ECETOC

Joint Assessment of Commodity Chemicals No. 38

Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3)

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THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced and are continuing to prepare reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a producer, government official or consumer can be informed on the up-to-date position with regard to safety, information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review already exists; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed.

This document presents a critical assessment of the toxicology, the environmental fate and ecotoxicology of monochloroacetic acid (MCAA) CAS no. 79-11-8 and its sodium salt (SMCA) CAS no. 3926-62-3.

Where relevant the studies have been graded by the Task Force (TF) to reflect the degree of confidence that can be placed on the reported results. The criteria used to assess and categorise reliability are included in the Appendix to the report. Most of the Tables in the report include reference to the "code of reliability" (CoR) assigned by the TF.

1. SUMMARY AND CONCLUSIONS

Monochloroacetic acid (MCAA) is a strong acid which is freely soluble in water. It is synthesised in a closed system, and produced either in molten form at 60°C, as crystalline flakes, in solution (80%), or as the sodium salt (SMCA). MCAA and SMCA are used almost exclusively as intermediates for the synthesis of carboxymethylcellulose, herbicides, surfactants, thioglycolic acid and in other production processes where carboxylation is required.

Some release to the environmental compartments may occur during production, transport and downstream use. MCAA/SMCA is rapidly degraded in the atmosphere by OH radicals, although low concentrations of MCAA have been measured in areas remote from anthropogenic emissions (as exemplified by pre-industrial ice samples). This is thought to be due to natural occurrence in the environment. If released into soil MCAA/SMCA will initially partition into the aqueous phase. MCAA/SMCA exists in water in the ionised state as the monochloroacetate anion; its properties will therefore be those of the salt in solution.

Monochloroacetate is readily biodegradable. It is rapidly degraded aerobically and anaerobically in soil and in the aquatic environment and will not exist as such for more than a few days. Due to its low K_{oc} MCAA will not absorb into sediment and the log K_{ow} -3.47 indicates that bioaccumulation of SMCA in aquatic flora and fauna is unlikely to occur to any significant extent.

The results of laboratory ecotoxicity studies on MCAA, where high concentrations are employed and the pH is significantly modified, are not relevant to environmental conditions where the compound will exist as the monochloroacetate anion. In acute studies on aquatic fauna and bacteria, the species most sensitive to SMCA has been shown to be the protozoan *Tetrahymena pyriformis* with a 9-hour IC_{50} of 83 mg/l. In chronic studies the bacteria *Vibrio fischeri* had the highest sensitivity with a 22-hour NOEC of 10 mg/l. However, algae are the most sensitive aquatic species. The lowest E_bC_{50} is 0.025 mg/l and the lowest 72-hour NOEC is 0.0058 mg/l for *Scenedesmus subspicatus.*

The few data available indicate a significant toxicity for terrestrial organisms, based on accidental exposure and an oral LD_{50} of 75 mg/kg SMCA for the Gray Lag goose (*Anser anser)*.

It is known that there have been five fatal and two non-fatal human cases of severe acute intoxication after accidental dermal exposure to MCAA, and one fatal case after ingestion. Ten percent or more of the body surface was involved in the five fatal injuries by dermal exposure, and between 5 and 10 % in the 2 non-fatal accidents. In a few other incidents, workers had more than 5 or even 10 % of their body

surface burned without any signs of systemic intoxication. Symptoms of systemic toxicity are delayed for about 1-3.5 hours after exposure. Vomiting occurs initially, followed by CNS disturbances (hyperexcitability, disorientation, convulsions), CNS depression and coma. Cardiovascular involvement occurs in all cases, with arrhythmia, tachycardia and cardiovascular shock. Increased blood creatinine levels are observed. The development of a severe metabolic acidosis is very difficult to overcome and death occurs within 4 hours to 7 days due to cardiovascular shock, renal failure and cerebral oedema. Early administration of phenobarbital or dichloroacetate is proposed as specific antidotal therapy to prevent the development of the MCAA-induced lactic acidosis.

MCAA is rapidly and extensively absorbed by all routes of administration. The acute toxicity data for SMCA suggest an absorption comparable to MCAA by the oral route and conversely, a limited absorption by the dermal route of exposure. The monochloroacetate anion and/or its metabolites are initially distributed in lipid-poor tissues (liver, kidney, stomach) and subsequently in lipid-rich tissues (brain, spinal cord, thymus, pancreas). Monochloroacetate is excreted unchanged in a fast elimination phase (t½ = 90 minutes in rat after sc injection) and is bound to glutathione, cysteine or protein or is eliminated as $C0_2$ in a slow phase (t½ = 500 minutes). Thirty-five to ninety percent of monochloroacetate and its metabolites are excreted in the urine of rats and mice within 24 hours after oral administration. In humans a half-life of about 15 hours has been found for the rapid excretion of monochloroacetate in the urine, following contamination of the skin with ^{14}C-MCAA. After 6 days, only trace amounts are detectable in the blood. Monochloroacetate is metabolised in mice and rats to thiodiacetic acid (via S-carboxymethyl glutathione and S-carboxymethyl cysteine) and, to a lesser extent, to glycolic acid and $C0_2$ (after enzymatic hydrolysis of the C-Cl bond).

MCAA and SMCA are toxic after oral administration (LD_{50} in rats: 55-200 mg/kg and 76-580 mg/kg, respectively). Systemic effects include body-weight loss, hypoactivity, dyspnoea, tremor, convulsion, and cyanosis, in addition to severe burns of the gastro-intestinal tract. MCAA can be absorbed through the skin in toxic and lethal amounts (LD_{50}: 180-800 mg/kg in rats and rabbits) and leads to clinical signs identical to those observed after oral administration. No mortality was observed in rats after dermal administration of 2000 mg SMCA/kg. Exposure of rats for less than 10 minutes to MCAA saturated vapour (generated at 75°C) induced eye and respiratory tract irritation but no mortality.

MCAA is corrosive to the skin and produces irreversible damage to the eyes. In contrast SMCA is not irritant to the skin and induces a reversible irritation in contact with the eyes. There are no indications that MCAA or SMCA possess skin sensitisation potential.

MCAA and SMCA administered orally in repeated doses for up to 3 months seem to have a species-dependent threshold for mortality of about 60 mg/kg/day in rats and 150 mg/kg/day in mice. Sub-lethal

doses of MCAA lead to changes in liver and kidney weights, histopathological lesions in liver and kidneys, and non-specific changes in various biochemical parameters clinically related to these organs. Cardiomyopathy has also been observed in rats. The NOAEL for long-term administration is also species-dependent and is 100 mg/kg/day in mice and 30 mg/kg/day in rats. No relevant data are available on inhalation and dermal exposures for establishing a NOAEL for those routes of administration.

MCAA has no genotoxic potential in bacterial mutagenicity studies, *in vitro* chromosomal aberration assays, *in vitro* and *in vivo* primary DNA damage assays or a mutation assay in germ cells of *Drosophila melanogaster*. In tests for gene mutations in mammalian cells, the results were conflicting and probably subject to artifacts due to pH shift. In a poorly-reported study, an increase in chromosomal aberrations and sperm shape abnormalities was observed in mice after intraperitoneal injection of MCAA. However, no clastogenic activity was detected in the newt (*Pleurodeles waltl* larvae*)* micronucleus test. Overall, the data available on MCAA do not demonstrate a genotoxic potential.

No increase in mortality from tumours or in tumour incidence was found in F344 rats and B6C3F1 mice in life-time oral carcinogenicity assays. The findings in mice of inflammation of the nasal epithelium, metaplasia of the olfactory epithelium and focal squamous cell hyperplasia of the forestomach were ascribed to the strong local irritant effect of MCAA.

Visceral but not skeletal foetal malformations were observed after the administration of high doses to pregnant rats during the most sensitive period of gestation. The results of other *in vivo* and *in vitro* assays suggest that this effect can be ascribed to maternal toxicity. Thus MCAA is not considered to be toxic to development.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 IDENTITY

Table 1: Monochloroacetic acid (MCAA) and its sodium salt (SMCA)

Characteristics	MCAA	SMCA
IUPAC name	Chloroacetic acid	Sodium chloroacetate
Synonyms	α-Chloroacetic acid Chloroethanoic acid Monochloroacetic acid	Sodium 2-chloroacetate
CAS name	Acetic acid, chloro-	Acetic acid, chloro-, sodium salt
CAS No	79-11-8	3926-62-3
EINECS No	201-178-4	223-498-3
EC No	607-003-00-1	607-158-00-5
EC classification	Toxic if swallowed, causes burns, very toxic to aquatic organisms [1)]	Toxic if swallowed, irritant to skin [2)]
EC labelling	T, N; R25-34-50, S(1/2)23-37-45 [1)]	T; R25-38, S(1/2)22-37-45 [2)]
Formula	$C_2H_3ClO_2$	$C_2H_2ClNaO_2$
Molecular mass	94.5	116.48
Structural formula	Cl — CH_2 — CO — OH	Cl — CH_2 — CO — O^-Na^+

1) EC, 1994
2) EC, 1993

2.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of MCAA and SMCA are given in Table 2.

MCAA

At room temperature, pure MCAA is a colourless, hygroscopic, crystalline solid, which occurs in monoclinically prismatic structures and exists in the α-, β-, γ-, and also possibly the δ-form. Of these

the α-form is the most stable and the most important industrially (Ullmannn, 1986). MCAA is highly soluble in water, ethanol, methanol, acetone and diethyl ether, but poorly soluble in hydrocarbons and chlorinated hydrocarbons.

Industrially, MCAA is produced either in the molten form, as crystalline flakes or in solution. A typical commercial sample of MCAA molten or flakes has a specified purity of ≥ 99.0% (m/m) and contains dichloroacetic acid (DCAA) (≤ 0.3% m/m), acetic acid (≤ 0.2% m/m), glycolic acid (≤ 0.2% m/m) and water (≤ 0.2% m/m). A typical commercial solution consists of MCAA (78-81% m/m) in water. It has a characteristic odour similar to that of vinegar.

SMCA

At room temperature SMCA consists of a white powder or granules with or without a slight odour depending on the specification; it is highly water soluble.

A typical commercial sample of SMCA has a specified purity of ≥ 97.5% (m/m) and contains sodium chloride (≤ 0.7% m/m), sodium dichloroacetate (≤ 0.3% m/m), sodium glycolate (≤ 0.8% m/m) and water (≤ 0.9% m/m).

Table 2: Physical and chemical properties

Parameter	MCAA	SMCA
Melting temperature		
Commercial form	61-65°C [1]	
α-form	62-63°C [1]	
β-form	55-56°C [1]	
γ-form	50-51°C [1]	
δ-form	43.8°C [1]	
Boiling temperature (1.013 hPa)	189°C [2]	
Density		
Liquid form (4°C/65°C)	1.3703 [1]	
Solid form (20°C/20°C)	1.58 [1]	850 kg/m^3 [6]
Vapour density (air = 1)	3.26 [3]	
Viscosity, dynamic (70°C)	2.16 mPa•s [1]	
Vapour pressure		
25°C	8.68 Pa [4]	
80°C	11 hPa [1]	
pKa (25°C)	2.85 [10]	
pH		
80% solution (20°C)	1 [5]	
50 g/l (20°C)		4.5-9 [6]
10 g/l		6.2-8.5 [7]
Surface tension (100°C)	35.17mN/m [4]	
Solubility in water (20°C)	80.8 g/100 g soln [1]	44 wt% [1]
	421 g/100g H_2O [1]	
Solubility (20°C) in solvents:		
acetone	2570 g/kg [4]	
methylene chloride	510 g/kg [4]	
benzene	260 g/kg [4]	
carbon tetrachloride	27.5 g/kg [4]	
Henry´s constant (25°C)	4.2 x 10^{-4} Pa.m^3/mol^{-1}	
Flash point (DIN 51 758, closed cup)	126°C [1]	~270°C [6]
Lower explosion limit (1.013 hPa)	8 vol% [1]	
Ignition temperature	470°C [1]	
log K_{ow}	0.22 [8]	-3.47 [9]
	0.34 [9]	

1) Ullmannn, 1986
2) Merk Index, 1976
3) Sax, 1984
4) Kirk-Othmer, 1983
5) Elf Atochem, 1995a
6) Clariant, 1997
7) Elf Atochem, 1996
8) Hansch and Leo, 1985
9) Syracuse, 1993
10) CRC Handbook, 1988-89

2.3 CONVERSION FACTORS

The conversion factors for concentrations of MCAA vapour in air (20°C, 1.013 hPa) are:

1 ppm = 3.92 mg/m^3
1 mg/m^3 = 0.26 ppm

2.4 ANALYTICAL METHODS

2.4.1 In air

MCAA vapour can be determined in air by collection on silica gel sorbent tubes, desorption with water and determination of the monochloroacetate anion by ion chromatography. The method has been validated with concentration of 0.35-29 mg/m^3 in 3-litre air samples. The absorbant capacity of the silica gel is in the range 3-4 mg MCAA/100mg, which allows for up to 8-hr sampling at concentrations > 40 mg/m^3 (Mason *et al*, 1986).

MCAA and SMCA dust may be monitored by sampling the total or respirable dust fraction, followed by similar desorption and measurement of MCAA content (Akzo Nobel, 1994).

Both the above methods may be employed either for fixed (spot) measurements or for personal sampling.

There is no specific method for measuring exposure to aerosols.

Alternatively MCAA can be collected on a quartz fibre filter impregnated with sodium bicarbonate; refrigeration of exposed filters or extraction of the filters soon after exposure is necessary to preserve the MCAA for subsequent determination. It has been suggested that in the determination of both MCAA vapour and salts, filter sampling may be more suitable than the silica gel tube (Mason *et al*, 1986). The Task Force is not aware of any data to support this suggestion.

2.4.2 In water

MCAA/SMCA can be determined in water by gas chromatography with electron-capture detection after derivatisation with either diazomethane or pentafluorobenzene bromide (detection limits respectively 1 and 10 μg/l) (Quick *et al*, 1992).

2.4.3 In biological media

In addition to the method described by Quick *et al* (1992) in Section 2.4.2, MCAA can be demonstrated in peripheral blood by gas chromatography/mass spectrometry after derivatisation to the methyl ester by reacting with the BF_3-methanol complex and extraction with methylene chloride. The limit of detection in plasma is 2.2 µM (Yan *et al*, 1997; Akzo Nobel, 1998).

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 PRODUCTION

3.1.1 MCAA

MCAA is synthesised in a closed system by the continuous chlorination of acetic acid in the liquid phase at elevated temperature. The reaction products are separated by distillation and the more volatile components (e.g. acetic acid) returned to the production process. The raw MCAA remains in the distillate and is purified either by catalytic hydrogenation (the by-product DCAA is converted to MCAA thereby) or by crystallisation (Ullmann, 1986; Kirk-Othmer, 1983).

3.1.2 SMCA

The further conversion of MCAA to SMCA with bicarbonate or sodium hydroxide is performed in either continuous or batch processes (Ullmann, 1986; Akzo Nobel internal data).

3.2 STORAGE

3.2.1 MCAA

Molten MCAA is stored under nitrogen at temperatures above 80°C in containers of vitrified steel. Contact with concentrated solutions of strong bases must be avoided because of the risk of an exothermic reaction and decomposition.

MCAA flakes should be protected from moisture and stored away from heat and ignition. It is recommended that the flakes are stored at temperatures below 50°C and stored and shipped in paper bags lined with polyethylene.

MCAA solution is stored in containers of stainless or vitrified steel, polyethylene, or polypropylene at temperatures below 40°C (Ullmann, 1986).

3.2.2 SMCA

SMCA powder should be protected from moisture and stored at temperatures below 50°C in paper bags lined with polyethylene (Elf Atochem, 1996).

3.3 TRANSPORT

3.3.1 MCAA

MCAA is transported “in-plant” in the liquid state through permanently-installed pipes. Outside the plant MCAA is transported in liquid form in heated tankers using compensation piping in filling and charging (Ullmann, 1986), or as flakes in paper bags lined with polyethylene.

3.3.2 SMCA

SMCA powder is shipped in paper bags lined with polyethylene (Elf Atochem, 1996).

3.4 USE

Currently MCAA and SMCA are used almost exclusively as intermediates for the synthesis of carboxymethyl cellulose, herbicides, surfactants, thioglycolic acid and in other production processes where carboxylation is required (Ullmann, 1986). Unpublished data (Table 3) from the three main European producers indicate that the production volumes of MCAA and SMCA are in the region of 160,000 and 27,000 tons/year respectively.

Table 3: Use pattern in the EU (1997)

Type of use	MCAA/SMCA (%)
Production of carboxymethyl cellulose	30-50
Production of herbicides (e.g. 2,4-dichloro-phenoxyacetic acid)	20-25
Production of surfactants (e.g. for shampoos and industrial cleaning agents)	5
Production of thioglycolic acid	10-16
Production of other carboxylated products	15-24

SMCA is used to a limited extent (<10 tons/year) in the UK and Ireland as a herbicide (EDAP, 1990).

The use of MCAA as a wart remover (Verzone™) was developed by a podiatrist in the Minneapolis area (USA) and is believed to have been only marketed locally (Rogers, 1995). The Task Force has no information on whether or not the product was removed from the market following the fatal accident described in Section 10.1.1.

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 ENVIRONMENTAL SOURCES/EMISSIONS

4.1.1 Natural sources

The existence of natural sources of MCAA is strongly suggested by its ubiquitous presence in the environment and in pre-industrial ice samples. There are no obvious atmospheric degradation pathways that could explain a direct formation of MCAA from chlorinated solvents.

However DCAA and trichloroacetic acid (TCAA) may be formed in the atmosphere from trichloroethylene (TCE) and perchloroethylene respectively by photochemical reactions. This has been demonstrated in laboratory experiments (Franklin, 1994). Of the levels present in the environment, about 90% of TCE and about 30% of perchloroethylene is thought to be of natural origin (ECSA, 1997). It has been suggested that the chlorine atoms produced in the marine boundary layer could react with unsaturated hydrocarbons of natural origin to produce MCAA. This hypothesis is being tested within the EU, 1998 "HALOBUD" project.

4.1.2 Anthropogenic emissions

Releases from production

There is a potential for the release to the environment of anthropogenic MCAA/SMCA during the production and processing of these compounds. Emissions should, however, be extremely low; any loss during production would enter the environment via air or water. Synthesis generally takes place in closed systems; any releases are neutralised before draining into waste-water-treatment plants. Release into the environment may occur as a result of local deposition of MCAA/SMCA dust particles during packaging, drying during the cooling process for molten MCAA or transformation of MCAA to SMCA; incidental amounts may be released when cleaning tubes after unloading tankers.

Other sources

MCAA occurs as a by-product in the chlorination of drinking water (See Section 6.1). It can also be formed in the degradation of higher chlorinated acetic acids (Zakordonets, 1987).

4.1.3 Concentrations in the environment

MCAA has been found in air, rain-water and surface water (Frank *et al*, 1995). Concentrations in urban air ranged from 10-5000 pg/m^3 and in rain-water from a few to 700 ppt (w/w) (Frank *et al*, 1995). MCAA has been found in snow in both the northern and southern hemispheres at levels of up to about 80 ppt (w/w) (Eurochlor, 1995). It has also been detected in ice samples of pre-industrial origin at levels of up to 27 ppt (w/w) (Eurochlor, 1995).

The amount of MCAA emitted in solution to the atmosphere and assumed to undergo local deposition is 3.1 kg/hour according to calculations carried out for a Swedish production site (KEMI, 1994). In Germany emissions of less than 500 kg/year to the atmosphere from production and processing have been indicated (BUA, 1994). This can be compared to 35,000 tonnes/year MCAA deposited by rain-water, assuming an average precipitation of 700 mm/year and a concentration of 0.1 ppb (w/w). In addition MCAA is likely to remain in the aqueous phase if emitted in solution due to its high water solubility.

Industrial emissions thus make a negligible contribution to the observed global background concentrations of MCAA in air and rain-water.

4.2 ENVIRONMENTAL DISTRIBUTION

An indication of the partitioning tendency of a chemical can be obtained using a Mackay level I calculation (Mackay, 1991). This basic model describes the distribution of a chemical over the various environmental compartments in a so-called “unit world”. The steady-state equilibrium conditions are calculated assuming a continuous chemical input, no transfer between compartments and no degradation of the chemical. The absolute values resulting from the calculation are not relevant, but the results can be used to identify compartments of potential concern.

The results for MCAA/SMCA presented in Table 4 are based on the values for SMCA, which are the environmentally-relevant data, i.e. vapour pressure 1.5 x 10^{-5} Pa, water solubility 44% (w/w), log K_{ow} – 3.47, molecular weight 116.48 g/mol.

Table 4: Mackay level 1 calculation

Compartment	%
Air	0.00
Water	100
Soil	0.00
Sediment	0.00

The results show that the tendency for MCAA/SMCA to partition into water is high and negligible into the other compartments.

4.3 ENVIRONMENTAL FATE AND BIOTRANSFORMATION

4.3.1 Atmospheric Fate

If emitted to the atmosphere, MCAA is degraded by OH radical attack and has a half-life of about 10 days, based on the Atmospheric Oxidation Programme (Meylan and Howard, 1993), and an OH average concentration of 10^6 molecules/cm^3 according to Atkinson's method (Kwok and Atkinson, 1995). This competes with the dissolution of MCAA in atmospheric water and further rain out. The lifetime for this process has been estimated to be about 10 days for species of high solubility (Giorgi and Chameides, 1985). From its structure it is anticipated that MCAA is unlikely to give stable products after OH radical attack but will be completely degraded to carbon dioxide and hydrochloric acid. If MCAA is emitted in aqueous solution in aerosols it is likely to remain in the aqueous phase because of its high solubility (Henry's constant 4.2 $.10^{-4}$ Pa. m^3/ $moles^{-1}$) (BUA, 1994).

4.3.2 Aquatic Fate

Monochloroacetate will be present predominantly in the aqueous phase in the aquatic environment and will not partition into sediment (Table 4). Based on biodegradation characteristics monochloroacetate is expected to be degraded rapidly and fully mineralised.

4.3.3 Terrestrial Fate

When released into soil monochloroacetate will initially partition into the aqueous soil phase. The biodegradation potential of monochloroacetate in soil is high, since it biodegrades rapidly both under aerobic and anaerobic conditions (Section 4.3.4). Based on its biodegradation characteristics under

aerobic conditions in soil (Section 4.3.4) monochloroacetate is expected to have a lifetime of only days to weeks in the soil. Thus, although the potential for mobility is high, under normal circumstances monochloroacetate is unlikely to reach ground water.

4.3.4 Biodegradation

Aerobic and anaerobic

MCAA/SMCA is readily biodegradable under aerobic conditions, as has been shown in a number of standard tests presented in Table 5.

The rapid biodegradation is exemplified by a standard closed bottle test using an unadapted inoculum from a sewage treatment plant (3 mg suspended solids/l). At a concentration of 10.3 mg/l MCAA/SMCA was rapidly degraded, reaching 60% biodegradation in about 10 days and 69% in 28 days (Akzo Nobel, 1988). MCAA/SMCA is degraded by greater than 70-90% within 5-10 days in laboratory biodegradation tests using sewage or acclimated sludge inocula (Zahn and Wellens, 1974 and 1980).

These results are in agreement with the findings of Slater *et al* (1979) who found a doubling time of the bacterial population of 4 hours when using MCAA as carbon and energy sources. This approaches the rates found for glucose. MCAA/SMCA is also degraded rapidly under anaerobic conditions, with measured rates of reduction of 86-90% within 2 days at 34 °C (Egli *et al*, 1989).

The presence of MCAA/SMCA degrading micro-organisms in soil has been demonstrated by the isolation of these organisms by Jensen (1957, 1959). This was confirmed by studies on the biodegradation of TCAA in soil in which TCAA was degraded via DCAA and MCAA. No accumulation of MCAA was observed, indicating that MCAA was degraded in soil more rapidly than TCAA. TCAA takes several weeks to disappear (Lignell *et al*, 1984). MCAA has been shown to degrade in soil within 2 weeks (Jensen, 1960).

Table 5: OECD tests for aerobic biodegradation

Type of test	Guideline	Days	Inoculum	MCAA (mg/l)	Result	Reference	CoR‡
Closed Bottle test	OECD 301 D	28	AS	10.3	69%	Akzo Nobel, 1988	1a
Modified Zahn-Wellens	OECD 302 B	8	AS industrial	570 mg DOC/l	100%	Hoechst, 1992a	1c
Modified Zahn-Wellens	OECD 302 B	10	AS industrial	1140	99%	Hoechst, 1992a	1c
Modified OECD	OECD 301 E	28	AS	5 (DOC)	100%	Gerike and Gode, 1990	2a
Modified Zahn-Wellens	OECD 302 B	28	AS	1000	100%	Gerike and Gode, 1990	2a
Modified MITI	OECD 301 C	21	AS	100	65%	MITI, 1992	2c
Modified Zahn-Wellens	OECD 302 B	6	AS industrial	1000*	90%	Zahn and Wellens, 1974	2c
Modified Zahn-Wellens	OECD 302 B	5.5	AS industrial	1000	>90%	Zahn and Wellens, 1980	2c
Modified OECD	OECD 301 E	7	AS	4.5	73%	Struijs and Stoltenkamp, 1990	2e
Modified OECD	OECD 301 E	7	AS	9	14-24%	Struijs and Stoltenkamp, 1990	2e
Modified OECD	OECD 301 E	28	AS	-	50-55%	Trénel and Kühn, 1982	4e

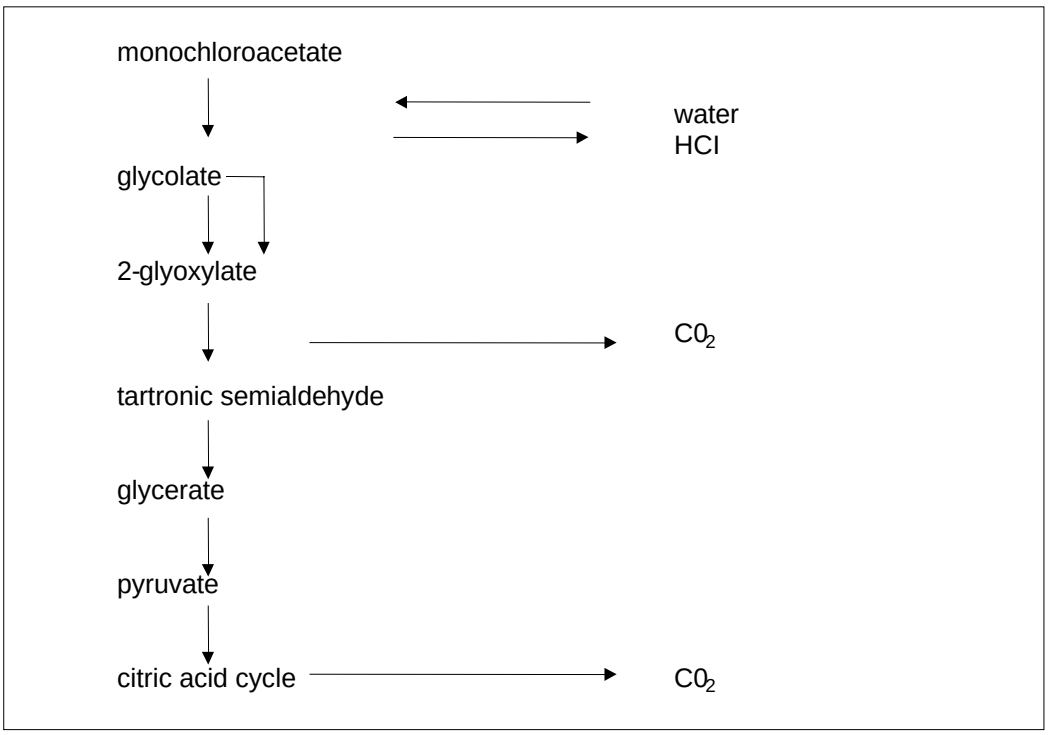
AS activated sludge
* SMCA
‡ see Page i and Appendix for explanation

Metabolic biodegradation pathway

The biodegradation of monochloroacetate under aerobic conditions is initiated by an enzymatic cleavage of the carbon-halogen bond. This hydrolysis is catalysed by two enzymes, namely haloalkanoic acid dehydrogenase and halido hydrolase (Hardman and Slater, 1981), resulting in hydrochloric and glycolic acid. In bacteria the glycolic acid is directly converted into glyoxylic acid, which is further converted via normal cell metabolic pathways to carbon dioxide, water and biomass. A schematic representation of the microbial metabolic pathway is presented in Figure 1.

Under anaerobic conditions monochloroacetate is degraded via glycolic acid. The hydrolysis of monochloroacetate is catalysed by a methanogenic mixed culture. The glycolic acid is converted to carbon dioxide and methane (Egli *et al*, 1989).

Figure 1: Microbial metabolic pathway of monochloroacetate



4.3.5 Bioaccumulation

Although no reference was found in the literature to concentrations of MCAA/SMCA in aquatic organisms, the value of the partition coefficient (log K_{ow}), calculated as -3.47 for SMCA, suggests that bioaccumulation is unlikely to occur to any significant extent.

4.3.6 Abiotic Degradation

Neither hydrolysis nor photolysis have been observed with monochloroacetate (Doughty and Derge, 1931; Kaliana and Kunze, 1938).

4.4 EVALUATION

An examination of the physico-chemical properties, release patterns and fate characteristics indicate that monochloroacetate is restricted almost exclusively to the aquatic compartment, does not persist in the environment due to rapid aerobic and anaerobic biodegradation, and does not bioaccumulate.

5. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

In some cases, the effects of MCAA were due to pH rather than to direct toxicity. At high concentrations the pH of the non-neutralised MCAA was outside the range supporting aquatic life. Such studies have been reviewed in this report, but have not been taken into account in the final evaluation.

Unless otherwise specified, all concentrations mentioned in the studies described below are based on MCAA, with the MCAA solution having been subsequently adjusted to an environmentally-acceptable pH. The MCAA was thus tested as the monochloracetate anion.

5.1 MICRO-ORGANISMS

An EC_{10} of 4630 mg/l for MCAA was reported in a 16-hour bacterial toxicity test carried out by Trénel and Kühn (1982). Gerike and Gode (1990) reported a 3-hour bacterial respiratory inhibition concentration of >1000 mg/l for MCAA using an adaptation of OECD Method 209, in which activated sludge was replaced with a monoculture of *Pseudomonas putida.* The concentration at which the efficacy of an OECD confirmatory test unit was reduced with respect to the control was also determined for the same substance and this too was close to the *P. putida* value. Weightman *et al* (1985) produced resistant strains of *P. putida* by culturing the parent PP3 strain on a solid medium containing monochloroacetate (unspecified) at a concentration of 1-2 g/l carbon. In 1993, Hoechst reported a study carried out earlier, in which an EC_{50} of 160 mg/l was found in a bacterial inhibition test using activated sludge; no effect was observed at 80 mg/l. However, the test procedure did not use a completely anaerobic or aerobic methodology and has since been discontinued. Moreover no details of the pH of the test solutions were included and the solutions might not have been adjusted to neutral. This test cannot therefore be considered as valid. In a later Zahn-Wellens test, also by Hoechst (1992a), no adverse effects on biodegradation rate were found with 1140 mg/l although there was a longer latency period (3 days) than was found for an identical test using a concentration of 570 mg/l where 10% biodegradation was observed within 1 day. No lower concentrations were tested, so no comparison of the rate of biodegradation can be obtained. 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 in this test.

A recent study (Radix *et al*, 1998) on the chronic bacterial toxicity of monochloroacetate to *Vibrio fischeri* resulted in a 22-hour NOEC of 10 mg/l and a 22-hour EC_{50} of 68.9 mg/l.

A test was also carried out on anaerobic bacteria by Egli *et al* (1989) who found that methanogenic bacteria, grown on a culture medium containing 10 mM (945 mg/l) neutralised MCAA, were completely

inhibited by this concentration, whereas controls without monochloroacetate produced methane within 24 hours. At concentrations of 1 mM (94.5 mg/l), neutralised MCAA caused a delay of one week to methanogenesis.

The toxicity of MCAA to protozoa appears to be higher than to prokaryotes. Sauvant *et al* (1995) developed a new technique for assessing toxicity to the protozoan, *Tetrahymena pyriformis,* using a small culture volume and found a 36-hour IC_{50} for growth of 16 mg/l for MCAA, compared to a 9-hour IC_{50} of 83 mg/l which was obtained using a standard flask culture technique.

A summary of the various studies on the toxicity of monochloroacetate on micro-organisms is provided in Table 6.

Table 6: Acute effects on micro-organisms

Organism	Parameter	Time (h)	MCAA (mg/l)	Reference	CoR‡
BACTERIA					
Pseudomonas putida	respiration inhibition	ns	>1000	Gerike and Gode, 1990	2a
	OECD CTU* perturbation	ns	750	''	
Pseudomonas putida	EC_{10}	16	4630	Trénel and Kühn, 1982	4e
Methanogenic bacteria culture	EC_{100}	24	945†	Egli *et al*,1989	2e
Activated sludge	EC_0	24	80	Hoechst, 1993	3c
	EC_{50}	24	160	''	
Activated sludge	Zahn-Wellens (NOEC)	24 **	570	Hoechst, 1992a	2a
Pseudomonas putida	microplate culture	10	1000-2000†	Weightman *et al,* 1985	2e
Vibrio fischeri	NOEC	22	10	Radix *et al*, 1998	1d
	EC_{50}	22	68.9	''	1d
PROTOZOA					
Tetrahymena pyriformis	IC_{50} flask	9	83	Sauvant *et al,* 1995	2e
	IC_{50} microplate	36	16	''	

† compound not specified
‡ see Page i and Appendix for explanation
ns not specified
* confirmatory test unit (CTU)
** time to onset of biodegradation

5.2 AQUATIC ORGANISMS

5.2.1 Algae

Algae appear to be the species most sensitive to monochloroacetate (Table 7). Three species have been tested at environmentally-relevant pH. Tests were carried out in different laboratories on *Scenedesmus subspicatus,* resulting in a 48-hour EbC_{50} of 0.028 (Kühn and Pattard, 1990) and a 72-hour EbC_{50} of 0.025 mg/l (Hoechst, 1992b). *S. quadricauda* was tested for 8 days, resulting in an EC_3 of 0.13 mg/l, which was considered to be the NOEC (Trénel and Kühn, 1982). The test period was unusual and insufficient details are available to enable the test results to be fully evaluated. *Selenastrum capricornutum* was tested by Eka Nobel (1993), resulting in an 72-hour ErC_{50} of 1.8 mg/l. No reason for the large difference between the closely-related species, *S. subspicatus and S. capricornutum,* was evident from the details provided.

An EC_0 of 0.0058 mg/l (Hoechst, 1992b) and a LOEC of 0.005 mg/l (Eka Nobel, 1993) have been reported respectively for *S*. *subspicatus* and *S. capricornutum*. The value of 0.005 mg/l quoted referred to a calculated EC_3 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. It should be noted that there was a 10-fold difference between the lowest and second lowest concentrations; thus the test did not conform with the OECD general guidelines of times 2.2 between concentrations.

Table 7: Effects on algae

Organism	Conc (mg/l)	pH	Time (h)	Result (mg/l)	Reference	CoR‡
Scenedesmus subspicatus	0.008-1.0	neutral	48	EbC_{50} = 0.028 EbC_{10} = 0.007 ErC_{50} = 0.07 ErC_{10} = 0.014	Kühn and Pattard, 1990	2d
Scenedesmus subspicatus	0.0058-0.1	neutral	72	EbC_{50} = 0.025 EbC_{10} = 0.006 EbC_0 (NOEC) = 0.0058 ErC_{50} = 0.033 ErC_{10} = 0.007 ErC_0 (NOEC) = 0.0058	Hoechst, 1992b	1b
Scenedesmus quadricauda	ns	ns	8 (d)	EC_3 = 0.13	Trénel and Kühn, 1982	4e
Selenastrum capricornutum	0.005-5.0	neutral	72	ErC_{50} = 1.8 ErC_{20} = 0.13 ErC_{10} = 0.06 LOEC = 0.005 NOEC < 0.005	Eka Nobel, 1993	3a

ns not specified
‡ see Page i and Appendix for explanation

5.2.2 Aquatic Invertebrates

In studies on *Daphnia magna* (Table 8), Akzo Nobel (1985) reported a 48-hour EC_{50} of 88 mg/l at a pH of 7.8-8.2, while Kühn *et al* (1989a) found a 24-hour EC_{50} of 99 mg/l and a 48-hour EC_{50} of 77 mg/l. Trénel and Kühn (1982) reported an EC_{50} of 427 mg/l in neutralised MCAA solution which reduced to 79 mg/l if non-neutralised (test period not reported). Elf Atochem (1988) found a nominal 24-hour EC_{50} of 180 mg/l for non-neutralised MCAA but of 800 mg/l for the salt. The pH of the highest concentration of the MCAA solution was 4.05 and this caused 100% immobilisation (250 mg/l), which implies that the EC_{50} was pH related. Radix (1998) reported a 48-hour NOEC of 40 mg/l for a reproduction study on *Brachionus calyciflorus* and a 48-hour EC_{50} of 68.9 mg/l.

Kühn *et al* (1989b) performed a 21-day reproduction study at neutral pH on *D. magna* and noted a NOEC (based on reproduction rate, time to appearance of first brood and adult mortality), at the measured concentration of 32 mg/l.

Table 8: Acute and chronic effects on aquatic invertebrates

Organism	Conc (mg/l)	pH	Time (h)	Result (mg/l)	Reference	CoR‡
Daphnia magna	50-300	neutral	24	EC_{50} >300	Akzo Nobel, 1985	1d
			48	EC_{50} = 88		
Daphnia magna	ns	ns	24	EC_{50} = 99	Kühn *et al,* 1989a	1c
			48	EC_{50} = 77		
Daphnia magna	ns	neutral	*	EC_{50} = 427	Trénel and Kühn, 1982	4e
		acidic	*	EC_{50} = 79		
Daphnia magna	100-250	acidic	24	EC_{50} = 180	Elf Atochem, 1988	1b
	500-1500	SMCA	24	EC_{50}·= 800†		
Daphnia magna	0.032-100	ns	21 (d)	NOEC reproduction = 32	Kühn *et al,* 1989b	1d
Brachionus calyciflorus	0-160	acidic (>5.5)	48	NOEC reproduction = 40	Radix, 1998	1d
			48	EC_{50} = 68.9		

* assumed to be 48-hour based on later publications by the same authors

† based on SMCA

‡ see Page i and Appendix for explanation

ns not specified

Further EC values on aquatic toxicity to the species *Gammarus pulex*, *Chironomus plumosus*, *Epeorus assimilis* and *Tubifex tubifex* and on the protozoa, *Vorticella campanula* were provided by Meinck *et al* (1977). However, as no exposure time or test conditions were reported, the reliability of the data cannot be established.

5.2.3 Aquatic Vertebrates

MCAA has a low toxicity for fish with LC_{50} values in the range of 369-2000 mg/l (Table 9). Akzo Nobel (1985) performed acute and sub-chronic tests on several aquatic fauna, adjusting the pH to neutral in each case, and found in all cases that toxicity was low. Their acute static test using the guppy (*Poecilia reticulata*) determined a 96-hour LC_{50} at a concentration of 369 mg/l. Other authors support these results. A study performed by CIT (1998a) gave a 96-hour LC_{50} of 370 mg/l for *Brachydanio rerio.* A 96-hour acute fish toxicity test (Hoechst, 1979f), resulted in a no-effect concentration for golden orfe (*Leuciscus idus melanotus)* $\geq$ 100 mg/l and total mortality at $<$ 500 mg/l (all animals died within 173 minutes, probably at least partly due to an unadjusted pH of 3.8). No LC_{50} could be derived as no intermediate concentrations were tested. Alabaster (1969) found a 48-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) at 900 mg/l and Applegate, *et al* (1957) observed a 24-hour no effect concentration $>$ 5 mg/l (the highest concentration tested) for 3 species of fish, bluegill sunfish (*Lepomis macrochirus*), trout (*Oncorhynchus mykiss*) and sea lamprey (*Petromyzon marinus*).

Table 9 : Acute and chronic effects on aquatic vertebrates

Organism	Conc (mg/l)	pH	Time (h)	Result (mg/l)	Reference	CoR‡
Brachydanio rerio	8.8-1000	neutral	96	LC_{50} = 370	CIT, 1998a	1a
Poecilia reticulata	100-1000	neutral	96	LC_{50} = 369	Akzo Nobel, 1985	1c
Leuciscus idus melanotus	1-500	neutral	96	LC_0 = 100	Hoechst, 1979f	3b
		acidic	96	LC_{100} = 500		
Oncorhynchus mykiss	ns	SMCA	24	LC_{50} = 2000	Alabaster, 1969	3b
			48	LC_{50} = 900		
Petromyzon marinus	ns	ns	24	no effect at 5	Applegate *et al,* 1957	3a
Oncorhynchus mykiss	ns	ns	24	no effect at 5	Applegate *et al,* 1957	3a
Lepomis macrochirus	ns	ns	24	no effect at 5	Applegate *et al,* 1957	3a
Brachydanio rerio	56-560	neutral	12 (d)	NOEC (embryo/larval) = 320 LOEC (embryo/larval) = 560	Akzo Nobel, 1985	3b
Brachydanio rerio	25-400	neutral	28 (d)	LOEC (Early life stage) =25	CIT, 1998b	1b

‡ see Page i and Appendix for explanation
ns not specified

A sub-chronic semi-static test was also carried out by Akzo Nobel (1985) in which zebra fish (*Brachydanio rerio*) embryos were exposed for a period of 12 days to a series of MCAA concentrations ranging from 56-560 mg/l at neutral pH; a NOEC of 320 mg/l was calculated. Mortality in the control group was about 25% over the test period. The study cannot be considered to be chronic as it did not continue beyond 12 days.

In an early life-stage study, following Guideline 210, performed at neutral pH on *B. rerio* by CIT (1998b), no NOEC was found. However, when the control mortality was subtracted from the data set, 15% mortality was found at 25mg/l, the lowest concentration tested.

5.3 TERRESTRIAL ORGANISMS

5.3.1 Field studies

Only one terrestrial study has been reported in which groups of Grey Lag geese (*Anser anser*) were deliberately exposed to SMCA (Christiansen and Dalgaard-Mikkelsen, 1961; CoR 2e). 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. Before death, the geese were unsteady on their feet and unable to support their heads upright. Based on a gavage study (6 geese), the same authors report an LD_{50} for SMCA of 75 mg/kg, with a NOEL of 50 mg/kg. Typically, clinical signs commenced after a 3-hour latency period and the geese developed intermittent convulsions 15-30 minutes before death.

5.3.2 Accidental exposure

Four cases of accidental exposure to SMCA have been described in the literature. In all cases the animals had been grazing on fields shortly after SMCA had been employed as a defoliant.

In an unconfirmed study (CoR 4e), cited by Christiansen and Dalgaard-Mikkelsen (1961), 170 geese were reported to have died several days after migrating one kilometre from treated pasture. Quick *et al* (1992; CoR 2e) reported an incident in which approximately 200 greenfinches (*Carduelis chloris*) fed on onion seeds from an SMCA-treated field sprayed late in the afternoon (100 birds of various other species were also implicated). The first birds died within a few hours and deaths continued throughout the night for a period of 21 hours after crop spraying. Many of the birds fell from trees; of those that were still alive when found, some were panting while others suffered muscle spasms. By extrapolation from the goose $LD_{50,}$ the authors calculated an LD_{50} for 30g greenfinches of 2.3 mg/bird, an amount which was estimated to be contained in 50µl herbicide spray.

Quick *et al* (1983; CoR 2e) described two separate incidents of cattle (species unknown) and sheep (species unknown) mortality after SMCA application to crops. In the first 10 cattle died after drinking water which had become contaminated after a worker had cleaned crop spraying equipment next to a farm drain overflow. In addition to SMCA, trifluralin had been used in the same equipment on the same day. The toxicity of trifluralin is reported to be lower than that of SMCA, however, and the autopsy noted findings which corresponded closely to SMCA poisoning (sc haemorrhages with venous congestion around the neck and thorax, congested heart with multiple epicardial and endocardial haemorrhages and oedematous lungs). The authors calculated an effect dose of 17-68 mg/kg. In the second case 2 ewes and 2 lambs were found dead after a contractor had mixed SMCA for crop spraying close to a standpipe in their field. The effect dose was calculated as 39-70 mg/kg SMCA. These doses are

thought to slightly underestimate the actual concentration as they were based on estimated rumeno-reticulum contents and in addition the rapid degradation of the substance was not taken into account.

No data on the ecotoxicity of MCAA/SMCA to other terrestrial organisms were found in the literature.

5.3.3 Plant toxicity

SMCA is a non-selective herbicide.

5.4 EVALUATION

Due to the necessity of evaluating environmentally-realistic conditions, effects evoked by the pH have not been taken into account in the evaluation despite the reliability category. Algae is the most sensitive aquatic group. The lowest observed 72-hour E_bC_{50} is 0.025 mg/l for *Scenedesmus subspicatus*, and the lowest chronic value is a 72-hour NOEC of 0.0058 mg/l. The toxicity of MCAA/SMCA to aquatic fauna and micro-organisms is low. In acute studies the most sensitive species has been shown to be the protozoan (*Tetrahymena pyriformis)* with an 9-hour IC_{50} of 83 mg/l. In chronic studies *Vibrio fischeri* had the highest sensitivity with a 22-hour NOEC of 10 mg/l. The few data available indicate a significant toxicity for terrestrial organisms based on accidental exposure and an oral LD_{50} of 75 mg/kg SMCA for geese.

6. HUMAN EXPOSURE LEVELS AND OCCUPATIONAL EXPOSURE STANDARDS

6.1 NON-OCCUPATIONAL EXPOSURE

Chlorinated drinking water is the main source of human exposure to MCAA and other chloroacetic acids (DCAA and TCAA) via the environment (Table 10). However, given the low rate of metabolism of DCAA and TCAA to MCAA (Larson and Bull, 1992), their contribution to MCAA exposure seems negligible.

Table 10 : Chloroacetic acids in drinking water

Country	# samples and origin of drinking water	Conc (µg/l)			Reference
		MCAA	DCAA	TCAA	
USA	2 (reservoir)	not reported	63-133	34-160	Uden and Miller, 1983
USA	35 (not specified)	<1-1.2	5.0-7.3	4.0-6.0	Krasner *et al, 1*989
USA	35 (not specified)	not detected	Total haloacetic acids (mainly DCAA and TCAA) mean: 17.3, range: 0.30-60.6		Nieminski *et al*, 1993
Australia	16 (15 surface, 1 ground water)	26-124 [1)]	1-41	<0.02-14	Simpson and Hayes, 1998
Netherland	23 (surface water)	not reported	0.2-3.0	0.1-1.4	Versteegh *et al*, 1990
France	15 (surface water)	not reported	0.8-13.3	0.8-11.6	Benanou *et al*, 1998
France	2 (water from dams)	not reported	50 and 62	8	Benanou *et al*, 1998
France	3 (ground water)	not reported	< 0.2	<0.1-0.1	Benanou *et al*, 1998

1) lowest and highest mean reported values

Relatively high MCAA concentrations can occasionally occur in drinking water, due to changes in the concentration and nature of dissolved organic material in the raw water supply, or to variations in the water-treatment process. The highest concentration that has been reported is 244 µg/l MCAA in drinking water in Australia (Simpson and Hayes, 1998). Such trace amounts of MCAA are of no particular concern in the context of human health according to the available toxicological data (see Section 9).

6.2 OCCUPATIONAL EXPOSURE

6.2.1 Skin

In industries producing or using MCAA, dermal exposure to liquid MCAA is accidental, resulting mainly from minor splashes. However, fatal intoxications have been reported after contamination of more than 10% of the body surface (see Section 10). After skin contamination there are difficulties in quantifying the relationship between the degree of exposure and MCAA in blood because of inherent uncertainties in estimating the amount of MCAA that has been absorbed.

There is a possibility of skin exposure to SMCA during the general handling of the product and in particular when manually opening and emptying bags of SMCA.

6.2.2 Inhalation

Inhalation exposure to MCAA may occur as vapour (maximum vapour concentration at saturation: 0.33 mg/l at 20°C), aerosol (from melts and aqueous solutions), dust, or a combination of all three. Exposure to SMCA may occur as dust or as an aerosol from solutions.

No exposure data are available in the published/open literature; Table 11 is a compilation of internal, industry data. So far as can be derived from the data, overall exposure is generally less than 1 mg/m^3.

Table 11: Occupational exposure monitoring results

Industrial category and/or activity	Year	Method	N	TWA or STV	Range (mg/m^3)	Mean (mg/m^3)
Operator during incident	1966	ns	1	STV, ns	15	
Production operators	1989	ns	ns	TWA		0.93
Technicians	1989	ns	ns	TWA		0.58
Lab technician	1989	ns	1	TWA	0.85	
Maintenance	1989	ns	ns	STV, ns		2
Not specified	1989	ns	4	TWA-4	0.5-1.6	0.8
Production: chlorination area	1990	PAS, ns	3	TWA		0.57
Production: chlorination area	1990	PAS, ns	1	STV	1.39	
Production: crystallisation area	1990	PAS, ns	2	TWA-8		2.47
Production: packaging area	1990	PAS, ns	2	TWA-8		0.35
Operators	1994	PAS *	23	TWA 5.5-7.5	nd (< 0.3)	
Warehouse men	1994	PAS *	2	TWA	nd (<0.3)	
Maintenance (shutdown)	1995	PAS, ns	ns	TWA	0.035-0.91	
Operators: control room	1995	PAS, ns	4	ns	<0.01-0.022	
Operator: doing rounds	1995	PAS, ns	8	ns	<0.01-7.9	
Operators: crop protection chemicals factory	1995	PAS, ns	3	TWA		<2
Maintenance	1995	ns	1	TWA	0.005	
Production: chlorination area	1995	PAS, ns	3	TWA-8		0.57
Production: crystallisation area	1995	PAS, ns	2	TWA-8		0.36
Operators: control room doing rounds	1996	PAS, ns	ns	TWA-8	<0.01	
Operator unloading MCAA	1996	PAS, ns	1	TWA-8	0.28	
Maintenance operator	1996	PAS, ns	1	TWA-8	0.13	
“Production”	1997	ns	10	TWA	0.005-0.823	
“Packaging”	1997	ns	4	TWA	0.005-0.293	
Not specified	1997	ns	2	TWA-7	<0.2	

PAS personal air sampling
TWA Time-Weighted Average
STV Short-Term Value
* method fully described
ns not specified
nd not detectable
N number of sample

6.3 OCCUPATIONAL EXPOSURE STANDARDS

Some countries have established occupational exposure standards. Examples of these are given below:

Country	Long-term exposure limit 8-h TWA	Short-term exposure limit 15-min-STEL	Skin Notation	Reference
UK	1.2 mg/m^3 (0.3 ppm)		Yes	HSE, 1998
NL	4 mg/m^3 (1 ppm)			SZW, 1996
S	4 mg/m^3 (1 ppm)	8 mg/m^3 (2 ppm)	Yes	AFS, 1993
USA	1 mg/m^3 (0.3 ppm)	4 mg/m^3 (1 ppm)	Yes	AIHA, 1984
D	The MAK-committee has proposed classifying MCAA as IIB (insufficient data to establish a MAK value) (Deutsche Forschungsgemeinschaft, 1997).			

6.4. EVALUATION

Exposure of the general population to MCAA is mainly through trace amounts in chlorinated drinking water. Industrial exposure is limited to a small group of workers. Dermal exposure is mainly incidental, while occupational inhalation exposure, so far as it can be derived from the available data, is generally less than 1 mg/m^3.

7. TOXICOKINETICS AND METABOLISM

7.1 ABSORPTION, DISTRIBUTION AND ELIMINATION

7.1.1 Human data

In a laboratory accident, a worker's fingers were contaminated with hot [^{14}C]-MCAA (estimated dose 200-1600 rad); the hands were washed within one minute of the accident. The degree of skin contamination fell from 10,000 βs/cm^2/sec immediately after contamination to zero within 10 days. A rapidly-excreted substance, which appeared to be mainly unchanged MCAA was found in the urine (half-life ~15 hours). In the slow phase (no information on half-life) the MCAA reacted with cysteine, glutathione or protein and was excreted in the urine (~ 330 µCi, ≅0.002 ml labelled MCAA). A similar amount of radioactivity was eliminated as carbon dioxide. Less than 20% of the radioactivity was found in the erythrocytes and about 80% in the plasma, 17.5 hours after the accident. After 6 days, only a small amount (0.16 µCi/ml) was detected in the blood (Dancer *et al*, 1965).

The levels of MCAA found in serum following accidental skin contamination are presented in Section 10.1.1.

7.1.2 Animal data

7.1.2.1 Oral administration

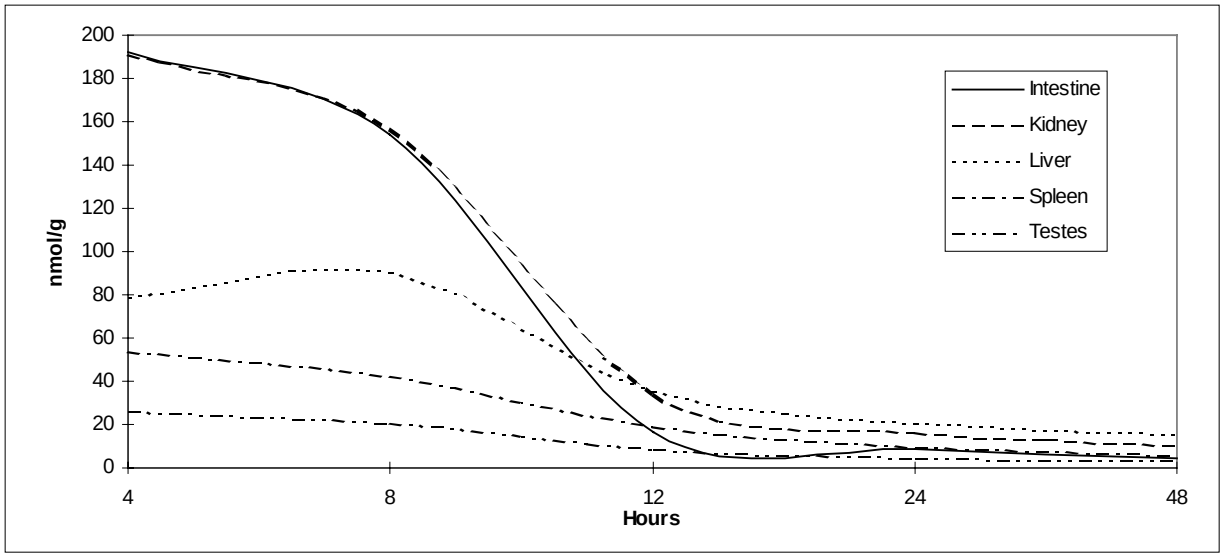
The data summarised in Table 12 indicate that MCAA is rapidly and extensively absorbed by the oral route. It is rapidly eliminated from the body with a half-life not exceeding 12 hours in non-nervous tissues and 26 hours in the CNS. MCAA-equivalent is excreted in the urine mainly during the first 24 hours.

Table 12: Excretion data following MCAA administration to rats and mice

Species	Exposure conditions	t½ (h)	Cumulative excretion of MCAA-equivalent in urine	Reference
Sprague-Dawley rats	single oral dose of 9.4 mg/kg[1-^{14}C]-MCAA	-	90% in 24h	Kaphalia *et al*, 1992
Sprague-Dawley rats	single oral dose of 0.06 mg/kg [1-^{14}C]-MCAA	7.7 (plasma) 2.2 (liver) 3.3 (kidney) 4.4 (testis) 4.0 (stomach) 9.0 (brainstem) 6.8 (hypothalamus) 21.0 (cerebellum) 13.5 (cerebral cortex)	51% in 24h 52.5% in 72h	Berardi, 1986
Swiss-Webster mice	single oral dose of 0.6, 150 or 250 mg/kg [1-^{14}C]-MCAA	1.3-1.5 (plasma) 0.4-1.9 (liver) 1.3-2.0 (kidney) 8.2-12.0 (testis) 0.4-0.5 (stomach) 15.0-19.0 (brainstem) 14.4-20.0 (hypothalamus) 24.0-26.0 (cerebellum) 14.0-17.0 (cerebral cortex)	32.0-59.3% in 24h 33.7-60.8% in 72h	

As shown in Figure 2, the distribution of [^{14}C]-label in different tissues also suggests that the MCAA is rapidly absorbed and eliminated from the body. The elimination phase appears to be fast for intestine and kidney as compared to other tissues. Maximum radioactivity was detected in intestine and kidney at 4 and 8 hours after treatment, followed by liver, spleen, testes, lung, brain and heart in decreasing order.

Figure 2: Distribution of [^{14}C]-MCAA in rat tissues



Sprague-Dawley rats were sacrificed at 4, 8, 12, 24 and 48 hours following a single oral dose 9.4 mg/kg [1-^{14}C]-MCAA by gavage (Kaphalia *et al*, 1992).

The distribution pattern of [1-^{14}C]-MCAA was studied after oral administration to Swiss-Webster mice at dose levels of 0.6, 150, and 250 mg/kg and in Sprague-Dawley rats at the dose level of 0.06 mg/kg. The results summarised in Table 13 indicate that the toxicokinetic properties of MCAA are dose-dependent. The highest maximum concentrations were seen in liver and kidney in both species, and also in spleen in mice. Much lower concentrations were observed in lung, heart, testis, and plasma. At 150 and 250 mg/kg, the maximum concentrations in the brain areas of mice were very close to the plasma concentration (Berardi, 1986).

Table 13: Maximum concentration of [1-^{14}C]-MCAA equivalents in rat and mouse brain and other tissues*

	Rat 0.06 mg/kg		Mouse 0.6 mg/kg		Mouse 150 mg/kg		Mouse 250 mg/kg	
Tissue/brain area	C_{max} (pmole/g)	t_{max} (h)	C_{max} (nmole/g)	t_{max} (h)	C_{max} (nmole/g)	t_{max} (h)	C_{max} (nmole/g)	t_{max} (h)
Hypothalamus	-	-	0.4 ± 0.1	4	687 ± 79	2	797 ± 322	1
Brainstem	-	-	0.3 ± 0.05	2	601 ± 61	2	690 ± 253	1
Cerebellum	-	-	0.3 ± 0.4	16	717 ± 65	2	905 ± 79	8
Cerebral cortex	-	-	0.2 ± 0.1	1	569 ± 103	2	632 ± 215	1
Rest of brain	-	-	0.2 ± 0.3	16	608 ± 112	2	734 ± 313	1
Plasma	179.4 ± 20.3	1	1.2 ± 0.2	1	703 ± 141	0.5	915 ± 296	0.5
Liver	3537.7 ± 874.9	2	23.2 ± 7.6	0.5	3137 ± 624	0.5	5645 ± 1811	1
Kidney	6414.1 ± 955.6	2	11.5 ± 3.1	1	2192 ± 753	1	2873 ± 582	1
Lung	203.9 ± 67.4	4	2.0 ± 0.5	1	762 ± 185	0.5	971 ± 225	1
Heart	110.2 ± 20.9	2	1.9 ± 0.9	0.5	630 ± 95	0.5	800 ± 275	1
Spleen	456.3 ± 75.6	2	4.7 ± 1.0	1	2805 ± 1399	1	4292 ± 1161	1
Testis	371.3 ± 79.7	2	1.7 ± 0.2	2	847 ± 220	2	1010 ± 236	8
Stomach	5073.0 ± 1423.9	0.5	20.7 ± 15.3	0.5	13249 ± 4990	1	24531 ± 6532	1
Duodenum	8172.4 ± 3234.1	0.5	28.5 ± 18.5	0.5	3037 ± 952	1	5841 ± 3538	1

* Berardi, 1986

A dose of 94 mg/kg [1-^{14}C]-MCAA was administered for 3 days and the rats were sacrificed 24 hours after the last dose to evaluate the bioaccumulating properties of MCAA and/or its metabolites in the tissues. The accumulation of [^{14}C]-label was less than expected. [^{14}C]-label determined in the dialysed plasma suggests an *in vivo* binding of [^{14}C]-label to plasma proteins where albumin accounted for about 65% as determined by affinity chromatography (Kaphalia *et al*, 1992).

7.1.2.2 Dermal administration

Pre-treatment of the skin of mice 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 solution (Berardi, 1986). These studies indicate that skin penetration is dependent on corrosivity rather than temperature.

7.1.2.3 Parenteral administration

Female albino mice received ip injections of [1-^{14}C]-MCAA with an activity of 2-4 mCi at doses of 70, 90 and 100 mg/kg. The amount of [^{14}C]-label in the urine, expired air and faeces was determined after 24, 48 and 72 hours. Within 72 hours, 82-88% had been recovered in the urine, 8% in the expired air and 0.2-0.3% in the faeces (which were contaminated with urine). The amount remaining in the body was 2-3% (Yllner, 1971).

The maximum plasma concentration was detected after 32 minutes following a sc injection of 53 mg/kg [2-^{14}C]-MCAA to Sprague Dawley rats. From the 2-phase elimination curve, the plasma half-life for the fast and slow phase was respectively 90 and 500 minutes. Approximately 50% of the administered radioactivity was excreted in the urine within 17 hours (Hayes *et al*, 1973).

Two hours after sc injection of 162 mg/kg [2-^{14}C]-MCAA to groups of 3 Sprague-Dawley rats, higher levels of radioactivity were measured in the liver and kidneys than in the plasma, while the levels in the heart and the brain were comparable with plasma levels. Subcutaneous injection of 53 mg/kg led to a similar distribution (Hayes *et al*, 1973).

Male Sprague-Dawley rats were injected in the tail vein with a tracer dose of 68 µg/kg [1-^{14}C]-MCAA. After 5 minutes and after 1, 4, 12, 24 and 48 hours, 3 rats at each time interval were sacrificed and subjected to whole-body autoradiography. At 5 minutes there was evidence of a rapid distribution of radioactivity to the liver, kidney cortex, stomach wall, salivary and tear glands, oesophagus, tracheal tissues, pancreas and certain ganglia of the peripheral nervous system and some accumulation in the brain. The radioactivity disappeared rapidly from the blood circulation. One hour after the administration of [1-^{14}C]-MCAA, the radioactivity was extensively excreted into the small intestine, the kidney contents and the urinary bladder. A high level of radioactivity was observed in the brain, spinal cord, thymus gland, myocardial tissue, salivary glands and tongue. After 4 hours, the liver and various other tissues

began to eliminate the radioactivity, while the brain (in particular the cerebellum), the spinal cord, the thymus and the pancreas had accumulated more radioactivity, and still continued to do so after 48 hours. These results support an early distribution of MCAA and/or its metabolites in hydrophilic tissues, and subsequent distribution in lipophilic tissues (Bhat *et al*, 1990).

7.2 BIOTRANSFORMATION

There are 2 different pathways for the breakdown of monochloroacetate in the organism (Figure 3). The main route is the formation of S-carboxymethyl glutathione and subsequently S-carboxymethyl cysteine (S-CMC), which is then metabolised to thiodiacetic acid (TDA). The second, less important metabolic pathway, is enzymatic hydrolysis of the C-CI bond, with subsequent formation of glycolic acid, which is mainly oxidised to CO_2. These metabolic pathways are inferred from the following studies:

- Following ip injections of [1-^{14}C]-MCAA to female albino mice, the 2 major 24-hour urinary metabolites were S-CMC (33-43% as the free compound and 1-6% conjugated) and TDA (33-42%). Also detected were monochloroacetate (6-22%), glycolic acid (3-5%) and oxalic acid (OA) (0.1-0.2%) (estimated by isotopic dilution analysis) (Yllner, 1971).
- After oral administration of 50 mg/kg non-labelled MCAA to 2 Wistar rats, TDA was identified as the major urinary metabolite, accounting for 61% of the administered dose after 24 hours (Green and Hathway, 1975).
- In mice, 30-40% of an oral dose of 100 mg/kg [^{14}C]-MCAA was excreted as TDA compared with 90% resulting from a comparable dose in rats. Most of the remainder of the dose in both species was accountable as N-acetyl-S-CMC (Jones and Hathway, 1978).
- Following a single oral dose of 250 mg/kg of [1-^{14}C]-MCAA to mice, 67% of the 24-hour urinary metabolite was S-CMC, 28% TDA, and 5% OA (Berardi, 1986).
- Five major metabolites (Table 14), namely S-CMC, monochloroacetate, OA, TDA, and an unknown metabolite, were identified in the plasma and cerebrospinal fluid (CSF) of Sprague-Dawley rats 75 minutes after treatment with [1-^{14}C]-MCAA (80 mg/kg, iv) (Mitroka, 1989).

Table 14: Radioactive metabolites in rat plasma and cerebrospinal fluid *

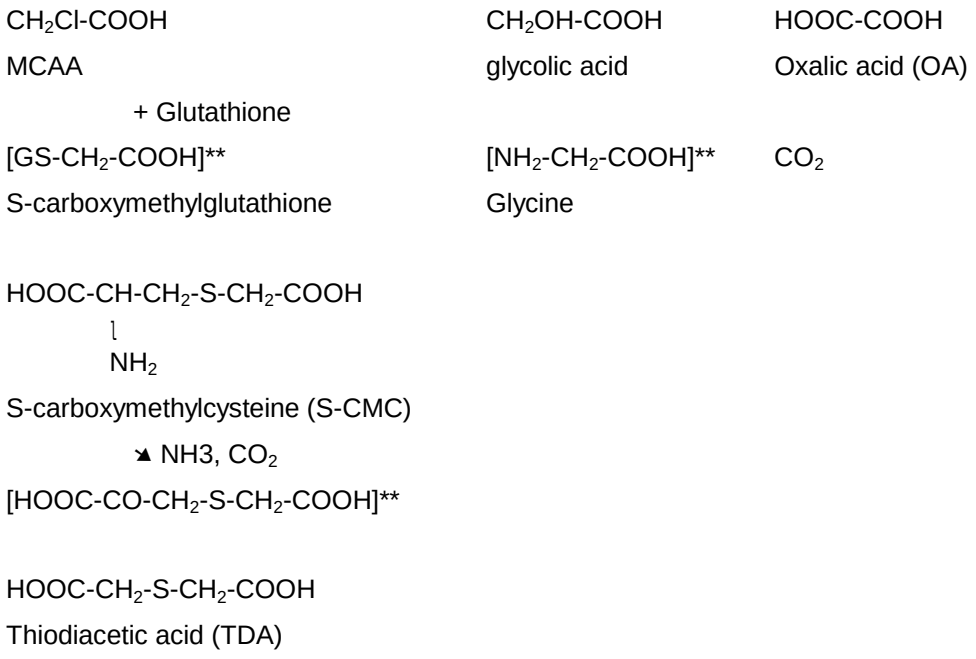
Radioactive Metabolite	Plasma (µmol/l) **	CSF (µmol/l) **
S-CMC	132 ± 16	7 ± 2
Unknown	8 ± 1	33 ± 6
MCAA	969 ± 97	1180 ± 117
OA	47 ± 10	13 ± 1
TDA	32 ± 7	12 ± 2
Total radioactivity	1453 ± 169	1069 ± 100†

* Mitroka, 1989

** 75 min after 80 mg/kg [1-^{14}C]-MCAA iv

† total radioactivity in brain expressed in µmol/kg

Figure 3: Suggested Metabolic Pathways of MCAA in the Mouse*



* Yllner, 1971, and Mitroka, 1989

** The compounds in brackets were not isolated

In vitro, MCAA inhibits rat liver glutathione-S-transferase by direct binding (Dierickx, 1984).

7.3 EVALUATION

MCAA is rapidly and extensively absorbed by all routes of administration; skin lesions due to corrosivity facilitate the entry of MCAA through the skin. MCAA and/or its metabolites are initially distributed in lipid-poor tissues (liver, kidney, stomach) and subsequently in lipid-rich tissues (brain, spinal cord, thymus, pancreas). MCAA is excreted unchanged in the urine in a fast elimination phase (t½ = 90 minutes in rat after sc injection) and is bound to glutathione, cysteine or protein or is eliminated as carbon dioxide in a slow phase (t½ = 500 minutes). In rats after oral administration, about 90% of the radioactivity is excreted in the urine after 24 hours. In humans, after contamination of the skin with ^{14}C-MCAA, a half-life of about 15 hours has been found for the rapid excretion of MCAA in the urine. MCAA is metabolised in mice and rats to TDA (via S-carboxymethyl glutathione and S-CMC) and, to a lesser extent, to glycolic acid and $C0_2$ (after enzymatic hydrolysis of the C-Cl bond).

8. BIOCHEMICAL AND PATHOPHYSIOLOGICAL MECHANISMS OF ACUTE MCAA INTOXICATION

These aspects have been reviewed in detail in an ECETOC document (1999).

8.1 INDUCTION OF LACTIC ACIDOSIS BY MCAA IN EXPERIMENTAL ANIMALS

Blood and cerebral lactic acidosis were observed in rodents dying of MCAA intoxication (Mitroka, 1989; Elf Atochem, 1995c). After iv injection of 40 or 80 mg/kg MCAA (as sodium salt) to rats, blood and CSF lactate concentrations increased progressively with time until death (see Section 9.1.4 and Table 18). CSF lactate levels were consistently higher and increased earlier than blood levels. Clinical signs of toxicity and mortality developed in direct relation to the increase of CSF lactate level.

Accumulation of lactate in the brain is primarily a consequence of the low capacity of the blood-brain barrier for the removal of lactate and there is no known transport mechanism that would accumulate lactate in the brain against this concentration gradient. Therefore, it is likely that the lactate accumulation in the brain is secondary to *in situ* pyruvate formation.

8.2 BIOCHEMICAL BASIS OF MCAA TOXICITY

Prolonged incubation of isolated rat heart mitochondria with monochloroacetate inhibits both pyruvate-dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (α-KGDH) enzyme complexes (van Hinsbergh and Vermeer, 1994), via an indirect inhibition through formation of oxalate from MCAA (Mitroka, 1989), or a direct inhibition through slow alkylation of sulfhydryl groups (van Hinsbergh and Vermeer, 1994).

Since the combined inhibition of PDH and α KGDH has a major impact on cellular energy production, the cell would then revert to anaerobic glycolysis, which results in lactate accumulation (van Hinsbergh, 1994).

Unpublished *in vitro* experiments with human endothelial cells have shown that monochloroacetate leads to a peculiar pattern of cell death, with a total cessation of cell protein synthesis secondary to a block in ATP synthesis (van Hinsbergh, 1992). This process could not be halted or ameliorated by giving intermediates of the Krebs cycle or by replenishing the product of pyruvate oxidation, acetyl-CoA, i.e ethanol, acetate or acetyl-L-carnitine (van Hinsbergh, 1991). This indicates that a block of the citric acid cycle at the aconitase level, similar to the mechanism of fluoroacetate poisoning, is unlikely to play a major role in the mechanism of toxicity of MCAA.

8.3 PATHOPHYSIOLOGICAL EFFECTS OF MCAA INTOXICATION

The time course and pattern of MCAA intoxication in man (see Section 10) is similar to that in most other species, including rodents, cattle and birds. The pattern of distribution found in rodents shows an initial fast distribution in lipid-poor tissues, followed by a slow but sustained uptake in lipid-rich tissue, notably the brain (see Section 7). This distribution pattern, followed by the slow development of the lactic acidosis, may explain the lag time between skin contamination and the appearance of the first CNS symptoms in man and animals. While cerebral or CSF lactate acidosis has not been demonstrated in man, systemic metabolic acidosis was found in several victims (see Section 10). Also, *in vitro* the effects of MCAA are much more evident in human endothelial cells than in other cells, e.g. liver, and this is consistent with the evidence of microvascular damage in the brain (Mitroka, 1989). Overall, it seems reasonable to assume that in man, as in rodents, cerebral lactic acidosis is the main cause of lethality.

9. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

9.1 ACUTE TOXICITY

9.1.1 Oral

In acute oral toxicity studies in which MCAA was dosed orally as a solution in water, the LD_{50} ranged from 55-200 mg/kg in rats (Maksimov and Dubinina, 1974; Pasquet and Mazuret, 1975; Hoechst, 1979a; Berardi, 1986) and was 260 mg/kg in mice (Berardi, 1986). High concentrations of MCAA caused severe burns to the stomach and this would contribute to the toxicity.

In most acute oral studies the MCAA solution was neutralised with NaOH or Na_2CO_3 to yield SMCA. The oral LD_{50} values for SMCA ranged from 76.2-580 mg/kg in rats (Woodard *et al*, 1941; Maksimov and Dubinina, 1974; Dubinina and Maksimov, 1976; Babanov *et al*, 1984), 165-415 mg/kg in mice (Woodard *et al,* 1941; Morrison, 1946; Babanov *et al*, 1984), and were 79.8 and 90 mg/kg in the guinea pig and rabbit, respectively (Woodard *et al*, 1941). The lower values may be due to the presence of some free acid in an incompletely neutralised solution of MCAA.

In general, clinical signs included body-weight loss, hypoactivity, dyspnea, tremor, convulsion, and cyanosis. Observation of the MCAA-surviving mice revealed that 20% of these animals exhibit some effects on front paw function, and 10% had clasping of the front paws (Berardi, 1986). These effects were attributed to histologically-demonstrated damage to the Purkinje cells, which has not been observed in other species.

Details of the acute oral toxicity studies cited above are provided in Table 15.

9.1.2 Dermal

MCAA is easily absorbed through the skin. The resulting mortality rate is dependent on the form and concentration used.

When tested as a 40-50% solution in water, the LD_{50} ranged from 305-800 mg/kg in rats (Pasquet and Mazuret, 1975; Hoechst, 1979c) and was 250 mg/kg in rabbits (Hoechst, 1979b); no mortality was reported in rats at 400 mg/kg with a 5% solution (Hoechst, 1979c).

When tested in the molten form, doses of 350 mg/kg and 660 mg/kg MCAA were lethal in rabbits when applied respectively for 15 minutes on 3% body surface or for 1 minutes on 5% body surface (Hercules, 1969a). A dose of 3560 mg/kg was lethal when applied for 15 minutes on 20% body surface of one dog (Hercules, 1969a). An LD_{50} of 490 mg/kg was reported in mice after a 3-minute exposure (Berardi, 1986).

The dermal LD_{50} in rabbits for solid MCAA under occlusive patch test was 178 mg/kg, and was greater than 200 mg/kg under semi-occlusive patch (Hercules, 1969b).

Apart from possible skin irritation/corrosion effects, the clinical signs of toxicity induced by MCAA were in all cases similar after dermal and oral exposure.

No decrease in the mortality rate was observed in rabbits when molten MCAA was washed off with sodium bicarbonate 1 minute after exposure (Hercules, 1969a). In rats, rinsing the exposed site with a 5% sodium bicarbonate solution, or application of sodium bicarbonate paste after a water rinse did not alter the mortality rate induced by molten MCAA or aqueous MCAA solutions (Berardi, 1986).

No mortality was observed in rats with a dermal dose of 2000 mg/kg SMCA (Hoechst, 1988a).

Details of the dermal studies cited above are provided in Table 16.

9.1.3 Inhalation

In a poorly-reported Russian study, an inhalation LC_{50} of 180 mg/m^3 was found in rats exposed to a condensed aerosol generated by heating MCAA at 95°C. Most of the deaths occurred within the first 24 hours. No mortality was observed at a vapour concentration of 5 mg/m^3 (Russian occupational exposure limit); the first signs of irritation and adverse effects appeared at 23.7 mg/m^3 and 93.6 mg/m^3 (aerosols) (Maksimov and Dubinina, 1974). No data on the exposure duration were included.

Inhalation for up to 10 minutes of MCAA-saturated vapour generated at 75°C (nominal concentration 27-31 mg/l) induced signs of ocular and respiratory tract irritation but no mortality in rats, mice or guinea-pigs (Hercules, 1969c and 1969d).

Details of the inhalation studies cited above are provided in Table 17.

9.1.4 Parenteral Routes

Parenteral routes of dosing yielded LD_{50} values comparable to those found when MCAA was given orally (Le Poidevin, 1965; Hayes *et al,* 1973; Bakishev, 1978; Hoechst, 1979d; Berardi, 1986; Elf Atochem, 1989 and 1995b).

Severe blood and cerebral lactic acidosis were observed in rats after MCAA intoxication by the iv route (Mitroka, 1989; Elf Atochem, 1995c). Clinical signs of toxicity and mortality were directly related to the increase in CSF lactate levels.

Details of the parenteral studies cited above are provided in Table 18.

9.1.5 Evaluation

MCAA was toxic in experimental animals by the oral and parenteral routes of administration, and could be absorbed rapidly through the skin in toxic and lethal amounts. SMCA (or neutralised MCAA) was not absorbed dermally but was of comparable toxicity to MCAA once in the body. Inhalation exposure to MCAA saturated vapour atmosphere for a few minutes induced respiratory tract irritation but no mortality in rats, mice or guinea pigs. The clinical signs of toxicity, which involved mainly the CNS, and mortality developed concurrently to a severe blood and CSF lactic acidosis.

Table 15: Acute oral toxicity data

Species	Exposure conditions	Result	Clinical signs	Reference	CoR‡
Rat (Wistar, 10/dose)	MCAA 1% in water	LD_{50} = 90.4 (73.6-112.0) mg/kg	apathy, disorders of balance, lacrimation, piloerection, excessively open eyes, prone position, squatting posture	Hoechst, 1979a	2e
Rat (SD, 4/dose)	MCAA in water (pH 1.2)	LD_{50} = 102 (51-204) mg/kg	CNS effects, death 1- 4h after MCAA administration	Berardi, 1986	2e
Rat (CD, 4/dose)	MCAA 6% in water	LD_{50} ~ 200 mg/kg	hypoactivity, dyspnea, cyanosis	Pasquet and Mazuret, 1975	3b
Rat (no details available)	MCAA 10% in water	LD_{50} = 55 (40.4-74.8) mg/kg	not reported	Maksimov and Dubinina, 1974	4d
Rat (5-20/dose)	MCAA soln neutralised with NaOH (pH 6-7)	LD_{50} = 76.2 (70.7-82.2) mg/kg	apathy, weight loss	Woodard *et al*, 1941	2e
Rat (no details available)	MCAA soln neutralised, no details available	LD_{50} = 580 (513-655) mg/kg	not reported	Maksimov and Dubinina, 1974	4d
Rat (no details available)	SMCA, no additional data available	LD_{50} = 410 mg/kg	not reported	Babanov *et al*, 1984	4a

‡ See Page i and Appendix for explanation

Table 15 (continued): Acute oral toxicity data

Species	Exposure conditions	Result	Clinical signs	Reference	CoR‡
Mouse (Swiss-Webster, 8-10/dose)	MCAA in water (pH 1.2)	LD_{50} = 260 (214-316) mg/kg	immobility, head bobbing, ataxia, hyperreactivity to stimuli, slight tremors, clasping of front paws, laboured respiration, death 3-6h after MCAA administration	Berardi, 1986	2e
Mouse (10/dose)	MCAA soln neutralised with NaOH (pH 6-7)	LD_{50} = 255 (196-334) mg/kg	apathy, weight loss	Woodard *et al*, 1941	2e
Mouse (no details available)	MCAA 5% soln neutralised with Na_2CO_3 (pH 7)	LD_{50} = 165 mg/kg	not reported	Morrison, 1946	3a
Mouse (no details available)	SMCA, no additional details available	LD_{50} = 415 mg/kg	not reported	Babanov *et al*, 1984	4a
Hamster (no details available)	no details available	LD_{50} = 430 (338-654) mg/kg	not reported	Dubinina and Maksimov, 1976	4d
Guinea pig (10/dose)	MCAA soln neutralised with NaOH (pH 6-7)	LD_{50} = 79.8 (71.8-88.6) mg/kg	apathy, weight loss	Woodard *et al*, 1941	2e
Rabbit (1-10/dose)	MCAA soln neutralised with NaOH (pH 6-7)	$LD_{50} \approx$ 90 mg/kg	apathy, weight loss	Woodard *et al*, 1941	2e

‡ see Page i and Appendix for explanation

Table 16: Acute dermal toxicity data

Species	Exposure conditions	Result	Clinical signs	Reference	CoR‡
Rat (Wistar, 6/dose)	MCAA 5% in water	no mortality at 400 mg/kg	apathy, lacrimation, piloerection, excessively open eyes, prone position, panting, miosis	Hoechst, 1979c	2e
Rat (Wistar, 6/dose))	MCAA 40% in water	LD_{50} = 305 (242-384) mg/kg	apathy, lacrimation, piloerection, excessively open eyes, prone position, panting, miosis	Hoechst, 1979c	2e
Rat (CD, 4/dose)	MCAA in water (up to 50%)	LD_{50} ~ 800 mg/kg	hypoactivity, dyspnea, cyanosis, skin corrosion	Pasquet and Mazuret, 1975	3b
Rat (Wistar, 10/dose)	SMCA mixed with 0.9% NaCl soln	LD_{50} >2,000 mg/kg	decreased activity, squatting posture, flanks hollow, stitled and staggering gait, irregular respiration, moist rales, diarrhoea	Hoechst, 1988a	1a
Rabbit (2/dose)	1- or 15-min contact of molten (60°C) MCAA on 1-4% of body surface then washing with soap and water	lethal when applied on 3% (0.26 ml/kg) body surface for 15 min or on 5% (0.48 ml/kg) body surface for 1 min	hypoactivity, dyspnea, prostration, skin necrosis	Hercules, 1969a	2e
Rabbit (2/dose)	1-min contact with molten (60°C) MCAA on 5-40% of the body surface then treatment with sodium bicarbonate (no details available on the procedure of treatment)	lethal when applied on 5% (0.47 ml/kg) body surface	not reported	Hercules, 1969a	2e

‡ see Page i and Appendix for explanation

Table 16 (continued): Acute dermal toxicity data

Species	Exposure conditions	Result	Clinical signs	Reference	CoR‡
Rabbit (10/dose)	200 mg/kg solid MCAA under semi-occlusive patch	2/10 rabbits died	not reported	Hercules, 1969b	2e
Rabbit (2/dose)	solid MCAA under occlusive patch	LD_{50} = 178 mg/kg	hypoactivity, skin necrosis	Hercules, 1969b	3b
Rabbit (6/dose)	MCAA 50% soln in NaCl 0.9%	LD_{50} ~ 250 mg/kg	apathy, disorders of balance, hyporeflexia, lacrimation, prone position, increased respiratory rate	Hoechst, 1979b	2e
Mouse (Swiss-Webster, 7-8/dose)	3-min contact with molten (65°C) MCAA then 2-min rinsing with water	LD_{50} = 490 (428-562) mg/kg	not reported	Berardi, 1986	2e
Dog (one)	15-min contact with molten (60°C) MCAA on 20% (3560 mg/kg) of body surface	lethal	not reported	Hercules, 1969a	2e

‡ see Page i and Appendix for explanation

Table 17: Acute inhalation toxicity data

Species	Exposure conditions	Result	Clinical signs	Reference	CoR‡
Rat, mouse, guinea-pig (3 of each)	MCAA saturated vapour at 75°C, 3-, 5-, or 10-min exposure	no mortality at 27 mg/l (nominal conc.)	nasal discharge, lung hyperaemia	Hercules, 1969c	2e
Rat, mouse, guinea-pig (2 of each)	MCAA saturated vapour at 75°C, 1-min exposure	no mortality at 31 mg/l (nominal conc.)	mild lacrimation, nasal discharge, dyspnea	Hercules, 1969d	2e
Rat (no details available)	MCAA aerosol, duration unknown	LC_{50} = 180 (146-221) mg/m^3	not reported	Maksimov and Dubinina, 1974	4d

‡ see Page i and Appendix for explanation

Table 18: Acute parenteral toxicity data

Species	Exposure conditions	Result	Clinical signs	Reference	CoR‡
Rat (5/dose)	sc (MCAA soln in water)	LD_{50} = 108 (88-133) mg/kg (at 24h) LT_{50} (at 162 mg/kg) = 130 (112-151) min	depression, lethargy, clonic and tonic convulsions	Hayes *et al*, 1973	2e
Rat (Wistar, 10/dose)	sc (MCAA 50% soln in NaCl 0.9%)	LD_{50} = 97.4 (89.9-105.5) mg/kg	apathy, stupour, disorders of balance, hyporelexia, salivation, piloerection, excessively open eyes, miosis, prone position, squatting tremor, increased respiratory rate	Hoechst, 1979d	2e
Mouse (Swiss-Webster, 8/dose)	sc (MCAA in water, pH 1.2)	LD_{50} = 150 (129-175) mg/kg	CNS effects	Berardi 1986	2e
Mouse (Swiss-Webster, 8/dose)	sc (MCAA soln buffered, pH 7.4)	LD_{50} = 130 (105-160) mg/kg	CNS effects	Berardi 1986	2e
Rat	ip (no details available)	LD_{50} = 154 mg/kg	not reported	Bakishev, 1978	3a
Mouse	ip (MCAA neutralised with Na_2CO_3)	LD_{50} = 269 mg/kg	not reported	Le Poidevin, 1965	3b
Rat (Sprague-Dawley, 5 male/dose)	iv (MCAA 20% soln in Na_2PO_4 neutralised with NaOH, pH 7)	LD_{50} = 75 (53-117) mg/kg	hypokinesia, sedation, dyspnea, lateral decubitus, suffocation, coma, death after 1-3h	Elf Atochem, 1995b	1a

‡ See Page i and Appendix for explanation

Table 18 (continued): Acute parenteral toxicity data

Species	Exposure conditions	Result	Clinical signs	Reference	CoR‡
Rat (Sprague-Dawley	80 mg/kg iv (MCAA 20 % soln in Na_2PO_4 neutralised with NaOH, pH7)	significant increase of blood and CSF lactate levels from 60 and 35 min after treatment, respectively	hypokinesia and sedation after 30-40 min, death after 1h	Elf Atochem, 1995c	1a
Rat (Sprague-Dawley)	80 or 40 mg/kg iv (MCAA 20% soln in Na_2PO_4 neutralised with NaOH, pH7)	significant increase of the blood lactate level from 60 min after treatment with 80mg/kg, and very slight increase at 40 mg/kg significant increase of the CSF lactate levels from 60 min and at 120 min after treatment with 80 and 40 mg/kg, respectively	ataxia, death after 1-2h	Mitroka, 1989	2e
Dog (2)	iv (100 mg/kg MCAA soln in water)	lethal	vomiting after 1-3h, convulsions after 6h, death after 10-24h	Elf Atochem, 1989	2e

‡ see Page i and Appendix for explanation

9.2 SKIN, EYE, RESPIRATORY TRACT IRRITATION AND SENSITISATION

9.2.1 Skin Irritation

MCAA induced corrosion and mortality when applied to the skin of rabbits for 24 hours (Hoechst, 1979g; Pasquet and Mazuret, 1975). A 0.05% solution was reported to be the threshold concentration for local skin effects (Maksimov and Dubinina, 1974). After occlusive application for 24 hours of a 10% solution of MCAA to the intact rabbit skin there was marked hyperaemia and slight oedema (Rodionova and Ivanov, 1979).

SMCA did not induce any signs of skin irritation when applied for 4 hours to the skin of rabbits (Hoechst, 1988b).

Details of the skin irritation studies cited above are provided in Table 19.

9.2.2 Eye Irritation

MCAA was extremely irritant to the rabbit eye (Hoechst, 1979g; Pasquet and Mazuret, 1975).

SMCA induced moderate irritation in the rabbit eye (Hoechst, 1988c).

Details of the eye irritation studies cited above are provided in Table 20.

9.2.3 Respiratory Tract Irritation

In the acute inhalation toxicity studies reported in Section 9.1.3 (Table 17), mild lacrimation, nasal discharge and dyspnea were observed in rats, mice, and guinea pigs exposed for 1-10 minutes to saturated vapour of MCAA generated at 75°C (Hercules, 1969c and d).

In a 4-month inhalation study in rats and guinea pigs exposed to concentrations of 20.8 and 5.8 mg/m^3 MCAA vapour (limited documentation, e.g. no information on daily exposure duration) signs of irritation and inflammation of the respiratory tract were seen at the higher concentration (Maksimov and Dubinina, 1974).

9.2.4 Sensitisation

Skin

An open epicutaneous test in rabbits did not indicate any skin sensitising effects of MCAA (induction: 10 drops of 5% MCAA soln/d to 6 cm^2 skin , challenge: 1 drop of 0.1-50% soln on day 30) (Maksimov and Dubinina, 1974).

None of the Dunkin-Hartley guinea pigs sensitised to ethyl monochloroacetate in a maximisation assay, cross-reacted with MCAA in a subsequent challenge (Braun and van der Walle, 1987).

Respiratory Tract

No data available.

9.2.5 Evaluation

Due to its low pKa value, MCAA was corrosive to the skin and produced serious irreversible damage to the eyes. Air saturated with MCAA vapour was irritant to the respiratory tract. There was no indication from the available data of a sensitising potential.

SMCA has been classified as a skin irritant R38 (EC, 1993) although available data do not support this classification. It was mildly irritant to the rabbit eye but did not warrant classification according to the Directive (EC, 1993).

Table 19: Skin irritation data

Species	Guideline	Exposure conditions	Result	Reference	CoR‡
Rabbit (6)	FDA	occlusive application of 500 mg MCAA paste (~250 mg/kg in 0.05 ml 0.9% NaCl soln) to intact/ abraded skin for 24h	all animals died within 24h. Skin of exposed site was indurated and discoloured	Hoechst, 1979g	1b
Rabbit (6)	FDA	occlusive application of 100 mg/kg MCAA in 0.05 ml 0.9% NaCl soln (dose selected to ensure no mortality) to intact skin for 24h	severe damage and corrosion of the skin	Hoechst, 1979g	1b
Rabbit (4)	similar to FDA	occlusive application of 500 mg of crystalline MCAA to intact/abraded skin for 24h	2 animals died within 24h. Severe erythema and oedema on intact/scarified skin. Primary irritation index: 7.66/8	Pasquet and Mazuret, 1975	1b
Rabbit (3)	OECD 404	semi-occlusive application of 500 mg SMCA (mixed with 0.18 ml 0.9% NaCl) to intact skin for 4h	no signs of irritation	Hoechst, 1988b	1a

‡ see Page i and Appendix for explanation

Table 20: Eye irritation data

Species	Guideline	Exposure conditions	Result	Reference	CoR‡
Rabbits (6)	FDA	instillation of 100 mg MCAA (as paste with 0.01 ml 0.9% NaCl soln) into conjunctival sac	severe signs of irritation; eyelids and mucous membranes discoloured and corroded. Study terminated after 24h	Hoechst, 1979g	1b
Rabbit (4)	similar to FDA	instillation of 100 mg crystalline MCAA into conjunctival sac	extremely irritant (mean scores at 24+48+72h: conjunctival redness 3, chemosis 3, cornea 4, iris not evaluated due to the corneal opacity). No recovery after 7 days	Pasquet and Mazuret, 1975	1b
Rabbit (3)	OECD 405	instillation of 100 mg SMCA into conjunctival sac	moderately irritant (mean scores at 24+48+72h: conjunctival redness 2.4, chemosis 1.7, cornea 1.0, iris 0.7) Reactions reversible within 7 days	Hoechst, 1988c	1a

‡ see Page i and Appendix for explanation

9.3 REPEATED DOSE TOXICITY

9.3.1 Oral

The repeated dose toxicity of MCAA and SMCA has been evaluated in rats by gavage (Table 21A), dietary (Table 22) and drinking water administration (Table 23) and in mice by gavage (Table 21B).

Various sub-acute and sub-chronic toxicity studies have been performed according to GLP and current EPA guidelines as preliminary studies to NTP 2-year chronic/carcinogenicity studies in rats and mice. A summary of these is given below.

In 16-day toxicity studies, MCAA was administered to F344 rats (7.5-120 mg /kg/d) and B6C3F1 mice [15 (males only), 30-240 or 480 (females only) mg/kg/d]. One of 5 male rats given 120 mg/kg died during the third day of dosing. Clear nasal discharge, lacrimation, or both, were observed in all MCAA-treated rats. All mice died within 2 days following a dose of 240 mg/kg or more MCAA. Hypoactivity, piloerection, ataxia, and lacrimation were observed in mice given 240 or 480 mg/kg. No MCAA-related gross or histopathological lesions were observed in rats and mice at necropsy (NTP, 1992).

In 13-week toxicity studies, MCAA was administered by gavage to F344 rats (30-150 mg/kg) and B6C3F1 mice (25-200 mg/kg). Compound-related deaths occurred mainly during the first weeks of treatment at the 4 highest dose levels in rats and at the highest dose in mice. The mean body-weight gain of rats and mice that survived treatment was similar to that of controls. A dose-related increase in liver and kidney function blood parameters as well as in relative liver and kidney weights was observed in rats only. There was a dose-related increase in the severity and incidence of cardiomyopathy in rats. This was stated to be related to inhibition of heart mitochondrial aconitase activity but there is no evidence to support this. No compound-related lesions were observed in mice. The results indicated that F344 rats were more sensitive than B6C3F1 mice; sexes within the species were equally sensitive. The NOEL for MCAA was estimated as 30 mg/kg for rats and 100 mg/kg for mice (NTP, 1992; Bryant *et al,* 1992).

As part of the 2-year chronic/carcinogenicity studies with F344 rats (Section 9.5) interim evaluations were conducted on rats given 15 or 30 mg/kg/day after 6 and 15 months of treatment. There were no significant treatment-related differences in mean body-weight gain, haematological and clinical chemistry parameters at necropsy at either evaluation period. Changes in kidney, brain, and heart weights occurred at 6-months which were not observed at 15-months (NTP, 1992; IRDC, 1985a).

In another 13-week toxicity study, Sprague-Dawley rats were administered 15-120 mg/kg neutralised MCAA by oral gavage. MCAA clearly induced toxicity particularly in males; at 120 mg/kg/day 30% of

females and 80% of males died, most within the first 2 days of treatment. Haemorrhagic and congested lungs (possibly post-mortem changes) were seen in the early deaths (1-3 days) whereas liver lesions were observed in later deaths. In addition, there was nephrotoxicity as evidenced by changes in kidney function parameters. Hepatotoxicity was indicated by increases in liver-function parameters. Both organs showed increased organ-to-body-weight ratios. Microscopic examination revealed a significant increase in chronic nephropathy and increased splenic pigmentation at 60 mg/kg in males. The LOAEL was concluded to be 15 mg/kg/d (Daniel *et al*, 1991). However, the variations observed in clinical chemistry at 15 and 30 mg/kg/d were very slight (probably in the range of historical control data), not dose-related, observed only in one sex, and not correlated with any microscopic lesions. The findings were thus in line with the NTP 13-week study which established a NOEL of 30 mg/kg/d.

Rats given 0.1% MCAA (~ 100 mg/kg/d) in the diet for 208 days showed reduced body-weight gain and reduced activity; doses up to 0.05% (~50mg/kg/d) produced no signs of toxicity. Gross examination of organs at necropsy revealed no abnormalities. There were no treatment-related effects on liver glycogen content or oxygen consumption in the liver, kidney and skeletal muscle (Fuhrman *et al*, 1955).

The relative toxicities of MCAA, DCAA and TCAA in drinking water were compared in a study by DeAngelo *et al* (1989) in which B6C3F1 mice and Sprague-Dawley rats were exposed to concentrations of 11-32 mM MCAA (pH 6.8-7.2) for 14 days (Table 23). Body-weight gain and liver weights at necroscopy were decreased at all dose levels in treated rats but not in mice. There was no MCAA-induced hepatic peroxisome proliferation in either species. In another drinking water study, 1.9 mM MCAA (pH 7.2-7.4) was administered for 90-day to Sprague-Dawley rats. Microscopic examination revealed minimal-to-mild treatment-related changes in the liver and the lungs, characterised respectively by a slight collagen deposition and portal vein dilatation and by minimal alterations, observed as foci of perivascular inflammation, on small pulmonary veins (Bhat *et al,* 1991). These effects are considered to be of low toxicological significance and are at variance with the results of other studies of longer duration and/or using higher dose levels.

9.3.2 Inhalation

A Russian long-term inhalation study (exact duration not clearly stated, but probably 4 months) with rats and guinea-pigs at concentrations of 5.8 and 20.8 mg/m^3 showed local irritant effects at the higher dose level (Section 9.2.3). With regard to systemic effects, the lower dose level produced only some early functional changes. At 20.8 mg/m^3 there was initial body-weight loss in both species and isolated findings (e.g. reduced oxygen consumption and decreased body temperature) which appeared to be

related to depressed metabolism (Maksimov and Dubinina, 1974; CoR 4d).

9.3.3 Evaluation

The systemic effects of MCAA were observed mainly in the liver and kidney as evidenced by a dose-related increase in the weight of the organs, non-specific changes in various biochemical parameters clinically related to these organs and in related histopathological lesions. The relevance of the isolated findings of cardiomyopathy in one of the 13-week studies on rats and of the minimal alterations reported in the lungs is uncertain. The NOAEL for long-term administration is species-dependent and was estimated to be 100 mg/kg/d in mice and 30 mg/kg/d in rats. It should be noted that the threshold of mortality after repeated administrations was in the range of the acute toxicity levels.

Table 21A: Repeat dose toxicity data by gavage in rat

Species	Dose/exposure conditions	Parameters studied/results	Reference	CoR‡
F344/N rat (5/sex/dose)	0, 7.5, 15, 30, 60 and 120 mg/kg/d MCAA in distilled water for 16 d (5 d/week)	*mortality*: 1/5 males at 120 mg/kg/d on day 3 of treatment *clinical signs*: ataxia, lacrimation, bradypnea, prostration, decreased limb tone; impaired grasping reflex in rat that died *body weight gain*: slight in males at 120 mg/kg/d *organ weights* (6 organs): no effects *histopathology* (~33 organs): no effects NOAEL: 60 mg/kg/d	NTP, 1992	1a
Sprague-Dawley rat (10/sex/dose)	0, 15, 30, 60 and 120 mg/kg/d MCAA in distilled water (adjusted to pH 7.0-7.5 with NaOH) for 90 d (7 d/week)	*mortality*: 8/10 males and 3/10 females at 120 mg/kg/d, mainly during first 3 days of treatment *body weight gain*: in males at 120 mg/kg/d *food and water consumptions*: no effects *haematology*: ↑ WBC at ≥ 30 mg/kg/d and segmented neutrophils at ≥ 60 mg/kg/d in females; monocyte counts in females at 15 mg/kg/d; ↑ monocyte counts in males at 15-60 mg/kg/d *serum clinical chemistry*: ↑ BUN in females at 120 mg/kg/d and in males at 15 and 30 mg/kg/d; ↑ creatinine levels in females at 30 and 60 mg/kg/d and in males at all doses; ↑ PO_4 in females at 120 mg/kg/d; increased Ca^{++} in males at 15 and 30 mg/kg/d; ↑ ALT in females at 120 mg/kg/d and in males at 15 and 30 mg/kg/d, ↑ AST in females at 120 mg/kg/d *organ weights* (9 organs): ↑ kidney and liver weight ratios in males and females at 60 mg/kg/d, and in females at 120 mg/kg/d *histopathology* (~ 40 organs): chronic nephropathy, splenic pigmentation and clear cell foci in liver in males at 60 mg/kg/d NOAEL: < 15 mg/kg/d according to the authors, 30 mg/kg/g according to the Task Force	Daniel *et al*, 1991	1b

‡ see Page i and Appendix for explanation ↑ increased decreased

Table 21A (continued): Repeat dose toxicity data by gavage in rat

Species	Dose/exposure conditions	Parameters studied/results	Reference	CoR‡
F344/N rat (20/sex/dose)	0, 30, 60, 90, 120 and 150 mg/kg/d of MCAA in distilled water for 90 d (5 d/week). Interim sacrifice weeks 4 and 8 (5 rat/dose)	*mortality**: all at 150 mg/kg/d,majority in week 1;all at 120 mg/kg/d, majority of females in week 1 and males in weeks 1-8; all but one at 90 mg/kg/d, majority in first 2 weeks and up to week 13; 2 males and 1 female at 60 mg/kg/d on weeks 1 and 11 respectively. *clinical signs*: sialodacryoadenitis in dosed and control rats related to viral infection *body weight gain**: no effects in surviving animals *haematology:* ↑ haematocrit, Hb, and WBC in males at 150 mg/kg/d on week 4; ↑ segmented neutrophil counts in males at 90-150 mg/kg/d on week 4 and lymphocyte counts in males at 30-120 mg/kg on week 8 (both indicative of a stress reaction) *serum clinical chemistry:* ↑ BUN in males at 90-150 mg/kg/d, and in females at 60-150 mg/kg/d on weeks 4 or/and 8 (probably not due to direct toxic effect); ↑ ALT and AST in both sexes at 60, 120 and 150 mg/kg/d on week 4; cholinesterase in males at 90 mg/kg/d on week 8 and at 30 and 60 mg/kg/d on week 13, and in female at all doses on weeks 4 and 8, and at 60 mg/kg/d on week 13 (may be related to the hepatotoxicity); ↑ thyroxin (T_4) in males at 90-150 mg/kg on week 4, and at 90 mg/mg/d on week 8 *organ weights* (8 organs): heart weight in both sexes at 60 mg/kg/d and in females at 30 mg/kg/d; ↑ liver weight in both sexes at 60 mg/kg/d, ↑ kidney weight in males at 60 mg/kg/d *histopathology* (full examination): cardiomyopathy in both sexes at 60-150 mg/kg/d. No peroxisome proliferation NOAEL: 30 mg/kg/d	NTP, 1992; Bryant *et al*, 1992	1a

‡ see Page i and Appendix for explanation ↑ increased decreased

* in animals not used in the interim evaluations

Table 21A (continued): Repeat dose toxicity data by gavage in rat

Species	Dose/exposure conditions	Parameters studied/results	Reference	CoR‡
F344/N rat (10/sex/dose/ sacrifice time)	0, 15, and 30 MCAA in distilled water for 6 or 15 months (5 d/week)	*mortality*: early mortality (3/sex/dose) *clinical signs*: none *body weight gain*: no effects in surviving animals *haematology*: no effects *serum clinical chemistry*: no effects *organ weights* at 6-months: relative kidney weights in females at both doses; ↑ relative kidney weight in males at 30 mg/kg/d; absolute and relative brain weights in females at both doses, ↑ relative heart weight in females at 30 mg/kg/d. No effects at 15-months *histopathology*: no treatment-related neoplastic or non-neoplastic lesions NOAEL: 30 mg/kg/d	NTP, 1992; IRDC, 1985a	1a

‡ See Page i and Appendix for explanation ↑ increased decreased

Table 21B: Repeat dose toxicity data by gavage in mice

Species	Dose/exposure conditions	Parameters studied/results	Reference	CoR‡
B6C3F1 mouse (5/sex/dose)	0, 15 (male only), 30, 60, 120, 240 and 480 (female only) mg/kg/d MCAA in distilled water for 16d (5 d/week)	*mortality*: 5/5 females at 480 mg/kg/d on days 1 and 2; 5/5 males and females at 240 mg/kg/d on days 1 and 2; *clinical signs*: lacrimation, ataxia, hypoactivity, bradypnea, bradycardia, hypothermia, prostration, piloerection, decrease limb tone, impaired grasping reflex in mice that died *body weight* gain: no effects *organ weights* (6 organs): no effects *histopathology* (~33 organs): no effects NOAEL: 120 mg/kg/d	NTP, 1992	1a
B6C3F1 mouse (20/sex/dose)	0, 25, 50, 100, 150, and 200 mg/kg/d MCAA in distilled water for 90 d (5 d/week). Interim sacrifice on week 4 and 8 (5 mice/dose)	*mortality* *: all males, majority during week 1 and 2/10 females, during weeks 1 and 5 at 200 mg/kg/d *clinical signs*: none *body weight gain* *: in females at 200 mg/kg/d *haematology*: no effects *serum clinical chemistry*: no effects, except cholinesterase in females at 150 and 200 mg/kg/d (may be related to liver toxicity) *organ weights* (7 organs): ↑ liver weight in females at 200 mg/kg/d *histopathology* (full examination) : liver lesions in animals that died during study (attributed to metabolic derangement in moribund animals). No evidence of peroxisome proliferation NOAEL: 100 mg/kg/d	NTP, 1992; Bryant *et al*, 1992	1a

‡ see Page i and Appendix for explanation ↑ increased decreased

* in animals not used in the interim evaluations

Table 22: Repeat dose feeding toxicity data

Species	Dose/exposure conditions	Parameters studied/results	Reference	CoR‡
Slonaker-Wistar rat (6 males/dose)	0, or 0.1% MCAA for 90d	↑ liver glycogen no effect on oxygen consumption in liver, cerebral cortex, kidney cortex and skeletal muscle	Fuhrman *et al*, 1955	2e
Slonaker-Wistar rat (6 males/dose)	0, 0.005, 0.01, 0.025, 0.05 and 0.1% MCAA for 208d	*body weight gain*: at 0.1% *food consumption*: marginal ↑ at 0.05 and 0.1% *mortality*: no treatment-related effects *histopathology* (heart, liver, spleen, adrenals, kidney, lung, stomach, intestine, pancreas, thyroid, bladder, and testes): no effects NOAEL: 0.05% (~ 50 mg/kg/d)	Fuhrman *et al*, 1955	2e

‡ see Page i and Appendix for explanation ↑ increased decreased

Table 23: Repeat dose drinking water toxicity data

Species	Dose/exposure conditions	Parameters studied/results	Reference	CoR‡
Sprague-Dawley rat, and B6C3F1 mouse (5-6 males of each species/dose)	34 mM NaCl (control), or 11, 21, and 32 mM MCAA (adjusted to pH 6.8-7.2 with NaOH) for 14d	*mean daily intakes*: 265, 386 and 482 mg/kg bw/d in mice and 170, 321 and 501 mg/kg bw/d in rats at concentrations of 11, 21 and 32 mM, respectively *body weight gain*: at all doses in rats. No effects in mice *relative liver weight*: at all doses in rats. No effects in mice *peroxisome proliferation*: no effects in either species NOAEL: >170 mg/kg/d in rats = 482 mg/kg/d in mice	DeAngelo *et al*, 1989	2e
Sprague-Dawley rat (5 males/dose)	0 or 180 mg/l (1.9 mM) MCAA (adjusted to pH 7.2-7.4 with NaOH) for 90d	*mean daily intake*: ~19 mg/kg bw/d *mortality*: none *clinical signs*: not reported *body weight gain*: no effects *organ weights*: no effects on liver or testis *histopathology*: minimal-to-mild collagen deposition and portal vein dilatation in the liver; some foci of perivascular inflammation in the lungs	Bhat *et al*, 1991	2e

‡ see Page i and Appendix for explanation decreased

9.4 GENOTOXICITY

9.4.1 *In vitro* assays

The genotoxicity of the monochloroacetate anion was evaluated in *in vitro* assays using MCAA and buffered culture media. Thus, the results can be considered to be applicable to SMCA.

9.4.1.1 Bacterial gene mutation assays

MCAA has been tested in a number of gene mutation assays on *Salmonella typhimurium* strains TA98, TA100, TA1530, TA1535, TA1537, and/or TA1538 (McCann *et al*, 1975; Malaveille *et al*, 1975; Bartsch *et al*, 1975 and 1980; Rannug *et al*, 1976; Elmore *et al*, 1976; Hoechst, 1979e; Mortelmans *et al*, 1986; NTP, 1992; Saito *et al*, 1995; JETOC, 1996; Giller *et al*, 1997), and in *Escherichia coli* strain WP2 *uvr*A (JETOC, 1996) using standard plate incorporation, liquid pre-incubation, and/or fluctuation protocols in the presence and the absence of metabolic activation. All these tests have demonstrated reproducibly that MCAA is not mutagenic.

Details of the above-mentioned studies are provided in Table 24.

9.4.1.2 Mammalian gene mutation assays

An increase in the mutation frequency at the thymidine kinase locus was observed in mouse lymphoma L5178Y $TK^{+/-}$ cells with and without metabolic activation at MCAA concentrations in culture media inducing cytotoxic effects and/or acidic pH shift (McGregor *et al*, 1987; NTP, 1992; Amacher and Turner, 1982). In another study on gene mutation with Chinese hamster V79 cells (in which the induction of 8-azaguanine-resistant and ouabain-resistant mutations was tested), there was no indication of mutagenic activity for MCAA without metabolic activation (Huberman *et al*, 1975).

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, the mutagenic activity observed with MCAA in the mouse lymphoma assays is questionable, and cannot be considered relevant in the assessment of its genotoxic potential.

Details of the above-mentioned studies are provided in Table 25.

9.4.1.3 Chromosomal aberration assays

MCAA did not induce chromosomal aberrations either with or without metabolic activation in Chinese hamster lung fibroblasts (CHL) (Sawada *et al*, 1987) and Chinese hamster ovary (CHO) cells (Galloway *et al*, 1987; NTP, 1992) even at concentrations inducing a cytotoxic effect (Table 26).

9.4.1.4 Primary DNA damage assays

Bacteria

No increase in DNA repair by MCAA was detected in the *umu* test on *Salmonella typhimurium* TA 1535/pSK1002 (Nakamura *et al*, 1987; Ono *et al*, 1991), in the SOS chromotest on *Escherichia coli* (Szegedi, 1989; Giller *et al*, 1997), in DNA repair assays with *Escherichia coli* WP2 and WP100 (*uvr*A$^-$ *rec*A$^-$) (Mamber *et al*, 1983 and 1984) in *Bacillus subtilis* strains (Elmore *et al*, 1976) or in the prophage induction test (inductest) with *Escherichia coli* WP2 (Mamber *et al*, 1984).

Details of the above-mentioned studies are provided in Table 27.

Mammalian cells

There was a significant increase in sister chromatid exchanges (SCEs) in CHO cells on exposure to MCAA at concentrations of 160 µg/ml or more without metabolic activation (no data are available on potential cytotoxicity). In the presence of metabolic activation, no increase was observed at the same concentrations (Galloway *et al*, 1987; NTP, 1992). In CHL cells, no SCEs were found at concentrations up to 250 µg/ml without metabolic activation, concentrations which are not cytotoxic (Sawada *et al*, 1987).

MCAA did not induce DNA strand breaks in cultured rat and mouse hepatocytes at concentrations below those that yielded cytotoxicity, and in the human lymphoblastic CCRF-CEM cells (Chang *et al*, 1992).

Details of above-mentioned studies are given in Table 28.

9.4.2 *In vivo* assays

In studies based on a poorly-described protocol, a significant increase of chromosomal aberrations was observed in the bone marrow of male and female Swiss mice 6-48 hours after a single ip dose of

up to 50 mg/kg MCAA, and 24 hours after 5 ip injections of 10 mg/kg/day MCAA. No increase in chromosomal aberrations, however, was observed 24 hours after oral or sc administration of 50 mg/kg MCAA. In addition, a slight, but not dose-related, increase of sperm shape abnormality was observed in male Swiss mice (3/group) 35 days after the administration (route and number of doses not reported) of up to 50 mg/kg (Bhunya and Das, 1987). The relevance of the results of this study cannot be fully determined due to the lack of detail provided.

No clastogenic effect on the peripheral blood erythrocytes was detected in *Pleurodeles waltl* larvae (newt micronucleus test) treated with MCAA concentrations of up to 40 µg/ml in water for 12 days (Giller *et al*, 1997).

No DNA strand breaks were induced 4 hours after a single oral administration of 1-10 mM/kg MCAA in an alkaline unwinding assay using livers of F344 rats and B6C3F1 mice and in splenocytes and epithelial cells derived from the stomach and duodenum of B6C3F1 mice (Chang *et al*, 1992).

No induction of recessive lethal mutations was found when MCAA (400 ppm in water) was administered for 3 days to *Drosophila melanogaster*. Injection of MCAA (900 ppm in water) caused a slight but not statistically-significant increase in mutation frequency. These latter results were considered by the authors to be of questionable significance (Foureman *et al*, 1994; NTP, 1992).

Details of the above-mentioned studies are given in Table 29.

9.4.3 Evaluation

There was no evidence of genotoxic potential in bacterial mutagenicity studies, in *in vitro* chromosomal aberration assays, in *in vitro* and *in vivo* primary DNA damage assays or in a mutation assay in germ cells of *Drosophila melanogaster*. In tests for gene mutations in mammalian cells, the results were contradictory and probably subject to artefacts due to changes in pH. In a poorly-reported study in mice increased chromosomal aberrations and sperm shape abnormalities were observed after ip injection . However, no clastogenic activity was detected after oral, ip or sc administration or in the newt micronucleus test.

In conclusion, the data available do not demonstrate a genotoxic potential on the part of MCAA/SMCA.

Table 24: *In vitro* bacterial gene mutation assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
Histidine reversion	*Salmonella typhimurium* strains TA100, TA1535, TA1537 and TA98	preincubation assay (20 min at 37°C), at ≤ 1000 µg/plate without S9 and ≤ 3,333 µg/plate with Aroclor 1254-induced rat/hamster liver S9	with S9, ≥ 2000µg/plate on TA1535 and TA1537 and at 3333 µg/plate on TA100 and TA98	no mutagenic activity	Mortelmans *et al,* 1986; NTP, 1992	1b
Histidine reversion	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537	preincubation assay (20 min at 37°C) ≤ 5000 µg/plate with/without phenobarbital and 5,6-benzoflavone-induced rat liver S9	≥ 2500 µg/plate	no mutagenic activity	JETOC, 1996	1b
Tryptophan reversion	*Escherichia* coli WP2 *uvrA*	preincubation assay (20 min at 37 °C) ≤ 5000 µg/plate with/without phenobarbital and 5,6-benzoflavone-induced rat liver S9	≥ 2500 µg/plate	no mutagenic activity	JETOC, 1996	1b
Histidine reversion	*Salmonella typhimurium* strains TA100, TA1535, TA1537 and TA98	plate incorporation assay at ≤ 500 µg/plate without S9 and ≤1000 µg/plate with Aroclor 1254-induced rat liver S9	with S9, 1000 µg/plate on TA1535 and TA1537	no mutagenic activity	Hoechst, 1979e	2b
Histidine reversion	*Salmonella typhimurium* strain TA1530	plate incorporation assay, 0.4, 4 and 40 µmol/ml soft agar with/without sodium phenobarbitone-induced mouse liver S9	≥ 4 µmol/ml	no mutagenic activity	Malaveille *et al*, 1975; Bartsch *et al*, 1980; Bartsch *et al*, 1975	2e
Histidine reversion	*Salmonella typhimurium* strain TA1535	pre-incubation assay (1h at 25°C) ≤500 mM without metabolic activation	≥ 100 mM	no mutagenic activity	Rannug *et al*, 1976	2e

‡ see Page i and Appendix for explanation

Table 24 (continued): *In vitro* bacterial gene mutation assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
Histidine reversion	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538	plate incorporation assay ≤ 1 mM without metabolic activation	not reported	no mutagenic activity	Elmore *et al*, 1976	2e
Histidine reversion	*Salmonella typhimurium* strain TA100	fluctuation assay ≤ 300 µg/ml without metabolic activation and ≥ 10,000 µg/ml with Aroclor-induced rat liver S9	bacteriotoxic at 100 µg/ml	no mutagenic activity	Giller *et al*, 1997	2e
Histidine reversion	*Salmonella typhimurium* strains TA100, TA1535, TA1537 and TA98	plate incorporation assay with/without Aroclor 1254-induced rat liver S9; no data on dose levels	not reported	no mutagenic activity	McCann *et al*, 1975	3a
Histidine reversion	*Salmonella typhimurium* strains TA98 and TA100	preincubation assay with/without rat liver S9 (no further details available)	no data available	no mutagenic activity	Saito *et al*, 1995	4a

‡ See Page i and Appendix for explanation

Table 25: *In vitro* mammalian gene mutation assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
Trifluorothymidine-resistant mutation	mouse L5178 Y $TK^{+/-}$ lymphoma cells	≤ 800µg/ml without metabolic activation	cytotoxic (≤ 15% of relative total growth) and acidic pH shift at ≥ 400µg/ml	increase of $TK^{+/-}$ mutant frequency at ≥ 400 µg/ml	McGregor *et al*, 1987; NTP, 1992	1b
Trifluorothymidine-resistant mutation	mouse L5178Y $TK^{+/-}$ lymphoma cells	≤ 1048.2 µg/ml with non-induced rat liver S9	cytotoxic (≤ 20% of cell survival) at ≥500 µg/ml)	slight increase of $TK^{+/-}$ mutant frequency at ≥ 500 µg/ml	Amacher and Turner, 1982	1d
Ouabain and 8-azaguanine-resistant mutation (HGPRT)	Chinese hamster V79 cells	≤ 2,100 µM without metabolic activation	not cyototoxic	no mutagenic activity	Huberman *et al*, 1975	3b

‡ see Page i and Appendix for explanation

Table 26: *In vitro* chromosomal aberration assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
Cytogenetic analysis	Chinese hamster ovary (CHO) cells	≤500 µg/ml without S9, ≤ 1600 µg/ml with Aroclor 1254-induced rat liver S9; 2-/12-h incubation at 37°C, respectively	not reported	no clastogenic activity	Galloway *et al*, 1987; NTP, 1992	1b
Cytogenetic analysis	Chinese hamster lung fibroblast (CHL) cells	6-h incubation with ≤500 µg/ml with/without PCB-induced rat liver S9	cytotoxic at 500 µg/ml with S9	no clastogenic activity	Sawada *et al*, 1987	2e

‡ see Page i and Appendix for explanation

Table 27: *In vitro* bacterial primary DNA damage assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
DNA repair	*Bacillus subtilis* strains 168M, Hcr-9, FB-13, and MC-1	≤1 mM without metabolic activation	not reported	no genotoxic activity	Elmore *et al*, 1976	2e
DNA repair	*Escherichia coli* strains WP2 and WP100 *uvr*A$^-$ *rec*A$^-$	≤4000 µg/ml with Aroclor-induced rat liver S9	not reported	no genotoxic activity	Mamber *et al*, 1983; Mamber *et al*, 1984	2e
umu test	*Salmonella typhimurium* strain TA1535/pSK1002	≤330 µg/ml with/ without phenobarbital and 5,6-benzoflavone-induced rat liver S9	not reported	no genotoxic activity	Nakamura *et al*, 1987	2g
umu test	*Salmonella typhimurium* strain TA1535/pSK1002	≤485.4 µg/ml with/ without phenobarbital and 5,6-benzoflavone-induced rat liver S9	not reported	no genotoxic activity	Ono *et al*, 1991	2g
SOS chromotest	*Escherichia coli* strain PQ37	≤3000 µg/ml with/ without Aroclor-induced rat liver S9	toxic at 300 µg/ml without S9; 1000 µg/ml with S9	no genotoxic activity	Giller *et al*, 1997	2e
SOS chromotest	*Escherichia coli*	no details on levels tested; no metabolic activation	not reported	no genotoxic activity	Szegedi, 1989	4a
Prophage-induction test (inductest)	*Escherichia coli* strain K12 λ lysogen (GY5027) *uvr*B$^-$ *env* A$^-$	≤2000 µg/plate with Aroclor-induced rat liver S9	not reported	no genotoxic activity	Mamber *et al*, 1984	2g

‡ see Page i and Appendix for explanation

Table 28: *In vitro* mammalian cell primary DNA damage assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
Sister chromatid exchange	Chinese hamster ovary (CHO) cells	≤500 µg/ml without S9, ≤1600 µg/ml with Aroclor 1254-induced rat liver S9; 2h incubation at 37°C	not reported	increase in SCE/chromosome at ≥160 µg/ml without S9; no increase with S9	Galloway *et al*, 1987; NTP, 1992	1b
Sister chromatid exchange	Chinese hamster lung fibroblast (CHL) cells	6h incubation ≤250 µg/ml without metabolic activation	no cytotoxic activity	no genotoxic activity	Sawada *et al*, 1987	2e
DNA strand breaks	F344 rat hepatocytes	treatment for 4h with 1, 5 and 10mM	cytotoxic (LDH release) at 5 and 10 mM	genotoxic activity at 5 and 10mM (secondary to cytotoxicity)	Chang *et al*, 1992	1d
DNA strand breaks	B6C3F1 mouse hepatocytes	treatment for 4h with 0.1, 1 and 10mM	cytotoxic (LDH release) at 10mM	genotoxic activity at 10mM (secondary to cytotoxicity)	Chang *et al*, 1992	1d
DNA strand breaks	human lymphoblastic CCRF-CEM cells	treatment for 2h with 1, 5 and 10mM	no cytotoxic activity	no genotoxic activity	Chang *et al*, 1992	1d

‡ see Page i and Appendix for explanation

Table 29: *In vivo* assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
Chromosomal aberration in blood (micronucleus assay)	*Pleurodeles waltl* larvae	≤40 µg/ml in water for 12d	toxic at 80 µg/ml in range-finding study	no clastogenic activity	Giller *et al*, 1997	2e
Chromosomal aberration in bone marrow (cytogenetic analysis)	10-12 week male and female Swiss mice	single ip (12.5, 25 and 50 mg/kg); sacrifice 6, 24 or 48h later	not reported	significant increase of chromosomal aberrations	Bhunya and Das, 1987	3a, 3b
		single po (50 mg/kg) or sc (50 mg/kg); sacrifice 24h later	not reported	no increase of chromosomal aberrations		
		5 repeated ip (10 mg/kg/d); sacrifice 24h after last injection	not reported	significant increase of chromosomal aberrations		
Primary DNA damage (DNA strand breaks)	male B6C3F1 mice	≤1 and 10mmol/kg, single dose po and sacrifice 4h later	not reported	no genotoxic activity in stomach or duodenum epithelial cells	Chang *et al*, 1992	1d
Primary DNA damage (DNA strand breaks)	male B6C3F1 mice	1 and 2 mmol/kg, single dose po and sacrifice 4h later	not reported	no genotoxic activity in liver or spleen	Chang *et al*, 1992	1d
Primary DNA damage (DNA strand breaks)	male F344 rat	1 mmol/kg, single dose po and sacrifice 4h later	5 and 10 mmol/kg reported as toxic	no genotoxic activity in liver	Chang *et al*, 1992	1d

‡ see Page i and Appendix for explanation

Table 29 (continued): *In vivo* assays

End-point	Test system	Exposure conditions	Toxicity	Genotoxicity	Reference	CoR‡
Sex-linked recessive lethal mutation	*Drosophila melanogaster* canton-S wild-type male	feeding: 400 ppm in water for 3d	not reported	no mutagenic activity	Foureman *et al*, 1994; NTP, 1992	1b
		injection: 900 ppm in water	not reported	slight and equivocal (p=0.06) increase in mutation frequency		
Sperm abnormality	10-12 week male Swiss mice	up to 50 mg/kg (route and number of doses not reported); sacrifice 35d after last treatment	not reported	slight (not dose-related) increase in % abnormal sperm	Bhunya and Das, 1987	3a, 3b

‡ see Page i and Appendix for explanation

9.5 CARCINOGENICITY

Details of the studies on mice and rats reported below are given in Tables 30 and 31 respectively.

Older studies have given no indication of carcinogenicity in various mouse strains following oral gavage (Bionetics,1968; Innes *et al,* 1969), dermal (van Duuren *et al*, 1974) or sc administration (van Duuren *et al*, 1974; Bionetics,1968).

More recently in 2-year oral carcinogenesis bioassays, rats and mice were given respectively 15 and 30 mg/kg MCAA or 50 and 100 mg/kg MCAA by gavage. Mortality was significantly increased in the high-dose groups of all animals and in the female rat low-dose group. Apart from a decreased body-weight gain in male rats and female mice in the high-dose group, there were no signs of systemic toxicity in the surviving animals. No excess incidence of tumours was found in either species. Inflammation of the nasal epithelium, metaplasia of the olfactory epithelium and focal squamous cell hyperplasia of the forestomach in the mice at the high dose groups were ascribed to the strong local irritant effect of MCAA (NTP, 1992; IRDC, 1985a and b).

In a study to compare the liver carcinogenity of chloroacetic acids (DeAngelo *et al*, 1997) rats were given MCAA in their drinking water at the initial concentrations of 0.05, 0.5 or 2 g/l. The highest concentration was reduced to 1.1g/l because of signs of toxicity after 24 weeks. Body-weight gain was significantly reduced in the higher-dose groups; absolute and relative liver and spleen weights were reduced in the two higher-dose groups. This was believed to reflect the relatively high systemic toxicity of MCAA, although no major histopathological abnormalities were reported. There was no decrease in survival rate as compared with controls, nor was there evidence of any increase in the frequency of tumours.

Evaluation

The results of the chronic studies on MCAA carried out according to current guidelines, gave no indications of carcinogenicity. This is supported by the findings of earlier studies of limited quality.

Table 30: Carcinogenicity in mice

Species	Exposure conditions	Parameters studied/results	Reference	CoR‡
B6C3F1 mouse (60 /sex/dose)	0, 50, or 100 mg/kg/d MCAA in distilled water by gavage for 2 years (5 d/week)	*survival at study termination*: 79, 65 and 38% in males, and 71, 67 and 76% in females at 0, 50 and 100 mg/kg/d respectively *body weight gain*: (8-11%) in females at 100 mg/kg/d during second year of study *clinical findings*: none *histological findings*: inflammation of nasal mucosa in males at 100 mg/kg/d, and in females at both doses; metaplasia of olfactory epithelium in females at 100 mg/kg/d; squamous hyperplasia of the forestomach at 100 mg/kg/d in both sexes no evidence of carcinogenicity	NTP, 1992; IRDC, 1985b	1a
B6C3F1 and B6AKF1 mouse (18/sex/strain)	46.4 mg/kg/d MCAA in distilled water by gavage from d 7-28 then 149 ppm in diet for 17 months	no evidence of carcinogenicity	Innes *et al*, 1969; Bionetics, 1968	3b
B6C3F1 and B6AKF1 mice (18/sex/strain)	single dose of 100 mg/kg MCAA sc at age 28 d; sacrifice 17 months later	no evidence of carcinogenicity	Bionetics, 1968	3b
ICR/Ha Swiss mouse (50 mice)	skin application of 2.0 mg MCAA in 0.1 ml acetone 3/week for 580 d	no evidence of carcinogenicity	van Duuren *et al*, 1974	3b
ICR/Ha Swiss mouse (50 mice)	0.5 mg MCAA in 0.05 ml tricaprylin sc, 1/week for 580 d	no evidence of carcinogenicity	van Duuren *et al*, 1974	3b

‡ See Page i and Appendix for explanation decreased

Table 31: Carcinogenicity in rats

Species	Exposure conditions	Parameters studied/results	Reference	CoR‡
F344/N rat (53 /sex/dose)	0, 15, or 30 mg/kg/d MCAA in distilled water by gavage for 2 years (5 d/week)	*survival at study termination*: 53, 40 and 32% in males, and 70, 38 and 51% in females at 0, 15 and 30 mg/kg/d respectively *body weight gain*: (5%) in males at 30 mg/kg/d during second year of study *clinical findings:* none no evidence of carcinogenicity	NTP, 1992; IRDC, 1985a	1a
F344 rat (50 males/dose)	via drinking water containing 2.0 g/l NaCl (control), or 0.05, 0.5 and 2.0 (reduced to 1.1 after 24 weeks due to toxicity) g/l MCAA (adjusted to pH 6.9-7.1 with NaOH) for 2 years; interim sacrifices on weeks 15, 30, 45, or 60, final sacrifice on week 104	*mean daily intake*: 3.5, 26.1 and 59.9 (time-weighted) mg/kg/d at 0.05, 0.5 and 2.0/1.1 g/l, respectively *survival rate:* no effect *water consumption*: at 0.5 and 1.1 g/l *body weight gain*: at 0.5 and 1.1 g/l *serum clinical chemistry*: no effects on AST and ALT *peroxisome proliferation*: no effects on week 15, 30, 45, 60, and 104 *hepatocyte proliferation*: no effects *organ weight*: spleen weight at 0.05 g/l and at 1.1 g/l; liver and kidneys weights at 0.5 and 1.1 g/l myocardial degeneration and chronic/active inflammation of the nasal cavities at 1.1 g/l no evidence of carcinogenicity	DeAngelo *et al*, 1997	1d

‡ see Page i and Appendix for explanation increased decreased

9.6 REPRODUCTIVE TOXICITY

9.6.1 *In vivo* data

Pregnant Long-Evans rats (~ 20/group) were given 0, 17, 35, 70 or 140 mg/kg MCAA (in distilled water, pH 6-7) by oral gavage on days 6-15 of gestation. There were no compound-related maternal deaths, but maternal weight gain was significantly reduced at 140 mg/kg. The mean percentage of resorbed implants/litter and the weight of live foetuses were comparable to controls. The mean frequency/litter of visceral malformations ranged from 1.2% (control) to 6.37% (140 mg/kg) (no further information available) but, according to the authors, these effects were not dose-related. At the highest dose level, incidences of malformations of the cardiovascular system (including levocardia, defect between ascending aorta and the right ventricle and ringed aortic arch) were significantly elevated as compared with controls. There were no skeletal malformations (Smith *et al*, 1990; CoR 4a).

MCAA was administered at a concentration of 1,570 ppm in drinking water (pH 7.0) to pregnant Sprague-Dawley rats from day 1 to 22 of pregnancy (equivalent to a mean daily intake of 193 mg/kg bw/d) in a study performed to assess the role of the metabolites of TCE, and dichloroethylene (DCE) in foetal cardiac teratogenic effects. Maternal and foetal variables showed no statistically-significant differences between MCAA and control groups (Johnson *et al*, 1998; CoR 2e).

In 13-week toxicity studies in rats and mice conducted by the NTP (1992) (see Section 9.3) there was no change in absolute or relative testis weight. No compound-related histopathological effects were observed in the testis or ovaries (Schwetz, 1993).

9.6.2 *In vitro* data

In a whole embryo culture assay to screen the developmental toxicity of a series of chloro- and bromoacetic acids, 3-6 somites staged CD-1 mouse embryos were exposed for 24 hours to MCAA concentrations ranging from 50-500 µM. During the study, the initial pH of the MCAA culture medium was carefully controlled and was similar to the control medium. Embryonic development was affected at 175 µM (neural tube, pharyngeal, and heart defects) and produced embryolethality at 250 µM. No effects were observed at 100 µM (Hunter *et al*, 1996; CoR 2e).

MCAA was studied to assess the practicability of the *Hydra pseudologactis* regeneration assay on the pre-screening of teratogenic potential. The concentration of 955 mg/l and 155 mg/l were 50% toxic for the polyps and 50% inhibitory to regeneration, respectively. Apparently, the pH of the culture medium was not neutralised, and it was not possible to be sure than the observed effects were due to MCAA and not due to pH shifts (Ji Yuan-tang *et al*, 1998; CoR 3b).

9.6.3 Evaluation

In a study for which it was not possible for the Task Force to assign a reliability factor as only an abstract was available, a slight increase in malformations of the cardiovascular system was observed in rats at the dose level of 140 mg/kg/d. The other available data support the assumption that this effect was related to maternal toxicity for the following reasons:

1) the highest dose investigated was close to the LD_{50} and induced maternal toxicity, 2) in another study no visceral malformations (including cardiac defects) were observed in the foetuses from pregnant rats receiving a higher but non-maternally toxic dose of MCAA, 3) malformations (including heart defects) were observed in cultured mouse embryos at concentrations significantly higher ($\geq$175 µM) than the maximum plasma concentration (1 µM) reported after oral administration of 250 mg/kg to mice (Berardi, 1986), 4) MCAA induces severe lactic acidosis (Mitroka, 1989); 5) it has been demonstrated that elevated foetal plasma lactate can affect the development of the foeutus (Powell and Brace, 1991; Bocking *et al,* 1991).

All these data support the conclusion that MCAA cannot be considered to have a direct toxic effect on development.

With regard to male and female fertility, no adverse effects on reproductive organs were found in sub-chronic studies in rats and mice.

9.7 EVALUATION

In addition to the corrosive properties of the acid form, the monochloroacetate anion is toxic by all routes of exposure once it is bioavailable in sufficient amounts. Severe blood and CSF lactic acidosis were observed in rodents dying from MCAA intoxication, secondary to an inhibition of both pyruvate-dehydrogenase and α-ketoglutarate dehydrogenase enzyme complexes (see Section 8). Clinical signs of toxicity and mortality developed in direct relationship to the increase in CSF lactate levels. No data are available to demonstrate the involvement of the lactic acidosis in the chronic toxicity of MCAA. Nevertheless, the early mortality observed at high doses in the repeated gavage test, but not observed at higher doses in the drinking water studies, might be related to the lower monochloroacetate blood peak levels (and hence lower blood lactic acidosis) resulting from drinking water administration as compared with those evoked by gavage administration.

No conclusive evidence for any sensitising, genotoxic, carcinogenic or reproductive toxicity potential was found in the toxicological data reviewed by the Task Force.

10. EFFECTS ON MAN

10.1 ACUTE TOXICITY

There have been no reports of acute toxic effects following exposure to SMCA.

Only 8 cases of severe systemic intoxication have been reported from exposure to MCAA by the oral route or by inhalation, dermally or by a combination of both (Table 32). These are described below.

10.1.1 Routes of exposure

Oral exposure

One case of acute oral intoxication has been reported in which a 5-year-old girl was accidentally given 5-6 cc of an 80% MCAA wart remover in mistake for medicine. She had no symptoms for 1.5 hours following ingestion but then developed refractory ventricular tachycardia, pulmonary oedema and a metabolic acidosis which did not respond to treatment. Despite intensive-care treatment she died 8 hours later. Whether or not there were neurological effects is uncertain from the case report. Autopsy revealed diffuse gastric erosions, fatty infiltration of the liver, pulmonary and cerebral oedema. MCAA levels of 100 µg/ml were found in the serum (Feldhaus *et al,* 1993 ; Rogers, 1995).

Inhalation exposure

There are no reliable reports of inhalation exposure to MCAA alone. In a fatal case reported by Zeldenrust (1951) a worker was splashed by a large amount of so-called “MCAA end-reaction fluid” from a process that is no longer used. An aerosol developed, probably containing large amounts of hydrochloric and acetic acid, sulphur dioxide and MCAA, as well as lesser amounts of anhydrides of chloroacetic acid and acetic acid, plus various sulphur-chloride compounds. The case history suggests that the worker removed the mask while still enveloped in the cloud of acid aerosol; his gas mask was later proven to be unsuitable to protect against acid vapours and aerosols. Systemic toxicity, as described in Section 10.1.2, occurred and he died 4 hours after the accident; the clinical history is only briefly described but is suggestive of CNS involvement (convulsions and coma). Post mortem examination showed mainly congestion and petechial haemorrhage of most organs, including the brain. Histologically there was necrosis of the alveolar walls and marked congestion of the lung tissue; serous liquid was found in alveoli. The author ascribed the fatality to inhalation of one or more toxic compounds, since the dermal lesions were not considered important. The systemic toxicity of MCA after dermal absorption was unknown at the time and the author's conclusion is not supported by later accidents,

which have demonstrated that fatalities can result from similar, relatively limited dermal exposure without pulmonary involvement (Kulling *et al*, 1992).

Dermal exposure

Seven cases of systemic toxicity have been reported following dermal contamination with MCAA, including the above-reported case (Zeldenrust, 1951), which was due to a combined dermal and inhalation exposure.

Ten percent or more of the body surface was involved in the 5 fatalities reported by Millischer *et al* (1987) while 5-10% body surface was splashed in 2 non-fatal accidents. In other accidents, workers have had more than 5 or even 10% body surface affected without any signs of systemic toxicity (Kulling, 1997). This discrepancy cannot be fully explained by factors such as time of exposure and temperature. Initial assessment may underestimate the severity of the skin lesion as both the area and degree may increase within 1-2 days (Vincenti, 1987 ; DKK, 1984).

Only limited data are available on the absorption of MCAA after skin contamination. MCAA has been found in serum after skin contamination of an area as small as 2%. An overview of currently available data of MCAA in blood, related to time after skin contact, is given in figure 4.

Figure 4: Serum MCAA levels after accidental dermal exposure

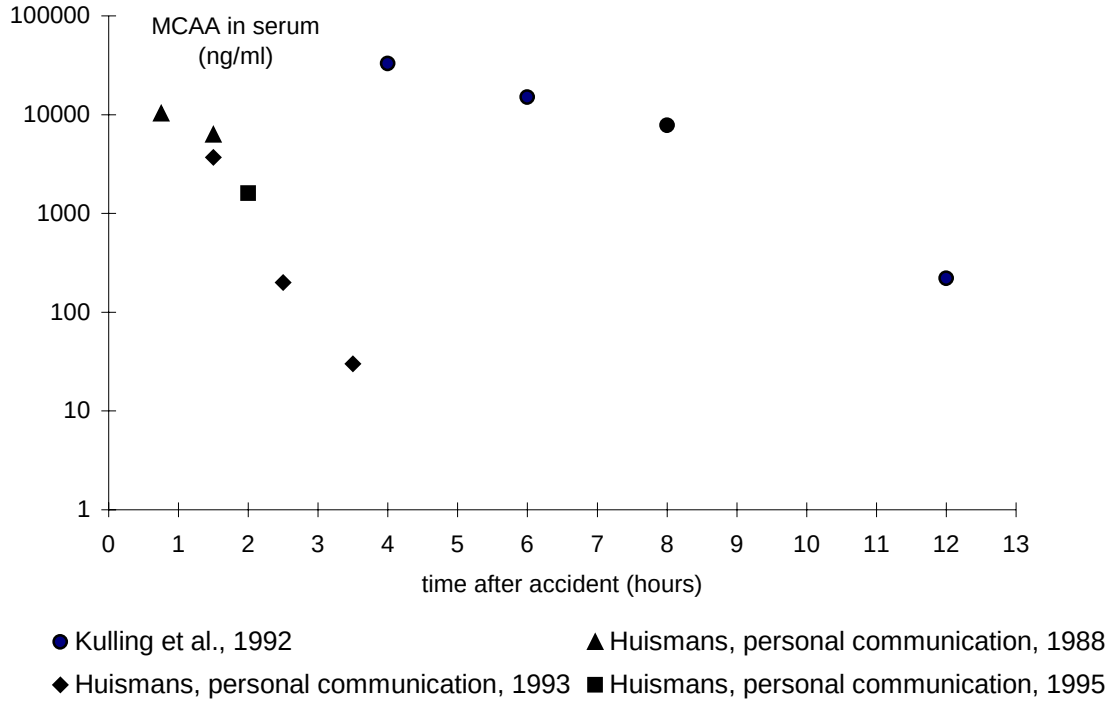


Table 32: Cases of systemic intoxication

Case report	Form of MCAA	Temperature	Route of intoxication	Intensity of exposure	Year	Reference
1	Solution	60 °C	inhalation/dermal	extensive dermal contamination	1949	Zeldenrust, 1951
2	Molten	60°C	dermal	10% body surface	1969	Hercules, 1969e; Mann, 1969; Christofano *et al*, 1970
3	Molten	>60°C	dermal	10% body surface	1980	Heckler, 1981
4	Solution 80%	warm	dermal	15% body surface	1984	DKK, 1984
5	Solution 80%	35°C	dermal	25-30% body surface	1986	Kulling *et al,* 1992
6	Molten	not reported	dermal	10% body surface	1975	Kusch *et al*, 1990
7	Molten	90°C	dermal	6-10% body surface	1985	Ruty, 1985; Contassot *et al*, 1987; Vincenti, 1987
8	Solution 80%	ambient	oral	5-6 cm^3	1993	Feldhaus *et al*, 1993; Rogers, 1995

10.1.2 Course of systemic intoxication

Clinical

Due to its corrosivity MCAA initially causes cutaneous damage (see Section 10.2.1). Signs of systemic poisoning develop after 1-3.5 hours (Millischer *et al*, 1987). In severe cases, different signs rapidly succeed one another as indicated below.

- Vomiting and occasionally diarrhoea are early signs of systemic intoxication (DKK, 1984 ; Hercules, 1969e ; Ruty, 1985; Kusch *et al,* 1990; Feldhaus *et al*, 1993).
- CNS involvement is then predominant, with excitation (Hercules, 1969e; Kulling *et al*, 1992; Contassot *et al*, 1987), disorientation (Contassot *et al,* 1987) or convulsions (Zeldenrust, 1951; DKK, 1984; Hercules, 1969e; Kulling *et al*, 1992), followed by CNS depression (Christofano *et al,* 1970) and coma (Zeldenrust, 1951; Hercules, 1969e; DKK, 1984; Kulling *et al,* 1992; Contassot *et al,* 1987). Signs of intracranial hypertension have been reported (Kulling *et al,* 1992) as well as alternating CNS excitation and depression (Kulling, 1997 ; Hercules, 1969e; Contassot *et al,* 1987).
- In all cases there is cardiac involvement. Arrhythmia (Hercules, 1969e; Kusch *et al*, 1990; Feldhaus *et al*, 1993; Contassot *et al,* 1987) and tachycardia (Kusch *et al*, 1990; Contassot *et al*, 1987; Feldhaus *et al*, 1993) have been described. Electrocardiographic changes indicated non-specific myocardial damage (Contassot *et al*, 1987; Kulling *et al,* 1992) or occasional premature ventricular contractions (Kusch *et al*, 1990). In most cases cardiovascular shock is observed (Hercules, 1969e; DKK, 1984; Kulling *et al,* 1992; Contassot *et al*, 1987; Rogers, 1995).
- Renal failure, seen within 12 hours (Kulling, 1997), is probably caused by cardiovascular shock and may be complicated by a tubular necrosis secondary to the impact of myoglobin or calcium oxalate, both of which may be due to rhabdomyolysis (DKK, 1984; Kulling *et al*, 1992; Kulling, 1997).

Two minors cases have been reported in which the only signs were vomiting and hypotension respectively (Huismans, 1998).

Details of the course of systemic intoxication are provided in Table 33.

Table 33: Clinical signs of systemic intoxication with MCAA

Clinical Signs	Case report *
GI tract	
nausea	(6); (7)
vomiting	(2); (4); (6); (7); (8)
diarrhoea	(7)
Respiratory tract	
cough	(1); (7)
pulmonary oedema	(1); (8)
Cardiovascular system	
arrhythmia	(2); (6); (7); (8)
tachycardia	(6); (7); (8)
cardiovascular shock	(2); (4); (5); (7); (8)
ECG alterations	(5); (7)
CNS	
convulsions	(1); (2); (4); (5)
confusion	(7)
excitation	(2); (5); (7)
depression	(2); (4); (7)
alternating excitation/depression	(2); (7)
coma	(1); (2); (4); (5); (7); (8)
intracranial hypertension	(5)
Kidneys	
anuria	(4); (5)

* For references to case reports see Table 32

Biological

A severe metabolic acidosis which is difficult to treat is the main biological sign (Vincenti, 1987; Contassot *et al,* 1987; Kulling *et al,* 1992; Feldhaus *et al*, 1993). Hypokalaemia has been reported (Contassot *et al*, 1987; Kusch *et al,* 1990; Hercules, 1969e; Kulling *et al,* 1992) and hypocalcaemia may appear the second day (Kulling *et al,* 1992). Increased transaminases levels, indicating extensive

tissue damage, were observed on the 2nd day (1st analysis) in a fatal case reported by Kulling *et al* (1992) but not on the first day in a non-fatal case (Vincenti, 1987). Myoglobinaemia (Kulling *et al,* 1992), leucocytosis (Hercules, 1969e) and coagulation disturbance (Ruty, 1985) have been reported; a hyperglycaemia observed in one case has no clear explanation (Contassot *et al*, 1987).

In several autopsies, haemorrhagic congestion has been observed (Zeldenrust, 1951 ; Mann, 1969; Kulling *et al*, 1992 ; Feldhaus *et al*, 1993). According to Kulling (1997) the main mechanism of MCAA toxicity is microvascular damage due to endothelial cellular damage. However, this is still only a hypothesis.

The above details are provided in tablular form in Table 34.

Table 34 : Biological data of systemic intoxications

Case report	Metabolic acidosis	Hypo-kalaemia	Hypo-calcaemia	Hyper-glycaemia	creatine kinase	ALAT	ASAT	Myoglo-binaemia	Reference
2		+							Hercules, 1969e; Mann, 1969; Christofano *et al*, 1970
5	+	+	+		+	+	+	+	Kulling *et al,* 1992
6		+							Kusch *et al*, 1990
7[@]	+	+		+	+				Ruty, 1985; Contassot *et al*, 1987; Vincenti, 1987
8	+								Feldhaus *et al*, 1993; Rogers, 1995

[@] Additional data : no haemoglobinuria, and LDH normal on the first day increased

ALAT alanine aminotransferase
ASAT aspartate aminotransferase

Prognosis

Prognosis is poor if the signs of systemic toxicity have already developed. Only 2 of 8 patients with systemic toxic effects survived (Millischer *et al*, 1987; Kusch *et al*, 1990 ; Contassot *et al*, 1987). Death occurred within 4 hours to 8 days (Millischer *et al*, 1987) as a result of cardiovascular shock, renal failure and cerebral oedema (Kulling *et al*, 1992). Details are presented in Table 35.

Table 35: Course of systemic intoxications with MCAA

Case report	Time until systemic signs	Time until death	Reference
1	1h	4h	Zeldenrust, 1951
2	not reported	11h	Hercules, 1969e; Mann, 1969; Christofano *et al*, 1970
3	not reported	18h	Heckler, 1981
4	65 min	6h	DKK, 1984
5	2h	8d	Kulling *et al,* 1992
6	45 min	No death	Kusch *et al*, 1990
7	3½h	No death	Ruty, 1985; Contassot *et al*, 1987; Vincenti, 1987
8	1½h	7½h	Feldhaus *et al*, 1993 ; Rogers, 1995

10.2 IRRITATION AND SENSITISATION

10.2.1 Irritation/corrosion

MCAA is corrosive and can damage skin, mucous membranes and eyes (BG Chemie, 1993; Kulling, 1997). In addition a thermal burn can be caused by the temperature of molten MCAA or hot MCAA solution. MCAA skin burns are in general first to second degree and have a peculiar white colour (J-C Besson, personal observation). After 24-48 hours the burns may be greater in extent and seriousness than originally perceived (Vincenti, 1987; Kulling, 1997).

Inhalation of MCAA fumes or aerosols is likely to cause damage of a similar nature to that caused by other acidic or corrosive substances (Watrous, 1947; BG Chemie, 1993; Kulling, 1997).

In general no adverse effects have been reported following skin contact with SMCA. However in one

factory where bags of SMCA were opened and emptied manually, on hot and humid days redness of the exposed skin was noted, especially on skin areas covered with sweat. No confirmation of this observation has been possible due to closure of this facility (C Braun, personal communication).

10.2.2 Sensitisation

No cases of allergic sensitisation have been reported following occupational exposure.

10.3 CHRONIC EFFECTS, CARCINOGENICITY, GENETIC AND REPRODUCTIVE TOXICITY

There are no human data available.

10.4 EVALUATION

MCAA is highly toxic following acute exposure and is corrosive to skin. If a sufficiently large area of skin is contaminated, signs of human systemic toxicity are similar to those found in other mammals, e.g. CNS and cardiovascular system involvement. Biochemically, an unmanageable metabolic acidosis is predominant, generally accompanied by signs of extensive non-specific tissue damage. Gross pathology and histology findings indicate vascular damage, but are otherwise non-specific. There have been no reports of sensitisation, chronic toxicity, carcinogenicity, genotoxicity or reproductive toxicity in humans.

No human data are available on the systemic toxicity of SMCA, but should absorption occur, its toxicity would be expected to be similar to that of MCAA. The only reported effect is redness of the skin following dermal exposure.

Animal toxicity studies have highlighted the relationship between the induction of a severe lactic acidosis and the development of clinical signs and mortality after acute MCAA intoxication (see Sections 8 and 9.1.4). Lactic acidosis is a common metabolic disorder usually rapidly fatal in humans (Stacpoole *et al,* 1983). We can suppose that severe lactic acidosis (which could be responsible for the unmanageable metabolic acidosis) was also involved in the cases of fatal human intoxication, although no clinical data are available to support this assumption.

11. FIRST AID AND SAFE HANDLING ADVICE

11.1 FIRST AID AND MEDICAL TREATMENT

Proposals for therapy of acute human MCAA acid intoxication are considered in detail in an ECETOC document (1999).

11.1.1 Skin exposure

11.1.1.1 MCAA

There is general agreement that dermal penetration is rapid and skin damage may be significantly more extensive than the initial assessment suggests. To prevent any significant skin penetration the skin should be rinsed immediately and intensively following exposure, even if little or no skin reaction is seen. Contaminated clothing and other items, such as wrist watches, should be removed (Vincenti, 1987; Kulling, 1997; Bruijnzeel *et al,* 1998).

Anecdotal clinical experience from the MCAA-producing companies, as well as inconclusive experimental evidence (Bruijnzeel *et al*, 1998), suggests that immediate bathing in a saturated bicarbonate solution has a beneficial effect on skin damage and possibly also on systemic effects (personal communications from Akzo Nobel and Clariant). Water should, however, always be used if more immediately accessible than sodium bicarbonate solution, as rapidity of treatment has been demonstrated to be of greater importance in the prevention of systemic toxicity from MCAA skin contamination.

A suitably-qualified person should always be consulted to estimate the area of the body surface affected. If the affected skin area is >1% of body surface (size of palm of hand) it has been recommended that the patient should be immediately transported to hospital after adequate decontamination and observed for at least 6 hours (Kulling, 1997). This is considered to be a rather conservative recommendation since in the reported cases of systemic toxicity at least 5% of the body surface was contaminated.

11.1.1.2 SMCA

Contaminated skin should be washed with soap and water (Elf Atochem, 1996). No further measures are warranted as SMCA is not absorbed through the skin and is, at worst, a mild irritant.

11.1.2 Eye exposure

The recommended treatment for MCAA and SMCA exposure is to flush the contaminated eye immediately with water for 15 minutes (Kulling, 1997).

A physician should always be consulted. First aid and medical treatment recommendations are based on generic procedures for ocular contamination with acids.

11.1.3 Inhalation

11.1.3.1 MCAA

The recommended procedure is to remove the worker to fresh air, administer oxygen and treat symptomatically as for other respiratory irritants (betamimetics, inhaled or systemic steroids) (Kulling, 1997). Medical aid should be summoned immediately.

11.1.3.2 SMCA

No specific recommendations are available for the treatment of inhalation exposure to SMCA.

11.1.4 Ingestion

Vomiting should not be induced if accidental ingestion of MCAA occurs. If the victim is conscious, rinsing of the mouth is recommended.

Professional medical assistance should always be sought urgently and gastric decontamination by orogastric or nasogastric tube performed as soon as possible (Kulling, 1997).

Based on generic first aid measures for treatment of ingestion of non-corrosive materials, induced vomiting may be acceptable after ingestion of SMCA.

Treatment of both SMCA and MCAA ingestion with water and/or an active carbon suspension has been suggested but no data are available on the effectiveness of either procedure. In case of unconsciousness, nothing should be given by mouth.

11.1.5 Systemic effects

11.1.5.1 MCAA

Systemic effects are likely to occur whatever the route of exposure to MCAA in situations where the monochloroacetate becomes biologically available in sufficient quantity (see Section 10). Currently only symptomatic treatment for metabolic acidosis and shock is used, which should be instituted as soon as signs of systemic intoxication appear. However, case histories demonstrate that symptomatic treatment is generally ineffective once metabolic acidosis has developed. Haemodialysis and possibly plasmapheresis have been stated to be of value, the latter in case of severe rhabdomyolysis (Kulling, 1997).

Experimental studies have demonstrated that the MCAA-induced toxicity was related to a severe lactic acidosis (see Section 8). DCAA has proved to be an effective drug in the treatment of metabolic lactic acidosis of diverse origin (Stacpoole *et al,* 1992). In spite of a lack of clinical experience in relation to MCAA intoxication, but also in view of the lack of effective alternatives, experts recommend that treatment with DCAA be initiated when more than 6% of the body surface is exposed to MCAA, or if MCAA has been ingested (Kulling 1997). This treatment should be given immediately to prevent the development of any clinical signs of systemic intoxication.

Based on animal experiments, phenobarbital could be considered as an alternative to DCAA (ECETOC, 1999). Its action is through a general reduction of brain cell metabolism, thus reducing glucose metabolism and subsequent lactic acid formation. However, there is no clinical experience in treating MCAA poisoning with phenobarbital. Since phenobarbital was less effective than DCAA in animal experiments and because human doses comparable to those effective in animals would require intensive-care therapy and artificial respiration, preference is given to the use of DCAA (Kulling, 1997).

11.1.5.2 SMCA

Significant amounts of SMCA can only be absorbed via the oral route. No clinical experience exists, but based on animal tests, once absorbed, SMCA is expected to lead to the same systemic effects as MCAA and the treatment principles for systemic MCAA intoxication described above are therefore applicable.

11.2 SAFE HANDLING

11.2.1 Safety at work

MCAA is synthesised in closed systems. Nevertheless exposure to MCAA may occur in situations such as sampling and maintenance or down-stream use. Contact with skin and eyes should be avoided using, for example, impermeable protective clothing (in some circumstances special polypropylene-coated protective clothing), acid-proof gloves and eye and face protection. Furthermore, inhalation of vapour and dust should be avoided; local mechanical exhaust ventilation to minimise exposure may be installed in the workplace .

11.2.2 Safety in storage

Storage conditions are described in Section 3. Safety concerns relate mainly to the potential for the spontaneous exothermic decomposition of MCAA.

In addition it should be recognised that good housekeeping is necessary in MCAA-handling areas to ensure that MCAA dust does not collect on elevated structures. Any liquefied dust could prove a potential danger to workers, particularly in the warehouse areas where no protective clothing is worn.

11.2.3 Fire safety and extinguishants

In the event of fire, MCAA and SMCA will generate hydrogen chloride. Fire-fighters should therefore use acid-resistant fire-fighting equipment (breathing apparatus and protective clothing) in dealing with such events.

Fires can be extinguished with foam, carbon dioxide or dry powders. Water mist is less suitable but where water is used it should be collected and disposed of in accordance with local regulations. In case of fire, exposed containers should be removed.

11.2.4 Protection against fire and explosion

The following precautions are recommended: no smoking, exclusion of all sources of ignition, and use of explosion-proof plant and equipment as laid down in national standards

11.3 MANAGEMENT OF SPILLAGE AND WASTE

MCAA spillage and waste should be taken to an authorised disposal site or incineration plant if necessary, after neutralisation (e.g. with sodium carbonate or slaked lime) to prevent the emission of hydrogen chloride. Dilution with water will prevent a temperature increase.

Empty MCAA containers must be disposed of in accordance with the local regulations.

MCAA is readily biodegradable. There will be no problems with sewage disposal provided that the MCAA concentration in waste water does not exceed 120 mg/l.

12. HAZARD CHARACTERISATION

12.1 ENVIRONMENT

Environmental fate

Monochloroacetate is readily biodegradable in the aquatic environment and is highly mobile in soil and sediment. It is therefore not considered to be persistent in the environment.

Ecotoxicity

Concentrations of MCAA found in the aquatic environment under normal conditions will not reduce the pH to environmentally unacceptable levels. At neutral pH, monochloroacetate is of low toxicity to aquatic fauna but does present a hazard to unicellular algae, with a NOEC of approximately 0.005 mg/l.

Lethality to terrestrial mammals and birds has also been recorded at doses estimated at approximately 75 mg/kg. No useful information has been found concerning toxicity to terrestrial invertebrates.

12.2 HUMAN HEALTH

Toxicokinetics

Human cases of accidental contamination and animal data indicate an extensive and rapid absorption of MCAA through the skin, and a rapid excretion in the urine either as unchanged MCAA or as reaction products with cysteine and glutathione, and in exhaled air as CO_2.

Acute toxicity

The major hazard of MCAA for human health comes from accidental dermal exposure. Several cases of fatal intoxication have been observed when 10% or more of the body surface was involved. In experimental animals, MCAA, but not SMCA, can be rapidly absorbed through the skin in toxic amounts. One human case and various animal data confirm that MCAA and SMCA are also toxic after oral administration. Although the acute data available in rats are insufficient to evaluate the toxicity by inhalation exposure, the absence of mortality observed in rats after a 10-minute exposure to saturated vapour of MCAA does not indicate a high risk for humans in case of brief accidental exposure.

Local effects

Industrial experience as well as animal studies have demonstrated that in addition to a potential for thermal burns with the molten form, MCAA is corrosive to the skin and eyes, and is irritant to the mucous membranes. In contrast, no such effects were reported with SMCA. The potential for skin sensitisation is low.

Repeat-dose effects

NOAELs of 30 and 100 mg/kg/d were determined respectively for rats and mice in oral 13-week studies with MCAA conducted according to GLP and current guidelines. Liver and/or kidneys were the target organs in both species. An interim sacrifice at 15 months, during a 2-year bioassay in rats, confirmed the absence of systemic toxicity at 30 mg/kg/d.

Genotoxicity

MCAA/SMCA has been tested extensively *in vitro*, and no evidence of genotoxic potential was demonstrated at levels of pH compatible with cell survival. In a study of low reliability, chromosomal aberrations were observed in bone marrow of mice after ip administration, but not after oral or sc administration of MCAA. In contrast, treatment with MCAA failed to induce DNA damage in the target organs of mice, gene mutations in *Drosophila melanogaster* and micronucleus in the blood of newts. The weight of available evidence does not give rise to concern with regard to genotoxicity of MCAA/SMCA.

Carcinogenicity

The results of GLP bioassays in rats and mice, conducted according to current guidelines, as well as some additional studies, support the conclusion that MCAA does not present a carcinogenic hazard.

Reproductive toxicity

No effect on reproductive organs was observed in sub-chronic toxicity studies in rats and mice. In the absence of skeletal malformation and further confirmation, the increase of cardiovascular system malformations observed in rats at maternally toxic oral dose level of 140 mg/kg/d, is not considered a direct specific toxic effect for development. No adverse effect on human reproduction is expected.

APPENDIX: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997) and Rosner (1994)

Code of Reliability (CoR‡)	**Category of reliability**
1	**Reliable without restriction**
1a	GLP guideline study (OECD, EC, EPA, FDA, etc...)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, etc...)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	**Reliable with restrictions**
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	**Not reliable**
3a	Documentation insufficient for assessment
3b	Significant methodological deficiences
3c	Unsuitable test system
4	**Not assignable**
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated (e.g. Russian)
4e	Documentation insufficient for assessment

‡ see Page i and Appendix for explanation

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LIST OF ABBREVIATIONS

CHL(s)	Chinese hamster lung fibroblasts
CHO(s)	Chinese hamster ovary cells
CNS	central nervous system
CSF	cerebrospinal fluid
CoR	code of reliability
DCAA	dichloroacetic acid
DCE	dichloroethylene
EbC_n	effect concentration on biomass
EC_n	a statistically-derived concentration which, over a defined period of exposure, is expected to cause a specified effect in n% of test population
ErC_x	effect concentration on specific growth
IC_{50}	immobilisation (Daphnia) or inhibition (algae) concentration
ip	intraperitoneal
iv	intravenous
α-KGDH	α-ketoglutarate dehydrogenase
LOAEL	lowest-observed-adverse effect level
LOEC	lowest-observed effect concentration
MCAA	monochloroacetic acid
NOAEL	no-observed-adverse effect level
NOEC	no-observed effect concentration
OA	oxalic acid
PDH	pyruvate dehydrogenase
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion

sc	subcutaneous
SCE(s)	sister chromatid exchange
S-CMC	S-carboxymethyl cysteine
SDCA	sodium dichloroacetate
SMCA	monochloroacetic acid, sodium salt
STEL	short-term exposure limit
TCAA	trichloroacetic acid
TCE	trichloroethylene
TDA	thiodiacetic acid
TWA	time-weighted average concentration

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