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# METHYL METHACRYLATE

CAS No: 80-62-6

EINECS No: 201-297-1

**Summary Risk Assessment Report**

**2002** **Special Publication I.01.67**

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# SUMMARY RISK ASSESSMENT REPORT

*Final report, 2002*

Germany

The Rapporteur for the risk assessment of methyl methacrylate (MMA) is the Federal Institute for Occupational Safety and Health.

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| | |
|---|---|
| **Date of Last Literature Search :** | **1995** |
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| **Final report:** | **2002** |

# PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance methyl methacrylate that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the original risk assessment report that can be obtained from the European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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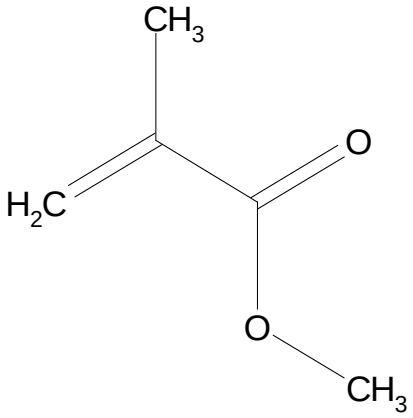
# 1 GENERAL SUBSTANCE INFORMATION

## 1.1 IDENTIFICATION OF THE SUBSTANCE

CAS no: 80-62-6
EINECS no: 201-297-1
IUPAC name: 2-Methyl-propenoic acid, methyl ester
Molecular weight: 100.12 g/mol
Molecular formula: $C_5H_8O_2$
Structural formula:




Synonyms: Methyl methacrylate (MMA)

## 1.2 PURITY/IMPURITIES, ADDITIVES

Purity: ≥ 99.8% w/w

Impurities: ≤ 0.05% w/w water
≤ 0.005% w/w methacrylic acid
≤ 800 ppm light fractions: acetone, methyl acetate, methanol, methacrylonitrile, methyl isobutyrate and methyl propionate
≤ 400 ppm heavy fractions: ethyl acrylate, butanols, methylhydroxy isobutyrate and succinic acid methyl ester (at ppm levels); diacetyl < 1 ppm

Additives: 2,4-dimethyl-6-tert-butylphenol (10-30 ppm), hydroquinone (HQ) (25-100 ppm) and the monomethylether of hydroquinone (MeHQ, synonym p-methoxy phenol) (2-100 ppm)

## 1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

| | |
|---|---|
| Physical state | Liquid at 20°C |
| Melting point | - 48°C (approx.) |
| Boiling point | 100-101°C at 1.013 hPa |
| Relative density | 0.9440 |
| Vapour pressure | 36-47 hPa at 20°C |
| Surface tension | 61 mN/m |
| Water solubility | 16 g/l at 20° C (approx.) |
| Partition coefficient | log Pow 0.67-0.7<br>log Pow 1.38 at 20°C (used for RAR) |
| Flash point | 10°C |
| Autoflammability | 430°C |
| Flammability | highly flammable |
| Explosive properties | not explosive |
| Oxidising properties | no oxidising properties |
| Henry's law constant | 26.3 · Pa · $m^3$ · $mol^{-1}$ |

## 1.4 CLASSIFICATION

Classification and labelling according to the 28th ATP of Directive 67/548/EEC[2]

| | | |
|---|---|---|
| Classification: | F; R11 | Highly flammable |
| | Xi; R37/38 | Irritating to respiratory system and skin |
| | R43 | May cause sensitisation by skin contact |
| Labelling: | F; Xi | |
| | R: 11-37/38-43 | S: (2-)24-37-46 |

Specific concentration limits: None

Note: D

[2] The classification of the substance is established by Commission Directive 2001/59/EC of 6 August 2001 adapting to the technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 225, 21.8.2001, p.1).

# 2 GENERAL INFORMATION ON EXPOSURE

At eight sites in the European Union, methyl methacrylate (hereafter referred to as MMA) is produced at tonnage of ≥ 5,000 t/a. The maximum production capacities per site are between 10,000 t/a up to nearly 200,000 t/a. According to industry statements for 1996, the total EU production capacity amounts to 610,000 t/a and the actual production volume to 470,000 t/a. Significant dynamics of the methacrylate-chemistry market with increasing trends at least in Germany are reported.

MMA is mainly used as an intermediate for the production of polymers (industrial category IC 11). The most important polymer types are cast acrylic sheets and moulding / extrusion compounds, besides emulsions, dispersions and solvent based polymers. Another significant use is the production of various methacrylate esters (industrial category IC 3), which are subsequently used for polymer production. Minor amounts are distributed and used as a monomer, e.g. in reactive resins, but even in these applications the MMA monomers eventually will be polymerised; the final polymerisation step takes place at the site of use.

About 2/3 of the total production quantity is sold to customers and not processed at the production sites.

MMA is produced commercially via the acetone cyanohydrine (methacrylamide sulphate) route or less through oxidation of isobutene or *tert*-butanol ($C_4$ route). A third, minor method uses ethylene as feed stock ($C_2$ route). Methacrylic acid produced by other routes also serves as key intermediate to MMA.

# 3 ENVIRONMENT

## 3.1 ENVIRONMENTAL EXPOSURE

Releases of MMA to the environment are to be expected mainly during production and processing with wastewater and exhaust gas as well as during the use of water based emulsion polymers, e.g. paints and varnishes.

Residual monomeric MMA-contents, which are the basis for release estimations from different polymeric products, are reported to range between 0.005 and 1.1 %.

Direct releases to agricultural or natural soil are not expected to a relevant extent.

The environmental behaviour of MMA is determined by the following characteristics:

- the estimated range of atmospheric half-life is 1.1 to 9.7 hours;
- MMA is readily biodegradable. Hydrolysis is not significant at neutral and acidic pH, but increases in the upper pH range;
- MMA is moderately volatile;
- the average $K_p$ value of 1.0 l/kg indicates no relevant adsorption onto sediment or soil.

Based on the physico-chemical properties of MMA, the air and to a much lower extent the hydrosphere are the preferred target compartments for distribution and neither relevant bioaccumulation nor geoaccumulation are expected. In wastewater treatment plants (WWTPs) 89.2 % of the substance are estimated to be removed predominately by biodegradation.

Predicted Environmental Concentrations (PEC) are calculated for the local aquatic environments of the production and processing sites using all site-specific information available. Data gaps are filled with default values proposed in the Technical Guidance Document (TGD). The resulting concentrations range between 0.004 µg/l and slightly above 10 µg/l with the exception of two production sites where no complete WWTPs are installed. For these sites realistic worst-case PEC calculations are performed on the basis of measured effluent concentrations and estimated site-specific or default dilution factors, resulting in PECs of 15.4 µg/l, 40 µg/l, and 360 µg/l, respectively.

MMA is also used as an external intermediate, i.e. about two thirds of the production quantity are sold within the EU to non producers/importers for processing at sites different from those considered above. A default calculation for external esterification at one fictitious single site gives a PEC of 15.6 µg/l. The main use area for MMA is the production of polymers, split to dry and wet polymerisation techniques. From dry polymerisation no relevant releases with wastewater to hydrosphere have to be assumed. For wet polymerisation a default calculation according to the TGD results in a PEC of 693 µg/l.

Due to actual data provided by Industry it is possible to supplement the generic scenario by specific information on this downstream use. The volumes of MMA used for wet polymerisation have been provided for 29 European sites covering 84,000 t/a, i.e. a good half of MMA externally used for wet polymerisation. Two sites covering a total amount of less than 2,000 t/a confirmed zero release to hydrosphere as a wastewater reutilization / recycling system is employed.

For all known sites where more than 1,000 t/a MMA are handled, PECs are calculated based on site-specific MMA tonnage, site-specific information on wastewater treatment and dilution as far as available, and default release factors. Resulting PECs range between 1.4 µg/l and 2,340 µg/l. With regard to received site-specific information, a processing volume of 10,000 t/a at one single site has to be assumed as realistic worst-case for unknown sites. For this generic site a PEC of 1,800 µg/l is calculated applying TGD default parameters.

Further exposure assessments are performed for formulation and private use of paints and for paper recycling, because the polymer emulsions and paper coatings may contain residual monomeric MMA. The resulting PECs amount to 1.83 µg/l, 0.015 µg/l and 0.73 µg/l, respectively.

No monitoring data for the aquatic environment are available.

No PEC estimation is performed for the sediment compartment, since no relevant adsorption of MMA onto sediment is expected.

For the atmosphere a generic PEC estimation for wet polymerisation by downstream users is representing the realistic worst-case for production and processing as well as for external processing like ester production, dry and wet polymerisation. Applying the respective emission factors proposed in the TGD, a local concentration of 381 µg/m³ in air in the vicinity of a generic site is calculated.

Local exposure of the atmosphere from manufacturing, formulation and use of polymers is expected to be significantly below the generic emissions calculated above for handling of the monomer and therefore additional quantification is not necessary.

Releases of MMA to soil are expected to occur through atmospheric deposition after local release to atmosphere. The input through sludge application on agricultural soil is considered negligible, as MMA does not partition to a significant extent to sewage sludge in WWTPs.

From the total annual deposition in vicinity of the generic worst-case site, the maximum equilibrium concentration in soil is calculated according to the procedure proposed in the TGD. The resulting bulk concentration in soil (natural soil and agricultural soil) is 41 µg/kg wwt, the respective porewater concentration is 41 µg/l.

The regional background concentrations calculated according to EUSES are low and do not contribute significantly to the local concentrations. The resulting values are:

| | | |
|---|---|---|
| $PECregional_{aquatic}$ | = | 0.14 µg/l |
| $PECregional_{air}$ | = | 0.05 µg/m3 |
| $PECregional_{agr.-soil}$ | = | 0.01 µg/kg (wwt) |
| $PECregional_{agr.-soil\ porewater}$ | = | 0.01 µg/l |
| $PECregional_{natural-soil}$ | = | 0.004 µg/kg (wwt) |

## 3.2 EFFECTS ASSESSMENT

For fish, only two relevant results from acute tests are currently available. For *Lepomis macrochirus*, a 96-h $LC_{50}$ of 191 mg/l is reported, for the rainbow trout *Oncorhynchus mykiss* a $LC_{50}$ of > 79 mg/l and a 96-h NOEC of 40 mg/l.

For invertebrates acute and long-term studies on Daphnia magna had been conducted and the most relevant EC value is the 21-d NOEC of 37 mg/l.

Among four algae toxicity tests, two tests run in open static systems are considered as not valid, and a third one was regarded as not valid after a critical re-evaluation revealed serious doubts concerning "true" MMA exposition. In a new study on *Selenastrum capricornutum* according to OECD-guideline 201 such doubts have been removed in most points. The highest test concentration of 110 mg/l caused growth inhibition below 50 %, the NOEC was 110 mg/l for growth rate as endpoint, and 49 mg/l for biomass as endpoint.

For derivation of the Predicted No Effect Concentration (PNEC) the lowest valid effect concentration, i.e. 37 mg/l from the long-term daphnid test, is divided by an assessment factor of 50 as proposed in the TGD for the present data basis: $PNEC_{aqua}$ = 740 µg/l.

The derivation of a PNEC for microorganisms is based on results from four non-standard tests on cell multiplication inhibition with protozoa and bacteria. For the three protozoa tests toxic threshold concentrations, i.e. $EC_5$ values between 178 mg/l and 556 mg/l are reported, for the bacterial test with *Pseudomonas putida*, an $EC_3$ of 100 mg/l is reported. Applying an assessment factor of 1 for this sensitive species according to the TGD, the $PNEC_{microorganisms}$ is set at 100 mg/l.

There are no relevant results with benthic organisms available and there is no need for performing an indicative quantitative risk assessment for the sediment compartment, because MMA shows no relevant adsorption and there are no monitoring data on MMA concentrations in sediment available.

It is not possible to derive a PNEC for the atmospheric compartment due to the lack of experimental data.

Data on effects to terrestrial organisms are not available. In an indicative risk assessment for the soil compartment, the aquatic PNEC of 740 µg/l can be used and compared to the concentration in soil pore water.

## 3.3 RISK CHARACTERISATION

The possible risks to microorganisms in wastewater treatment plants are evaluated for municipal and industrial facilities. For all considered scenarios the PEC/PNEC ratios are far below one and therefore no risk for the function of WWTPs is expected (**conclusion (ii)**).

**Conclusion (ii)** There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

For surface water a comparison between PEC and PNEC for all relevant exposure scenarios is performed. Based on the updated site-specific data all producing sites reveal PEC/PNEC ratios clearly below 1. There is at present no need for further information gathering or for limiting the risk beyond those measures which are already being applied (**conclusion (ii)**).

For four out of 29 known downstream user sites where MMA is used for wet polymerisation processes, as well as for the generic site scenario of wet polymerisation, PEC/PNEC ratios above one are calculated and a risk for the aquatic compartment has to be deduced on the basis of the present data configuration. Although an improvement of exposure data would be possible for the wet polymerisation scenarios, e.g. by performing effluent measurements, it is concluded that a sufficient and appropriate data basis cannot be acquired within an acceptable time frame and with acceptable efforts. Additionally, due to the dynamic methacrylate market, significant year-to-year variations of MMA tonnage used at individual sites hamper reliable PEC estimations.

It is concluded that local risk reduction measures have to be considered, if the MMA processing capacity for wet polymerisation exceeds 5,000 t/a at one single site. It should be noted that wastewater reutilization / recycling systems are applied by some known polymerisation sites, avoiding any significant MMA emission to hydrosphere. Sites applying such advanced process engineering would not require further consideration of risk reduction measures (**conclusion (iii)**).

**Conclusion (iii)** There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Regarding all other processing and use scenarios, no risk for the aquatic compartment is expected (**conclusion (ii)**).

From the current manufacturing and use of MMA, no risk for the sediment compartment is expected (**conclusion (ii)**).

Due to the fast atmospheric photooxidation and the low resulting concentrations in air, adverse effects on organisms and abiotic effects upon the atmosphere, like global warming and ozone depletion are not expected from MMA.

From an indicative risk assessment for the soil compartment no risk is deduced for the present data configuration and there is no need for further testing and/or gathering of exposure information (**conclusion (ii)**).

MMA does not present indications of a bioaccumulation potential. A risk characterisation for secondary poisoning is not required.

# 4 HUMAN HEALTH

## 4.1 HUMAN HEALTH (TOXICITY)

### 4.1.1 Exposure Assessment

#### 4.1.1.1 Occupational Exposure

MMA is primarily used as a chemical intermediate which is further processed to polymers. This is also true for applications where the final polymerisation step takes place at the site of use (e.g. use of adhesives). Main products are cast acrylic sheets, moulding, extrusion, emulsion and dispersion polymers, methacrylate esters and reactive resins. The further processing of MMA is predominantly performed at the site of the producers. The remaining quantity is further processed at sites of customers, which may belong to the large-scale chemistry as well as to the plastics industry and smaller formulation companies.

The substance is used in reactive resins preparations counting up to 80 % MMA which are applied in industrial and skilled trade sectors e.g. as floor coatings, adhesives, and dental products. Methyl methacrylate may be a residual component in paints and varnishes and may be released during thermal processing of polymeric MMA (PMMA).

The exposure assessment is based on measured data and literature data (limited), expert judgement and estimations according to the EASE model.

With regard to inhalative exposure, exposure to methyl methacrylate in vapour form is of primary concern here. Since most producers give no information about appropriate glove types or recommend glove materials providing only limited protection, dermal exposure has to be considered too.

The following occupational exposure limits (8-h TWA) are established for methyl methacrylate:

| | | | |
|---|---|---|---|
| AUS, B, FIN, F, USA (NIOSH/OSHA, ACGIH) | | 410 mg/m$^3$ | 100 ml/m$^3$ |
| DK | | 307 mg/m$^3$ | 75 ml/m$^3$ |
| D | | 210 mg/m$^3$ | 50 ml/m$^3$ |
| NL | | 200 mg/m$^3$ | 50 ml/m$^3$ |
| | 1.5.1999: | 100 mg/m$^3$ | 25 ml/m$^3$ |
| Sweden | | 200 mg/m$^3$ | 50 ml/m$^3$ |
| Switzerland | | 210 mg/m$^3$ | 50 ml/m$^3$ |
| UK | | 208 mg/m$^3$ | 50 ml/m$^3$ |

Within the EU, the lowest short-term level (D) amounts to 210 mg/m$^3$ (50 ml/m$^3$) and the highest (F) to 820 mg/m$^3$ (200 ml/m$^3$).

**Table 4.1** lists the relevant exposure data of methyl methacrylate which lead to concern during occupational risk assessment.

Table 4.1 Summary of exposure data

| Area of production and use | Form of exposure | Activity | Duration and frequency | Inhalation exposure | | Dermal exposure | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Shift average [mg/m$^3$] | Method | Level of exposure [mg/cm$^2$/day] | Exposed area [cm$^2$] | Shift average [mg/p/day] | Method |
| Chemical industry | | | | | | | | | |
| 1. MMA production | vapour (liquid) | production, packaging, drumming maintenance | shift length / daily and short term | 18<br>87 [1)] | 90$^{th}$ percentile workpl. measur.<br>short-term (15 min) measur. | 0.1- 1 | 420 (palms of two hands) | 42 – 420 | EASE [2)] |
| 2. PMMA production | vapour (liquid) | polymerisation , maintenance packaging | 4 hours / daily and short term | 28<br>79 [1)] | 90$^{th}$ percentile workpl. measur.<br>short-term(5 min) measur. | 0.1- 1 | 420 (palms of two hands) | 42 – 420 | EASE [2)] |
| 3. Transesterification | vapour (liquid) | production, filling | 4 hours / daily and short term | 10<br>33 [1)] | 90$^{th}$ percentile workpl. measur.<br>short-term (5 min) measur. | 0.1- 1 | 420 (palms of two hands) | 42 – 420 | EASE [2)] |
| 4. Cast sheet production | vapour (liquid) | cast filling, waste handling | 4 hours / daily and short term | 148.5<br>412 [1)] | 90$^{th}$ percentile workpl. measur.<br>short-term (15 min) measur. | 0.1- 1 | 420 (palms of two hands) | 42 – 420 | EASE [2)] |
| 5. Production of adhesives | vapour (liquid) | production, packaging | 4 hours / daily | 57 | 90$^{th}$ percentile workpl. measur. | 0.1- 1 | 420 (palms of two hands) | 42 – 420 | EASE [2)] |
| 6. Production of reactive resins | vapour (liquid) | mixing, packaging, maintenance | 4 hours / daily | 119 | 90$^{th}$ percentile workpl. measur. | 0.1- 1 | 420 (palms of two hands) | 42 – 420 | EASE [2)] |

Table 4.6 continued overleaf

Table 4.6 continued Summary of exposure data

| Area of production and use | Form of exposure | Activity | Duration and frequency | Inhalation exposure | | Dermal exposure | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Shift average [mg/m³] | Method | Level of exposure [mg/cm²/day] | Exposed area [cm²] | Shift average [mg/p/day] | Method |
| Industrial area | | | | | | | | | |
| 7. Production of adhesives, casting resins and floor coating materials | | filling, mixing, cleaning | 4 hours / daily (assumed) | 21 – 105 (with LEV)<br>210 – 420 (without LEV) | EASE<br>EASE | 0.1 – 1 | 420 (palms of two hands) | 42 – 420 | EASE |
| 8. Production of paints and varnish | vapour (liquid) | filling sampling mixing | no information / daily | 146 (with LEV)<br>120 (without LEV) | 95th percentile workpl. measur.“ | 0.1 – 1 | 420 (palms of two hands) | 42 – 420 | EASE |
| 9. Use of adhesives in plastics, electronics and glass industry (60 % MMA) | vapour (liquid) | mixing bonding coating | shift length / daily (assumed) | 83 (with LEV)<br>132 (without LEV) | 95th percentile workpl. measur. “ | 0.06 – 0.6 | 210 (fingers) | 12.6 – 126 | EASE |
| Skilled trade area | | | | | | | | | |
| 10. Use of adhesives (bonding small areas) (60 % MMA) | vapour (liquid) | mixing, coating, bonding | shorter than shift length, not daily (assumed) | 11 | 50 % percentile [3]) workpl. measur. | 0.06 – 0.6 | 210 (fingers) | 12.6 – 126 | EASE |
| 11. Floor coating (20 % MMA) | vapour (liquid) | Priming, transfer, mixing, covering, sealing | shift length / not daily | 1,045 | 95 % percentile workpl. measur. | 0.2 – 1 | 840 (hands) | 168 – 840 | EASE |

Table 4.6 continued overleaf

Table 4.6 continued Summary of exposure data

| Area of production and use | Form of exposure | Activity | Duration and frequency | Inhalation exposure | | Dermal exposure | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Shift average [mg/m³] | Method | Level of exposure [mg/cm²/day] | Exposed area [cm²] | Shift average [mg/p/day] | Method |
| Use of casting resins | | | | | | | | | |
| 12. Medical applications | vapour (liquid) | filling, mixing, applicating | about 2 h / daily (assumed) and short term | 4<br>420 [6)] | literature data<br>short-term,(10 min) measur. | 0 – 0.08 | 210 (fingers) | 0 – 16.8 | EASE |
| 13. Orthopaedic workshops | vapour (liquid) | filling, mixing, applicating | shift length / daily | 61 (with LEV)<br>187 (without LEV) | expert judg. [4)]<br>expert judg. [4)] | 0.08 – 0.8 | 420 (palms of two hands) | 34 – 336 | EASE |
| 14. Dental laboratories and surgeries | vapour (liquid) | filling mixing applicating | about 2 h / daily<br>short term<br>about 2 h / daily<br>short term | 6 (with LEV)<br>42 (with LEV)<br>110 (without LEV)<br>600 (without LEV) | expert judg. [4)]<br>short-term (10 min) measurement<br>expert judg. [4)]<br>short-term (10 min) measurement | 0.08 – 0.8 | 50 (fingertips) | 4 – 40 | EASE |
| 15. Manufacturing of lenses | vapour (liquid) | filling mixing applicating | no information / not daily | 4.2 – 42 | literature data | 0.08 – 0.8 | 50 (fingertips) | 4 – 40 | exp. judg. analogous to dental |
| 16. Ornamental decoration | vapour (liquid) | filling mixing applicating | no information / not daily | 83 – 374 | literature data | 0.08 – 0.81 | 420 (palms of two hands) | 34 – 336 | exp. judg. analogous to ortho-paedic |

[1)] short-term concentration, no shift average value
[2)] worst case, immediate skin contact because of unsuitable glove material
[3)] measurement collective comprises bonding large and small areas, for skilled trade sector bonding small areas is assumed
[4)] expert judgement of a reasonable worst case from the given / measured data

#### 4.1.1.2 Consumer exposure

Polymers manufactured with methyl methacrylate as co-monomer are used in consumer products. Using dispersion paints and 2-component adhesives consumers may be exposed only to residual monomers.

- Dispersion paints

  Assuming the use of dispersion paints 6 events/year with 13.6 kg/event results in an average inhalation concentration per event of 2.0 mg/m$^3$. The dermal exposure via skin amounts to ~ 0.4 mg/event, whereas that from vapours (~ 0.19 µg/event) is considered to be negligible. The total internal dose rate is expected to be lower than 0.01 mg/kg bw/d (yearly average).

- 2-component adhesives

  Assuming the appropriate use of the adhesive (1 g of product for 1 hour, 4 events per year) a maximum concentration of 6.8 mg/m$^3$ was estimated using the SCIES model. Taking into consideration that most of the monomeric MMA will polymerise during the use, the residual monomer available for inhalation is much lower. Thus, an acute exposure by inhalation can be neglected.

#### 4.1.1.3 Humans exposed via the Environment

Man can be exposed indirectly to methyl methacrylate via the environment mainly by air and drinking water. An intake of a total daily dose of 0.132 mg/kg bw/d is calculated for the local scenario and of 17 ng/kg bw/d for the regional scenario, respectively.

### 4.1.2 Effects Assessment

Methyl methacrylate (MMA) is rapidly absorbed after oral or inhalatory administration. *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. After inhalation exposure to rats, 10 to 20 % of the substance is deposited in the upper respiratory tract where it is metabolised. Activities of local tissue esterases of the nasal epithelial cells may be lower in man than in rodents.

Toxicokinetics seems to be similar in humans and experimental animals. After arthroplasty using methyl methacrylate-based cements, exhalation of unchanged ester occurs to a greater extent than after i.v., i.p. or oral administration. After oral or parenteral administration methyl methacrylate is further metabolised by physiological pathways with the majority of the administered dose being exhaled as $CO_2$. Conjugation with GSH or NPSH plays a minor role in methyl methacrylate metabolism and only occurs at high tissue concentrations.

Acute toxicity of methyl methacrylate by the oral, dermal, and inhalative routes is low as judged by several reported tests with different species: The oral $LD_{50}$ for rats, mice, and rabbits is found to exceed 5,000 mg/kg body weight. Acute inhalation toxicity for rats and mice is described by $LC_{50}$ values of > 25 mg/l/4 hours. Acute dermal toxicity is reported for rabbits to exceed 5,000 mg/kg.

Skin and respiratory irritation are reported for subjects exposed to monomer methyl methacrylate. The substance has been shown to produce severe skin irritation when tested undiluted on rabbits skin using a 4-hour and up to a 24-hour exposure period. There are indications from studies in animals that methyl methacrylate can be irritating to the respiratory system. In contact with eyes methyl methacrylate has shown to produce only weak irritation of the conjunctivae. The available data indicate that MMA is not corrosive to skin or eyes. Methyl methacrylate is classified as irritating to respiratory system and to the skin (R 37/38).

There are numerous reports on skin sensitisation in certain occupational environments, where frequent and prolonged unprotected skin contact with preparations containing monomeric MMA was common practice. In the literature, cases of sensitisation of patients with implanted acrylic bone cement, of patients with hearing aids and of persons using synthetic fingernails have been reported. In skin sensitisation studies, guinea pigs showed a positive sensitisation rate. It was concluded that methyl methacrylate had a moderate to strong sensitising potential in experimental animals**.** Methyl methacrylate is classified as R 43 (May cause sensitisation by skin contact).

A small number of case studies have attempted to link MMA exposure with occupational asthma. Authors reported only immediate responses which were most likely due to an airways irritation. While an immunological mechanism may be deduced in a few cases, the majority of cases do not seem to indicate a mechanism resulting in respiratory sensitisation, but due to irritative reactions. It was concluded that there was no convincing evidence that methyl methacrylate was a respiratory sensitiser in humans. Thus, the R-phrase R 42 is not warranted, however, possible non-specific asthmatic responses due to respiratory tract irritation cannot be excluded and labelling with R 37 is sufficient for the protection of humans.

Assessment of the available animal toxicological data indicates that the lead effect caused by methyl methacrylate is a degeneration of the olfactory region of the nose being the most sensitive target tissue. For this effect, a NOAEC of 104 mg/m$^3$ (25 ppm) in a two-year inhalation study in rats was identified but only slight effects on the olfactory tissues have been observed at 416 mg/m$^3$ (100 ppm). The animal data showing degeneration / atrophy / replacement of the olfactory epithelium are considered to be relevant for predicting possible health effects on humans.

The most sensitive adverse effect was lower final body weights in rats at MMA doses of 400 ppm and higher and in mice at 500 ppm and higher. In subchronic inhalation studies, systemic toxic effects were seen in rats at doses > 1,000 ppm, respectively in mice at doses > 500 ppm including degenerative and necrotic lesions in liver, kidney, brain, and atrophic changes in spleen and bone marrow. These effects were not seen in chronic studies up to 1,000 ppm. Higher mortality rates were seen in rats subchronically exposed to high doses of MMA (>2,000 ppm), however early deaths in mice were seen in a subacute study at doses of 500 ppm and higher. Oral administration to rats resulted in a NOAEL of 200 mg/kg bw/d.

*In vitro* MMA has the potential for induction of mutagenic effects, especially clastogenicity, however, this potential seems to be limited to high doses with strong toxic effects. Furthermore, the negative *in vivo* micronucleus test and the negative dominant lethal assay indicate that this potential is probably not expressed *in vivo*.

There is no relevant concern on carcinogenicity in humans and animals. Epidemiology data on increased tumour rates in exposed cohorts were of limited reliability and cannot be related to MMA as the solely causal agent. Therefore there are no reasons to assume that MMA should be considered to be carcinogenic in humans.

The available human data on sexual disorders in male and female workers are not considered for risk assessment of reproductive toxicity due to the uncertain validity of these studies. Definite assessment of possible impairment of fertility will be provided from a 2-generation inhalation study planned in the USA for the near future. At present data of limited value from a dominant lethal study with short-term inhalation exposure are available. With this study design methyl methacrylate did not reveal an effect on male fertility in mice when animals had been exposed to up to 9,000 ppm for a period of 5 days before mating.

From the available developmental toxicity investigations, including an inhalation study according to OECD Guideline 414, no teratogenicity, embryotoxicity or fetotoxicity has been observed at exposure levels up to and including 2,028 ppm (8,425 mg/m$^3$). The studies using the intraperitoneal route of administration that produced some inconsistent results, are of questionable significance.

### 4.1.3 Risk Characterisation

#### 4.1.3.1 Workers

##### 4.1.3.1.1 General remarks on calculations and extrapolations relevant for the workplace risk assessment

The toxicity profile of methyl methacrylate is mainly determined by its tissue damaging properties at the site of entry. The concentration-dependent severity of skin and airways irritation is thus the main subject of quantitative evaluation during risk assessment at the workplace.

For methyl methacrylate short- and long-term inhalative data from rats and mice are available. Thus data adjustment for the purposes of workplace risk assessment concentrates on species extrapolation from animal data to humans. One main discussion point in the past addressed the question whether rats were more sensitive to lesions in the olfactory region of the nose than humans according to species differences in site-specific metabolic capacity and local air-flow characteristics.

For methyl methacrylate a PBPK-model was developed, which allows to address local concentrations in the nose of different species but until now the model is not sufficiently validated for a founded quantification of species differences between rats and humans. For the time being data from rat inhalative studies are thus judged to be relevant for humans. This includes systemic toxicity as well as local effects. Calculation of MOS values therefore does not include species-specific adjustment factors.

Margin of Safety (MOS) values concerning inhalation toxicity are calculated by directly using experimental data. Nevertheless they can be considered as adjusted to humans.

##### 4.1.3.1.2 Occupational risk assessment

Inhalation of vapour and skin exposure are the relevant routes of exposure at workplaces.

This report concentrates on the main points of concern with regard to the risk characterisation at workplaces.

Irritation/Corrosivity

*Inhalation*

From human case reports, it is demonstrated that acute occupational exposure to high air concentrations of methyl methacrylate might result in signs of airway irritation. An air concentration without irritating effects cannot be derived from this data.

In rats single inhalation exposures to 410 mg/m$^3$ (100 ppm) for 2 or more hours resulted in irritating effects in the respiratory tract. In this acute study a level without effects was not identified, but studies with repeated application indicate that the irritation threshold for short-term exposure does not significantly differ from that for long-term exposure. Therefore the chronic irritation threshold of 25 ppm (100 mg/m³) is used as the NAEC for the purpose of risk assessment.

From the exposure assessment several scenarios with short-term inhalation are identified (**Table 4.1**) which are compared to the NAEC. In addition exposure situations which are of longer duration throughout a shift but do not occur daily are evaluated.

In each case that exposure levels exceed the inhalation threshold, resulting in MOS values below 1 acute respiratory irritation is anticipated to occur. Because of sufficient information on dose-response-relationship MOS values greater than 1 are not considered of concern (see Section *Repeated dose toxicity, inhalation).*

For the evaluation of risks by acute irritation scenarios with long-term repeated exposures are equally relevant. The evaluation of respiratory irritation for these scenarios is explicitly addressed in the Section *Repeated dose toxicity, inhalation.* Consequently conclusion (iii) concerning acute respiratory irritation additionally applies for all scenarios that come up with conclusion (iii) for *Repeated dose toxicity, inhalation*. Exposure scenarios which give rise to conclusion (iii) are listed below (**conclusion (iii)** applies to scenarios 4, 6, 7 without LEV, 8 with and without LEV, 9 without LEV, 11, 12, 13 without LEV, 14 without LEV, 16; see **Table 4.2**).

**Conclusion (iii)** There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Sensitisation

*Dermal*

MMA may cause sensitisation by skin contact. This assessment is based on experimental animal data and supported by human experience. The data do not allow to estimate sensitisation potency, thus the concentration of a dilution without sensitising properties cannot be identified, but it is known by the nature of the effect that even low exposures might lead to sensitisation.

According to the concentration limit for classification and labelling it is assumed for risk assessment purposes that preparations containing ≥ 1 % MMA are sensitising to human skin.

At the listed workplaces (see **Table 4.1***)* relevant dermal exposure cannot be excluded thus rising the possibility of skin sensitisation by occupational exposure against concentrated MMA or preparations containing ≥ 1 % MMA.

Allergic contact dermatitis is considered to be a severe health problem. For MMA case reports of skin sensitisation underline the fact that risk reduction measures beyond those already applied have to be considered (**conclusion (iii)** applies to scenarios 1-16).

Repeated dose toxicity

*Inhalation, local effects*

For the assessment animal and human data are available.

The primary effect in experimental animals is respiratory tract irritation and degeneration, the olfactory epithelium of the nasal cavity being the most sensitive target tissue. Comparison of the subacute and chronic rat inhalation studies with methyl methacrylate supports the conclusion that long-term inhalation leads to an increase of multiplicity of lesions and locations affected, however the respiratory tract irritation threshold does not change with duration of exposure.

In a 2-year study in rats, a NOAEC of 25 ppm (100 mg/m$^3$) was established for nasal irritation, only slight adverse effects were observed at 100 ppm (410 mg/m$^3$). There were no experimental exposure levels between 25 and 100 ppm and therefore it is impossible to be more precise.

The main problem in methyl methacrylate risk assessment is species extrapolation from rodents to humans. Rodents show a nasal anatomy and respiratory physiology different from humans. These differences will influence the toxicokinetics of substances in the upper respiratory tract. PBPK modelling suggests that humans are less sensitive than rodents. The PBPK data on MMA generated to date are not considered robust enough to be used as a quantitative basis for establishing a human NOEL for nasal effects.

It should be recognised that human studies are available for the specific exposure scenario of acrylic cast sheet production (scenario 4). These worker health data indicate that exposure levels up to 50 ppm MMA are not associated with respiratory symptoms or olfactory dysfunction. Short-term exposure to higher levels of MMA vapour caused increased incidences of cough, throat irritation and mild airway obstruction.

The comparison of the rat and human health data does not point to a substantial difference in species sensitivity. The rat irritation threshold level of 25 ppm or somewhat higher is not contrary to the human evidence indicating no olfactory or respiratory dysfunction up to 50 ppm. Due to the understandable limitations of the human health studies the occurrence of morphological alterations in the upper respiratory tract cannot be excluded with certainty.

The relevance of the human health data is not considered to be sufficient to justify the assumption of an overall human NAEC of 50 ppm. Occupational risk assessment thus relies on an anticipated human NAEC of 25 ppm (100 mg/m³).

The NAEC is compared with the information on long-term inhalation exposure with a daily frequency as indicated in **Table 4.1**. Since there is considerable knowledge on dose-response-relationship of MMA, MOS values greater than 1 are not considered of concern.

There are certain working areas in production and use of MMA where MOS values < 1 indicate concern (**conclusion (iii)** applies to scenarios 4, 6, 7 without LEV, 8 with and without LEV, 9 without LEV, 13 without LEV, 14 without LEV)

*Inhalation, systemic effects*

From repeated inhalation studies in rats and mice the most sensitive toxic effect besides that at the respiratory tract is reported to be dose-dependent growth retardation starting at air concentrations of 400 ppm (1,640 mg/m$^3$) in female rats. Beginning with exposures of 500 ppm for just a few days lethality occurred in mice and at higher air concentration similarly in rats. In other studies however lethality was not observed to the same extent. The NOAEC for systemic effects was estimated to 100 ppm (410 mg/m$^3$).

For risk assessment purposes a systemic NAEC of 100 ppm (410 mg/m$^3$) is anticipated to be relevant for humans. The MOS values for systemic effects by repeated inhalation are calculated. Long-term exposure scenarios are used as outlined in **Table 4.1**. In addition shift average values are considered which occur repeatedly but not every day. Assessment of these scenarios seems justified with reference to the time schedule of the early deaths in the animal studies.

A discussion could be started about which margin of safety should give rise to concern. For respiratory tract irritation with a NAEC of 25 ppm and marginal local effects starting at 100 ppm a MOS of less than 1 was judged critical. Relative to this, the difference between NAEC and LAEC for systemic toxicity (100 ppm and 400 ppm, respectively) at the first view seems similar, however at air concentrations of 500 ppm early deaths occurred which cannot be excluded to be substance-related and thus have to be taken into consideration. In summary, MOS values below 3 are judged to be of concern for systemic toxicity in occupational risk assessment.

The highest value for chronic inhalation exposure is estimated for floor coating in the skilled trade area with an exposure level of 1,045 mg/m³ resulting in a MOS value of about 0.4 thus clearly leading to concern even though exposure is not reported to be daily (**conclusion (iii)** applies to scenarios 4, 7 without LEV, 8 with LEV, 11, 13 without LEV, 16).

*Combined exposure (dermal and inhalation)*

In addition to route-specific risks, health effects due to combined exposure (inhalation and dermal contact) are to be assessed. There are several workplace activities which lead to combined dermal and inhalation exposure.

The combined risk assessment for inhalation and dermal exposure did not identify exposure scenarios at risk additional to those already determined during inhalation risk assessment (**conclusion (iii)** applies to scenarios 4, 7 without LEV, 8 with LEV, 11, 13 with LEV, 16).

The conclusions of the occupational risk assessment are summarised in **Table 4.2**.

Table 4.2 Conclusions of the occupational risk assessment of MMA [1)]

| No. [2)] | Area of production and use | Specification | Irritation / Corrosivity (inhal.) [3)] | Sensitisation (dermal) | Repeated dose tox. (inhalation local effects) [4)] | Repetaed dose tox. (inhalation systemic effects) [5)] | Repeated dose tox. (combined exposure) [6)] |
|---|---|---|---|---|---|---|---|
| Chemical industry | | | | | | | |
| 1 | MMA production | | | iii | | | |
| 2 | PMMA production | | | iii | | | |
| 3 | Transesterification | | | iii | | | |

Table 4.2 continued overleaf

Table 4.2 continued Conclusions of the occupational risk assessment of MMA

| No. [2] | Area of production and use | Specification | Irritation / Corrosivity (inhal.) [3] | Sensitisation (dermal) | Repeated dose tox. (inhalation local effects) [4] | Repetaed dose tox. (inhalation systemic effects) [5] | Repeated dose tox. (combined exposure) [6] |
|---|---|---|---|---|---|---|---|
| 4 | Cast sheet production | | iii | iii | iii | iii | iii |
| 5 | Production of adhesives | | | iii | | | |
| 6 | Production of reactive resins | | iii | iii | iii | | |
| Industrial area | | | | | | | |
| 7 | Production of adhesives, casting resins and floor coating materials | with LEV | | iii | | | |
| | | without LEV | iii | iii | iii | iii | iii |
| 8 | Production of paints and varnishes | with LEV | iii | iii | iii | iii | iii |
| | | without LEV | iii | iii | iii | | |
| 9 | Use of adhesives in plastics, electronics and glass industry (60% MMA) | with LEV | | iii | | | |
| | | without LEV | iii | iii | iii | | |
| Skilled trade area | | | | | | | |
| 10 | Use of adhesives (bonding small areas) (60% MMA) | | | iii | | | |
| 11 | Floor coating (20% MMA) | | iii | iii | | iii [7] | iii [7] |
| Use of casting resins | | | | | | | |
| 12 | Medical applications | | iii | iii | | | |
| 13 | Orthopaedic workshops | with LEV | | iii | | | |
| | | without LEV | iii | iii | iii | iii | iii |
| 14 | Dental laboratories and surgeries | with LEV | | iii | | | |
| | | without LEV | iii | iii | iii | | |
| 15 | Manufacturing of lenses | | | iii | | | |
| 16 | Ornamental decoration | | iii | iii | | iii [7] | iii [7] |

(1) Blank fields: conclusion (ii) is applied, conclusion (iii): there is a need for limiting the risks; risk reduction measures which are being applied shall be taken into account
(2) Exposure scenarios are listed according to Table 4.1, further information refer to that table
(3) MOS calculated with NAEC = 100 mg/m³, conclusion (iii) for MOS < 1
(4) MOS calculated with NAEC = 100 mg/m³, conclusion (ii) for MOS < 1
(5) MOS calculated with NAEC = 410 mg/m³, conclusion (iii) for MOS < 3
(6) Only systemic effects considered, conclusion (iii) for MOS < 3
(7) Scenarios with repeated but not daily exposure

#### 4.1.3.2 Consumers

Repeated dose toxicity

Following the exposure assessment, the consumer may be exposed to MMA via inhalation, whereas oral and dermal exposure can be neglected. The described human exposure scenarios (dispersion paints and 2-component adhesives) do not represent real chronic scenarios. The NOAEC for local effects of 25 ppm (100 mg/m$^3$) used for the MOS is derived from a two-year inhalation study in rats. Because MMA acts primarily at the nasal cavity, systemic effects have not been considered. Taking into account the worst-case exposure scenarios the margin of safety is judged to be sufficient (**conclusion (ii)**).

**Conclusion (ii)** There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Reproductive toxicity

Following the exposure assessment, the consumer may be mainly exposed to MMA via inhalation. The limited data did not give evidence for adverse effects on fertility. In developmental toxicity studies with methyl methacrylate a specific teratogenic, embryo- or fetotoxic potential could not be revealed. Thus it can be concluded that there is no concern for consumers (**conclusion (ii)**).

#### 4.1.3.3 Humans exposed via the environment

Repeated dose toxicity

For the risk characterisation the total daily intakes for the local scenario and the regional one are compared with an oral NOAEL of 200 mg/kg bw/d which was derived from the two-year drinking water study in rats. The MOS expressed by the magnitude between the calculated exposures and the NOAEL is considered to be sufficient for both scenarios. Thus, the substance is of no concern in relation to humans exposed via the environment (**conclusion (ii)**).

Reproductive toxicity

Following the exposure assessment, there is no evidence for relevant exposure to methyl methacrylate via the local and the regional scenario. The limited data did not give evidence for adverse effects on reproductive organs. In developmental toxicity studies a specific teratogenic, embryo- or fetotoxic potential could not be revealed. Thus it can be concluded that there is no concern in relation humans exposed via the environment (**conclusion (ii)**).

### 4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

**Conclusion (ii)** There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

# 5 RESULTS

## 5.1 ENVIRONMENT

A potential risk to the local aquatic environment is identified from wet polymerisation processes by downstream users of monomeric MMA (default calculations for generic site and four out of 29 known sites).

For the processing sites with PEC/PNEC ratios above one, the PEC calculations are essentially based on default calculations. Therefore, an improvement of exposure data is possible for the wet polymerisation scenarios, e.g. by performing sufficiently detailed effluent measurements. However, keeping in mind reported year-to-year variations of used MMA tonnages by factors of up to 27, it seems questionable if appropriate effluent monitoring data can be achieved with reasonable expenditure of time and money. Reliable data have to meet the requirement of being representative for all possible utilisation factors (related to used MMA tonnage) of a specific site overall capacity for wet polymerisation processes.

On the effects side of the risk assessment data improvement is possible because an assessment factor of 50 is used for the PNEC derivation and it might be possible to lower the PNEC by further testing, i.e. the assessment factor can be lowered to 10 if a long-term fish test is performed. But regarding the locally limited risks that are identified due to the specific scenario this kind of data improvement is not proposed.

It is concluded, that local risk reduction measures have to be considered, if the MMA processing capacity exceeds 5,000 t/a at one single site. It should be noted, that wastewater reutilisation / recycling systems are applied by some known polymerisation sites, avoiding any significant MMA emission to hydrosphere. Sites applying such advanced process engineering would not require further consideration of risk reduction measures.

**Conclusion (iii)** There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (ii) applies for effects on wastewater treatment plants, sediment, atmosphere, soil, and secondary poisoning. It also applies to the aquatic compartment regarding all production sites, the processing scenarios esterification and dry polymerisation, and the relevant use scenarios formulation of paints, private use of paints, and paper recycling.

**Conclusion (ii)** There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

## 5.2 HUMAN HEALTH

### 5.2.1 Human health (toxicity)

#### 5.2.1.1 Workers

There is a need for limiting the risks of MMA concerning skin sensitisation and respiratory tract irritation at several workplaces in the chemical industry, industrial area and skilled trade and during use of casting resins. For certain inhalation exposure scenarios systemic toxicity gives in addition rise to concern. Risk reduction measures at the community level are recommended.

**Conclusion (iii)** There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

#### 5.2.1.2 Consumers

**Conclusion (ii)** There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

#### 5.2.1.3 Humans exposed via the environment

**Conclusion (ii)** There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

### 5.2.2 Human health (risks from physico-chemical properties)

**Conclusion (ii)** There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.