EUROPEAN COMMISSION
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MONOCHLOROACETIC ACID (MCAA)

CAS No: 79-11-8

EINECS No: 201-178-4

Summary Risk Assessment Report

2005 **Special Publication I.04.221**

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2005

The Netherlands

Rapporteur for the risk assessment of monochloroacetic acid (MCAA) is the Ministry of Housing, Spatial Planning and the Environment (VROM) and the Ministry of Social Affairs and Employment (SZW), in consultation with the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organisation for Applied Scientific Research (TNO) and the National Institute of Public Health and Environment (RIVM), by order of the rapporteur.

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance monochloroacetic acid (MCAA) that has been prepared by The Netherlands 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 comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

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

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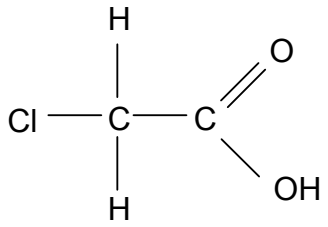
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number:	79-11-8
EINECS Number:	201-178-4
IUPAC Name:	2-Chloro-ethanoic acid
Synonyms:	α-Chloroacetic acid, Chloressigsauer, Chloroethanoic acid, chlorethansauere, MCA, MKhUK, Monochloressigsauere, Monochloroacetic acid, Monochloroethanoic acid, Chloroacetic acid, MCAA
Molecular weight:	94.5 g/mol
Molecular formula:	$C_2H_3ClO_2$

Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity:	>99%	
Impurities:	dichloroacetic acid (Cas no. 79-43-6)	<0.3%
	acetic acid (Cas no. 64-19-7)	<0.2%
	Fe (Cas no. 7439-89-6)	<0.0005%
	Pb (Cas no. 7439-92-1)	<0.0001%
Additives:	none	

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value
Physical state	solid
Melting point	61.5-62.3°C, 120°C (SMCA)
Boiling point	189°C at 1,013 hPa
Relative density	1,580 kg/m^3 at 20°C
Vapour pressure	<1 hPa at 20°C, 8.7 Pa at 25°C, 11 hPa at 80°C
Water solubility	4210 g/l at 20°C, 820 g/l (SMCA)
pH in water	3.2 (100 mg/l)
Granulometry	MCAA flakes: 8.5% <1,000 µm 18.6% 1,000-3,150 µm 42.5% 3,150-6,300 µm 23.9% 6,300-10,000 µm 6.5% >10,000 µm
Dissociation constant (pKa)	2.85 at 25°C
Flash point	126°C (melt), not applicable in view of aggregation point
Autoflammability temperature	460-470°C
Flammability	not flammable, according to EU-guideline
Explosive properties	not explosive
Oxidising properties	not oxidising
Solubilty in other solvents	soluble in ethanol, benzene, chloroform, ether
Partition coefficient n-octanol/water (log value)	≤0.2 (measured and calculated)
Surface tension	35.2 mN/m at 100°C

1.4 CLASSIFICATION AND LABELLING

The data submitted do fulfil the basic requirements as specified in Annex VIIA of Directive 67/548/EEC. With regard to the physico-chemical properties, classification and labelling is not indicated.

Current Classification according to Annex 1:

T, N, R25-34-50, S23-37-45-61

In its meeting of May, 2003 the Commission Working Group on the Classification of Dangerous Substances decided that MCAA should be classified and labelled as follows:

Classification

T; R23/24/25	Toxic by inhalation, in contact with skin and if swallowed
C; R 34	Causes burns
N; R50	Very toxic to aquatic organisms

Specific concentration limits:

C≥ 25%:	T, N ; R23/24/25-34-50
10%≤C<25%:	C ; R20/21/22-34
5%≤C<10%:	Xn ; R20/21/22-36/37/38
3%≤C<5%:	Xn ; R20/21/22

Labelling

T; N
R: 23/24/25-34-50
S: (1/2)-26-36/37/39-45-61-63

2 GENERAL INFORMATION ON EXPOSURE

Production

The chemical industry can both produce monochloroacetic acid (hereafter referred to as MCAA) and the sodium salt of monochloroacetic acid (SMCA). SMCA is obtained by converting MCAA with caustic soda.

In the European Union MCAA is produced by three companies at five different locations. Two companies have each two production locations. The total EU production volume of MCAA for 1999 was 145,000 tonnes/annum. According the industry there was no import from outside the EU in 1999. The estimated total export was about 25,000 tonnes/annum. The use volume, i.e. production and import minus export, within the EU was therefore about 120,000 tonnes/annum.

Three production companies convert MCAA into the salt. For 1999 the SMCA production was 26,000 tonnes/annum. The estimated total export of SMCA was about 9,800 tonnes/annum. The use volume, i.e. production and import minus export, within the EU was therefore about 16,000 tonnes/annum.

Uses

MCAA is mainly used as a chemical intermediate for the synthesis of other products. Major applications of MCAA are related to the production of:

- carboxymethylcellulose (CMC), carboxymethyl starch
- crop protection chemicals (like 2,4-D and MCPA)
- plastics
- thioglycol acid (TGA)
- sodium salt of MCAA
- other products such as esters and amides

SMCA is mainly used as a chemical intermediate for the production of:

- amphoteric surfactants (e.g. shampoos and industrial cleaning agents);
- pigments;
- dyes (indigo);
- printing inks, paints, lacquers and varnishes;
- pharmaceuticals (caffeine, vitamin B6);
- CMC.

A number of minor applications of MCAA and SMCA occur as well.

Some quantitative data are available on the distribution of the various downstream uses of MCAA and SMCA as a chemical intermediate. No figures are available on the use volumes of minor applications.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General Discussion

MCAA/SMCA may be released by industry into the environment during its production and processing as intermediate. The emission of MCAA/SMCA will occur via air and water. However, in view of the low vapour pressure and high water solubility, MCAA/SMCA is expected to end up mainly in the water compartment.

MCAA may also be released by unintentional sources. For instance, MCAA can be formed (indirectly) in the atmosphere from industrial chlorinated chemicals. Besides anthropogenic sources, MCAA is also expected to be formed *de novo* in the environment.

General characteristics of MCAA which are relevant for the exposure assessment are given below.

General

MCAA has a pKa of 2.86 at 25°C and therefore the substance will be completely ionised at environmentally relevant pHs. The log K_{ow} for MCAA and SMCA is 0.22 and –3.47, respectively. As MCAA is completely ionised at environmental pHs the physico-chemical data of water dissolved SMCA will be used for the risk assessment. The log K_{ow} of -1 is considered not to be valid for estimating the bioconcentration factors. Therefore, no risk assessment is made for secondary poisoning and certain indirect exposure routes for humans.

Degradation

Both MCAA and SMCA hydrolyse very slowly. Direct photolysis of MCAA in air and water is not expected, because it does not absorb UV radiation above 290 nm. The photo-oxidation rate of MCAA with OH-radicals was estimated with a QSAR (DT50 of 58 days). The direct photolysis competes with the dissolution of MCAA in atmosphere and further rain out. The rain out of MCAA was estimated to take about 10 days. Dry deposition of MCAA from air can also take place.

On the basis of a number of standardised biodegradation tests it can be concluded that MCAA/SMCA is readily degradable. A biodegradation rate constant of 1 h^{-1} or DT50 of 0.0289 days (TGD-default) is used for the model calculations for the Waste Water Treatment Plant (WWTP). This value was overwritten, however, for all MCAA/SCMA production and processing sites based on submitted high measured removal rates. The suggested default half-life of 15 days for biodegradation in surface water for ready biodegradable substances according to the TGD (1996) is used (only relevant for the regional exposure assessment).

For degradation in soil, a default DT50 value (TGD) of 30 days is used. This default biodegradation rate for soil is at the upper end of an experimentally derived DT50 range (3 to 33 days).

Distribution

According to the TGD (1996) a Henry's Law constants of $1.9 \cdot 10^{-4}$ and $1.2 \cdot 10^{-3}$ Pa. m^3/mol at 20°C can be calculated for MCAA and SMCA, respectively. The calculated Henry's Law

constants indicate that volatilisation of MCAA/SMCA from surface water will not occur at significant levels.

With regard to the adsorption of MCAA and SMCA in a soil-water system, organic-water partition coefficients (K_{oc}) of 4 and 3.16 have been calculated using the QSAR for organic acids and non-hydrophobics, respectively. Adsorption to soil is thus not expected to occur.

On the basis of the water solubility of MCAA/SMCA and the low log K_{ow}, no bioaccumulation is expected (see above).

3.1.2 PECs at production and processing

The environmental exposure assessment of MCAA will be based on the expected releases of the substance during the following life cycle stages:

The environmental exposure assessment of MCAA will be based on the expected releases of the substance during the following life cycle stages:

I. Production, including captive use
II. Processing – chemical intermediates (off-site)
III. Formation of MCAA as by-product (indirect via industrial sources)
IV. Non industrial sources/natural occurrence

For production and use local PECs were calculated based on the TGD principles using both default information and site-specific data. In addition to these estimated PECs also a number of local and regional monitoring data are available for MCAA in various environmental compartments (mainly (rain) water and soil).

The regional PEC for surface water is calculated to be 68 ng/l. This value falls within the range of the available measured regional background data as found in Switzerland, Germany and Sweden (20-400 ng/l). The monitoring data, however, comprise both the natural background sources of MCAA, the anthropogenic (non MCAA related) sources and the emissions from MCAA producers and users. The contribution of MCAA producers and users to the background is expected to be negligible (see Section 3.3).

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3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

The available short-term EC50-values and long-term NOEC-values for daphnia and fish in neutralised medium, range between 10-1,000 mg/l. The short and long-term results for algae are all < 1 mg/l, except for one EC50-value. Therefore algae are considered the most sensitive species when compared to fish and invertebrates.

The lowest long-term test result is the NOEC of 5.8 µg/l for *S. subspicatus*. Two NOECs for additional algae species support the lowest obtained NOEC value of 5.8 µg/l. The NOEC for *S. subspicatus* of 5.8 µg/l is therefore used for the derivation of the PNEC. An assessment factor of 10 is applied, because long-term studies are available for three different trophic levels. This leads to a $PNEC_{surface\ water}$ of 0.58 µg/l. In addition to the laboratory data also an *in situ* aquatic mesocosm study with MCAA was available. The results of this mesocosm study can, however, not be used to modify the PNEC of 0.58 µg/l. This is because planktonic green algae, being the most sensitive group from the laboratory studies, were not taken into account.

Since no data on sediment-dwelling organisms are available, the equilibrium partitioning method is used to derive the $PNEC_{sediment}$. The $PNEC_{sediment}$ is calculated to be 0.4 µg/kg wwt.

A number of short-term toxicity studies for MCAA with bacteria and protozoa are available. The results show that bacteria are less sensitive than protozoa. The lowest observed IC50 of 16 mg/l for protozoa will be used for derivation of the $PNEC_{micro\text{-}organisms}$. An assessment factor of 10 is considered to be appropriate, resulting in a PNEC for micro-organisms of 1.6 mg/l

Terrestrial compartment

A seedling emergence/growth test with three plant species is the only terrestrial ecotoxicity test suitable for deriving a $PNEC_{terrestrial}$. This test resulted in a 21-day NOEC of 3.2 mg/kg dwt. A time average NOEC of 0.6 mg/kg dwt (assuming a first order rate degradation during the 21-day experiment) can be estimated based on the neutral soil DT50 value of 66 hours. Both values are used in the PNEC derivation (and risk characterisation). The seedling emergence/growth test can be considered as a chronic test which would result in an assessment factor of 100 following the TGD. This results in PNECs soil of 32 µg/kg dwt and 6 µg/kg dwt (time average).

Atmosphere

No data available.

Non compartment specific effects relevant to the food chain

Bioaccumulation/secondary poisoning is considered not to be relevant for MCAA/SMCA

3.3 RISK CHARACTERISATION

General

Chloroacetates, including monochloroacetates, are found ubiquitously in the environmental compartments. It is expected that the non-industrial formation of MCAA plays an important role here (e.g. chlorination of ethene). The MCAA levels found in surface waters are sometimes rather close (0.45 µg/l) or even slightly above (0.64 µg/l; Japan) the current PNEC

surface water of 0.58 µg/l. MCAA levels in rain water are exceeding this PNEC even in many cases. A comparable, even more pronounced situation occurs for the terrestrial ecosystem, i.e. high measured background data (n.d.-164 µg/kg dwt) in comparison with the PNEC soil (32 µg/kg dwt). It should be stated however that the number of soil monitoring data is very limited compared to the water data.

Table 3.1 presents the local PEC/PNEC ratios for, respectively, the production and processing stages of MCAA. Details will be discussed in this section.

Table 3.1 Local PEC/PNEC ratios

Scenario	$PEC/PNEC_{micro-organisms}$	$PEC/PNEC_{aqua}$	PEC/PNEC soil*
Production/processing site I-A1	< 0.01	0.1	0.1
Production/processing site I-A2	< 0.01	0.1	0.1
Production site I-B1	<0.01	1	0.1
Production site I-B2	< 0.01	0.9	0.4
Production site I-C	18.7	5,250	0.1
Processing sites II (max. value)	0.27	0.7	0.2

* Only PEC/PNEC ratios with the lowest PNEC soil of 6 µg/kg dwt are given.

Aquatic compartment (incl. sediment)

The local PECs in surface water exceed the PNEC surface water for two MCAA production/processing sites (I-B1 and I-C). For one of these sites (I-C) the PEC/PNEC ratio is >1 for the STP as well. Although the PEC/PNEC ratio equals 1 for site I-B1, actual monitoring data in the vicinity of site I-B1 are found to exceed the present PNC for surface water. For both sites industry has indicated that the efficiency of the local WWTP will be improved, but up to now no data are available to verify this statement (**conclusion (iii)**). For the remaining scenarios, including the regional one, the PEC/PNEC ratios are below 1 (**conclusion (ii)**).

Terrestrial compartment

For soil in all exposure scenarios the PEC/PNEC is <1, irrespective of the selected PNEC **(conclusion (ii)**). This conclusion is supported by available measured data for one of the sites.

Measured regional background levels in Sweden were found to be between n.d and 164 µg/kg dwt. This range exceeds the current terrestrial PNEC of 32 µg/kg (and 6 µg/kg). More information is needed on the split-up between natural and anthropogenic emission sources of these background levels before a final conclusion about the potential risk to the terrestrial ecosystem can be drawn (**conclusion (i)**). It is emphasised that this **Conclusion (i)** is not related to the industrial production and use of MCAA (unintentional sources).

Atmosphere

As no PNEC for air could be derived, no risk characterisation is carried for the atmospheric compartment. Acidification and ozone depletion are not considered relevant for MCAA/SMCA.

Non compartment specific effects relevant to the food chain

Not relevant. See Section 3.3.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

Monochloroacetic acid (MCAA) as a raw material is mainly used in the production of carboxymethylcellulose, crop protection chemicals, thioglycol acid, and a variety of other products. MCAA is also used as a component in paint removal baths. There are no indications that MCAA today is still an ingredient of graffiti removers.

MCAA is marketed in various forms: as a solid (powder or flakes), in molten form (kept at a temperature > 80°C) or as 80% dilution in water. For these forms of packaging, exposure estimates are made.

Occupational exposure may occur in industries where MCAA is produced or is used as a raw material or as an intermediate. Routes of exposure are by inhalation and by dermal contact. Ocular exposure due to hand-eye contact is not very likely because of the corrosive nature of the substance and will perhaps only occur during incidents. The relevant populations exposed are workers in the chemical industry, workers active in processing MCAA and workers formulating and using paint removal products.

From the uses of MCAA as mentioned the following scenarios for exposure were discussed:

Scenario 1: The production of MCAA

Relevant activities to exposure during production are routine procedures in the production process, cleaning and maintenance and packaging of the product. Exposure may occur by accidental projection of the substance during the process (risk of skin contact). During packaging there may be exposure to dust (risk of skin contact and inhalation). For exposure during production, sufficient data were available for an estimate of inhalation exposure. During handling (packaging) of MCAA as a solid, the estimates of analogous substances were used, together with the few measured data on ‘packaging’. For handling MCAA in liquid form (molten or as 80% solution), the lower side of the estimated range of the EASE model was taken as a typical value. The upper value was taken as a worst case approach. Dermal exposure in this scenario is considered to occur only accidentally.

Scenario 2: The use of MCAA in synthesis

MCAA may be used as a raw material or as an intermediate for the production of other products. It is assumed that MCAA will be fully converted into another chemical substance. Exposure to MCAA, in the commercially available forms, is possible when the substance is added to a reaction mixture. For the estimate of inhalation exposure, the ranges of the estimate by the EASE model were used for risk characterisation. The lower value of the range was taken as typical value and the upper value was taken as worst case.

In handling MCAA in the liquid form, the same procedure was followed: the lower value of the range was used as a typical value and the upper range value as a reasonable worst case. Dermal exposure in this scenario is considered to occur only accidentally.

Scenario 3: Formulation of paint removers

MCAA is also used in paint stripping baths, in combination with other solvents like methylene chloride and formic acid. Production of paint removers takes place in mixing vessels where the ingredients are added and mixed and then packed into smaller units. Exposure may occur when transfer lines are coupled or de-coupled from the system. Adding MCAA to the mixing system may represent a worst case situation, because then undiluted MCAA is handled. For the estimate of inhalation exposure, the ranges of the estimate by the EASE model were used for risk characterisation. The lower value of the range was used as a typical value and the upper range value as a reasonable worst case.

Dermal exposure in this scenario is considered to occur only accidentally.

Scenario 4: Use of paint removers

The paint stripping solutions, as described under Scenario 3 are used undiluted. The volume of the paint stripping baths may differ, but the baths may be used for large objects. In that kind of use, old layers of paint are removed by dipping the objects by means of a fork-lift truck or a tackle into the solution where it rests for several hours to soak. After that, the objects are sprayed by hand with water under high pressure to remove the dissolved paint, which may result in an aerosol containing the ingredients of the bath. It is assumed that during spraying of the objects with water a dilution factor of 100 is reached. For inhalation exposure, the ranges of the estimate by the EASE model were be used for risk characterisation. The lower value of the range (without use of PPE) was used as a typical value and the upper range value as a reasonable worst case.

Dermal exposure for single contact during spraying of objects to remove the residue paint remover was estimated with the EASE model and a dilution factor.

Table 4.1 Conclusions of the occupational exposure assessment

Scenario	Activity	Frequency days/year	Duration hours/day	Reasonable worst case		Typical concentration		Dermal	
				mg/m^3	Method	mg/m^3	Method	$mg/cm^2/day$	dose (mg/day)
1 Production of MCAA									
- production	Full shift	200-300	6-8	0.1	Measured	0.1*	Measured	n.e.	n.e.
	Short term	200-300	0-0.5	0.25	Measured			n.e.	n.e.
	Cleaning and Maintenance	up to 25	6-8	negl.	EASE	negl.	EASE	n.e.	n.e.
- packaging of solids	Full shift	200-300	6-8	0.32	Analogue	0.16	Analogue	n.e.	n.e.
	Short term	200-300	0-0.5	1.0	Expert			n.e.	n.e.
- transfer of molten MCAA	Full shift	200-300	6-8	1.2	EASE	0.2	EASE	n.e.	n.e.
	Short term	200-300	0-0.5	2.4	Expert			n.e.	n.e.
- transfer of 80% MCAA	full shift	200-300	6-8	1.2	EASE	0.2	EASE	n.e.	n.e.
	short term	200-300	0-0.5	2.4	Expert			n.e.	n.e.
2 Use of MCAA									
- use of solids	full shift	100-200	6-8	0.125	Calculated	0.05	Calculated	n.e.	n.e.
	handling	100-200	1-2	0.5	EASE	0.2	EASE	n.e.	n.e
- use of molten MCAA	full shift	100-200	6-8	0.3	Calculated	0.05	Calculated	n.e.	n.e.
	handling	100-200	1-2	1.2	EASE	0.2	EASE	n.e.	n.e.
- use of 80% MCAA	full shift	100-200	6-8	0.3	Calculated	0.05	Calculated	n.e.	n.e.
	handling	100-200	1-2	1.2	EASE	0.2	EASE	n.e.	n.e.
3 Formulation of paint removers	full shift	1-10	6-8	0.1	Calculated	0.025	Calculated	n.e.	n.e.
	handling	1-10	0-1	0.9	EASE	0.2	EASE	n.e.	n.e.
4 Use of paint removers	full shift	100-200	6-8						
	-without PPE			10	Calculated	5	Calculated	0.15	3000
	-with PPE			1.0	Calculated	0.5	Calculated	0.015	300
	handling	100-200	1-2						
	-without PPE			39	EASE	20	EASE	n.e.	n.e.
	-with PPE			3.9	EASE	2.0	EASE	n.e.	n.e.

Consumer exposure

There is no intentional consumer exposure. Negligible exposure was expected from wart remover, herbicides, amphoteric surfactant and paint strippers as information on the exposure can hardly be substantiated. The use as an anti-microbiological agent in food is not applicable in Europe anymore. One consumer product in Sweden that contained SMCA was in a hand wash detergent. This exposure resulted in 0.0336 mg/day.

Humans exposed via the environment

Local exposure of MCAA to the environment at production and processing sites may occur. For both the local and regional scale, human intake occurs via air, drinking water or leaf crops. Exposure via root crops and cows was considered negligible and could not be calculated, because of the ionising properties of MCAA. On a local scale a production site caused a high intake via drinking water and one processing site caused a high intake via leaf crops. These sites caused the highest total daily intake, 0.0794 and 0.066 mg/kg bw/day, respectively. For the regional scale, the total daily intake was calculated to be $1.41 \cdot 10^{5}$ mg/kg bw/day.

4.1.2 Effects assessment

In the data set animal as well as human studies are available. Most of the studies were not performed according to current standards, and were in some cases not suitable to be used in risk assessment.

After oral exposure of rats to ^{14}C-MCAA at least 90% was absorbed from the gastro-intestinal tract based on the amount excreted in urine in 24 hours. After oral exposure in mice, the absorption from the gastro-intestinal tract amounts ±60% (based on excretion in urine after 72 hours). The toxicity data on inhalation do not give any conclusion on the inhalation absorption rate or percentage. Based on the high toxicity in one inhalation study and the low molecular weight of MCAA, inhalation absorption of 100% is used in the risk characterisation. The toxicity data indicate a rapid absorption via the skin of rats, rabbits, and human. Based on the available data no dermal absorption rate or percentage could be established. Therefore, 100% dermal absorption is assumed in the risk characterisation.

After absorption, the radiolabel was rapidly distributed. The highest concentrations of radiolabel appeared in the intestine, kidneys, and liver. Radiolabel also appeared in the central nervous system and thus passed the blood-brain-barrier. Different doses and exposure routes were tested but did not show any difference in distribution patterns. Repeated exposure to high doses of ^{14}C-MCAA resulted in a significant increase in radioactivity in tissues compared to single exposure. Plasma disappearance of radioactivity was biphasic after subcutaneous exposure. The radiolabel was rapidly eliminated, mainly via urine. Other excretory routes were expired air and faeces. After oral exposure in rats 90% of the administered dose was recovered in urine within 24 hours, after ip injection (100% absorption) 82-88% within 3 days, and after sc exposure 50% by 17 hours after administration. In humans (one case), a half-life of about 15 hours has been found for excretion in urine, after contamination of the skin with ^{14}C-labelled MCAA.

Two metabolic pathways for MCAA were suggested. A major one with an initial formation of S-carboxymethyl glutathione which is converted to S-carboxymethylcysteine, part of which is further metabolised to thiodiacetic acid. In addition, a minor one involving probably enzymatic hydrolysis of the carbon-chlorine bond resulting in the formation of glycolic acid

which is mainly oxidised to carbon dioxide. Investigation of single intravenous administration of a subtoxic and a toxic dose in rats (10 and 75 mg/kg bw, respectively) revealed non-linear kinetics to start between these two dose levels. The abrupt onset of coma/death in the high dose group in contrast to no toxicity at all in the low dose group is due to a rapid overwhelming of the detoxification capacity of the liver.

No information is available on the toxicokinetics, metabolism, and distribution of MCAA after inhalation exposure.

MCAA can inhibit different enzymes: acetate oxidation, aconitase, pyruvate carboxylase, pyruvate-dehydrogenase, a-ketoglutarate dehydrogenase and glutathione S-transferase (GST). It was suggested that the inhibition of the aconitase activity could have influenced the development of cardiomyopathy. Furthermore, it was suggested that the inhibition of pyruvate carboxylase inhibits the gluconeogenesis. Also, as MCAA inhibits pyruvate-dehydrogenase and a-ketoglutarate dehydrogenase, at least in vitro, the combined inhibition of both enzymes could lead to impaired cellular energy production and conversion to anaerobic glycolysis, resulting in lactate accumulation. Regarding the inhibition of GST, it was concluded that the major interaction of MCAA was a direct covalent binding to GST. It was assumed that this binding could have a protective function against MCAA. The GST binding is also one of the steps in the metabolism of MCAA, therefore it can be concluded that MCAA inhibits its own metabolism.

MCAA induced acute neurotoxic effects in experimental animals after exposure by different routes and needs to be classified as toxic by inhalation, in contact with skin and if swallowed. Human data also indicate a high acute dermal toxicity of pure MCAA; several case studies described the occurrence of severe systemic effects a few hours after accidental dermal exposure to MCAA.

MCAA is corrosive to the skin and induces a risk of serious damage to the eyes. Respiratory irritation was observed at 23.7 mg/m^3 in rats. The threshold for respiratory (sensory) irritation in humans was reported to be 5.7 mg/m^3. Based on wide practical experience with MCAA in the absence of any case reports on allergy, it is concluded that no indications for sensitising effects exist.

No suitable dermal and inhalation repeated-dose toxicity studies are available. Oral repeated-dose toxicity studies with 16-day, 13-week, and chronic exposure to MCAA were available. Within the limited study design of the 16-day toxicity studies (by gavage), the NOAEL in rats was 7.5 mg/kg bw/day, and in mice 60 mg/kg bw/day, both based on lacrimation. A NOAEL could not be derived from the results of a 13-week repeated-dose toxicity study with rats (by gavage). Changes in the weight of the heart, liver, kidneys, and clinical chemistry values were observed at the lowest dose level tested, i.e., 30 mg/kg bw/day. An increased liver weight and decreased activity of serum cholinesterase were observed in mice exposed during 13-weeks by gavage. The NOAEL for mice was 100 mg/kg bw/day. Main target organs of MCAA after prolonged oral administration are liver in both rats and mice, and heart and kidneys in rats. In the chronic toxicity studies, effects on the nasal mucosa, growth depression, and decreased survival became more apparent. The effects on the heart disappeared at lower dose levels in repeated-dose toxicity studies with longer study duration. Based on the data available, rats appeared to be more sensitive for the toxic effects of MCAA than mice. An NOAEL of 3.5 mg/kg bw/day derived from the 2-year drinking water study performed by DeAngelo et al. (1997) in rats is used as starting-point for the risk characterisation. At this level, no effect on survival, body weight, liver, kidneys, or (non-)neoplastic lesions was found.

Based on the available data it is concluded that MCAA is not a genotoxic compound.

No evidence of carcinogenic activity of MCAA was found in rats and mice after oral administration in drinking water or by gavage. Besides, no evidence for carcinogenic activity after repeated dermal exposure (during 580 days) was found in female mice. Carcinogenicity studies by inhalation exposure were not available.

A reproductive toxicity study with MCAA was not available. However, in the oral (sub)chronic repeated-dose toxicity studies with rats and mice, no effects were found on the male and female reproductive organs. With respect to developmental toxicity, in a study, aimed at the investigation of fetal cardiac teratogenicity, in rats exposed to 193 mg/kg bw/day the only effect observed was a decrease in maternal average weight gain during pregnancy. No developmental toxicity was observed in this study. However, since no skeletal malformations or effects on the brain were examined, no definite conclusion regarding possible developmental toxicity of MCAA can be drawn on the basis of this study. Furthermore, concern with respect to developmental toxicity of MCAA is indicated based on a summary report of a developmental test with rats, a Hydra regeneration assay, and a whole CD-1 mouse embryo culture test. In the first and latter, indications for effects on the heart of the embryo were found. A complete test report of the developmental toxicity study (Smith et al., 1990) was never published. Taking these various aspects into consideration, a developmental toxicity study should be performed.

4.1.3 Risk characterisation

4.1.3.1 Workers

Warning: It is noted that molten/liquid MCAA is very dangerous for dermal exposure. Following accidental dermal exposure to molten/liquid MCAA, fatal and non-fatal cases of severe acute systemic intoxication have been reported.

For the purpose of risk characterisation, it is assumed that inhalation of dust and skin contacts are the main routes of exposure. Oral exposure is not considered to be a significant route of exposure under normal working practices. If applicable, quantitative risk assessment is performed by calculation of the MOS (the ratio between NOAEL/LOAEL and exposure levels) and comparison of this value with the minimal MOS. This minimal MOS is established via assessment factors, taking into account inter- and intraspecies differences, differences between experimental conditions and the exposure pattern of the worker, type of critical effects, dose-response relationship, confidence in the database, and correction for route-to-route extrapolation. A risk is indicated when the MOS is lower than the minimal MOS. In case of combined exposure the calculations are based on internal NOAELs and systemic exposure levels.

An overview of the occupational risk characterisation for MCAA is given in **Table 4.2**.

In the scope of the assessment of existing substances, repeated dermal exposure to corrosive concentrations is not assessed. It is assumed that due to the corrosive effects, workers are protected from repeated dermal exposure and only accidental exposure may occur. In the case of MCAA, the effects of direct dermal contact are known to be very severe. Therefore, techniques and equipment (including PPE) are used that provide a very high level of protection from direct dermal contact. Eye protection is obligatory for activities where direct handling of MCAA occurs.

If the required skin and eye protection is strictly adhered to, skin and eye contact in scenario's 1, 2, and 3 is considered to occur only accidentally, so **conclusion (ii)** is justifiable for dermal exposure and eye contact in these scenarios. For Scenario 4 'use of paint removers' it assumed that PPE is not always strictly used and that the type of PPE used in this scenario provides a lower level of protection, therefore dermal exposure and eye contact to MCAA in this scenario cannot be excluded (for conclusions see the different end points).

Given the effects observed in the sensitisation studies and the mutagenicity tests, it is concluded that MCAA is of no concern for workers with regard to skin sensitisation and mutagenicity (**conclusion (ii)**). There are no reasons for concern with regard to systemic carcinogenicity (**conclusion (ii)**). Risk characterisation of local carcinogenicity can only be performed with studies performed with relevant exposure routes.

Acute toxicity

Dermal exposure (Scenario 4)

Starting-point for the risk characterisation for short-term dermal exposure is the LD50 value <400 mg/kg bw for pure MCAA. The minimal MOS required for acute occupational exposure using this LD50-values is >>22[2]. Comparison of the minimal MOS and the calculated MOSs (see **Table 4.2**) indicates that, based upon the present information, acute toxic effects due to acute dermal exposure cannot be excluded for Scenario 4 with and without the use of PPE. **Conclusion (iii)**.

Inhalatory exposure

Starting-point for the risk characterisation for short-term inhalation exposure are the LC50-values of the rat as determined by Maksimov and Dubinina (1974), i.e. 180 mg/m^3, and by Streeter (1987), i.e. >259 mg/m^3. The minimal MOS required for acute occupational exposure using these LC50-values is >>9[3]. Comparison of the minimal MOS and the calculated MOSs (see **Table 4.2**) indicates that, based upon the present information, acute toxic effects due to acute inhalation exposure cannot be excluded for all scenarios (**conclusion (iii)**) except the subscenarios 'Production of MCAA: production and cleaning and maintenance' and 'Use of MCAA: use of solids'.

Irritation and corrosivity

Scenario 4: Dermal irritation

Given the serious corrosive properties of MCAA and the anticipated dermal exposure in Scenario 4 (without the use of PPE), it is concluded that MCAA is of concern for workers with regard to local skin effects (**conclusion (iii)**). In case PPE would be strictly used, there would be no concern for workers with regard for local skin effects.

Respiratory irritation

In a limited reported study respiratory (sensory) irritation was observed in humans at a concentration of 5.7 mg/m^3. Using this effect level of 5.7 mg/m^3 and an arbitrary factor of 3 for the extrapolation to a no-effect-level, results in a no-effect-concentration of 2 mg/m^3. Comparison of this concentration with the reasonable worst case short term and full-shift

[2] Minimal MOS acute dermal toxicity >>22 = 2.4 · 3 (interspecies) · 3 (intraspecies) · >>1 (type of critical effect) · >>1 (dose-response)

[3] Minimal MOS acute inhalatory toxicity >>9 = 3 (interspecies) · 3 (intraspecies) · >>1 (type of critical effect) · >>1 (dose-response)

concentration levels indicates that the occurrence of respiratory (sensory) irritation cannot be excluded in the subscenarios 'Production of MCAA – transfer of molten MCAA and transfer of 80% MCAA' (**conclusion (iii)**) and the scenario 'Use of paint removers' with as well as without PPE. **Conclusion (iii)**.

Scenario 4: Eye irritation

Given the eye irritating properties of MCAA and the possible eye contact in Scenario 4 (without the use of PPE), it is concluded that MCAA is of concern for workers with regard to eye irritation (**conclusion (iii)**). In case PPE would be strictly used, there would be no concern for workers with regard for eye-irritation.

Repeated-dose toxicity

Dermal exposure (Scenario 4)

Starting-points for the risk characterisation for workers exposed by skin contact for systemic effects is the NOAEL of 3.5 mg/kg bw/day from the 2-year drinking water study performed by DeAngelo et al. (1997) in rats. The minimal MOS required for chronic occupational exposure using this NOAEL is 40[4]. Comparison of the minimal MOS and the calculated MOSs (see **Table 4.2**) indicates that systemic effects due to (possible) repeated dermal exposure in Scenario 4, with and without the use of PPE, can not be excluded. **Conclusion (iii)**.

Inhalatory exposure

Starting-points for the risk characterisation for workers exposed by inhalation for systemic effects is the NOAEL of 3.5 mg/kg bw/day from the 2-year drinking water study performed by DeAngelo et al. (1997) in rats. The minimal MOS required for chronic occupational exposure using this NOAEL is 40[5]. Comparison of the minimal MOS and the calculated MOSs (see **Table 4.2**) indicates that, based upon the present information, systemic toxicity due to repeated inhalation exposure cannot be excluded for the subscenarios 'Production of MCAA: transfer of molten MCAA and transfer of 80% MCAA' and for Scenario 4 'Use of paint removers' (**conclusion (iii)**). It might be possible that in some industrial premises worker protection measures are already being applied, but it should be realised that PPE has already been taken into account for estimation of the exposure levels.

Combined exposure

The total body burden (systemic dose) is determined by uptake after dermal as well as inhalation exposure to MCAA. In general, a risk characterisation for systemic effects for combined exposure introduces a lot of uncertainties, e.g., due to differences in build-up of the internal exposure after both exposure routes and due to difficulties in the choice of the most appropriate toxicity study as starting point. In case of MCAA, the 2-year drinking water study performed by DeAngelo et al. (1997) in rats is used as starting point for both the risk characterisation after dermal and inhalation exposure. Therefore, it is considered justifiable to estimate the risk for combined exposure, starting with the NOAEL of 3.5 mg/kg bw/day. In view of the dermal and inhalation exposure estimates, no additional concern is derived from combined dermal and inhalation exposure.

[4] Minimal MOS dermal repeated dose toxicity 40 = 3 · 4 (interspecies) · 3 (intraspecies) · 1.1 (absorption differences (100% dermal/90% oral)

[5] Minimal MOS dermal repeated dose toxicity 40 = 3 · 4 (interspecies) · 3 (intraspecies) · 1.1 (absorption differences (100% inhalation/90% oral)

Reproductive toxicity

There are no indications for effects on fertility found in the oral (sub)chronic repeated-dose toxicity studies with rats and mice. However, indications for developmental toxicity due to oral MCAA exposure were found. A full developmental toxicity study should be performed. From a risk assessment point of view, **conclusion (i)** is justified. However, waiting the outcome of the Risk Reduction Strategy the required test is put ‘on hold' (**conclusion (i) ‘on hold’,** waiting for the Risk Reduction Strategy).

Table 4.2 Overview of the conclusions with respect to occupational risk characterisation

Scenario's	**Scenario 1 – Production of MCAA**										**Scenario 2 - Use of MCAA**						**Scenario 3 - Formulation of paint removers**		**Scenario 4 - Use of paint removers**			
Subscenario's	**production**		**cleaning and maintenance**		**packing of solids**		**transf. molten MCAA**		**transfer of 80% MCAA**		**use of solids**		**use of molten MCAA**		**use of 80% MCAA**				**without PPE**		**with PPE**	
	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.	MOS	concl.
Acute toxicity																						
-dermal	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	<9.3	iii	<93	iii
-inhalation	720	ii	high	ii	180	iii	75	iii	75	iii	360	ii	150	iii	150	iii	200	iii	4.6	iii	46	iii
Local toxicity after single or repeated exposure																						
-dermal	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	iii	n.a.	ii
-inhalation	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	iii	n.a.	iii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	iii	n.a.	iii
-eye	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	iii	n.a.	ii
Sensitisation	conclusion ii																					
Repeated dose toxicity																						
Systemic																						
-dermal	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	0.08	iii	0.8	iii
-inhalation	245	ii	high	ii	77	ii	20	iii	20	iii	196	ii	82	ii	82	ii	245	ii	2.5	iii	25	iii
-combined	245	ii	high	ii	77	ii	20	iii	20	iii	196	ii	82	ii	82	ii	245	ii	0.08	iii	0.8	iii
Mutagenicity	conclusion ii																					
Carcinogenicity	n.a.	Ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii	n.a.	ii

Table 4.2 continued overleaf

Table 4.2 continued Overview of the conclusions with respect to occupational risk characterisation

Scenario's	**Scenario 1 – Production of MCAA**										**Scenario 2 - Use of MCAA**						**Scenario 3 - Formulation of paint removers**		**Scenario 4 - Use of paint removers**			
Subscenario's	**production**		**cleaning and maintenance**		**packing of solids**		**transf. molten MCAA**		**transfer of 80% MCAA**		**use of solids**		**use of molten MCAA**		**use of 80% MCAA**				**without PPE**		**with PPE**	
Reproductive toxicity *	n.a.	I	n.a.	i	n.a.	i	n.a.	i	n.a.	i	n.a.	i	n.a.	i	n.a.	i	n.a.	i	n.a.	i	n.a.	I
Flammability	Conclusion ii																					
Explosive properties	Conclusion ii																					
Oxidising properties	Conclusion ii																					

n.a. = not applicable * Conclusion i 'on hold' waiting for the Risk Reduction Strategy

4.1.3.2 Consumers

Starting point for the risk characterisation is the minimal dermal exposure to SMCA in a hand wash detergent for which an external exposure of 0.56 µg/kg bw/day was calculated assuming 60 kg bw for a consumer. Because the absorption of SMCA through the skin is considered 100%, this external exposure level results in an internal exposure of 0.56 µg/kg bw/day.

Starting point for the risk assessment for the repeated dose toxicity is the oral NOAEL of 3.5 mg/kg bw/day from the 2-year drinking water study with rats. Comparison of this value with the calculated human systemic exposure level of 0.56 µg/kg bw/day results in a MOS of 6,250. This MOS indicates no concern for consumers, taking into account intra- and interspecies differences and the use of a NOAEL of a 2-year study.

MCA is a non-genotoxic substance (**conclusion (ii)**) and there are no clear reasons of concern for carcinogenicity (**conclusion (ii)**). No indications for effects on fertility are found (**conclusion (ii)**). However, indications for developmental toxicity due to oral MCAA exposure were found. A developmental study should be performed (**conclusion (i) 'on hold'**, waiting for the Risk Reduction Strategy).

4.1.4 Humans exposed via the environment

The margins of safety for inhalation exposure at local and regional scale for man exposed via the environment are sufficiently large, resulting in a **conclusion (ii)** for repeated dose toxicity. MCA is a non-genotoxic substance (**conclusion (ii)**) and there are no clear reasons of concern for carcinogenicity (**conclusion (ii)**). No indications for effects on fertility are found (**conclusion (ii)**). However, indications for developmental toxicity due to oral MCAA exposure were found. A developmental study should be performed (**conclusion (i) 'on hold'**, waiting for the Risk Reduction Strategy).

The main exposure route for man indirectly exposed is oral. Starting point for the risk characterisation for the local scale are a production and processing site, which show the highest total daily intakes of 0.0794 and 0.066 mg/kg bw, respectively. For the regional scale the total daily intake is $1.41 \cdot 10^{-5}$ mg/kg bw. Assuming and oral absorption of 100% for humans these total daily intake values can directly be used for systemic exposure. Starting point for the risk characterisation for repeated dose toxicity is the NOAEL of 3.5 mg/kg bw/day from the 2-year drinking water study with rats. Taking into account inter- and intra species differences and the use of a NOAEL of a 2-year study, the margin of safety for this production site the MOS (44) is too low for exposure via drinking water. Therefore **conclusion (iii)** is considered more appropriate (see conclusion for the environment). For this processing site with a high emission to air a possible risk for repeated dose toxicity after oral exposure may be observed as the MOS (53) of this site is considered to be too low. The main exposure for man at this site is via eating leaf crops. The concentration in the leaf crops is caused by deposition of MCAA from air (**conclusion (iii)**). This scenario is based on the generic TGD defaults. For the regional scale the margins of safety are judged to be sufficient, taking into account inter- and intra-species differences and the use of a NOAEL of a 2-year study (**conclusion (ii)**).

MCAA is a non-genotoxic compound (**conclusion (ii)**) and there are no clear reasons of concern for carcinogenicity (**conclusion (ii)**). No indications for effects on fertility are found (**conclusion (ii)**). However, indications for development toxicity due to oral MCAA exposure were found. A developmental toxicity study should be performed (**conclusion (i) 'on hold'**), waiting for the Risk Reduction Strategy.

4.1.4.1 Combined exposure

Since several scenarios described in the previous sections caused concern for either workers or public at large, it seems not useful to characterise the risk more specifically after combined exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Given the physico-chemical data, MCAA is considered not to form a risk with respect to flammability, explosive and oxidising properties for either workers (**conclusion (ii)**), consumers (**conclusion (ii)**) or humans exposed indirectly via the environment (**conclusion (ii)**).

5 RESULTS

5.1 ENVIRONMENT

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

This conclusion (unintentional sources) applies because substantial MCAA levels are measured in various environmental compartments, wet deposition, surface water and soil. These regional/continental background concentrations exceed the corresponding PNEC in some cases, especially in soil. Further research is needed to investigate, quantitatively, the origin of these MCAA levels (natural versus anthropogenic).

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

This conclusion applies because the local PECs in surface water exceed the PNEC for MCAA production/processing site I-B1 and site I-C. In case of site I-B1 the conclusion is based on monitoring data. For site I-C the PEC/PNEC is >1 for the STP as well. For both sites industry has indicated that the efficiency of the local WWTP will be improved, but up to now no data are available to verify this statement.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Warning: It is noted that molten/liquid MCAA is very dangerous for dermal exposure. Following accidental dermal exposure to molten/liquid MCAA, fatal and non-fatal cases of severe acute systemic intoxication have been reported.

Conclusion (i) There is a need for further information and/or testing.

This conclusion is ‘on hold’ (waiting for the Risk Reduction Strategy) is reached because a developmental toxicity study should be performed.

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

This conclusion is reached because:

- acute toxic effects after short-term dermal exposure cannot be excluded for Scenario 4 ‘Use of paint removers’;
- acute toxic effects after short-term inhalation exposure cannot be excluded for all scenarios except the subscenarios 'Production of MCAA: production and cleaning and maintenance’ and the scenario ‘Use of MCAA: use of solids’;
- the occurrence of dermal and eye irritation cannot be excluded in Scenario 4 ‘Use of paint removers’(without the use of PPE);
- the occurrence of respiratory (sensory) irritation cannot be excluded in the subscenarios ‘Production of MCAA: transfer of molten MCAA and transfer of 80% MCAA’ and the scenario ‘Use of paint removers’;

- systemic effects after repeated dermal exposure cannot be excluded for Scenario 4 'Use of paint removers';
- systemic effects after repeated inhalation exposure cannot be excluded for the subscenarios 'Production of MCAA: transfer of molten MCAA and transfer of 80% MCAA' and for the scenario 'Use of paint removers'.

It might be possible that in some industrial premises these worker protection measures are already applied. However, it should be realised that PPE has already been taken into account for the estimation of the exposure levels.

In relation to all other potential adverse effects and the worker population, it is concluded that based on the available information at present no further information/testing on the substance is needed.

Consumers

Conclusion (i) There is a need for further information and/or testing.

This conclusion 'on hold' (waiting for the Risk Reduction Strategy) is reached because a developmental toxicity study should be performed.

Humans exposed via the environment

Conclusion (i) There is a need for further information and/or testing.

This conclusion 'on hold' (waiting for the Risk Reduction Strategy) is reached because a developmental toxicity study should be performed.

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

This conclusion is reached because:

- for local production scenario I-C a possible risk for repeated dose toxicity after oral exposure may be observed. The main exposure for humans at this site is via drinking water (see also conclusion environment).
- for one of the processing sites (off-site) II with a high emission to air a possible risk for repeated dose toxicity after oral exposure may be observed. The main exposure for humans at this site is via eating leaf crops. The concentration in the leaf crops is caused by deposition of MCAA from air.