

*Recommendation of the Scientific Committee
on Occupational Exposure Limits
for
Monochloroacetic Acid*

8 hour TWA	-
STEL (15 min)	-
Additional classification	-

1. SUBSTANCE IDENTIFICATION

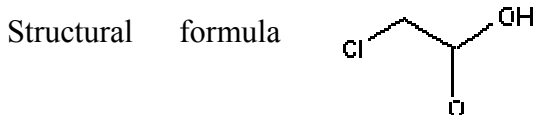
Monochloroacetic acid

Synonyms 2-Chloro-ethanoic acid, 2-chloroacetic acid, chloroethanoic acid, MCA, MKhUK, monochloroacetic acid, monochloroethanoic acid, chloroacetic acid, MCAA

EINECS No. 201-178-4

CAS No. 79-11-8

Molecular formula $C_2H_3ClO_2$



MWt 94.5 gmol^{-1}

Conversion factors At 25°C $1 \text{ ppm} = 3.86 \text{ mgm}^{-3}$; $1 \text{ mgm}^{-3} = 0.26 \text{ ppm}$

EU Classification: T; R23/24/25 (Toxic by inhalation, in contact with skin and if swallowed)

C; R34 (Causes burns)

N; R50 (Very toxic to aquatic organisms)

N for $C \geq 25\%$

Specific concentration (c) limits

$c \geq 25\%$ (swallowed)	T, R23/24/25 (Toxic by inhalation, in contact with skin and if swallowed) C; R34 (Causes burns)
$10\% \leq c < 25\%$ (swallowed)	R20/21/22 (Harmful by inhalation, in contact with skin and if swallowed) C; R34 (Causes burns)
$5\% \leq c < 10\%$	Xn; R20/21/22-36/37/38 (Harmful by inhalation, in contact with skin and if swallowed; irritating to eyes, respiratory system and skin)
$3\% \leq c < 5\%$	Xn; R20/21/22 (Harmful by inhalation, in contact with skin and if swallowed)

This document is based on the EU RAR (2005) and the references therein.

2. PHYSICO-CHEMICAL PROPERTIES

MCAA is a solid with a melting point of 61.5-62.3°C and a boiling point of 189°C at 1013 hPa. It has a relative density of 1580 kgm⁻³ at 20°C and a vapour pressure of 8.7 Pa at 25°C. Its solubility in water is 4210 g/L at 20°C and a solution of 100 mg/L has a pH of 3.2. It has a pKa of 2.85 at 25°C. In a typical sample of MCCA flakes, most particles (91.5%) were greater than 1 mm in diameter.

3. OCCURRENCE/USE

In Europe, MCAA is mainly produced by the chlorination of liquid acetic acid at temperatures between 85 and 120°C in the presence of an acetic anhydride and/or acetylchloride catalyst. The reaction product is purified by either selective dechlorination of dichloroacetic acid by treatment with hydrogen gas in the presence of a catalyst such as palladium and subsequent distillation, or by recrystallisation from suitable solvents. An alternative production process involves heating equal weights of trichloroethylene and sulphuric acid to 130-140°C followed by distillation of MCAA arising from the reaction.

The EU RAR estimated that 145,000 tonnes per year of MCAA are produced in Europe and 120,000 tonnes per year used.

The main use of MCAA is as a chemical intermediate for the synthesis of products such as carboxymethylcellulose, crop protection chemicals, plastics, thioglycol acid and the sodium salt of MCAA (used in detergents, pigments, dyes, inks and pharmaceuticals). Other minor uses include as a constituent of paint removing products, as a component in

coatings used for cans containing food, as a wart remover, as a caustic agent in medicine and as an analytical reagent.

4. METHODS OF EXPOSURE MONITORING AND ANALYSIS

The US National Institute for Occupational Safety and Health has published an appropriate method for the monitoring and analysis of MCAA in workplace air (NIOSH Method 2008, Issue 2, 1994). The method involves sample collection on a silica gel tube and analysis by ion chromatography. The estimated limit of detection is $0.4 \mu\text{g m}^{-3}$.

5. HEALTH EFFECTS

5.1 Toxicokinetics

No data are available describing the inhalation toxicokinetics of MCAA. MCAA is rapidly absorbed following skin contact or ingestion. Animal data indicate that about 90% of an ingested dose is absorbed and the RAR assumed that 100% absorption occurs through the skin or respiratory tract. More recently Saghir and Rozman (2003) investigated the uptake of radio-labelled MCAA (dissolved in acetone, 250mg/ml) through the skin in rats. Most of the dose (125 mg/kg) rapidly penetrated into the skin (>95% within 15 minutes) from where it was slowly released to become more widely distributed within tissues. The penetration of MCAA through the skin, when applied in aqueous solution, has not been reported.

Radiolabel studies have demonstrated that MCAA is rapidly distributed following absorption with the highest concentrations arising in the intestine, kidneys and liver. Radiolabelled MCAA also appeared in the central nervous system having passed through the blood-brain barrier. Different routes of administration and exposure regimes did not affect the distribution of the radiolabel. Repeated exposure to high doses of radiolabelled MCAA resulted in a significant increase in radioactivity compared to a single exposure.

The main route of metabolism for MCAA involves the initial formation of S-carboxymethyl glutathione which is converted to S-carboxymethylcysteine, part of which is further metabolised to thiodiacetic acid. A lesser metabolic pathway may involve enzymatic hydrolysis of the carbon-chlorine bond resulting in the formation of glycolic acid that is mainly oxidised to carbon dioxide.

The main route of elimination of MCAA following oral or intravenous administration is via the urine. In studies with radio-labelled MCAA in rats reviewed by the EU RAR, about 90% of the radiolabel was recovered in urine within 24 hours of oral administration of 9.5 mg/kg and 82-88% was recovered in 3 days following intravenous administration. The recovery of radiolabel from mice was lower – 34-61% in the 72 hours following oral administration. A more recent study in rats recovered 64-72% of the dose in urine within 32 hours of oral (aqueous solution) or dermal (acetone solution) administration (Saghir and Rozman, 2003). Tissue concentrations of the radiolabel were initially lower

following oral administration of 225 mg/kg than 10 mg/kg and this was attributed to retention of most of the higher dose for up to 8 hours in the stomach.

MCAA inhibits a range of enzymes and also interacts with lipids. MCAA may be incorporated into phospholipids and conjugates with cholesterol to form cholesteryl chloroacetate.

5.2 Acute toxicity

Human data

There are no human data for inhalation exposure to MCAA.

The EU RAR reviewed several reports of severe adverse effects including death following accidental skin contact with molten or highly concentrated MCAA. Death may follow contact with 5% of the body surface (Pirson *et al*, 2003). Reported symptoms include vomiting, tachycardia other cardiac effects and coma. Following these accidents death typically occurred between 4 to 18 hours after exposure, although in some cases not until 7 or 8 days after exposure.

Animal data

Several industry studies in which animals were exposed by inhalation to MCCA were reviewed in the EU RAR. Rats, mice and guinea pigs were exposed to average concentrations of 31,000 mgm⁻³ for one minute followed by exposure to 27,000 mgm⁻³ for three, five and ten minutes. Mild lacrimation and nasal discharge were observed in all animals after the one minute exposure and immediately after exposure commenced in the five and ten minute exposure studies. Some increased blood flow in the lungs was revealed on necropsy. Another study exposed rats to MCCA vapour at a concentration of 259 mgm⁻³ for one hour. During exposure all rats squinted and appeared slightly lethargic. Transient weight loss was observed following exposure that may have been a non-specific response to stress but no mortality or exposure-related pathologic changes were observed during a two week follow up period. The EU RAR considered another study that reported the LC₅₀ for rats as 180 mgm⁻³ to be inadequately described.

The acute oral studies reviewed by the EU RAR were generally not reported in detail. Acute LD₅₀ values for rats were between 55 and 277.7 mg/kg and for mice 260-300 mg/kg. Symptoms reported in rats included neurobehavioural effects, lacrimation and pulsing respiration. Mice were reported to show tremors, respiratory depression, paralysis and, occasionally, convulsions. Saghir and Rozman (2003) commented that difference between doses that caused no overt toxicity in rats (up to 200 mg/kg by oral administration) and a dose that caused 100% mortality (450 mg/kg) is relatively small.

In studies of acute toxicity following skin contact with MCCA, the LD₅₀ was found to depend on both the total quantity applied and the concentration. An LD₅₀ of 305 mg/kg was reported in rats for a 40% solution of MCCA. An LD₅₀ of 250 mg/kg was reported in rabbits for a 50% solution. Effects following dermal application included neurobehavioural effects, lacrimation and respiratory difficulties

5.3 Irritation

Maksimov and Dubinina (1974) reported some effects for respiratory irritation in Guinea pigs and rats at 5.8 mgm^{-3} , but without providing any further details. More severe respiratory irritation in rats was observed at a concentration of 20.8 mgm^{-3} .

Experimentally, MCAA induces skin irritation or corrosion and eye irritation. A number of case reports describe chemical burns in humans following skin contact with MCAA.

5.4 Sensitization

There have been no reports of respiratory or dermal sensitisation to MCAA following occupational exposure. MCAA did not cause dermal sensitisation in a poorly reported animal study cited by the EU RAR and no respiratory data were identified. The corrosive properties of MCAA have hampered investigations of sensitisation.

5.5 Repeated dose toxicity

Human data

No studies of the effects of workplace exposure to MCAA have been undertaken and there have been no case reports describing adverse effects following exposure to MCAA in workplace air.

Animal data

No inhalation data were reviewed by the EU RAR. RTECS lists two inhalation studies in rats and guinea pigs published in the USSR in the 1970s that reported a LOEL of 20.8 mgm^{-3} for intermittent exposure over 17 weeks in both species. Reported effects included changes in the kidney, bladder or urinary system and in the number of pigmented or nucleated red blood cells. No experimental details are available and the studies are not available for review.

Prolonged oral administration of MCAA is associated with adverse effects in the liver in both rats and mice and the kidney and heart in rats (Table 1). Effects on the heart disappeared in the lower dose groups in the longer term studies. In two year studies, reduced weight gain, decreased survival and inflammation of the nasal mucosa were observed with a LOAEL of 15 mg/kg/day and a NOAEL of 3.5 mg/kg/day .

Table 1: Repeated oral dose experiments reviewed by the EU RAR

Species	Duration	Dose mg/kg/day	NOEL mg/kg/day	LOEL mg/kg/day	Effects	Study
Rats	16 days	0, 7.5, 15, 30, 60, 120	7.5	15	Lacrimation	NTP (1992)
Mice	16 days	0, 15, 30, 60, 120, 240	120	240	Mortality of all animals in the highest dose group associated with lacrimation, ataxia, reduced activity, slowed breathing and heart beat, hypothermia, prostration, piloerection, decreased limb tone and impaired grasping reflect	
Mice	16 days	0, 30, 60, 120, 240, 480	6	120	Lacrimation	
Rat	13 weeks	0, 30, 60, 90, 120, 150	<30	30	Changes in heart, liver and kidney weights and clinical chemistry values (increased blood urea, ASAT, ALAT), increased thyroxine levels (males exposed to 90+ mg/kg/day), decreased serum cholinesterase; Cardiomyopathy and mortality at doses > 60 mg/kg/day	
Mice	13 weeks	0, 25, 50, 100, 150, 200	100	150	Increased liver weight, decreased serum cholinesterase activity	
Rats	103 weeks	0, 15, 30	<15	15	Decreased survival, acute inflammation of the nasal mucosa	
Mice	103 weeks	0, 50, 100	<50	50	Acute inflammation of the nasal mucosa	
Rats	104 weeks	0, 3.5, 26.1, 59.9	3.5	26.1	Reduced weight gain in the mid and high dose groups; some changes in liver enzymes and mild hepatocellular necrosis in high dose group; myocardial degeneration and inflammation of the nasal cavities of high dose animals at 104 weeks	DeAngel o <i>et al</i> (1997)

5.6 Mutagenicity

The EU RAR concluded that MCAA is not genotoxic. It gave negative results in most *in vitro* and *in vivo* assays.

5.7 Carcinogenicity

There are no human carcinogenicity data.

Two year studies in which rats were exposed to up to 59.9 mg/kg/day and mice were exposed to up to 100 mg/kg/day in drinking water found no evidence of carcinogenicity (EU RAR). No evidence of papillomas or carcinomas was found after repeated dermal application of MCCA (0.2mg in 0.1 ml acetone, 3 times a week for 580 days) in female mice.

The EU RAR concluded that there was insufficient evidence to classify MCCA as a carcinogen.

5.8 Reproductive toxicity

There are no human reproductive toxicity data.

No information is available about the effects of MCAA on animal fertility. No effects were found on male or female reproductive organs in the repeated dose experiments described above (Section 5.5). Two developmental studies were reviewed by the EU RAR. Pregnant rats exposed to 193 mg/kg/day in drinking water showed a decreased average weight gain, no effects on the number and weight of fetuses were found. In another study, pregnant rats exposed to 140 mg/kg/day showed a reduced weight gain and an increase in malformations of the cardiovascular system. No skeletal malformations or other effects were found. The data did not meet the requirements of Directive 67/548/EEC (Classification, packaging and labelling of dangerous substances) and the EU RAR recommended that a further developmental study should be performed.

RECOMMENDATION

MCCA is rapidly absorbed and widely distributed following ingestion or skin contact. No information about uptake following inhalation is available, although it is assumed that it is also readily absorbed in the respiratory tract. The main route of metabolism involves the initial formation of S-carboxymethyl glutathione, conversion to S-carboxymethylcysteine and some further metabolism to thiodiacetic acid. The main route of elimination is via the urine.

The effects of inhaled MCAA are not well established. A report by Maksimov and Dubrinina (1974) mentions some irritation to occur in Guinea pigs and rats at 5.8 mg/m³, and significant respiratory irritation at 20.8 mg/m³, but without providing supporting details. The studies are poorly reported and the data may not be reliable. The threshold for respiratory irritation in humans is not known.

In medium to long term experiments, oral administration of MCAA was associated with effects on the cardiovascular system, respiratory system and liver function. The LOEL from these experiments was 15 mg/kg/day in rats and the NOEL was 3.5 mg/kg/day (NTP, 1992, DeAngelo *et al*, 1977).

MCAA is irritating to the skin and eyes and there have been a number of reported cases of chemical burns arising from contact with MCAA. Accidental skin contact has also been associated with systemic toxicity and death. There is no evidence that MCAA is a skin sensitizer.

There is evidence that MCAA easily penetrates the skin when dissolved in acetone. However, similar data for aqueous solutions are not available.

MCAA is not considered genotoxic or likely to cause cancer. There are insufficient data to determine whether it is a developmental toxicant, although the EU RAR recommended further research in this area.

In essence, the primary effect of MCAA is local irritancy. A threshold for irritation of the airways is not supported by available data. Oral studies have been conducted in mice and rats, but these do not allow conclusions regarding a threshold of respiratory irritation.

Under these conditions, it is not possible to set a health-based OEL.

Due to lack of appropriate data, a recommendation of a skin notation cannot be made.

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