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# SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

**Opinion on the results of the Risk Assessment of:**

## MONOCHLOROACETIC ACID (MCCA)
## HUMAN HEALTH PART

**CAS N° : 79-11-8**

**EINECS N° : 201-178-4**

**Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]**

**Adopted by the CSTEE during the 39th plenary meeting of 10 September 2003**

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[1] Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

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## INTRODUCTION

Monochloroacetic acid (MCAA) is mainly used as chemical intermediate. Together with its sodium salt 170,000 tonnes are annually produced in Europe. Exposure to MCAA is mainly occupational during production, use in synthesis, formulation of paint removers, or use of paint removers. There is very little evidence of any use of MCAA in consumer products.

### Terms of Reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report

2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

## GENERAL COMMENTS

The human health part of the document is of very good quality. The CSTEE is in agreement with all of the risk characterisation conclusions presented in the RAR, although the Committee has not followed the report's use of minimal MOS-values.

## SPECIFIC COMMENTS

### *Exposure assessment*

Three European companies in five different locations produce MCAA and its sodium salt (SCMA). The total EU production of MCAA for 1999 was 145,000 tonnes and for SMCA 26,000 tonnes. There is no import from outside EU, whereas 25,000 tonnes of MCAA and 9,800 tonnes of SMCA are exported. MCAA is chiefly produced either by chlorination of acetic acid or hydrolysis of trichloroethylene. MCAA is mainly used as a chemical intermediate for the synthesis carboxymethylcellulose, crop protection chemicals, plastics, thioglycolic acid, SCMA and other esters and amides. SCMA is chiefly used as a chemical intermediate for the production of amphoteric surfactants, pigments, dyes, printing inks, paints, lacquers and varnishes, some pharmaceuticals and carboxymethylcellulose.

Four major occupational exposure scenarios are described in the RAR: 1) The production of MCAA, 2) use of MCAA in synthesis, 3) formulation of paint removers, and 4) use of paint removers. A typical value for inhalation exposure during production based on measured data is 0.1 mg/m$^3$, whereas a reasonable worst case is described as 1 mg/mg$^3$, and a possible short-term value of 2.5 mg/m$^3$ may be reached. Applying proper protective equipment, the worst case and short-term exposure level may be reduced to 0.1 and 0.25 mg/mg$^3$, respectively. Production is a continuous process, the number of persons involved is estimated to be 200-300. Dermal exposure is considered to occur only accidentally.

Modelling of inhalation exposure from solid MCAA during synthesis is estimated to be 2 mg/m$^3$ as a typical value and 5 mg/m$^3$ as a worst case value, these levels can be reduced to 10% by the use of protective equipment. The corresponding values when handling MCAA in liquid form is estimated to 2.0 mg/m$^3$ and 11.8 mg/m$^3$, respectively. Including a reduction of 90% due to protective equipment and duration of two hours per day, typical and worst case full shift exposure is 0.05 and 0.3 mg/m$^3$, respectively. Dermal exposure is considered to occur only accidentally.

Modelling of MCAA inhalation exposure during formulation of paint removers has been calculated to 0.2 mg/m$^3$ (typical)-1.2 mg/m$^3$ (worst case). Assuming a duration of one hour per day and use of protective equipment, this leads to a full-shift worst case level of 0.1 mg/m$^3$ and a typical value of 0.02 mg/m$^3$. Dermal exposure is considered to occur only accidentally.

When MCAA is used as a paint remover, ranges of exposure have been estimated to 20 (typical)-39 (worst case) mg/m$^3$, and 2.0-3.9 mg/m$^3$, respectively, when protective equipment is used. Dermal exposure for single contact has been estimated to 3000 mg/day, 300 mg/day when dermal protective gloves are used.

With respect to consumer exposure, industry does not support applications of MCAA which are not related to the use as an intermediate. However, some consumer use has been identified, but this can be considered mostly as negligible. One product in Sweden was identified that contains 0.04% SMCA in a hand-wash detergent. If this is assumed to be used once daily, the total exposure will be 0.034 mg/day. The RAR states that a potential use of MCAA as a paint stripper by consumers cannot be substantiated.

There is potential indirect exposure to MCAA via air, leaf crops (via accumulated deposits from air) or drinking water (either surface water or groundwater) both at the local and the regional scale. The measured or calculated data results in doses in the low microgram per kg per day-range or lower.

## Effects assessment

### *Toxicokinetics and biochemical effects.*

No information is available on the toxicokinetics of MCAA after inhalation exposure. After oral exposure of rats to MCAA, at least 90% were absorbed from the gastro-intestinal tract. Rapid absorption via the skin is indicated, but no dermal absorption rate or percentage could be established. After intravenous administration of radiolabelled MCAA in rats, the radiolabel was rapidly eliminated, mainly via urine (90% of the dose within 24 hours). A major route of metabolism via glutathione conjugation is indicated, with initial formation of S-carboxymethylglutathione which is converted to S-carboxymethylcysteine, part of which is further metabolised to thiodiacetic acid. MCAA can inhibit a number of different enzymes including aconitase (possibly involved in the development of cardiomyopathy) and pyruvate carboxylase (inhibition of gluconeogenesis). MCAA

binds covalently to glutathione transferase inhibiting its own metabolism. High doses of MCAA can lead to alkylation of total sulfhydryls in rat liver and kidney.

***Acute toxicity***

Following accidental dermal exposure to molten/liquid MCAA, fatal and non-fatal cases of severe acute systemic intoxication in workers have been reported. MCAA fulfils the classification criteria for toxic by inhalation, in contact with skin and if swallowed (inducing acute neurotoxic effects), although the studies underlying data for classification presumably were not performed to accepted test guidelines.

***Irritation/corrosion***

MCAA is considered to be a strong corrosive agent to the skin and can induce serious damage to eyes and skin. Only limited information is available on the respiratory tract irritating effects of MCAA. On study reports a threshold for respiratory irritation to 5.7 mg/m$^3$ in humans.

***Sensitisation***

There are no acceptable animal sensitisation studies with MCAA available. However, based on the wide practical experience with the substance and the absence of any case reports of allergy, the RAR considers that further testing is not required. Also, testing for sensitisation potential will be hampered by the corrosive properties of the substance. There are no indications available with respect to any respiratory allergic potential.

***Repeated-dose toxicity***

In a 13-week repeat-dose gavage study in rats, a NOAEL for MCAA could not be derived since there were changes in the weight of the heart, liver and kidneys, and in clinical chemistry values at the lowest dose level tested (30 mg/kg bw/day). Dose-related cardiomyopathy was found in both sexes at 60 mg/kg bw/day and above. In mice exposed during 13 weeks by gavage, a NOAEL was identified at 100 mg/kg bw/day (increased liver weight and decreased serum cholinesterase activity as critical endpoints). A NOAEL of 3.5 mg/kg bw/day was derived from a 2-year drinking water study in rats.

***Genotoxicity***

MCAA does not induce point mutations or primary DNA damage in bacteria, nor chromosome aberrations or DNA strand breaks in mammalian cells *in vitro*. Some positive TK$^+$/TK$^-$ assays were reported with mammalian cells. *In vivo* oral administration did not induce DNA strand breaks in spleen, liver, stomach or duodenum of mice or in liver of rats. MCAA is reported to induce sperm abnormalities and chromosome aberrations in bone marrow in mice, however, the description of these studies is limited (only reported in an abstract). MCAA had no genotoxic potential in a germ cell mutation assay with *Drosophila melanogaster*. Based on the available data, the RAR concludes that MCAA is not a genotoxic compound.

***Carcinogenicity***

*Human carcinogenicity data*

Data on carcinogenicity in humans due to exposure to MCAA are not available.

*Animal carcinogenicity data*

The carcinogenic potential of MCAA was studied in oral studies with rats and mice by gavage, in male rats by administration in drinking water, in female mice by skin contact. The RAR concludes that there is no evidence for carcinogenic activity of MCAA.

### *Toxicity for reproduction*

*Reproductive toxicity*

A fertility study with MCAA was not available. No treatment-related effects were found on the reproductive organs of both male and female mice and rats in 13-16 days gavage studies (rats up to 150 mg/kg bw/day, mice up to 240 mg/kg bw/day) or in 103-week gavage studies (rats up to 30 mg/kg bw/day, mice up to 100 mg/kg bw/day), or in rats receiving MCAA in drinking water during 104 weeks (up to 1.1 g/l).

*Developmental toxicity*

Data on toxicity for reproduction in humans were not available. In a limited study examining possible cardiac teratogenicity in rats, no effects were seen at a dose of 193 mg/kg bw/day. However, cardiovascular effects have been described, although a complete study report is not available. There are also indications of developmental toxicity from a *Hydra* regeneration assay and a whole mouse embryo culture test. The RAR concludes that a developmental toxicity study should be performed, and based on the outcome of this study, a fertility study may be considered.

## Risk characterisation

### *Workers*

The RAR has compared the various MCAA exposures in occupational settings with "minimal MOS-values" presented in Annex 5. These minimal MOS-values and their corresponding assessment (uncertainty) factors are taken from a TNO-report (Hakkert et al., 1996). The minimal MOS-values for acute toxicity, >>9 for inhalation exposure and >>22 for dermal exposure are derived from inhalation LC50- and dermal LD50-values, respectively. For chronic dermal, chronic inhalation and combined inhalation and dermal exposure, a minimal MOS (overall assessment factor) of 40 is used. Here the RAR uses an interspecies assessment factor of 12 and an intraspecies factor of 3. In addition, a route-to-route extrapolation factor of 1.1 is used, based on a measured oral absorption value of 90% and a default inhalation and dermal absorption of 100%. The intraspecies factor of 3 rather than the conventional default factor 10 is based on a presumed smaller interindividual variation in workers than in the general population. The CSTEE has in its evaluation directly used the calculated MOS-values, rather than comparing these with the proposed minimal MOS-values in the RAR.

### *Acute toxicity*

For the dermal route, estimated worker exposures have been compared with a dermal LD50 value in rabbits of <400 mg/kg bw for pure MCAA. Since the dermal exposure in use scenarios 1, 2 and 3 is considered to occur only accidentally, the RAR finds ***conclusion ii*** justifiable. For use of paint removers, MOS values between the LD50 value and systemic doses were calculated to be between <9.3 and <93, therefore a ***conclusion iii*** is drawn. For the inhalation route, packing of solids (MOS 180), transfer of molten (MOS 75) and 80% MCAA (MOS 75), use of molten (MOS 150) and 80% MCAA (MOS 150), formulation of paint removers (MOS 200), as well as use of paint removers (with (MOS 46) or without (MOS 4.6) protective equipment), all were considered to

have MOS-values of concern when they were compared with the minimal MOS-value. Thus, ***conclusion iii*** was concluded for these scenarios. The CSTEE supports the conclusions in the RAR with respect to acute toxicity, since the variously estimated exposure levels were related to LC50/LD50-doses, thus requiring a larger MOS than when MOS-values are derived from NOAEL-doses.

***Irritation/corrosion***

When there is dermal exposure during use of paint removers containing MCAA, there is concern for workers with regard to local skin effects when protective gloves are not used (***conclusion iii***). The CSTEE agrees to this. Since eye protection is obligatory for activities where direct handling of MCAA occurs, ***conclusion ii*** is warranted.

***Sensitisation***

Based on wide practical experience with MCAA, there are no concerns for dermal sensitisation effects.

***Repeated-dose toxicity***

For dermal exposure in the use of paint removers-scenario, MOS-values have been calculated to be between 0.08 and 0.8, thus the RAR ***conclusion iii*** is supported when compared with the minimal MOS of 40. With respect to repeated inhalation exposure the following MOS-values were calculated for scenarios below the minimal MOS-value of 40: transfer of molten or 80% MCAA during production, both 20; and use of paint removers without protective equipment 2.5, with 25. Thus, ***conclusion iii*** is presented in the RAR, the CSTEE agrees with this.

***Genotoxicity***

The CSTEE agrees with the conclusion of the RAR that MCAA is not a genotoxic compound.

***Carcinogenicity***

The CSTEE agrees with the RAR that there is no evidence for carcinogenic activity of MCAA.

***Reproductive toxicity***

The CSTEE agrees with the RAR that a full developmental toxicity study should be performed (***conclusion i***). Based on the outcome of this study, a fertility study may be needed. The RAR proposes to put the requirement for a developmental toxicity study 'on hold', waiting the outcome of a Risk Reduction Strategy.

***Consumers***

The hand washing detergent scenario with SMCA was the only relevant risk characterisation scenario for consumers. For this, a daily exposure of $5.6 \times 10^{-4}$ mg/kg bw was calculated, giving a MOS of 6250. The RAR argues for ***conclusion i*** with respect to reproductive toxicity as was done for some worker exposure scenarios, since a full developmental toxicity study is lacking. In principle, this conclusion may be warranted, however, it appears highly unlikely that any developmental toxic effect of MCAA would be so potent as to create a concern (i.e. a NOAEL of <56 μg/kg bw/day).

***Man exposed indirectly via the environment***

MOS-values for inhalation exposure via the environment have been calculated to 2298 and higher, therefore there is no concern for human safety. Daily exposure via drinking water at the local scale related to air emission from one production site, yields a MOS of 44. Consumption of leaf crops contaminated from one processing site gives a MOS of 53. Thus, for both of these scenarios the RAR proposes ***conclusion iii***, the CSTEE is in agreement with this. No health safety concerns are found at the regional scale.

Additional information on the presence of MCAA in the environment related to emission of other chemicals and/or possible natural formation has been requested in the environment part of the RAR. The potential consequences of this for humans indirectly exposed through the environment should therefore be considered.