MONOCHLOROACETIC ACID

Document History
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I. IDENTIFICATION[1,2]

Chemical Name: Monochloroacetic acid
Synonyms: Chloroacetic acid; monochloroethanoic acid; chloroethanoic acid; MCA
CAS Number: 79–11–8
Other Designations: UN1750 (liquid); UN1751 (solid)
Molecular Formula: $C_2H_3ClO_2$
Structural Formula: Cl — CH_2 — COOH

II. CHEMICAL AND PHYSICAL PROPERTIES

Physical State: white or colorless to light brown, volatile, deliquescent crystals (3 or 4 crystalline forms) or 80% aqueous solution[3]
Molecular Weight: 94.50[3]
Conversion Factors: 1 ppm = 3.87 mg/m^3
1 mg/m^3 = 0.259 ppm[4]
Boiling Point: 189°C (372°F)[5]
Melting Point: 63°C (144°F) for alpha form, 55–56°C (157–158°F) for beta form, 50°C (148°F) for gamma form[3]
Vapor Pressure: 0.75 mmHg at 20°C (68°F)[6]; 1 mmHg at 43°C (109°F)[1]
Vapor Density: 3.26 (air = 1)[5]
Saturated Vapor Concentration: 987 ppm at 20°C (68°F)[6] and 1316 mmHg at 43°C (109°F)[1] [calculated]
Odor Threshold and Description: 0.045 ppm[4]; penetrating, burning odor[5]
Flammability Limits: LEL = 8% by volume[5]
Flash Point (closed cup): 126°C (259°F)[5]
pKa: 2.86[1]
pH: <1[6]
Specific Gravity: 1.58 at 20°C (68°F)[1]
Solubility: Very soluble in water, soluble in alcohol, acetone, ether, chloroform, carbon disulfide, and benzene[1,6]
Stability: Decomposes at high temperatures forming phosgene and hydrogen chloride[3]
Reactivity and Incompatibilities: MCA is a strong organic acid that is incompatible with strong bases, strong oxidizing agents, strong reducing agents and most common metals.[5,6]

III. USES AND VOLUME

MCA is used as an intermediate in the production of carboxymethylcellulose, ethyl chloroacetate, glycine, glycolic acids and esters, Vitamin B6, indigoid dyes, 1- and 2-naphthylacetic acids, amphoteric surfactants, synthetic caffeine, sarcosine, thioglycolic acid, EDTA, 2,4-D and 2,4,5-T as well as in the manufacture of other herbicides, preservatives, and bacteriostats.[3,4,7]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Oral

LD_{50}, mouse: 255 mg/kg[8]
LD_{50}, mouse: 260 mg/kg[9]
LD_{50}, mouse: 165 mg/kg[10]
LD_{50}, rat: 76 mg/kg[11]
LD_{50}, rat: 108 mg/kg[9]
LD_{50}, guinea pig: 80 mg/kg[11]

In LD_{50} studies, groups of 8–10 male Swiss-Webster mice were orally administered 80, 93, 124, 125, 165, 200, 222, 295, 318, 500, or 800 mg/kg MCA. A small number of mice surviving dosages of 260 mg/kg (LD_{50}) or 380 mg/kg (LD_{80}) exhibited neurological damage to their front paws and hind legs, which caused difficulty in walking. In the most severe cases, many of the mice had arched backs, severe tremors, and convulsions and died within 48-hours after MCA treatment. The damage appeared to be permanent in the survivors and there was no improvement up to 6 months after treatment. These studies also suggested that the lethal effects of MCA and the physical deficits observed in survivors might be associated with impairment of the blood-brain barrier function.[9]

2. Eye

Rabbit: concentrated solution was highly irritating and produced severe conjunctival burns.[12]

Rabbit: eye washed with 10% or 50% MCA solution showed conjunctival irritation and corneal damage; eye washed with 1% MCA solution showed trace of conjunctival irritation, which completely healed within 24-hours.[12]

The vapor, mist or liquid can cause moderate to severe irritation or tissue damage, depending on the concentration of the acid and duration of contact. Permanent injury, including blindness, may occur. There is no human information available, but MCA vapor is reported to have produced corrosive tissue damage in an animal test.[13]

3. Skin

a. Absorption

LD_{50}, rabbit, skin: 650 mg/kg (closed patch test); 178 mg/kg (dry flake MCA)[14]
LD_{50}, rat, skin: 305 mg/kg[14]
LD_{50}, rabbit, skin: 250 mg/kg[14]

Reported skin toxicity tests were as follows:

In all animal species tested, when MCA was applied to 5% of the skin at tested concentrations, death uniformly resulted in spite of rapid washing with water, sodium bicarbonate, and/or pre- or post-anesthesia of the animals.[15]

Solid MCA at room temperature produces a dermal LD_{50} after a 24-hour occluded contact of approximately 180 mg/kg for rats and dogs. The dermal LD_{50} by DOT Class B Poison Protocol was >200 mg/kg.[15]

Molten 60°C MCA applied to 15% of the body surface of a dog caused the following clinical changes: decreased blood glucose and WBC; increased BUN, SGOT, SGPT, and ventricular block.[15]

Molten 60°C MCA in contact with 20% of the body surface of a mongrel dog for 15 minutes at 4100 mg/kg was lethal.[15]

Molten 60°C MCA in contact with 5% or greater of the body surface of rabbits for 1 minute at 760 mg/kg was lethal.[15]

b. Irritation

Rabbit: concentrated MCA was highly corrosive; 0.05% MCA was irritating.[12]

Wistar rats (3 males and 3 females): 1 mL/kg of MCA was applied (unoccluded) to shaved skin of the back; minimum concentration that showed moderate or severe effects was 5%.[16]

ddY Mice (3 males and 3 females): 1 mL of MCA was applied (unoccluded) to shaved skin of the back; minimum concentration that showed moderate or severe effects was 5–20%.[16]

Application of a 4.3% solution of MCA (dose of 100 mg/kg) produced redness and swelling. A 43% solution (dose of 1000 mg/kg produced corrosive tissue damage and death in most animals.[14]

c. Sensitization

No data available.

4. Inhalation

LC_{50}, rat: 47 ppm (reported as 180 mg/m^3); duration of exposure not given[8]

5. Other

In male rats dosed subcutaneously with MCA in aqueous solutions at a dosage of 162 mg/kg (LD_{90}), the following clinical symptoms were observed: respiratory depression, clonic and tonic convulsion, and enlarged livers and spleens were found at necropsy.[10] The total sulfhydryl concentration in rat liver and kidney was significantly decreased. MCA also inhibited (^{14}C) acetate oxidation in *in vitro* studies using rat tissue from these animals.

B. Genotoxicity

MCA was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98, with or without S9 activation, or in related in vitro mutagenicity assays.[17-23] MCA was also negative in the SOS chromotest (*E. coli* PQ37, with and without S9 activation), Ames fluctuation test (*S. typhimurium* TA100), and the newt micronucleus test (*Pleurodeles waltl*).[24]

In the L5178Y/TK mouse lymphoma forward cell mutation assay, MCA (99%) mutant counts were significantly greater than control levels in at least one test with S9 activation.[25] In another L5178Y/TK assay, where MCA was only tested in the absence of S9 activation, significant mutagenic responses were obtained for two of three tests conducted.[26]

MCA was tested in Chinese hamster ovary (CHO) cells for the induction of chromosome aberrations and sister chromatid exchanges (SCE), with and without exogenous metabolic activation. The SCE

test was positive without activation. Slight, but not significant, increases in aberrations were seen without and with S9 activation.[27] Additional chromosomal aberration and sister-chromatid exchange (SCE) tests *in vitro* on MCA were carried out using a Chinese hamster cell line (CHL). MCA showed cytotoxicity, but did not induce chromosomal aberrations or SCEs, with and without S9 mix, in these tests.[28]

MCA was ineffective in inducing DNA strand breaks in cultured rat and mouse hepatocytes and human CCRF-CEM cells at concentrations below those that yielded cytotoxicity.[29]

MCA was negative or gave equivocal results in a sex-linked recessive lethal (SLRL) assay following feeding or injection of adult *Drosophila melanogaster* males.[30]

Based on a weight-of-evidence, the NTP concluded that the potential for MCA to cause DNA damage and mutagenicity is probably low.[31]

C. Metabolism and Pharmacokinetics

Distribution of MCA was studied in rats given a single oral dose of 0.1 mmole/kg of body weight [1-^{14}C] MCA, by gavage. The animals were sacrificed at 4, 8, 12, 24, and 48 hours after treatment. The distribution of ^{14}C-label, determined in different tissues, suggests that MCA is rapidly absorbed and eliminated from the body. The elimination phase appears to be faster for the intestine and kidney as compared to other tissues. Maximum radioactivity was detected in the intestine and kidney at 4 and 8 hours following the treatment that was followed by the liver, spleen, testes, lung, brain and heart in a decreasing order. Urinary excretion of MCA and/or its metabolites was found to be ~90% of the dose in 24 hours. The absorption and elimination phases were augmented to some extent in other tissues, as a significant amount of radioactivity was detected even at 48 hours following the exposure.[32]

Metabolites of MCA identified in urine of mice include S-carboxymethylcysteine, thiodiacetic acid (thiodiglycolic acid), glycolic acid, and oxalic acid. In both rats and mice, the major percentage (>60%) of the administered dose is excreted as thiodiglycolic acid and S-carboxymethylcysteine.[33]

MCA is readily absorbed through the skin. A worker exposed to heated ^{14}C-labeled MCA on his fingers showed in a blood sample taken 17.5 hours after the accident a ^{14}C concentration considerably lower than in a 24-hour urine sample. The half time for excretion of MCA was reported to be 15 hours. The primary excretion product was considered to be unmetabolized MCA, while a smaller proportion reacted with glutathione and was excreted in conjugated form and as CO_2 in exhaled air. A single intraperitoneal dose of ^{14}C-labeled MCA (0.1 g/kg) was given to mice; 82–88% of the radioactivity was excreted in urine and 8% in exhaled air within 3 days.[4]

D. Developmental/Reproductive Toxicity

Pregnant Long-Evans rats were dosed by oral intubation on gestation Days 6–15 with 0, 17, 35, 70, or 140 mg/kg/day MCA in distilled water. There were no clear signs of maternal toxicity; however, maternal weight gain was significantly reduced at 140 mg/kg/day. The mean percentage of resorbed implants per litter and the weight of live fetuses did not differ from controls. Malformations of the cardiovascular system were significantly elevated over the controls at 140 mg/kg/day (NOAEL = 70 mg/kg/day). No skeletal malformations were observed.[34]

A study was performed in pregnant Sprague-Dawley rats during organogenesis to determine if trichloroethylene (TCE), dichloroethylene, their metabolites (including MCA), and related compounds were responsible for cardiac teratogenesis. The drinking water concentration for MCA was 1,570 ppm, which was equivalent to a dosage of 193 mg/kg/day. There was no evidence of teratogenicity in the litters of 10 maternal animals exposed to MCA.[35]

The developmental toxicity of MCA and other haloacetic acids were tested using whole embryo culture (CD-1 mouse) for a 24-hour study. Exposure to MCA affected embryonic development at concentrations as low as 175 uM (16.5 mg/L) and produced embryolethality (41% of embryos) at a 250 uM concentration. At the 250 uM (23.6 mg/L) concentration, the incidence of arch and heart defects were similar to the incidence of neural tube defects (NTDs).[36,37]

E. Subacute

B6C3F$_1$ male mice and Sprague-Dawley male rats (5–6 per group) were provided drinking water containing 11 to 32 mM (1 to 3 g/L) MCA for 14 days. The calculated average daily dosages for B6C3F$_1$ mice drinking water containing 11, 21, and 32 mM MCA over a 14-day period were 265, 386, and 482 mg/kg/day, respectively. For the Sprague-Dawley rat, the corresponding average daily dosages were 170, 321, and 501 mg/kg/day. Rat liver weights were depressed in a dose-dependent manner, but mouse liver weights were not

affected. MCA did not have any significant effect on peroxisome proliferation.[38]

F344/N rats (groups of 5 of each sex) were orally administered 0, 7.5, 15, 30, 60 or 120 mg/kg/day MCA in deionized water by gavage for a total of 12 doses over the course of 16 days. Male $B6C3F_1$ mice (groups of 5) were administered MCA doses of 0, 15, 30, 60, 120, or 240 mg/kg/day and female $B6C3F_1$ mice (groups of 5) were administered doses of 0, 30, 60, 120, 240, or 480 mg/kg/day 12 times over a 16-day period. A clear nasal discharge and/or lacrimation were observed in all groups of rats. At 120 mg/kg/day, 1/5 male rats and at >240 mg/kg/day all mice died. Hypoactivity, piloerection, ataxia, and lacrimation were observed in mice given 240 or 480 mg/kg. CNS effects such as impaired grasping reflex, muscular incoordination, prostration and slow breathing were observed in the rats and mice that died. No compound-related gross or microscopic lesions were observed in rats or mice. [31]

F. Subchronic Toxicity

Groups of 20 F344 rats and 20 $B6C3F_1$ mice of each sex were administered MCA once daily, 5 days per week, in water by gavage for up to 13 weeks. Doses used were 0, 30, 60, 90, 120, or 150 mg/kg for rats and 0, 25, 50, 100, 150, or 200 mg/kg for mice. Compound-related deaths occurred at the three highest dose levels in rats and at the highest dose level (200 mg/kg) in mice. Mean body weights of treated groups of rats and mice surviving until the end of the study were similar to controls. A dose-related increase in BUN, alanine aminotransferase, aspartate aminotransferase, as well as a dose-related increase in the relative liver and kidney weights was observed in rats, but not in mice. A dose-related increase in the incidence and severity of cardiomyopathy occurred in rats. This lesion may be related to the inhibition of heart mitochondrial aconitase activity. No compound-related lesions were observed in mice. The NOAEL was estimated as 30 mg/kg for rats and 100 mg/kg for mice.[33]

Groups of 10 male and 10 female Sprague-Dawley rats were administered sodium monochloroacetate (SMCA) [sodium salt of MCA] by daily gavage for 90 consecutive days. Doses used were 0, 15, 30, 60, and 120 mg/kg/day. SMCA clearly induced toxicity in both males and females, with the greatest severity in the males. Both the liver and kidneys were identified as target organs. At 120 mg/kg/day, 30% of females and 80% of males died, most within the first 2 days of treatment. Hemorrhagic and congested lungs (possibly a post-mortem change) were seen in the early deaths (1–3 days), whereas liver lesions were observed in the later deaths. In addition, there was nephrotoxicity as evidenced by elevated creatinine, blood calcium, and BUN levels. Based on the observation of toxicity at all treatment levels in males, a lowest-observed-adverse-effect-level (LOAEL) of 15 mg/kg per day is proposed for a 90-day exposure to SMCA by oral gavage to the Sprague-Dawley rat. Effects noted at the 15 mg/kg per day dose included significantly decreased monocyte counts in females; increased monocyte counts in males; increased BUN, creatinine, and blood calcium levels in males; increases in alanine aminotransferase (ALN) in males; and an increased incidence of microscopic lesions of the heart in males.[39]

MCA, dichloroacetic acid (DCA), and trichloroacetic acid (TCA) were administered in a 90-day drinking water study in male Sprague-Dawley rats (5 per group). The results of the study indicated that, relative to their respective LD_{50} values, DCAA is more toxic than TCA, and MCA is least toxic. The MCA dose at 1.9 mM was at approximately 1/4 of the LD_{50} value of 76 mg/kg. After 90 days, the rats were sacrificed for gross and microscopic evaluations. MCA exposed animals did not exhibit any significant change in body weight (95.2% of control). A slight weight decrease liver (90.3% of control) was noted for the MCA exposure. At necropsy, no gross lesions were observed, with the MCA exposed group having the least microscopic lesions noted.[40]

In a Russian study, 75 rats and 18 guinea pigs were exposed for 4 months to 5.8 mg/m^3 and 20.8 mg/m^3 MCA. Inhalation by rats and guinea pigs to 20.8 mg/m^3 MCA produced a reduction in body weight, inflammation of the lungs, reduced blood hemoglobin levels, lowering of rectal temperature, and decreased oxygen uptake. A concentration of 5.8 mg/m^3, determined to be the study LOAEL, produced milder toxic effects. This study was poorly reported and analytical procedures were not described.[8,12]

G. Chronic Toxicity and Carcinogenicity

Male Slonaker rats were fed 50, 100, 250, 500, or 1000 ppm of MCA for 208 days. Rats fed 1000 ppm had significantly decreased body weight. No tissue change (gross or microscopic lesions) could be attributed on autopsy to MCA feeding. The 500 ppm NOAEL and 1000 ppm LOAEL identified in this study are equivalent to about 20 and 40 mg/kg/day, respectively, for a male rat with a dietary intake of 0.02 kg food per day.[41]

Groups of 50 male F344/N rats were exposed for 104 weeks to MCA in the drinking water at 0.05, 0.5 or 2 g/L of MCA. The 2 g/L dosage was lowered in stages to 1 g/L when the animals began to exhibit signs of toxicity. A time-weighted mean daily MCA concentration of 1.1 g/L was calculated this dosage over the 104-week exposure period. Time-weighted mean daily doses based on water consumption were 3.5, 26.1, and 59.9 mg/kg/day, respectively for MCA. Spleen weights were increased in the low-dose group and decreased in the high-dose group. Significant dose-related decreases in relative or absolute liver, kidney and testes weights were observed in the mid- and high-dose groups. Non-neoplastic hepatic changes were, for the most part, spontaneous and age-related. No evidence of hepatic neoplasia was found at any of the MCA doses.[42]

In NTP 2-year oral studies, groups of 70 of each sex of F344/N rats were given 0, 15, or 30 mg/kg/day (5 times/week) MCA, while groups of 60 of each sex of $B6C3F_1$ mice were given 0, 50, or 100 mg/kg/day (5 times/week) MCA via aqueous gavage. At the high doses, the body weights of male rats and female mice were reduced. Survival of high-dose male rats and mice was significantly reduced, as was survival of all dosed female rats. No significant degenerative lesions of the heart were observed in rats, despite the observation of cardiomyopathy in the 13-week studies at 60 mg/kg/day. This lack of cardiac effects may be due to the lower doses used in the 2-year studies. There was no compound-related increase in the incidence of neoplasms or non-neoplastic lesions in rats given MCA for 2 years. Similarly, there was no MCA-related increase in the incidence of neoplasms in male or female mice, and malignant lymphoma occurred with a significant negative trend in dosed female mice. Non-neoplastic lesions of the nasal mucosa, olfactory epithelium, and the forestomach were observed in dosed male and female mice (LOAEL = 50 mg/kg/day). There was no evidence of carcinogenic activity for MCA in male or female F344/N rats given 15 or 30 mg/kg, and there was no evidence of carcinogenic activity in male or female $B6C3F_1$ mice given 50 or 100 mg/kg MCA.[31]

MCA applied to or injected under the skin of mice (50 mice per group) was not carcinogenic in two studies. In the first study, repeated dermal applications of 2 mg MCA in 0.1 mL of acetone 3 times/week for 80 days to the shaved skin of female ICR/Ha Swiss mice did not produce either carcinomas or skin papillomas among the treated animals.[43] In the second study, subcutaneous injections of 0.05 mg of MCA in 0.5 mL of tricaprylin once/week for 580 days produced 3 sarcomas among 50 test mice, which was well within the background rate for the ICR/Ha Swiss mice tested. These reached statistical significance because the 100 control mice showed no tumors.[43] Maximal tolerated oral doses of 46.4 mg/kg MCA (in distilled water) via gavage daily for 21 days, followed by 149 ppm/day in the diet for 17 months did not cause cancer or any other signs of toxicity in mice (18 mice/sex/hybrid strain).[44]

V. HUMAN USE AND EXPERIENCE

A number of human fatalities have been attributed to MCA poisoning. The deaths in most cases were due to percutaneous absorption of MCA; molten MCA was particularly toxic:

10% body burns — MCA at 58°C[15]
Full body drench — MCA at 60°C[45]

Death occurred within 18 hours in the case with 10% body burns. The mechanism of morbidity and death is not known and specific antidotes and/or treatments that can reverse clinical processes, once initiated, are also unknown.[15,45]

Clinical signs in the incident involving whole body drenching included: first degree burns of the skin, coughing and spitting up of blood, convulsions, loss of consciousness, and death within 4 hours. Autopsy revealed the following in the case of full body drenching: first degree burns on the body; hemorrhage of the lungs, pleural membranes, liver, kidney, brain, and mucous membranes of the bronchia; point-shaped bleeding between the soft membranes of the brain; and the right heart cavities were dilated and filled with blood.[45]

A case of accidental lethal MCA oral-route poisoning occurred in a 5-year old girl inadvertently given a teaspoonful of Verzone, a wart remover composed of MCA. The girl immediately vomited, collapsed, and experienced unmanageable metabolic acidosis and cardiac arrhythmia. Death occurred within 6 hours. Autopsy showed only fatty infiltration of the liver and marked gastric mucosal hyperemia.[46]

A 38-year old male was splashed with an 80% MCA solution on 25–30% of his body surface. In addition to epidermal and superficial dermal burns, features of systemic poisoning occurred within a few hours including disorientation, agitation, cardiac failure, and coma. He later developed severe metabolic acidosis, rhabdomyolysis, renal insufficiency and cerebral edema, and died due to uncal (hippocampal gyrus) herniation on Day 8. The 4-hour post-exposure plasma MCA concentration was 33 mg/L, confirming skin absorption. In addition to its corrosive action, MCA

probably blocks the Kreb's cycle and may also react with sulfhydryl groups in enzymes, causing severe tissue damage in energy-rich organs.[47]

A 45-year old male was sprayed on the back of both legs with molten 90% MCA. He entered a safety shower in <30 seconds, where he remained for 10 minutes before being transported to the plant medical facility, where he showered for an additional 25 minutes. It was estimated that the body surface involved was 10%. Nausea and vomiting developed in 30 to 45 minutes, but consciousness remained normal. During the first 6 hours after hospitalization, he experienced tachycardia and "occasional" premature ventriculations (PVC). The PVCs did not return after 2–3 days. Initial therapy consisted of intravenous (IV) fluid replacement, IV potassium chloride, high dose corticosteroids, and diuretics. He subsequently recovered and was discharged 4 days after the incident occurred. It was unclear whether survival was related to the treatment regimen and/or prompt showering or some other combination of circumstances. The fact that he developed vomiting, tachycardia, and PVCs suggests that his level of exposure was adequate to cause systemic toxicity; however, it is possible that these clinical signs were stress-related.[48]

The threshold for the perception of mucous membrane irritation in humans was reported as 5.7 mg/m^3 (1.5 ppm).[8] There has been a reported instance of vapors of MCA causing corneal epithelial injury. The concentration and/or duration of exposure were not reported.[13]

VI. RATIONALE

MCA is a strong acid that causes severe burns and is corrosive to the skin. It can also produce burns of the eye and irritation of the respiratory tract. It is acutely toxic via the oral, dermal and inhalation routes in experimental animals. Genotoxicity studies were equivocal. However, based on the weight-of-evidence, MCA is considered to have a low potential to produce genotoxic effects. In the 2-year NTP gavage studies, there was no evidence of carcinogenic activity for MCA in male or female F344/N rats given 15 or 30 mg/kg. Cardiomyopathy was observed in a 90-day study in rats (NOAEL = 30 mg/kg/day). There was no evidence of carcinogenic activity for MCA in male or female B6C3F$_1$ mice given 50 or 100 mg/kg. Non-neoplastic changes in the nasal mucosa and forestomach were observed in female mice at 15 mg/kg/day. This is equivalent to an 8-hour inhalation exposure for workers of approximately 100 mg/m^3. There are no known reliable long-term inhalation studies upon which to base an OEL. Poorly documented reports state that the perception of mucous membrane irritation in humans has been reported to be at 5.7 mg/m^3 (1.5 ppm). An OEL guide of 0.5 ppm (1.9 mg/m^3) is recommended to protect against possible irritation and other local and systemic effects. This recommendation is consistent with the OEL calculated from the pKa.[49] Insufficient data were available to support a short-term exposure limit. Skin exposure to molten MCA presents a life-threatening hazard and death has occurred as a result of skin absorption. Therefore, a "skin" notation has been assigned to MCA, to highlight the potential for significant toxicological effects following skin absorption.

VII. RECOMMENDED OEL

0.5 ppm (1.9 mg/m^3) 8-hour TWA, Skin

VIII. REFERENCES

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