrylate may be initiated again to address the remaining concern(s).

The available information showed clastogenic effect *in vitro*. The *in vivo* micronucleus assays do not enable the evaluating MSCA to convincingly dismiss the *in vitro* concern. Based on the available data, no conclusion can be drawn on the classification of methyl methacrylate for genotoxicity.

7.9.6. Carcinogenicity

7.9.6.1 Oral route

Two oral chronic studies were provided in the dossier.

In the first study by Borzelleca *et al*. (1964), 25 male and female albino (Wistar) rats were administered to 6, 60 or 2000 ppm (corresponding to 0.37 mg/kg/d, 3.7 mg/kg/d, 124 mg/kg/d for males and 0.48 mg/kg/d, 4.86 mg/kg/d, 162 mg/kg/d for females) of methyl

methacrylate in the drinking water daily ad libitum for 2 years. The concentrations of the low- and mid-dose groups were increased to 7 and 70 ppm at the beginning of the fifth month of the study. There was only an increased kidney/body-weight ratio in female rats exposed to 2000 ppm of methyl methacrylate, considered to be a functional adaptation in response to the significantly reduced water intake noted. There was no compound related effect on body weight, food consumption, macroscopic and histopathological examinations.

In the second study by Borzelleca *et al.* (1964), methyl methacrylate was administered daily during 2 years by capsule to 2 male and 2 female dogs. The doses were equivalent to that achieved by dietary concentrations of 0, 10, 100, 1000 - 1500 ppm (corresponding to ca. 0.04, 0.41 and 4.1-6.2 mg/L, respectively) dissolved in corn oil. The highest tested dose was reduced to 500 ppm on day 2, 0 ppm on day 3-13 and 300 ppm on day 14 due to vomiting, and then increased to 1200 ppm at week 5 and to 1400 ppm at week 7 to 1500 ppm at week 9. A decrease in body weight gain was observed in the 1000 and 1500 ppm groups. In addition, there was a statistically significant decrease in spleen to body weight ratios only in the 100 ppm group. The biological significance of this finding was not apparent in the absence of a dose-response relationship. There was no compound related effect on haematological and histopathological examinations.

In conclusion, these studies performed in dogs and rats revealed no increase of neoplastic lesions. However the reliability of these studies is limited due to their non-conformance with current carcinogenicity test guidelines (e.g., histopathological examination was performed on a limited number of organs and low number of animals).

7.9.6.2 Inhalation route

- **Animal Data**

Four studies by inhalation route were available in the registration dossier.

In the first study by Chan *et al.* (1988, NTP 1986c), fifty B6C3F1 mice were exposed to vapours of methyl methacrylate by whole body, 6h/day, 5 day/week during 2 years. The doses used were 0, 500 and 1000 ppm. Animals were killed at 113-114 weeks of age. The examinations were performed following the OECD guideline 451. No difference in survival rate between treated and untreated groups was observed. No significant histopathological findings, other than in the respiratory tract, were observed. Histopathological signs of irritation in the upper respiratory tract were present in all dose groups. At the highest dose, in males, inflammatory responses were also seen in the lungs. During most of the second year of the study, the mean body weights of treated male mice and high-dose female mice were 10-18% lower than those of the controls. Therefore, a LOAEC of 500 ppm is set for non-neoplastic local and systemic effects. Concerning carcinogenic effects, no treatment-related tumours were observed and a NOAEC for carcinogenic effects of 1000 ppm is proposed. Therefore, a NOAEC of 1000 ppm is set for carcinogenic effects.

In a second study by Chan *et al.* (1988, NTP 1986d), F344/N rats were exposed to methyl methacrylate (purity >99%; containing 0.04 mg/l equivalent to 10 ppm monomethylethyl ether of hydroquinone as an inhibitor of polymerization) by inhalation, 6 hours a day, 5 days a week for 102 weeks. Males received 0, 2.1, 4.2 mg/l (equivalent to 500 or 1,000 ppm) and female received 0, 1.0 or 2.1 mg/l (equivalent to 250 or 500 ppm). Animals were killed at 111-112 weeks of age. The examinations were performed following the OECD guideline. No significant differences of the survival rates were observed between any groups. The primary finding in this study was inflammation of rat nasal cavity as well as olfactory epithelial degeneration at all exposure levels in male and female rats. At 500 and 1000 ppm in males, signs of inflammation were also seen in lungs. An increase of incidence of focal or multifocal fibrosis was observed for females exposed to 500 ppm. Mean body

weight was reduced in females at 500 ppm (6-11%) and in males (5-10%) at 1000 ppm. These decreases were considered due to reduced food consumption due to nasal irritation and damage of olfactory epithelium. Therefore, a LOAEC of 250 ppm is proposed for non-neoplastic local effects and a NOAEC of 500 ppm for males and 250 for females for non-neoplastic systemic effects. No treatment-related tumors were observed. The marginal increase in the incidence of mononuclear-cell leukaemia observed in female rats (control 11/50; low-dose 13/50; high-dose 20/50) fell within the range of values seen in historical controls. Therefore, a NOAEC of 1000 ppm in males and 500 ppm in females is set for carcinogenic effects.

In a combined chronic toxicity and carcinogenicity study on methyl methacrylate performed by R. (1979, re-evaluated L. in 1992), methyl methacrylate vapours were administered to 70 rats/sex/group for six hours per day, five days per week, for 104 weeks at 0, 25, 100 or 400 ppm (corresponding to ca. 0.10, 0.41 and 164 mg/L, respectively). The mortality rates for treated groups were comparable to the control group. A body weight reduction was observed in females exposed to 400 ppm. Two males (1/49 at 100 ppm and 1/47 at 400 ppm) had a small solitary polypoid mass attached to the lateral wall of one side of the anterior nasal cavity. Both animals had also a chronic inflammation of the respiratory epithelial region. The R. (1979) report study considered the polypoid masses to be unlikely related to methyl methacrylate exposure because they were not significantly increased in comparison to controls and the findings were not confirmed by other studies. A NOAEC of 400 ppm (1640 mg/m3) is proposed for non-neoplastic systemic effects and carcinogenic effects and a NOAEC of 25 ppm (104 mg/m3) is proposed for non-neoplastic local effects. In contrast, the results were reviewed by L. (1992) and came to the conclusion that both masses, composed of well-differentiated pseudoglandular structures arising from respiratory epithelium, can be diagnosed as adenomas. In addition, it can be noted that historical data show that adenomas from respiratory epithelium are very rare tumours in rats with a spontaneous rate of 0-0.1% for F344 male and female rats (Haseman *et al*., 1990). In conclusion, it cannot be completely excluded that the adenoma observed are related to treatment even if there is no evidence of a dose-response relationship.

In another study by Lomax *et al.* (1997), methyl methacrylate was administered by inhalation at 25, 100 and 400 ppm to Golden hamsters with groups of 53-56 males and 56-59 females exposed to 0, 25, 100 or 400 ppm (0, 102.5, 410 or 1,640 mg/m³) of methyl methacrylate for 6 h/d, 5 d/week for 78 weeks (18 months) (no interim sacrifice). At the high-dose, body weight decreased and mortality increased in high dose males. After week 60, males exposed to 400 ppm and to 25 ppm had significantly lower body weight during some weeks. There was no treatment-related effect on clinical signs, haematology and gross pathology. Frequent observations from all of the dose groups (including the control group) included focal discoloration of the lungs and liver as well as cystic growths on the liver. There were no exposure-related neoplastic or non-neoplastic lesions recorded. Histological changes were similar between the high dose and control groups and were typical of hamsters of this age and strain. It was noted by the authors that the hamster nasal cavities were "exceptionally free of lesions." Therefore a non-neoplastic systemic NOAEC of 100 ppm (0.41 mg/l) and a NOAEC for carcinogenic effects of 400 ppm are proposed.

In conclusion, there is no consistent carcinogenic effects observed in the chronic animal studies (rats, hamsters, mice) exposed to methyl methacrylate via the inhalation route. Among the 4 studies, only one study reported possible carcinogenic effect, such as 2 adenomas in nasal cavity of rats, one in two different dose groups, without any clear dose-response relationship. Based on this dataset, IARC in 1994 concluded that there is evidence suggesting the lack of carcinogenicity of methyl methacrylate in experimental animals. The eMSCA is of the opinion that there is no carcinogenicity potential for methyl methacrylate.

- **Human data**

Cohort studies are available. They described the exposure of cast acrylic sheet manufacturing workers since this type of industry has historically a potential for an exposure to high levels of methyl methacrylate. These studies are available below.

A retrospective mortality study has been conducted among workers exposed to the vapour phase of methyl methacrylate , low percentages of ethyl acrylate (EA) and volatile by-products of the methyl methacrylate and EA polymerization process in acrylic sheet manufacture in two US plants. Detailed analyses of colorectal cancer mortality were performed for each of the three cohorts (cohort I: 3,934 white males employed between 1933 and 1945; cohort II: 6,548 white males hired between 1946 and 1986; cohort III: 3,381 white males hired between 1943 and 1982). Exposure was estimated on the basis of a job-specific semi-quantitative rating scale. Mortality from colon cancer was significantly increased in cohort I and non-significantly increased in cohort III. The risk for colon cancer was highest in the most exposed workers, who worked extensively in the early 1940s. No regular increase according to years elapsed since first exposure or intensity of exposure was observed for colon cancer. The rate for rectal cancer was increased in cohort I (Walker et al., 1991). Some evidence of increased death rate from respiratory cancer or non-malignant respiratory disease was reported for cohort III (Study report #13 (1987)).

Another retrospective mortality study (Collins *et al.*, 1989) included a cohort of 2671 male workers employed between 1951 (1957 respectively) and 1974 in two acrylic fibre production plants. Only 1561 men of the cohort at mean concentrations below or equal to 1 ppm were exposed to methyl methacrylate . A small excess of respiratory cancer was reported. There was no significant increase in the number of cancer deaths.

In a cohort study by Tomenson (1994), colorectal cancer was as expected (17 observed deaths versus 16.9 expected) and respiratory cancer mortality was lower than expected (SMR=93). Mortality due to stomach cancer was increased by approximately one third.

In 1994, IARC concluded based on these data that there is inadequate evidence in humans.

A critical review of the epidemiology literature including the cohorts studies described above on the potential cancer risks of methyl methacrylate (Tomenson *et al.*, 2005) is available. The authors conclude that excesses of respiratory, stomach and colorectal cancers were observed in some cohorts of workers exposed to methyl methacrylate . But there was no robust evidence to suggest that methyl methacrylate exposure was responsible for the excess of respiratory and stomach cancer, and it is more likely that they resulted from unexplained contributions from lifestyle exposure such as cigarette smoking and diet.

The excess of colorectal cancer in Early Bristol workers (highly exposed to methyl methacrylate) remains unexplained (absence of relationship between cancer and duration of exposure, plant located in an area with high colorectal cancer rates but US mortality rate was used to SMR) and the possibility that a link between methyl methacrylate exposure and colorectal cancer exists in humans cannot be ruled out.

Overall, the epidemiological data do not provide consistent evidence on the carcinogenic effect in humans, nevertheless a link between methyl methacrylate exposure and colorectal cancer exists in humans and therefore a risk cannot be totally ruled out. The studies did not allow a strong association of increased tumour rates in a distinct organ or several organs to methyl methacrylate as the responsible agent.

Overall conclusion on carcinogenicity

No carcinogenic potential was detected in inhalation studies in rats, mice, dogs and hamsters, except 2 polyps observed in rats, for which it cannot be excluded they could be related to irritant properties of the substance.

In humans, some respiratory and stomach cancers were reported however rather to be related to cigarette smoking. Only a role of methyl methacrylate in the observed colorectal cancer cannot be totally ruled out. The tumours reported cannot be linked to methyl methacrylate as the solely causal agent. Otherwise, these epidemiology data were of limited reliability leading to inadequate evidence of carcinogenicity in humans. In any case, if methyl methacrylate would contribute to cancer (e.g. colorectal cancer), it would be more likely via an irritating mechanism.

In conclusion, based on the available data, no further action is foreseen under SEv or classification frameworks.

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

7.9.7.1 Effects on fertility

In a two generation reproduction toxicity study by Study report #3 (2009c), methyl methacrylate was administered to groups of 25 male and 25 female healthy young Wistar rats (F0 parental generation) as an aqueous preparation by stomach tube at the following concentrations: 0; 50; 150 and 400 mg/kg body weight/day.
The mid- and high-dose parental animals (150 and 400 mg/kg bw/d) showed clinical signs of test-substance related effect: the only relevant clinical observation was temporary salivation during a short period after dosing. From the temporary, occurring immediately after dosing it is likely that this finding was induced by a bad taste of the test substance. It is, however, not considered to be an adverse toxicologically relevant finding.
In the mid- and high-dose (150 and 400 mg/kg bw/d) F0 generation animals, dose-related intermittent reductions of food consumption were noted, either during premating, gestation and lactation phases of this study. Less significant changes were noted for the F1 generation animals where the effects were limited to the high-dose group.
High dose F1 parental males had statistically significantly lower body weights during several study segments, which led to a statistically significant reduction of the mean terminal body weight.
High dose F1 parental females had statistically significantly lower body weights during the first weeks after weaning. This weight decrease during major phases of sexual maturation could explain the apparent marginal delay of vaginal patency. This minor delay did, however, not result in any corroborative pathological findings nor adversely affect F1 female cyclicity, fertility and reproduction. Thus, an effect of the test substance on female sexual maturation is not assumed.
Pathological examinations did not reveal any test-substance-related changes in gross lesions, changes in differential ovarian follicle counts or microscopic findings, apart from an increase in kidney and liver weights in male and female animals in both generations which is presumably related to the treatment. There was no histopathological lesion observed that could explain the weight increase. It is regarded to be an adaptive change, most likely caused by an increase in metabolic activity in the two organs, which does not lead to histopathological findings.
In F0 generation parental animals, an increase of the relative weights of epididymis and seminal vesicle, statistically significant at 400 mg/kg/d and higher testis weight at all doses were observed. In the F1 generation parental animals, a statistically significant increase of epididymis weight was observed at all doses.
However, there were no indications from clinical examinations as well as gross and histopathology, that the administration of methyl methacrylate adversely affected the fertility or reproductive performance of the F0 or F1 parental animals up to and including

a dose of 400 mg/kg bw/day. Estrous cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, and gross and histopathological findings of these organs (including differential ovarian follicle counts in the F1 females) were comparable between the rats of all test groups and ranged within the historical control data of the test facility.
All data recorded during gestation and lactation in terms of embryo-/fetal and pup development gave no indications for any developmental toxicity in the F1 and F2 offspring up to a dose level of 400 mg/kg bw/day. Up to this dose level, the test substance did not adversely influence pup viability and pup body weights. Sex ratio and sexual maturation was not directly affected at any dose level, inclusive the high-dose group (400 mg/kg bw/day).
A reproduction NOAEL of 400 mg/kg/d and a developmental toxicity NOAEL of 400 mg/kg/d are proposed.
The NOAEL for general, systemic toxicity was determined to be 50 mg/kg bw/day for the P and F1 parental rats, based on adverse effects on food consumption observed at the LOAEL of 150 mg/kg bw/day in the P parental females.

In the literature some alerts on endocrine disruption were found. But these data (summarized below) are not sufficient to conclude on potential endocrine disruption properties of methyl methacrylate, especially as the two generation study available is of good reliability and no alert is identified.
In the study by Stepanov *et al. (*1991*),* chronic effect of small concentrations of methyl methacrylate by inhalation (at the level of a maximum permissible dose of 50 mg/m^3 and in its 10-fold excess) after short-term enhancement of the hypothalamo-hypophyseo-gonad system (in one month after exposure to a dose at maximum permissible concentration) is quickly followed by suppression of its function. The use of methyl methacrylate for 4 months revealed a decrease in ovarian mass, the blood level of progesterone and a rise of secretion of FSH and LH with a simultaneous decrease in the level of gonad-releasing hormone in the mediobasal hypothalamic structures. It indicates a primary gonad damage of the reproductive system and preservation of a normal reaction of the hypothalamo hypophyseal factor which responded by activation of the feedback loop.
Fakhouri *et al.* (2008a*)*, showed in their study that methyl methacrylate mixed with water at four different concentrations is able to affect the histological structure of testicular tissues and seminal vesicle on male rats. The target population was composed by 60 male Sprague-Dawley rats. They were divided into five different groups: The first group (n=15) designated as the control group and four experimental groups (n=45). Experiments were conducted by exposing the four experimental groups to methyl methacrylate administered *per os* mixed with water at different concentrations (4%, 8%, 16%, 32%). The exposure duration was eight months. The testicles and the seminal vesicles were then extracted, dissected, fixed in Bouin liquid fixative and were submitted for histopathological examination.
Seven out of 10 rats to which the methyl methacrylate was administrated at a concentration of 32% showed partial seminal vesicle atrophy. The seminal vesicles in the remaining rats showed normal histology in all specimens. Testis, epididymis and vas deferens showed normal histology in all rats.
The data in this study showed that methyl methacrylate administered at high concentration is associated to seminal vesicle atrophy. These findings could suggest that this effect could be the result of either a direct effect of methyl methacrylate on testosterone levels, or through its possible action on other organs involved in testosterone metabolism and seminal vesicle trophicity such as the hypophysis.

In another study, Fakhouri *et al.* (2008b) showed that methyl methacrylate is able to modify the testosterone level.
On the same population than the previous study, blood was obtained before and at the end of the exposure and the measurement of the testosterone level was made using EIA test.
The exposure of rats at a moderate concentration of methyl methacrylate (16%) showed an increase in testosterone level of 60% ($p = 0.003$) while the other groups showed a decrease of testosterone level. The control group showed a decrease of 44.8% ($p = 0.001$),

the rats exposed at 4% showed a decrease of 67.7%, those exposed at 8% showed a decrease of 432% , the rats exposed at 32% showed a decrease of 71.7% .
Despite the fact that methyl methacrylate at low concentration was rapidly hydrolyzed in blood due to the nonspecific carboxylesterase and metabolized at high concentration by the liver, its effects on testosterone level were significant. These preliminary results showed an interference of the methyl methacrylate with the testosterone hormonal equilibrium that could be an interesting target for further investigations.

Nishihara *et al.* (2000), tested the ligand-dependent interaction of two proteins, a hormone receptor and a coactivator, and hormonal activity is detected by ß galactosidase activity. In this study the estrogen receptor, ERα, and the coactivator, TIF2 were used.
The results are evaluated by relative activity, expressed as REC10 (10% relative effective concentration), that is the concentration of the test chemical showing 10% of the agonist activity of 10^{-7} M E2 which is the optimum concentration for E2. When the activity of the test substance was higher than REC10 within the concentration tested, the chemical was judged as positive. When it was judged to be negative, the highest tested dose was reported.
For methyl methacrylate , the REC10 of E2 is 3*10-10M and the REC10 of methyl methacrylate is superior to 1*10-3 M. In this context, the result is considered as negative. However, as mentioned in the literature report, this test may give false negative results for endocrine disruptors which:

- act via receptors other than ERα
- involve a pathway other than via receptor-mediated gene expression
- act as antagonist
- act after being metabolized by animal cells
- have inhibitory activity against the galactosidase assay and biocidal activity against the yeast cell cannot be transported into cell, resulting a cellular concentration below the sensitivity level.

Altogether, these different publications do not allow to draw a coherent conclusion on a possible endocrine disruptive activity of methyl methacrylate.

7.9.7.2 Developmental toxicity

Three studies of good reliability to assess developmental effects of methyl methacrylate were provided by the registrants, two by inhalation and one by oral route.

In a Study report #4 (2009d) methyl methacrylate was tested in rabbits by oral route. The test substance was administered to 25 Himalayan rabbits at 0, 50, 150 and 450 mg/kg/d from gestation day 6 through GD28.
No effect on maternal toxicity was observed, except:

- Reduced food consumption (-18%) and body weight gain (-31%) at 450 and reduced food consumption (-13%) and body weight gain (-27%) at 150 mg/kg/d.

No test substance related adverse effects on gestational parameters were observed.
Various external, soft tissue and skeletal malformations occurred throughout all test groups, including control. All individual malformations are present in the historical control data, with the exception of lateral pouches in the tongue of 2 fetuses (150 and 450 groups). They showed neither a consistent pattern since a number of morphological structures of different ontogenic origin were affected, nor a clear dose response relationship. The overall incidence of malformations was comparable to the historical control data.
One external (paw hyperflexion), two soft tissues (absent lobus inferior medialis and mal positioned carotid branch) and/or a broad range of skeletal variations occurred in all test groups including the controls.

All fetal and litter incidences for these variations and the corresponding mean percentages of affected fetuses/litter were not significantly different from the concurrent control and their frequency is comparable to the historical control data.
A spontaneous origin is also assumed for all unclassified external, soft tissue and skeletal cartilage observations which were observed in fetuses of all test groups including controls. Distribution and type of these findings do not suggest a relation to treatment.
Therefore, a NOAEL of 50 mg/kg/d for maternal toxicity and 450 for developmental toxicity are proposed.

methyl methacrylate was also tested in both rats and mice by inhalation route.

In the study report #14 (1991) methyl methacrylate was administered by inhalation exposure to 5 groups of 27 rats at concentration of 0, 99, 304, 1178 and 2028 ppm (0.41, 1.2, 4.8, 8.3 mg/L) for 6h/day on days 6 to 15 of gestation. All doses were administered by a whole body inhalation exposure. Observations were performed according to the OECD guideline 414. No treatment related deaths were noted. The only clinical sign noted was a minimal increase in the incidence of scant feces at 2028 ppm. Losses in maternal body weight or decrease in maternal body weight gain and decreases in maternal feed consumption were noted at all exposure levels tested. The decreases in maternal body weight at 99 and 304 ppm were minimal and transient since they occurred only during the first 2 days of exposure and returned to control values by the next weighing period. The body weight and feed consumption values returned to control values for all groups during the post exposure period (GD16-20). At 1178 and 2028 ppm, treatment related effects included losses in maternal body and/or decreased body weight gain throughout the exposure period (GD 6-16) and decrease corrected maternal body weight gain.
No embryo or foetal toxicity was observed and no increase in the incidence of malformations or variations was noted at exposure levels up to 2028 ppm.
Therefore, a systemic NOAEC of 1.02 mg/L and a teratogenicity NOAEC of 8.3 mg/L are proposed.

In the studyreport #16 (1976) mice were exposed to methyl methacrylate by inhalation route during day 4 to day 13 of gestation, 6 hours per day at 0, 116 and 400 ppm. No signs of maternal toxicity were reported. Additionally, there were no significant differences between control and exposed groups in viability, gross abnormalities or skeletal and visceral abnormalities of the off spring.

The evaluating MSCA considers that there is no concern for reproductive toxicity.

7.9.8. Hazard assessment of physico-chemical properties

There are no chemical groups associated with explosive properties present in the molecule; therefore the substance is non explosive.

Methyl methacrylate is a highly flammable liquid. Its Flash point is <23 °C and boiling point >35 °C.

The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.

The substance is highly flammable, but does not contain structures associated with oxidising properties.

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

Since originally, a study was requested by evaluating MSCA to clarify the concern regarding genotoxicity, it was judged that no definitive DNEL or DMEL could be identified. No risk assessment has therefore been performed.

DNEL or DMEL may be derived in a further evaluation if the proposed immediate follow-up of a harmonized classification of methyl methacrylate as respiratory sensitizer will not be adopted.

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

As stated above and based on the available information:

The substance needs to be classified as Flam. Liq. 2, H225 and has already a harmonized classification as such.

The registered substance is not acutely toxic by oral, dermal or inhalation route.

The substance has to be classified as Skin Irrit. 2, H 315 and has already an harmonized classification as such.

There is sufficient information to classify the substance as a skin sensitizer and methyl methacrylate has already a harmonized classification as Skin Sens. 1, H317. Additionally based on the human data the evaluating MSCA concluded that the substance needs to be classified as Resp. Sens. 1, H334 and a harmonized classification dossier has been submitted to ECHA in September 2018 for this endpoint.

The substance needs to be classified as STOT SE 3, H335 and has already a harmonized classification as such.

A concern was raised regarding mutagenicity during the evaluation, nevertheless following the discussion during the MSC, no further test has been requested.

There are no concerns for either carcinogenicity, fertility or developmental toxicity.

7.10. Assessment of endocrine disrupting (ED) properties

There is no concern identified for potential ED properties of methyl methacrylate.

7.11. PBT and VPVB assessment

Not assessed since the evaluation was targeted to human health concerns.

7.12. Exposure assessment

The exposure assessment was not evaluated. Nevertheless it should be noted that the updated harmonised classification, if agreed, may have an impact on how to handle the substance, its uses and the subsequent exposures.

7.13. Risk characterisation

Not evaluated. The evaluation focused on hazards only. Indeed, when the classification will be harmonised, conditions of use of the substance will be impacted and the subsequent risk characterisation as well.

7.14. References

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