MONOCHLOROACETIC ACID
(CAS Reg. No. 79-11-8)

ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)

February 2006

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

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EXECUTIVE SUMMARY

Monochloroacetic acid (MCAA) is a colorless crystalline material, which is highly soluble in water and soluble in organic solvents. Its vapor pressure at room temperature is moderate with reported values between 0.2 hPa (crystalline substance) and 10 hPa (solution in water). MCAA has a pungent odor.

MCAA is produced by chlorination of acetic acid or hydrolysis of trichloroethene using sulfuric acid. The world production capacity was estimated at 362,500 metric tons/year in 1987. MCAA or its sodium salt, sodium monochloroacetate, are used primarily in the industrial production of carboxymethyl-cellulose, herbicides, thioglycolic acid as well as in the production plastics, pharmaceuticals, flavors, cosmetics and other organic chemicals.

MCAA is an acid (pK_a 2.85) and therefore can cause eye and skin irritation upon contact with a diluted MCAA solution and skin corrosion and conjunctival burns upon contact with more concentrated solutions. The systemic toxicity of MCAA is caused by inhibition of enzymes of the glycolytic pathway and the tricarboxylic acid cycle. This metabolic blockage damages organs with a high energy-demand, such as heart, CNS and muscles, and leads to metabolic acidosis due to the accumulation of lactic acid and citric acid in the body.

No studies are available reporting severe toxic effects in humans after inhalation exposure to MCAA. Mortality was reported in a child after oral uptake of 5-6 ml of an 80 % MCAA solution (Rogers, 1995). Several lethal accidents have been reported, in which workers were dermally exposed to hot, liquid MCAA. An inadequately described study reported an irritation threshold of 1.48 ppm (Maksimov and Dubinina, 1974); no respiratory tract irritation, effects on lung function parameters or irritation of skin and mucous membranes were reported for >33 workers potentially exposed to MCAA concentrations between <0.13 ppm for 3 hours and 0.31 ppm for 7 hours (Clariant GmbH, 2000).

The only animal study reporting lethal effects after inhalation exposure was an inadequately described study in which a LC_{50} of 46.8 ppm for 4 hours was reported for rats (Maksimov and Dubinina, 1974). Several studies report lethal effects after oral exposure with LD_{50} values mostly between 50-200 mg/kg for rats, mice and guinea pigs. In a single inhalation experiment on rats, eye squint and slight lethargy were observed during exposure to an analytical concentration of 66 ppm for 1 hour (Dow Chemical Co., 1987). In an inadequately reported study, an irritation threshold in rats of 6.16 ppm and a NOEL for histological changes in the respiratory tract in rats and guinea pigs of 1.5 ppm after 4 months have been reported (Maksimov and Dubinina, 1974).

No relevant studies of adequate quality were available for the derivation of the AEGL-1. Therefore, AEGL-1 values were not recommended due to insufficient data. Due to the lack of an adequately performed study reporting an odor threshold for MCAA, no level of distinct odor awareness (LOA) was derived.

The AEGL-2 was based on a single inhalation study in rats (Dow Chemical Co., 1987) in which eye squint and lethargy were observed in rats exposure to 66 ppm for 1 hour. A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability because 1) the effect level was considered below that of an AEGL-2, 2) because the available data on acute oral lethality do not

point at a large interspecies variability for more severe (lethal) effects, and 3) because of the limited toxicodynamic variability as the enzymes inhibited by MCAA do not vary considerably within and between species. An uncertainty factor of 3 was applied for intraspecies variability because of the limited toxicokinetic variability with respect to local effects and because of the limited toxicodynamic variability with respect to systemic effects since the enzymes inhibited by MCAA do not vary considerably within and between species. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.

No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended.

The AEGLs are summarized in the table below.

SUMMARY TABLE OF AEGL VALUES FOR MONOCHLOROACETIC ACID [a]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	N.R.[b]	N.R.	N.R.	N.R.	N.R.	Insufficient data
AEGL-2 (Disabling)	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)	eye squint and lethargy in rats (Dow Chemical Co., 1987)
AEGL-3 (Lethal)	N.R.	N.R.	N.R.	N.R.	N.R.	Insufficient data

[a] Skin contact with molten MCAA or MCAA solutions should be avoided; dermal penetration is rapid and fatal intoxications have been observed when 10 % or more of the body surface was involved.
[b] not recommended due to insufficient data

References

Clariant GmbH, 2000. Unpublished. Letter of Dr. Kreiling dated 23.08.2000.

Dow Chemical Co., 1987. Monochloroacetic acid: an acute vapor inhalation limit study with Fischer 344 rats. Unpublished report, Dow Chemical Company, Midland, USA.

Maksimov G.G. and O.N. Dubinina, 1974. Materials of experimental substantiation of maximally permissible concentration of monochloroacetic acid in the air of production area. *Gigiena Truda i Professional nye Zabolevarija* 9, 32-35.

178 Rogers D.R., 1995. Accidental fatal monochloroacetic acid poisoning. *American Journal of Forensic*
179 *Medicine and Pathology* 16, 115-116.

1. INTRODUCTION

Monochloroacetic acid (MCAA) is a colorless crystalline material, which is highly soluble in water and soluble in organic solvents.

MCAA is produced by a) chlorination of acetic acid or b) hydrolysis of trichloroethene using sulfuric acid (BUA, 1994). A) the chlorination of acetic acid is carried out in liquid phase at temperatures between 85 and 120 °C. Acetic anhydride and/or acetylchloride may be used as catalysts. The chlorination product contains considerable amounts of acetic acid and/or dichloroacetic acid. Purification takes place either by selective dechlorination of dichloroacetic acid and subsequent distillation, or by recrystallization from suitable solvents (ECB, 2003). B) trichloroethylene and sulphuric acid are heated to 130-140 °C in the reactor. A mixture of trichloroethylene and sulphuric acid is continuously fed to the bottom of the reactor. The chloroacetic acid and sulphuric acid are permitted to overflow into a cascade, where the chloroacetic acid is distilled at 20 mm Hg and the sulphuric acid is recycled. The hydrolysis of trichloroethylene yields high-purity monochloroacetic acid, but has the disadvantage of utilising a relatively more expensive starting material (ECB, 2003).

The world production capacity was estimated at 362,500 metric tons/year in 1987 (KEMI, 1994). In Europe about 145,000 metric tons were produced in 1999 (ECB, 2003); in the US about 39,000 metric tons were produced in 1989 (UN, 1996). Imports into the US comprised about 17,000 metric tons of chloroacetic acids in 2003 (USITC, 2004). The TRI database (DHHS, 2004) lists 17 sites in the US where production and/or use of MCAA causes emissions to the air.

MCAA is pumped in molten form (about 80 °C) or as 80 % aqueous solution through pipes on industrial sites and is also transported in molten form in tank trucks and rail tank cars between industrial sites (ECETOC, 1999; ECB, 2003). Therefore, an inhalation exposure during accidental releases cannot be ruled out (ECETOC, 1999), although no case of severe intoxication by inhalation has been published in the literature.

MCAA or its sodium salt, sodium monochloroacetate, are used primarily in the industrial production of carboxymethylcellulose, herbicides, thioglycolic acid as well as in the production of plastics, pharmaceuticals, flavors, cosmetics and other organic chemicals (KEMI, 1994; ECB, 2003).

Haloacetic acids, including MCAA, are a group of chemicals that are formed along with other drinking water disinfection byproducts (e.g. trihalomethanes) when chlorine or other disinfectants used to control microbial contaminants in the water, react with naturally occurring organic and inorganic matter in water. Depending on the amount of bromide in the source water varying amounts of chlorinated, brominated and mixed bromochlorohaloacetic acids are produced. The U.S. EPA (1998) has published the Stage 1 Disinfectants/Disinfection Byproducts Rule to regulate a group of five haloacetic acids at a maximum contaminant level of 0.06 mg/l (60 ppb) annual average. A very small inhalation exposure might result from this water contamination. Xu and Weiser (2003) have measured an aerosol-bound concentration of 6.3 ng/m³ of haloacetic acids during showering with water containing 250 µg/l haloacetic acids .

Chemical and physical properties of MCAA are listed in Table 1.

TABLE 1: CHEMICAL AND PHYSICAL DATA		
Parameter	**Value**	**Reference**
Molecular formula	$ClCH_2$-COOH ($C_2H_3ClO_2$)	NTP, 1992
Molecular weight	94.5 g/mol	NTP, 1992
CAS Registry Number	79-11-8	NTP, 1992
Physical state	solid	NTP, 1992
Color	colorless	NTP, 1992
Synonyms	Chloroacetic acid; monochloroethanoic acid; chloroethanoic acid; Monochloressigsäure; Chlorethansäure	UN, 1996; Greim, 1998
Vapor pressure	0.1 mm Hg (at 20 °C) ca. 0.2 hPa (crystalline substance at 20 °C) 1 hPa (at 20 °C) 10 hPa (solution in water at 20 °C) 1 mm Hg (at 43 °C) 4.4 hPa (liquid at 65 °C) 8.23 mm Hg (at 80 °C) 10 mm Hg (at 81 °C) 40 mm Hg (at 109.2 °C) 100 mm Hg (at 130.7 ° C) 400 hPa (at 169 °C)	Dow Chemical Co., 1987 Greim, 1998 IUCLID, 1996 IUCLID, 1996 Weast, 1984 IUCLID, 1996 Dow Chemical Co., 1987 Weast, 1984 Weast, 1984 Weast, 1984 Weast, 1984
Density	1.58 g/cm³ (solid) 1.3707 g/cm³ (liquid)	UN, 1996
Melting point	63 °C (α-crystalline form, common form) 56.2 °C (β-crystalline form) 52.5 °C (γ-crystalline form)	Weast, 1984
Boiling point	187.8 °C (α-crystalline form) 187.9 °C (β-crystalline form) 187.8 °C (γ-crystalline form)	Weast, 1984
Solubility	very soluble in water (4210 g/l at 20 °C); soluble in methanol, ethanol, acetone, ether, dioxane, DMF, DMSO	IUCLID, 1996; BG Chemie, 1992; Weast, 1984
Acidity, pK_a	2.85	Weast, 1984
Odor	pungent odor	ICPS & CEC, 1993
Explosive limits in air	no data	
Conversion factors	1 ppm = 3.92 mg/m³ (at 1013 hPa, 25 °C) 1 mg/m³ = 0.26 ppm (at 1013 hPa, 25 °C)	BG Chemie, 1992

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Deaths after inhalation of MCAA have not been reported in the literature (ECETOC, 1999). Lethal effects have occurred after oral intoxication and after dermal exposure to hot, liquid MCAA (ECETOC, 1999; IUCLID, 1996; BUA, 1994). Some of these incidences are described in the following paragraphs.

Studies with non-inhalation exposure

Feldhaus et al. (1993) and Rogers (1995) reported a case study of a fatal acute oral exposure. A 5-year old girl was accidentally given 5-6 ml of an 80 % MCAA containing wart remover. After 1.5 hours post exposure, she developed refractory ventricular tachycardia, pulmonary edema and acidemia. The patient died 8 hours post-ingestion despite medical intervention. An autopsy revealed diffuse gastric erosions, fatty infiltration of the liver and pulmonary and cerebral edema. The post mortem MCAA concentration in serum was 100 mg/l as determined by gas chromatography/mass spectroscopy. The exposure corresponds to an oral dose of about 200-240 mg/kg (see Section 7.1).

Fatal cases and life-threatening poisonings in workers have been described after skin contact (IUCLID, 1996; BUA, 1994): Christofano et al. (1970) reported a case, in which about 10 % of the body surface was contaminated with warm MCAA solution. Although the contaminated skin was immediately rinsed with water for more than 1 hour, first-grade burns, anxiety, restlessness and shock developed, followed by death about 10 hours after the accident. Ruty et al. (1987) reported on the case of a 47-year-old worker, whom pressurized, molten (about 90 °C) MCAA squirted on both legs. Although the legs were immediately rinsed with water, 6 % of the body area showed first-grade burns. Four hours after the accident, nausea, vomiting, cardiovascular shock, unconsciousness and coma developed. Arrhythmia, hypotension and severe metabolic acidosis were found. The patient was treated with ethanol, an effective antidot for fluoroacetic acid intoxications. His symptoms ameliorated after 24 hours and the patient returned to work 3 months later. Kulling et al. (1992) reported the case of a 38 year-old man who was splashed with an 80 % MCAA solution on 25-30 % of his body surface. On admission to hospital 1 hour after the accident, he had epidermal and dermal superficial burns and showed slight disorientation. One hour later, he developed agitation, cardiac failure and coma. He later developed severe metabolic acidosis, rhabdomyolysis, renal insufficiency and cerebral edema and died on day 8 after the accident due to severe CNS damage.

2.2. Nonlethal Toxicity

Clariant GmbH (2000) reported that routine medical examinations of workers of two plants, producing MCAA and sodium monochloroacetate, respectively, revealed no respiratory tract irritation, effects on lung function parameters or irritation of skin and mucous membranes. The number of potentially exposed workers was 33 in one plant and not stated for the other. Concentrations of MCAA and sodium monochloroacetate, respectively, were measured at individual workplaces about every 1 to 2 years between 1991 and 2000. Measurements were carried out either as area or personal sampling by

drawing a defined volume of air through a 0.01 mol/l sodium hydroxide solution during a time period between 275 and 430 minutes followed by ion chromatography analysis. Results are given in Table 2.

TABLE 2: RESULTS OF MCAA MEASUREMENTS AT WORKPLACE; adopted from Clariant GmbH, 2000

Plant	Workplace situation	Individual MCAA concentrations measured between 1991 and 2000	No. workers and exposure time per workshift
SMCA [a] production	area of rollers for production of MCAA flakes	area sampling; 1, <1, <1, 1, 1, 1, 1 mg/m³ (MCAA measured) (0.26, <0.26, <0.26, 0.26, 0.26, 0.26, 0.26 ppm)	1 person for 1 hour
SMCA production	filling of MCAA flakes	personal sampling; <1, 1.2, 1, <1, 1 mg/m³ (MCAA measured) (<0.26, 0.31, 0.26, <0.26, 0.26 ppm)	max. 4 persons for 7 hours
SMCA production	SMCA mixer	area sampling; 0.81, 0.89 mg/m³ (SMCA measured) (0.21, 0.23 ppm)	1 person for 1 hour
SMCA production	filling of bags with SMCA	personal sampling; 0.49, 0.45, <0.40 mg/m³ (SMCA measured) (0.13, 0.12, <0.10 ppm)	1 person for 6 hours
MCAA production	round and sampling men workarea in five different buildings	personal sampling; <1, <1, <1,<1,<1, <1, <1, <1,<1,<1, 0.8, <0.5, <0.5, <0.5, <0.5, <0.5, <0.5 mg/m³ (MCAA measured) (<0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, <0.26, 0.21, <0.13, <0.13, <0.13, <0.13, <0.13, <0.13 ppm)	8 persons for 3 hours

[a] SMCA; sodium monochloroacetate

Maksimov and Dubinina (1974) and Rodionova and Ivanov (1979) reported an irritation threshold for humans of 5.7 mg/m³ (1.48 ppm) (for this study an exposure time of 1 minute was stated in Izmerov et al., 1982). The experimental details were not described by the authors.

An odor threshold of 0.01 ppm cited from an unpublished correspondence from Dow Chemical Co. was reported by AIHA (1993). Oelert and Florian (1972) cited an odor threshold of 0.045 ppm; however, the authors did not state whether this value was taken from the literature or whether and how they measured the odor threshold.

Knapp (1923) reported a case in which occupational exposure to MCAA had resulted in severe damage of the cornea (keratitis traumatica), but did not provide details of the exposure.

298 ***Studies with non-inhalation exposure***

299 Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 ml of a 0.05 %
300 MCAA solution in water did not result in adverse effects in three human volunteers. The exposure
301 corresponds to an oral dose of about 2.1 mg/kg/day (see Section 6.1).

302 **2.3. Developmental/Reproductive Toxicity**

303 No studies documenting developmental or reproductive effects of MCAA in humans were
304 identified (IUCLID, 1996; Medline and Toxline search November 2003).

305 **2.4. Genotoxicity**

306 No studies documenting genotoxic effects of MCAA in humans were identified (IUCLID, 1996;
307 Greim, 1998; Medline and Toxline search November 2003).

308 **2.5. Carcinogenicity**

309 No studies documenting carcinogenic effects of MCAA in humans were identified (IUCLID,
310 1996; Greim, 1998; Medline and Toxline search November 2003).

311 **2.6. Summary**

312 No studies are available reporting severe toxic effects in humans after inhalation exposure to
313 MCAA. An inadequately described study reported an irritation threshold of 1.48 ppm (Maksimov and
314 Dubinina, 1974; Rodionova and Ivanov, 1979); no respiratory tract irritation, effects on lung function
315 parameters or irritation of skin and mucous membranes were reported for >33 workers potentially
316 exposed to MCAA concentrations between <0.13 ppm for 3 hours and 0.31 ppm for 7 hours (Clariant
317 GmbH, 2000). Mortality was reported in a child after oral uptake of 5-6 ml of an 80 % MCAA solution
318 (Feldhaus et al., 1993; Rogers, 1995). Several lethal accidents have been reported, in which workers were
319 dermally exposed to hot, liquid MCAA or aqueous MCAA solutions (ECETOC, 1999, IUCLID, 1996;
320 BUA, 1994).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Several studies are available that report oral lethal doses of MCAA in different animal species. The oral lethality data are summarized in Table 3. Only one study reporting lethal effects after inhalation exposure was located.

3.1.1. Non-human Primates

Studies with non-inhalation exposure

In a metabolic study, Dow Chemical Co. (1976) administered MCAA intravenously to one male rhesus monkey. The animal was given 75 mg/kg on day 1 and 200 mg/kg on day 2. It died 2 hours after the second dose. No signs of toxicity other than vomiting were reported, the cause of death remained undetermined. [Note: The study would be ethically unacceptable nowadays.]

3.1.2. Rats

Maksimov and Dubinina (1974) observed no deaths in albino rats exposed at 5 mg/m³ (1.3 ppm) MCAA vapor (the authors stated that this was the maximum achievable vapor concentration at 20 °C). When MCAA was heated to 95 °C and rats were exposed to the condensed aerosol, the authors reported a LC_{50} of 180 (146-221) mg/m³ (46.8 ppm) for 4 hours (exposure duration taken from Izmerov et al., 1982). The experimental details were not described by the authors.

Studies with single non-inhalation exposure

Hoechst AG (1979a) administered 1 %(w/v) solutions of MCAA in water to groups of 10 female Wistar rats that were deprived of food for 16 hours before and 2 hours after gavage. The post exposure observation period was 14 days. Mortality rates were 0/10 animals at a dose of 40 mg/kg, 2/10 at 63 mg/kg, 5/10 at 100 mg/kg and 10/10 at 160 mg/kg. Death occurred between 128 minutes and 24 hours after gavage. Symptoms before death included restlessness, crouching, balance disturbance, prone position, passiveness, drowsiness, incomplete eyelid closure, discharge from the eyes and dyspnea. Gross pathologic examination revealed brownish-red livers with prominent lobular structuring and light-red to pink spotted lungs. In surviving animals, the same symptoms occurred to a lesser extent, but were not observed longer than until 48 hours after exposure. Using Probit analysis, an oral LD_{50} of 90.4 mg/kg (95 % C.I. (95 % confidence interval) 73.6-112 mg/kg) was calculated by the study authors.

Using subcutaneous injection of a 50 % solution of MCAA in saline, a LD_{50} of 97.4 (89.9-105.5) mg/kg was reported for Wistar rats (10 animals/group) (Hoechst AG, 1979d). Dermal LD_{50} were 305 (242-384) mg/kg for a 40 % non-neutralized MCAA solution in water (Hoechst AG, 1979e) and >2000 mg/kg for sodium monochloroacetate in saline (Hoechst AG, 1988c).

Berardi (1986) reported an oral LD_{50} of 102 mg/kg (95 % C.I. 51-204 mg/kg) using groups of 4 Sprague-Dawley rats and gavage of a non-neutralized MCAA solution in water.

Woodard et al (1941) reported an oral LD_{50} of 76.2 mg/kg (95 % C.I. 70.7-82.2 mg/kg) using a neutralized MCAA solution and groups of 5 to 20 rats (strain not specified).

Maksimov and Dubinina (1974) investigated oral LD_{50} values in albino rats administered a 10 % of MCAA solution. A value of 55 mg/kg was found when the acid solution was used, and a value of 580 mg/kg was determined for the neutralized solution. No experimental details were provided.

Using subcutaneous injection, Hayes et al. (1973) determined a LD_{50} in groups of 5-10 male Sprague-Dawley rats of 108 mg/kg (95 % C.I. 88-133 mg/kg).

Using intravenous injection of a 20 % MCAA solution in phosphate buffer, pH 7, Elf Atochem (1995) reported a LD_{50} of 75 (53-117) mg/kg in Sprague-Dawley rats. Clinical signs were hypokinesia, sedation, dyspnea, lateral decubitus, suffocation, coma and death (after 1-3 hours).

Mitroka (1989) reported the following 24-hour mortality rates in Sprague-Dawley rats injected intravenously with 20, 40, 80 and 100 mg/kg neutralized MCAA solution: 0/6, 1/6, 4/5 and 6/6 animals, respectively. Intoxication was characterized by a fixed posture, slight tremors, hyperreactivity to stimuli and a dark ruddy eye color. Death usually occurred 1-4 hours after treatment. Death was usually preceded by slow, labored respiration, wheezing, gasping for breath and unconsciousness. No consistent differences were observed in the gross appearance of organs of untreated and treated animals upon necropsy.

Using MCAA administration via implanted mini pumps, Rozman (2000a) found that the relationship between dose and time to MCAA-induced coma in male Sprague-Dawley rats followed the C x T = k relationship. The time-dose combinations were between about 125 mg/kg for about 60 minutes to about 50 mg/kg for about 120 minutes. The details of these experiments are not provided in the publication and have not been published until now.

3.1.3. Mice

Studies with single non-inhalation exposure

Berardi (1986) reported an oral LD_{50} of 260 mg/kg (95 % C.I. 214-316 mg/kg) using groups of 8-10 Swiss-Webster mice and gavage of a non-neutralized MCAA solution in water. Reported symptoms included immobility, head bobbing, ataxia, hyperreactivity to stimuli, slight tremors, clasping of front paws, labored respiration. Death occurred 3-6 hours after MCAA administration. Using dermal application of molten (65 °C) MCAA for 2 minutes followed by rinsing with water, a LD_{50} of 490 (428-562) mg/kg war found. After subcutaneous injection of MCAA into Swiss-Webster mice (8 animals/group), reported LD_{50} values were 150 (129-175) mg/kg for non-neutralized MCAA solution in water and 130 (105-160) mg/kg for neutralized MCAA solution.

Woodard et al (1941) found an oral LD_{50} of 255 mg/kg (95 % C.I. 196-334 mg/kg) using a neutralized MCAA solution and groups of 10 mice (strain not specified).

Morrison and Leake (1941) published an oral LD_{50} of 165 mg/kg for MCAA in mice.

Mitroka (1989) reported the following 24-hour mortality rates in Swiss-Webster mice injected intravenously with 100, 125, 160 and 200 mg/kg neutralized MCAA solution: 0/7, 1/4, 5/7 and 4/4 animals, respectively. Signs of intoxication appeared within 2 hours of treatment. Intoxication was characterized by a fixed posture, slight tremors, hyperreactivity to stimuli and a dark ruddy eye color. Death usually occurred 3-12 hours after treatment. Death was usually preceded by slow, labored respiration, wheezing, gasping for breath and unconsciousness. No consistent differences were observed in the gross appearance of organs of untreated and treated animals upon necropsy.

3.1.4. Other Species

Studies with single non-inhalation exposure

Woodard et al (1941) reported an oral LD_{50} of 79.8 mg/kg (95 % C.I. 71.8-88.6 mg/kg) for guinea pigs (10 animals/group) and about 90 mg/kg for rabbits (1-10 animals/group) using a neutralized MCAA solution (respective strains not specified).

Dalgaard-Mikkelsen and Rasmussen (1961) evaluated oral toxicity in cattle. Doses of 0, 50, 100 and 150 mg/kg were given to one animal each by stomach tube. A dose of 50 mg/kg resulted in inappetence of 24 hours duration. A dose of 100 mg/kg produced severe symptoms of intoxication with anorexia, ruminal atony, diarrhea and fibrillar muscle twitchings. The animal recovered within 2 weeks. Administration of 150 mg/kg caused colic, diarrhea, generalized fibrillar muscle twitching and dyspnea. The animal died 9 hours after dosing.

Christiansen and Dalgaard-Mikkelsen (1961) gave doses of 50 mg/kg by oral gavage to two geese. No symptoms were observed. The same animals were given 75 mg/kg two weeks later. After 3 hours, incoordination and seizures were observed; the animals died after 4 to 6 hours.

TABLE 3: SUMMARY OF ACUTE ORAL LETHAL DOSES IN LABORATORY ANIMALS

Species	Dose (mg/kg)	Study Type/Size	Type of MCAA solution	Signs and Symptoms	Reference
cattle	100	1 animal	no details reported	anorexia, ruminal atony, diarrhea, fibrillar muscle twitchings, survived	Dalgaard-Mikkelsen and Rasmussen, 1961
	150	1 animal		colic, diarrhea, generalized muscle twitching, dyspnea, death after 9 h	
rabbit	≈ 90	LD_{50} (no details reported)	neutralized solution	apathy	Woodard et al., 1941
guinea pig	79.8	LD_{50} (10 animals/group)	neutralized solution	apathy	Woodard et al., 1941

Species	Dose (mg/kg)	Study Type/Size	Type of MCAA solution	Signs and Symptoms	Reference
rat	102	LD_{50} (4 rats/group)	non-neutralized solution in water	central nervous system effects, death after 1-4 h	Berardi, 1986
rat	90.4	LD_{50} (10 rats/ group)	1 % solution in water	restlessness, crouching, balance disturbance, prone position, passiveness, drowsiness, incomplete eyelid closure, discharge from the eyes and dyspnea	Hoechst AG, 1979a
rat	76.2	LD_{50} (5-20 rats/group)	neutralized solution	apathy	Woodard et al., 1941
rat	55 580	LD_{50} (no details reported) LD_{50} (no details reported)	10 % non-neutralized solution in water 10 % neutralized solution	not reported	Maksimov and Dubinina, 1974
mouse	260	LD_{50} (8-10 mice/group)	non-neutralized solution	immobility, ataxia, slight tremors, labored respiration, death after 3-6 h	Berardi and Snyder,1983
mouse	255	LD_{50} (10 mice/group)	neutralized solution	apathy	Woodard et al., 1941
mouse	165	LD_{50} (no details reported)	no details reported	respiratory paralysis	Morrison and Leake, 1941
goose	50 75	2 animals same animals, two weeks later	no details reported	no symptoms incoordination, seizures, death after 4-6 h	Christiansen and Dalgaard-Mikkelsen, 1961

3.2. Nonlethal Toxicity

A limited number of studies describe nonlethal effects after inhalation exposure. Signs of irritation were observed after inhalation and after oral exposure of animals to MCAA.

3.2.1 Rats

Dow Chemical Co. (1987) exposed a group of 6 female and 6 male Fisher 344 rats to MCAA vapor by inhalation for 1 hour. The test material was vaporized into a stainless steel and glass 112 l Rochester-type inhalation chamber. The targeted concentration was 1000 ppm MCAA. The nominal chamber concentration was calculated based on the amount of test material used and the total air passed through the chamber during each exposure period. The nominal concentration was 964 ppm. The analytical concentration in the chamber was determined by taking an air sample from the chamber by pulling air through a glass tube containing silica gel during exposure and subjecting this sample to ion chromatography. The actual analytical concentration of MCAA vapor during exposure was calculated to be 66 ppm. It was stated that an analytical concentration of 1000 ppm was not feasible due to "substantial recrystallization of MCAA in the presence of room temperature (23 °C) air".

During all exposures, all rats (12/12) showed eye squint and slight lethargy. While in the text the expression "slight lethargy" is used, "lethargy" is used in the corresponding table. "The observations [prior to and after exposure] included an evaluation of fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity was also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as slight lethargy and other signs of altered central nervous system function." During the two-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remainder period (day 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

Hercules (1969a) exposed groups of 3 rats, mice and guinea pigs by inhalation to MCAA-saturated vapor generated at 75 °C (nominal concentration 27000 mg/m³; 7020 ppm). No deaths occurred after exposure for 3, 5 or 10 minutes, while nasal discharge and lung hyperemia were observed. In a similar study involving exposure of groups of 2 rats, mice and guinea pigs to saturated MCAA vapor (nominal concentration 31000 mg/m³; 8060 ppm) mild lacrimation, nasal discharge and dyspnea, but no mortality, was found (Hercules, 1969b). No experimental details were reported. The relevance of these studies is compromised by the fact that no information about the analytical concentrations was provided.

Maksimov and Dubinina (1974) reported an irritation threshold in rats of 23.7 mg/m³ (6.16 ppm) based on changes in the respiration rate. The exposure duration and other experimental details were not stated by the authors.

Studies with repeated inhalation exposure

Maksimov and Dubinina (1974) exposed 75 rats and 18 guinea pigs at 5.8±3.0 and 20.8±1.0 mg/m³ (1.5±0.8 and 5.4±0.3 ppm) MCAA over a period of 4 months (probably continuous exposure, exact exposure conditions were not stated by the authors). In the high dose group the following observations were made: a reduction in body weights of guinea pigs and rats during the second and tenth week; a reduction in oxygen uptake on day 3 and 15; a lowering of the rectal body temperature on day 2 and 15; a reduction in the chloride concentration in urine at the end of the second month and hemoglobinemia in the forth month. The pathomorphological investigation revealed inflammatory changes in the respiratory organs and tracheal catarrh, bronchitis and bronchopneumonia. In the low dose group only very slight effects were found: a lower oxygen uptake on the third day; a lower rectal

temperature on the 7th and 14th day and a reduction in the chloride concentration of the urine in the forth month. Morphological examinations revealed only slight effects on the respiratory organs, which were not considered significant compared to the control group by the authors. The experimental details were not described by the authors.

Studies with repeated non-inhalation exposure

NTP (1992) exposed groups of 5 male and 5 female F344 rats by gavage to 0, 7.5, 15, 30, 60 and 120 mg/kg MCAA in water once daily for a total of 12 dose days over a 16-day period. One male rat of the high dose group died on the third day of dosing (symptoms observed within 4 hours after dosing were lacrimation, prostration, bradypnea, decreased limb tone, ataxia and an impaired gasping reflex); no other deaths occurred. Lacrimation was also observed in males receiving 60 or 120 mg/kg and females receiving 15 mg/kg or higher. No gross or histologic lesions were observed.

Bryant et al. (1992), also described in NTP (1992), exposed groups of 20 male and 20 female F344 rats to oral doses of 0, 30, 60, 90, 120 or 150 mg/kg MCAA in water by gavage once daily, 5 d/w for up to 13 weeks. All rats receiving 120 or 150 mg/kg and all but one receiving 90 mg/kg died before the end of the exposure period. Other deaths included two male rats and one female rat receiving 60 mg/kg and one female rat receiving 30 mg/kg. A complete pathologic and histopathologic examination on all early deaths and all surviving animals at the end of the exposure period was done. The final mean body weights of rats surviving to the end of the study were similar to those of the controls. Relative heart weights of male and female rats in the 60 mg/kg groups as well as those of female rats in the 30 mg/kg group were significantly lower than controls. Relative weights of liver and kidney of male and female rats at 60 mg/kg were significantly greater than those of the controls. Blood urea nitrogen was increased in a dose-related trend in males at 90-150 mg/kg and in females at 60-150 mg/kg. Male rats at 150 mg/kg and females at 60, 120 and 150 mg/kg had a significant increase in serum alanine aminotransferase activity compared to controls. Chemical related degenerative and inflammatory changes (including cardiomyopathy) were observed in the hearts of male and female rats receiving 60, 90, 120 or 150 mg/kg. Acute or subacute cardiomyopathy was observed in rats in these dose groups that died before the end of the study and was considered to be the cause of death in these animals. No cardiomyopathy or other histological effects were observed at a dose of 30 mg/kg.

Bhat et al. (1991) gave a neutralized solution of 1.9 mmol/l MCAA in water as drinking water to male Sprague-Dawley rats (number not stated) for 90 days. On day 90, body weights were not significantly reduced compared to controls (426.8 ± 22.1 g vs. 448.2 ± 22.8 g); liver weights were reduced (13.25 ± 0.64 g vs. 14.68 ± 0.78 g). Minimal to mild morphological liver alterations were observed (enlarged portal veins, increased numbers of bile ducts, areas of edema and inflammatory cells surrounding the portal veins). Increased perivascular inflammation compared to controls was observed in the lungs. The dose tested was equivalent to about 20 mg/kg/day (BIBRA, 1997).

Daniel et al. (1991) administered the sodium salt of MCAA by oral gavage for a period of 90 consecutive days to Sprague-Dawley rats. Groups of 10 male and 10 female rats received daily doses of 0, 15, 30, 60 or 120 mg/kg. At 120 mg/kg, 30 % of females and 80 % of the males died, 7 of the 11 deaths occurred within the first 3 days of treatment, while the other 4 deaths occurred between the 14th and 90th day. In the early deaths hemorrhagic and congested lungs were observed but considered a postmortem

change. In the later deaths liver lesions were found. One male in each of the 60 and 15 mg/kg groups died. No apparent dose-response related differences between treated and control groups in body or organ weights were found with the exception of significant increased liver and kidney weights in females at 120 mg/kg. Relative liver weights were increased in both females and males at 60 and 120 mg/kg. Histopathologic examination revealed a significantly increase in chronic renal nephropathy and increased splenic pigmentation at 60 mg/kg/day (120 mg/kg/day group excluded due to mortality). In female, but not in male rats, significantly increased numbers of white blood cells were found at 30, 60 and 90 mg/kg and sporadic, but not dose-related changes in subpopulations (lymphocytes and monocytes) were seen at doses of 15 mg/kg or higher. Increased blood urea nitrogen levels in females at 120 mg/kg and in males at 15 and 30, but not 60 and 120 mg/kg as well as increased creatinine levels in females at 15 and 30, but not at 60 and 120 mg/kg and in males at all dose levels were found.

3.2.2. Mice

Studies with repeated non-inhalation exposure

NTP (1992) exposed groups of 5 male and 5 female B6C3F_1 mice by gavage to MCAA in water once daily using doses of 0, 15, 30, 60, 120 and 240 mg/kg for males and 0, 30, 60, 120, 240 and 480 mg/kg for females for a total of 12 dose days over a 16-day period. All mice receiving 240 mg/kg or higher died within 2 days; no other deaths occurred except for one male in the 15-mg/kg group. Clinical findings in animals that died included lacrimation, ataxia, hypoactivity, bradypnea, bradycardia, hypothermia, prostration, piloerection, decreased limb tone and impaired gasping. Lacrimation was also observed in females receiving 120 mg/kg. No changes in organ weights and gross or histologic lesions were observed.

Bryant et al. (1992), also described in NTP (1992), exposed groups of 20 male and 20 female B6C3F_1 mice to oral doses of 0, 25, 50, 100, 150 or 200 mg/kg MCAA in water by gavage once daily, 5 d/w for up to 13 weeks. All mice receiving 200 mg/kg died or were killed moribund before the end of the exposure period (all but two died within the first week). Two males given 200 mg/kg and one female given 100 mg/kg died from gavage trauma; two male controls died from unknown causes. With the exception of females receiving 200 mg/kg, the mean body weights of dosed mice were similar to those of controls. Cholinesterase levels were significantly decreased in female mice receiving 150 or 200 mg/kg at weeks 8 and 13. No chemical related lesions were observed in mice of either sex. Hepatocellular vacuolization was seen in mice in the 200-mg/kg group that died during the study. No effects were observed at a dose of 100 mg/kg.

3.3. Developmental/Reproductive Toxicity

No studies evaluating developmental or reproductive toxic effects after inhalation exposure were located in the literature (Medline and Toxline search November 2003).

Studies with non-inhalation exposure

Smith et al. (1990) exposed pregnant Long-Evans rats to 0, 17, 35, 70 and 140 mg/kg (daily gavage) during gestational day 6 to 15. The body weight increase was significantly reduced in the highest exposure group. No effects on the number of resorptions and birth weight was found. The rate of visceral

545 malformations (especially of the heart and cardiovascular system) was between 1.2 % in controls and 6.4
546 % in the highest dose group, but no dose-dependency was observed. No skeletal malformations were
547 found. This study has only been published as an abstract and no details were reported.

548 Johnson et al. (1998) exposed pregnant Sprague-Dawley rats during gestational days 1-22 to 1570
549 ppm MCAA in drinking water as well as to other halogenated hydrocarbons. The authors calculated the
550 dose for exposure to MCAA as 33 mg/kg/day. No signs of maternal toxicity were observed. No effects on
551 the number of mean implantation sites and resorption sites was found. MCAA produced no cardiac
552 abnormalities. Of the substances tested only trichloroacetic acid caused a significant increase in the
553 number of cardiac abnormalities.

554 Bhunya and Das (1987) injected single doses of 12.5, 25 and 50 mg/kg MCAA intraperitoneally
555 into groups of 3 male Swiss mice. After 35 days an increased number of malformed sperm was found in
556 the two highest dose groups.

557 **3.4. Genotoxicity**

558 In genetic toxicity testing in the NTP study (NTP, 1992), MCAA was not mutagenic in
559 Salmonella typhimurium strains TA100, TA1535, TA1537 and TA98 (with and without metabolic
560 activation using rat liver S9 mix). It induced trifluorothymidine resistance in L5178Y mouse lymphoma
561 cells in the absence of S9 mix and induced sister chromatid exchanges in Chinese hamster ovary cells in
562 the absence of S9 mix, but not in its presence. MCAA did not induce chromosomal aberrations in Chinese
563 hamster ovary cells (with and without activation). MCAA administered in feed was negative for the
564 induction of sex-linked recessive lethal mutations in germ cells of male Drosophila melanogaster, while
565 results were equivocal when MCAA was administered by injection.

566 Several other reports on negative results in assays for mutations in bacteria and positive as well as
567 negative results in tests for mutations and sister chromatid exchanges in eucaryotic cells in vitro have
568 been published (see BG Chemie, 1992; IUCLID, 1996; ECETOC, 1999).

569 Bhunya and Das (1987) injected 12.5, 25 and 50 mg/kg one time or 5 times 10 mg/kg MCAA
570 intraperitoneally into male and female Swiss mice. A significantly increased rate of chromosomal
571 aberrations was observed for all doses after 6-120 hours in the bone marrow. No effect was seen 24 hours
572 after oral gavage or subcutaneous injection of 50 mg/kg.

573 **3.5. Carcinogenicity**

574 In a NTP carcinogenicity study (NTP, 1992) male and female F344 rats were given 0, 15 or 30
575 mg/kg and male and female $B6C3F_1$ mice were given 0, 50 and 100 mg/kg by gavage of a MCAA
576 solution in water for 5 days/week for 2 years. In both species there was no evidence of carcinogenic
577 activity of MCAA. In mice, but not in rats, a dose-dependent increase in inflammation of the nasal
578 mucosa and metaplasia of the olfactory epithelium was found, as well as squamous metaplasia of the
579 forestomach.

DeAngelo et al. (1997) performed a 2-year carcinogenicity study in F344 rats. Animals were given 50, 500 and 2000 mg MCAA/l in drinking water. Due to severe inhibition of body weight gain, the high dose was reduced to 1500 mg/l at 8 weeks and further to 1000 mg/l at 24 weeks. The authors calculated time-weighted mean daily doses of 3.5, 26.1 and 59.9 mg MCAA/kg/day. They found no significant differences in animal survival between the control and treatment groups. No increased incidence of neoplastic lesions were found.

3.6. Summary

The only animal study reporting lethal effects after inhalation exposure was an inadequately described study in which a LC_{50} of 46.8 ppm for 4 hours was reported for rats (Maksimov and Dubinina, 1974). Several studies report lethal effects after oral exposure. LD_{50} data presented in Table 3 are mostly between 50-200 mg/kg for rats, mice and guinea pigs. In addition, lethal doses in other species were 200 mg/kg in a rhesus monkey (Dow Chemical Co., 1976), 150 mg/kg in a cow (Dalgaard-Mikkelsen and Rasmussen, 1961) and 75 mg/kg in geese (Christiansen and Dalgaard-Mikkelsen, 1961).

In a single inhalation experiment on rats, eye squint and slight lethargy were observed during exposure at 66 ppm for 1 hour (Dow Chemical Co., 1987). In an inadequately reported study, an irritation threshold in rats of 6.16 ppm and a NOEL for histological changes in the respiratory tract in rats and guinea pigs of 1.5 ppm after 4 months have been reported (Maksimov and Dubinina, 1974).

After repeated oral gavage for 2 weeks, lacrimation was observed in male rats receiving 60 or 120 mg/kg and in female rats receiving 15 mg/kg or higher (NTP, 1992). In experiments performed in parallel, lacrimation was also observed in female mice receiving 120 mg/kg (NTP, 1992). In subchronic studies using oral exposure by gavage or drinking water, a doses of 30 mg/kg in rats and 100 mg/kg in mice had no or only minor effects (Bryant et al., 1992; NTP, 1992; Bhat et al., 1991; Daniel et al., 1991).

The study by Smith et al. (1990) suggests that high doses of MCAA (close to the LD_{50} in other rat strains) can cause maternal toxicity and malformations in the offspring. The effect on fertility upon intraperitoneal injection (Bhunya and Das, 1987) requires further studies using other exposure routes. There is no evidence of genotoxic potential in bacterial mutagenicity studies, in in-vitro chromosomal aberration tests, in in-vitro and in-vivo primary DNA damage assays. Gene mutation tests in mammalian cells gave contradictory results and in one study increased chromosomal aberrations were found after intraperitoneal injection in mice. No carcinogenic activity of MCAA was found in mice and rats after oral administration of MCAA by gavage or drinking water.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No quantitative absorption rate data are available for inhalation exposure. An oral absorption rate of 82 % (^{14}C recovery in urine was 70 %) was found in a rat that was given 1-^{14}C-labelled MCAA (Dow Chemical Co., 1976). A rate of 90 % in 24 hours for the cumulative excretion of MCAA in urine was reported in Sprague-Dawley rats after an oral dose of 9.4 mg/kg 1-^{14}C-labelled MCAA (Kaphalia et al., 1992). Berardi (1986) reported values for cumulative excretion in urine of 51 % in 24 hours and 52.5 % in 72 hours in Sprague-Dawley rats and 32.0-59.3 % in 24 hours and 33.7-60.8 % in 72 hours in Swiss-Webster mice. Lethal effects in humans after dermal contact with liquid MCAA indicate a considerable dermal absorption.

Yllner (1971) injected doses of 0.07, 0.09 and 0.1 g/kg 1-^{14}C-labelled MCAA subcutaneously into mice and measured radioactivity after 24, 48 and 72 hours in urine, faeces and expired air. Within 72 hours, 82-88 % of the radioactivity were eliminated in urine, 8 % via the lungs and 0.2-0.3 % in faeces and 2-3 % remained in the body. The main metabolites found in urine were S-carboxymethyl-L-cysteine (33-43 % in free form and 1-6 % as glutathione conjugate) and thiodiacetic acid (33-42 %) as well as MCAA (6-22 %), glycolic acid (3-5 %) and oxalic acid (0.1-0.2 %). The authors suggested two metabolic pathways: 1) conjugation with glutathione resulting in formation of S-carboxymethyl-glutathione which can be further metabolized to S-carboxymethyl-L-cysteine and further on to thiodiacetic acid and 2) enzymatic hydrolysis of the chlorine-carbon bond and formation of glycolic acid that can be degraded completely to carbon dioxide.

In the urine of rats thiodiglycolic acid, but not S-carboxymethyl-L-cysteine was found. However, according to the study, S-carboxymethyl-L-cysteine may have been present in bile, but could not be identified unequivocally (Dow Chemical Co., 1976).

Hayes et al. (1972; 1973) injected 162 mg/kg 1-^{14}C-labelled MCAA subcutaneously into rats. After 2 hours higher radioactivity was found in kidneys and liver than in plasma, while heart and brain had similar levels as plasma. A similar distribution was found after administration of 53 mg/kg. A biphasic elimination curve was observed with half-life times of 90 minutes and 17 hours.

The fact that rodents can be exposed for long periods of time (90 days or 2 years) (Bryant et al., 1992; NTP, 1992; Daniel et al., 1991; DeAngelo et al., 1997) at daily doses close to the oral LD_{50} (see Table 3) argues for rapid clearance of MCAA after each exposure.

4.2. Mechanism of Toxicity

The biochemical basis of systemic MCAA toxicity is the inhibition of single enzymes of the glycolytic and tricarboxylic acid metabolic pathways. The blockage of these metabolic processes results in inhibition of energy metabolism (ATP generation) and in the accumulation of lactic acid in the glycolytic pathway, which causes metabolic acidosis.

Prolonged incubation of isolated rat heart mitochondria with MCAA inhibits both pyruvate dehydrogenase and α-ketoglutarate dehydrogenase (van Hinsbergh and Vermeer, 1994), via an indirect inhibition through formation of oxalate from MCAA (Mitroka, 1989), or a direct inhibition through slow alkylation or sulfhydryl groups (van Hinsbergh and Vermeer, 1994). Since the inhibition of these enzymes of the glycolytic (pyruvate dehydrogenase) and tricarboxylic acid (α-ketoglutarate dehydrogenase) metabolic pathways has a major impact on cellular energy production, the cell would then revert to anaerobic glycolysis, which results in lactate accumulation (van Hinsbergh and Vermeer, 1994). In vitro, MCAA inhibited oxidation of radiolabelled acetate to carbon dioxide by rat liver homogenate (Hayes et al., 1973), indicating an inhibitory effect on the tricarboxylic acid cycle. Blockade of aerobic energy metabolism can be expected to especially damage organs and tissue with a high energy-demand, such as heart, CNS and skeletal muscles (Kulling et al., 1992).

It has been suggested that in analogy to monofluoroacetic acid, MCAA could also inhibit the tricarboxylic-acid-cycle enzyme aconitase (IUCLID, 1996). Experimental evidence suggests organ-specific differences with respect to aconitase inhibition by MCAA and monofluoroacetic acid: about 1.5-2 hours after oral administration of 24, 48 or 96 mg MCAA/kg to F344 rats, an inhibition of aconitase was detected in the heart (54, 55 and 46 % inhibition, respectively), but not in the liver (0 % inhibition at all doses), while monofluoroacetic acid inhibited aconitase in both organs (4.0, 10.5 and 21.0 % inhibition, respectively; same inhibition in both organs) (NTP, 1992; Bryant et al., 1992). These findings suggest, that different isoenzymes with different susceptibility to the inhibitory effect of MCAA are expressed in the two organs. In the experiments, no dose-response relationship was revealed: a 33-55 % inhibition was found after doses between 4 and 150 mg/kg.

After intravenous injection of 40 or 80 mg/kg MCAA (neutralized solution in phosphate buffer) to rats, blood and cerebrospinal fluid lactate concentrations increased progressively with time until death (1-2 hours after dosing) (Mitroka, 1989). In the blood, a significant increase in lactate concentrations was found for the 80-mg/kg dose starting at 60 minutes, while a very slight increase was seen for the 40-mg/kg dose. In the cerebrospinal fluid, significant increases were found for the 40-mg/kg dose from 120 minutes and for the 80-mg/kg dose from 60 minutes (Mitroka, 1989). The accumulation of lactate in the brain can contribute to the lethal effects of MCAA, especially since the removal of lactate from the brain via the blood-brain barrier is slow. The damage of the blood-brain barrier by MCAA has also been shown by Berardi (1986) and Berardi et al. (1987): nearly lethal doses administered orally to mice (257 and 380 mg/kg) led to an increased entry of radiolabeled dopamine and inulin into all brain regions; in addition, red blood cells were found in the brain parenchyma. The associated neurologic dysfunction was characterized by front paw rigidity. At doses that caused no or little mortality (80, 118 and 174 mg/kg) the concentration of radioactive inulin did not differ from controls.

Unlike monofluoroacetate and like monoiodoacetic acid, MCAA can bind to sulfhydryl groups (van Hinsbergh and Vermeer, 1994; Yllner, 1971; Hayes et al., 1973). After oral administration, MCAA was shown to bind to sulfhydryl groups in the kidney and liver of rats. Direct inhibition of sulfhydryl groups in the kidney may account for the anuria present in animals receiving toxic levels of MCAA, which could contribute to enzyme inhibition and renal dysfunction (Hayes et al., 1973). Renal insufficiency was also found in humans after oral intoxication (Kulling et al. 1992) and renal nephropathy was found after subchronic oral exposure in rats (Daniel et al., 1991).

MCAA causes severe local effects on skin and eyes: after occlusive application of 100 and 500 mg MCAA paste (solution in 0.05 ml 0.9 % NaCl) to the skin of rabbits, corrosion (at both doses) and mortality (all animals died at the higher dose) were observed (Hoechst AG, 1979f). After occlusive application for 24 hours of a 10 % solution to the intact rabbit skin, there was marked hyperemia and edema (Rodionova and Ivanov, 1979). Sodium monochloroacetate did not produce any signs of irritation when applied for 4 hours to the skin of rabbits (Hoechst AG, 1988d). While MCAA was extremely irritant to the rabbit eye (instillation of 100 mg MCAA as paste into conjunctival sac; Hoechst AG, 1979f), sodium monochloroacetate induced moderate irritation (instillation of 100 mg sodium monochloroacetate into conjunctival sac; Hoechst AG, 1988d). From this it can be expected that inhalation of MCAA vapor or MCAA aerosol can cause local irritation and tissue damage in the respiratory tract either by local decrease of the pH or by local enzyme inhibition.

4.3. Structure-Activity Relationships

4.3.1. Studies Using Alkyl Esters of MCAA

Hoechst AG (1988a) determined the acute inhalation toxicity of chloroacetic acid methyl ester. Groups of 5 female and 5 female Wistar rats were exposed whole-body for 4 hours in an exposure chamber at 90, 210, 315 and 385 ppm. The concentration in the exposure chamber was measured by infrared spectroscopy using a Miran analyzer and by gas chromatography. The post-exposure observation period was 14 days. Mortality rates were 0/10 animals at 90 and 210 ppm, 7/10 at 315 ppm and 10/10 at 385 ppm. Death occurred between 270 minutes and 6 days after exposure.

Torkelson et al. (1971) exposed groups of 4-5 female rats in an exposure chamber to different concentrations of chloroacetic acid methyl ester for different exposure times. The following mortality rates were observed for different exposure periods: 2/4 animals at 1000 ppm for 1 hour, 4/5 at 2000 ppm and 0/4 at 500 ppm for 2 hours, 5/5 at 2000 ppm, 5/5 at 500 ppm and 0/4 at 250 ppm for 4 hours, and 0/4 at 100 ppm at 7 hours. The authors noted severe irritation at 250-1000 ppm and slight irritation at 100 ppm. In rabbits, 7- and 4-hour exposures to 100 ppm caused delayed conjunctival and corneal irritation, while 50 ppm did not cause eye irritation.

Studies with repeated inhalation exposure

Hoechst AG (1988b) exposed groups of 10 female and 10 male Wistar rats repeatedly to chloroacetic acid methyl ester at 0, 10, 33 and 100 ppm (6 h/d, 5 d/w, total of 20 exposures). Mean concentrations measured in the exposure chamber by a Miran infrared analyzer were 10.4, 32.3 and 100.1 ppm, respectively. Gross morphological and histological examinations were performed in half of the animals after the last exposure and in the other half after a 14-day recovery period. At 10 ppm narrowed palpebral fissures were observed only during the first exposure, which was interpreted as a sign of irritation. Additional signs in the 33-ppm group were sneezing and increased hair grooming, which were observed only during individual exposures. Additional signs in the 100-ppm group were incoordination, retracted flanks, irregular respiration, passiveness and standing hair, some of which persisted until the next morning and into the recovery period. A decreased food consumption and body weight increase and significantly increased relative lung weights were found in the 100-ppm group. No histopathological alterations or differences in hematological and clinical chemistry parameters were observed.

Studies with non-inhalation exposure

Hoechst AG (1979b) determined the acute oral toxicity of chloroacetic acid ethyl ester administered to groups of 10 female Wistar rats by gavage of a 5 %(w/v) solution in sesame oil. The post exposure observation period was 14 days. Mortality rates were 0/10 animals at a dose of 80 mg/kg, 2/10 at 125 mg/kg, 5/10 at 200 mg/kg and 10/10 at 315 mg/kg. Death occurred between 136 minutes and 24 hours after gavage. Symptoms before death included crouching, balance disturbance, prone position, and passiveness. No abnormal findings were observed in gross pathologic examinations. Using Probit analysis, a LD_{50} of 180 (151-215) mg/kg was calculated by the authors.

Using the same study design, a 0.5%(w/v) solution of chloroacetic acid methyl ester in sesame oil was used (Hoechst AG, 1979c). Mortality rates were 0/10 animals at doses of 50 and 80 mg/kg, 4/10 at 100 mg/kg, 8/10 at 125 mg/kg and 10/10 at 200 and 315 mg/kg. Using Probit analysis, a LD_{50} of 107 (95 % C.I. 97.2-121) mg/kg was calculated by the authors.

4.3.2. Studies with Other Monohaloacetic Acids

Hayes et al. (1973) found that the subcutaneous LD_{50} for three haloacetic acids varied considerably in rats and that toxicity is probably caused by differing mechanisms. LD_{50} (95 % C.I.) were 5 (4-6) mg/kg for monofluoroacetic acid, 60 (54-67) mg/kg for monoiodoacetic acid and 108 (88-133) mg/kg for MCAA. The mean time to death was 130 (112-151) minutes for MCAA, 310 (292-360) minutes for monofluoroacetic acid and 480 (343-672) minutes for monoiodoacetic acid. MCAA and monoiodoacetic acid, but not monofluoroacetic acid, significantly reduced the total sulfhydryl concentration in rat liver at a LD_{90} dose after 5 % of the time to death. In vitro, MCAA did not alcylate sulfhydryl groups of cysteine.

In mice, Morrison and Leake (1941) found oral LD_{50} values of 63 mg/kg for monoiodoacetate, 100 mg/kg for monobromoacetate and 165 mg/kg for MCAA.

4.3.3. Conclusions from Structure-Activity Relationships

Several studies evaluated the toxicity of monochloroacetic acid esters on rats. While the LD_{50} values for oral administration are comparable to the LD_{50} values for MCAA (see Table 3), lethal effects after inhalation exposure to monochloroacetic acid esters occurred at considerable higher concentrations: while Maksimov and Dubinina (1974) reported a 4-hour LC_{50} of 46.8 ppm for MCAA, a 4-hour exposure at 210 ppm chloroacetic methyl ester did not result in deaths and at 315 ppm, 7/10 rats died (Hoechst AG, 1988a). This difference suggests toxicokinetic and toxicodynamic differences between MCAA and its alkyl esters. Compared with MCAA, local effects of its esters are less likely, because a) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value; and b) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first; although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to monochloroacetic esters compared to MCAA. In

summary, the inhalation studies using monochloroacetic acid esters cannot be used as supportive evidence for MCAA data.

Oral lethality data for different monohaloacetic acids found a considerable difference in LD_{50} values. These findings and the probable differences in biochemical mechanism presented in Section 4.2 argue for different toxicodynamic properties of the different monohaloacetic acids and do not support the use of data on other monohaloacetic acids as supportive evidence for MCAA data.

4.4. Other Relevant Information

4.4.1. Species Variability

With regard to lethal effects, it has been suggested that these are mediated by damage of the blood-brain barrier and by metabolic acidosis, which is especially due to lactate accumulation in the brain which, in turn is secondary to inhibition of single enzymes of the glycolysis and tricarboxylic acid cycle (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and aconitase). Since these enzymes are evolutionary highly conserved, a limited interspecies variability can be assumed. The available oral lethality data support this conclusion and indicate that the variability in LD_{50} values is small: LD_{50} values for different species (mean values of LD_{50} values given in Table 3) were 90 mg/kg for rabbits, 79.8 mg/kg for guinea pigs, 80.9 mg/kg for rats (mean of all LD_{50}s except the 580 mg/kg value) and 227 mg/kg in mice; moreover, one cattle survived an oral dose of 100 mg/kg showing only moderate toxic effects (another died at 150 mg/kg) (Dalgaard-Mikkelsen and Rasmussen, 1961) and a rhesus monkey survived intravenous injection of 75 mg/kg (and died after another dose of 200 mg/kg the next day) (Dow Chemical Co., 1976). It should be noted that good data are available for two of these species only, namely rats and mice, and that the difference between these two species is also in line with what can be expected on the basis of a standard body weight$^{0.75}$ scaling. No data are available that would suggest a large species difference for local effects in the respiratory tract.

4.4.2. Intraspecies Variability

With regard to lethal effects, it has been suggested that these are mediated by damage of the blood-brain barrier and by metabolic acidosis, which is especially due to lactate accumulation in the brain which, in turn is secondary to inhibition of single enzymes of the glycolysis and tricarboxylic acid cycle (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and aconitase). Since these enzymes are housekeeping enzymes, which are required for energy metabolism and show a constant expression level, a limited intraspecies variability can be assumed. The available oral lethality data support this conclusion and indicate that the variability in LD_{50} values within individual species is small because the reported LD_{50} values for differed species varied within each species by less than a factor of 2 (see Table 3). Some variation is indicated by the finding that repeated oral exposure of rats to 120 mg/kg/day led to death in 8/10 males, but only in 3/10 females (Daniel et al., 1991). The contribution to death of local effects in the respiratory tract upon inhalation is unknown.

At lower concentrations that do not lead to systemic effects, MCAA is irritating to the eye and mucosal surfaces. The mechanism for this effect may involve both, local lowering of the pH value and local metabolic blockage by enzyme inhibition. A limited interindividual variability can be assumed for

this local effect because it involves direct effects on the tissue (acidity) or effects on highly conserved enzymes, which are expected not to differ considerably between individuals.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Clariant GmbH (2000) found no respiratory tract irritation, effects on lung function parameters or irritation of skin and mucous membranes in >33 workers potentially exposed to MCAA concentrations between <0.13 ppm for 3 hours and 0.31 ppm for 7 hours.

Maksimov and Dubinina (1974) and Rodionova and Ivanov (1979) reported an irritation threshold for humans of 5.7 mg/m³ (1.48 ppm) (for this study an exposure time of 1 minute was stated in Izmerov et al., 1982). The experimental details were not stated by the authors and, therefore, evaluation of the studies is impossible.

Reported odor thresholds are 0.01 ppm, cited from an unpublished correspondence from Dow Chemical Co. in AIHA (1993), and 0.045 ppm (Oelert and Florian, 1972) (in the latter study it was unclear if the value was cited from the literature or measured by the authors).

5.2. Animal Data Relevant to AEGL-1

Maksimov and Dubinina (1974) reported an irritation threshold in rats of 23.7 mg/m³ (6.16 ppm) based on changes in the respiration rate.

After exposure of rats and guinea pigs at 5.8 and 20.8 mg/m³ (1.5 and 5.4 ppm) MCAA over a period of 4 months (probably continuous exposure, exact exposure conditions were not stated by the authors) slightly reduced body weights, effects on metabolism (reduced oxygen uptake and lower rectal body temperature); kidney function (reduced chloride concentration in urine and hemoglobinemia) and inflammatory alterations of respiratory organs were found in the high dose group. In the low dose group only very slight effects (lower oxygen uptake and lower rectal temperature, lower urine chloride concentration) were found (Maksimov and Dubinina, 1974).

5.3. Derivation of AEGL-1

No definitive study was available for the derivation of AEGL-1 values.

The human irritation threshold reported by Maksimov and Dubinina (1974) was inadequately described and, therefore, was not considered an adequate basis for the derivation of AEGL-1 values. The report by Clariant GmbH (2000) was not considered an adequate basis because the depth of the routine medical examination was not reported and the time point of the examination was not linked to an actual exposure assessment. Moreover, the exposure assessment using about 1 to 2 measurements per year was considered insufficient.

Therefore, due to insufficient data, AEGL-1 values were not recommended.

Due to the lack of an adequately performed study reporting an odor threshold for MCAA, no level of distinct odor awareness (LOA) was derived.

836 **TABLE 4: AEGL-1 VALUES FOR MONOCHLOROACETIC ACID**

837 AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
838 AEGL-1	N.R. [a]	N.R.	N.R.	N.R.	N.R.

839 [a] not recommended due to insufficient data

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 ml of a 0.05 % MCAA solution in water did not result in adverse effects in three human volunteers. Assuming a body weight of 70 kg and 0.05 % as 500 mg/l, this oral exposure corresponds to a daily dose of

500 mg/l x 0.3 l/d x 1/70 kg = 2.1 mg/kg/day

6.2. Animal Data Relevant to AEGL-2

Dow Chemical Co. (1987) exposed a group of 6 female and 6 male Fischer 344 rats to MCAA vapor by inhalation for 1 hour. The targeted concentration was 1000 ppm MCAA and the nominal concentration was 964 ppm, however, the analytical concentration of MCAA vapor during exposure was found to be 66 ppm. It was stated that a concentration of 1000 ppm could not be achieved due to "substantial recrystallization of MCAA in the presence of room temperature (23 °C) air". During exposure, all rats squinted and appeared "slightly lethargic" (stated in the text) / "lethargic" (stated in the tables). During the two-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remainder period (day 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

6.3. Derivation of AEGL-2

For the derivation of AEGL-2 values, the study in rats by Dow Chemical Co. (1987) was used because it was the only relevant inhalation study available. Exposure of rats to 66 ppm for 1 hour resulted in eye squint and in some lethargy, which might be interpreted as an effect on the central nervous system. No severe effects occurred. There is some uncertainty as to the exposure because of the large discrepancy between the nominal exposure concentration of 964 ppm and the analytically measured exposure concentration of 66 ppm. The authors did not discuss whether recrystallization of MCAA took place completely outside the exposure chamber (i.e. before the air stream entered the chamber) or whether uptake of recrystallized MCAA by routes other than inhalation (e.g. dermal and oral uptake after deposition on the hair) might have occurred. In case of an additional exposure, the measured air concentration of 66 ppm and be regarded as an conservative exposure assumption. The AEGL-2 values were based on a 1-hour exposure to 66 ppm.

Time scaling using the equation $C^n * t = k$ was done to derive the other exposure duration-specific values. Due to lack of a definitive data set, an n of 3 was used in the exponential function for extrapolation from the experimental period (1 hour) to shorter exposure periods and an n of 1 was used for extrapolation to longer exposure periods. The calculations of exposure concentrations scaled to AEGL-2 time periods are shown in Appendix A.

A total uncertainty factor of 10 was used. An uncertainty factor of 3 was applied for interspecies variability because 1) the effect level was considered below that of an AEGL-2, 2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects (see Section 4.4.1), and 3) because of the limited toxicodynamic variability as the enzymes inhibited by

MCAA do not vary considerably within and between species. An uncertainty factor of 3 was applied for intraspecies variability because of the limited toxicokinetic variability with respect to local effects and because of the limited toxicodynamic variability with respect to systemic effects since the enzymes inhibited by MCAA do not vary considerably within and between species.

The values are listed in the Table 5 below.

TABLE 5: AEGL-2 VALUES FOR MONOCHLOROACETIC ACID

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-2	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)

885 ## 7. DATA ANALYSIS FOR AEGL-3

886 ### 7.1. Human Data Relevant to AEGL-3

887 No reports on deaths after inhalation of MCAA are available in the literature. Fatal cases and life-
888 threatening poisonings in workers have been described after skin contact (Kulling et al., 1992; IUCLID,
889 1996; BUA, 1994), however, exact doses have not been reported.

890 Only one study reporting lethality after oral uptake was located: Feldhaus et al. (1993) and
891 Rogers (1995) reported the case of a 5-year old girl that was accidentally given 5-6 ml of an 80 % MCAA
892 containing wart remover, resulting in a dose of 4.0-4.8 g MCAA corresponding to 200-240 mg/kg
893 assuming a body weight of 20 kg. The girl died 8 hours post-ingestion despite medical intervention. An
894 autopsy revealed diffuse gastric erosions, fatty liver and pulmonary and cerebral edema. The post mortem
895 MCAA concentration in serum was 100 mg/l (assuming a serum volume of 750 ml, this concentration
896 corresponds to a total MCAA amount of about 75 mg in serum) as determined by gas chromatography/
897 mass spectroscopy.

898 Morrison and Leake (1941) reported that daily oral exposure for 60 days to 300 ml of a 0.05 %
899 MCAA solution in water did not result in adverse effects in three human volunteers. Assuming a body
900 weight of 70 kg and 0.05 % as 500 mg/l, this oral exposure corresponds to a daily dose of
901 500 mg/l x 0.3 l/d x 1/70 kg = 2.1 mg/kg/day.

902 ### 7.2. Animal Data Relevant to AEGL-3

903 Maksimov and Dubinina (1974) reported a LC_{50} in rats of 180 (146-221) mg/m³ (46.8 ppm) for 4
904 hours without providing experimental details. Assuming a body weight of 0.3 kg for rats (EPA, 1986), a
905 pulmonary absorption rate of 100 % and deriving a respiration rate using the allometric relationship
906 published by EPA (EPA, 1988)
907 ventilation rate (m³/d) = 0.80 x body weight (kg) $^{0.8206}$ (EPA, 1988)
908 ventilation rate = 0.80 x 0.3 $^{0.8206}$ = 0.298 m³/d
909 the corresponding dose can be calculated as:
910 dose (mg/kg) = exp. conc. (mg/m³) x ventilation rate (m³/d) x exp. time (d) x 1/body weight (kg)
911 dose = 180 mg/m³ x 0.298 m³/d x 4/24 d x 1/0.3 kg = 29.8 mg/kg.

912 Hercules (1969a; 1969b) reported that exposure of rats, mice and guinea pigs to MCAA-saturated
913 vapor generated at 75 °C (reported nominal concentrations 7020-8060 ppm) for up to 10 minutes resulted
914 in irritation (mild lacrimation, nasal discharge), dyspnea and lung hyperemia, but did not cause lethality.
915 Since no experimental details, especially no analytical concentrations, were reported these studies provide
916 little meaningful information.

917 Oral LD_{50} data are presented in Table 3. Hoechst AG (1979a) administered doses of 0, 40, 63,
918 100 and 160 mg/kg MCAA to groups of 10 female Wistar rats using gavage of 1 %(w/v) solutions of
919 MCAA in water. Using Probit analysis, a LD_{50} of 90.4 (95 % C.I. 73.6-112) mg/kg was calculated by the
920 authors. The very high LD_{50} of 580 mg/kg for neutralized MCAA solution found in rats by Maksimov and
921 Dubinina (1974) will not be considered further because 1) this value is much higher than other values

reported for neutralized MCAA solutions (see Table 3), which are similar to non-neutralized MCAA solutions and 2) due to inadequate data presentation it can not be excluded that neutralization was carried out by addition of sodium hydroxide (solid or as solution) to the acidic MCAA solution; this could give rise to high pH either locally in the solution or temporarily due to overtitration and thus cause nucleophilic substitution (hydrolysis) of the chlorine moiety in MCAA resulting in reaction to the much less toxic glycolic acid.

7.3. Derivation of AEGL-3

For the derivation of AEGL-3 values, no relevant and well-documented LC_{50} studies were available.

Although oral lethality data in animals are available, these were not used as a basis for derivation of AEGL values because of the uncertainty regarding local effects of MCAA in the respiratory tract. Several mechanistic aspects point at a possible role of local effects: a) MCAA has a pK_a of 2.85 and thus is a strong acid, which may cause irritation and local tissue damage by its acidity alone; b) MCAA can bind to sulfhydryl groups (van Hinsbergh and Vermeer, 1994; Yllner, 1971; Hayes et al., 1973), e.g. those of reduced glutathione, and may thus cause lung damage through glutathione depletion; and c) during inhalation exposure, local concentrations of MCAA in the respiratory tract could cause local tissue damage by enzyme inhibition already in doses lower than those required for systemic effects in oral studies.

Experimental findings support a possible local effect on the respiratory tract: a) the available inhalation studies report effects on the respiratory tract, i.e., Hercules (1969a) reported lacrimation, nasal discharge, dyspnea and lung hyperemia in rats and Maksimov and Dubinina (1974) reported inflammation in the respiratory organs, tracheal catarrh, bronchitis and bronchopneumonia in rats; and b) MCAA causes severe local damage to skin and eyes (Hoechst AG, 1979f; 1988d; see Section 4.2).

Unfortunately, in the only LC_{50} study located in the literature (Maksimov and Dubinina, 1974), data presentation is inadequate. Since pathological findings were not reported it remains unknown if rats died from local lung tissue destruction or from systemic toxicity (i.e. acidosis affecting CNS or heart). With respect to systemic effects, it could be argued that the rat LC_{50} value of 46.8 ppm for 4 hours (Maksimov and Dubinina, 1974), corresponding to a dose of 29.8 mg/kg (see Section 7.2), is not supported by studies reporting oral LD_{50} values around 90 mg/kg for rats (see Table 3 and Fig. 1). However, as discussed above a higher toxicity of MCAA for the inhalation route compared to the oral route cannot be ruled out. The data presented in Figure 1 suggest that upon inhalation exposure lethal effects might occur at lower doses compared to oral exposure.

Inhalation studies using monochloroacetic acid esters revealed no mortality after 4-hour exposure to up to 210 or 250 ppm (Hoechst AG, 1988a; Torkelson et al., 1971). These data were not considered relevant for the derivation of AEGL-3 values, because compared with MCAA local effects of its esters are less likely, because a) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value; and b) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first; although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the

deposited ester will enter systemic circulation before it is hydrolyzed and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to monochloroacetic esters compared to MCAA.

Due to the inadequate presentation of the only LC_{50} available (Maksimov and Dubinina, 1974) and the uncertainties of a route-to-route extrapolation, no AEGL-3 values were derived.

TABLE 6: AEGL-3 VALUES FOR MONOCHLOROACETIC ACID

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-3	N.R. [a]	N.R.	N.R.	N.R.	N.R.

[a] not recommended due to insufficient data

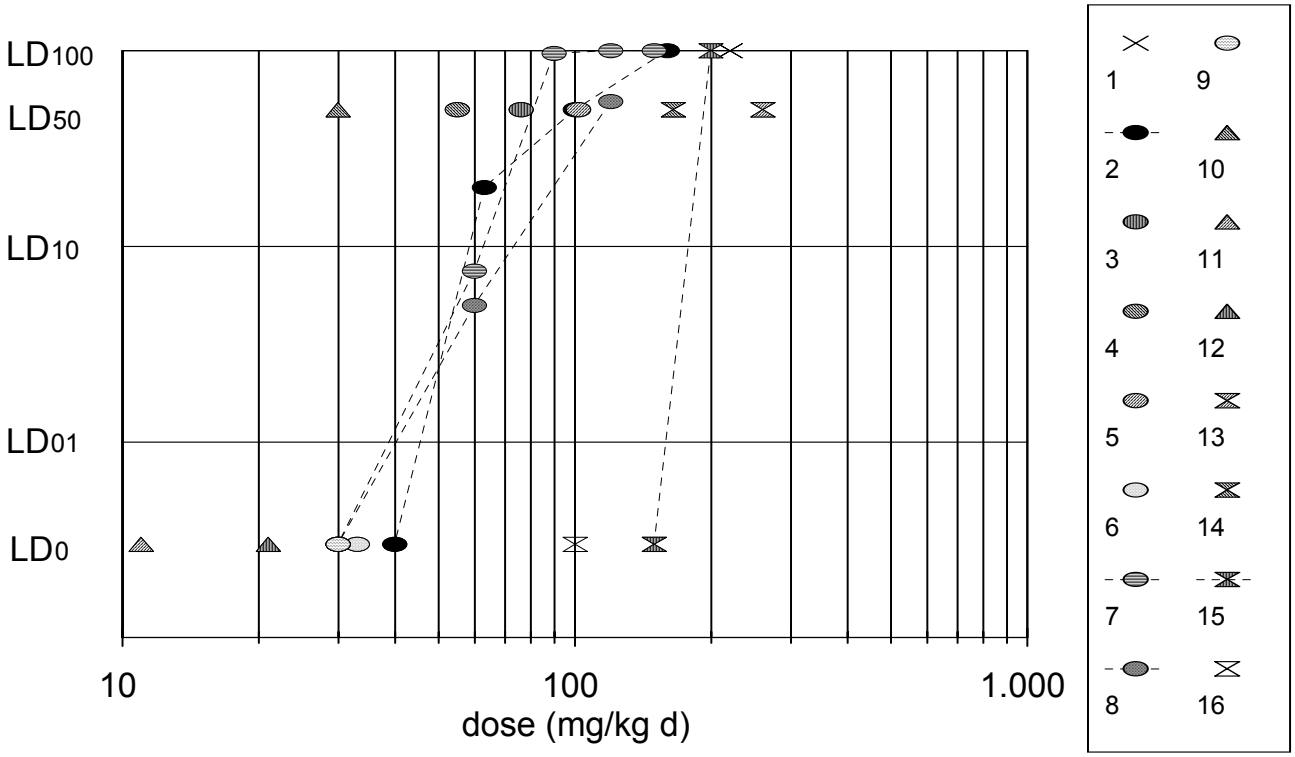


FIGURE 1: RELATIONSHIP BETWEEN MCAA DOSE AND LETHAL EFFECTS

All exposures (including single and repeated inhalation exposures and single oral exposures) were converted to daily doses. LD_0 designates a NOEL for lethality.

1 human case, single oral exposure; Feldhaus et al. (1993); Rogers (1995)
2 rat, single oral exposure; Hoechst AG (1979a)
3 rat, oral LD_{50}; Woodard et al. (1941)
4 rat, oral LD_{50}; Maksimov and Dubinina (1974)
5 rat, oral LD_{50}; Berardi (1986)
6 rat, subacute oral exposure; Johnson et al. (1998)
7 rat, subchronic oral exposure; Bryant et al. (1992); NTP (1992)
8 rat, subchronic oral exposure; Daniel et al. (1991)
9 rat, chronic oral exposure; NTP (1992)
10 rat, inhalation LC_{50}; Maksimov and Dubinina (1974)
11 rat, acute inhalation exposure; Dow Chemical Co. (1987)
12 rat, subchronic inhalation exposure; Maksimov and Dubinina (1974)
13 mouse, oral LD_{50}; Berardi (1986)
14 mouse, oral LD_{50}; Morrison and Leake (1941)
15 mouse, subchronic oral exposure; Bryant et al. (1992); NTP (1992)
16 mouse, chronic oral exposure; NTP (1992)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for various levels of effects and various time periods are summarized in Table 7. They were derived using the following key studies and methods.

No relevant studies of adequate quality were available for the derivation of the AEGL-1 value. Therefore, due to insufficient data, AEGL-1 values were not derived.

The AEGL-2 was based on a single inhalation study in rats (Dow Chemical Co., 1987) in which eye squint and lethargy were observed in rats exposed at 66 ppm for 1 hour. A total uncertainty factor of 10 was used. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.

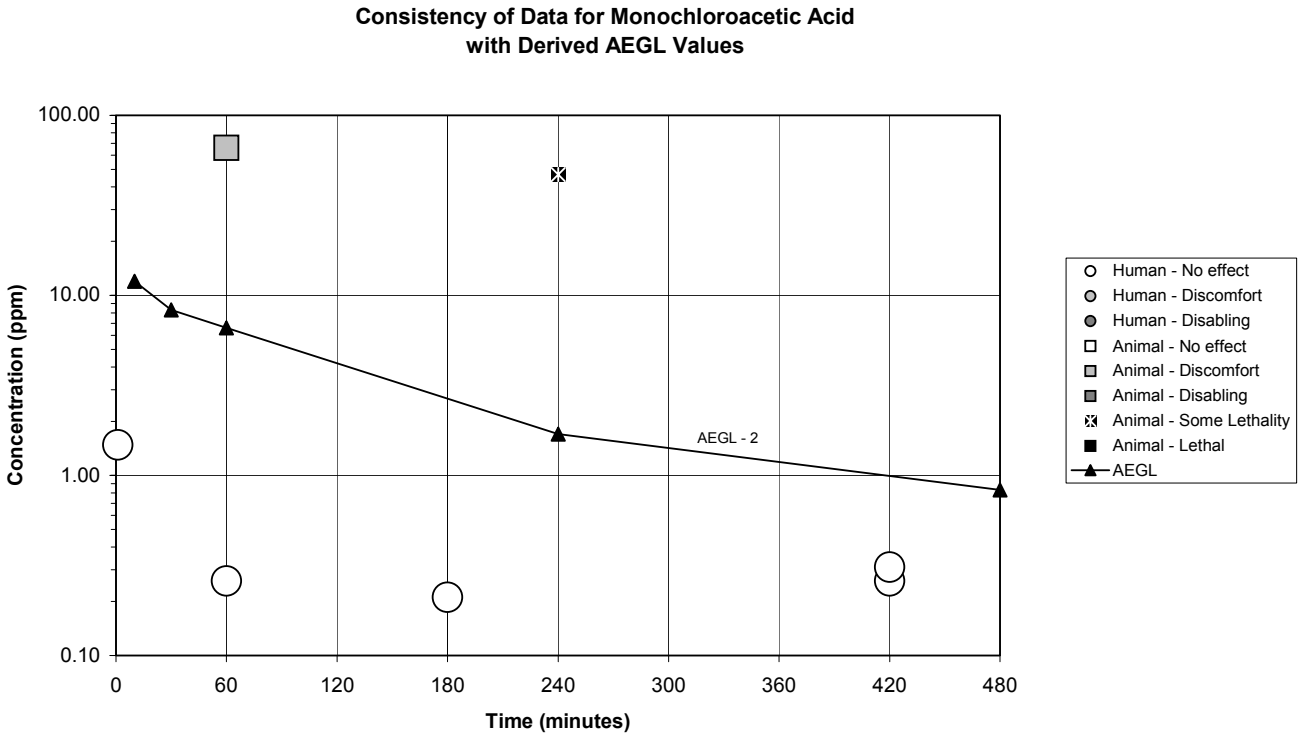
No relevant studies of adequate quality were available for the derivation of the AEGL-3 value. Therefore, due to insufficient data, AEGL-3 values were not derived.

TABLE 7: SUMMARY/RELATIONSHIP OF AEGL VALUES [a]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	N.R. [b]	N.R.	N.R.	N.R.	N.R.
AEGL-2 (Disabling)	12 ppm (47 mg/m³)	8.3 ppm (33 mg/m³)	6.6 ppm (26 mg/m³)	1.7 ppm (6.7 mg/m³)	0.83 ppm (3.3 mg/m³)
AEGL-3 (Lethal)	N.R.	N.R.	N.R.	N.R.	N.R.

[a] Skin contact with molten MCAA or MCAA solutions should be avoided; dermal penetration is rapid and fatal intoxications have been observed when 10 % or more of the body surface was involved.
[b] not recommended due to insufficient data

All inhalation data are summarized in Figure 1 below. The data were classified into severity categories chosen to fit into definitions of the AEGL level health effects. The category severity definitions are "No effect"; "Discomfort"; "Disabling"; "Lethal"; "Partial lethality" (at an experimental concentration in which some of the animals died and some did not, this label refers to the animals which did not die) and "AEGL". Note that the AEGL-2 values are designated as triangles.



1019 **FIGURE 2: CATEGORICAL REPRESENTATION OF ALL MCAA INHALATION DATA**

1020 **8.2. Comparison with Other Standards and Criteria**

1021 Existing limit and guideline concentrations are shown in Table 8. The proposed occupational
1022 exposure limits for Sweden is 1 ppm (with skin notation) and a STEL of 2 ppm (with skin notation)
1023 (KEMI, 1994). Maksimov and Dubinina (1974) recommended 1 mg/m³ (0.26 ppm) as the Russian
1024 occupational exposure limit.

TABLE 8. EXTANT STANDARDS AND GUIDELINES FOR MONOCHLOROACETIC ACID

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	N.R.	N.R.	N.R.	N.R.	N.R.
AEGL-2	12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm
AEGL-3	N.R.	N.R.	N.R.	N.R.	N.R.
REL-TWA (AIHA)[a]					0.26 ppm 1 mg/m³
STEL (AIHA)[b]	1.0 ppm (4 mg/m³) for 15 min				
MAK (Germany)[c]					1.0 ppm
MAC-Peak Category (The Netherlands)[d]					1.0 ppm (4 mg/m³)

[a] **AIHA-TWA (American In dustrial Hygiene Association, 1984)** (AIHA, 1993) is defined as the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[b] **AIHA-STEL (American In dustrial Hygiene Association, 1984)** (AIHA, 1993) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday.

[c] **MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association]) is defined analogous to the ACGIH-TLV-TWA. The peak category is 1, MCAA has a skin notation (BMA, 2000).

[d] **MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration - Peak Category])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the AIHA-TWA.

8.3. Data Adequacy and Research Needs

Definitive, high-quality studies assessing health effects of MCAA after single or repeated inhalation exposure in humans or experimental animals are not available. Due to insufficient data, AEGL-1 and AEGL-3 values were not derived.

The derivation of AEGL-2 was based an a single 1-hour inhalation exposure study on rats using a single concentration level.

Single inhalation exposure studies focusing on lethal effects in animals and irritative effects in animals and humans would allow for more precisely defining the thresholds for the three AEGL levels.

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APPENDIX A

Time Scaling Calculations for AEGLs

AEGL-2

Key study:	Dow Chemical Co. (1987)
Toxicity endpoint:	Rats were exposed for 1 hour at an analytical MCA concentration of 66 ppm, no other concentrations were tested. During exposure all rats squinted and appeared slightly lethargic.
Scaling:	$C^3 \times t = k$ for extrapolation to 30 minutes and 10 minutes $k = 66^3$ ppm^3 x 1 h = 287496 ppm^3 h C x t = k for extrapolation to 8 hours and 4 hours k = 66 ppm x 1 h = 66 ppm h
Uncertainty factors:	Combined uncertainty factor of 10. 3 for interspecies variability 3 for intraspecies variability
Calculations:	
10-minute AEGL-2	C^3 x 0.167 h = 287496 ppm^3 h C = 119.85 ppm 10-min AEGL-2 = 119.85 ppm /10 = 12 ppm (47 mg/m^3)
30-minute AEGL-2	C^3 x 0.5 h = 287496 ppm^3 h C = 83.15 ppm 30-min AEGL-2 = 83.15 ppm/10 = 8.3 ppm (33 mg/m^3)
1-hour AEGL-2	C = 66 ppm 1-hour AEGL-2 = 66 ppm/10 = 6.6 ppm (26 mg/m^3)
4-hour AEGL-2	C x 4 h = 66 ppm h C = 16.50 ppm 4-hour AEGL-2 = 16.50 ppm /10 = 1.7 ppm (6.7 mg/m^3)
8-hour AEGL-2	C x 8 h = 66 ppm h C = 8.25 ppm 8-hour AEGL-2 = 8.25 ppm /10 = 0.83 ppm (3.3 mg/m^3)

1258 **APPENDIX B**

1259 **Derivation Summary for Monochloroacetic Acid AEGLs**

ACUTE EXPOSURE GUIDELINES FOR MONOCHLOROACETIC ACID (CAS NO. 79-11-8)

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
N.R.	N.R.	N.R.	N.R.	N.R.

Reference: Not applicable

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale:
No definitive study was available for the derivation of AEGL-1 values. The human irritation threshold reported by Maksimov and Dubinina (1974) was inadequately described and, therefore, was not considered an adequate basis for the derivation of AEGL-1 values. The report by Clariant GmbH (2000) was not considered an adequate basis because the depth of the routine medical examination was not reported and the time point of the examination was not linked to an actual exposure assessment. Moreover, the exposure assessment using about 1 to 2 measurements per year was considered insufficient. Therefore, due to insufficient data, AEGL-1 values were not recommended.

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Data Adequacy:
Adequate human or animal data relevant for the derivation of AEGL-1 values are not available.

ACUTE EXPOSURE GUIDELINES FOR MONOCHLOROACETIC ACID (CAS NO. 79-11-8)

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
12 ppm	8.3 ppm	6.6 ppm	1.7 ppm	0.83 ppm

Reference: Dow Chemical Co., 1987. Monochloroacetic acid: an acute vapor inhalation limit study with Fischer 344 rats. Unpublished report, Dow Chemical Company, Midland, USA.

Test Species/Strain/Sex/Number: Rat / Fisher 344 / 6 female and 6 male

Exposure Route/Concentrations/Durations: Inhalation / 66 ppm (analytical concentration) / 1 hour

Effects:
During all exposures, all rats (12/12) showed eye squint and slight lethargy. While in the text the expression "slight lethargy" is used, "lethargy" is used in the corresponding table. "The observations [prior to and after exposure] included an evaluation of fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity was also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as slight lethargy and other signs of altered central nervous system function." During the two-week observation period, MCAA-exposed rats lost weight initially (day 2) and regained weight during the remainder period (day 4-15). Gross pathologic examination of rats revealed no exposure-related effects.

Endpoint/Concentration/Rationale:
For the derivation of AEGL-2 values, the study in rats by Dow Chemical Co. (1987) was used because it was the only relevant inhalation study available. Exposure of rats to 66 ppm for 1 hour resulted in eye squint and in some lethargy, which might be interpreted as an effect on the central nervous system, but no severe effects. There is some uncertainty as to the exposure because of the large discrepancy between the nominal exposure concentration of 964 ppm and the analytically measured exposure concentration of 66 ppm. The authors did not discuss whether recrystallization of MCAA took place completely outside the exposure chamber (i.e. before the air stream entered the chamber) or whether uptake of recrystallized MCAA by routes other than inhalation (e.g. dermal and oral uptake after deposition on the hair) might have occurred. In case of an additional exposure, the measured air concentration of 66 ppm and be regarded as an conservative exposure assumption. The AEGL-2 values were based on a 1-hour exposure to 66 ppm.

Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3 - because 1) the effect level was considered below that of an AEGL-2, 2) because the available data on acute oral lethality do not point at a large interspecies variability for more severe (lethal) effects, and 3) because of the limited toxicodynamic variability as the enzymes inhibited by MCAA do not vary considerably within and between species. Intraspecies: 3 - because of the limited toxicokinetic variability with respect to local effects and limited toxicodynamic variability with respect to systemic effects since the enzymes inhibited by MCAA do not vary considerably within and between species.
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Insufficient data
Time Scaling: The exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.
Data Adequacy: The only available single inhalation study in animals was used for the derivation of AEGL-2 values. In this study, neither different exposure concentrations nor different exposure durations were employed. The derived values are supported by an older subchronic study in humans daily oral exposures to MCAA.

ACUTE EXPOSURE GUIDELINES FOR MONOCHLOROACETIC ACID (CAS NO. 79-11-8)

AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
N.R.	N.R.	N.R.	N.R.	N.R.

Reference: Not applicable

Test Species/Strain/Sex/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale:
For the derivation of AEGL-3 values, no relevant and well-documented LC_{50} studies were available. Although oral lethality data in animals are available, these were not used as a basis for derivation of AEGL values because of the uncertainty regarding local effects of MCAA in the respiratory tract. Several mechanistic aspects point at a possible role of local effects: a) MCAA has a pK_a of 2.85 and thus is a strong acid, which may cause irritation and local tissue damage by its acidity alone; b) MCAA can bind to sulfhydryl groups, e.g. those of reduced glutathione, and may thus cause lung damage through glutathione depletion; and c) during inhalation exposure, local concentrations of MCAA in the respiratory tract could cause local tissue damage by enzyme inhibition already in doses lower than those required for systemic effects in oral studies. Experimental findings support a possible local effect on the respiratory tract: a) the available inhalation studies report effects on the respiratory tract, and b) MCAA causes severe local damage to skin and eyes.
Unfortunately, in the only LC_{50} study located in the literature (Maksimov and Dubinina, 1974), data presentation is inadequate. Since pathological findings were not reported it remains unknown if rats died from local lung tissue destruction or from systemic toxicity (i.e. acidosis affecting CNS or heart). Inhalation studies using monochloroacetic acid esters were not considered relevant for the derivation of AEGL-3 values, because compared with MCAA local effects of its esters are less likely, because a) the esters are not acidic and thus do not cause local effects by lowering the tissue pH value; and b) local effects due to glutathione binding or enzyme inhibition can be expected to be smaller because the esters have to get hydrolyzed enzymatically to free MCAA first; although quantitative data for the hydrolysis are lacking, it is likely that due to its rapid distribution in the body, much of the deposited ester will enter systemic circulation before it is hydrolyzed and thus the concentration of MCAA in respiratory tract tissue is likely to be much smaller during inhalation exposure to monochloroacetic esters compared to MCAA.
Due to the inadequate presentation of the only LC_{50} available (Maksimov and Dubinina, 1974) and the uncertainties of a route-to-route extrapolation, AEGL-3 values were not recommended due insufficient data.

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: Not applicable
Data Adequacy: Adequate animal data relevant for the derivation of AEGL-3 values are not available.