European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

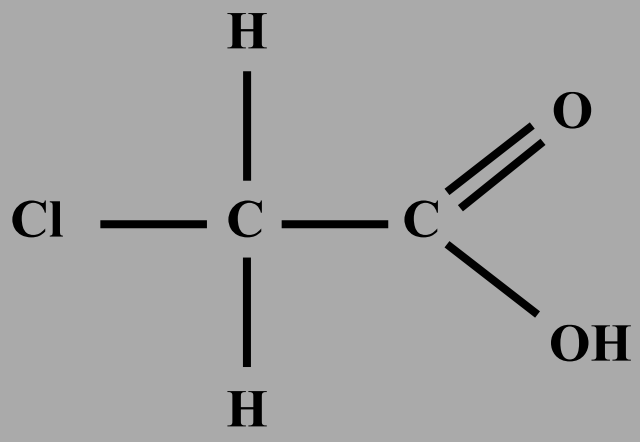
Existing Substances

European Union Risk Assessment Report

CAS No: 79-11-8

EINECS No: 201-178-4

monochloroacetic acid (MCAA)



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European Union Risk Assessment Report

MONOCHLOROACETIC ACID (MCAA)

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RISK ASSESSMENT

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MONOCHLOROACETIC ACID (MCAA)

CAS No: 79-11-8

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RISK ASSESSMENT

Final Report, 2005

The Netherlands

Rapporteur for the risk evaluation of monochloroacetic acid is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and 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 Organization for Applied Scientific Research (TNO) and the National Institute of Public Health and Environment (RIVM), by order of the rapporteur.

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Date of Last Literature Search:	**2000**
Review of report by MS Technical Experts finalised:	**2002**
Final report:	**2005**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

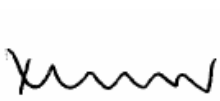
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Roland Schenkel
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[1] O.J. No L 084, 05/04/1993 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No:	79-11-8
EINECS No:	201-178-4
IUPAC Name:	Monochloroacetic acid

Environment

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

This conclusion (unintentional sources) is reached 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 is reached 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.

Human Health

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 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 sub-scenarios '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 sub-scenarios '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 sub-scenarios '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 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 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 man 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 man at this site is via eating leaf crops. The concentration in the leaf crops is caused by deposition of MCAA from air.

CONTENTS

ANNEXES

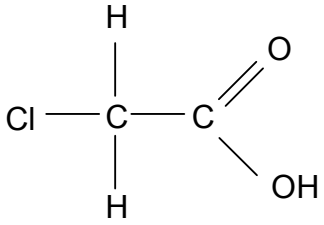
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 79-11-8
EINECS No: 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
CA-Index name: Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, tetrasodium salt
Empirical formula: $C_2H_3ClO_2$
Molecular weight: 94.5 g/mol

Structural formula



1.2 PURITY/IMPURITIES, ADDITIVES

Purity	:	>99%	
Impurity	:	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 Physico-chemical properties of MCAA

Property	Result	Comments
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	*

Table 1.1 continued overleaf

Table 1.1 continued Physico-chemical properties of MCAA

Property	Result	Comments
Surface tension	35.2 mN/m at 100°C	* In view of this value and the water solubility, the material should be regarded as surfacially active at room temperature.
Water solubility	4,210 g/l at 20°C 820 g/l (SMCA)	*
pH in water Dissociation constant (pKa)	3.2 (100 mg/l) 2.85 at 25°C	* *
Solubility in other solvents	soluble in ethanol, benzene, chloroform, ether	*
Partition coefficient n-octanol/water (log value)	≤0.2	* measured and calculated value
Flash point	126°C (melt)	not applicable, in view of aggregation state
Flammability	not flammable, according to EU-guideline	**
Autoflammability temperature	460-470°C	*
Explosive properties	not explosive	**
Oxidising properties	not oxidising	**
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	Determined by sieving

* One or several values found in literature, all in the same range, not all methods are specified
** Conclusion based on theoretical, and/or structural considerations

These data are mainly derived from CRC (1995), Hoechst AG (1982, 1993a/b, 1997a/b), KEMI (1994) and ECETOC (1999). Tests according to OECD or EU guidelines were not available. However, the data available were considered suitable for evaluation.

Conclusion

The data submitted do fulfill 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.

1.4 CLASSIFICATION

Classification according to Annex I

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

2.1 PRODUCTION

2.1.1 MCAA and SMCA

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 this chapter the production of both MCAA and SMCA will be considered.

MCAA

In the European Union MCAA is produced by three companies at five different locations (see **Table 2.1**). 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.

SMCA

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.

Table 2.1 Production sites of MCAA and SMCA (>1,000 tonnes/year) in the EU

Company[1]	Location
Akzo Nobel Chemicals	Hengelo, The Netherlands Skoghall, Sweden
Atofina	St. Auban, France
Clariant	Hürth, Germany Gersthofen, Germany

1. Producing company BUNA GmbH or BSL GmbH in Germany and Metsa Serla Chemicals in Finland were included in the HEDSET data. The German company was shut down in 1992 and therefore not included in the RAR. The producer in Finland did not produce MCAA during the last year.

2.1.2 Production process

There are two major commercial processes for the production of MCAA:

1 Chlorination of acetic acid

In this process acetic acid is chlorinated in the liquid phase at temperatures between 85 and 120°C. Acetic anhydride and/or acetylchloride may be used as catalysts. The chlorination product contains considerable amounts of acetic acid and/or dichloroacetic acid. Purification takes place either by selective dechlorination of dichloroacetic acid (by treatment with hydrogen

gas in the presence of a catalyst such as palladium) and subsequent distillation or by recrystallisation from suitable solvents.

2 Hydrolysis of trichloroethylene

In this process equal weights of trichloroethylene and sulphuric acid are heated to 130-140°C in the reactor. A mixture of trichloroethylene and sulphuric acid is continuously fed to the bottom of the reactor. The chloroacetic acid and sulphuric acid are permitted to overflow into a cascade, where the chloroacetic acid is distilled at 20 mm Hg and the sulphuric acid is recycled. The hydrolysis of trichloroethylene yields high-purity monochloroacetic acid, but has the disadvantage of utilising a relatively more expensive starting material.

The four companies that supplied data are all producing MCAA by the chlorination of acetic acid. It is a continuous process in a closed system (Letter from Company A, 1997). However, one company applies a batch process in a closed system (Letter from Company D, 1997).

Conversion of MCAA into SMCA

The process of a possible further conversion of MCAA to the sodium salt (SMCA) with sodium bicarbonate or sodium hydroxide is conducted in either a continuous or a batch process (ECETOC, 1999).

2.2 USE PATTERNS

MCAA is mainly used as a chemical intermediate for the synthesis of other products.

Major applications of MCAA are related to the production of (SIDS, 1994; ECETOC, 1999; BUA, 1993):

- 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.

Other and minor applications of MCAA (SIDS, 1994; ECETOC, 1999) are:

- constituent in acidic paint remover or graffiti remover; however, ‘open use applications’ of these products are not supported by industry;
- can coating for food (i.e. as modifier for resins) (Registered as food contact material; SCF, 1999);
- escharotic agent;
- wart remover;
- analytical reagent.

No figures are available on the use volume of these minor applications.

According to SIDS (1994) and ECETOC (1999), 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.

Furthermore, the salt of MCAA is used (< 10 tonnes/year) as an active ingredient for herbicides and is known to be registered in the UK and Ireland (ECETOC, 1999).

The current environmental risk assessment primarily focuses on the use of MCAA and SCMA as a chemical intermediate (IC/UC: 3/33). Minor applications such as paint remover, escharotic agent, anti-microbial additive for food, wart agent and analytical reagent are not considered relevant for the environmental risk assessment. Usage of SCMA as a herbicide is very low (see above) and continuation of application is questionable. A phase out is foreseen within Pesticide Regulation 91/414/EEC (from July 2003).

Three production companies of MCAA and SMCA have presented their distribution figures for downstream uses in five main groups (see **Table 2.2**). The distribution of the downstream uses only considers the use of MCAA and SMCA as a chemical intermediate.

Table 2.2 Use of MCAA and SMCA as a chemical intermediate within the European Union (Risk Assessment Group, 2000)

Use of MCAA as a chemical intermediate in:	Percentage (%)
Production of carboxymethylcellulose (CMC)	43
Production of crop protection chemicals (CPC)	14
Production of surfactants/cleaning agents	13
Production of thioglycolic acid (TGA)	10
Production others (e.g. esters, sodium salt of MCAA, amides)	20

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General

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 (see below).

MCAA may also be released by unintentional sources. For instance, MCAA can be formed (indirectly) in the atmosphere from industrial chlorinated chemicals (see Section 3.1.1.1).

Besides anthropogenic sources, MCAA is also expected to be formed *de novo* in the environment (see Sections 3.1.1.2.2.1 and 3.1.1.3.1).

General characteristics of MCAA and SMCA which are relevant for the exposure assessment are discussed in the following subsections. Within the OECD HPVC programme MCAA and SMCA were earlier evaluated by sponsor country Sweden. This resulted in a SIDS initial assessment report (SIDS, 1994). Besides this OECD report also a review from BUA on MCAA/SMCA (1993) and an ECETOC report (March 1999) are available. The three reports give a comprehensive description of the different environmental degradation routes. A summary of the various routes is presented below. None of the described data has been re-evaluated by the rapporteur.

Partitioning

Dissociation constant (pKa)

MCAA has a pKa of 2.86 at 25°C and therefore the substance will be completely ionised at environmentally relevant pHs (BUA, 1993 and SIDS, 1994). Both SMCA and MCAA can thus be treated as anion under general environmental conditions with pH 6-7. The physico-chemical results of the water dissolved salt are therefore used as input for the EUSES-model (see also log K_{ow}).

Log K_{ow}

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. For pragmatical reasons a log K_{ow} of -1 will be used as input for the PEC calculations. It should be noted that selecting lower log K_{ow} values (< -1) would not affect the output of the calculations. Investigation of pH dependence of the log K_{ow} is not considered relevant because MCAA is completely ionised at relevant pHs (see also the pKa).

Use of log K_{ow} for partition coefficients, distribution WWTP and bio concentration factors

Many estimation routines are based on the octanol-water partition coefficient. It should be noted that for ionic substances, the K_{ow} may not be an accurate predictor for estimating the partition coefficients, the distribution within a WWTP and the bio concentration factors. However, MCAA/SMCA is highly soluble and no sorption is expected for MCAA/SMCA. The selected

log K_{ow} of -1 (see log K_{ow}) is therefore considered acceptable for estimating the partition coefficients and the distribution pattern within a WWTP. A quantitative risk assessment can thus be made for water, air and soil compartment. On the other hand a log K_{ow} of -1 is considered not to be valid for estimating the bio-concentration factors. Therefore, no risk assessment is made for secondary poisoning and certain indirect exposure routes for humans (see indirect exposure).

Degradation

Hydrolysis

Both MCAA and SMCA hydrolyse very slowly. After 30 days and at 20°C only 0.01% of MCAA is hydrolysed (BUA, 1993 and SIDS, 1994).

Photodegradation

Direct photolysis of MCAA in air and water is not expected, because it does not absorb UV radiation above 290 nm (BUA, 1993 and SIDS, 1994). A photo-reactor study showed that MCAA photodechlorinates very slowly in air-saturated solutions. However, in the presence of radiosensitisers such as p-cresol and tryptophan, which generate superoxide anion radicals ($O_2^{\bullet}$), the rate of dechlorination increases (SIDS, 1994). The photo-oxidation rate of MCAA with OH-radicals (concentration $5 \cdot 10^5$ molecules/cm^3) can be estimated with a QSAR (Atkinson; TGD 1996). The estimated DT50 for MCAA is 58 days. This value is further used in the risk assessment. No stable metabolites are expected to occur after photolysis. MCAA will probably be further degraded into carbon dioxide and hydrochloric acid.

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 (ECETOC, 1999). Dry deposition of MCAA from air can also take place (De Leeuw, 1999).

MCAA emitted into aqueous solution in aerosols will probably remain in the aqueous phase because of its high solubility (ECETOC, 1999).

Biodegradation

All available biodegradation test results are presented in **Table 3.1**.

Ready and inherent biodegradation tests

There are seven studies available on ready biodegradability. These were conducted according to OECD-guidelines no. 301B-E. Four results clearly indicated MCAA to be readily biodegradable, i.e. 60-70% within a time-window of 10-14 days. This result is also supported by the inherent biodegradation results. In all five inherent tests (no.3, 4, 6, 8 and 9) MCAA was (nearly) 100% biodegraded between 6 and 28 days.

Anaerobic biodegradation tests

In three out of four anaerobic biodegradation tests with adapted methanogenic bacteria MCAA was > 86 % mineralised after 2 days, into methane, CO_2 and chloride ions.

Degradation in soil

Degradation in soil will occur. In the SIDS-report (1994) estimates are given for degradation rates of MCAA in soil under various environmental conditions. These estimates are based on experimental data from Jensen (1959). The highest degradation rate is estimated for a neutral soil at 15^{o}C (half life of 66 hours), whereas the lowest rate (half life 800 hours = 33 days) is given for acid soil at 7^{o}C.

Table 3.1 Biodegradation results for MCAA (aerobic). (References cited in ECETOC report, 1999)

No.	Type of test	Guideline	Days	Inoculum	MCAA (mg/l)	Result	Reference**
1	Closed Bottle test	OECD 301 D	28	AS	10.3	69 %	Akzo Nobel, 1988
2	Closed Bottle test	OECD 301 D	28	AS	5	100%	Gerike and Gode, 1990
3	Modified Zahn-Wellens	OECD 302 B	8	AS industrial	570 mg DOC/l	100 %	Hoechst, 1992a
4	Modified Zahn-Wellens	OECD 302 B	10	AS industrial	1,140	99 %	Hoechst, 1992a
5	Modified OECD	OECD 301 E	28	AS	5 (DOC)	100 %	Gerike and Gode, 1990
6	Modified Zahn-Wellens	OECD 302 B	28	AS	1,000	100 %	Gerike and Gode, 1990
7	Modified MITI	OECD 301 C	21	AS	100	65 %	MITI, 1992
8	Modified Zahn-Wellens	OECD 302 B	6	AS industrial	1,000*	90 %	Zahn and Wellens, 1974
9	Modified Zahn-Wellens	OECD 302 B	5.5	AS industrial	1,000	>90 %	Zahn and Wellens, 1980
10	Modified OECD	OECD 301 E	7	AS	4.5	73 %	Struijs and Stoltenkamp,1 990
11	Modified OECD	OECD 301 E	7	AS	9	14-24%[1]	Struijs and Stoltenkamp, 1990
12	Modified OECD	OECD 301 E	28	AS	-	50-55%	Trénel and Kühn, 1982

AS activated sludge
* SMCA
** All references were cited in ECETOC report (1999)
1. According to the authors MCAA appeared inhibitory to the mixed flora.

Conclusion (degradation)

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 will be overwritten, however, for all MCAA/SCMA production and processing sites based on submitted high measured removal rates. One company measured an average removal rate of 99.93% of SMCA/MCAA in their WWTPs. This figure is based on 7 measurements on the ratio influent versus effluent concentration at three different WWTPs (range 99.83-99.98%). In line with this finding Wettstrom (1993) reported a reduction rate of MCAA/SCMA of ≥ 98% in the waste water treatment plant of a Swedish MCAA production facility. The same company also performed removal rate measurements in a modern STP which receives most of the sewage from municipal sources, but some industries discharge as well. Twenty-four hour mixed samples were collected and analysed twice, giving an average elimination of 99.84%. Another company measured the removal rate of MCAA/SCMA in a partly municipal WWTPs. The measured elimination rate was reported to be more than 99.99%. The data suggest that there is practically no difference between the removal rate in industrial WWTPs and municipal STPs. In the current risk assessment a default removal rate of 99.9% is used, for both adapted, industrial WWTPs and communal (unadapted) STPs.

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). The Rapporteur realises that, based on the above-mentioned discussion on degradation in STPs, this is a conservative approach.

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 the DT50 range given in the SIDS report (3 to 33 days).

Distribution

Water-air

According to the TGD (1996) 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 value of the salt is used for further calculations. This value is probably smaller because SMCA is a salt, but for calculating this value, the vapour pressure (8.7 Pa at 25°C) of MCAA was used. The calculated Henry's Law constants indicates that volatilisation of MCAA/SMCA from surface water will not occur at significant levels. This conclusion can be supported with Mackay Level 1 calculations. These calculations indicate that MCAA/SMCA will end up 100% in the water compartment (ECETOC, 1999).

Soil-water

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. For this QSAR calculation log K_{ow} values of 0.22 and –1 were used for MCAA and SMCA, respectively. Adsorption to soil is thus not expected to occur. The K_{oc} value of 3.16 (salt) is used for the risk assessment.

Soil-air

MCAA has a pKa of 2.86 at 25°C and therefore will be completely ionised at environmental pHs. Loss of MCAA from soil to air is probably not relevant.

Air-Soil/Water

MCAA in aerosols will be subjected to dry deposition and undergoes slow photodechlorination.

Accumulation

On the basis of the water solubility of MCAA/SMCA, no bioaccumulation is expected.

3.1.1 Exposure scenarios

3.1.1.1 General

The environmental exposure assessment of MCAA and SMCA 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)

Non-intentional sources are also discussed such as indirect formation of MCAA via industrial precursors or natural occurrence (3-4).

III Formation of MCAA as by-product (indirect via industrial sources)
IV Non industrial sources/natural occurrence

For the release in the environment MCAA and SMCA are considered together as one substance. Both SMCA and MCAA are treated as anion of MCAA under general environmental conditions with pH 6-7 (see also Section 3.1.1 for pKa and log K_{ow}). Therefore, physico-chemical data of SMCA will be used as input for EUSES-model. (The MCAA toxicity results obtained in neutralised media are used for the PNEC derivations).

No calculations are performed for the sediment compartment. According to TGD (1996) no quantitative risk characterisation is needed for sediment when no measured data are available, either for the determination of $PEC_{sediment}$ or for the calculation of $PNEC_{sediment}$ A quantitative risk assessment can be made for water, air and soil compartment. However, no PECs are estimated for secondary poisoning (see Section 3.1.1: use of log Kow for bio concentration factors).

3.1.1.2 Local exposure assessment

3.1.1.2.1 Production, including captive use (site specific) (I)

In Section 2.1 it is mentioned that there are three producers of MCAA within the EU. Two producers each have two production locations. In total there are thus five locations where production (> 1,000 tonnes/annum) of MCAA takes place. At all these production locations

MCAA is further processed as a chemical intermediate. However, mostly not the whole amount of produced MCAA is allocated for internal chemical intermediate use. The remaining part is exported either outside the EU or sold to other processing industries within the EU. Other processing industries also use MCAA mainly as a chemical intermediate.

The processing of MCAA into SMCA and the use of MCAA as chemical intermediate is covered in the production scenarios in case of captive use. The emissions during off-site processing are presented as no. II "Processing of chemical intermediates (site specific scenario)" (see Section 3.1.1.2.2).

It should be noted that the calculated PEC_{local} values include the regional background concentration. Therefore, the calculated PEC_{local} should be regarded as: $PEC_{local} = C_{local} + PEC_{regional}$. The $PEC_{regional}$ will be discussed in Section 3.1.1.3.1.

For each production location site specific data on emission (kg/day) is available which is presented in **Table 3.2.** For confidentiality reasons not all information is presented in this table. With the input of **Table 3.2** the local Predicted Environmental Concentrations (PECs) are calculated which are also presented in this table. The calculations of PECs are carried out according to the TGD, applying the EUSES 1.0 model. The PECs for each site are also presented in **Table 3.2**. For sites I-A1, I-A2, I-B1 and I-B2 the MCAA concentrations in WWTP effluent and in surface water were found to be below the detection limit (industry information). The detection limits for sites I-A1 and I-A2 was 5 µg/l. Site I-B1 used a detection limit of 0.5 µg/l and site I-B2 and I-C used detection limits of 100 and 1,000 µg/l, respectively. Additional studies on the occurrence of MCAA in soil and water near site I-B2 used analytical methods with a detection limit for soil of 15 ng/g (Von Sydow et al., 2001). In the analysis of surface water concentrations the detection limit of the analytical method used was 5 ng/l (Grimvall et al., 1995). The ECETOC report (1999) mentions detection limits for MCAA of either 1 or 10 µg/l depending on the method. It is clear that there is a great difference in the applied analytical methods between the individual companies. The analytics of detecting MCAA, however, require the greatest care as the substance NOECs are in the low µg/l range (see section Effect assessment).

The measured concentrations for site I-C are relatively high when compared to other sites. According to industry the WWTP of this site was not fully functioning in that period. In the mean time an emission reduction campaign has started covering a major refurbish and refitting of the WWTP, reducing losses of MCAA to water by regrouping the sewage pipe system and recovery of MCAA for incineration rather than to waste water.

All scenarios (also for off-site processing; see next section) refer to the production and use of MCAA as a chemical intermediate (IC/UC 3/33). If no site-specific dilution factor is submitted, then, according to the TGD, for this category a larger river flow (60 m^3/s) could be used, resulting in a larger default dilution factor. However, as one of the scenarios (I-C) has a site-specific dilution factor of 9.8, the application of a higher dilution factor is felt to be not adequate in case of MCAA. Therefore the dilution factor of 10 is used in those scenarios for which no site-specific dilution factor was submitted.

Table 3.2 Input data for the local exposure assessment and local PECs at production, including captive use (I). Site specific information is presented in bold.

Company-site specific data	**I-A1**	**I-A2**	**I-B1**	**I-B2**	**I-C**
Annual production (t/a)	Confidential	confidential	Confidential	Confidential	confidential
Industry and use category	3 33 (SCMA*)	3 33 (ester/amides)	3 33 (SCMA**)	3 33 (SCMA***)	3 33 (SCMA****)
Main category	Ib Continuous and closed system	Ib Continuous and closed system	Ib Continuous and closed system	Ib Continuous and closed system	Ib Continuous and closed system
Fraction released to waste water	$1.45.10^{-3}$	$9.97.10^{-4}$	Not relevant	Not relevant	Not relevant
Number of days	365	365	350	300	300
Release air (kg/d)	0.015	0.02	0.51 (IND) 17 (ERI-96)	48 SMCA	2.8
Release waste water (kg/d)	198	62.8	1057 (IND) 460 (ERI-95) 0 (ERI-96)	236 SMCA	717.6[2]
Removal rate in WWTP (%)	99.94	99.98	99.99	99[4]	99.9 (D)
WWTP effluent flow (m^3/day)	22,157	3,020	28,120	527,040	24,000
Flow receiving water (m^3 /day)	$9.07.10^7$ (IND)	$3.46.10^6$	Unknown	Unknown	211,680[1]
Dilution	4095 (IND)	1145 (IND)	5 (C)	10	9.82
PEC in effluent (μg/l)	5.36 (C) < det. level (5 μg/l)	4.17 (C) < det. Level (5 μg/l)	2.63 (C) Not detectable (not given)	4.48 (C) < det. Level (0.1 mg/l)	29,900 (C) 22,000-35,000 M
PEC surface water (μg/l)	0.0697 (C)	0.072 (C)	0.595 (C) <0.5-0.8 (d.l. 0.5 μg/l)	0.516 (C) 6-21 ng/l[5] (d.l. 5 ng/l)	3,050 (C)
PECair (μg/m^3)	$4.41 \cdot 10^{-3}$ (C)	$5.80 \cdot 10^{-3}$ (C)	0.118 (C)	11 (C) 1.5 (M)	0.64 (C) <2.7 ng/m^3(M)
PECsoil 30 days (mg/kg_{wwt})	$1.17 \cdot 10^{-4}$ (C)	$1.17 \cdot 10^{-4}$ (C)	$1.36 \cdot 10^{-4}$ (C)	$1.95 \cdot 10^{-3}$ (C)	$2.23 \cdot 10^{-4}$ (C)

1 The WWTP effluent release into the river x (flow of 211,700 m^3/day). This is followed by the confluent the y (flow of 72,000 m^3/day at 1.2 km) and river z (at 4.8 km). Only the dilution in river x is accounted for. Measured concentration in the river z is below detection limit of 1 mg/l.

2 Emission to surface water

3 Dilution factor is unknown. The waste water is collected in a pre-settling pond which subsequently discharges into a lake. As a consequence the default dilution factor is used.

4 Waste water is not treated in a WWTP or STP, therefore the removal rate was chosen to be a factor of ten lower than the default value, giving a removal rate of 99%, which still might be considered rather high, taking account of the local situation.

5 Measured in receiving lake, no information on sample locations with respect to production site, 3 measurements.

* This site converts all produced MCAA into SMCA.

** This site converts part of the produced amount MCAA into SMCA.

*** This site converts part of the produced MCAA into SMCA. The emission data only refer to SMCA.

**** This site converts only 8000 t/year into SMCA. The emission data refer to MCAA. There is no emission data available for SMCA-production.

(ERI) Emission Registration Information 1995/1996 (The Netherlands).

(D) Default; (IND): Industry; (C): calculated by Rapporteur; (M): Measured

3.1.1.2.2 Processing industry-chemical intermediates (off-site use) (II)

As described in the previous section, a number of production companies also directly (on-site) process MCAA as an intermediate for manufacturing SMCA, CMC and others (see **Table 2.2**).

Exposure information for the remaining downstream users is collected by the three producers. The aggregated information (maximum PEC values) for the off-site processing of MCAA/SMCA is presented in **Table 3.3**. More detailed information can be found in Annexes 1, 2 and 3.

In Section 2.1.1 the total use volume (MCAA and SMCA) was estimated at 135,872 tonnes/year within the European Union. About 30,000 tonnes/year is covered by the on-site processing locations. The total processing volume reported in the submitted site specific emission scenarios for external down stream users adds up to 100,890 tonnes/year. The total processing volume for which emission estimates have become available is nearly 131,000 tonnes/year. This gives a difference of about 5,000 tonnes/year with the original total estimate in Section 2.1, which is believed to be caused by uncertainties like different reporting years. The available data are thus considered to be representative for the entire use of MCAA and no additional generic scenario is felt to be needed.

According to the TGD (1996) the emission factor for main category Ic is 0. However, an average emission factor of 0.0005 can be calculated from the site specific emission factors. Atmospheric emissions can be expected during cleaning operations with water. MCAA is a strong acid and the reaction of strong acids with water is highly exothermic resulting in MCAA vapour release. For this reason, in case site-specific data are lacking for atmospheric emissions, the value of 0.0005 is used as a default instead of the TGD value.

Table 3.3 Local PECs at off-site processing (II). Only maximum values are given. Details can be found in Annexes 1, 2 and 3.

	Maximum value
PEC_{STP}	428 µg/l
PEC water	0.38 µg/l
PEC soil	1.0 µg/kg dwt
PEC air	5.3 µg/m^3

Release during use of end products

Remains of MCAA in end products such as CMC, esters, SMCA and amide are zero or < 0.1% (Letter from Company A, 1997). Release from use of end products is not considered in the further risk assessment, because it is expected to be negligible.

3.1.1.2.3 Releases from non-intentional industrial sources and natural sources (III-IV)

Non-intentional industrial sources (III)

MCAA might be released from the paper and pulp industry during bleaching processes. The only release data for this type of process is a maximum concentration of 6 g/l to the aeration basin of the WWTP in Finnish pulp and paper mills (Sarlin et al., 1999). This figure, however, is characterised as an accidental release. MCAA concentrations under normal conditions are not

available. According to industry bleaching with chlorine is rapidly decreasing as alternatives are available.

The formation of MCAA has also been observed after disinfection of drinking water (see consumer exposure). In addition, in flue gasses from municipal waste incinerators in Sweden MCAA were measured (HSDB, 1996).

Natural occurrence (IV)

See Section 3.1.1.3.1 on diffuse emissions.

3.1.1.2.4 Measured local data

Measurements were performed at the sites I-B1 (water) and I-B2 (water and soil) to estimate environmental concentrations.

At site I-B1 MCAA concentrations in surface water were measured both upstream and downstream from the WWTP outlet (Industry, 2001). The upstream concentrations were all below the detection limit (0.5 μg/l), whereas downstream measurements indicated higher levels of MCAA in the surface water. Three out of five samples were below the detection limit, but two downstream samples showed levels in the range of 0.6-0.8 μg/l and 0.5-0.6 μg/l.

Grimvall et al. (1995) measured MCAA levels between 6 and 21 ng/l (n=3) in the Swedish lake Vänern which receives the waste water of site I-B2. The measurements were part of a larger monitoring campaign in the southern part of Sweden. It was concluded that the MCAA levels in lake Vänern did not differ from those in the other lakes in the area. No correlation was found between the distance to the factory and the measured concentrations. The concentrations, ranging up to 106 ng/l are therefore assumed to represent the regional background MCAA concentrations (see also Section 3.1.1.3.1). Von Sydow et al. (2001) recently measured the MCAA concentrations in soil in the vicinity of site I-B2 and in two different reference locations in southern Sweden. The concentrations of MCAA in soil ranged from n.d. to 160 ng/g (detection limit: 15 ng/g). Furthermore, similar to the situation for MCAA levels in surface water, no correlation was found between the MCAA soil levels and the distance to the site. Apparently, there is a significant background concentration of MCAA (and other chloroacetates) in the environment. See also Section 3.1.1.3.1.

3.1.1.3 Regional and continental exposure assessment

3.1.1.3.1 Releases from diffuse sources

Chloroacetic acids, including MCAA have been measured in the atmosphere, soil and water (see section on monitoring data). The global dispersion of MCAA is illustrated by the fact that it was detected in pre-industrial glacial ice samples and in snow samples of remote areas (e.g. Antarctica). Grimvall et al. (1995) further showed that there is no pronounced difference in concentration between snow from the northern and southern hemisphere. They concluded that the universal occurrence, including remote areas, of MCAA at more or less similar levels is a strong indication that natural sources account for a significant part of the observed background concentrations. In line with this ECETOC (1999) suggested that “chlorine atoms produced in the marine boundary layer could react with unsaturated hydrocarbons of natural origin to produce MCAA”. On the other hand anthropogenic sources have been suggested as well. MCAA and also

di-, and trichloroacetic acid may be formed in the atmosphere by photochemical reactions with anthropogenic chlorinated hydrocarbons or salt aerosols (SIDS, 1994). According to the Rapporteur it is possible that MCAA is formed via certain precursors. However, the MCAA formation in atmosphere via precursors such as chlorinated solvents, is not expected to occur at large amounts. Scott and Alaee (1998) measured MCAA in the Canadian environment, but they considered current understanding about the occurrence of MCAA in the environment (and haloacetic acids in general) as insufficient to draw any conclusion about their potential source. Neitzel et al. (1998) tended towards the occurrence of halogenated acetic acids, including MCAA, in the environment being caused by anthropogenic sources. Reimann et al. (1996a) concluded that the fact that MCAA concentrations in plant products are similar throughout the globe cannot be interpreted as a proof for a natural origin (see Section 4.1.1.4). They suggested that acids can be formed from long-lived, equably distributed precursors in the atmosphere, such as chlorinated solvents. The ECETOC report (1999) summarised that there are no obvious atmospheric degradation pathways that could explain a direct formation of MCAA from chlorinated solvents.

In a recent review Frank (2001) investigated the possible sources of MCAA in the environment. He concluded that MCAA has both natural and industrial sources, but that it is inconceivable that the atmospheric burden stems from industrial sources. Several possible routes (tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane and ethene) for MCAA formation were analysed and the chlorination of ethene was estimated to be of great importance. Ethene emissions are of natural and anthropogenic origin (Frank, 2001). Slooff et al. (1991) reported that on a global scale most emitted ethene originates from natural production (74%). Plants and micro-organisms produce and emit large amounts of ethene. In the CCDM report (2000) anthropogenic ethene air emissions were estimated for the Netherlands (1999 data). Traffic contributes to 64% of the total anthropogenic ethene emission (7,130 tonne/annum out of total of 11,100 tonnes/annum), whereas industry 'only' emits 1,540 tonnes/annum (14%). Estimations for the natural emissions of ethene were not given in the CCDM report. Frank (2001) does not discuss the sources of chlorine (Cl-radicals) in the environment, but it is clear that like ethene these can have both a natural and anthropogenic background.

Some rough estimates have been made about the magnitude of some MCAA fluxes in the environment.

ECETOC (1999) calculated that 35,000 tonnes/year MCAA is deposited by rain-water. For this calculation an average precipitation of 700 mm/year and a MCAA concentration of 0.1 ppb (w/w) were used. SIDS (1994) stated: "The natural annual contribution to the total exposure to the environment is calculated to be 0.07-0.7 mg/m^2 (based on 700 mm rain per year and natural background level of 0.1-1 μg/l)."

Reimann (1996a): "An annual wet deposition in Zurich of 1 mg/m^2 of MCAA and about 140 μg/m^2 of TCA is calculated based on the data between September 1994-1995. Extrapolated for the territory of Switzerland, this amounts to an annual deposition of 46 tonnes of MCAA and 6 tonnes of TCA". For this calculation an annual rain fall of 1500 l/m^2.year, an annual wet deposition of MCAA of 1 mg/m^2 and a Swiss region of + 40,000 km^2 was used. The rapporteur estimates an annual deposition in Europe of 250-2,500 tonnes/year. For this calculation an average precipitation of 700 mm/year, a MCAA background concentrations of 0.1-1 ppb (w/w) and a EU region of 32,36169 km^2 was used (0.1 μg/l · 700 l/m^2 · 3,236169 km^2). The MCAA rain water figures that were mentioned in the SIDS document compare fairly well with the more recent Reimann (1996a) data as presented in **Table 3.6**. The total emission to air from production and processing sites within Europe (see **Table 3.2** and **3.3** for site specific sites)

amounts to approximately 57 tonnes (190 kg/day · 300 days). This is much lower than the calculated natural background figure of 250-2,500 tonnes/year for the EU.

In conclusion: at present no unequivocal conclusion can be drawn about the origin of MCAA in the environment, although the latest review by Frank (2001) points to the importance of non-industrial sources. The contribution of MCAA production and processing to the total MCAA burden is expected to be marginal at the regional/global scale. Further investigation is however needed for a more detailed identifying of the potential precursors (anthropogenic and natural).

3.1.1.3.2 Regional and continental PECs

EUSES 1.0 (according to the TGD, 1996) has been used for calculating the regional PEC values for the different environmental compartments. The input for the regional assessment is the emissions to air and waste water. Diffuse (unintentional) emissions are not taken into account for the regional exposure assessment as there are no reliable quantitative release estimates (see previous section). More importantly, these background concentrations seem to originate largely from natural sources (see Section 3.1.1.3.1). This section thus only focuses on the regional exposure assessment for (intentional) MCAA producers and users.

For calculating the regional exposure firstly the total EU (continental) emission values are determined. To obtain continental emission values all emission values for the local sites are summed up (production, including captive use (I) and off site processing (II). (see Section 3.1.1.2.1). The total continental emission values are presented in **Table 3.4**.

The total regional emissions are based on the largest local site-specific emissions, which are 48 kg/day to air, 1,057 kg/day to waste water and 2.36 kg/day to surface water. The very high value of 718 kg/day for the emission of site I-C to surface water is not considered relevant for this purpose as it is most probably due to the temporary disfunctioning of the WWTP (exception). For a comparison regional emissions are calculated with the 10% rule, which are 20.7 kg/day to air, 403 kg/day to waste water and 72.2 kg/day (this value includes the high emission of 718 kg/day for site I-C) to surface water. Except for surface water these values are lower than the largest local emission values. The used regional emission values are printed bold in **Table 3.4**. The resulting regional PEC values are presented in **Table 3.5**.

Table 3.4 Total continental emission values (EU)

		Emission air	Emission waste water	Emission surface water
		(kg/day)	(kg/day)	(kg/day)
I-A1	Local production (and processing) site	0.0150	198	0.118
I-A2	Local production (and processing) site	0.0200	62.8	0.0125
I-B1	Local production (and processing) site	0.514	1,057[1)]	0.0740
I-B2	Local production (and processing) site	48[1)]	236	2.36[1)]
		(kg/day)	(kg/day)	(kg/day)
I-C	Local production (and processing) site	2,8	0	718
II	Down stream users[2)]	139	2,280	2.19
	Total EU	190	3,833	722

1) These largest local emission values are the input for the regional assessment.
2) Only sum is given, individual data can be found in Annexes 1, 2 and 3.

Table 3.5 Regional PEC values

PEC air (μg/m^3)	$2.38 \cdot 10^{-4}$
PEC surface water (μg/l)	0.068
PEC sediment (mg/kg$_{wwt}$)	$4.4 \cdot 10^{-5}$
PEC agricultural soil (mg/kg$_{wwt}$)	$6.76 \cdot 10^{-5}$
PEC natural soil (mg/kg$_{wwt}$)	$1.16 \cdot 10^{-4}$

3.1.1.3.3 Measured regional data in environment

This section contains monitoring data for MCAA in the various environmental compartments. **Table 3.6** gives MCAA concentrations in the aquatic compartment, including ice, snow, surface water leaching water, ground water, rain water and sediment. MCAA has been detected in snow and rain water at levels around 0.1-2 μg/l. MCAA concentrations in surface waters were found in the range between 0.005 and 0.6 μg/l. **Table 3.7** shows some atmospheric MCAA monitoring data. Soil data are hardly available.

In Section 3.1.1.2.1 some attention was already paid to the large differences in detection limits being reported by the individual companies. The application of various analytical methods for detecting MCAA in the environment will also hamper a precise comparison of the data reported by different authors in **Table 3.6**. According to Frank (2001) the reliability of MCAA determinations in monitoring studies cannot be judged when the potential for abiotic and biotic degradation of MCAA in samples and calibration standard solutions, the size and variability of blank levels, the potential for artificial MCAA-formation, yields of recovery and derivatisation, and their contributions to analytical results are not addressed.

Table 3.6 Measured regional data of MCAA in the aquatic compartment.

Location	Type of site	Levels observed	Year	Reference
Sweden	"detected in the spent chlorination liquor from the bleaching of sulphite pulp" (L)	0.1-0.7 g/ton pulp	< 1986	HSDB, 1996
Japan	Surface water (lake) Sediment (lake)	0.64 (μg/l) 1.6-3.3 (μg/kg)	<1984?	SIDS, 1994
-	Pre-industrial origin ice samples	27 ppt (w/w)~ 27 ng/l	-	Eurochlor, 1995 (Cited in: ECETOC, 1999
Antarctica	Pre-industrial glacial ice water	0.1-1.0 (μg/l)	-	SIDS, 1994
Northern and southern hemisphere	Snow	Up to 120 ng/l	-	Grimvall et al., 1995
	Rain water	Few-700 ppt (w/w)	-	Frank et al., 1995
Swiss, Zürich Swiss, rural (terrestrial)	Rain waters Rain waters Alptall – rural Alptall-Open-field Alptall-Forest canopy runoff	500 ng/l 0.2-2.1 μg/l +0.1-1.1 μg/l +0.3-1.8 μg/l +0.1-1.2 μg/l	1993-summer 1994-1995 (monthly)	Reimann, 1996a
Germany and Austria	-	300-4,300 ng/l	1993-1994	Cited by Reimann, 1996a
Germany (11 sampling stations; urban and rural areas)	Rain water (n=203) Leaching water (n=245) Ground/spring water (n=182)	<0.5 µg/l (93% of samples; 0.5-<1 µg/l (7% of samples) <0.5 µg/l (90% of samples; 0.5-<1.9 µg/l (10% of samples) <0.5 µg/l (96% of samples; 0.5-<1 µg/l (4% of samples)	1992-1995	Schleyer, 1996
Canada	Lake water (3 lakes) Ground water (2 locat.) Rain water (2 locat.) Snow (3 locat.)	0.15-0.49 µg/l (n=7) <0.06 –0.06 µg/l (n=2) 0.77 - 0.78 µg/l (n=2) 0.29-0.83 µg/l (n=3)	1996	Scott and Alaee, 1998
Germany	River Elbe River Elbe bank filtrate	< 1 µg/l (=det. Limit) < 2 µg/l	1997/1997	Neitzel, 1998
Germany	Direct measurements in German surface water	<5-66 ng/l average <30 ng/l	<1995	Frank et al., 1995
Sweden	Lake Hageltorpsgölen Bergskärret	300 ng/l (surface water) 300 ng/l (surface water)	2000	Von Sydow et al., 2001

Table 3.6 continued overleaf

Table 3.6 continued Measured regional data of MCAA in the aquatic compartment

Location	Type of site	Levels observed	Year	Reference
Germany and Ireland	Bayreuth (D) Mace Head (Irl) Clean air station	2.5 µg/l (average rain water) 0.5-3.5 µg/l (rain water)		Frank et al., 1995
Germany and Ireland	Surface waters: Elbe (Wittenberg, D) Mistelbach (Bayreuth, D) Lough Skannive (Mace Head, Irl) Lough Ahalia (Mace Head, Irl) North Sea (Hutum)	 250 ± 17 ng/l 200 ± 7 ng/l 310 ± 35 ng/l 320 ± 6 ng/l 430 ± 18 ng/l	1995	Klein: cited in: Frank, 2001
Switzerland	 Rain and snow (n=73) Rivers (n=80) Midland lakes (n=20) Mountain lakes (n=8) Moor water (n=3)	Average range (in ng/l) 1,780 60-7,170 107 <6-320 153 40-242 215 71-417 389 247-476	1996-1997	Berg et al., 2000
Sweden	Lake Vänern and selection of lakes in southern Värmland	<5 – 106 ng/l average 21 ng/l	1994	Grimvall et al., 1995

- data unknown
L local scale

Table 3.7 Measured regional data of MCAA in the atmospheric compartment

Location	Type of site	Levels observed	Year	Reference
Sweden (Boras)	Flue gases from municipal incinerator (L)	3.2-7.8 µg/m^3	(< 1987)?	HSDB 1996
Germany (and Ireland)	Tübingen and Bayreuth (D) Mace Head (Irl) (clean air station)	0.1-3.3 ng/m^3 0.6 ng/m^3	1993-1996	Klein: cited in: Frank, 2001
-	Urban air	10-5,000 pg/m^3	-	Frank et al., 1995 (cited in: ECETOC, 1999)

- data unknown

On the atmosphere data, Frank (2001) concluded the following: "The results indicate that MCAA is an ubiquitous atmospheric component. The atmospheric burden of air masses at remote locations (Mace Head) are in the same range, or even higher, than those found in samples collected close to densely populated areas. This must be interpreted as an indicator of MCAA being released from non-anthropogenic sources, or as the result of a slow formation from a ubiquitously distributed precursor. However, the fact that the southern hemispheric data tend to

be in the same range or higher than northern hemispheric data suggest that 1,1,1,-trichloroethane is unlikely as precursor".

Concentrations in precipitation tend to be higher than those in surface water. This confirms that atmosphere is an important source of halogenated acetic acids (including MCAA) and that precipitation is most likely the major transfer mechanism to the biosphere. Recent (> 1994) and reliable (according to Frank (2001)) surface water concentrations are generally found to be within the range of 20-400 ng/l. Similar to atmosphere, MCAA levels in the hydrosphere (precipitation and surface water) do not show great differences between remote (rural) areas and urban (industrialised) areas.

Industry calculated a background concentration between 0.2 and 75 ng/l in surface water from atmospheric input e.g. via rain. The estimation is as follows: The background input for the EU was estimated to be 1,250 tonnes using a natural background level in rain of 0.5 µg/l. The direct input to surface water was estimated to be 37% of the total input e.g. 460 tonnes/year, of which 30% reaches the surface water through the ground water and 7% reaches the surface water directly through rain. This calculated mass flow of MCAA was used to calculate the average background concentration in the EU using EUSES. For biodegradation in surface water a worst case DT50 of 15 days (TGD, default) and a best case DT50 of 1hour (TGD default for STP) were used. The resulting background concentrations for the first case were calculated to be 75 ng/l and for the second case to be 0.2 ng/l.

In Section 3.1.1.2.4 the results of a recent MCAA soil monitoring program around a Swedish MCAA producer and a reference area were reported. Levels were found to be between n.d. (< 15 ng/g) and 164 ng/g and no correlation was found with potential anthropogenic sources. It should be recognised that the data set for soil MCAA monitoring data is very limited.

3.1.1.3.4 Comparison of measured and calculated data

The regional PEC in the present RAR 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). It is also within the range of the industry estimate of 0.2-75 ng/l.

It is important to realise however that the above-mentioned comparison of the calculated PEC regional with the actual monitoring data is of lesser relevancy (apples to pears comparison). This because the calculated PEC only focuses on the amounts of MCAA from (intentional) MCAA producers. The monitoring data on the other hand 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 however expected to be negligible (see Section 3.1.1.3.1). There seems to be some contradiction on this point as the estimated PEC regional is not negligible in comparison with the available monitoring data. It should be realised however, that the PEC regional includes a number of uncertainties, e.g. the estimated emission input or the selected fate parameters (e.g. degradation rates).

3.2 EFFECTS ASSESSMENT

3.2.1 General

The subsequent paragraphs only contain the summarised results of the ecotoxicity studies with MCAA and SMCA. These have already been reviewed by Sweden within the OECD SIDS-program for HPVCs (1994) and by BUA (1993). In addition, an ECETOC report No. 38 (1999) was available. These sources were checked in order to ensure that "key studies" were incorporated in the underlying report. None of these studies is re-evaluated by the rapporteur.

Most of the aquatic toxicity tests were conducted in neutralised medium (pH 7-9.6). As the pH of the medium is always above the pKa (= 2.8) MCAA is fully dissociated and can be considered as a salt dissolved in water. In neutralised medium MCAA was tested as monochloroacetate anion.

3.2.2 Aquatic compartment

3.2.2.1 Toxicity to fish

The short-term toxicity studies with MCAA/SMCA and freshwater fish are summarised in **Table 3.8**.

Table 3.8 Short-term toxicity of MCAA/SMCA to freshwater fish

No.	Species	Exp. (h)	LC50 (mg/l)	Method	Anal. y/n* pH range	Reference
	MCAA					
1	*Pimephales promelas*	96	145	Unknown (semi-static)	no data no data	SIDS, 1994
2	*Leuciscus idus melanotus*	96	>100[1] LC0= 100	In house method (static)	n 8.3-8.7	BUA, 1993
3	*Brachydanio rerio*	96	370	No data	no data neutral	ECETOC, 1999
4	*Poecillia reticulata*	96	369	NEN 6504 (static)	no data 8.0-8.3	BUA, 1993
	SMCA					
1	*Oncorhynchus mykiss*	48	900	Unknown (semi-static)	no data no data	SIDS, 1994
2	*Rasbora heteromorpha*	96	1,400	Unknown	no data no data	SIDS, 1994

[1] At 500 mg/l all fish died, probably due to the low pH at this concentration (pH 3.8).
* Anal. y/n: Analysis yes/no

MCAA (short-term)

Table 3.8 shows that for MCAA the short-term LC50-values for fresh water fish range from 145-370 mg/l. All tests were performed in neutralised medium except for test No. 1. Two tests

(no. 1 and 2) tests are not considered reliable, because no data are given for the test conditions. Nevertheless, the results of these tests are useful as supporting data. The test results for the four different fish species are all in the same order of magnitude.

SMCA (short-term)

The LC50-values of SMCA ranged from 900 to 1,400 mg/l. Test no. 1 is not considered reliable because the described method was not in accordance with EU/OECD guidelines. The reliability of test no. 2 is unknown. Nevertheless, the LC50-values support the obtained results for MCAA, in the sense that they are higher than 100 mg/l.

In the SIDS report (1994) an additional LOEC-value for sublethal effects for *Oncorhynchus mykiss* was available (Walterson et al, 1980). A LOEC of 20 mg/l was obtained, but no information on exposure period, test method and test conditions was given.

Several non–standard toxicity tests are available which were not considered reliable or useful for the RAR (SIDS, 1994). These tests were not included in the BUA- and ECETOC reports either.

MCAA (long-term)

In addition to the base set short-term information for fish, also two long-term studies are available for *Brachydanio rerio* (**Table 3.9**). In the first sub-chronic test fish were exposed for 12 days to concentrations ranging from 56-560 mg/l at neutral pH. In the control group 25% mortality was found. This value exceeds the validity criterium for control group mortality of < 20% according to OECD-guidelines. In study no. 2 only a LOEC was given. However, according to TGD (1996) a NOEC of 12.5 mg/l can be derived from this LOEC (LOEC/2: see footnote **Table 3.9**).

Table 3.9 Long-term toxicity of MCAA to fresh water fish

No.	Species	Exp. (days)	NOEC (mg/l)	Method	Anal. y/n* pH range	Reference
1	*Brachydanio rerio*	12 (days)	NOEC=320[1] LOEC=560	-Sub-chronic -Inhouse SOP	n 8.0-8.2	ECETOC, 1999
2	*Brachydanio rerio*	28 (days)	LOEC=25[2] NOEC=12.5	OECD no.210; ELS test	no data neutral	ECETOC, 1999

1 endpoints were mortality, embryonal and larval malformations and swimming behaviour
NB. According to SIDS this study is performed with SMCA!!

2 No NOEC was found. When the control mortality was taken into account, 15% mortality was found at 25 mg/l. The test concentrations ranged from 25-400 mg/l. According to TGD (1996) a NOEC can be derived when a LOEC > 10 and 20% effect is found. The calculated NOEC is LOEC/2.

* Anal. y/n: Analysis yes/no

3.2.2.2 Toxicity to aquatic invertebrates

The short-term toxicity studies with MCAA/SMCA and freshwater invertebrates are summarised in **Table 3.10**.

Table 3.10 Short-term toxicity of MCAA/SMCA to fresh water invertebrates

No.	Species	Exp. (h)	LC50 (mg/l)	Method	Anal. y/n* pH range	Reference
	MCAA					
1	*Daphnia magna*	48	EC0 =55	unknown	no data	BUA, 1993
2	*D. magna*	24 48	99 77 (71-85)	DIN 38412 Part II	no data pH>=7[3]	BUA, 1993
3a	*D. magna*	24[4]	79	unknown	no data acidic	BUA, 1993
3b	*D. magna*	24[4]	427	Unknown	-n -neutral	ECETOC, 1999
4	*D. magna*	24	180	ISO 6341	-no data -no data[5]	SIDS, 1994
5	*D. magna*	48	75[1]	No data	-no data no data	SIDS, 1994
6	*D. magna*	24 48	>300 88	NEN 6501	no data 8.1-8.2	BUA, 1993
7	*Brachionus calyciflorus*	48	68.9 NOEC=40[2]	No data	no data acidic(>5.5)	ECETOC, 1999
	SMCA					
1	*Daphnia magna*	24	800	ISO 6341	no data no data	SIDS, 1994

1. Not clear whether the medium is neutralised
2. NOEC for reproduction
3. According to ECETOC report (1999), pH is not specified.
4. According to ECETOC report (1999), exposure time is assumed to be 48 hours.
5. Not clear whether the medium is neutralised. According to ECETOC report (1999), pH was in acidic range.

* Anal. y/n: Analysis yes/no

MCAA (short-term)

There are six short-term toxicity tests with MCAA available for *Daphnia magna.* One test (no. 3) is conducted in both non- and neutralised medium. For tests no. 4 and 5 the pH is not given. The 24- or 48 hours EC50 for *D. magna* in neutral and acid medium ranged between 77-427 and 68.9-79 mg/l, respectively. For tests no. 4 and 5, for which the pH value is unknown, the 24- or 48 hour EC50 *D. magna* ranged between 75-180 mg/l. In addition to the *D. magna* studies, a 48-hour EC50 of 68.9 mg/l and NOEC of 40 mg/l for *Brachionus calyciflorus* was found.

The results of MCAA in neutral and acidic medium are in the same order of magnitude, apart from test no. 3b, which showed less toxicity, i.e. an EC50 of 427 mg/l.

SMCA (short-term)

For one test with *Daphnia magna* a 48-hour EC50-value of SMCA 800 mg/l was found.

MCAA (long-term)

In addition to the base set information for *Daphnia magna*, also one long-term study is available (**Table 3.11**).

Table 3.11 Long-term toxicity of MCAA to fresh water invertebrates

No.	Species	Exp. (days)	NOEC (mg/l)	Method	Anal. y/n* pH range	Reference
1	*Daphnia magna*	21 (days)	NOEC=32[1]	Other (draft guideline from Umweltbundesamt, 1984, reproduction study)	y neutral	BUA, 1993

1. endpoint was reproduction rate, time to appearance of first brood and adult mortality
* Anal. y/n: Analysis yes/no

3.2.2.3 Toxicity to aquatic plant (e.g. algae)

The short- and long-term toxicity studies with MCAA/SMCA and freshwater plants are summarised in **Tables 3.12** and **3.13**.

MCAA Short-term studies

Two studies with *Scenedesmus subspicatus* were independently performed at two different laboratories. The obtained results for biomass and growth were within the same range, i.e. 25-28 µg/l for biomass and 30-70 µg/l for growth (48-72-hour EC50-values). A third study with *Pseudokirch Neriella subspicatus* showed a 72-hour EC50 for growth of 1,800 µg/l.

MCAA Long-term studies

Long-term results for three different algae species are presented in **Table 3.13**. The 72-hour NOEC-value for *S. subspicatus* is 6 µg/l. The 48-hour for EC10 (biomass and growth) value for this species (test no.4) is in the same order of magnitude i.e. 7-14 µg/l. In test no. 2 the reported 72-hour EC3 was 5 µg/l which was based on a calculation. The obtained EC3 was considered as a LOEC or NOEC <5 µg/l. A 8-day test with *Scenedesmus quadricauda* resulted in a LOEC of 130 µg/l, which indicates less toxicity. This non-standard test could not be fully evaluated. No explanation was found for the difference in test results between the two species, *Scenedesmus quadricauda* and *Scenedesmus subspicatus.*

Algae are shown to be most sensitive to MCAA/SMCA in comparison with fish and invertebrates. This sensitivity is in accordance with the use of SMCA as a herbicide (see Section 2.2 Use Patterns).

Table 3.12 EC50-data of MCAA for freshwater plants

No.	Species[a]	Exp. (hours)	EC50 (mg/l)	Method	Anal. y/n* pH range	Reference
1	*Scenedesmus subspicatus*	72 hours	0.025[1]	OECD 201	n 7.7-8.1	BUA, 1993
	S. subspicatus	72 hours	0.033[2]	"	"	"
2	*S. subspicatus*	48 hours	0.028[1]	DIN 38,412 Part 9	n 8.1-9.6	BUA, 1993
	S. subspicatus	48 hours	0.07[2]	"	"	"
3	*Pseudokirch-Neriella subspicata*[3]	72 hours	1.8[2]	ISO 8,692	no data 7.4-7.5	ECETOC, 1999

A According to expert judgement the species can be considered as three different species.
1. biomass
2. growth rate
3. former name was *Selenastrum capricornutum*
* Anal. y/n: Analysis yes/no

Table 3.13 NOEC-data of MCAA for fresh water plants

No.	Species	Exp. (hours)	NOEC (mg/l)	Method	Anal. y/n* pH range	Reference
1	*Scenedesmus quadricauda*	8 days	0.13 (=EC3)[1]	Other (non-standard)	n no data	ECETOC, 1999
2	*Pseudokirch-Neriella subspicata*[4]	72 hours	0.005 (=EC3) (EC10 =0.06[2,3])	ISO 8,692	no data 7.4-7.5	ECETOC, 1999
3	*Scenedesmus subspicatus*	72 hours	0.0058	OECD 201	n 7.7-8.1	BUA, 1993
4	*Scenedesmus subspicatus*	48 hours	0.007 (EC10 biomass) 0.014 (EC10 growth)	DIN 38,412 Part 9	n 8.1-9.6	BUA, 1993

1. EC3 was considered to be the LOEC. The NOEC < 0.13 mg/l.
2. ECETOC (1999): "The value of 0.005 mg/l quoted referred to a calculated EC3 and was therefore indicated as a LOEC. However since no statistical analysis was carried out to investigate whether or not the difference from controls was significant, the result should be considered as a NOEC." The rapporteur considers the NOEC < 0.005 mg/l.
3. biomass
4. former name was *Selenastrum capricornutum*
* Anal. y/n: Analysis yes/no

3.2.2.4 PNEC for the aquatic compartment (incl. sediment)

The 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 (herbicide) when compared to fish and invertebrates.

The lowest long-term test result is the NOEC of 5.8 μg/l for *S. subspicatus*. This value should be taken into consideration for derivation of PNEC. However, according to TGD (1996): "If a chemical shows specific toxicity to algae, the algae NOEC determined from the base-set should be supported by a second algae species test". Within the data set there are two tests with other species, *P. subspicata* and *S. quadricauda*, which showed NOEC-values of <5.0 and <130 μg/l, respectively. These tests are considered as not fully reliable. However, these two NOECs do support the lowest obtained NOEC value if 5.8 μg/l. The lowest obtained NOEC for *S. subspicatus* of 5.8 μg/l will be 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 $PNEC_{aquatic}$ of 0.58 μg/l.

Recently the results of an *in situ* aquatic mesocosm study with MCAA were submitted (summary report; Basseres, 2002a). The effects of MCAA on invertebrate communities and periphytic algae were examined in experimental flow through channels in France. Besides a control, three different MCAA concentrations (50, 250 and 1,250 μg/l; nominal values) were used in the study. The following ecological endpoints were investigated: Shannon-Weiner diversity index, abundance and biodiversity (richness) of benthic invertebrates and oligochaetes, and Shannon-Weiner diversity index, biodiversity (richness) and the pollution sensitivity index (IPS) of diatoms. The authors reported the LOEC and NOEC of this study to be 775 μg/l and 236 μg/l, respectively (actual concentrations). The principal question is, however, whether this mesocosm study is useful for the (generic) PNEC water derivation of MCAA.

From the data in the present RAR it is clear that algae (green algae) are the most sensitive taxonomic group: the difference in toxicity between algae and fish/invertebrates amounts to several orders of magnitude. This finding is not that surprising taking into account that MCAA is a known herbicide. The current PNEC (0.58 μg/l) is thus based on the green algae NOEC (Scenedesmus subspicatus: NOEC of 5.8 μg/l) using an assessment factor of 10. A factor of 10 may be used in this case as more than one algae species has been tested in the laboratory and NOECs are available for fish and invertebrates as well. This factor 10 should take into account the (remaining) uncertainties on the lab-to-field extrapolation.

In the submitted mesocosm study the focus is on invertebrates and oligochaetes and for the primary producers initially only diatoms were recorded. The authors of the mesocosm study stated that the reason for the selection of diatoms is that: 'they are the main representatives of algae in a dynamic mesocosm'. Diatoms are not green algae, however, and although they also contain chlorophyll, we have no conclusive data about the difference in sensitivity between diatoms and green algae (Dr P. vd Brink, 2002, pers. comm.). We therefore consider the absence of planktonic green algae in the mesocosm study as an important shortcoming for using it for the derivation of a (generic) PNEC. In an additional summary report (Basseres, 2002b) on the same study, new, but limited information was provided on the response of green algae in the mesociosm study. The submerged glass plates, initially only used for scoring diatoms, were re-analysed on the presence/diversity of green algae. Due to the sampling technique, however, only periphytic algae, in particular filamenteous algae, could be detected. Here again, however, the difference in sensitivity between planktonic green algae and periphytic, filamenteous green algae is unknown. Planktonic algae may be less relevant for (fast)flowing water systems, but the generic PNEC in the EU RA should protect other, i.c. stagnant water ecosystems (lakes, ditches etc.) as well.

In conclusion we think that, despite the elegancy of the test system, the mesocosm study cannot be used to modify the current PNEC of 0.58 μg/l. This because planktonic green algae, being the

most sensitive group from the laboratory studies, were not taken into account. The uncertainties on the lab-to-field extrapolation in the current PNEC are therefore not elucidated yet.

No in-depth evaluation of the summary report of mesocosm study was performed by the Rapporteur. The comprehensive study report is not available yet.

PNEC for sediment-dwelling organisms

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 (EUSES). The rapporteur realises that the validity of this PNEC for sediment is questionable as it is based on partition coefficients. The use of partition coefficients in the case of MCAA is uncertain (see Section 3.1.1).

3.2.2.5 Toxicity to micro-organisms (e.g. bacteria)

The short-term toxicity studies for MCAA with bacteria and protozoa are summarised in **Table 3.14**. Several tests (n=12) with different species are available. However, only 9 tests (no. 1, 3-5, 7, 9-12) seem to be reliable and useful for the risk assessment. The NOECs for *P. putida* from different tests (no. 4 and 5) are in the same range, i.e. > 1,000 mg/l. In tests no. 1, 3 and 7 mixed populations of bacteria were found to be more sensitive than *P. putida*. The lowest NOEC and EC50 for bacteria is 80 and 160 mg/l, respectively. For protozoa the lowest observed IC50 is 16 mg/l.

Table 3.14 Toxicity of MCAA to micro-organisms

No.	Species	Exp. (hours)	NOEC (mg/l)	Method	Anal. y/n* pH range	Reference
	Bacteria					
1	Activated sludge Bacteria	No data	750	OECD confirm. Test	no data no data	ECETOC, 1999
2	Activated sludge	24[1]	570	Zahn-Wellens test	no data no data	ECETOC, 1999
3	Domestic sewage sludge	24 hours	80[2]	ETAD ferm. Tube method	no data no data	BUA, 1993
4	*Pseudomonas putida*	18 hours	4,630 (EC10)	Cell multi-plication inhibition	no data neutralised	ECETOC, 1999
5	*Pseudomonas putida*	3 hours	> 1,000	OECD 209	no data no data	ECETOC, 1999
6	*Vibrio fischeri*	22 hours	10 68.9 (EC50)	Other[3]	no data no data	ECETOC, 1999

Table 3.14 continued overleaf

Table 3.14 continued Toxicity of MCAA to micro-organisms

No.	Species	Exp. (hours)	NOEC (mg/l)	Method	Anal. y/n* pH range	Reference
	Bacteria					
7	Domestic sewage sludge	24 hours	160[4]	ETAD ferm. Tube method	no data no data	BUA, 1993
7a	Activated sludge (industrial; adapted))	10 minutes	600 (pH of 3, not adjusted) 12,000 (neutralised with NaOH)	Oxygen uptake rate (OUR)	No Yes	Sarlin et al., 1999
8	Methanogenic bacteria culture, adapted	24 hours	945[5] (EC100)	Methane production	no data neutralised	ECETOC, 1999
9	*Pseudomonas putida*	10 hours	1,000-2,000[6]	Microplate	no data no data	ECETOC, 1999
	Protozoa					
10	*Tetrahymena pyriformis*	9 hours	83	Flask test	no data no data	ECETOC, 1999
11	*Tetrahymena pyriformis*	36 hours	16	Microplate technique	no data no data	ECETOC, 1999
12	*Tetrahymena pyriformis*	3 hours	626	Acute tox. Test	no data no data	ECETOC, 1999
	Tetrahymena pyriformis	6 hours	510	Acute tox. Test	no data no data	ECETOC, 1999
	Tetrahymena pyriformis	9 hours	106	Acute tox. Test	no data no data	ECETOC, 1999

1. Time to onset of biodegradation. The NOEC for the latency period of 10% biodegradation can however be considered to be 570 mg/l. There was no pre-adaptation of the activated sludge.
2. Compound not specified.
3. Probably a MICROTOX test. *Vibrio fischeri* is a salt-water species.
4. ECETOC (1999): "the test procedure did not use a completely anaerobic or aerobic methodology and has been discontinued. Test solutions might not have been adjusted to neutral conditions."
5. At 94.5 mg/l, neutralised MCAA caused a delay of one week to methanogenesis. Control showed methane production within 24 hours.
6. Activated sludge respiration inhibition test performed with *P. putida*. Activated sludge was replaced with a monoculture of *Pseudomonas putida*. Resistant strains of *P. putida* by culturing the parent PP3 strain on a solid medium containing MCAA (unspecified) at a concentration of 1-2 g/l carbon.

* Anal. y/n: Analysis yes/no

3.2.2.6 PNEC for micro-organisms

The results show that bacteria are less sensitive than protozoa. Protozoa are regarded as additional species for derivation of a $PNEC_{micro\text{-}organisms}$ (Doc. ECB4/TRI/98). 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.

PNEC $_{\text{micro-organisms}}$ = 1.6 mg/l.

3.2.3 Terrestrial environment

3.2.3.1 Toxicity to soil dwelling organisms

No data available.

3.2.3.2 Toxicity to terrestrial plants

SMCA is a non-selective herbicide. A pesticide manual, however, indicates that SMCA is a selective contact herbicide with broad spectrum against broad leafed weeds. SMCA as a herbicide is applied via spray. Concerning the mode of action the SIDS report (1994) mentioned: "halogenated acetates are theoretically able to alkylate the sulfhydryl or amino groups in enzymes".

SMCA is also used in combination with atrazine for total weed control on uncultivated land.

In the SIDS report (1994) an LC100 of 6.7 g/m^3 soil for terrestrial plants was given. The effect concentration was based on the recommended herbicide dose applied via spraying in agriculture (20 kg/ha to a 0.3 m depth).

Study with pine seedlings

In two studies, pine seedlings (*Pinus sylvestris)* were exposed to MCAA and trichloroacetic acid (TCAA) (Shroder et al., 1997; Sutinen et al., 1997). In the abstract of the first study, titled as "Exposure to Chlorinated Acetic Acids: Responses of Peroxidase and Gluthathione S-Transferase Activity in Pine Needles" the following is cited: "During long-term exposure of pine (*Pinus sylvestris* L.) seedlings to trichloro- and monochloroacetic acids via root uptake or acid mist treatments, both substances were removed from the plant tissues by metabolic activity. None of the treated plants exhibited visible stress at concentrations used. In addition, the exposure to both substances led to dramatic changes in the activity of xenobiotic detoxification enzymes (peroxidase and gluthatione S-transferase) in the needles of the plants".

In the abstract of the second study, titled as "Long-term exposure of Scots pine seedlings to monochloroacetic and trichloroacetic acid: Effects on needles and growth" the following is cited: "The effects of monochloroacetic acid (MCAA) and trichloroacetic acid (TCA) exposures on Scots pine seedlings were studied. The exposures, with two dose levels for TCA and one for MCAA, were done simultaneously via the roots and the foliage during two consecutive simulated growing seasons. An increase in potassium concentration in current-year needles exposed to lower TCA dose after the first exposure season, and an increase in the nitrogen concentration, as well as a decrease in the transpiration rate and in the total chloroplast area, were noted in the current-year needles exposed to MCAA after the second exposure season and these changes were statistically different form the control. These results may be due to charge compensation and hormonal changes induced by subtoxic levels of TCA and MCAA." Several endpoints were examined within this study such as: chlorophyll concentration, transpiration rate, growth, nutrient concentrations and microscopic studies on mesophyll tissue (e.g. number of chloroplasts, starch grains etc).

The seedlings in both studies were exposed via roots and to foliar mist by applying 5 ml of 1 mg/l (0.005 mg MCAA) and 10 ml of 5 mg/l MCAA (0.19 mg/m^3), respectively. MCAA was not measured in the needle samples. No EC50 or NOEC value can be derived from these studies.

Recently an OECD 208(A) Seedling Emergence and Seedling Growth test was carried out with MCAA. One monocotyledon (oat, Graminae) and two dicotyledons (rape, Brassicaceae) and red clover (Leguminosae) were tested. The test was conducted with the concentrations 0, 1.0, 3.2, 10, 32 and 100 mg/kg dwt. For shoot height a lowest NOEC of 3.2 mg/kg dwt was found for red clover. For fresh weight a similar result was found, whereas for seed emergence a lowest NOEC of 3.2 mg/kg dwt with oat as most sensitive species. The test substance was mixed with the soil and after the start of the experiment no renewal takes place. MCAA is known to be (bio)degraded rather fast in soil (DT50 of 66 hours in neutral soil at 15ºC) and one may question the amount of MCAA during the experiment. The duration of the experiment is 21 days and no analytics were carried out. The aspect of MCAA loss will be discussed in the section on the derivation of the PNEC soil.

3.2.3.3 Toxicity to soil micro-organisms

No data available.

3.2.3.4 PNEC for terrestrial compartment

The $PNEC_{terrestrial}$ can be estimated in two different ways: 1) from the PNEC for aquatic organisms using the equilibrium partitioning and 2) from the plant experimental data.

1) The equilibrium partitioning approach according to TGD. EUSES generates a $PNEC_{terrestrial}$ of 0.11 µg/kg wwt.

$PNEC_{terrestrial}$ = 0.1 µg/kg WWT

Similar to the PNEC for sediment, also the validity of the PNEC soil for MCAA is questionable as it is based on partition coefficients (see Section 3.1.1).

2) The 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. The limitations of this test, in particular the potential loss of the substance during the experiment, were discussed in Section 3.2.3.2. Rather than only expressing the NOEC on the initial, nominal concentration, it is considered relevant to calculate (and use) an average test concentration as well. 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 will be 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. Although chronic data are only available for one trophic level it can be expected that plants will be most sensitive to MCAA This because of MCAA's characteristics as herbicide which is supported by the finding that algae were found to be most sensitive among the aquatic species. For these reasons an assessment factor of 10 could be suggested. As a worst case approach a factor of 100 is (initially) proposed, resulting in PNECs of 32 µg/kg dwt and 6 µg/kg dwt (time average).

The 'experimental' PNEC is much higher than the one based on equilibrium partitioning. Due to the large uncertainties around the PNEC based on equilibrium partitioning, preference is given to the experimental PNEC.

In the seedling emergence/growth test the plants were exposed to MCAA via the soil (OECD 208A). However, MCAA is known to be a contact herbicide and therefore the exposure route via spraying (leafs) may be considered as most sensitive. The relevancy of the seedling emergence/growth test may therefore be questioned as deposition plays an important role for this chemical. The (ir)relevancy of the seedling emergence/growth test for the risk assessment of MCAA is further discussed in Section 3.3 Risk characterisation. An alternative approach that is based on the effective dose of MCAA (20 kg/ha) will be presented as well to overcome the shortcomings of the current $PNEC_{terrestrial}$.

3.2.3.5 Other organisms

Bees

In a pesticide manual MCAA was indicated as toxic to bees (Tomlin, 1997).

3.2.3.6 PNEC for plants (atmospheric compartment)

MCAA/SMCA is known for its phytotoxic properties, but the available set of data for the atmospheric compartment is considered not suitable to derive a PNEC.

3.2.3.7 Abiotic effects (atmosphere)

According to RIVM expert judgement acidification and ozone depletion are not considered relevant for MCAA/SMCA.

3.2.3.7.1.1. Non compartment specific effects relevant to the food chain (secondary poisoning)

Toxicity to birds

Two field studies with geese are cited in ECETOC (1999). Regarding the first study ECETOC states: "The geese suffered no ill effects when simply moving around an SMCA-treated pasture without feeding, but 4/6 died within 24 hours of ingesting treated plants in a second pasture sprayed with 20 kg/hectare and 3/6 died after feeding on plants dosed at 40 kg/hectare".

In the second (gavage) study with geese a LD50 of 75 mg/kg body weight was reported for SMCA (ECETOC, 1999). The NOEL in this study was 50 mg/kg b.w.

In the SIDS-report (1994) a LD50 (? days) of 81 mg/kg body weight for a hen was given. It was unknown whether the LD50 refers to SMCA or MCAA. In the SIDS report it was stated that SMCA/MCAA was "classified toxic to poultry".

Toxicity to birds and cattle (accidental exposure)

In ECETOC report (1999) accidents of SMCA-herbicide were described with geese and greenfinches exposed on a sprayed field. Some of the birds were found dead within a few hours or days or showed several clinical signs.

In addition, in accidents with cattle, amongst other sheep, similar effects were found. The authors (Quick et al, 1993; cited in ECETOC report) calculated effect doses of 17-68 mg/kg and 39-70 mg/kg SMCA for two different incidents with cattle.

PNEC derivation

As stated in Section 3.1.1, bioaccumulation/secondary poisoning is considered not to be relevant for MCAA/SMCA. Furthermore, no PNEC is needed because the PEC cannot be estimated (see use of log K_{ow} for bioconcentration factors).

3.3 RISK CHARACTERISATION

3.3.1 Added risk approach

Chloroacetates, including monochloroacetates, are found ubiquitously in the environmental compartments. According to Frank (2001) the non-industrial formation of MCAA plays an important role (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.

If the regional background observed MCAA levels would be mainly due to natural sources, then 'simply' using the derived PNEC in the risk characterisation without further attention would not be correct. Ecosystems would probably have adapted to a considerable part of these natural background levels of MCAA. An option for performing a risk characterisation could then be the use of the 'added risk approach' (Struijs et al., 1997; see also EU RAR on zinc and zinc compounds). The use of the added risk approach implies that only the anthropogenic amount of a substance is considered to be relevant for the effect assessment. A possible contribution of the natural background concentration to toxic effects is ignored.

The Frank study (2001) is clear in its conclusion that the contribution of emissions from the MCAA industry (production and users) to the observed regional/continental MCAA background levels is negligible. The study is less clear, however, to what extent these background levels originate from natural or anthropogenic (non MCAA related) sources. Due to this uncertainty the added risk approach, which basically assumes that the background is natural, can not be followed in the current RAR on MCAA.

3.3.2 Aquatic compartment

The $PNEC_{micro\text{-}organisms}$ and $PNEC_{aquatic}$ were set at 1.6 mg/l and 0.58 µg/l, respectively. These values are compared with the PEC_{wwtp} and $PEC_{surface\ water}$ for the various environmental exposure scenarios. **Table 3.15** shows these PEC/PNEC ratios.

Table 3.15 Local PEC/PNEC ratios for micro-organisms (WWTP) and aquatic organisms

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

At production site I-C both the PEC/PNEC for the WWTP and surface water are larger than 1. Industry has indicated that the WWTP of site I-C was not functioning properly at the time of the submission of their release data. This was confirmed by later measurements. A number of steps will be (or have been) taken to reduce MCAA losses into the local environment. The measures are: 1) major refurbishing and refitting of the local WWTP, 2) reducing the losses of MCAA to an absolute minimum and regrouping the sewage pipe system so that all waste water from the plant passes through the WWTP and 3) recovery of MCAA for incineration rather than to waste water. As at this moment there is no information about the effectiveness of these measures **conclusion (iii)** is considered most appropriate for site I-C. Industry indicated that a new monitoring campaign will be launched after the completion of the technical steps for reducing MCAA emissions to surface water (first half of 2003).

The PEC/PNEC equals 1 for site I-B1. Local monitoring data (downstream discharge outlet of site I-B1) on two out of five sampling days however were found to 0.6-0.8 and 0.5-0.6 µg/l. The corresponding PEC/PNEC range then becomes 0.9-1.3, indicating that the PNEC may be exceeded in the vicinity of site I-B1. The Rapporteur realises that the number of monitoring data is very limited, but argues that if in a five-day monitoring campaign the PNEC can already be exceeded, this may occur more often during a year. In addition, higher PECs, and thus larger PEC/PNEC ratios than 1.3 may occur as well. For these reasons **conclusion (iii)** is considered most appropriate for site I-B1. Industry has stated that the local WWTP of site I-B1, a municipal STP, is currently being reconstructed by the local authorities and this will further increase its removal capacity. The expected termination date of the upgrade is February 2003 and a further monitoring campaign will be carried out by industry to confirm approved biodegradation of MCAA a soon as the work is completed.

For the remaining scenarios the PEC/PNEC for both STP and surface water are below 1: **conclusion (ii)**. For site I-B2 this conclusion is supported by local monitoring data.

All measured regional background concentrations for surface water in the EU are below the PNEC surface water: **conclusion (ii)**.

(Note: Now the calculated PEC regional of 68 ng/l is used as background for the local exposure assessment (see Section 3.1.1.3.4). Selecting another regional background value, for example a value between 20 and 400 ng/l based on the range of measured MCAA levels, would not alter the conclusions of the risk assessment. This because for site I-B1 and I-B2 the current

conclusions are supported by local (site specific) monitoring data. For site I-C the regional background is negligible to the local emissions, whereas for sites IA1 and IA2 the local emissions are so low that the PEC is nearly completely determined by the regional background (PEC/PNEC < 1). The only borderline case would be the maximum value of the processing sites (II). Only if a background higher than 260 ng/l would be used then the local assessment would result in a PEC/PNEC of slightly above 1. With a (maximum) background value of 400 ng/l the PEC/PNEC would become 1.2. It is considered too speculative however to follow this line of reasoning due to the many uncertainties about a.o. the 'real' background for this specific site and the unknown natural part of the regional background concentrations (see Section 3.3.1).

3.3.3 Atmosphere

As no PNEC for air could be derived, no risk characterisation is carried for the atmospheric compartment. Deposition is taken into account in Section 3.3.4 (terrestrial compartment).

Acidification and ozone depletion are not considered relevant for MCAA/SMCA.

3.3.4 Terrestrial compartment

The calculated PECs in soil are compared with the PNECs soil of 32 and 6 µg/kg dwt.

Table 3.16 shows the PEC/PNEC ratios for soil.

Table 3.16 Local PEC/PNEC ratios for soil

Scenario	PEC/PNEC soil PNEC 32 µg/kg	PEC/PNEC soil PNEC 6 µg/kg
Production/processing site I-A1/II-A1	0.1	0.05
Production/processing site I-A2/II-A2	0.1	0.05
Production site I-B1	0.1	0.05
Production site I-B2	0.1	0.4
Production site I-C	0.1	0.05
Processing sites (maximum)	0.1	0.2

For soil in all exposure scenarios the PEC/PNEC is <1, irrespective of the selected PNEC: **conclusion (ii)**. The measured soil concentration in the vicinity of site I-B2 was found to be below the detection limit (< 15 ng/g) which confirms **conclusion (ii)** for this particular site.

In Section 3.2.3.4 the relevancy of the exposure route in the seedling emergence test was discussed. The point is that MCAA is a contact herbicide and based on this mode of action the exposure route via leafs may be more sensitive than the root exposure in the seedling emergence/growth test. The local exposure assessment for MCAA for the terrestrial compartment is entirely determined by atmospheric deposition which may make the 'classical' approach for the soil risk characterisation in this particular case discutable. As an alternative approach, the local deposition around MCAA production and processing sites will be compared with the available, quantitative information on MCAA as contact herbicide. Only a recommended spraying dose of 20-25 kg/ha is available. The maximum deposition rate for the MCAA production/processing sites is 0.024 mg/m^2/d for site I-B2. The recommended dose of 20-25 kg/ha is equal to 2-2.5 g/m^2. The difference therefore amounts to about a factor 100,000. The Rapporteur is aware of the limitations of this comparison (e.g. acute, high dose effect versus

continuous, low dose exposure), but nevertheless some thoughts can be given on the 'safety margin' of 100,000. The recommended dose corresponds, by definition, with an LC90 or LC100. An extrapolation from such a LC100 towards a NOEC should be made and, although not much data is available to the Rapporteur on the full dose-effect curve of MCAA for terrestrial plants, a factor of 100 is considered to be acceptable for this. (The dose-effect relationships in the seedling emergence/growth test support this choice). An additional assessment factor of 10 may be relevant for interspecies variation, leaving a factor 100 for the remaining uncertainties. (Note that extrapolation from lab to field is not necessary in this case, as the recommended dose is based on field data). This is considered to be sufficient. **Conclusion (ii)** as drawn above for all exposure scenarios based on the 'classical' approach is thus supported by this alternative assessment.

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 **conclusion (i)** is not related to the industrial production and use of MCAA (unintentional sources).

3.3.5 Non compartment specific effects relevant to the food chain

No risk characterisation is carried out for secondary poisoning (see use of log K_{ow} for estimation of bioconcentration factors).

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General introduction

Monochloroacetic acid (MCAA) as a raw material is a colourless, highly hygroscopic powder, with a sharp odour. It has a low vapour pressure at room temperature and is soluble in water and in common organic solvents. Chapter 2 contains detailed information on the use categories of MCAA. The substance is mainly used in the production of carboxymethylcellulose (CMC), crop protection chemicals (like 2,4-D and MCPA), thioglycol acid (TGA), surfactants (e.g. for shampoos and industrial cleaning agents), dyes (indigo), pharmaceuticals (caffeine, vitamin B6) and a variety of other products. The substance is marketed as a powder or flakes, as a concentrated solution in water, methanol or ethanol, but also in molten form, as its Na-salt or as the methyl ester (Kirk-Othmer, 1982).

In **Table 4.1** an overview of occupational limit values for MCAA is given.

Table 4.1 Occupational limits values for MCAA

Country/ Organisation	8-hour TWA (in mg/m³)	15 min. STEL (in mg/m³)	Remarks	References
United Kingdom/HSE	1.2	-	skin notation	HSE, 1998
Deutsche Forschungsgemeinschaft	-	-	under revision; for the time being, it was not possible to establish a TWA-value	Deutsche Forschungsgemeinschaft, 1998
The Netherlands	4	-	skin notation	SZW, 1997
Sweden	4	8	skin notation	AFS, 2000
USA	1	4	skin notation	AIHA, 1984

4.1.1.2 Occupational exposure

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 population exposed is workers in the chemical industry, active in processing MCAA. These processes include production and use of the substance, drumming or adding various forms of MCAA or transfer from and to tanks, and cleaning and maintenance of the used equipment.

MCAA is also used as a component in paint removal baths. There were no indications that MCAA today is still an ingredient of graffiti removers. For the latter it seems that it is no more in use, due to more strict environmental regulations.

The following data (if available) are used for occupational exposure assessment:

- physico-chemical data of MCAA, such as physical appearance and vapour pressure at room temperature;
- data regarding the production process and use pattern of the substance and the amount of the substance in the products;
- exposure control pattern in the relevant industries (from the HEDSET or other sources);
- exposure data from the HEDSET or other sources (literature, exposure databases);
- results from exposure models if applicable (EASE model); in the exposure models the above mentioned types of data are used.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Documents and agreements made at official Meetings of Competent Authorities (TGD, 1996). Internal dose depends on external exposure and the percentage of the substance that is absorbed (either through the skin or through the respiratory system).

The exposure is generally assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment as based on potential exposure indicates that risks are to be expected, the use of personal protective equipment may be one of the methods to decrease actual risks, although other methods (technical and organisational) are to be preferred. This is in fact obligatory following harmonised European legislation.

Knowledge of affectivity of PPE in practical situations is very limited. Furthermore, the affectivity is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonably effective use of proper PPE for skin exposure may reduce the external exposure by 85%. For respiratory protection the efficiency depends largely on the type of protection used. Without specific information, a tentative reduction efficiency of 90% may be assumed, equivalent to the assigned protection factors for supplied-air respirators with a half mask in negative pressure mode (NIOSH, 1987). Better protection devices will lead to higher protection. Imperfect use of the respiratory protection will lower the practical protection factor compared to the assigned factor. These estimations of reduction are not generally applicable "reasonable worst-case" estimations, but indicative values based on very limited data. They will generally not be used directly in the exposure and risk assessment. Furthermore, the reduction of external exposure does not necessarily reflect the reduction of absorbed dose. It has to be noted, that the use of PPE can result in a relatively increased absorption through the skin (effect of occlusion), even if the skin exposure is decreased. This effect is very substance-specific. Therefore, in risk assessment it is generally not possible to use default factors for reduction of exposure as a result of the use of PPE.

In some specific situations the model estimates with normal assumptions for input parameters or measured values outside of PPE in the assessed exposure scenarios are expected not to lead to a reasonable assessment of exposure. For situations with high risk of direct acute effects, such as manual handling of corrosive substances and hot materials, or possible inhalation exposure of substances with severe acute effects on the respiratory tract, the total level of containment given by all exposure control measures is assumed to be higher than for similar scenarios with other substances. In these cases, for estimating exposure an extra protection is assumed. According to the new Technical Guidance Document (Draft 2001) the Assigned Protection Factors (APF) given by the BS 4,275 for the relevant type of RPE should be used to calculate exposure with RPE from the exposure without RPE. To protect the worker from MCAA a semi- mask with a P2 filter or a full mask with a P3 filter is used depending on the form (liquid or powder) of the substance. Assigned protection factors according to BS 4,275 are respectively 10 and 20. For the

purpose of this exposure assessment an assigned protection factor of 10 for all scenarios is assumed.

For inhalation exposure these values are calculated for specific tasks or activities that lead to high exposure levels only. For other activities in the same scenario, e.g. background exposure, no additional protection is assumed. The extra protection can be reached by a combination of technical and organisational control measures and personal protective equipment. If the extra protection is reached (mainly) by using personal protective equipment, this is an unwanted situation that should be changed by further technical and organisational control measures.

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 incidental 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. Thus, dermal contact will only occur accidentally, with the exception of Scenario 4.

The MCAA Industry Risk Assessment Group consists of three companies. Four companies supplied data on physico-chemical properties, production and exposure. Their total production is estimated to be roughly 80% of the total European production (Feenstra and De Voogt, 1986). It may therefore be concluded that this document is representative for the European Industry as a whole.

From the uses of MCAA as mentioned the following scenario's for exposure will be discussed:

Scenario 1: The production of MCAA
Scenario 2: The use of MCAA in synthesis
Scenario 3: Formulation of paint removers
Scenario 4: Use of paint removers

Because MCAA is a very corrosive substance, and dermal or inhalation exposure may cause severe health effects, it is assumed that appropriate personal protective equipment is used during all activities in production and formulation. Ocular exposure, due to hand-eye contact, is assumed not to occur because of the corrosive properties of the substance and the use of PPE. It is assumed that single dermal exposure and inhalation exposure will be reduced to 10% of the potential exposure. The results for exposure using analogous substances or models will be dealt with accordingly.

4.1.1.2.1 The production of MCAA (Scenario 1)

There are two major commercial processes for the production of MCAA:

1 Chlorination of acetic acid

In this process acetic acid is chlorinated at temperatures between 85 and 120°C. Acetic anhydride and/or acetyl chloride may be used as catalysts. The chlorination product contains appreciable amounts of acetic acid and/or dichloroacetic acid. Upgrading takes place either by selective dechlorination of dichloroacetic acid (by treatment with hydrogen gas in the presence of a catalyst such as palladium) and subsequent distillation or by recrystallisation from suitable solvents.

2 Hydrolysis of trichloroethylene

In this process equal weights of trichloroethylene and sulfuric acid are heated to 130-140°C in the reactor. A mixture of trichloroethylene and sulfuric acid is continuously fed to the bottom of the reactor. The chloroacetic acid and sulfuric acid are permitted to overflow into a cascade still, where the chloroacetic acid is distilled at 20 mm Hg and the sulfuric acid is recycled. The hydrolysis of trichloro ethylene yields high-purity MCAA but has the disadvantage of utilising a relatively more expensive starting material.

The four companies that supplied data are all producing MCAA by the first mentioned process, the chlorination of acetic acid. In-plant transport of MCAA is carried out in the liquid state through permanently installed pipes, while transport outside the plant is in heatable tankers. Filling and charging processes are by compensation pipe.

The process is run in a completely closed system. Normally, all workers wear a protective suit. When samples are taken, special protective gloves and goggles are worn. If there is a danger of splashing, a safety shield is used additionally. During repairs, or if MCAA has to be handled directly, a special propylene-coated protective clothing is used. To prevent exposure local mechanical exhaust ventilation is used.

Relevant activities to exposure during production are routine procedures in the production process, cleaning and maintenance, and quality control sampling, 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). MCAA is marketed in various forms: as a solid (powder or flakes) or in molten form (kept at a temperature > 80°C) or as an 80% dilution in water. For these forms of packaging, exposure estimates are made.

Measured data

Production

Data on exposure were received from four companies (company A-D, 1998, company B and C, 2000). The results are summarised in Annex 4. No additional data on exposure were found in literature or European databases. The measured data concern only inhalation exposure. Dermal exposure is only described in literature, when accidental spilling took place, causing severe health problems. Most data are personal air samples, reported as TWA-values over a whole shift. Some short term values are mentioned, including one high exposure level due to an incident. The activities during measurements are also mentioned. Operators during production are frequently measured. In one company (company A), repeated measurements were done in subsequent years with the same population. From the table it may be concluded that analytical methods may have improved, because accuracy seems to improve and the limits of detection tend to be more sensitive in recent years.

For operator exposure, the data range from 0.005 to 7.9 mg/m^3. Most of the measured values are in the lower part of the range. Short term exposure values were 2 and 3.5 mg/m^3 (N=2). During unloading of MCAA, a value of 0.28 mg/m^3 was measured.

Maintenance

Two measurements were reported during maintenance: 2 mg/m^3 as a short term value and 0.13 mg/m^3 (8-hour TWA) for a maintenance operator.

Packaging

Company B mentions data for measurements during bagging and packaging. The range is <0.005-0.39 mg/m^3 (N=7). The median of the packaging samples was 0.005 mg/m^3 and three samples were < 0.005 mg/m^3. The physical form of MCAA during packaging was not mentioned. Company C mentions production in a packaging area with exposure levels of 0.35 mg/m^3 (TWA, N=2). More samples were reported in the period 1991-2000. The average during packaging (N=5) was 0.8 mg/m^3 and during bagging (N=3) it was 0.5 mg/m^3.

Models and analogous substances

Cleaning and maintenance

It is assumed that in cleaning and before maintenance (when installations have to be opened), facilities and equipment are flushed with a suitable solvent (for instance water). In view of the high solubility of MCAA, the maximum concentration of the residual is assumed to be 1%. Inhalation exposure is therefore expected to be negligible.

Dermal exposure is considered to occur only accidentally.

Packaging of solids

MCAA is packed as a solid in 25 kg paper bags, 136 kg fibre drums or 1,000 kg big bags. Inhalation exposure to vapour (Vp = 0.02 kPa), assuming non-dispersive use and the presence of local exhaust ventilation (LEV) is estimated to be in the range of 0.5-3 ppm (2-11.8 mg/m^3). Dust exposure is estimated by EASE to be 0-1 mg/m^3, based on low dust technique with LEV. Low dust technique is assumed based on the specific equipment used for preventing emission as far as possible. The filling of the 25 kg bags and the palletisation are automatic processes. The bagging installation is protected from the rest of the building with Plexiglas housing with exhaust dust control. The total inhalation exposure ranges from 2-12.8 mg/m^3.

In literature, total dust concentrations during bag filling range from 0.15-45 mg/m^3 (Lansink et al., 1996). These concentrations apply for manual bag filling and are very high values in the respective studies, probably due to poor dust control. For automatic bag filling operations, exposure ranges from 0.6 to 1.6 mg/m^3 (Lansink et al., 1996, number of measurements not mentioned). A tentative "reasonable worst-case" for manual bag filling with local exhaust ventilation is 10 mg/m^3. It has to be considered however, that plant conditions and control measures influence the exposure. The use of PPE is assumed to further reduce exposure with 90%.

Dermal exposure during drumming or bagging is considered to occur only accidentally.

Transfer of liquids

A usual method of transportation of MCAA is in molten form (> 80°C) or as an 80% solution in water (> 40°C). Vapour pressures mentioned are not very consistent. In particular, different vapour pressures are mentioned for aqueous solutions. For the exposure assessment for molten MCAA, a value of 1.3 kPa (80°C) is used and for the 80%-liquid a value of 0.019 kPa (40°C).

Molten MCAA

For assessment of exposure during tank filling, the EASE model is used. Since the system of filling tanks is described as a closed system, it is possible that short term exposure may be possible when pipes are uncoupled or other attachments are made. In the model the opening of a system is usually described as 'breaching for sampling or maintenance'. Assuming a temperature of 80 °C and a vapour pressure of 1.3 kPa, the inhalation exposure is estimated to be 0.5-3 ppm (2.0-11.8 mg/m^3). Dermal exposure is considered to occur only accidentally.

MCAA, 80% solution

It is assumed that for filling tanks with MCAA as an 80% solution the same conditions apply as for using molten MCAA. The process temperature is assumed to be 40°C and the vapour pressure to be 0.019 kPa. The inhalation exposure range estimated by the model is 0.5-3 ppm (2.0-11.8 mg/m^3).

Dermal exposure is considered to occur only accidentally.

Conclusions

For exposure during production, sufficient data are available for an estimate of inhalation exposure. Since these data are supplied by several producers in Europe, measured in the course of several years, they may be considered to be representative. From the data it is estimated that a typical value for exposure during production is 0.1 mg/m^3. A reasonable worst case value of 1 mg/m^3 is concluded. A short term value of 2.5 mg/m^3 is concluded (all based on measured data). It is assumed, that no respiratory protective equipment is used during background exposure situations. In the other situations, proper PPE will reduce the reasonable worst-case exposure and the short term exposure to 0.1 and 0.25 mg/m^3.

The reported data for maintenance did not describe in detail the activity during which the measurements were performed. The result of the estimate with the EASE model for exposure is used for risk characterisation: negligible inhalation exposure. During the handling (packaging) of MCAA as a solid, the estimates of the analogous substances are used, together with the few measured data on 'packaging' (no exact description of the work has been mentioned). It is assumed that the drumming will be an automated process. As a typical value, the upper side of the measured range of analogous substances is taken: 1.6 mg/m^3. The reasonable worst-case of 10 mg/m^3 was not for an automated process, but for manual work in the presence of LEV. It is more appropriate to regard this value as a short term exposure. For a worst case value, twice the typical value is taken: 3.2 mg/m^3. It is assumed that respiratory protection is used to prevent acute effects on the respiratory system. A protective effect of 90% is assumed, which reduces the typical value to 0.16 mg/m^3, the reasonable worst-case situation to 0.32 mg/m^3 and the short term value to 1.0 mg/m^3.

For handling MCAA in liquid form (molten or as an 80% solution), the lower side of the estimated range (EASE) is taken as a typical value: 2 mg/m^3. The upper value is taken as a worst case approach: 11.8 mg/m^3. The short term value is estimated as twice the worst-case value: 23.6 mg/m^3. A reduction of 90% due to the use of protective equipment is assumed, which reduces the typical concentration, the reasonable worst-case and the short term concentrations to 0.2, 1.2 and 2.4 mg/m^3 respectively (all expert judgement). This estimate is assumed to be for a whole shift, since there is no information on job times.

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

Production is a continuous process which takes, 24 hours/day, 7 days/week, and 365 days/year. Packaging is in a two-shift system during five days per week. The number of persons involved in production is estimated to be 200-300.

4.1.1.2.2 Use of MCAA in synthesis (Scenario 2)

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 (usually without weighing (comp A)) to a reaction mixture. Like in Scenario 1, the results of the exposure estimate by the model are for this situation reduced by 90% (due to the use of protective equipment) for use in risk characterisation. The factor is based on expert judgement and is used to account for the protective effect of PPE that will be used because of the corrosive nature of MCAA.

Measured data

No measured data are available for the use of MCAA in various processes.

Models and analogous substances

Solid MCAA

Addition of powder may lead to the emission of dust, depending on the dustiness of the substance and on the proper use of adequate local exhaust ventilation (LEV). Exposure levels estimated by the EASE model, assuming the presence of proper local exhaust ventilation, are up to 2-5 mg/m^3 (reasonable worst-case estimate).

Bag dumping of other substances is described several times in the literature. Total dust exposures reported vary from 0.1 to 15.9 mg/m^3, while respirable dust varies from < 0.1 to 5 mg/m^3. These data are for situations with LEV. Without LEV exposures are stated to be much higher, but actual data to verify this were not reported by the available sources.

Comparing the reported data for analogues with the estimates by the EASE model it appears that the estimation with LEV does not represent a reasonable worst case. This may be due to the use of not highly efficient ventilation systems in some of the sources studied. A reasonable worst case estimate for total dust exposure levels due to weighing and dumping of powders, using more or less efficient LEV is 10 mg/m^3. However, due to the corrosive nature of the substance and the well equipped industries involved, it may be assumed that effective LEV will be used for handling of MCAA. Furthermore, it is assumed that PPE, with a protective effect of 90% is used.

Dermal exposure is considered to occur only accidentally.

Molten MCAA

The assumption of non-dispersive use and direct handling is usually done for substances that are non-corrosive. Details of the way in which MCAA is added to reaction mixtures are not known, but it is very likely that measures have been taken to reduce inhalation exposure, for instance by means of very good local exhaust ventilation. If LEV is present, the estimated exposure is 0.5-3 ppm (2-11.8 mg/m^3). Handling the liquid may take place during two hours per day, using

personal protective equipment. This will reduce full-shift to 0.05-0.3 mg/m^3 ((2-11.8) · 0 .1 · 2/8).

Dermal exposure is considered to occur only accidentally.

MCAA, 80%-solution

Assuming that good LEV is present and that exposure only takes place during coupling and decoupling of transfer lines, the inhalation exposure levels are estimated by the EASE model to be 0.5-3 ppm (2.0-11.8 mg/m^3). Handling the 80%-solution may take place during two hours per day, using personal protective equipment. This will reduce the concentration range to 0.04-0.2 mg/m^3 ((2.0-11.8) · 0.1 · 0.8 · 2/8).

Dermal exposure is considered to occur only accidentally.

Conclusions

It is assumed that during handling of MCAA measures will be taken to reduce exposure in the form of good local exhaust ventilation and personal protection because of the corrosive nature of the substance. When using solids, the mentioned reasonable worst-case value in the use of the analogous substance of 10 mg/m^3 is probably an overestimate because of the corrosive nature of MCAA. The ranges of the estimation by the EASE model will be used instead for risk characterisation: 2-5 mg/m^3. The lower value of 2 mg/m^3 is taken as typical value and the upper value 5 mg/m^3 as worst-case value. Including a reduction of 90% due to PPE, these values reduce to 0.2 and 0.5 mg/m^3. Assuming duration of two hours per day and zero exposure during the rest of the day, typical and worst-case full shift exposure is 0.05 and 0.125 mg/m^3 respectively.

In handling MCAA in the liquid form, the same procedure is followed: the lower value of the range is used as a typical value (2.0 mg/m^3) and the upper range value as a reasonable worst case (11.8 mg/m^3). Including a reduction of 90% due to PPE, these values reduce to 0.2 and 1.2 mg/m^3. Assuming duration of two hours per day and zero exposure during the rest of the day, typical and worst-case full shift exposure is 0.05 and 0.3 mg/m^3 respectively.

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

4.1.1.2.3 Formulation of paint removers (Scenario 3)

MCAA is also used in paint stripping baths, in combination with other solvents like methylene chloride and formic acid. The content of MCAA in paint stripper may vary from 2.5-10%. Production of paint removers takes place in mixing vessels where the ingredients are added and mixed and then packed into smaller units. The size of these units is from 1 litre up to tankers of 1,000 litres. Filling of the mixing vessel as well as the products units is done mainly in automated systems. 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.

Because no measured values or suitable comparison with analogous data is possible, the exposure will be estimated with the EASE model.

Inhalation exposure during coupling and decoupling of transfer lines is estimated with EASE to be 0.5-3 ppm (2-11.8 mg/m^3), assuming no aerosol formation, non-dispersive use and a vapour pressure of 0.02 kPa. With a protection factor of 90%, exposure reduces to 0.2-1.2 mg/m^3.

Dermal exposure is considered to occur only accidentally.

Conclusions

The ranges of the estimation by the EASE model will be used for risk characterisation: 0.2-1.2 mg/m^3. The lower value of the range is used as a typical value and the upper range value as a reasonable worst case. Assuming a duration of one hour per day and the use of PPE which reduces concentrations with 90%, this leads to full-shift reasonable worst case level of 0.1 mg/m^3 and a typical value of 0.02 mg/m^3.

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

4.1.1.2.4 Use of paint removers (Scenario 4)

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.

Because no measured values or suitable comparison with analogous data is possible, the exposure will be estimated with the EASE model.

Inhalation exposure, estimated by EASE assuming aerosol formation, wide dispersive use and direct handling, with a vapour pressure of 0.002 kPa (0.02 · 10%), is 500-1,000 ppm (1,950-3,900 mg/m^3). With a dilution factor of 100 the exposure is 20-39 mg/m^3. Since the use of personal protective equipment cannot be guaranteed (especially in small and medium sized enterprises) and no threshold value for the corrosiveness of MCAA could be assessed from the available data, the assessment is performed with and without PPE. If PPE is used in the present scenario, exposure would be reduced by 90% and exposure would be 2-3.9 mg/m^3.

Dermal exposure to the spray solution, assuming wide dispersive use, direct handling and extensive contact is 5-15 mg/cm^2/day (product). A dilution factor of 100 is assumed, leading to an estimate of 0.005-0.015 mg/cm^2/day MCAA. Assuming an exposed area of 20,000 cm^2 (the whole body), the exposure to MCAA would be 1,000–3,000 mg/day. Since the use of personal protective equipment cannot be guaranteed (especially in small and medium sized enterprises) and no threshold value for the corrosiveness of MCAA could be assessed from the available data, the assessment is performed with and without PPE. If PPE is used in the present scenario exposure would be reduced by 90 % and exposure would be 100–300 mg/day.

Conclusions

For inhalation exposure, the ranges of the estimation by the EASE model will be used for risk characterisation: 20-39 mg/m^3. If respiratory protective equipment is used exposure would be 2-3.9 mg/m^3.The lower value of the range (without use of PPE) is used as a typical value and the

upper range value as a reasonable worst case. Assuming duration of two hours per day, this leads to a full-shift reasonable worst case level of 10.0 mg/m^3 and a typical value of 5 mg/m^3. If respiratory protective equipment is used the full-shift reasonable worst case level would be 1.0 mg/m^3 and a typical value would be 0.5 mg/m^3.

Dermal exposure for single contact during spraying of objects to remove the residue paint remover is estimated to be 3,000 mg/day. When dermal protective equipment is used exposure is estimated to be 300 mg/day. This estimate is also assumed to be relevant for repeated exposure, due to the high level of dilution and the type of process involved.

Table 4.2 Conclusions of the occupational exposure assessment

Scenario	Activity	Frequency days/year	Duration hours/day	Reasonable worst-case		Typical concentration		Dermal	
				mg/m³	Method	mg/m³	Method	mg/cm²/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	EASE	0.2	EASE	n.e.	n.e.
			1-2						
- 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	full shift	1-10	6-8	0.1	Calculated	0.025	Calculated	n.e.	n.e.
removers	handling	1-10	0-1	0.9	EASE	0.2	EASE	n.e.	n.e.

Table 4.2 continued overleaf

Table 4.2 continued 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)
4 Use of paint removers	full shift	100-200	6-8						
	-without PPE			10	Calculated	5	Calculated	0.15	3,000
	-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.

All values mentioned in the Table include an assumed reduction of 90% by PPE (BS 4275), because of the assumed direct effect at relatively high exposure levels, except the typical value for production

* The typical value for production is expected not to lead to acute effects and therefore not to urge workers to wear PPE

negl negligible
meas data taken from measurements
EASE estimate with the EASE model
analogue based on measurements on analogous substances
expert expert judgement
n.e. not estimated; due to the corrosive properties of MCAA, dermal exposure is considered to occur only accidentally

4.1.1.3 Consumer exposure

MCAA or its sodium salt (SMCA) is mainly used as intermediate in several industrial uses (see Section 2.2). The presence of MCAA in consumer products was unknown in Denmark (Product Register Denmark, June 1997) but known in the US (US Product Register, October 1997). MCAA or SMCA were not available in the inventory of ingredients used in cosmetic products (EC, 1996). Industry does not support applications of MCAA which are not related to the use as intermediate. However, some consumer use has been identified, but this use can be considered mostly as negligible (see below). For one scenario the exposure was quantified. Possible consumer exposure:

1) MCAA or its sodium salts have been used as an anti-microbiological additive in food and as a wart remover. Information on both uses was scarce (SIDS, 1994).

1a) Only one early reference was found on the use of MCAA in wine (Haller and Junge, 1971). It is therefore expected that MCAA is not used in wine anymore and need not be considered. The use of MCAA as an anti-microbiological agent in breweries was forbidden as high amounts were detected in beers (50 mg/l) in 1986 in Germany and caused the "beer scandal" (Reimann et al., 1996). Sendra and Todo (1990) analysed seventeen European beers for monohaloacetic acids content and no acids were found. The detection limit for MCAA was 0.1 ppm (100 µg/l). Reimann et al. (1996) showed that MCAA amounts in beers found in 1996 were not applied intentionally. MCAA is not registered as an anti-microbiological agent in the Netherlands (Pesticide Databank, 2002). In Germany the substance is not allowed as a food additive (Anonymus, 1992). In the USA MCAA is not expected to be used as such any more (NTP, 1992). However, the use as an anti-microbiological agent is still known in the US (Product Register, October 1997). Anyway, the use of MCAA as an anti-microbiological agent in Europe is considered not applicable anymore.

1b) With respect to the use of MCAA as a wart remover one reference was found describing an accident with Verzone that contained MCAA. It was believed that this wart remover was available on the local market only (Rogers, 1995). Steele et al. (1988) showed the MCAA effectiveness as a wart remover in pre-clinical treatment. MCAA is not used as such in the Netherlands (Informatorium, 1999). In Europe there is apparently only one wart remover containing MCAA in use (a product called Acetocaustin). This product seems to be available in Germany and Switzerland and sold over the counter. Consumer exposure can be considered negligible.

2) SMCA is registered as an herbicide in Ireland and the UK. It can be used in several cabbage crops, onions and leek as well as for fruits. From the pesticides guides from the UK and Ireland, it seems to be used by farmers but not by consumers (EDAP, herbicides, 1990; UK-MAFF, Pesticides, 1997; UK Pesticide Guide, 1998). It is not registered as a pesticide in the Netherlands. In the US it is also used as herbicide (US Product Register, October 1997). Although registered, it appears that the actual use as an herbicide is rather limited, as much better alternatives are available. Consumer exposure can be considered negligible.

3) The use of MCAA as a paint stripper or graffiti remover is mentioned in SIDS (1994) but no quantitative information was available. Sweden stated that MCAA is not used as a paint stripper anymore. For workers such use is identified. However, no information is available on the actual consumer use of MCAA as a paint stripper or graffiti remover. In addition, industry has stated and informed their downstream users that MCAA should not be used as such. Therefore the use of MCAA as a paint stripper by consumers cannot be substantiated.

4) SIDS (1994) mentions the use of SMCA as amphoteric surfactant in detergents but no quantitative information was available at that moment. This use is also known in the US (Product Register, October 1997). Cetinkaya (1991) determined SMCA in body cleaning products and other amfoteric surfactants. As no further information is available and SMCA is not a surfactant itself but only used for making surfactants the exposure via consumer products can be considered negligible.

5) In Sweden one consumer product was identified that contains 0.04% SMCA in a hand wash detergent. This level corresponds to 40 mg SMCA/kg hand wash detergent. Using a dilution factor of 100 (e.g. 100 g of detergent (TGD value) in a bucket of 10 L water, the skin is exposed to 0.004 mg/cm^3 of substance. The skin is only exposed to a 0.01 cm thickness layer of product in contact with the skin. Therefore the exposure is 0.00004 mg/cm^2. The exposed area is 840 cm^2 (hands on both sides), resulting in a total exposure of 0.0336 mg/event. Assuming that hand washing detergent is used once daily; the total exposure will be 0.0336 mg/day. This value will be taken across to the risk characterisation.

6) The EU Scientific Committee on Food has evaluated the occurrence of MCA in can coatings for aqueous foodstuffs. According to the Committee, an amount of MCA equivalent to 50 μg/kg food is acceptable (SCF, 1999). The evaluation by SCF is considered sufficiently adequate to cover this exposure to MCA. Hence, no exposure estimate is derived for the occurrence of MCA in food contact material.

4.1.1.4 Indirect exposure via the environment

General

In view of the solubility of MCAA, 0% is directed to sludge (see Distribution –WWTP, 3.1.1) and indirect exposure will thus not occur via sludge application and following routes. Besides, the log K_{ow} cannot be used for ionised chemicals (see Section 3.1.1) for secondary poisoning. This means that the indirect exposure of MCAA via the environment is limited to exposure via:

1. air;
2. leaf crops, which may accumulate MCAA via the deposition from air;
3. drinking water derived from either surface water or groundwater.

Ad 2) It is assumed that the concentration in leaf crops is solely derived from deposition from air. It is noted, that in EUSES the route air → soil → plant root → plant leaf cannot be separated from the route air → plant leaf. However, the model states which fraction of the total amount that is present in plant leafs comes from air. Hence it is possible to exclude irrelevant routes for plants manually, afterwards. In addition, to take into account that plant tissues will metabolise MCAA, a degradation rate in the plant has been incorporated into the EUSES calculations. This is based on a study with bean cell cultures, indicating that in the whole plant MCAA is metabolised at a rate corresponding to a DT50 of 3 days (Scholl, 1993). DT50 values in spruce were twice as high (Braun, personal communication with industry), but bean cell cultures are considered more representative for vegetables.

Ad 3) The concentration in groundwater is derived from the deposition of MCAA and subsequent leaching through the soil.

Local scale

The EUSES calculations of the concentration of MCAA in air, drinking water and leaf crops are shown in **Table 4.3**. For all production and processing sites for which site-specific information was available (**Table 3.2** and **3.3**), only those sites are mentioned with an emission to air of >12 kg MCAA/day. An emission of < 12 kg MCAA/day leads to air and groundwater concentration not showing a potential risk. Neither do sites with an emission of < 12 kg MCAA/day show a potential risk via the leaf crops. Sites that show minor concentrations in the surface water or ground water (< 1 µg/L) were also not taken into account as these sites did not show a potential risk either. These conclusions were drawn from a pre-screening assessment. For the processing off-sites, only one site was found that had an emission to air of > 12 kg/day that is 20 kg/day. All the processing off-sites have concentrations in drinking water < 1 ug/l.

The total exposure of humans via the environment is totally attributed to the concentration in leaf crops for site I-BI, I-B2 and one processing site (off-site) II. For site I-C it is the concentration in drinking water derived from surface water that mainly attributes to the total exposure. The values in **Table 4.3** are used in the risk characterisation.

Table 4.3 Human intake of MCAA from air, drinking water and food at the local scale*

	I-B1 MCAA (SMCA)	I-B2 MCAA (SMCA)	I-C MCAA (SMCA)	Processing (off-site) II
Conc. in air in mg/m3	$0.118 \cdot 10^{-3}$	0.0015	$6.4 \cdot 10^{-4}$	$5.3 \cdot 10^{-3}$
Mg/kg bw/day	$3.37 \cdot 10^{-5}$	$4.29 \cdot 10^{-4}$	$1.83 \cdot 10^{-4}$	0.0015
Conc. in drinking water in mg/l	$7.83 \cdot 10^{-4}$	0.0112	2.5**	$5.8 \cdot 10^{-3}$
Mg/kg bw/day	$2.24 \cdot 10^{-5}$	$3.2 \cdot 10^{-4}$	0.0715	$1.66 \cdot 10^{4}$
Conc. in leaf crops in mg/kg	0.0827	1.05	0.45	3.75
Mg/kg bw/day	0.0014	0.018	0.0077	0.0642
Total daily intake in mg/kg bw/day	0.00148	0.019	0.0794	0.066

* The concentration of MCAA in air, drinking water and leaf crops is shown. The daily amount of uptake of air (20 m^3/day, 100% absorption), water (2 l/day) and leaf crops (1.2 kg WWT/day) is multiplied with the concentrations in these media. The exposure to the public at large at the local scale in mg/kg bw/day is calculated assuming a body weight of 70 kg.

** The concentration is derived from annual concentration in surface water.

Regional scale-EUSES data

The EUSES calculation for the regional scale is based on all scenarios. The regional exposure is included in **Table 4.4**.

Regional scale-measured data

In Germany MCAA was measured in urban air. The concentrations ranged from 10-5,000 pg/m^3 (ECETOC, 1999). In addition, in Germany and Ireland values ranging from 100-3,300 pg/m^3 were found. For the exposure assessment the maximum value of 5,000 pg/m^3 will be used as a worst case approach. MCAA may be found as a by-product during the disinfecting process of drinking water. The occurrence of MCAA in drinking water was a reason for testing MCAA in the NTP program for carcinogenicity (NTP, 1992). Reimann et al. (1996) detected MCAA in several beers and food not intentionally treated with MCAA. The exposure via drinking water is described in scenario A. The exposure via beers and food is described in scenario B.

Scenario A: Exposure via drinking water

In a 1990 survey in the Netherlands MCAA was not detected as a disinfectant by-product in drinking water (Versteegh et al., 1990; Peters et al., 1990). Maximum levels of 0.3-0.6 ug/l MCAA were detected in drinking water after disinfections with hypochlorite. This value was referenced in a report from the Dutch Board on the Authorisation of Pesticides (CTB) on Alfa Laval 1997 (registration nummer 7366 N). In France MCAA was also not found in samples from surface water and groundwater to be used for drinking water (Benanou et al., 1998). Krasner et al. (1989) investigated 35 treatment facilities in the USA on disinfectant by-products and found a maximum MCAA amount of 1.2 µg/l. Nieminsky et al. (1993) found a total of haloacetic acids of 17 µg/l in Utah. The amount of MCAA was not determined in this study. In Australia the guideline value for chloracetic acid is 150 µg/l, but values between 10-244 µg/l were found. The value of 150 µg/l was met at 2 sites; all other sites were below 150 µg/l (Simpson and Hayes, 1998). Reimann et al. (1996) detected 1 µg/l MCAA in drinking water in Switzerland.

The value of 1 µg/l from Reimann et al. (1996) is taken into account for the risk characterisation for the EU. It is noted that in Australia 150 µg/l is used as an upper limit for MCAA in drinking water.

Scenario B: Contamination in beers and food with MCAA from unknown origin

Reimann et al. (1996) determined MCAA in several beers and crops. In vegetables from a biological farmer, MCAA concentrations varied from 5.3 µg/kg in carrot and 3.8 µg/kg in cabbage to <0.7 µg/kg in tomato. In fruits, MCAA values were all lower than 0.7 µg/kg. The concentrations that were found in home made bread (Switzerland) varied from 2.3 to 11.9 µg/kg. Concentrations in 6 beers from different countries varied from 0.2 (Mexico) to 2.6 µg/l (Switzerland). MCAA found in fruits and grains from other parts of the world (e.g. Asia) varied between 1 and 7 µg/kg. Interestingly, crops and fruits from all over the world contain more or less similar amounts of MCAA. These MCAA levels in fruit and crops did most probably not result from intentional use (herbicide) as the substance was also detected in products from biological farms. Up to now the origin from MCAA in crops remains unclear. Reimann et al. (1996) concluded that the fact that MCAA concentrations in plant products are similar throughout the globe cannot be interpreted as a proof for a natural origin. They suggested that acids can be formed from long-lived, equably distributed precursors in the atmosphere, such as chlorinated solvents.

The information of Reimann et al. (1996) on the exposure will be used for the regional scale:

Root crops:	5.3 µg/kg WWT
Leaf crops:	3.8 µg/kg WWT + grains 7 µg/kg = 10.8 µg/kg

Table 4.4 Human intake from air, drinking water and food at a regional scale*

Regional + consumption per day	Concentration according to:		Exposure to the public at large (mg/kg bw/day)	
Route:	EUSES	Field data (ref**)	EUSES	Field data
Air (pg/m^3)	238	5,000 (1)	$6.8 \cdot 10^{-8}$	$1.4 \cdot 10^{-6}$
Drinking water (mg/l)	$3.9 \cdot 10^{-4}$	0.001 (2)	$1.11 \cdot 10^{-5}$	$2.9 \cdot 10^{-5}$
Leaf crops (mg/kg WWT)	$1.88 \cdot 10^{-4}$	0.0108 (2)	$2.9 \cdot 10^{-6}$***	$1.9 \cdot 10^{-4}$
Root crops (mg/kg WWT)	Not applicable	0.0053 (2)	Not applicable	$2.9 \cdot 10^{-5}$
Total			$1.41 \cdot 10^{-5}$	$2.4 \cdot 10^{-4}$

* The concentration of MCAA in air, drinking water and leaf crops is shown according to EUSES calculation and Reimann et al. (1996). The daily amount of uptake of air (respiratory volume 20m^3/day, 100% absorption), water (2 l/day), leaf crops (1.2 kg wwt/day) and root crops (0.384 kg wwt/day), is multiplied with the concentrations in these media. The exposure to the public at large at the local scale in mg/kg bw/day is calculated assuming a body weight of 70 kg.

** References: 1: ECETOC (1999); 2: Reimann et al. (1996)

*** For the calculation of the intake via leaf crops only the fraction derived from air was taken into account (89%)

It can be seen that the EUSES estimation for the regional scale for air and drinking water is similar to the data derived from Reimann et al. (1996). For leaf crops the EUSES estimates are much lower. Other sources than the sources mentioned here are possibly relevant. Reimann et al. (1996) indicated that MCAA are possibly breakdown products from other industrial chemicals. The release from non-intentional industrial sources and natural sources is also discussed in Section 3.1.1.3.1.

The values in **Table 4.4** are used in the risk characterisation.

4.1.1.5 Combined exposure

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

4.1.2 Effects assessment (Hazard identification and dose (concentration)-response (effect) relationship)

4.1.2.1 Toxico-kinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

Oral

In 35 male Sprague Dawley rats given a single oral dose of 0.06 mg/kg of [1-^{14}C]-MCAA (1.0 μCi, gavage), radioactivity in plasma, liver, kidney, heart, testis, and spleen peaked at 1-2 hours after administration, and declined rapidly ($t_{1/2}$ = 2-7 hours). However, radioactivity in brain, although present in lower levels than in other organs, continued to rise up to 8 hours and plateaued through 24 hours. The data indicates that MCAA is rapidly absorbed by the oral route.

Excretion in the urine occurs mainly during the first 24 hours (51% of administered dose) (Berardi and Snyder, 1983; Berardi, 1986a).

In a second experiment male Swiss-Webster mice (n = 6/dose group) were treated orally with a single dose of 0.6, 150, or 250 mg/kg of [1-^{14}C]-MCAA (1.0 μCi). It was found that MCAA is rapidly absorbed by the oral route, rapidly eliminated from the body with a half-life not exceeding 12 hours in non-nervous tissues and 26 hours in the CNS. The elimination phase appears to be fast for intestine and kidney as compared to other tissues. After 24 hours 32.0-59.3% of administered MCAA was excreted in the urine, after 72 hours 33.7-60.8% MCAA-equivalent was excreted in urine. The major urinary metabolites found were S-carboxymethyl-L-cysteine and thiodiacetic acid. The distribution patterns of MCAA in mice indicate that the toxicokinetic properties of MCAA are dose-dependent. At 150 and 250 mg/kg, the maximum concentrations in the brain areas of mice were very close to the plasma concentration (Berardi, 1986a).

Buphendra et al. (1992) studied the distribution of MCAA in 15 male Sprague-Dawley rats given a single oral dose of 0.1 mmole/kg body weight (equivalent to 9.5 mg/kg bw) [1-^{14}C]-MCAA, by gavage (vehicle not reported). The animals (three/time point) were sacrificed at 4, 8, 12, 24, and 48 hours following the treatment. Urinary excretion of MCAA and/or its metabolites was found to be 90% of the administered dose in 24 hours. The urinary excretion and the distribution of ^{14}C-label, determined in different tissues (see **Table 4.5**), suggest that MCAA is rapidly absorbed and eliminated from the body. The elimination phase appears to be faster for intestine and kidney as compared to other tissues. Highest levels of radioactivity were detected in intestine and kidney at 4 and 8 hours following the treatment, followed by lower levels in liver, spleen, testes, lung, brain, and heart in decreasing order.

Table 4.5 Distribution of ^{14}C-label in different tissues of rats treated with a single oral dose of 0.1 mmole/kg bw [1^{14}C]CAA

	Hours after treatment				
Tissues	4	8	12	24	48
Intestine	192.1 ± 8.8	154.0 ± 4.5	16.1 ± 0.8	8.5 ± 0.6	4.0 ± 0.1
Kidney	191.5 ± 13.8	156.3 ± 4.8	33.6 ± 1.3	16.1 ± 0.3	10.5 ± 0.6
Liver	79.0 ± 0.9	90.5 ± 3.0	35.4 ± 1.3	21.1 ± 0.8	15.5 ± 0.2
Spleen	53.7 ± 2.0	42.4 ± 5.3	19.3 ± 0.5	9.4 ± 0.4	6.2 ± 0.4
Testes	26.0 ± 1.1	21.0 ± 1.2	8.7 ± 0.7	4.2 ± 0.2	3.8 ± 0.1
Lung	24.0 ± 0.6	24.6 ± 0.9	14.8 ± 2.0	8.4 ± 0.5	7.6 ± 0.1
Brain	16.4 ± 0.9	18.9 ± 0.5	14.5 ± 0.5	7.8 ± 0.6	4.5 ± 0.4
Heart	12.3 ± 0.2	10.6 ± 0.5	6.1 ± 0.3	4.6 ± 0.5	4.3 ± 0.2

The values are mean ± SD of three animals expressed as nmole/g tissue

To two other groups of male rats (n=3/group), a single oral dose of 1 mmole/kg bodyweight (equivalent to 95 mg/kg bw) [1-^{14}C]-MCAA was given, by gavage (vehicle unknown), daily for 1 or 3 days. The animals were sacrificed at 24 hours following the doses 1 and 3 to study the distribution of [1-^{14}C]-MCAA in tissues. The ^{14}C-label in different tissues at 24 hours following single exposure were 1.4 to 3.8 folds higher in rats treated with 1 mmole/kg bodyweight [1-^{14}C]-MCAA than those found in rats treated with 0.1 mmole/kg bodyweight [1-^{14}C]-MCAA (see **Table 4.6**). The distribution patterns were found to be comparable. There was also a significant increase in ^{14}C-label present in different tissues 24 hours following three high doses of [1-^{14}C] MCAA as compared to those given the same single high dose, except for liver and spleen. The

data indicate a dose-dependent accumulation of MCAA in tissues. The excretion in urine after the administration of the high doses was not reported. In addition, no detailed data on the tissue distribution of the 3 daily high doses were reported.

Table 4.6 Distribution pattern of ^{14}C-label in different tissues after 24 hr of single oral doses of 0.1 and 1.0 mmole/kg bw [1-^{14}C] MCAA to rats (Buphendra et al., 1992)

	Doses (mmole/kg bw)		Ratio of ^{14}C-label (1.0/0/1)
Tissues	0.1	1.0	
Kidney	16.1	57.7	3.6*
Liver	21.1	53.7	2.5*
Intestine	8.5	32.1	3.8***
Lung	8.4	18.9	2.3**
Spleen	9.4	17.8	1.9*
Heart	4.6	13.5	2.9**
Brain	7.8	10.7	1.4*
Testes	4.2	8.0	1.9

Values are mean values of 3 animals in each group and expressed as nmole/g tissue.
P-values: * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001 for differences between the two dose levels.

Dermal

Pre-treatment of the skin of mice (Swiss-Webster) for 2 minutes with 400 mg/kg of molten (65°C) MCAA increased significantly the skin absorption of a dose of 0.6 mg/kg [1-^{14}C]-MCAA applied for 3 minutes to the same site as compared to non-pre-treated skin. However, 6 hours after dermal application of 282 mg/kg [1-^{14}C]-MCAA as an aqueous solution at 25°C or 65°C for 3 minutes, the radioactivity in the plasma, whole brain, skin, and urine of mice was not significantly greater with the 65°C solution as compared to the 25°C (Berardi, 1986a).

Subcutaneous

In male Sprague-Dawley rats (n = 3) administered a single sc dose of 162 mg/kg bw [2-^{14}C]-MCAA (vehicle was not reported), radioactivity was found in greater concentrations in liver and kidney than in plasma (4-128 minutes after treatment). Total radioactivity in heart and brain was similar to that in plasma.

A dose of 53 mg/kg bw [2-^{14}C]-MCAA distributed similarly to the high dose. Peak plasma levels were reached at 32 minutes after administration of the low dose. Plasma disappearance of radioactivity, given at the low dose (53 mg/kg), was biphasic (approximately rapid phase half-life: 90 minutes; slow phase: 500 minutes). Kidney cortex and medulla had similar ^{14}C-MCAA levels. Approximately 50% of the administered radioactive dose (53 mg/kg bw) was recovered in urine by 17 hours after MCAA administration (Hayes et al. 1973).

Intraperitoneal

Yllner (1971) reported that 3 days following intraperitoneal injection of 70, 90, or 100 mg [1-^{14}C]-MCAA (dissolved in water) in female mice (strain and n not reported), 82-88% of the administered dose was eliminated in the urine, 8% was eliminated in expired air as CO_2, and 0.2-3% was eliminated in the faeces; 2-3% of the administered dose remained in the animal. Examination of the urine by paper chromatography showed 2 major metabolites of MCAA,

S-carboxy-methyl-L-cysteine (33-43% free and 1-6% conjugated) and thiodiacetic acid (33-42%), and small amounts of glycolic acid (3-5%) and oxalic acid (0.1-0.2%). The authors suggested two metabolic pathways for MCAA (see **Figure 4.1**): 1) 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, and 2) a minor one involving probably enzymatic hydrolysis of the carbon-chlorine bond with the formation of glycolic acid which is mainly oxidised to carbon dioxide.

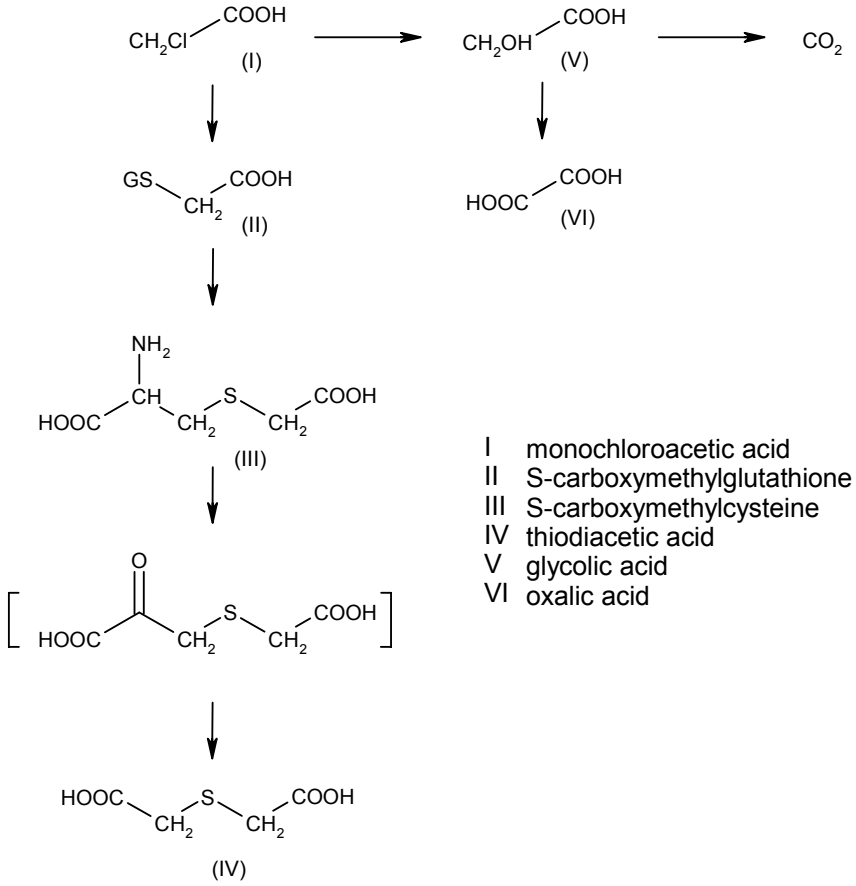


Figure 1 Suggested metabolic pathways of MCAA in the mouse. The compounds in brackets were not isolated (Yllner, 1971)

Intravenous

In a whole body autoradiography study by Bhat et al. (1990) Sprague Dawley rats (3/group, sex unknown) were given a single i.v. dose of 0.07 mg/kg bw [1-^{14}C]-MCAA (in 10% Na_2CO_3) and were sacrificed after 5 minutes, 1, 4, 12, 24, and 48 hours. The radioactivity was rapidly removed from the circulation. Already at 5 minutes high levels of ^{14}C-activity were observed in the liver and the excretory systems. MCAA and/or its metabolites were present in the excretory organ walls, such as kidney cortex and stomach walls; in certain areas of the brown fat such as in the upper dorsal areas of the neck and high levels of ^{14}C-activity were present in the myocardial tissues. At 1 hour following administration of [^{14}C]-MCAA, radioactivity was extensively excreted into the small intestinal lumen. The presence of [^{14}C]-MCAA in the brain, thymus, salivary glands, and tongue was prominent at 1 hour. After 4 hours the liver and other tissues started to eliminate most of the radioactivity. Contrary to other tissues, in the central nervous system, thymus, and pancreas the radioactivity appeared at later time periods. It was suggested that MCAA and/or its metabolites accumulate into hydrophilic tissues at earlier time periods and

into carboxymethylcysteine tissues at later times. The limited reported study provided no information on the actual MCAA concentrations in the different tissues.

Distribution, metabolism and excretion of MCAA were examined in adult male rats at a sub toxic and at a toxic dose (10 and 75 mg/kg bw, respectively), administered i.v. as [^{14}C]-MCAA (Saghir et al., 2001). Biliary excretion was studied in additional bile duct canulated rats. In the intact rats, plasma and other tissues, organs and the contents of some of them (stomach, small intestine, and colon) were analysed for radiolabel. Plasma and urine (including urine bladder contents) were analysed as well for MCAA as such. In addition, metabolites were analysed for in bile and urine. Plasma data were analysed by a compartmental modelling method. The best fit of the data was obtained by using a two-compartment model rather than a one- or three-compartment model. In the range finding experiment (10-125 mg/kg bw) that was included, the onset of toxicity was very abrupt. No apparent signs of toxicity were observed up to 50 mg/kg bw, whereas 43% of the rats died at 60 mg/kg bw and >50% at 70 mg/kg bw, preceded by coma. Mean time to coma and death was 70 and 75 min, respectively. Doses between 70 and 100 mg/kg bw induced almost the same mortality, no dose response was apparent. Doses of $\geq$110 mg/kg bw caused 100% mortality. Most of the animals that went into coma and did not die within 90 minutes of dosing regained consciousness suddenly and recovered.

Upon i.v. administration of 10 and 75 mg/kg bw, doses that were chosen to investigate kinetics, a very rapid distribution to tissues was observed for radiolabel as well as MCAA. After 5 minutes only 0.6 and 1.0% of dose/ml remained in the systemic circulation at low and high dose, respectively. Most of the radiolabel associated with plasma was parent MCAA and binding of radioactivity to red blood cells was negligible (<0.08% of the dose/g). For many organs, a t_{max} of <15 minutes or even <5 minutes was observed. Only in the contents of the small intestines and in urine, t_{max} values were larger, i.e. 45 minutes and $\geq$16 hours, respectively. Furthermore, the AUC (area under the curve) of total and parent MCAA in plasma (versus time) was 22 to 23 times higher at a dose of 75 than at a dose of 10 mg/kg bw instead of the expected 7-to 8-fold quotient (representing the ratio of the doses), reflecting the slower distribution and/or clearance at the higher dose. A higher percentage of radiolabel was found in liver and kidneys at the sub toxic compared to the toxic dose. Concentrations of radiolabel in plasma, liver, heart, lungs and brown fat paralleled each other, especially in the 10 mg/kg bw dose group, whereas those in brain and thymus were somewhat delayed compared to plasma. Concentrations in liver peaked at $\leq$5 minutes and at 15 minutes in the low and high dose group, respectively. Those in kidneys peaked at 45 minutes and at 4 hours, respectively. Elimination rate constant and distribution rate constant were greatly reduced at the toxic dose. Elimination of the toxic dose was further retarded due to increased retention of MCAA in the peripheral compartment as indicated by increased mean residence time in most tissues. This was reflected in a very large fraction of the dose being found in the gastrointestinal tract contents, almost all of which was reabsorbed. Attempts to reduce toxicity at 100 mg/kg bw by blocking the enterohepatic circulation (and thus renewed exposure) with activated charcoal or cholestyramine failed. Biliary excretion of MCAA metabolite(s) turned out to be a detoxification step. Radioactivity found in bile was associated with one metabolite, being more polar that the parent compound. A very large fraction of the dose (73 and 59% in the low and high dose group) was found in urine, 55 to 68% of which was parent MCA. The rate-determining step in the toxicity of MCA was identified as its detoxicification by the liver as data clearly demonstrate that the abrupt onset of coma/death in MCAA exposed rats is due to a rapid overwhelming of the detoxification capacity of the liver.

Inhibition of enzymes

Hayes et al. (1973) reported an experiment on the inhibition of [1-^{14}C]-acetate oxidation *in vitro* by MCAA. MCAA was reported to be an uncompetitive inhibitor of acetate oxidation.

Bryant et al. (1992) studied the influence of a single dose of 24, 48, and 96 mg MCAA/kg bw administered by gavage on aconitase activity in heart and liver in female F344 rats (experimental groups: n=3; control group: n=6), because monofluoroacetic acid (MFAA) is a known inhibitor of this mitochondrial enzyme. Aconitase activity was measured in liver and heart that were removed 1.5-2 hours after dosing. MCAA inhibited the aconitase activity in the heart, however, not in the liver. According to the authors, the inhibition of the aconitase activity may probably have influenced the development of cardiomyopathy, as was observed in a 13-week repeated-dose toxicity study with rats (NTP, 1992).

In rat liver slices *in vitro*, MCAA at 0.1 mM inhibited the incorporation of label from [U-^{14}C]-alanine into glucose, without affecting production of ketone bodies or $^{14}CO_2$. It was suggested that the data indicate that MCAA may inhibit gluconeogenesis by specific inhibition of pyruvate carboxylase (Doedens and Ashmore, 1972).

Dierickx (1984) studied the *in vitro* interaction of a.o. MCAA with rat liver glutathione S-transferase (GST). In the study glutathione and 1-chloro-2,4-dinitrobenzene were used as substrates. MCAA inhibited the GST activity in crude extracts in a dose dependent manner. Each of the different GST isoenzymes was inhibited. The inhibition was dose dependent but not linear. It was concluded that direct covalent binding to GST is the major interaction mechanism. This binding could have a protective function against MCAA. The data on toxicokinetics and metabolism showed that binding to GST is one of the steps in the metabolism of MCAA. Therefore it might be concluded that MCAA is an inhibitor of its own metabolism.

MCAA inhibits both pyruvate-dehydrogenase (PDH) and a-ketoglutatarate dehydrogenase enzyme (KGHD) in isolated rat heart mitochondria but only after prolonged incubation. The exact mechanism of inhibition is still unknown. Since the combined inhibition of PDH and a-KGHD has a major impact on cellular energy production, the cell would then revert to anaerobic glycolysis, resulting in lactate accumulation (ref. in ECETOC, 1991).

Interaction with lipids

Bhat and Ansari (1988) investigated the interaction of MCAA with lipids using [^{14}C]-MCAA *in vitro* by incubation of rat liver microsomes with MCAA in the presence of co-enzyme A and adenosine triphosphate. They found that most of the radioactivity was incorporated into phospholipids.

In a second study Bhat and Ansari (1989) studied the covalent interaction of MCAA with rat liver lipids *in vivo*. Rats were administered a single oral dose of 8.75 mg/kg (50 μCi) of [1-^{14}C]chloroacetic acid. The animals were sacrificed after 24 hours. Lipids extracted from the livers were separated into neutral lipids and phospholipids by solid-phase extraction using sep-pak silica cartridges. It was shown that MCAA can conjugate with cholesterol to form cholestryl chloroacetate. MCAA reacts preferentially with neutral lipids. The effect of such conjugation reactions on the cell membrane and their contribution to toxicity is presently unknown, but should be more prone to retention than excretion, because the conjugate is a more lipophilic product.

Interaction with sulfhydryl groups

Hayes et al. (1973) studied the *in vivo* and *in vitro* interaction of MCAA with cysteine sulfhydryl groups. MCAA did not significantly alkylate sulfhydryl groups of cysteine *in vitro*. *In vivo* total sulfhydryl content in rat liver was decreased about 30% by oral LD90 doses of MCAA. Brain and heart sulfhydryl values were not affected by oral LD90 doses. MCAA binding in rat liver occurred in protein and nonprotein fractions. MCAA binding to total sulfhydryl groups in rat liver increased with time. Total sulfhydryl content was reduced to approximately 50% of the control value by 120 minutes. Rat kidney cortex and medulla also showed significant decrease of total sulfhydryl content from 84 to 120 minutes after MCAA treatment. Alkylation of brain and heart sulfhydryl groups was not affected at these times.

4.1.2.1.2 Studies in humans

Dancer et al. (1965) reported a case of human skin contamination with hot chloroacetic acid labelled with carbon-14. After the incident, measurements were made of skin contamination in the blistered areas and determinations of ^{14}C-label in blood, expired air, and urine were carried out. No signs of erythema or other damage were observed and the wound healed within the normal time. Approximately 300 μCi of ^{14}C-label (equivalent to 0.002 ml MCAA) was excreted in urine and it was calculated that a similar quantity was eliminated in breath. A half-life of about 15 hours was found for the excretion of MCAA in urine. In a sample of blood taken 17.5 hours after the incident, less than 20% of the activity was associated with the separated red cells, most remained in the plasma. The ^{14}C concentration in this blood sample was much less than that in urine collected during the first 24 hours suggesting that the transfer of activity from the blood to urine must have been very rapid. After 6 days only a small amount was detectable in blood. A percentage of dermal absorption cannot be deduced.

4.1.2.1.3 Conclusion

It should be noted that most of the available studies on the toxicokinetics, metabolism, and distribution of MCAA are limitedly reported and most of the studies were performed with relatively high doses (nearby the LD50 values). No information is available on the toxicokinetics, metabolism, and distribution of MCAA after inhalation exposure. Limited qualitative human data after dermal exposure were obtained from a case study.

After oral exposure of rats to ^{14}C-MCAA at least 90% was absorbed from the gastro-intestinal tract. The toxicity data available (see Section 4.1.2.2) 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. 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.

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. The pattern of distribution shows an initial fast distribution into rather lipid-poor tissue, followed by uptake into lipid-rich tissues such as the brain. 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 sc exposure.

Upon i.v. administration of ^{14}C-MCAA in rats, distribution of radiolabel was very rapid (t_{max} <15 minutes for almost all organs). Furthermore, the AUC (area under the curve) of total and parent MCAA in plasma (versus time) was 22 to 23 times higher at a dose of 75 than at a dose of 10 mg/kg bw instead of the expected 7-to 8-fold quotient (representing the ratio of the doses), reflecting the slower distribution and/or clearance at the higher dose. A more than proportional amount of MCAA was found in liver and kidneys in the high dose groups, reflecting overwhelming of the detoxification and excretion capacity, respectively, at the toxic dose.

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. After oral exposure in mice, 34-61% was excreted in urine after 72 hours. In humans (one case), after contamination of the skin with ^{14}C-labelled MCAA, a half-life of about 15 hours has been found for excretion of radiolabel in urine, with quantitatively similar excretion via urine and breath.

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.

MCAA can inhibit different enzymes: acetate oxidation, aconitase, pyruvate carboxylase, pyruvate-dehydrogenase, a-ketoglutarate dehydrogenase, and glutathione S-transferase. 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 glutathione S-transferase 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. Because GST binding is also one of the steps in the metabolism of MCAA it can be concluded that MCAA inhibits its own metabolism.

MCAA can also interact with lipids. It was found that MCAA mostly incorporated into phospholipids. Besides, it was shown that MCAA can conjugate with cholesterol to form cholestryl chloroacetate. The effect of such conjugation reactions was suggested to be more prone to retention than excretion, because the conjugate is a more lipophilic product.

High doses (LD90) of MCAA can lead to the alkylation of total sulfhydryls in rat liver and kidney.

4.1.2.2 Acute toxicity

The results of the relevant acute toxicity studies are summarised in **Table 4.7.**

Table 4.7 Acute toxicity

Route	Species	LD50/LC50	Unity	Reference
Oral (gavage, 1% conc. in water)	rat (female, Wistar)	90	mg/kg bw	Hoechst AG (1979a)
Oral	rat (sex and strain unknown)	277.5	mg/kg bw	Kurcatov and Vasileva (1976)
Oral (gavage, 10% concentration)	rat (sex and strain unknown)	55	mg/kg bw	Maksimov and Dubinina (1974)
Oral	mouse (male, Swiss-Webster)	260	mg/kg bw	Berardi et al. (1987)
Oral	mouse (male, strain unknown)	300	mg/kg bw	Berardi and Snyder (1983)
Inhalation (exposure time not reported, according to KEMI (1994) 4 hours)	rat (sex and strain unknown)	180	mg/m^3	Maksimov and Dubinina (1974)
Inhalation (1 hour)	rat (male and female F344)	>259	mg/m^3	Streeter et al. (1987)
Dermal (1%, 5%, and 40% concentration in 0.9% NaCl)	rat (female, Wistar)	1% c.: >100 5% c.: >400 40% c.: 305	mg/kg bw	Hoechst AG (1979b)
Dermal (50%concentration in 0.9% NaCl)	rabbit (sex unknown, Albino-Himalayan)	250	mg/kg bw	Hoechst AG (1979c)
Subcutaneous (50% concentration in 0.9% NaCl)	rat (female, Wistar)	97.4	mg/kg bw	Hoechst AG (1979d)
Subcutaneous	rat (male, Sprague-Dawley))	5	mg/kg bw	Hayes et al. (1972)
Subcutaneous	rat (sex and strain unknown)	108	mg/kg bw	Hayes et al. (1973)
Subcutaneous	mouse (male, Swiss Webster)	130	mg/kg bw	Berardi (1986a)
Subcutaneous	mouse (male)	150	mg/kg bw	Berardi and Snyder (1983)
Intravenous	rat (male, Sprague-Dawley)	75	mg/kg bw	Elf Atochem (1995)

4.1.2.2.1 Studies in animals

Oral

The LD50 values for rats varied between 55 and 277.5 mg/kg bw (Hoechst AG, 1979a; Kurcatov and Vasileva, 1976; Maksimov and Dubinina, 1974). The LD50 values for mice varied between 260-300 mg/kg bw (Berardi et al., 1987; Berardi and Snyder, 1983).

Details of most studies are lacking and several of the cited references are old or the abstracts only are available. However, it can be concluded that MCAA should be classified as toxic if swallowed.

After an oral dose of 40, 63, 100, or 160 mg/kg bw by gavage in 10 female Wistar rats per dose group mortality occurred between 120 minutes and 24 hours after exposure (LD50: 90 mg/kg bw). The clinical symptoms observed in moribund animals were: neurobehavioral effects, lacrimation, and pulsing respiration. The same effects, but less severe, were observed in surviving rats, they recovered within 48 hours. The macroscopic changes observed in dead

animals were discolorations of the liver, lung, stomach, and spleen. In surviving animals no macroscopic effects were observed (Hoechst AG, 1979a). The LD50 value of 55 mg/kg bw was observed after a single oral exposure (gavage) to a 10% solution of MCAA. According to the authors the mortality was caused by local damage, however, not further explained (Maksimov and Dubinina, 1974). After a single oral dose of 320-380 mg/kg bw in mice, front paw rigidity in 10% of the survivors was observed. Animals with front paw rigidity were killed 48 hours and 2, 5, and 8 weeks after MCAA exposure. Histological examination of the brain tissue suggested damage of the blood-brain barrier (BBB) as early as 48-hours post-treatment because of the presence of red blood cells outside the capillaries in several brain regions, especially the cerebellum. This was confirmed by the increase of iv injected [^{14}C]-inulin and [^{3}H]-dopamine into all brain regions of mice administered 300 mg/kg bw MCAA, orally. According to the authors the damage of the BBB of mice is associated with both the neurological dysfunction and death. The LD50 in this study was calculated to be 260 mg/kg bw, the LD80 was 380 mg/kg bw (Berardi et al., 1987; Berardi, 1986a+b). Male mice orally administered 300 mg/kg bw MCAA (= LD50 value) showed tremors, respiratory depression, and occasionally tonic and clonic convulsions. Some survivors had a Straub tail, severe tremors, and front limb paralysis after 24 hours (after exposure) (Berardi and Snyder, 1983).

Inhalation

Two acute vapour inhalation toxicity studies on MCAA with albino rats (Charles River), white mice (Swiss), and guinea pigs (English) were reported by Hercules Inc. (1969c+d). In the studies a vapour of MCAA was generated with undiluted MCAA heated to 75°C. Animals were subsequently exposed to a test atmosphere of 24°C at average concentrations of $3.1 \cdot 10^4$ mg/m^3 for one minute (2 animals per species) and $2.7 \cdot 10^4$ mg/m^3 for three, five, and ten minutes (3 animals per species); no control groups were used. No deaths were observed among any test animals. Mild lacrimation and nasal discharge were noted among all animals at 5-60 minutes after the one minute exposure and immediately during the five and ten minutes exposure. Necropsies revealed some lung hyperemia. The results of the studies cannot be used for the EC classification of MCAA due to the short exposure times and the limited number of animals per test group.

One acute inhalation study with male and female F344 rats (n=6/sex) was reported by Streeter et al. (1987). The physical characteristics of MCAA limited the analytical vapour concentration to 66 ppm; a saturated atmosphere (at 20°C) contains approximately 137 ppm MCAA. After a 1 hour exposure to 66 ppm, in-live animal observations and animal body weights were monitored. During exposure, all rats squinted and appeared slightly lethargic. Following exposure, transient urine stained perineum and weight loss was observed and was indicated to be typical non-specific stress-related responses to exposure. No mortality or exposure-related pathologic changes were observed at the end of a two week post-exposure period. The 1 hour LC50 of MCAA was concluded to be greater than 66 ppm (259 mg/m^3).

In another study the LC50 value for the rat was found to be 180 mg/m^3 (exposure duration not indicated; 4 hour exposure duration is mentioned in KEMI, 1994) (Maksimov and Dubinina, 1974). Details of this study are lacking, as well as a description of symptoms of toxicity. MCAA should be classified as very toxic after inhalation given the results of these acute toxicity studies.

Dermal

In a study by Hoechst AG (1979b), 6 female Wistar rats per group were dermal exposed to different doses of MCAA (50 and 100 mg/kg bw in a 1% concentration; 200 and 400 mg/kg bw

in a 5% concentration; 200, 280, 400, and 2,000 mg/kg bw in a 40% concentration) to equal surface areas (ca. 30 cm^2). The study was performed under occlusion. None of the animals exposed to 1% or 5% concentrations of MCAA died (LD50 values >100 mg/kg bw and >400 mg/kg bw, respectively). Deaths occurred within 3.5-24 hours after exposure to 280, 400, 2,000 mg/kg bw in the 40% concentration (no further details were described). Rats in moribund condition showed neurobehavioral effects, lacrimation, and respiratory difficulties. All dead animals showed macroscopic changes in lungs and bowels. In addition, in the 2,000 mg/kg bw dose group, discolouration of the skin at the application site was observed. None of the survivors showed effects within 48 hours after exposure and at sacrifice after 48 hours no macroscopic effects were observed. In this study, an LD50 of 305 mg/kg bw (based on a 40% concentration) was found. It was noted that the dermal toxicity both depends on the concentration (in %) and on the dose of exposure (in mg/kg bw).

In a second acute dermal toxicity study of Hoechst AG (1979c), 6 Albino-Himalayan rabbits (sex unknown) were exposed to different doses of a 50% concentration of MCAA (63, 125, 250, and 500 mg/kg bw). The application area was not reported. The study was performed under occlusion. In this study deaths occurred between 260 minutes and 24 hours after exposure (no further details). The animals showed neurobehavioral effects, lacrimation, high respiratory frequency, and local irritation/corrosion of the skin in the highest dose group (500 mg/kg bw). The only dose-related effects at lower doses (63, 125, 250 mg/kg bw) were a higher respiratory frequency, local irritation/corrosion, and animals specifically lying on their stomachs. The survivors did not show any symptoms. In this study, an LD50 of 250 mg/kg bw was found. Based on these studies, 40% and 50% concentrations of MCAA should be classified as toxic in contact with skin.

Millischer et al. (1988) described a study in which 5-10 NZW rabbits were exposed to molten pure MCAA (dose not mentioned) at 60°C directly applicated on the shaved skin (back side, 100 cm^2). The contact duration was 90 to 300 seconds and the skin was rinsed with water during 120 seconds after exposure. The experimental conditions were similar to that occurring in accidental skin splashing in workers. After exposure mortality occurred in all animals within a few hours (within 5-12 hours after 90 seconds of exposure; within 2.5-7.5 hours after 300 seconds). Biochemical changes observed in moribund animals were: hyperglycemia and strong acidosis. These effects are similar to observations in human (Millischer, 1987, see relevant section). In contrast to humans slight hyperkalemia was noted in rabbits. Increased length of skin contact before washing off MCAA induced a more rapid death in animals.

In a study by Hercules Inc. (1969a) two experiments were performed. In the first experiment, 2 male albino New Zealand rabbits per group were exposed to non-molten MCAA to the shaved abdominal skin (about 10 percent of the total body surface) at dose levels of 79.0, 118.5, 177.8, and 266.7 mg/kg bw under occlusive conditions. The test substance (in solid state) was not moistened with water or a vehicle. Twenty-four hours after application the plastic sheeting was taken off and all residual material removed. Observations for mortality, local skin reactions, and behavioural abnormalities were continued for a total of 14 days following the skin applications. No animals died in the two lowest dose groups, one died in the 177.8 mg/kg bw dose group and both animals in the high dose group died. Hyperactivity was noted among all animals in the two highest dose groups within one hour after application. After 24 hours all survivors appeared normal. At the end of the contact period necrosis was noted at the site of contact of MCAA. No improvement was noted after 14 days. The results of this experiment cannot be used to determine a LD50 value due to the small dose groups tested and because the test-substance was not moistened before application to the skin. In the second experiment non-molten MCAA was applied to the back of ten albino rabbits (five males and five females) at a level of 200 mg/kg

bw. The test-substance was not moistened with water or a vehicle. The sites were occluded loosely with gauze. After a 24-hour contact period, the gauze and the residual material were removed. The animals were observed for mortality for a rather short period of 48 hours. Two of the five females died and all male animals survived. In a second study by Hercules Inc. (1969b), 2 male albino New Zealand rabbits per group were dermally exposed to different doses of molten MCAA and different surface areas. The doses ranged from 0.2 to 10 ml and exposed body surface areas were 1, 3, 5, 10, 20, or 40 percent. Also different contact times were used and some animals were therapeutically treated with sodium carbonate at the end of the contact period. In one experiment the animals were anesthetised by intravenous injection of urethan at a level of 1.0 ml/kg bw prior to application of molten MCAA. In the same study, one mongrel dog was dermally exposed to 2.6 ml/kg bw (equivalent to 4,108 mg/kg bw) molten MCAA on 20% of the total body surface for 15 minutes and died within 4 hours. A summary of the mortality data incurred in the different experiments with rabbits is presented in **Table 4.8**.

Table 4.8 Summary of mortality data observed in the study of Hercules Inc. (1969b)

Exposed surface area	Dose	Mortality			
% of total body surface area exposed	total dose in mg/kg bw	I 15-minute contact + wash with sodium carbonate	II 1-minute contact + wash with sodium carbonate	III 15-minute contact + wash with sodium carbonate (other sample)	IV 1-minute contact + wash with sodium carbonate (other sample)
1.0	126-174	0/2	-	0/2	-
3.0	395-490	2/2	0/2	2/2	0/2
5.0	600-901	2/2	½	-	-
10.0	1,580-2,054	2/2	2/2	-	-
20.0	3,318-4,108	3/3*	2/2	-	-
40.0	5,372-6,636	2/2	2/2	-	-

* the additional animal in this group was a mongrel dog

Deaths were observed when either ≥3% of the total body surface area was exposed to 0.25 ml/kg bw (equivalent to 395 mg/kg bw) of MCAA for 15 minutes or ≥5% of the total body surface area was exposed to 0.57 ml/kg bw (equivalent to 901 mg/kg bw) for one minute. Washing the exposure site with soap and water, treatment with sodium bicarbonate, no treatment of any kind, or pre-exposure anesthesia did not appear to have any beneficial effects. Hypoactivity was noted among all animals immediately after application of MCAA. Two or three hours later, dyspnea and prostration were noted. Severe oedema, wrinkling, and necrosis were noted at the site of contact of MCAA within 15 minutes after application. Necropsy of the animals that died revealed extensive dilatation of the vascular system. The skin at the site of contact of MCAA was necrotic. There were no histologic changes which can be specifically attributed to the compound. Based on the mortality data no LD50 value for MCAA can be determined due to the small dose groups.

In another experiment reported by Hercules Inc. (1971) it was determined whether prompt treatment with parenteral sodium bicarbonate would reverse or alter the lethal consequence of topically applied MCAA. Six albino New Zealand rabbits (sex unknown) were dermally exposed to 2,000 mg/kg bw molten MCAA till death, 6 rabbits were exposed to 2,000 mg/kg bw for 5 minutes, and a group of 6 rabbits was exposed to 1,000 mg/kg bw molten MCAA for 5 minutes. After the 5 minutes of exposure an infusion with saline (3 animals) or bicarbonate

(3 animals) was given. All animals without treatment with sodium bicarbonate died within 3 hours. All animals with treatment of sodium bicarbonate died within 5.5 hours. Based on the results of the three experiments it was concluded that sodium bicarbonate parenterally administered to rabbits treated with a topical lethal dose of MCAA does not reverse the lethality of the test material under the regarding experimental conditions.

In an experiment to investigate whether ethanol can be used as antidote of MCAA toxicity (Millischer et al., 1988) high exposure doses were used so that rabbit skin contamination with MCAA was normally always fatal to the animals. No details of the study design were reported. In the circumstances of the experiment ethanol was unable to prevent death, even with maximum ethanolisation (3 g/l in blood). The mean mortality delay was higher in rabbits infused with ethanol after MCAA exposure than in rabbits not infused with ethanol. It seems that blood glucose, potassium, and HCO^-_3 were slightly less modified in ethanolised animals than in non-ethanolised animals.

Subcutaneous

LD50 values for rats varied between 5 and 108 mg/kg bw (Hayes et al., 1972; Hoechst AG, 1979d; Hayes et al., 1973) and for mice the LD50 values were found to be 130 mg/kg bw (Berardi, 1986a) and 150 mg/kg bw (Berardi and Snyder, 1983). Details of most studies are lacking or only abstracts are available, and several of the cited references are dated. In some cases the study was not aimed at the determination of the acute toxicity of MCAA.

An LD50 of 97.4 mg/kg bw in female Wistar rats was observed in a study reported by Hoechst AG (1979d). In this study 10 rats/group were subcutaneously exposed to 80, 100, 125, 200, or 315 mg/kg bw (based on a 50% concentration of MCAA). Deaths occurred within 172 minutes and 3 days after exposure. The effects observed were neurobehavioral effects, higher respiratory frequency, local effects on site of injection (grey brown coloured skin and muscles), and macroscopic changes of the liver (brownish coloured and strong bloody) and the small bowel (red coloured). None of the survivors did show any clinical or macroscopic changes.

Intravenous

An LD50 of 75 mg/kg bw (95% confidence interval limits: 53-117 mg/kg bw) in male Sprague-Dawley rats was observed in a study reported by Elf Atochem (1995). In this study six groups of 5 male Sprague-Dawley rats received MCAA by intravenous injection at doses of 30, 50, 70, 80, or 90 mg/kg bw. Hypokinesia, sedation, dyspnea, lateral decubitus, suffocation and/or coma were noted from 30-40 minutes after dosing, in almost all animals given 50, 70, 80, or 90 mg/kg bw. Only hypokinesia and sedation were noted in animals given 30 mg/kg bw. These signs were considered as indicative of central nervous system toxicity. Deaths were 0/5, 1/5, 1/5, 2/5, and 5/5 in the 30, 50, 70, 80, and 90 mg/kg bw group, respectively. Most deaths occurred at the day of administration. Body weight loss was noted in one of the 4 surviving animals of the 70 and 80 mg/kg bw group. All dead animals were macroscopically examined. No treatment-related changes were observed.

In a range finding experiment (10-125 mg/kg bw) that was included in an i.v. toxicokinetic study, the onset of toxicity was very abrupt. No apparent signs of toxicity were observed up to 50 mg/kg bw, whereas 43% of the rats died at 60 mg/kg bw and >50% at 70 mg/kg bw, preceded by coma. Mean time to coma and death was 70 and 75 minutes, respectively. Doses between 70 and 100 mg/kg bw induced almost the same mortality, no dose response was apparent. Doses of $\geq$110 mg/kg bw caused 100% mortality. Most of the animals that went into coma and did not die

within 90 minutes of dosing regained consciousness suddenly and recovered (Saghir et al., 2001).

4.1.2.2.2 Studies in humans

Oral

Feldhaus et al. (1993) and Rogers (1995) shortly described a case of oral-route poisoning of a 5-year old girl. By mistake, a teaspoonful of a wart remover containing 80% MCAA was ingested by the girl. The victim immediately vomited and soon collapsed. 1.5 hours after the ingestion, unmanageable metabolic acidosis and cardiac arrhythmias developed. Eight hours after the ingestion, the girl died. Autopsy showed pulmonary and cerebral edema, fatty infiltration of the liver, and marked gastrid mucosal hyperemia.

Dermal

Ruty et al. (1988) described a case of human systemic poisoning from percutaneous absorption. By accident, a 47-year-old worker was suddenly splashed on both legs (approximately 6% of the body surface) with molten MCAA under pressure. After exposure, burns of first degree became apparent. The general physical condition of the man was good. However after 4 hours, digestive signs appeared insidiously in the form of nausea with vomiting within half an hour. Later, cardiovascular shock occurred with progressive neurological symptoms consisting of loss of consciousness and alternation of excitation and depressive phases. The patient became comatose and had a cardiac arrhythmia. His blood systolic pressure was 70, his cardiac pulse 120, and the worker had a normal temperature. A very high persistent metabolic acidosis was observed. In addition to classical reanimation treatment and massive infusion of buffer solution an antidote treatment with ethanol was given. No steady state ethanol concentration in blood was observed but a health improvement was observed. After 24 hours the patient was considered saved. The burns healed after a long period (2-3 months).

Ethanol was thought to be able to act as an acetate donor. Acetate formed during the metabolism of ethanol could compete with chloroacetate, preventing its incorporation in the Krebs cycle. It could not be concluded whether the improvement in health was the result of the antidote treatment or not.

Another case was reported by Kusch et al. (1990). A 45-year old man was accidentally sprayed on both legs with molten 90% MCAA. After the accident a safety shower was activated immediately, the victim remained in the shower for 10 minutes. Following the shower ice was applied to the burned areas and he was placed in bed. The estimate of the body surface involved was 10%. Over the next 30-45 minutes the man developed nausea and vomiting. His level of consciousness had been normal during the time he was treated and observed at the medical facility. During the transportation to the hospital the man had 3 episodes of emesis. In the first 6 hours after admission he showed a tachycardia of 100-120 beats per minute and occasional premature ventricular contractions. He displayed an initial hypokalemia.

The burns on the legs were partially thickened (first and second degree) and did not expand or increase in depth following admission. The patient was treated iv with KCl, high dose corticosteroids, and diuretics and after 2 days orally with potassium and prednisone. It was unclear whether the patient survived because of the treatment regimen employed or whether this survival was related to prompt washing following exposure or some combination of

circumstances. The fact that the patient developed vomiting, tachycardia, and 'occasional premature ventricular contractions' is evidence that this level of exposure was adequate to cause systemic toxicity following skin exposure.

Kulling et al. (1992) described a case of fatal systemic poisoning after skin exposure to MCAA. A 38-year old man was splashed with an 80% monochloroacetic acid solution on 25-30% of his body surface. In addition to epidermal and superficial dermal burns, features of systemic poisoning occurred within a few hours including disorientation, agitation, cardiac failure, and coma. The patient later developed severe metabolic acidosis, rhabdomyolysis, renal insufficiency, and cerebral edema, and died due to cerebral herniation on day 8. The 4 hour post exposure plasma MCAA concentration was 33 mg/L confirming skin absorption.

Another case described by Kulling et al. (1992) was a 25-year old man who was splashed with MCAA (concentration not reported) at 60°C. The man suffered from extensive epidermal burns of the face, the neck, upper chest, groins, and legs. One hour after the accident he developed a cough with bloody sputum and convulsions. He became unconscious and died 4 hours later. Autopsy revealed signs of alveolar damage and petechial hemorrhages in the pericardium and pleura and dilatation of the right heart. It was suggested that the patient probably also had inhaled the substance, which might have contributed to the rapid onset of severe symptoms and the fatal outcome.

Millischer et al. (1987) described seven cases of systemic poisoning with molten or concentrated solutions of MCAA resulting from accidental skin contact. The body surface involved was usually around 10%, but sometimes less. Mainly legs were affected. Burns varied from first to third degree. In general, the burns were less extensive and serious when evaluated immediately after the accident. After a few hours, the intensity of the burns shifted to second or third degree and the surface affected was increased. The clinical signs were first digestive (vomiting) then neurological (excitation phases, convulsions). Cardiovascular shock was followed by loss of consciousness progressing into coma. The first signs occurred within 1 to 3 hours after skin contact. Biological changes were primarily a severe acidosis with hyperglycemia and hypokalemia. Low urinary output and elevated phosphocreatine kinase were observed. Death mostly occurred 4 to 18 hours after skin contact, except one case where death occurred after 7 days. Organ lesions found at autopsy were non specific: a variety of organs were affected, including the liver, brain, kidney, and heart.

Braun and Walle (1987) described a case of a 23-year old chemical technician who spilt MCAA over the dorsum of his right hand and forearm. The solution contained 1.5 M MCAA in ethanol 94%. The arm was rinsed with water for 10 minutes; despite this, erythema and small blisters appeared in the first hour. The lesions healed in 10 days with small scars. After 14 days, itchy vesicles appeared at the site of the scars.

On day 28 the patient was patch tested with the international standard series and the MCAA solution 1% in methanol 70%. A strong 4+ reaction was observed to the MCAA solution. Two control persons were negative. According to the authors the ethylester of MCAA (EMCA) was suspected as the causative agent (MCAA + ethanol may react to EMCA and water). On day 49, patch testing was performed with 1% EMCA (purity 99.9%) in acetone and ethanol and 1% MCAA in aq. Strong 4+ reactions were observed to the patches with EMCA, MCAA was negative.

4.1.2.2.3 Conclusion

Although it is presumed that animal studies were not performed according to OECD or EU guidelines and most data were of older date and only limited reported, the rapporteur considers the amount of data available sufficient to fulfil the Annex VIIA requirements for acute toxicity.

Based on the available data on acute toxicity the Commission Working Group on the Classification of Dangerous Substances decided that MCAA should be classified as toxic (T) by inhalation, in contact with skin and if swallowed.

The R-phrase 23/24/25 ('toxic by inhalation, in contact with skin and if swallowed') is applicable for pure MCAA.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

Skin and eye irritation

MCAA is reported to induce skin irritation or corrosion and eye irritation in all studies provided (Hoechst AG, 1979e; Maksimov and Dubinina, 1974; Christofano et al., 1970). Details of most studies are lacking. In the study performed by Hoechst AG (1979), 500 mg MCAA in 0.05 ml NaCl (0.9% solution) was applied to the intact shaved and abraded skin (2.5 cm^2) of 6 Albino-Himalayan rabbits under occlusive conditions. After exposure, all animals died, therefore a second test was performed in which 6 rabbits were dermally exposed (occlusive conditions, intact skin) to 150-250 mg MCAA (based on a dose of 100 mg/kg bw, a bodyweight of 1.5-2.5 kg, and a 50% MCAA solution in 0.9% NaCl) for 24 hours. The exposure resulted in severe skin irritation and corrosion (the effects were irreversible). The skin-irritation scores were not mentioned. In this publication also an eye-irritation test was reported with 6 rabbits. The dose instilled in the eyes was 100 mg in 0.01 ml NaCl (0.9% solution) and resulted in severe eye irritation. The eye-irritation scores were not reported. Based on these data MCAA is considered to be corrosive to the skin and to induce a risk of serious damage to the eyes.

Respiratory tract

In two acute vapour inhalation toxicity studies reported by Hercules Inc. (1969c+d; see Section 4.1.2.2. Acute toxicity), mild lacrimation and nasal discharge were noted among all animals tested.

In a limited reported acute inhalation study in rats respiratory irritation was observed at a concentration of 23.7 mg/m^3. No further details were reported (Maksimov and Dubinina, 1974).

4.1.2.3.2 Studies in humans

Data on irritating properties of MCAA are already described in Section 4.1.2.2 'acute toxicity'. In all human cases of MCAA exposure dermal burns were reported, demonstrating that accidental skin contact with molten or concentrated solutions of MCAA resulted in chemical burns that varied from first to third degree (Millischer et al., 1987). Even activation of a safety shower immediately after accidental skin contact with molten 90% MCAA could not prevent

from development of first and second degree burns at the site of contact (Kusch et al., 1990). Maksimov and Dubinina (1974) reported that the threshold for respiratory (sensory) irritation in humans amounts 5.7 mg/m^3. No further details were reported.

4.1.2.3.3 Conclusion

Although the available animal studies were not performed according to OECD or EU guidelines, and most data were of older date and only limited reported, the rapporteur considers the data available sufficient to fulfil the requirements for irritation testing of MCAA to eyes and skin. MCAA is considered to be corrosive to the skin (R34) and to induce a risk of serious damage to the eyes (Xi, R41). The symbol Xi and sentence R41 are not included in the label, because of the classification as corrosive with sentence R34. In that case, a risk of serious damage to eyes is considered implicit.

Only limited information is available on the respiratory tract irritating effects of MCAA. Respiratory irritation was observed at 23.7 mg/m^3 in rats. The threshold for respiratory (sensory) irritation is reported to be 5.7 mg/m^3 in humans (Maximov and Dubinina, 1974).

4.1.2.4 Corrosivity

As already mentioned in Section 4.1.2.3 (irritation) MCAA is considered to be corrosive to the skin.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

The only information available on the sensitising properties of MCAA was a short description of a sensitisation study in a Dutch translation of a report written by Maksimov and Dubinina (1974). This report described an open epicutaneous test performed with rabbits (n = unknown). The rabbit skin was treated with a 5% MCAA solution once a day for 30 days (induction) and followed by different concentrations of MCAA (one drop of a 0.1, 1, 5, 10, and a 50% MCAA solution; challenge). In this reference it was concluded that MCAA has no sensitising properties. However, due to the limited reporting this study is not considered reliable for the evaluation of the sensitising potential of MCAA.

There are no data on respiratory sensitisation of MCAA.

4.1.2.5.2 Studies in humans

In the Section ‘acute toxicity’ one case-study of Braun and Walle (1987) described a patch test with MCAA and its ethylester (EMCA). 28 days after exposure to MCAA in ethanol (dose unknown) the patient was patch tested with the international standard series and a 1% MCAA solution in 70% methanol. A strong 4+ reaction was observed to the MCAA solution. Two control persons were negative. According to the authors the ethylester of MCAA (EMCA) was suspected as the causative agent (MCAA + ethanol may react to EMCA and water). On day 49, patch testing with 1% EMCA (purity 99.9%) in acetone and ethanol and 1% MCAA in aq

resulted in strong 4+ reactions to EMCA; MCAA was negative. Based on this case-study the sensitising properties of MCAA cannot be excluded.

On the other hand, over forty years of production and handling of MCAA has not produced a single case of contact allergy to MCAA. Relatively large numbers of people have sustained both minor and major skin injuries, resulting in 2nd to 3rd degree burns. These conditions are ideal for the induction of contact allergy, yet allergy has never been described. Additionally, also the use of MCAA as a wart remover had not resulted in any documented contact allergic response (Industry Risk Assessment Group, 2000).

4.1.2.5.3 Conclusion

The data submitted are not considered acceptable with regard to the basic requirements as specified in Annex VIIA of Directive 67/548/EEC. However, based on the wide practical experience with MCAA and the absence of any case reports on allergy under ideal conditions for the induction of contact allergy, it is concluded that further testing is not required. Moreover, a proper evaluation of the sensitisation potential of MCAA will be hampered by the corrosive properties of the substance.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

The results of the repeated-dose toxicity studies most relevant for risk assessment are summarised in **Table 4.9** (see also Section 4.1.2.8 ‘Carcinogenicity’).

Table 4.9 Oral repeated-dose toxicity

Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Effects	Reference
Oral toxicity				
study 1: subacute, rat (5 d/wk, 12 doses over 16 days, gavage; 0, 7.5, 15, 30, 60, 120 mg/kg bw/day)	7.5	15	Lacrimation	NTP, 1992
study 2: subacute, male mice (5 d/wk, 12 doses over 16 days, gavage; 0, 15, 30, 60, 120, 240 mg/kg bw/day)	120	240	mortality, clinical signs	NTP, 1992
study 3: subacute, female mice (5 d/wk, 12 doses over 16 days, gavage; 0, 30, 60, 120, 240, 480 mg/kg bw/day)	60	120	Lacrimation	NTP, 1992
study 4: semichronic, rat (13 wk, 5 d/wk, gavage; 0, 30, 60, 90, 120, 150 mg/kg bw/day)	<30	30	changes in heart, liver, and kidney weights and clinical chemistry values; at doses ≥60 mg/kg bw/day: cardiomyopathy and mortality	NTP, 1992
study 5: semichronic, mice (13 wk, 5 d/wk, gavage; 0, 25, 50, 100, 150, 200 mg/kg bw/day)	100	150	increased liver weight, decreased serum cholinesterase activity	NTP, 1992
study 6: carcinogenicity (*), rats (103 wk, 5 d/wk, gavage; 0, 15, 30 mg/kg bw/day)	<15	15	decreased survival, acute inflammation of the nasal mucosa	NTP, 1992
study 7: carcinogenicity (*), mice (103 wk, 5 d/wk, gavage; 0, 50, 100 mg/kg bw/day)	<50	50	acute inflammation of the nasal mucosa	NTP, 1992
study 8: carcinogenicity (*), rats (104 wk, daily, drinking water; 0, 3.5, 26.1, 59.9 mg/kg bw/day)	3.5	26.1	changes in body weight	DeAngelo et al., 1997

* Description of study is provided in Section 4.1.2.8 'Carcinogenicity'.

Oral

In a range-finding study by the NTP (1992; study 1 in **Table 4.9**), 5 to 6 weeks old F344/N rats (5/sex/group) received MCAA by gavage in deionised water for 16 days (administration schedule: daily for 5 days/week). Doses were 0, 7.5, 15, 30, 60, and 120 mg/kg bw/day. One high dose male died on day 3. This animal showed increased lacrimation, prostration, bradypnea, decreased limb tone, ataxia and impaired grasping reflex within 4 hours after dosing. Lacrimation was also observed in the 60 and 120 mg/kg bw/day and 15 to 120 mg/kg bw/day groups for males and females, respectively. It is not mentioned by the authors if the occurrence of this effect was dose-related. There were no significant changes in body weight (gain). Gross examination at autopsy or full histopathology did not reveal lesions attributable to MCAA. Within the limited study design, the NOAEL is 7.5 mg/kg bw/day based on lacrimation observed at higher dose levels.

In another 16-day study (NTP, 1992; study 2 and 3 in **Table 4.9**), 7 to 8 weeks old male B6C3F1 mice (5/group) were exposed under the same exposure regimen to 0, 15, 30, 60, 120, and 240 mg/kg bw/day and female B6C3F1 mice (5/group) to 0, 30, 60, 120, 240, and 480 mg/kg bw/day (NTP, 1992). All male mice dosed with 240 mg/kg bw/day and female mice dosed with 240 or 480 mg/kg bw/day, died within two days. Clinical signs in these animals included lacrimation, ataxia, hypoactivity, bradypnea, bradycardia, hypothermia, prostration, piloerection, decreased limbtone, and impaired grasping reflex. No treatment-related effects were found on mean final body weight, absolute and relative organ weights, and at macro- and microscopic examination for both males and females. In the 120 mg/kg bw/day group (females) lacrimation was observed. Within the limited study design, the NOAEL is 60 mg/kg bw/day for female mice, based on lacrimation, and 120 mg/kg bw/day for male mice, based on clinical signs and mortality.

A 13-week study in rats was performed by NTP (NTP, 1992; study 4 in **Table 4.9**). F344/N rats (6-7 weeks old) were administered MCAA in deionised water for 13 weeks by gavage. Twenty animals/sex/group were dosed with MCAA at 0, 30, 60, 90, 120, and 150 mg/kg bw/day. At week 4 and 8, an interim evaluation was performed (5 animals/sex/group). Haematology, clinical chemistry, and urinalysis were performed at the interim evaluation and at the end of the study. All rats in the 120 and 150 mg/kg bw/day group, 19/20 in the 90 mg/kg bw/day group, and 2 males and 1 female in the 60 mg/kg bw/day group died before the end of the study. Treatment-related and dose-related cardiomyopathy was considered the cause of death in the decedents. Given the high mortality in the highest dose groups, the results are mainly reported for the 0, 30, and 60 mg/kg bw/day groups. No treatment-related effects on mean body weight (gain) and clinical findings were observed. Absolute heart weight was decreased at 60 mg/kg bw/day in both sexes, while relative heart weight was decreased at 60 mg/kg bw/day in males and at 30 and 60 mg/kg bw/day (dose-related) in females. Absolute liver weight was increased at 60 mg/kg bw/day in males and relative liver weight was increased at 30 and 60 mg/kg bw/day (dose-related) in males and at 60 mg/kg bw/day in females. Relative kidney weight was increased at 30 and 60 mg/kg bw/day (dose-related) in males. Blood urea nitrogen was dose-related increased at 90 to 150 mg/kg bw/day in males and at 60 to 150 mg/kg bw/day in females. There was a dose-related increase in ASAT and ALAT in males and females at 60 to 150 mg/kg bw/day. The increases were not statistically significant at all dose levels and all time points. Thyroxin (T4) levels were increased in male rats at 90, 120, and 150 mg/kg bw/day in week 4 and at 90 mg/kg bw/day in week 8. Serum cholinesterase activity was decreased in males at 30 and 60 mg/kg bw/day after 13 weeks, in all female dose groups after 4 and 8 weeks, and in females of the 60 mg/kg bw/day group after 13 weeks. The decreased serum cholinesterase activity may have been a result of liver toxicity, or direct inhibition of this enzyme by MCAA or

its metabolites. In addition, females showed decreased plasma levels of total protein (from 30 mg/kg bw/day), albumin (at 60 mg/kg bw/day), calcium (30 and 60 mg/kg bw/day), and sodium (from 30 mg/kg bw/day) after 8 and/or 13 weeks. Plasma potassium was increased after 13 weeks at 60 mg/kg bw/day in females and at 30 and 60 mg/kg bw/day in males. Hematocrit, hemoglobin, and erythrocyte counts were increased in male rats receiving 150 mg/kg bw/day for 4 weeks. Neutrophil counts were increased in males given 90, 120, and 150 mg/kg bw/day for 4 weeks. After 8 weeks of MCAA administration, lymphocyte counts were decreased in males of the 30, 60, 90, and 120 mg/kg bw/day groups. At necropsy of the rats that died during the study, blood or clear red fluid in the thoracic cavity and congestion of the lungs were observed. Dose-related cardiomyopathy was found in both sexes at 60 mg/kg bw/day and above. A NOAEL cannot be derived from the results of this study.

B6C3F1 mice (7-8 weeks old) were exposed to MCAA in deionised water for 13 weeks by gavage to 0, 25, 50, 100, 150, and 200 mg/kg bw/day (20 mice/sex/dose; NTP, 1992; study 5 in **Table 4.9**). All male and 2 female mice died in the 200 mg/kg bw/day group, 2 males and 1 female due to gavage trauma. Hepatocellular cytoplasmic vacuolisation was found in 5 males and 1 female that died in the highest dose group. Mean body weight gain was decreased in the surviving females in the highest dose-group. Absolute and relative liver weights were (not dose-related) increased in females in the 100 and 200 mg/kg bw/day group, but not in the 150 mg/kg bw/day group. The changes in liver weight at 100 mg/kg bw/day were not considered as toxicologically significant because the effect was minimal and no effects were found on other liver parameters. Serum cholinesterase activity was decreased in females of the 150 and 200 mg/kg bw/day group at 8 and 13 weeks after initiation of dosing, possibly as a result of liver toxicity, or direct inhibition of this enzyme by MCAA or its metabolites. No treatment-related effects were found at necropsy or histopathology in survivors. Within the limited study design, the NOAEL is 100 mg/kg bw/day. The liver appeared to be the target organ in mice in this study.

In the above NTP studies, rats appeared to be more sensitive for the toxic effects of MCAA than mice. Clear sex differences were not found. Histopathology was performed; however, details are not presented in the report.

DeAngelo et al. (1989) studied the species sensitivity to the induction of peroxisome proliferation by chloroacetic acids. Male B6C3F1 mice and male Sprague-Dawley rats were exposed to MCAA in their drinking water during 14 days. Concentration levels were 0, 11, 21, and 32 mM (calculated average intake 0, 265, 386, and 482 mg/kg bw/day; water consumption was not measured) for mice and 0, 11, 21, and 32 mM (calculated average intake 0, 170, 321, and 501 mg/kg bw/day; water consumption was not measured) for rats. The number of mice surviving and used for analysis per concentration level were 6, 5, 6, and 6, respectively, and for rats 6, 6, 6, and 5 (initial group sizes are not given). In mice there were no significant effects of MCAA on body weight, relative liver weight, and peroxisome proliferation. In rats, however, a dose-related statistically significant decrease in body weight and relative liver weight was found at all concentration levels. Rats showed no treatment-related effects on peroxisome proliferation parameters. No other observations were made in this study. Within the limited study design, it appears that male mice were less sensitive to MCAA administration in drinking water compared with male rats.

Fuhrman et al. (1955) administered MCAA in diet to Wistar rats in the three experiments below. It is noted that the authors do not report any data on the stability of MCAA in the diet. In the NTP repeated-dose toxicity studies (NTP, 1992), the gavage route of administration was chosen because MCAA was unstable in feed formulations, as determined by gas chromatographic analysis. Therefore, the results of the Fuhrman studies should be interpreted with caution.

Fuhrman et al. (1955) administered MCAA in diet to male weanling albino Wistar rats for 208 days (6 animals/group). Dose levels were 0.005, 0.01, 0.025, 0.05, and 0.1% (equivalent to 2.5, 5, 12.5, 25, and 50 mg/kg bw/day). A control group was included. The study design was limited. The following parameters were investigated: body weight, food consumption, general appearance, behaviour, macro- and microscopy of heart, liver, spleen, adrenals, kidney, lung, stomach, intestine, pancreas, thyroid, bladder, and testes. Haematology and clinical chemistry were not included in the study design. Organ weights were not determined. A statistically significant decrease in rate of growth was observed in the highest dose group, while the amount of food ingested per rat per day was somewhat higher. Five animals died in the 0.005, 0.01, 0.025, and 0.05% groups due to injury (not specified) or pneumonia. At necropsy, no treatment-related macro- and microscopic lesions were observed. Within the limited study design, the NOAEL is 25 mg/kg bw/day based on the reduced growth rate in the highest dose group.

In a second experiment Fuhrman et al. (1955) studied the effect of a diet containing 0.1% MCAA on the activity of 2.5 months old Wistar rats in running cages (2 groups, 6 rats/group). After 40 days of training and conditioning (day 1-40), the first test period started (day 41-60). At day 61, the diets were interchanged. So, each rat served as his own control. After a recondition period (day 61-67), the second test period started (day 68-88). A small but statistically significant decrease in average running distance run was found during MCAA treatment compared to control treatment.

In the third experiment Fuhrman et al. (1955) studied the effect of 90 days feeding of 0.1% MCAA on liver glycogen and oxygen consumption of samples of liver, cerebral cortex, kidney cortex, and skeletal muscle. Six young adult male Wistar rats were fed the diet containing MCAA and 6 without MCAA. No effect of MCAA in diet on liver glycogen and on the oxygen consumption was found.

MCAA was administered in drinking water to male Sprague-Dawley rats (5 in experimental and 5 in control group) for 90 days (Bhat et al., 1991). The concentration was 1.9 mM (equivalent to 19 mg/kg bw/day). The dose solutions were prepared such that each rat received ca. ¼ of the LD50. Body weight in the experimental group was 95.2% of the control. No statistically significant changes in organ weights were observed. Light-microscopic examination of the major organs revealed variable degrees of alteration in the lung (foci of perivascular inflammation) and liver (minimal collagen disposition, minimal to mild portal vein dilation/extension). No morphological changes were observed in other organs. Haematology and clinical chemistry were not performed. Because of the limited study design, this study cannot be used to derive a NOAEL/LOAEL for risk assessment. However, it is noted that the results are not contradictory to the results of the studies by the NTP (1992).

No evidence of carcinogenic activity of MCAA was found in rats and mice after oral administration in drinking water or by gavage. An NOAEL of 3.5 mg/kg bw/day is found in a 2-year drinking water study performed by DeAngelo et al. (1997; see Section 4.1.2.8 ‘Carcinogenicity’). At this level, no effect on survival, body weight, or (non-) neoplastic lesions was found.

Inhalation

Reliable repeated-dose toxicity studies by inhalation exposure were not available.

Dermal

Reliable repeated-dose toxicity studies by skin contact were not available.

4.1.2.6.2 Studies in humans

Data on toxicity after repeated exposure of humans to MCAA were not available.

4.1.2.6.3 Conclusion

The data submitted are considered acceptable with regard to the basic requirements as specified in Annex VIIA of Directive 67/548/EEC. The available oral repeated-dose toxicity data permit risk characterisation for repeated exposure. No suitable studies are available to assess toxicity after repeated dermal and inhalation exposure.

Increased mortality is observed in several studies. The dose levels at which mortality is observed is close to the LD50-values. As mortality was relatively high in the first days/week of exposure, this effect is considered merely an acute toxic effect.

Oral repeated-dose toxicity studies with 16-day and 13-week 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. An NOAEL could not be derived from the results of 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. Dose-related cardiomyopathy was found in both sexes at 60 mg/kg bw/day and above. An increased liver weight and decreased serum cholinesterase activity were observed in mice exposed during 13-weeks by gavage, the NOAEL was 100 mg/kg bw/day.

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 (see Section 4.1.2.8 'Carcinogenicity'). At this level, no effect on survival, body weight, or (non-) neoplastic lesions was found.

Main target organs of MCAA after prolonged oral administration are liver in both rats and mice, and heart and kidneys in rats. Additionally, growth depression, decreased survival, and inflammation of the nasal mucosa were observed in the carcinogenicity studies. 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.

4.1.2.7 Mutagenicity

In **Table 4.10** details of the mutagenicity tests are summarised.

4.1.2.7.1 *In vitro* studies

Bacterial tests

MCAA was not mutagenic in Salmonella typhimurium strains (TA 98, TA100, TA 102, TA 104, TA1535, TA1537, and TA1538) and E coli strains (WP2*uvr*A and WP2*uvr*A/pKM101) with or without exogenous metabolic activation (S9) (Giller, 1997; JETOC, 1996; Hoechst AG, 1979f; Bartsch et al., 1975; Malaveille et al., 1975; McCann et al., 1975; NTP, 1992; Mortelmans et al., 1986; Rannung et al., 1976; Bartsch and Montesano, 1975; Bartsch et al., 1976). MCAA did not

cause preferential killing of a DNA repair-deficient strain of Escherichia coli (WP100) over the wild type strains WP2 (NTP, 1992; Mamber et al., 1983) and it was inactive when tested for prophage induction in lysogenic strain of E. coli K12 WP2 (NTP, 1992). These findings indicated that exposure to MCAA did not induce DNA damage in these test systems. In addition, MCAA did not induce *umu* gene expression in Salmonella *typhimurium* strain TA1535/psK1002 WP2 (NTP, 1992; Nakamura et al., 1987; Ono et al., 1991). No positive response in the PQ37 strain was given by MCAA tested in the E. coli SOS chromo test (without metabolic activation) (Giller, 1997).

Mammalian cells studies

MCAA did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster lung fibroblast cells in the presence or in the absence of S9 activation (NTP, 1992; Sawada et al., 1987). In Chinese hamster V79 ovary cells, a dose-related increase in sister chromatid exchanges was observed without S9 although no induction of chromosome aberrations was observed after treatment with or without S9, (Galloway et al., 1987; NTP, 1992). MCAA caused no induction of 8-azaguanine- and ouabain-resistant mutants in an *in vitro* HGPRT assay with Chinese hamster V79 cells (Huberman et al., 1975). MCAA did not induce DNA strand breaks in primary cultures of rat and mouse hepatocytes or in human CCRF-CEM cells (Chang, 1992). At cytoxic concentrations, a positive response was obtained in the mouse lymphoma L5178Y cell assay for the induction of trifluorothymidine resistance, with and without S9 activation (Amacher and Turner, 1982; McGregor et al., 1987). Below cytotoxic concentrations, the response was negative and in general, an acidic pH shift was noted at cytotoxic concentrations. It is well known that changes in pH may lead to increased mutation frequencies, but neither of the two mutation assays with mouse lymphoma cells did include appropriate controls for the possible influence of changes in pH under the test conditions used, thereby hampering the evaluation of the relevance of the positive test results.

It is well established that genotoxic irrelevant effects might occur under culture conditions resulting in cytotoxicities and pH shifts (Oberly and Garriott, 1996; Clive et al., 1995; Cifone et al., 1987). Consequently, taking this, the negative findings in the bacterial mutagenicity assays and the fact that a positive mouse lymphoma assay response occurs only at cytotoxic concentrations into consideration, the mutagenic activity observed with MCAA in the mouse lymphoma assays is questionable.

4.1.2.7.2 *In vivo* studies

Amphibia studies

MCAA showed no clastogenic activity in a new micronucleus test with Pleurodeles waltl larvae (Giller, 1997).

Drosophila melanogaster studies

MCAA administered in feed was negative for the induction of sex-linked recessive lethal mutations in germ cells of male Drosophila melanogaster; however, when it was administered by injection the results were equivocal (Foureman, 1994; NTP, 1992).

Mammals studies

There is an abstract of one study on the induction of cytogenetic abnormalities in bone marrow and on induction of morphological abnormalities in sperm cells of Swiss mice exposed ip, po, or sc to MCAA (Bhunya and Das, 1987). Bhunya and Das (1987) concluded that dose- and route-dependent varieties of bone marrow chromosome anomalies and different abnormal headed sperms were induced by MCAA. However, the results of these experiments cannot be evaluated, due to the very limited description of the experiment, the results, and the classification of the abnormalities.

MCAA did not induce DNA strand breaks in spleen, duodenum, and stomach of mice, or livers of mice and rats treated orally *in vivo* (Chang et al., 1992).

4.1.2.7.3 Conclusion

Although inadequacies in reporting were noted, the data available are sufficient to fulfil the Annex VIIA requirements for mutagenicity. Unless indicated otherwise, the vast majority of the mutagenicity data is based on valid studies, either according to or in line with recent guidelines.

MCAA does not induce point mutations or primary DNA damage in bacteria, or chromosome aberrations or DNA strand breaks in mammalian cells *in vitro.* MCAA gave positive results in several TK+/TK- assays with mammalian cells *in vitro*. However, it is possible that the positive results are due to a pH-effect rather than a direct mutagenic effect of MCAA. *In vivo* oral administration of MCAA did not induce DNA strand breaks in spleen, liver, stomach or duodenum of mice or in liver of rats treated orally. MCAA is reported to induce sperm abnormalities and chromosome aberrations in bone marrow in mice. The relevance of these positive findings is not clear because of the limited description of the study. Since the overall toxicity profile of MCAA did not point to carcinogenicity and because there is no structural alert it is concluded that no additional genotoxicity test is required.

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

Table 4.10 Relevant *in vitro* and *in vivo* mutagenicity tests

I Bacterial tests

Cell type	Protocol	metabolic activation	Concentration	toxic concentration	result	comments	reference
S. typhimurium TA98, TA100, TA1535, TA1537	Ames test (plate incorporation)	with and without (rat liver S9)	0.8-1,000 μg/plate	not reported	-		Hoechst AG (1979)
S. typhimurium TA1530	Ames test	with and without (rat liver S9)	1.1-108 μmol/plate	10.8 μmol/plate	-		Bartsch et al. (1975)
S. typhimurium TA1530	Ames test	with and without (rat liver S9)	0.4-40 μmol/ml	4 μmol/ml	-		Malaveille et al. (1975)
S. typhimurium TA98, TA100, TA1535, TA1537	Ames test	with and without (rat or human liver S9)	not reported	not reported	-		McCann et al. (1975)
S. typhimurium TA98, TA100, TA1535, TA1537	Ames test	with and without (rat or hamster liver S9)	10-3,333 μg/plate	>3,333 μg/plate	-	.	NTP (1992)
S. typhimurium TA1535	Ames test	without	0.1 –1,000 mM (3 plates/conc.)	>10 - <500 mM	-		Rannung et al. (1976)
S. typhimurium TA1530	Ames test	with and without (mouse liver fraction)	0.4-40 μmol/ml	<4 μmol/ml	-		Bartsch and Montesano (1975)
S. typhimurium TA98, TA100, TA102, TA104, TA1535, TA1537, and TA1538/ E coli WP2*uvr*A and WP2*uvr*A/pKM101	Ames test (pre incubation)	with and without (rat liver S9)	9.77-5,000 μg/plate	2,500 μg/plate	-		JETOC (1996)

Table 4.10 continued overleaf

Table 4.10 continued Relevant *in vitro* and *in vivo* mutagenicity tests

Cell type	Protocol	metabolic activation	Concentration	toxic concentration	result	comments	reference
S. typhimurium TA100	Ames fluctuation test	with (rat liver S9) without (rat liver S9)	0.3-300 μg/ml 30-10,000 μg/ml	100 μg/ml 3000 μg/ml	- -		Giller (1997)
S. typhimurium TA1535/pSK1002	*Umu* test	with and without (rat liver S9)	≤330 μg/ml	not reported	-	primary DNA damage	Nakamura et al. (1987); NTP (1992)
S. typhimurium TA1535/pSK1002	*Umu* test	with and without (rat liver S9)	485.4 μg/ml	not reported	-	primary DNA damage	Ono et al. (1991)
E coli WP2 (wild type)/WP100 ($uvrA^-$ $recA^-$)	rec assay, qualitative and quantitative spot tests and quantitative suspension	with and without (rat liver S9)	3 conc. (conc not reported)	not applicable	-	primary DNA damage	Mamber et al. (1983); NTP (1992)
E coli PQ 37	SOS-chromotest	with and without (rat liver S9)	1-3,000 μg/ml 3-3,000 μg/ml	300 μg/ml 1,000 μg/ml	- -	maximum induction factor 1.05 maximum induction fcator 1.16	Giller (1997)

II Mammalian cells, *in vitro*

Cell type	protocol	metabolic activation	Concentration	toxic concentration	result	comments	reference
Chinese hamster lung fibroblast cells	CA	with and without (rat liver S9)	60-500 μg/ml	500 μg/ml (+S9)	-		NTP (1992); Sawada et al. (1987)
	SCE	with and without (rat liver S9)	60-500 μg/ml	not reported	-		

Table 4.10 continued overleaf

Table 4.10 continued Relevant *in vitro* and *in vivo* mutagenicity tests

Cell type	protocol	metabolic activation	Concentration	toxic concentration	result	comments	reference
CHO cells	CA SCE	with and without (S9) with and without (S9)	50-500 μg/ml 50-500 μg/ml (-S9) 50-1,600 μg/ml (+S9)	not reported not reported	- + -	A dose related increase in SCE was observed without S9.	Galloway et al. (1987); NTP (1992)
Chinese hamster V79 cells	HPRT assay (8-azaguanine- and ouabain resistance)	without	<2.1mM (ca. 200 μg/ml)		*	MCAA did not induce an increase of 8-azaguanine or ouabain-resistant mutants up to the highest concentration tested. The number of mutants was expressed per number of survivors. The highest concentration resulted in a cloning efficiency of 94%. The publication does not give further details on concentrations tested and results obtained with MCAA. The highest concentration tested was not sufficiently high for the assessment of possible mutagenic properties of MCAA in this test system.	Huberman et al. (1975)
Mouse lymphoma L5178Y cells	TK^+/TK^- assay	with (rat liver S9), uninduced 5% in activation mix	exp. 1: 330.0- 784.9 μg/ml (dilution factor 0.93) exp. 2: 139.4-1048.2 μg/ml (dilution factor 0.75)	exp. 1: 330.0 μg/ml (=LC50) exp. 2: 139.4 μg/ml (LC50=186.0 μg/ml)	* *	Exposure time: 3 hours. Steep dose response curve in cytotoxic concentration range, i.e., a doubling in mutants was seen at survival ≤ 18% at concentration ≥546.7 μg/ml (exp.1) and ≤ 19% at concentrations ≥589 μg/ml and above (exp.2). Positive results could be a pH-effect. Inappropriate study design for assessment of this possible effect.	Amacher and Turner (1982)

Table 4.10 continued overleaf

Table 4.10 continued Relevant *in vitro* and *in vivo* mutagenicity tests

Cell type	protocol	metabolic activation	Concentration	toxic concentration	result	comments	reference
Mouse lymphoma L5178Y cells	TK^+/TK^- assay	without	31.3-800 μg/ml	125-800 μg/ml	*	Exposure time: 4 hours Lowest observed effect dose: 400 μg/ml The $MF_{test}/MF_{control}$ ratio's amounted to 2.7 and 3.1, and the relative total growth values to 15 and 8% in experiment 1 and 2, respectively. Positive result may well be a pH-effect as the phenol red indicator in the Fischer's medium changed colour from pink to yellow at 400 μg/ml.	McGregor et al. (1987); NTP (1992)
Rat hepatocytes (Fischer 344, male) and mouse hepatocytes B6C3F1, male)	DNA strand breaks (alkaline elution)	not applicable	0, 1, 5, and 10 mM for 4 hours	5 mM	1 mM: - ≥ 5 mM: see comments	The results obtained at 5 mM (rat hepatocyte) and 10 mM (rat and mouse hepatocyte) pointed to an increase in DNA strand breaks occurring secondarily to cytotoxicity as demonstrated by the concurrent LDH release in the culture medium.	Chang (1992)
human lymphoblastic cell line (CCRF-CEM)	DNA strand breaks (alkaline elution)	without S9	0, 1, 5, and 10 mM for 2 hours	> 10 mM	-		Chang (1992)

III Amphibia, *in vivo*

Species	Test	concentration	toxic concentration	Result	Comments	reference
Pleurodeles waltl larvae (blood erythrocytes)	newt micronucleus test (15 larvae/concentration)	10, 20, 40 μg/ml in swimming water	80 μg/ml	Result: -	No increase in the incidence of micronucleated erythrocytes was observed.	Giller (1997)

Table 4.10 continued over leaf

Table 4.10 continued Relevant *in vitro* and *in vivo* mutagenicity tests

IV Drosophila melanogaster, *in vivo*

Species	Test	experimental	Result	Comments	reference
Drosophila melanogaster	Sex-linked recessive lethal test	dose: 900 ppm (injection) dose: 400 ppm (feed, 72 hours)	Result: +/- Result: -	MCAA injected induced an equivocal response.	Foureman (1994); NTP (1992)

V Mammals, *in vivo*

Species	Test	Experimental	Result	Comments	reference
Swiss mice (n and sex not reported)	Chromosome aberrations in bone marrow cells (n = 300 cells/group)	dose i.p. (sacrifice time): 1*12.5 mg/kg (24 hrs after treatment); 1*25 mg/kg (24 hours after treatment); 1*50 mg/kg (6,24,48 hours after treatment); 5*10 mg/kg (120 hrs after treatment) dose p.o. (sacrifice time): 1*50 mg/kg (24 hours after treatment) dose s.c. (sacrifice time): 1*50 mg/kg (24 hours after treatment)	*	% of cells with aberrations including “breaks” and “chromatid deletion including rings” (no further details) increased in all treatment groups. Test not suitable for evaluation a.o. due to limited description of the experiment, the results, and the classification of the abnormalities (only abstract available).	Bhunya and Das (1987)
Swiss mice (n= 3 males/dose group)	Sperm abnormality test	dose: 1* 12.5 mg/kg ; 1*25 mg/kg; 1*50 mg/kg, route unknown Sacrifice time 35 days after treatment	*	Test not suitable for evaluation a.o. due to limited description of the experiment, the results, and the classification of the abnormalities (only abstract available).	Bhunya and Das (1987)
Charles River mice (B6C3F1, male, n=2)	DNA strand breaks in liver, spleen, duode-num, and stomach	dose p.o. (sacrifice time): a single dose of 1-10 mmole/kg in distilled water (4 hours after treatment)	-		Chang (1992)
rat (Fischer 344, male, n not reported)	DNA strand breaks in liver	dose p.o. (sacrifice time): a single dose of 1, 5, 10 mmole/kg in distilled water (4 hours after treatment)	- (at 1 mmol/kg)	No data were available on mutagenicity at higher doses. The animals of the 5 and 10 mmole/kg dose groups did not survive.	Chang (1992)

* test not suitable for evaluation

4.1.2.8 Carcinogenicity

Studies in animals

Oral

F344/N rats, 70/sex/group, were exposed to MCAA in deionised water by gavage during 5 days/week for 103 weeks at doses of 0, 15, and 30 mg/kg bw/day (NTP, 1992; study 6 in **Table 4.9**). For interim evaluations, 10 and 7/sex/dose were killed at 6 and 15 months, respectively.

At a 6 month evaluation (10/sex/dose), relative heart weight was increased in high-dose females and relative kidney weight was increased in high-dose males and decreased in low- and high-dose females. Absolute brain weight was decreased in low- and high-dose females, while relative brain weight was decreased in low-dose females only. These changes were not found at the 15 month evaluation (7/sex/dose). Neoplasms related to administration of MCAA were not found at the interim kills. Survival was decreased in the high-dose males and the low- and high-dose females (mean number of survival days and percentage survival at the end of the study: males: 577, 570, and 528 days; 53, 40, and 32% and females: 591, 544, and 545 days; 70, 38, 51% for, respectively, 0, 15, and 30 mg/kg bw/day). No significant macro- or microscopic lesions were found in any of the decedents and indications for gavage trauma were not found. Mean body weight was decreased in the high-dose males during the second year. A statistically significant positive trend in uterine endometrial stromal polyps was found (1/53, 7/53, and 9/53 at 0, 15, and 30 mg/kg bw/day). This finding was not considered clear evidence of carcinogenicity, because this lesion is a common background finding and its incidence in the present control group was unusually low. Moreover, there was no decrease in time of appearance or evidence of malignant transformation. Nonneoplastic lesions that occurred more frequently in the test groups were lung congestion (females: 1/53, 6/53, 13/53 and males: 2/53, 6/53, 10/53 for respectively, 0, 15, and 30 mg/kg bw/day group), acute inflammation of the nasal mucosa in females (0/52, 6/53, and 5/48 for 0, 15, and 30 mg/kg bw/day, respectively) and squamous metaplasia in the nose in males (0/52, 0/53 and 6/53 for 0, 15, and 30 mg/kg bw/day). These changes in the lungs and nose could have resulted from a reflux of gavage solution. Based on the results of this study, there is no clear evidence of carcinogenic activity for male and female F344/N rats. The NOAEL is <15 mg/kg bw/day based on decreased survival and acute inflammation of the nasal mucosa. Haematology and clinical chemistry were not included in the study design. Complete histopathology was performed.

B6C3F1 mice, 60/sex/group, were exposed under the same exposure regimen as the rats to 0, 50, and 100 mg/kg bw/day (NTP, 1992; study 7 in **Table 4.9**). Mean body weight was decreased in high-dose females during the second year. There were no treatment-related clinical signs. Survival was statistically significantly decreased in high-dose males (mean number of survival days and percentage survival at the end of the study: 683, 627, and 530 days, and 79, 65, and 38%, for 0, 50, 100 mg/kg bw/day, respectively). Males showed no treatment-related neoplastic lesions (complete histopathology was performed). In females, a dose-related decrease in the incidence of malignant lymphomas was observed, i.e., 29/60, 18/60, 13/60 for 0, 50, and 100 mg/kg bw/day, respectively. Squamous cell papillomas occurred in the forestomach of two high-dose females. In high-dose males and females, forestomach squamous cell hyperplasia was statistically significantly increased. The incidence of acute nasal inflammation was increased in high-dose males (3/60, 7/59, and 24/60 for respectively, 0, 50, and 100 mg/kg bw/day), and low-

and high-dose females (5/60, 15/60, and 31/60 for respectively 0, 50, and 100 mg/kg bw/day). In addition, high-dose females showed increased incidences of metaplasia of the olfactory epithelium in the nose and of per vascular lymphocytic infiltration in the lungs, and congestion of the lungs occurred more frequently in high-dose males. The metaplasia of the olfactory epithelium in the nose and congestion of the lungs are considered to have resulted from a reflux of gavage solution rather than from a systemic effect via the oral route. Based on the results of this study, there is no clear evidence of carcinogenic activity for male and female B6C3F1 mice. No other effects were found. It is noted that haematology, clinical chemistry and determination of organ weights were not included in the study design. Within the limited study design, the NOAEL for local toxicity is <50 mg/kg bw/day and for systemic toxicity 50 mg/kg bw/day based on findings in the forestomach, and the decreased body weight and survival, respectively.

DeAngelo et al. (1992) performed a drinking-water study to evaluate the carcinogenicity of chloroacetic acids in male F344 rats. Concentration levels tested were 0.05, 0.5, and 2 g MCAA/l (equal to time-weighed mean daily doses of 3.6, 28, and 69 mg/kg bw/day). MCAA was administered for 100-104 weeks. Evaluations were made for mortality, body weight gain, organ weight, gross pathology, and histopathology on selected tissues (not specified). There was no treatment related pathology for MCAA although a dose related body weight gain depression and increased mortality at the high dose were seen. It was concluded in this study that MCAA is not carcinogenic in male rats. However, only an abstract of this study was available.

DeAngelo et al. (1997; study 8 in **Table 4.9**) studied in rats the potential carcinogenicity of MCAA administered in the drinking water. Male F344/N rats (50/group) were exposed to 0, 0.05, 0.5, and 1.1 g/l (equal to time-weighed mean daily doses of 0, 3.5, 26.1, and 59.9 mg/kg bw/day) for 104 weeks. Interim gross examination of body, liver, kidneys, spleen, and urinary bladder and microscopic examination of the liver, kidneys, spleen, and testes was performed at week 15, 30, 45, and 60 (total number of animals killed: 21, 18, 18, and 21 for 0, 0.05, 0.5, and 1.1 g/l, respectively). No effect on survival was found after 104 weeks. Body weight and water consumption were significantly depressed at 0.5 and 1.1 g/l. Body weights were lowered 13% and 38%, respectively, compared to the control value. Water consumption was 77 mg/kg bw/day (time-weighted mean) in controls compared 56 mg/kg bw/day both in the mid and high dose groups. Relative and absolute liver weights and absolute kidney weights were decreased (dose-related) in the 0.5 and 1.1 g/l groups. Relative testes weight was significantly increased in the 0.5 and 1.1 g/l groups, while the absolute testes weights in these groups did not differ statistically significantly from controls. The changes in the weights of the liver, kidneys, and testes were not accompanied by treatment-related histopathological changes and are considered secondary to the growth depression in these groups (Feron et al., 1973; Oishi et al., 1979). Mean relative and absolute spleen weight were statistically significantly increased in the 0.05 g/l group whereas spleen weights in the 0.5 and 1.1 g/l group were decreased (only statistically significantly at 1.1 g/l). The variation in spleen weight amongst and within the groups paralleled the variation in the incidence of mononuclear cell leukaemia in these groups (i.e., the incidence of mononuclear cell leukaemia was 24, 48, 17, and 4% for, respectively, the 0, 0.05, 0.5 and 1.1 g/l group). This suggests that the increased mean spleen weight in the 0.05 g/l group reflected the increase in the weight of the spleen of animals affected by leukaemia rather than a direct toxic effect of MCAA on the spleen. The considerable decrease in spleen weight at 1.1 g/l can be ascribed to the marked growth depression at this level. Histopathology did not reveal significant increases in the prevalence of neoplastic lesions. In the high-dose group at week 104, an increased incidence of myocardial degeneration and chronic inflammation of the nasal cavities was observed. No treatment-related effects were found on plasma ASAT and ALAT levels (measured at 104 weeks), or on peroxisome and hepatocyte proliferation (measured at the interim and final

sacrifice periods). It is noted that this study focussed at the detection of liver carcinogenicity/toxicity, and did not include haematology and clinical chemistry (except for plasma ASAT and ALAT). It was concluded by the authors of the publication that no evidence of hepatic neoplasia was found. The NOAEL after 104 weeks of exposure is 0.05 g/l (3.5 mg/kg bw/day) based on growth depression and decreased water consumption. There were no tumours or treatment-related changes found during the interim evaluation.

Inhalation

Carcinogenicity studies by inhalation exposure were not available.

Dermal

The carcinogenic potential of MCAA was studied by Van Duuren et al. (1974). Female ICR/Ha Swiss mice (6-8 weeks old) were exposed to MCAA by skin application (experiment 1) and by s.c. injection (experiment 2). The animals were examined regularly. Complete autopsy was performed, except for the cranial region. Histopathology was performed on all abnormal appearing tissues and organs. Hematology and clinical chemistry were not investigated. In both experiments, an effect on survival was not found. In the first experiment 2.0 mg MCAA in 0.1 ml acetone was applied in the intercapsular region of 50 mice, 3 times a week during 580 days. In none of the mice local papillomas or carcinomas were found. In the second experiment MCAA was injected weekly (0.5 mg in 0.05 ml tricaprylin) during 580 days in the left flank of 50 mice. A not statistically significant increase in local sarcomas was found (3/50 mice exposed to MCAA versus 1/50 in control group). Other local malignant tumours, squamous cell carcinomas or adenocarcinomas were not found. A vehicle control (n=50) and an untreated group (n=100) were included in both experiments. No further details on results were provided, for example, the results of the histopathology performed were not presented. It is noted that the administration route used in experiment 2 is not considered relevant for risk characterisation.

Based on the results of experiment 1, no evidence of carcinogenic activity for female mice is found.

4.1.2.8.1 Studies in humans

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

Miscellaneous

MCAA had no significant effect on Mouse type I interferon induction by Newcastle disease virus. The induction of type I interferon has been shown to be inhibited by several carcinogenic chemicals (Sonnenfeld et al., 1980).

4.1.2.8.2 Conclusion

The carcinogenic potential of MCAA was studied in oral studies with rats and mice by gavage, and in male rats by administration in drinking water. Based on the results of these studies no evidence of carcinogenic activity of MCAA was found after oral administration.

Besides oral administration, a carcinogenicity study by skin contact was available. Local papillomas or carcinomas were not found after repeated dermal application of MCAA in the

intrascapular region of female mice. Based on the results of this study, it is concluded that no evidence for carcinogenic activity after repeated dermal exposure was found in female mice.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Reproductive (fertility) toxicity

A reproductive toxicity study was not available. From repeated dose toxicity studies the following information was retrieved. No treatment-related effects were found on the reproductive organs of both male and female B6C3F1 mice and F344/N rats in 16-days (rats up to 120 mg/kg bw/day; mice up to 240 mg/kg bw/day), 13-week (rats up to150 mg/kg bw/day; mice up to 200 mg/kg bw/day) and 103-week (rats 0, 15 or 30 mg/kg bw/day; mice 0, 50 or 100 mg/kg bw/day) gavage studies. Examined where clitoral or preputial gland (rats), mammary gland, ovary, prostate gland, testis with epididymis, and uterus without biologically significant findings. A dose-related statistical increase in the incidence of uterine endometrial stromal polyps was observed in the 103-week study in female rats (2/60, 7/57, and 10/60). However, the incidence of these lesions in controls was unusually low, and the incidence in females receiving MCAA was lower than the mean historical control rate (116/252 or 20.6%, range 10-38%). Further, the only malignant endometrial stromal neoplasm occurred in the control group. For these reasons, the marginal increase in uterine stromal polyps in dosed female rats was not considered to be related to the administration of MCAA (NTP, 1992). Bhat et al. (1991) did not observe morphological changes in testes after administration of MCAA in drinking water for 90 days to rats (concentration 1.9 mM, equivalent to 19 mg/kg bw/day). No toxicological relevant changes in testes weight were found in rats receiving MCAA in drinking water (0.05, 0.5 or 1.1 g/l) during 104 weeks. The highest concentration in drinking water was 2.0 g/l in the beginning and lowered to 1 g/l when toxicity signs appeared (1.1 g/l is the time-weighted mean daily dose) (DeAngelo et al., 1997).

Developmental toxicity

In a study aimed at the investigation of fetal cardiac teratogenicity, 10 female Hsd:Sprague Dawley rats were exposed to MCAA in drinking water during pregnancy (20 days). The concentration level was 1,57 ppm (equivalent to 193 mg/kg bw/day). A control group of 55 pregnant rats was included in the study. No treatment related maternal mortality was observed. The average weight gain during pregnancy was decreased. No effect was found on the number of implantation sites, resorption sites, and live and dead fetuses. Fetal weight, placental weight, Crown/Rump length, and external morphology were analysed of the fetuses. No effects, including effects on the heart, were found. Skeletal malformations and effects on the brain were not examined in this study as of the limited study design (Johnson et al., 1998).

Furthermore, only a short communication on another developmental study was available (Smith et al., 1990). It is reported that pregnant Long-Evans rats (number of animals: unknown) were dosed MCAA by oral intubation on gestation days 6 to 15 with 0, 17, 35, 70, or 140 mg/kg bw/day in distilled water. Maternal weight gain was statistically significantly reduced in the highest dose group. No treatment-related maternal mortality was observed. Furthermore, no treatment-related effects were reported on organ weights, mean percentage of resorbed implants

per litter, and the weight of live fetuses. According to the abstract, the percentage of soft tissue malformations was increased, however not dose-related. No skeletal malformations were found. In the highest dose-group a statistically significant increase of malformations of the cardiovascular system, comprising predominantly levocardia, was found. An NOAEL for developmental and maternal toxicity to be used in the risk characterisation cannot be established, because of the limited reporting. This study was never fully published.

CD-1 mouse embryos (3-6 somites staged) were exposed *in vitro* to MCAA for 24-26 hours (Hunter et al., 1996). The tested MCAA concentrations in deionised water were 0, 50, 100, 175, 250, 350, and 500 µM. The number of embryos cultured for each concentration level was 34, 5, 21, 28, 34, 10, and 10, respectively. In this study an indication for developmental toxicity was found. All embryos died in the two highest concentration groups. In the 250 µM group, 14 of the 34 embryos died. Eye effects and somite dysmorphology were not observed. A statistically increased number of malformations were found in the 175 and 250 µM group, 39.3% and 70%, respectively. Neural tube defects were found in 39.3% and 50% of the embryos in the 175 and 250 µM group, respectively. A statistically decreased number of somites was also found at these concentration levels (19.4 and 19.6, respectively). Pharyngeal arch and heart defects were found at 250 µM in 40% and 65% of the embryos, respectively. The benchmark concentration, based on a 5% incidence of neural tube defects, was 90 µM.

Yuan-Tang et al. (1998) studied the teratogenic potential of chlorinated drinking water disinfection by-products by using *Hydra* digestive region regeneration test. MCAA was one of the substances studied. A positive and negative control was included. After 72 hours of exposure, the toxic concentration for 50% of the polyps (T_{50}) and the concentration 50% inhibitory to regeneration (I_{50}) were, respectively, 955 and 155 mg/l. The negative control values were 2,500 and 2,450 mg/l, respectively. The positive control values were 95 and 35 mg/l, respectively. Based on the results of this study, it was concluded that MCAA has high regeneration toxicity with teratogenicity in *Hydra* digestive region.

4.1.2.9.2 Studies in humans

Data on toxicity for reproduction in humans were not available.

4.1.2.9.3 Conclusion

The data submitted does not fulfil the basic requirements as specified in Annex VIIA of Directive 67/548/EEC. No effects were found on the male and female reproductive organs of experimental animals after oral (sub-)chronic exposures (see 4.1.2.6 'Repeated-dose toxicity). In a study aimed at the investigation of 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. In a short communication (Smith et al., 1990), developmental toxicity (cardiovascular effects) due to oral MCAA exposure is described although, unfortunately, a complete study report was never published. Furthermore, indications for developmental toxicity were found in *Hydra* regeneration assay and whole CD-1 mouse embryo culture test. All in all, the endpoint of developmental toxicity is not sufficiently covered. Moreover, indications for effects on the heart are present. A developmental study should be performed: **conclusion (i)**. Based on the results of that developmental toxicity study,

the performance of a one- or two-generation study may be considered. The already required developmental toxicity test can be put 'on hold' waiting for the Risk Reduction Strategy: **conclusion (i)** 'on hold'.

4.1.2.10 Other data

4.1.2.10.1 Toxicity mechanism

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. The pattern of distribution of MCAA shows an initial fast distribution into rather lipid-poor tissue, followed by uptake into lipid-rich tissues such as the brain (ECETOC, 2001; see also Section 4.1.2.1).

The time-course and pattern of MCAA intoxication in man is similar to that in other species, including rodents. The characteristics of the distribution patterns of MCAA and the slow development of lactic acidosis may explain the time lag observed between accidental skin contamination in man and the appearance of the first CNS symptoms. So far, clinicians have been unaware of the possible role of cerebral and systemic lactate acidosis and consequently have not determined CSF and/or serum lactate levels. However, a severe metabolic acidosis has been found in several victims. Also, the effects of MCAA *in vitro* are reported to be much higher in human endothelial cells than in other cells (e.g. liver epithelial cells) (ref. in ECETOC, 2001).

Overall, it is suggested that cerebral lactic acidosis, in combination with the subsequently developing systemic lactic acidosis, is the main cause of lethality (ECETOC, 2001).

Influence on blood-brain barrier / Antidotes

Mitroka (1990) used animal models (rats and mice) to evaluate potential antidotes for human exposure to MCAA. Dichloroacetic acid (DCAA) and phenobarbital (PB) but not ethanol or phenytoin, were found to be effective antidotes to MCAA in rats. DCAA (100 mg/kg, ip) administered to rats 15 minutes after a LD80 of MCAA (80 mg/kg, iv) consistently reduced the mortality to 0%, while PB reduced the mortality to less than 20%. Both DCAA and PB were found to be similarly effective to mice. The hypothesis that PB reduces mortality in MCAA treated rats by altering the metabolic disposition of MCAA was evaluated and rejected. They also investigated the relationship between altered blood-brain barrier permeability and death in MCAA treated rats. Treatment with MCAA (80 mg/kg, iv) was associated with a significant (50%) increase in the permeability of the rat blood-brain barrier to [^{125}I]-BSA. The effect was not altered by treatment with PB, however, suggesting that the altered blood-brain barrier permeability does not have an important role in the lethal effect of MCAA in rats. Furthermore, they studied the effect of MCAA on brain carbohydrate metabolism *in vivo*. Cerebrospinal fluid (CSF) and blood lactic acid concentrations increased in MCAA treated rats, and the increase in CSF levels was dose related. In individual MCAA treated rats, CSF lactate concentrations paralleled the time course of ataxia and a discrete threshold for death (18 mmol/L) was observed. The relationship between excess brain lactate levels and death in MCAA treated rats was investigated further. Hypoxia increased brain lactate and mortality in MCAA treated rats. Both PB and DCAA which decreased mortality in MCAA treated rats, decreased brain lactate levels in MCAA treated rats.

Based on the results of these studies the authors concluded that PB and DCAA are effective antidotes to MCAA intoxication in rats and mice, and that the lethal effect of MCAA in rats is essentially associated with an excessive accumulation of lactic acid in CSF. It is suggested that the effect of MCAA on the blood-brain barrier function and death are distinct, however this is in contrast with the results of an acute toxicity study in mice reported by Berardi (1986 and 1987) (see Section 4.1.2.2). In this study it was concluded that the damage of the blood-brain barrier of mice is associated with both neurological dysfunction and death.

4.1.2.10.2 Conclusion

Dichloroacetic acid (DCAA) and phenobarbital (PB) were found to be effective antidotes to MCAA in rats. Because PB treatment did not alter the blood-brain barrier (BBB) permeability it was assumed that the increase in BBB permeability did not have an important role in the lethal effect of high doses of MCAA in rats. A relationship was found between excess brain lactate levels and death in MCAA treated rats. Both antidotes (PB and DCAA) decreased the brain lactate levels in MCAA treated rats.

The increased lactate levels in the brain are not necessarily a direct effect of MCAA. It can also be a consequence of inhibition of the oxidation processes (such as in the mitochondria). The increased lactate levels might also be apparent in other organs, but has probably a more critical effect in the brains.

4.1.3 Risk characterisation

4.1.3.1 General aspects

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), after contamination of the skin with ^{14}C-labelled MCAA, a half-life of about 15 hours has been found for excretion in urine.

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 after oral exposure and as very toxic after inhalation and dermal exposure. 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. Based on the results of that developmental toxicity study, the performance of a one- or two-generation study may be considered.

4.1.3.2 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.

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and inhalation routes of exposure.

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 incidental 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. Thus, dermal contact will only occur accidentally, with the exception of Scenario 4.

Acute toxicity

MCAA is classified as toxic after oral exposure and as very toxic after inhalation and dermal exposure (see **Table 4.7**). For occupational risk assessment the short-term exposure levels are compared with the LD50 or LC50 values.

Dermal exposure

The 40-50% concentrations of MCAA are classified as toxic in contact with skin. An LD50-value of 250 mg/kg bw (rabbit) was found for this concentration. Despite a variety of other data on toxicity after acute dermal exposure that were available, an LD50 value for pure molten and non-molten MCAA could not be derived. The data indicated an LD50 value <400 mg/kg bw for pure MCAA. This value is used in the risk characterisation. In Annex 5 the assessment factors used to establish the minimal MOS are given (**Table II-2**). There is concern when the MOS is lower than the minimal MOS.

In Scenario's 1, 2 and 3, dermal exposure is considered to occur only accidentally, so **conclusion (ii)** is justifiable. In Scenario 4 'Use of paint removers', the systemic doses due to estimated dermal exposure are 43 (without PPE) and 4.3 mg/kg bw/day (with PPE), assuming a worker body weight of 70 kg (see **Table 4.2**). The MOSs between the LD50-value (<400 mg/kg bw/day) and the systemic doses are calculated to be <9.3 and <93, respectively. Based on comparison of these MOSs with a minimal MOS of >>22, **conclusion (iii)** is drawn for Scenario 4 (with as well as without PPE). Systemic effects due to acute dermal exposure can not be excluded.

Inhalation 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. Comparison with the estimated short-term exposure levels (see **Table 4.2**), is presented in **Table 4.11**. The MOSs between the LC50-values and the inhalation exposure levels are mentioned in **Table 4.11**. The MOSs are evaluated by comparison with the minimal MOS (>>9). In Annex 5 the assessment factors used to establish the minimal MOS are given (**Table II-1**). There is concern when the MOS is lower than the minimal MOS.

Given the MOSs for acute inhalation exposure as mentioned in **Table 4.11**, it is concluded, based upon the present information, that acute toxic effects due to acute inhalation exposure cannot be excluded for all scenarios except the sub-scenarios 'Production of MCAA: production and cleaning and maintenance' and 'Use of MCAA: use of solids'. It is noted that the data available for evaluation of acute inhalation exposure are limited (details on study design or results are lacking) and no upper limit of the minimal MOS can be established. Risk reduction measures are necessary: **conclusion (iii)**. It might be possible that in some industrial premises worker protection measures are already being applied. Although some subscenarios with exposure of about 1 mg/m^3 may be considered borderline scenario's for **conclusion (iii)**, this conclusion is considered justified because PPE has already been taken into account for estimation of the exposure levels unless indicated otherwise.

Table 4.11 Occupational risk assessment for MCAA for acute toxicity after inhalation exposure

Occupational exposure scenario	Short-term exposure estimate in mg/m^3 (duration 0-0.5 hr)	MOS[A]	Conclusion[B]
1. Production of MCAA			
- production	0.25	720, >1036	ii
- cleaning and maintenance	negl.	high	ii
- packing of solids	1.0	180, >259	iii
- transfer of molten MCAA	2.4	75, >108	iii
- transfer of 80% MCAA	2.4	75, >108	iii
2. Use of MCAA			
- of solids	0.5	360, >518	ii
- of molten MCAA	1.2	150, >216	iii
- of 80% MCAA	1.2	150, >216	iii
3. Formulation of paint removers	0.9	200, >288	Iii
4. Use of paint removers			
*without PPE	39	4.6, >6.6	iii
*with PPE	3.9	46, >66	iii

A) Based on LC50 of 180 mg/m^3 (exposure duration 4 h according to KEMI, 1994) and >259 mg/m^3 (1 hour), and the short-term inhalation exposure levels;
B) Based on comparison of the MOS with a minimal MOS of >>9.

4.1.3.2.1 Irritation and corrosivity

Dermal irritation after single and repeated exposure

MCAA is considered to be a strong corrosive agent. Workers can be exposed to corrosive concentrations. However, the data available do not permit quantitative risk characterisation. Given the effects observed in the skin irritation studies with rabbits and data available on human accidental exposure to pure MCAA or concentrated MCAA solutions, it is concluded that

MCAA is of concern for workers. However, in Scenario's 1, 2 and 3, dermal exposure to MCAA is considered to occur only accidentally if the required protection is strictly adhered to so **conclusion (ii)** is justifiable. In Scenario 4 ('Use of paint removers'), use of PPE will normally prevent exposure to MCAA. However, without the use of PPE exposure to diluted (100-fold) solutions may occur. Given the serious corrosive properties of MCAA, it is concluded that MCAA is of concern for workers with regard to local skin effects in this scenario without the use of PPE: **conclusion (iii)**.

Respiratory irritation after single or repeated exposure

No reliable data are available for (quantitative) risk characterisation of possible respiratory irritation of MCAA after single or repeated exposure. In a limited reported study respiratory (sensory) irritation was observed in humans at a concentration of 5.7 mg/m^3. A no-effect-level is not available for this end point. Using the 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 concentration levels presented in **Table 4.2** indicates that the occurrence of respiratory (sensory) irritation cannot be excluded in the sub-scenarios '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)**.

Eye irritation

Theoretically, MCAA is of concern for workers with regard to eye effects, because of the effects observed in the acute eye irritation study in rabbits and the classification as a 'risk of serious damage to the eyes'. However, eye protection is obligatory for activities where direct handling of MCAA occurs. If the required protection is strictly adhered to, exposure will occur only incidentally, so **conclusion (ii)** is justifiable for all scenarios except Scenario 4 without PPE.

4.1.3.2.2 Sensitisation

Based on wide practical experience with MCAA and the absence of any case reports on allergy, it is concluded that no indications for sensitising effects exist: **conclusion (ii)**.

4.1.3.2.3 Repeated-dose toxicity

Dermal exposure

Conclusions regarding the risk characterisation for local effects after repeated exposure to MCAA are described in the paragraph 'irritation and corrosivity'.

Starting-points for the risk characterisation for workers exposed by skin contact for systemic effects are (a) the NOAEL of 3.5 mg/kg bw/day from the 2-year drinking water study performed by DeAngelo et al. (1997) in rats, and (b) the estimated dermal exposure levels for the different occupational scenarios (see Section 4.1.1.2 and **Table 4.2**). Given the estimated frequency of exposure (200-300 days/year for production and 100-200 days/year for use), chronic exposure is assumed for risk characterisation. The MOSs are evaluated by comparison with the minimal MOS (40). In Annex 5 the assessment factors used to establish the minimal MOS are given (**Table II-3**). There is concern when the MOS is significantly lower than the minimal MOS.

In Scenario's 1, 2 and 3, dermal exposure is considered to occur only accidentally, so **conclusion (ii)** is justifiable. In Scenario 4 'Use of paint removers', the systemic doses due to the dermal exposure estimate of 3,000 (without PPE) and 300 mg/day (with PPE) are 43 and 4.3 mg/kg bw/day, respectively, assuming a worker body weight of 70 kg and 100% dermal absorption. The MOSs between the oral NOAEL (3.5 mg/kg bw/day) and the systemic doses are calculated to be 0.08 and 0.8, respectively. Based on comparison of these MOSs with a minimal MOS of 40, **conclusion (iii)** is applicable for Scenario 4. Systemic effects due to repeated dermal exposure can not be excluded.

Inhalation exposure

Starting-points for the risk characterisation for workers exposed by inhalation for systemic effects are (a) the NOAEL of 3.5 mg/kg bw/day from the 2-year drinking water study performed by DeAngelo et al. (1997) in rats, and (b) the estimated inhalation exposure levels for the different occupational scenarios (see Section 4.1.1.2 and **Table 4.2**). Given the estimated frequency of exposure (200-300 days/year for production and 100-200 days/year for use), chronic exposure is assumed for risk characterisation. The MOSs between the NOAEL and the inhalation exposure levels are mentioned in **Table 4.12**. The MOSs are evaluated by comparison with the minimal MOS (40). In Annex 5 the assessment factors used to establish the minimal MOS are given (**Table II-4**). There is concern when the MOS is significantly lower than the minimal MOS.

Given the MOSs for inhalation exposure as mentioned in **Table 4.12**, it is concluded that, based upon the present information, systemic toxicity due to repeated inhalation exposure cannot be excluded for Scenario 1 in 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.

Table 4.12 Risk assessment for MCAA for repeated-dose toxicity after respiratory exposure

Scenario/sub-scenario	Estimated respiratory exposure in mg/m^3 (mg/kg bw/day)[A]	MOS[B]	Conclusion[C]
1. Production:			
- production	0.1 (0.01)	245	ii
- cleaning and maintenance	negl.	high	ii
- packing of solids	0.32 (0.05)	77	ii
- transfer of molten MCAA	1.2 (0.2)	20	iii
- transfer of 80% MCAA	1.2 (0.2)	20	iii
2. Use of MCAA			
- use of solids	0.125 (0.02)	196	ii
- use of molten MCAA	0.3 (0.04)	82	ii
- use of 80% MCAA	0.3 (0.04)	82	ii
3. Formulation of paint removers	0.1 (0.01)	245	ii
4. Use of paint removers			
*without PPE	10 (1)	2.5	iii
*with PPE	1.0 (0.1)	25	iii

A) Between brackets: estimated inhalation exposure in mg/kg bw/day assuming a worker body weight of 70 kg and a respiratory volume of 10 m^3 for a working day;
B) Based on an oral NOAEL in rats of 3.5 mg/kg bw/day and the inhalatory exposure level;
C) Based on comparison of the MOS with a minimal MOS of 40.

4.1.3.2.4 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.

4.1.3.2.5 Mutagenicity

Based on the available data it is concluded that MCAA is not a genotoxic compound: **conclusion (ii)**.

4.1.3.2.6 Carcinogenicity

Given the results from the carcinogenicity studies, it is concluded that there are no clear reasons for concern for workers with regard to systemic carcinogenicity after dermal or inhalation exposure: **conclusion (ii)**. Risk characterisation of local carcinogenicity can only be performed with studies performed with relevant exposure routes.

4.1.3.2.7 Toxicity for reproduction

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).

4.1.3.2.8 Occupational limit values

In **Table 4.1** an overview of occupational limit values for MCAA is given. Only the UK has published a basis for setting an OEL (HSE, 1996). Respiratory (sensory) irritation was determined as the critical effect. A threshold for this effect was reported at 1.5 ppm (5.7 mg/m^3; based on human data). An 8-hour TWA of 0.3 ppm (1.2 mg/m^3) should provide adequate protection against such irritation and was considered to provide adequate protection against systemic effects (HSE, 1996). It is noted that the assignment of the skin notation is justified based on the data available for this risk characterisation.

More recently, systemic effects were observed in a 2-year drinking water study in rats (NOAEL 3.5 mg/kg bw/d). Based on these data, it is recommended to reconsider the current values, taking into account all available toxicological data.

4.1.3.3 Consumers

The hand washing detergent scenario is the only relevant scenario for the risk characterisation. For all other products and uses the exposure is considered negligible.

Repeated dose toxicity

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.

For the hand washing detergent scenario a daily exposure of 0.0336 mg SMCA was calculated, that is $5.6 \cdot 10^{-4}$ mg/kg bw assuming 60 kg bw for a consumer. The margin of safety between this NOAEL and the estimated exposure level is 6,250. Taking into account inter- and intra-species differences, the margin of safety for the hand washing detergent scenario are judged to be sufficient. Therefore there is no indication for concern for human safety: **conclusion (ii)**.

Mutagenicity

Based on the data available, it is concluded that MCAA is not a genotoxic compound. Therefore there is no concern for human safety: **conclusion (ii)**.

Carcinogenicity

Given the results from the carcinogenicity studies, it is concluded that there are no clear reasons for concern for consumers exposed via the environment with regard to systemic carcinogenicity after inhalation exposure: **conclusion (ii)**.

Reproductive toxicity

There are no indications for effects on fertility. However, indications for developmental 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).

4.1.3.4 Humans exposed via the environment

4.1.3.4.1 Inhalation exposure

Repeated dose toxicity

The starting points for the risk characterisation for repeated dose toxicity are the estimated exposure levels via air (see **Table 4.3** and **4.4**) and the NOAEL of 3.5 mg/kg bw/day from the 2-year drinking water study with rats (in view of the absence of repeated inhalation toxicity studies). The margins of safety between this NOAEL and the estimated exposure levels are given in **Table 4.13**.

Table 4.13 Margins of safety for local and regional scale

		Intake of MCAA via air, (mg/kg bw)	MOS
Local	Production: I-B1	$3.37 \cdot 10^{-5}$	103,857
	Production: I-B2	$4.29 \cdot 10^{-4}$	8,166
	Production: I-C	$1.83 \cdot 10^{-4}$	19,140
	Processing (off site) II (only one site)	0.0015	2,298
Regional	EUSES	$6.8 \cdot 10^{-8}$	$5.1 \cdot 10^{7}$
	ECETOC (1999)	$1.4 \cdot 10^{-6}$	$2.5 \cdot 10^{6}$

The air concentration calculated with EUSES and based on a submitted atmospheric release estimate leads to a margin of safety > 100.

The margins of safety for the sites in **Table 4.13** indicate no concern for human safety after inhalation, taking into account intra- and interspecies variation and the use of a NOAEL from a chronic study. For all other sites originally mentioned in **Table 3.2** and **3.3** the air concentrations are lower than those from the sites mentioned in **Table 4.13** and therefore the margins of safety are larger than the ones mentioned here: **conclusion (ii)**.

At the regional scale the margins of safety are also sufficiently large. Therefore there is no indication for concern for human safety: **conclusion (ii)**.

Mutagenicity

Based on the data available, it is concluded that MCAA is not a genotoxic compound. Therefore there is no concern for human safety: **conclusion (ii)**.

Carcinogenicity

Given the results from the carcinogenicity studies, it is concluded that there are no clear reasons for concern for man exposed via the environment with regard to systemic carcinogenicity after inhalation exposure: **conclusion (ii)**.

Reproductive toxicity

There are no indications for effects on fertility. However, indications for developmental 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).

4.1.3.4.2 Total daily intake (exposure via inhalation and via food)

Repeated dose toxicity

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.

Table 4.14 Margins of safety for local and regional scale

		Total daily intake (mg/kg bw*)	MOS
Local	Production: I-B1	0.00148	2,365
	Production: I-B2	0.019	184
	Production: I-C	0.0794	44
	Processing off site II (only one site)	0.066	53
Regional	EUSES	$1.41 \cdot 10^{-5}$	$2.5 \cdot 10^{5}$
	Field data	$2.4 \cdot 10^{-4}$	$1.5 \cdot 10^{4}$

* The total daily intake is derived from **Table 4.3** and **4.4** and is based on the intake of air, drinking water and leaf crops. For Field data, root crops are also taken into account.

** As for this site the reported air concentration is considered unrealistically high, no further risk characterisation has been carried out.

Taking into account inter- and intra species differences the margins of safety for production site I-C the MOS is too low for exposure via drinking water. Therefore **conclusion (iii)** is considered more appropriate (see conclusion for the 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 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 values of EUSES and Reimann et al. (1996) are used for the risk characterisation, including the margins of safety between the NOAEL and the estimated exposure levels (see **Table 4.4**). Taking into account inter- and intra-species differences, the margins of safety for the regional scale are judged to be sufficient. Therefore there is no indication for concern for human safety: **conclusion (ii)**.

Mutagenicity

Based on the data available, it is concluded that MCAA is not a genotoxic compound. Therefore there is no concern for human safety: **conclusion (ii)**.

Carcinogenicity

Given the results from the carcinogenicity studies, it is concluded that there are no clear reasons for concern for man exposed via the environment with regard to systemic carcinogenicity after oral or inhalation exposure: **conclusion (ii)**.

Reproductive toxicity

There are no indications for effects on fertility. However, indications for developmental 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).

4.1.3.5 Combined exposure

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

4.1.4 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 via the environment - **conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

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

This conclusion (unintentional sources) is reached 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 is reached 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.

5.1.1 HUMAN HEALTH

5.1.2 Human health (toxicity)

5.1.2.1 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.

Conclusion (i) There is 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 sub-scenarios '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 sub-scenarios ‘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 sub-scenarios ‘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.

Table 5.1 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**			
Sub-scenario'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.	li	n.a.	li	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	li	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.	li	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.	li	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.	li	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.	li	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	li	high	ii	77	ii	20	iii	20	iii	196	ii	82	ii	82	ii	245	ii	2.5	iii	25	iii
-combined	245	li	high	ii	77	ii	20	iii	20	iii	196	ii	82	ii	82	ii	245	ii	0.08	iii	0.8	iii

Table 5.1 continued overleaf

Table 5.1 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**			
Sub-scenario'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**	
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
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

5.1.2.2 Consumers

Conclusion (i) There is 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.

5.1.2.3 Humans exposed via the environment

Conclusion (i) There is 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 man 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 man at this site is via eating leaf crops. The concentration in the leaf crops is caused by deposition of MCAA from air.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 tonnes/annum)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives

JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic

PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst-Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category
UDS	Unscheduled DNA Synthesis

UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organisation
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Annex 1 Input data for exposure assessment and local PECs for water at down stream users supplied by Company C.

Location	1	2	3	4	5	6	Total
Application	TGA	CMC	CAC	CMC	Herbicides	Caffeine	
Country	FRA	FRA	CHE	ITA	GBR	DEU	EU
Processing per year (tpa)	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	27,000
Processing days	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	
Processing per day (tpd)	19.4	19.4	9.7	11.1	8.3	6.9	
Release factor	0.007	0.007	0.0005	0	0.007	0.007	
Release rate to waste water (kg/day)	136.1	136.1	4.9	0.0	58.3	48.6	384
Removal rate (%)	99.9	99.9	99.9	99.9	99.9	99.9	
Mass flow in WWTP effluent (mg/s)	1.58	1.58	0.06	0	0.68	0.56	
Release to water (kg/day)	0.14	0.14	0.005	0	0.06	0.05	0.384
PEC effluent (ug/l)	68.1	68.1	2.4	0	29.2	24.3	
River MNQ (m3/s)	7.33	147	0.23	0	25.17	420	
PEC local aquatic (ng/l)	283.1	78.9	312.8	0.0	95.0	69.5	
Release factor air	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	
Release to air (kg/day)	9.7	9.7	4.9	5.6	4.2	3.5	37.5
PEC local air (ug.m-3)	2.23	2.23	1.11	1.27	0.96	0.80	
PEC local soil (mg.kgwwt-1)	$5.57 \cdot 10^{-4}$	$5.57 \cdot 10^{-4}$	$3.36 \cdot 10^{-4}$	$3.68 \cdot 10^{-4}$	$3.05 \cdot 10^{-4}$	$2.73 \cdot 10^{-4}$	

Annex 2 Input data for exposure assessment and local PECs for water at down stream users supplied by Company B. Highest site specific values are presented in bold.

Location	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Application	CMC	AGRO	CMC	AGRO	AGRO	SURF	CMC	SURF	OTHER	SURF	CMC	OTHER	SURF	CMC	AGRO	SURF	
Country	NLD	AUT	NLD	GBR	DNK	GER	SWE	FRA	CHE	ESP	FIN	CHE	GBR	NLD	NLD	ESP	EU
Processing per year (tpa)	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	51,800
Processing days	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	
Processing per day (tpd)	6.3	3.6	7.2	15.3	9.7	6.3	15.7	10.0	10.0	2.2	40.0	6.4	6.7	15.1	8.6	8.7	
Release factor water	0	0	0.007[1]	0	0	0	0.014	0.007	$6.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-8}$	0.02	0	$9.2 \cdot 10^{-5}$	0.01	0	0	
Release rate to waste water (kg/d)	0.0	0.0	51	0.0	0.0	0.0	214	70	0.68	$6.2 \cdot 10^{-8}$	857	0	0.61	180	0	0	1373
Removal rate (%)	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	
Mass flow in WWTP effluent (mg/s)	0.00	0.00	0.59	0.00	0.00	0.00	2.48	0.81	0.01	0.00	9.92	0.00	0.01	2.08	0.00	0.00	15.89
Release to water (kg/day)	0	0	0.0506	0	0	0	0.214	0.0700	$6.8 \cdot 10^{-4}$	$6.2 \cdot 10^{-11}$	0.85714	0	$6.1 \cdot 10^{-4}$	0.180	0	0	1.373
PEC effluent (ug/l)	0	0	25.3	0	0	0	107.145	35	0.34	$3.1 \cdot 10^{-8}$	428.57	0	0.305	90	0	0	
River MNQ (m3/s)	750	680	50	0.21	0.21	0.21	61[3]	10	333	1.39	31	6.7	3.35	185	750	0.21	
PEC local aquatic (ng/l)	68.2	68.2	79.9	68.2	68.2	68.2	109	149.2	68.2	68.2	388.2	68.2	70.3	79.5	68.2	68.2	
Release to air (kg/day)	3.1	1.8	0.0	7.6	4.9	0.0	7.9	5.0	5.0	1.1	20.0	3.2	3.3	7.5	4.3	0.0	74.8
PEC local air (ug/m-3)	0.72	0.41	0.00	1.75	1.11	0.0002	1.80	1.15	1.15	0.25	4.58	0.73	0.76	1.73	0.99	0.0002	
PEC local soil (mg.kgwwt-1)	$2.58 \cdot 10^{-4}$	$1.95 \cdot 10^{-4}$	$1.16 \cdot 10^{-4}$	$3.42 \cdot 10^{-4}$	$3.36 \cdot 10^{-4}$	$1.16 \cdot 10^{-4}$	$4.62 \cdot 10^{-4}$	$1.7 \cdot 10^{-4}$	$2.42 \cdot 10^{-4}$	$1.39 \cdot 10^{-4}$	$9.98 \cdot 10^{-4}$	$2.17 \cdot 10^{-4}$	$2.55 \cdot 10^{-4}$	$4.62 \cdot 10^{-4}$	$3.11 \cdot 10^{-4}$	$1.16 \cdot 10^{-4}$	

Annex 3 Input data for exposure assessment and local PECs for water at down stream users supplied by Company A.

Location of customer	1	2	3	4	5	6	7	8	9	10	Total
Product produced	CMC	CMC	CMC	CMC	CMC	CMS	CMC	CMC	CMC	CMC	
Country	DE	DE	DE	DE	DE	DE	DE	DE	DE	DE	DE
Processing per year (tpa) in 1998-2000	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	19090
Processing days	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	Conf.	
Processing per day (tpa)	22.22	5.56	6.25	5.69	0.94	5.42	4.72	1.11	0.56	0.56	
Release factor	0.01	0.01	0.0001	0.01	0.01	0	0.01	0.01	0.01	0.01	
Discharge to WWTP (kg/d)	222.22	55.56	0.63	56.94	9.44	0	47.22	11.11	5.56	5.56	414
Removal rate (%) in WWTP	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	99.9	
Mass flow in WWTP effluent (mg/s)	2.57	0.64	0.01	0.66	0.11	0	0.55	0.13	0.06	0.06	4.79
Release to water (kg/day)	0.2222	0.06	0.001	0.06	0.009	0	0.05	0.01	0.006	0.0	0.41
PEC effluent (ug/l)	111	27.8	0.31	28.5	4.72	0.00	23.6	5.56	2.78	2.78	
River flows MNQ (m3/s)	238	266	0.23	60	1050	2.2	87	40.2	6.1	1.5	
PEC local aquatic (ng/l)	79.01	70.62	99.65	79.18	68.30	68.20	74.48	71.40	78.74	111.07	
Release factor air	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	
Release to air (kg/day)	11.1	2.8	3.1	2.8	0.5	2.7	2.4	0.6	0.3	0.3	26.5
PEC local air (ug.m-3)	2.55	0.64	0.72	0.65	0.11	0.62	0.54	0.13	0.06	0.06	
PEC local soil (mg.kgwwt-1)	$6.2 \cdot 10^{-4}$	$2.42 \cdot 10^{-4}$	$2.58 \cdot 10^{-4}$	$2.45 \cdot 10^{-4}$	$1.37 \cdot 10^{-4}$	$2.39 \cdot 10^{-4}$	$2.23 \cdot 10^{-4}$	$1.41 \cdot 10^{-4}$	$1.29 \cdot 10^{-4}$	$1.29 \cdot 10^{-4}$	

Annex 4 Worker exposure

Table II-1 Worker exposure data

Year	Job title/Activity	Method/number of samples	Exposure levels (mg/m³)	Duration of sample/distribution	Reference and remarks
1989	Operators	ns/ns	0.93	TWA, mean	Company A
	Technicians	ns/ns	0.58	TWA, mean	
	Laboratory	ns/1	0.85	TWA, mean	
	Maintenance	ns/ns	2	STV	
1994	Operators	PAS/23	< 0.3	TWA (5.5-7.5 h)	LOD=0.3
	Warehouse	PAS/2	< 0.3	TWA	
	Operator room	PAS/3	< 0.3	TWA	
1995	Operators doing rounds	PAS/8	< 0.01-7.9	ns	
	Operators in control room	PAS/4	< 0.01-0.022	ns	
	Operators crop protection chem.	PAS/3	< 2	TWA	External audit*
1996	Operators in control room and doing rounds	PAS/ns	< 0.01	TWA, whole shift	
	Operators unloading MCAA	PAS/1	0.28	TWA, whole shift	
	Maintenance operator Operator during incident	PAS/1 ns	0.13 15	TWA, whole shift STV	
1997	Production	ns/10	0.0005-0.823 0.005	Range Median	Company B 8 samples <0.005
	Packaging	ns/4	0.005-0.293 0.005	Range Median	3 samples <0.005
2000	Bagging area Supervisor Outdoor operator	PAS/3 PAS/3 PAS/3	0.088 0.39 0.33 0.019 < 0.014 < 0.014 1.70 0.19 0.14		Company B
1990	Production: chlorination area	PAS/3	0.57	TWA	Company C
	Production: chlorination area	PAS/1	1.39	STV	
	Production: crystallisation area	PAS/2	2.47	TWA	

Table II-1 continued overleaf

Table II-1 continued Worker exposure data

Year	Job title/Activity	Method/number of samples	Exposure levels (mg/m3)	Duration of sample/distribution	Reference and remarks
	Production: packaging area	PAS/2	0.35	TWA	
	Maintenance	ns/1	0.005	TWA	
1995	Operators in chlorination area	PAS/3	0.57	TWA	
	Operators in crystallisation area	PAS/2	0.36 3.5	TWA STV	
1991-2000 MCAA SMCA	 Packing Bagging Production Production Bagging Mixing	 PAS/5 PAS/3 STAT/7 PAS/17 PAS/3 STAT/2	 0.8 0.5 0.9 0.4 0.6 0.8	 average average average average average average	Company C
1989	Chem. Ind.	ns/4	0.5-1.6 0.8 1.6	TWA-4 Median 95-%	Company D
1997	Chem. Ind.	ns/2	< 0.2	TWA-7	
1995	Maintenance (shutdown)	PAS/ns	0.035-0.91	TWA	ECETOC, 1999
1966	Operator during incident	ns/1	15	STV	ECETOC, 1999

* values below LOD noted as half of LOD
TWA Time Weighted Average over a full shift
STV Short Term Value
LOD Limit of Detection
ns not specified
95-% 95-percentile

Annex 5 Establishment of the minimal MOSs used for the worker risk characterisation

In the Tables below calculations of the minimal MOS-values via assessment factors are given. The assessment factors are based upon the report of Hakkert et al. (1996).

Table II-1 Assessment factors applied for the calculation of the minimal MOS for acute toxicity after acute inhalation exposure (rat)

Aspect	Assessment factors
Interspecies differences[a]	3
Intraspecies differences	3
Differences between experimental conditions and exposure	1
Type of critical effect[b]	>>1
Dose response	>>1
Confidence of the database	1
Overall	>>9

a) Extrapolation based on differences in caloric demands, together with a factor 3 for remaining uncertainties.
b) It is noted that the MOS values are calculated for a severe effect (lethality). It is expected that other toxic effects after acute exposure might occur at lower concentrations than the lethal concentrations.

Table II-2 Assessment factors applied for the calculation of the minimal MOS for acute toxicity after acute dermal exposure (rabbit)

Aspect	Assessment factors
Interspecies differences[a]	2.4 · 3
Intraspecies differences	3
Differences between experimental conditions and exposure	1
Type of critical effect[b]	>>1
Dose response	>>1
Confidence of the database	1
Overall	>>22

a) Extrapolation based on differences in caloric demands, together with a factor 3 for remaining uncertainties.
b) It is noted that the MOS-values are calculated for a severe effect (lethality). It is expected and described in the studies available, that other toxic effects after acute exposure might occur at lower concentrations than the lethal concentrations.

Table II-3 Assessment factors applied for the calculation of the minimal MOS for systemic effects after chronic dermal exposure based on a 2-year drinking water study in rats

Aspect	Assessment factors
Interspecies differences[a]	4 · 3
Intraspecies differences	3
Differences between experimental conditions and exposure	1
Type of critical effect	1
Dose response	1
Confidence of the database	1
Route-to-route extrapolation	1.1
Overall	40

a) Extrapolation based on differences in caloric demands, together with a factor 3 for remaining uncertainties.
b) For route-to-route extrapolation correction is made by differences between oral absorption in oral toxicity studies and worker exposure relevant dermal absorption. Based on the information available a value of 90% holds for oral absorption. For dermal absorption a default value of 100% is used.

Table II-4 Assessment factors applied for the calculation of the minimal MOS for systemic effects after chronic inhalation exposure based on a 2-year drinking water study in rats

Aspect	Assessment factors
Interspecies differences[a]	4 · 3
Intraspecies differences	3
Differences between experimental conditions and exposure	1
Type of critical effect	1
Dose response	1
Confidence of the database	1
Route-to-route extrapolation	1.1
Overall	40

a) Extrapolation based on differences in caloric demands, together with a factor 3 for remaining uncertainties.
b) For route-to-route extrapolation correction is made by differences between oral absorption in oral toxicity studies and worker exposure relevant inhalation absorption. Based on the information available a value of 90% holds for oral absorption. For inhalation absorption a default value of 100% is used.

Table II-5 Assessment factors applied for the calculation of the minimal MOS for systemic effects after chronic combined exposure based on a 2-year drinking water study in rats

Aspect	Assessment factors
Interspecies differences[a]	4 · 3
Intraspecies differences	3
Differences between experimental conditions and exposure	1
Type of critical effect	1
Dose response	1
Confidence of the database	1
Route-to-route extrapolation[b]	1.1
Overall	40

a) Extrapolation based on differences in caloric demands, together with a factor 3 for remaining uncertainties.
b) For route-to-route extrapolation correction is made by differences between oral absorption in oral toxicity studies and worker exposure relevant dermal or inhalation absorption. Based on the information available a value of 90% holds for oral absorption. Both for dermal absorption and inhalation absorption default values of 100% are used.

European Commission

EUR 21403 EN **European Union Risk Assessment Report**
Monochloroacetic acid (MCAA), Volume 52

Editors: S.J. Munn, R. Allanou, K. Aschberger, F. Berthault, O. Cosgrove, M. Luotamo, S. O'Connor, S. Pakalin, A. Paya-Perez, G. Pellegrini, S. Scheer, B. Schwarz-Schulz, S. Vegro.

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Environment and quality of life series

The report provides the comprehensive risk assessment of human health part of the substance Monochloroacetic acid (MCAA). It has been prepared by The Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The environmental risk assessment for MCAA concludes that there is concern for the aquatic ecosystem and for microorganisms in the sewage treatment plants arising from production and processing at two sites. There is a need for further information to investigate, quantitatively, the sources (not related to MCAA production/processing) of the regional and continental MCAA background levels measured in various environmental compartments.

The human health risk assessment for MCAA concludes that there is concern for workers and for humans exposed via the environment. For consumers, for workers and for humans exposed via the environment there is a need for further information regarding the reproductive toxicity. This conclusion is on hold awaiting the outcome of the risk reduction strategy.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

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monochloroacetic acid (MCAA)

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