Human Acute Intoxication from Monochloroacetic Acid: Proposals for Therapy

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European Centre for Ecotoxicology and Toxicology of Chemicals
4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium.

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1. SUMMARY

Monochloroacetic acid is an industrial chemical, used mainly for carboxylation reactions. It is handled either in molten form at 600 C, as crystalline flakes or in highly concentrated aqueous solutions. Monochloroacetic acid is readily absorbed after oral or dermal exposure. As it is a strong acid, it is corrosive. It can also induce severe systemic intoxication.

Following accidental dermal exposure, 27 fatal (7 described in detail) and 15 non-fatal cases of severe acute systemic intoxication have been reported. The body surface involved was usually 10% or higher in the fatal cases and 5-10% in two of the non-fatal accidents. In one fatal and 13 non-fatal accidents, only the two hands (3-5% of body surface) were involved, but contact was unusually long. In a few other incidents, workers had up to 10 % of their body surface burned without any signs of systemic intoxication. At least another 20 cases have been mentioned in the literature. Following accidental ingestion, one fatality has been described in detail.

Symptoms are delayed for about one to three and a half hours following exposure. Vomiting occurs initially, followed by central nervous system disturbances (hyperexcitability, disorientation, convulsions), central nervous system depression and coma. There is cardiovascular involvement in all cases, with arrhythmia, tachycardia and cardiovascular shock. Blood creatinine levels are increased. In several cases, a severe metabolic acidosis has been observed; this is difficult to overcome and death generally occurs within four hours to seven days due to cardiovascular shock, renal failure and cerebral oedema. Data from animal and *in vitro* experience indicate that, due to inhibition of pyruvate-dehydrogenase and a-ketoglutarate hydrogenase enzyme complexes, clinical signs of toxicity and mortality develop directly in relation to an increase of cerebrospinal fluid lactate levels. Limited clinical data in humans and reproducible experimental data in rodents indicate that lactic acidosis is the main mechanism leading to toxic effects.

It has been suggested that sodium bicarbonate solution is more effective than water for decontamination of the skin following exposure to monochloroacetic acid. There is, however, no clear experimental evidence to support this assumption. For practical purposes it is more important that decontamination begins as soon as possible, whether water or sodium bicarbonate solution is used.

In the 1970s, various compounds from different therapeutic classes were investigated in experimental animals towards finding an effective antidote for monochloroacetic acid poisoning. These included antidotes for monofluoroacetic intoxication, sulphydryl donors, cytochrome P450 modulators, cholinergic, serotoninergic, GABAergic, and dopaminergic agonists and antagonists. None proved effective.

The identification at the end of the 1980s of the role of lactic acidosis in monochloroacetic acid toxicity, opened the door for research into effective antidotes. Dichloroacetate, and to a lesser degree phenobarbitone, were identified as effective in reducing mortality and in decreasing lactate accumulation in the blood and cerebral spinal fluid of rats and

mice following sub-lethal intoxication with monochloroacetic acid. Dichloroacetate acts directly on the involved enzyme systems while phenobarbitone probably acts through a non-specific "hibernation" effect.

Based on the above data, a clinical workshop established a protocol for the treatment of monochloroacetic acid intoxication. The protocol, which has been incorporated by IPCS-INTOX into their Poison Information Monograph on MCAA (IPCS-INTOX, 2001), proposed the early administration of dichloroacetate (50 mg/kg, iv) as specific antidotal therapy to prevent the development of monochloroacetic acid-induced lactic acidosis. The Task Force supports this proposal and recommends improving the availability of dichloroacetate. Additionally the Task Force considers that if dichloroacetate is not available, treatment with phenobarbitone might be considered, provided that intensive care facilities are available.

2. INTRODUCTION

The toxicological properties of monochloroacetic acid (MCAA) and its sodium salt (SMCA) have been recently and extensively reviewed (ECETOC, 1999). Since publication of the ECETOC review, the Task Force has become aware of several additional cases of intoxication in Asia; this information has been incorporated in the present document.

Synopsis of ECETOC JACC Report No. 38

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

MCAA is rapidly and extensively absorbed following all routes of administration. The acute toxicity data for SMCA suggest a rate of absorption comparable to MCAA by the oral route, but limited absorption dermally. The monochloroacetate anion and/or its metabolites are initially distributed in lipid-poor tissues (liver, kidney, stomach) and subsequently in lipid-rich tissues (brain, spinal cord, thymus, pancreas). Monochloroacetate is excreted unchanged in a fast elimination phase ($t_{½}$ = 90 minutes in rat after sc injection) and is bound to glutathione, cysteine or protein or is eliminated as carbon dioxide in a slow phase ($t_{½}$ = 500 minutes). Following oral administration, 35-90% of monochloroacetate and its metabolites are excreted in the urine of rats and mice within 24 hours. In a human case of accidental contamination of the skin with 14C-MCAA, a half-life of about 15 hours was found for the rapid excretion phase of monochloroacetate in the urine; after six days, only trace amounts were detectable in the blood. Monochloroacetate is metabolised in mice and rats to thiodiacetic acid (TDA) (via S-carboxymethyl glutathione and S-carboxymethyl cysteine) and, to a lesser extent, to glycolic acid and carbon dioxide (after enzymatic hydrolysis of the C-Cl bond).

MCAA and SMCA are toxic after acute oral administration (rat LD50 between 55-200 mg/kg and 76-580 mg/kg, respectively). Systemic effects include loss of body-weight, hypoactivity, dyspnoea, tremor, convulsion, and cyanosis. In addition MCAA causes severe burns of the gastrointestinal tract. MCAA can be absorbed through the skin in toxic and lethal amounts (LD50 between 180-800 mg/kg in rats and rabbits); clinical signs are identical to those observed after oral administration. No mortality was observed in rats after dermal administration of 2000 mg/kg SMCA. Exposure of rats for less than 10 minutes to MCAA saturated vapour (generated at 75°C) induced eye and respiratory tract irritation but no mortality.

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

In repeated oral administration studies of up to three months in rodents, MCAA and SMCA have a species-dependent threshold for the induction of death of around 60 mg/kg/d in rats and 150 mg/kg/d in mice. Sub-lethal doses of MCAA lead to changes in liver and kidney weights, histopathological lesions in liver and kidneys, and non-specific changes in various biochemical parameters clinically related to these organs. Cardiomyopathy has also been observed in rats. The no-observed-adverse effect level (NOAEL) for long-term administration is also species-dependent and is 30 and 100 mg/kg/d in rats and mice respectively. No relevant data are available on inhalation or dermal exposure.

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

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

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

Preamble to present report

Since 1949, several fatal accidents have been reported due to MCAA intoxication. No effective treatment has been established to date. The MCAA producers have been actively searching for an effective treatment.

In 1997 a workshop was organised by the European MCAA producers, in close cooperation with EAPCCT (European Association of Poison Centres and Clinical Toxicologists). Participants and their affiliations are listed in Appendix 1. This workshop discussed the data presented in this report which were available at that time and agreed a protocol for the treatment of monochloracetic acid intoxication. This protocol was submitted to IPCS in the form of a PIM (Poison Information Monograph) for inclusion in its INTOX data base.

In order to present and evaluate the scientific data underlying the recommendations of the workshop protocol, a toxicology/medical sub-group of the ECETOC Task Force which produced JACC Report No. 38, was given the following Terms of Reference:

- collect and review all data on cases of human intoxication to monochloroacetic acid (MCAA) and its sodium salt (SMCA);
- review the mechanisms of toxic action and potential antidote treatment;
- write a paper on MCAA intoxication suitable for publication in a scientific journal.

The following sections describe the clinical and experimental data, based on which the use of dichloroacetate (DCA), or alternatively phenobarbitone (PB), is proposed as a potentially effective antidote.

3. EXPERIENCE WITH ACCIDENTAL HUMAN ACUTE INTOXICATIONS

No reports of acute intoxications following exposure to SMCA have been traced. However, over the past five decades, several reports of cases of acute systemic intoxication due to MCAA have been reported, most of them following accidental dermal exposure.

Following exposure to MCAA by ingestion, inhalation or dermal contact, 43 cases of acute systemic intoxication (as opposed to local irritation) have been reported (ECETOC, 1999; Toyama 1999; Wang Kongfu *et al*, 1997), 28 of which were fatal. Detailed descriptions are available for 8 fatal and 15 non-fatal cases. The clinical and biochemical signs were consistent in all cases. The Task Force is also aware of several other accident reports that have not been published.

3.1 Oral Exposure

Only one case of acute oral intoxication has been reported. Despite intensive-care treatment, the patient died within eight hours; autopsy revealed diffuse gastric erosions, fatty infiltration of the liver, pulmonary and cerebral oedema. At post-mortem a monochloroacetate level of 100 µg/ml was detected in serum (Feldhaus *et al*, 1993; Rogers, 1995).

3.2 Combined Dermal and Inhalation Exposure

There has been one report of acute MCAA intoxication after inhalation exposure. However the worker also inhaled other irritants and his body was splashed extensively with MCAA. This was also a fatal accident (Zeldenrust, 1951).

3.3 Dermal Exposure

Dermal exposure accounted for 41 cases of systemic poisoning, of which 26 were fatal. Details are available for six of these fatalities. In five of the fatalities at least 10% of the body surface was contaminated (ECETOC, 1999; Toyama, 1999); in the one remaining case, exposure was limited to both hands but duration was exceptionally long (Wang Kongfu *et al*, 1997). In two non-fatal cases reported by Millischer *et al* (1987) 5-10% of the body surface was involved, while hands and wrists (3-5%) were exposed in 13 non-fatal cases reported by Wang Kongfu *et al* (1997). Due to its corrosive properties MCAA initially causes cutaneous damage, usually consisting of first to second degree burns with a typical whitish colour. The initial assessment may underestimate the severity of the skin lesion as both the area and degree of these may increase after a day or two.

Several case reports have been published in the open literature (Zeldenrust, 1951; Christofano *et al*, 1970; Ruty, 1985; Kulling *et al*, 1992; Feldhaus *et al*, 1993). Three case reports that are less easily accessible are summarised below.

1. A 52 year old Japanese male operator slipped and fell on his left side into a fresh spill of molten MCA (installation temperature ~ 68° C), resulting from a drain valve having been left open accidently. He ran into the plant control room to report the

accident, then showered for approximately 15-20 minutes. He was then taken to hospital, arriving approximately 45 minutes post-accident (p-a). At that time he was conscious and his blood pressure was 123/71 mm Hg. The chemical burn on the left side of the torso and left upper leg was an estimated 10% of body surface, with third degree burns on the leg. Nausea and vomiting occurred shortly after admission. An iv line with saline was established and hydrocortisone succinate and famotidine administered intravenously. Forty-five minutes after admission, the victim lost consciousness, blood pressure and peripheral oxygen saturation dropped and, despite shock treatment with uristatin and dopamine, his heart stopped beating about 4 hours after admission (~ 6 hr p-a). Intensive attempts at recussitation failed and the victim was formally declared dead 5 hours after admission (7 hr p-a). Serum electrolytes and biochemistry were normal at the time of admission. No autopsy was carried out (Toyama, 1999).

2. Fourteen Chinese workers were engaged in manually unloading wet bags (inadequately labelled for hazard) containing MCAA. After 30 minutes, the workers experienced itching and burning pain on their hands. After rinsing the hands and donning cotton gloves they continued working for another one and a half hours. On taking off the then totally-drenched cotton gloves, the men noted blisters on their hands and wrists with increasing itching and burning pain. Five hours after starting work, nine men were admitted to hospital with intolerable pain and an inability to stand ; all complained of dizziness, palpitations and some of nausea. One victim became nauseated, dysphoric and drowsy 10 hours after stopping work. His blood pressure decreased, heart rate increased, and breathing difficulties and cardiac arrhythmia developed; he died 6 hours later. His serum potassium was normal (no further clinical details available). It was estimated that 3-5% skin area was involved in all cases, but the fatality apparently also had burns on his feet and head (no further details available). In the 13 survivors, the skin injuries progressed, with the skin becoming swollen, discoloured, and hard and shiny, with serous fluid oozing from blisters and cracks. After about four weeks, the affected skin was cast off in a glove-like fashion. It is unknown if there was permanent scarring (Wang KongFu *et al*, 1997). The authors also state that at least another 20 fatal skin intoxications have been reported in the Chinese literature.

3. A 23 year old black male accidently submerged his left leg in a drum of molten MCAA (temperture ~ 58° C). As the drum was overturned, the right leg was also splashed with MCAA. Rinsing commenced immediately and continued for 45 minutes. About 75 minutes p-a, nausea and vomiting developed, and the victim became drowsy, although still responsive. Four hours p-a the respiration rate increased and tachyarrhythmia developed. During transport to the hospital, the patient became severely agitated and had to be restrained. Shortly after admission (~ 4hr 15min p-a) the victim became unconscious with no pulse or measurable bloodpressure. Pulse and blood pressure, but not consciousness, recovered after intensive shock treatment, which included glucose solution and saline by iv drip, corticosteroids and antihistamines. After recovery, respiration was fast and wheezy, later deveoping into coarse rales. Serum potassium was about half the normal level,

and potassium was added to the iv drip. Gradually, the patient's condition deteriorated, with signs of pulmonary congestion, low blood pressure and increased pulse rate; he died about 11 hours 40 minutes p-a. At autopsy, the total burn area on both legs was established at 20% and petechial haemorrhages were seen on chest and shoulders; heart, lungs and thymus showed congestive haemorhaging and the liver was congested. No brain autopsy was performed. The cause of death was recorded as MCAA poisoning (Hercules, 1969a; Mann, 1969)

3.4 Characteristics of Systemic MCAA Intoxication

The clinical signs of systemic poisoning generally develop one to three and a half hours after exposure (Millischer *et al*, 1987; Toyama, 1999). Vomiting and occasionally diarrhoea are early signs of systemic intoxication (Hercules, 1969a; DKK, 1984; Ruty, 1985; Kusch *et al*, 1990; Feldhaus *et al*, 1993). Thereafter central nervous system (CNS) involvement is predominant, with excitation, disorientation or convulsions, followed by CNS depression and coma (Zeldenrust, 1951; Hercules, 1969a; Christofano *et al*, 1970; DKK, 1984; Contassot *et al*, 1987; Kulling *et al*, 1992; Wang Kongfu *et al*, 1997;Toyama, 1999). In severe cases the signs rapidly succeed one another. Intracranial hypertension has also been reported (Kulling *et al*, 1992).

In all cases there was cardiac involvement with arrhythmia and tachycardia (Hercules, 1969a; Contassot *et al*, 1987; Kusch *et al*, 1990; Feldhaus *et al*, 1993; Wang Kongfu *et al*, 1997). Electrocardiographic changes indicated non-specific myocardial damage (Contassot *et al*, 1987; Kusch *et al*, 1990; Kulling *et al*, 1992). In most cases cardiovascular shock has been observed (Hercules, 1969a; DKK, 1984; Contassot *et al*, 1987; Kulling *et al*, 1992; Feldhaus *et al*, 1993; Wang Kongfu *et al*, 1997; Toyama, 1999) and this probably caused the renal failure seen within 12 hours (Kulling, 1997). The latter may be complicated by a tubular necrosis, due to the impact of myoglobin or of calcium oxalate, both presumably secondary to rhabdomyolysis (DKK, 1984; Kulling *et al*, 1992; Kulling, 1997).

In two non fatal minor cases only vomiting and hypotension were observed (Huismans, 1998).

A severe acidosis is the main biochemical sign of systemic MCAA intoxication (Contassot *et al*, 1987; Vincenti, 1987; Kulling et al, 1992; Feldhaus *et al*, 1993); in at least two cases this was established to be metabolic in origin. Hypokalaemia has been observed frequently (Hercules, 1969a; Contassot *et al*, 1987; Kusch *et al*, 1990; Kulling *et al*, 1992) and hypocalcaemia reported once on the second day (Kulling *et al*, 1992). In two cases creatine kinase levels were increased (Vincenti, 1987; Kulling *et al*, 1992;). High transaminase levels were found in one fatal case, but the first analysis was not performed until the second day (Kulling *et al*, 1992). The degree of increase of these enzymes is indicative of extensive tissue damage (Kulling, 1997). No increased transaminase levels were found on the first day in a non-fatal case in which there were signs of systemic intoxication (Vincenti, 1987). Myoglobinaemia (Kulling *et al*, 1992), leucocytosis (Hercules, 1969a) and coagulation disturbance (Ruty, 1985; Vincenti, 1987) have been reported. Hyperglycaemia was present in one case (Contassot *et al*, 1987).

Prognosis is poor once signs of systemic toxicity have developed, as evidenced by 28/43 fatalities in patients with systemic toxic effects (Wang Kongfu *et al*, 1997; ECETOC, 1999; Toyama, 1999). The time until death varied from four hours to eight days (Millischer *et al*, 1987; Wang Kongfu *et al*,1997; Toyama, 1999). In several autopsies, haemorrhagic congestion was observed in brain, heart, and lungs (Zeldenrust, 1951; Mann, 1969; Kulling *et al*, 1992; Feldhaus *et al*, 1993).

Table 13 (Appendix 2) summarises the clinical signs, biochemistry and autopsy outcomes of systemic MCAA intoxication.

4. BIOCHEMICAL AND PATHOPHYSIOLOGICAL MECHANISMS OF ACUTE MCAA INTOXICATION

4.1 Clinical Signs of MCAA Toxicity in Rats

In two independent studies with male rats, clinical signs of toxicity were observed over a period of 15 days after a single iv injection of 80 mg/kg MCAA (Elf Atochem, 1995a, 1998b). This dose level was slightly in excess of the LD50 (75 mg/kg; Elf Atochem, 1995a) and induced a high rate of mortality. Table 2 summarises the clinical signs observed at different time intervals after dosing in a total of 14 rats treated in these experiments.

The first significant clinical signs of toxicity (hypokinesia, sedation and dyspnoea) and the first death were observed after 45 minutes. After 2 hours, all rats were affected and the mortality exceeded 50%. The clinical signs regressed after three hours and all surviving rats were asymptomatic with the exception of one rat in which piloerection, emaciation, dyspnoea, chromodacryorrhea and round back were observed until its death on day 15.

Table 1 : Clinical signs of toxicity in rats (initial number = 14) after iv injection of 80 mg/kg MCAA (from Elf Atochem, 1995a, 1998b)

Time	**Minutes**			**Hours**							**Days**													
	15	30	45	1	1.5	2	2.5	3	4	5	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Number of surviving rats	14	14	13	11	10	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5
Death			1	2	1	4																		1
No clinical signs	13	12	9	1	1	0	1	1	3	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Piloerection													1	1	1	1	1	1	1	1	1	1	1	
Emaciation													1	1	1	1	1	1	1	1	1	1	1	
Hypokinesia		1	4	7	2	3	2	4	2															
Sedation			1	4	6	4	2	1	1	1					1	1								
Dyspnoea			2	4	5	4	3	2	1						1	1	1	1	1	1	1	1	1	
Chromodacryorrhea		1	1							1	1	1					1	1	1	1	1	1	1	
Suffocation						1		1																
Ventral and/or lateral decubitus				1	4	6	4																	
Round back													1	1	1	1	1	1	1	1	1	1	1	

4.2 Induction of Lactic Acidosis by MCAA in Rats

Blood and cerebral lactic acidosis have been observed in rodents dying of MCAA intoxication (Mitroka, 1989; Elf Atochem, 1995b). Figures 1 and 2 illustrate the time course of the lactate accumulation in blood and cerebrospinal fluid (CSF) respectively, following iv injection of 40 or 80 mg/kg MCAA (as sodium salt) to rats. Blood and CSF lactate levels increased with time until death. Mortality was not observed earlier than 60 min after MCAA injection. Lactate levels increased earlier and were consistently higher in the CSF than in blood. Clinical signs of toxicity appeared after a latency period of 45 min (Section 4.1) and developed in direct relation to the increase in CSF lactate levels (Elf Atochem, 1995a, b).

There is no known transport mechanism that would accumulate lactate in the brain against the concentration gradient. The lactate accumulation in the brain is thus likely to be secondary to pyruvate formed *in situ* (Mitroka, 1989).

Figure 1 : Time and dose-related effects of MCAA on blood lactate concentration in rats

Figure 1a: Elf Atochem, 1995b

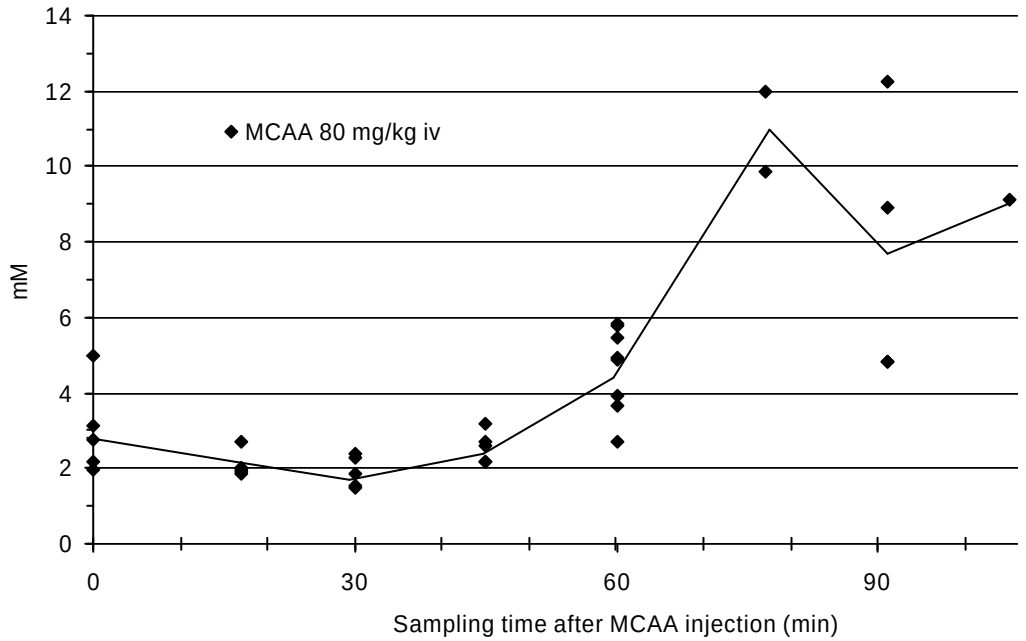


Figure 1b: Adapted from Mitroka, 1989

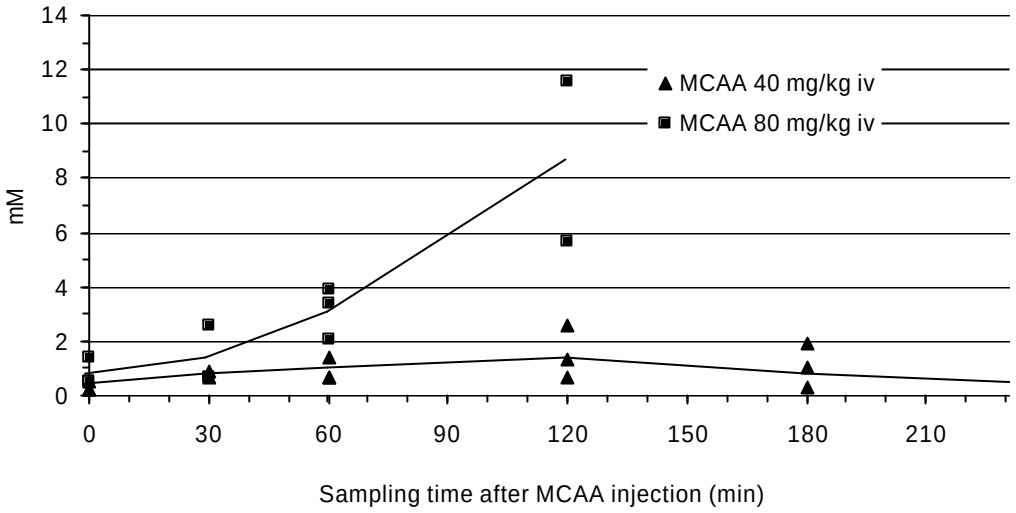


Figure 2 : Time and dose-related effects of MCAA on CSF lactate concentration in rats

Figure 2a: Elf Atochem, 1995b

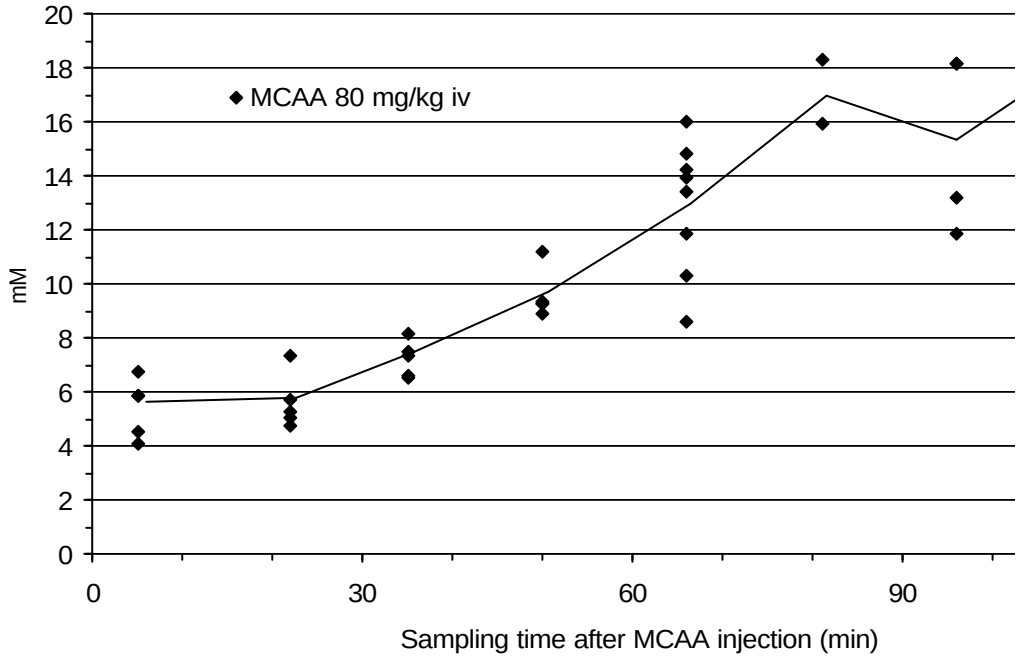
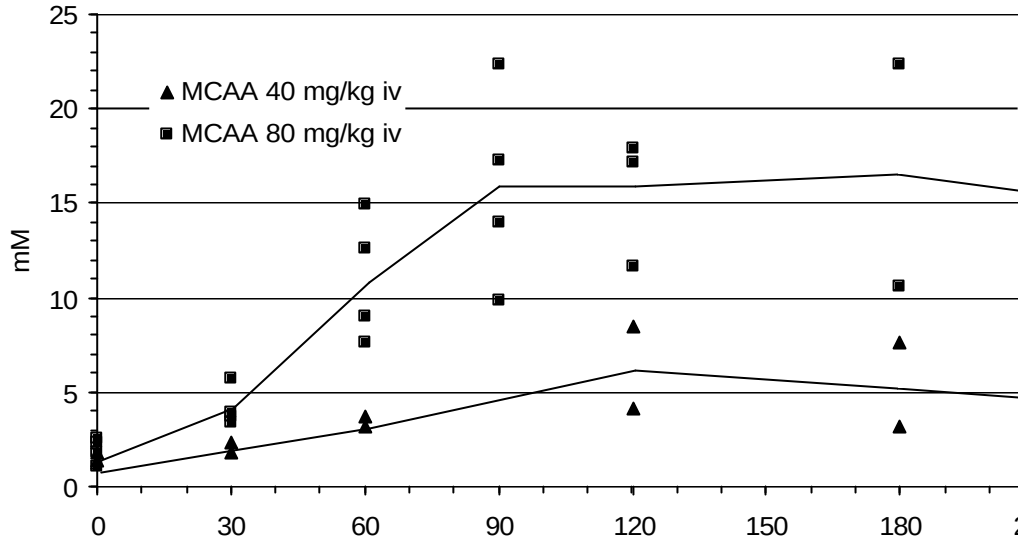


Figure 2b: Adapted from Mitroka, 1989



4.3 Biochemical Basis of MCAA Toxicity

MCAA inhibits both pyruvate-dehydrogenase (PDH) and a-ketoglutarate dehydrogenase (a-KGDH) enzyme in isolated rat heart mitochondria but only after prolonged incubation (van Hinsbergh and Vermeer, 1994). The exact mechanism of inhibition is still unknown; indirect inhibition through formation of oxalate from MCAA has been suggested (Mitroka, 1989), as well as direct inhibition through the slow alkylation of sulphydryl groups (van Hinsbergh and Vermeer, 1994). Since the combined inhibition of PDH and a-KGDH has a major impact on cellular energy production, the cell would then revert to anaerobic glycolysis, resulting in lactate accumulation (van Hinsbergh and Vermeer, 1994).

Under normal conditions, PDH is inactivated by phosphorylation through PDH-kinase, and is activated by dephosphorylation (through a phosphatase). It has been shown with isolated rat mitochondria that after pre-incubation with MCAA, the PDH activity could be partly restored by DCA. DCA is thought to block PHD kinase, thus locking the enzyme in its active state (van Hinsbergh and Vermeer, 1994). The outcome is dependent on the percentage of PDH being inhibited i.e. if the PDH has been totally inhibited, then the further blocking of the kinase will have no effect. The effect is also dependent on the presence of adenosine triphosphate (ATP), required for phosphorylation. The effects are small due to the different time-courses of the individual steps. As the kinase is rather unstable in the isolated mitochondria, this system is not ideal for demonstrating the effects under study. Nevertheless, small but significant effects confirming activation of PDH and a-KGDH activities by DCA have been found (van Hinsbergh and Vermeer, 1994).

Unpublished in vitro experiments with human endothelial cells have shown that monochloroacetate leads to a peculiar pattern of cell death, with a total cessation of cell protein synthesis secondary to a block in ATP synthesis. This process could not be halted or ameliorated by giving acetate donors (e.g. ethanol, acetate), intermediates of the Krebs cycle (e.g. pyruvate, a-ketoglutarate, L-glutamate) or by replenishing the product of pyruvate oxidation, acetyl-CoA, by incubation with acetyl-L-carnitine (van Hinsbergh, 1991). Given the experimentally observed lifesaving effects of DCA in MCAA-poisoned rodents (Mitroka, 1989; Régnier, 1997), it may be concluded that the combined PDH and a-KGDH inhibition are of major importance in MCAA poisoning, and that a block of the citric acid cycle at the aconitase level, if indeed present, would play only a minor role in the mechanism of toxicity.

Similar findings in kidney and liver epithelial cells, showing a dose-dependent increase in lactate and pyruvate levels directly related to cell viability, are supportive of the hypothesis that the above-mentioned enzyme systems are involved (Dartsch *et al*, 2000).

4.4 Pathophysiological Effects of MCAA Intoxication

The time-course and pattern of MCAA intoxication in man (Section 3.4) is similar to that in other species, including rodents, dogs, cattle and birds. The pattern of distribution found in rodents shows an initial fast distribution in lipid-poor tissues, followed by a slow but sustained uptake in lipid-rich tissues, notably the brain (Berardi, 1986; Bhat *et al*, 1991). The characteristics of the distribution pattern of MCAA and the slow development of lactic acidosis may explain the time lag observed between accidental skin contamination in man and the appearance of the first CNS symptoms. So far, clinicians have been unaware of the possible role of cerebral and systemic lactate acidosis and consequently have not determined CSF and/or serum lactate levels. However, a severe metabolic acidosis has been found in several victims. Also, the effects of MCAA *in vitro* are much higher in human endothelial cells than in other cells (e.g. liver epithelial cells); this is consistent with the evidence of microvascular damage in the brain (Mitroka, 1989).

Overall it is reasonable to assume that, in man as in rodents, cerebral lactic acidosis, in combination with the subsequently developing systemic lactic acidosis, is the main cause of lethality.

5. EXPERIMENTAL STUDIES SUPPORTING THE SKIN DECONTAMINATION RECOMMENDATIONS

Two studies have investigated the effectiveness of dermal decontamination following exposure to MCAA.

Four New Zealand albino rabbits were exposed (5% of body surface) to molten MCAA (0.48 ml/kg) for 1 minute. Two were then rinsed with soap and water and two with sodium bicarbonate solution. One of the two rabbits died in each case (Hercules, 1969b). The study does not allow a conclusion on the efficacy of sodium bicarbonate decontamination on account of the small number of animals and the excessive dose of MCAA used.

Using a full blood perfused pig ear model, Bruijnzeel *et al* (1998) applied radiolabelled ^{14}C-MCAA for one, three and ten minutes. MCAA readily permeated the skin, even after one minute exposure. The uptake in blood (mg MCAA/min/cm^2) reached a steady-state after 45-60 minutes and did not fall significantly until after another 60 minutes, indicating considerable diffusion from intradermal stores into the blood stream. After a 30-minutes decontamination with distilled water or a saturated sodium bicarbonate solution ("90g/l), the amount of MCAA remaining in the skin was 5 and 4% respectively. The effectiveness of both decontaminants decreased with increasing exposure time to MCAA. Although there was a statistically-significant difference between the rinsing with water and rinsing with sodium bicarbonate solution, the difference was small, and would probably not be noticeable in real-life accident situation. There is general agreement, however, that the skin must be rinsed immediately and intensively seconds after accidental exposure; even if little or no skin reaction is seen at the time, skin damage may be significantly more extensive later. For practical purposes the choice between water or sodium bicarbonate solution is less important than initiating decontamination immediately.

6. ANTIDOTES PREVIOUSLY INVESTIGATED IN EXPERIMENTAL STUDIES

Of the considerable number of possible antidotes that have been tested, the rationale for choice could be deduced to originate from presumed similarities to other substances or from known biochemical effects; for other substances the rationale for testing is unknown.

6.1 Investigations of Treatments Used in Monofluoro-acetate Intoxication

Initially studies were designed to test the hypothesis that MCAA acted in the same manner as monofluoroacetate, i.e. by disrupting the Krebs cycle (Table 2). Glycerol monoacetate, used in the treatment of monofluoroacetate poisoning (Chenoweth *et al*, 1951), was administered sc to rats immediately following MCAA intoxication. No protection against MCAA toxicity was observed; indeed high doses of glycerol monoacetate appeared to enhance the toxic effects of MCAA (Gibson and Hayes, 1971).

Ethanol has also been proposed as a potential antidote for MCAA intoxication (Ruty, 1985) based on early studies reporting beneficial effects by the partial inhibition of the formation of toxic metabolites and reactivation of the Krebs cycle in dogs poisoned with monofluoroacetate (Hutchens *et al*, 1949; Chenoweth *et al*, 1951). Ethanol was administered (Table 2) either by ip injection to mice after an oral dose of MCAA (Berardi, 1986), by gavage to rats after an iv injection of MCAA (Mitroka, 1989), by iv infusion to rabbits after a dermal application of MCAA (Elf Atochem, 1987), or orally to Beagle dogs 30 minutes before and repeatedly after the iv injection of a lethal dose of MCAA (Elf Atochem, 1989). The first three of those four experiments failed to demonstrate a protective effect of ethanol against MCAA mortality, however the ethanol treatment protected Beagle dogs from convulsive seizures and muscle tetany, and increased survival by up to 50%.

In conclusion, neither glycerol monoacetate nor ethanol is an effective antidote for MCAA intoxication.

Table 2 : Investigations of antidotes used in monofluoroacetic acid intoxication

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Male Sprague-Dawley rats 162 mg/kg sc	glycerol monoacetate 15-90 mmole/kg s.c. immediately following MCAA	 no protection at 15 and 30 mmole/kg potentiation of MCAA toxic effects at 60 and 90 mmole/kg	Gibson and Hayes, 1971
Swiss-Webster mice 380 mg/kg po (LD_{80})	ethanol 1200 mg/kg ip 0, 1 and 3 hr after MCAA 1700 mg/kg ip 0, 1 and 3 hr after MCAA	 no protection increased % MCAA lethality	Berardi, 1986
Male Sprague-Dawley rats 80 mg/kg iv (LD_{80})	ethanol 5 g/kg po immediately after MCAA	 no protection	Mitroka, 1989
New Zealand rabbits 2 ml molten MCAA on 100 cm^2 (4-5% of the body surface) (LD_{100}) for 1.5 or 5 min followed by a 2-min rinse with lukewarm water	ethanol iv infusion at 10% in NaCl 0.9% to maintain an alcohol level of 0.5-1 g/l iv infusion at 20% in NaCl 0.9% to maintain an alcohol level of 3 g/l	 no protection no protection but increased time until death in 50% of animals (6h30 versus 5h15 in control)	Elf Atochem, 1987
Beagle dogs 100 mg/kg iv (LD_{100})	ethanol 5 ml/kg (40% in water) 30 min before MCAA and repeated administrations after MCAA to maintain an alcohol level of 2 g/l during 8 hr	 protection against convulsive seizures with muscle tetany. 4/8 dogs survived	Elf Atochem, 1989

6.2 Sulphydryl Donors

Hayes *et al* (1973) demonstrated that MCAA inhibits liver and kidney sulphydryl groups *in vivo*. Certain sulphydryl donor reagents, such as glutathione, cysteine, dimercaprol (Gibson, 1973), N-acetylcysteine, and 2,3-dimercapto-succinate (Berardi, 1986) were tested as antidotes for MCAA poisoning (Table 3). None was effective.

6.3 Cytochrome P450 Modulators

Cytochrome-P450-inducing pretreatment during the previous days with phenobarbitone (PB) or treatments with cytochrome-P450 inhibitors such as SKF-525A or cobalt chloride, or the aldehyde dehydrogenase inhibitor disulfiram, did not significantly decrease MCAA-induced lethality in mice (Table 4; Berardi, 1986).

6.4 Cholinergic Agonists and Antagonists

The central cholinergic agonist, oxotremorine, and the peripheral cholinergic agonist, neostigmine, significantly increased mortality, while the cholinergic agonist physostigmine and the cholinergic antagonist, atropine, did not significantly reduce mortality in mice treated with lethal doses of MCAA (Table 5; Berardi, 1986).

6.5 Serotoninergic Agonists and Antagonists

The serotoninergic agonists p-methoxyphenyl-ethylamine (5-HT agonist), chloroimipramine (5-HT-uptake inhibitor), and fluoxetine (5-HT-uptake inhibitor), the serotoninergic antagonists, cyproheptadine (5-HT antagonist), and fenfluramine (5-HT depletor), and the serotoninergic neurotoxin, p-chloroamphetamine, were ineffective in protecting mice from the lethal effects of MCAA (Table 6; Berardi, 1986).

Table 3: Sulphydryl donors

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Male Sprague-Dawley rats	glutathione		Gibson, 1973
162 mg/kg sc (LD_{90})	200 mg/kg sc with MCAA	no protection	
	100 mg/kg sc + MCAA and 50 mg/kg sc 45 and 90 min after MCAA	no protection	
	100 mg/kg sc with MCAA then every 30 min	no protection	
Male Sprague-Dawley rats	cysteine		Gibson, 1973
162 mg/kg sc (LD_{90})	250 (free base) mg/kg + MCAA then 125 mg/kg every 30 min	no protection	
	250 (HCl) mg/kg 30 min before MCAA	no protection	
	125 (HCl) mg/kg + MCAA then 62.5 mg/kg/hr	no protection	
Male Sprague-Dawley rats	dimercaprol (BAL)		Gibson, 1973
162 mg/kg sc (LD_{90})	50 mg/kg 30 min before MCAA	no protection	
	75 mg/kg 30 min before MCAA	no protection	
Swiss-Webster mice	N-acetylcysteine		Berardi, 1986
380 mg/kg po (LD_{80})	600 mg/kg ip 0, and 1hr after MCAA	no protection	
	1000 mg/kg ip 1hr before MCAA	no protection	
Swiss-Webster mice	2,3-dimercapto-succinate		Berardi, 1986
380 mg/kg po (LD80)	46 mg/kg ip 0 and 3hr after MCAA	no protection	

Table 4: Metabolic modifiers

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Swiss-Webster mice 380 mg/kg po (LD_{80})	disulfiram 200 or 300 mg/kg po 2, 24, and 48hr before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	SKF 525A 25 mg/kg ip 30 min before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	PB 80 mg/kg ip 24, 48, and 72hr before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	cobalt chloride 25 mg/kg ip 10 min before MCAA	no protection	Berardi, 1986

Table 5: Cholinergic agonists and antagonists

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Swiss-Webster mice 320 or 385 mg/kg po (LD_{80})	oxotremorine 0.6 mg/kg ip 15 min before MCAA	increased lethality; decreased time to death	Berardi, 1986
Swiss-Webster mice 385 mg/kg po (LD_{80})	neostigmine 0.2 mg/kg ip 15 min before MCAA	increased lethality; decreased time to death	Berardi, 1986
Swiss-Webster mice 385 mg/kg po (LD_{80})	physostigmine 0.5 mg/kg ip 15 min before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 385 mg/kg po (LD_{80})	atropine 30 mg/kg ip 15 min before MCAA	no protection; decreased time to death	Berardi, 1986

Table 6: Serotoninergic agonists and antagonists

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Swiss-Webster mice 380 mg/kg po (LD_{80})	p-methoxyphenyl-ethylamine 60 mg/kg ip 15 min before MCAA 60 mg/kg ip 0, 1, 2, 3, 4, and 5 hr after MCAA	 decreased % mortality increased % mortality	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	chloroimipramine 10 mg/kg ip 30 min before MCAA	 no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	fluoxetine 5 mg/kg ip 2 hr before MCAA	 no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	cyproheptadine 5 mg/kg ip 30 min before MCAA	 no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	enfluramine f10 mg/kg ip 3.5 hr before MCAA	 no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	p-chloroamphetamine 10 mg/kg ip 48 hr before MCAA	 no protection	Berardi, 1986

6.6 Gabaergic Agonists and Antagonists

Treatment with the GABAergic (c-amino butyric acid) agonists, valproate, aminooxyacetate, diazepam, and chlordiazepoxide, or with the GABAergic antagonist (+)bicuculline, did not protect mice against MCAA mortality (Table 7; Berardi, 1986).

6.7 Dopaminergic Agonists and Antagonists

Neither the dopaminergic antagonists, reserpine and chlorpromazine, nor the dopaminergic agonist, L-dopa, protected mice against MCAA-induced lethality; indeed in some cases the time before death was decreased (Table 8; Berardi, 1986).

6.8 Miscellaneous Antidotes

Other antidote treatments such as the diuretic furosemide (Gibson, 1973), the nor-epinephrine uptake inhibitors, amitriptyline and D-amphetamine, the opiate receptor blocker, naloxone, the anticonvulsant, phenytoin, the adrenal steroid, dexamethasone (Berardi, 1986), the pH buffers, sodium bicarbonate (Hercules, 1971), and sodium acetate (Mitroka, 1989) have been tested to evaluate the hypothesis that acetate anions compete with monochloroacetate anions). None has proved effective against MCAA intoxication (Table 9).

The potential antidote activity of 2-chloropropionic acid (2-CP) (45 or 90 mg/kg iv), a PDH activator and lactate lowering agent (Leroux et al, 1980), was evaluated in rats 15 minutes after intoxication with MCAA (80 mg/kg iv) (Table 10; Elf Atochem, 1998a). Blood lactate levels were significantly decreased in 2-CP treated rats compared with MCAA-intoxicated rats (Figure 3), but mortality was not influenced. The inherent toxicity of 2-CP might account for the absence of beneficial effects on survival. Alternatively, lowering blood lactate levels alone may not be sufficient to prevent fatalities.

Table 7: GABAergic agonists and antagonists

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Swiss-Webster mice 380 mg/kg po (LD_{80})	valproate 300 mg/kg ip 1 hr before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	aminooxyacetate 25 mg/kg ip 6 hr before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	diazepam 15 mg/kg ip 15 min before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	chlordiazepoxide 20 mg/kg ip 30 min before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	(+)bicuculline 1 mg/kg sc 30 min before MCAA and 5.5, and 7.5 hr after MCAA	no protection	Berardi, 1986

Table 8: Dopaminergic agonists and antagonists

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Swiss-Webster mice 380 mg/kg po (LD_{80})	reserpine 1.5 mg/kg ip 3 hr before MCAA	no protection	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	chlorpromazine 5mg/kg ip 30 min before MCAA	no protection; decreased time to death	Berardi, 1986
Swiss-Webster mice 380 mg/kg po (LD_{80})	L-dopa1 100 mg/kg ip 30 min before MCAA	no protection; decreased time to death	Berardi, 1986

Table 9: Miscellaneous antidote treatments

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
Male Sprague-Dawley rats	furosemide		Gibson, 1973
162 mg/kg sc	100 mg/kg po with MCAA	no protection	
	50 mg/kg by infusion 5 min before MCAA injection	no protection	
Swiss-Webster mice	amitriptyline		Berardi, 1986
380 mg/kg po (LD_{80})	10 mg/kg ip 2x daily (3 days) and 90 min before MCAA	no protection	
Swiss-Webster mice	D-amphetamine		Berardi, 1986
380 mg/kg po (LD_{80})	4 mg/kg sc 1 hr before MCAA and 2.5 hr after MCAA	increased % lethality	
Swiss-Webster mice	naloxone		Berardi, 1986
380 mg/kg po (LD_{80})	1 mg/kg sc 20 min before MCAA and 2.5 and 5.5 hr after MCAA	no protection	
	10 mg/kg sc 30 min before MCAA and 5.5 hr after MCAA	no protection	
Sprague-Dawley rats	phenytoin		Mitroka, 1989
80 mg/kg iv (LD_{80})	80 mg/kg ip 15 min after MCAA	no protection	
Swiss-Webster mice	dexamethasone		Berardi, 1986
380 mg/kg po (LD_{80})	0.6 mg/kg ip 0 and 3 hr after MCAA	no protection	

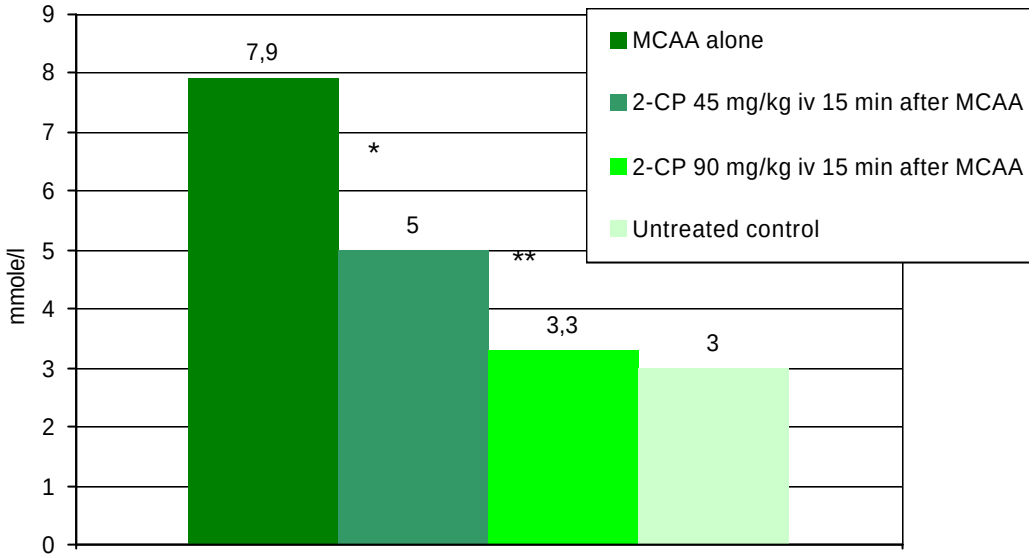
Table 9 (continued): Miscellaneous antidote treatments

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality	Reference
New-Zealand rabbits 2.0 g/kg (molten) dermally (no rinsing)	sodium bicarbonate iv infusion (20 drops/min) 1.3% soln. starting 10 min after MCAA	no protection	Hercules, 1971
New-Zealand rabbits 1.0 or 2.0 g/kg (molten) dermally for 5 min (rinsing)	sodium bicarbonate iv infusion (20 drops/min)1.3% soln. starting 10 min after MCAA	no protection	Hercules, 1971
Sprague-Dawley rats 100 mg/kg iv	sodium acetate 50 mEq/hr/kg iv infusion	no protection (no effect on time to death)	Mitroka, 1989

Table 10: 2-Chloropropionic acid

Species/dose MCAA	Antidote/mode of administration	Effect on MCAA lethality and toxicity	Reference
Sprague-Dawley rats	2-CP		Elf Atochem,1998a
80 mg/kg iv	45 mg/kg iv 15 min after MCAA	2/6 rats survived, all rats presented early clinical signs and 1/2 surviving rats presented in addition delayed clinical signs (versus 1/12 survival with persistent clinical signs in MCAA controls)	
	90 mg/kg iv 15 min after MCAA	1/6 ratsurvived without clinical signs, all rats presented early clinical signs (versus 1/12 survival with persistent clinical signs in MCAA control)	

Figure 3 : Effect of 2-CP administered 15 min after MCAA intoxication (80 mg/kg iv) on blood lactate levels measured 90 min after dosing of rats (Elf Atochem, 1995b, 1998a)



* p<0.05, ** p<0.01 (Dunnett test, n=6-12)/MCAA alone

6.9 Conclusion

Various chemicals, other than DCA or PB, have been investigated to test the different hypotheses for effective antidotes against MCAA toxicity. This has included acetate donors to combat the alleged inhibition of the Krebs cycle (similar to treatment of monofluoroacetate intoxication), sulphydryl-group donors to combat the demonstrated binding of MCAA to enzymatic-thiol groups, and a variety of neuro-active and miscellaneous substances. None, other than DCA or PB, has proved effective.

7. EFFICACY AND SAFETY OF DICHLOROACETATE FOR TREATMENT OF MCAA INTOXICATION

7.1 Mode of Action and Pharmacodynamics

Early studies on the pharmacological activity of DCA were performed with the diisopropylammonium salt. After it became clear that the DCA ion was the active moiety, most research was done with the sodium salt (Stacpoole *et al*, 1998b).

DCA enhances the activity of the pyruvate dehydrogenase complex (PDHc) in virtually all mammalian cells (Whitehouse *et al*, 1974). PDHc consists of several enzymes and is located in the inner mitochondrial membrane. It catalyses the oxidation of pyruvate to acetyl CoA. This is the rate-limiting step in the aerobic oxidation of glucose, pyruvate and lactate in animal cells.

The enzymes responsible for the activation and inactivation of PDHc are PDH-phosphatase and PDH-kinase respectively. PDH-kinase phosphorylates and thus inactivates PDHc, PDH-phosphatase dephosphorylates and thus activates PDHc. DCA appears to reduce the activity of PDH-kinase. This inhibition locks PDHc in its active unphosphorylated form (Stacpoole et al, 1998b). DCA is easily transported across cell membranes via the monocarboxylate carrier (Jackson and Halestrap, 1996) and is concentrated in the mitochondria (Stacpoole, 1989). Hence the inhibiting effect of DCA occurs rapidly after its administration.

Stacpoole (1989) suggested that DCA, by reactivating the enzymatic conversion of pyruvate to acetyl-CoA, primed the Krebs cycle with acetyl groups and the respiratory chain with electrons (donated by the reducing equivalents generated in the reactions catalysed by the PDHc and Krebs cycles). This promotes ATP synthesis in the cell, a process that consumes glucose and lactate and also enables the cell to survive impending energy failure. Studies have established DCA as a potent lactate-lowering agent in man, with little or no acute toxicity at the required dose levels (Bersin and Stacpoole, 1997).

As systemic intoxication by MCAA is thought to be the consequence of a cerebral lactic acidosis (Section 4), DCA appears to be a potential antidote.

7.2 Experimental Basis for Recommendation of DCA as Antidote

Rats or mice received various amounts of DCA (as sodium salt) as a single iv dose, at the same time or following a single iv dose of MCAA, previously established to be the LD_{80} (Mitroka, 1989; Elf Atochem, 1998a, b; Table 11). When DCA was administered at high doses (110 mg/kg) within 15 minutes of the MCAA administration, survival was close to 100% in all cases. The animals exhibited none of the clinical signs normally observed in MCAA-intoxicated animals (Elf Atochem, 1998a). A later administration of DCA (³ 30 min after MCAA) or the administration of a lower dose of DCA (50 mg/kg) resulted in a lower antidote efficacy. Nevertheless survival was still significantly higher than in untreated animals.

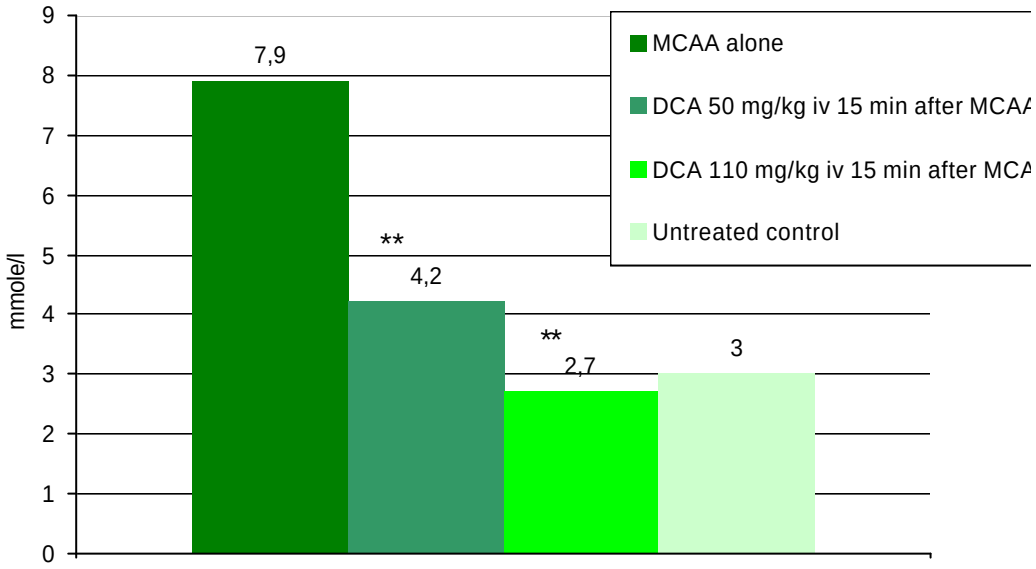
Only the early administration (< 15 min) of DCA after MCAA injection inhibited significantly the lactate rise in blood (Figure 4) and in CSF (Figure 5) (Mitroka, 1989; Elf Atochem, 1998a). At high DCA doses (110 mg/kg) the lactate levels were comparable with those of untreated control animals.

Table 11: Experimental studies with DCA as potential antidote for MCAA intoxication

Species/MCAA dose	DCA dose/mode of administration	Effect on MCAA lethality and toxicity	Reference
Sprague-Dawley rats 80 mg/kg iv	110 mg/kg iv with MCAA	12/12 rats survived on day 1 (versus 0/12 survival in MCAA controls)	Mitroka, 1989
	110 mg/kg iv 15 min. after MCAA	8/8 rats survived on day 1 (versus 2/8 survivals in MCAA controls)	
Sprague-Dawley rats 80 mg/kg iv	50 mg/kg iv 15 min after MCAA	5/6 rats survived on day 8, all rats presented early clinical signs and 1/5 surviving rat presented in addition delayed clinical signs (versus 1/12 survival with persistent clinical signs in MCAA controls)	Elf Atochem, 1998a
	110 mg/kg iv 15 min after MCAA	6/6 rats survived on day 8 without early or delayed clinical signs (versus 1/12 survival with persistent clinical signs in MCAA controls)	
Sprague-Dawley rats 80 mg/kg iv	110 mg/kg iv 45 min after MCAA	8/10 rats survived on day 15, 6/8 surviving rats presented early clinical signs and 2/8 were without clinical signs (versus 2/10 survivals without persistent or delayed clinical signs in MCAA controls)	Elf Atochem, 1998b
Swiss-Webster mice 160 mg/kg iv	220 mg/kg iv with MCAA	13/14 mice survived on day 1 (versus 4/14 in MCAA controls)	Mitroka, 1989
	220 mg/kg iv 30 min after MCAA	7/8 mice survived on day 1 (versus 2/8 in MCAA controls)	

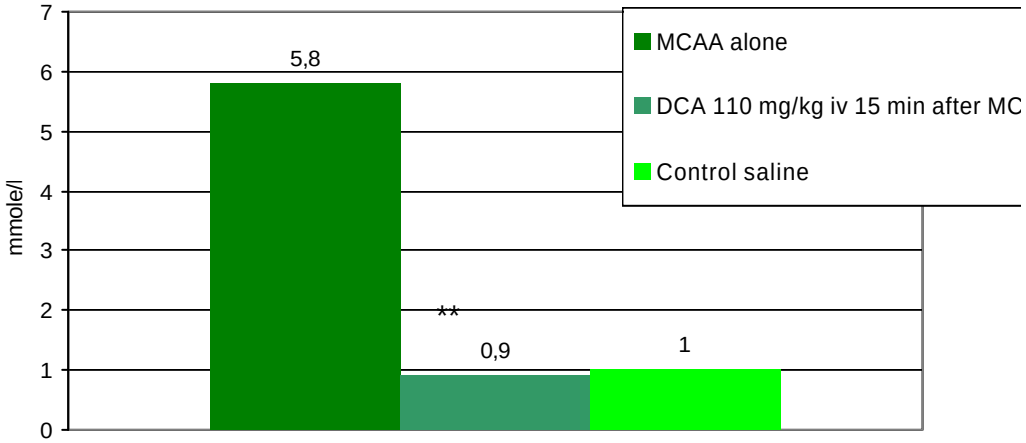
Figure 4: Blood lactate levels in rats after MCAA intoxication (80 mg/kg iv) and DCA treatment

Figure 4a : Effect of DCA administered 15 min after MCAA intoxication on blood lactate levels measured 90 min after MCAA dosing (Elf Atochem, 1995b, 1998a)



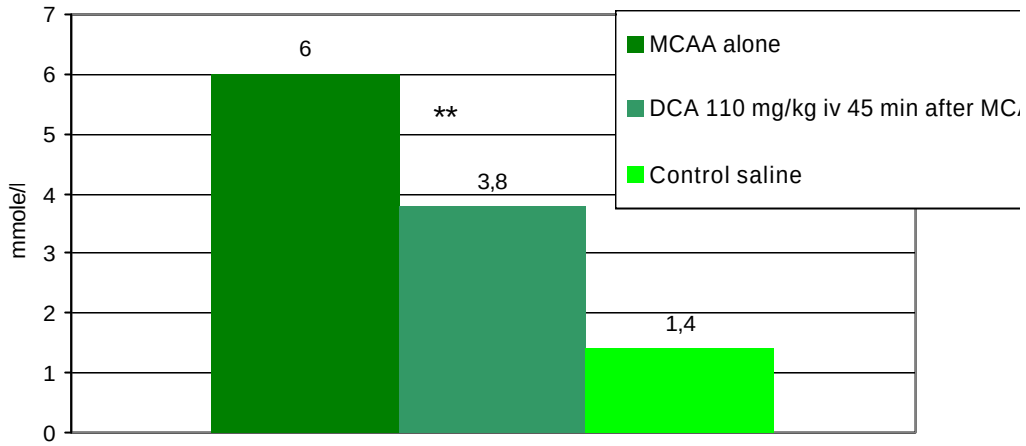
** p? 0.01 (Dunnett test, n=6-12)/MCAA alone

Figure 4b : Effect of DCA administered 15 min after MCAA intoxication on blood lactate levels measured 75 min after MCAA dosing (adapted from Mitroka, 1989)



** p? 0.01 (Bonferroni's test, n=5-7)/MCAA alone

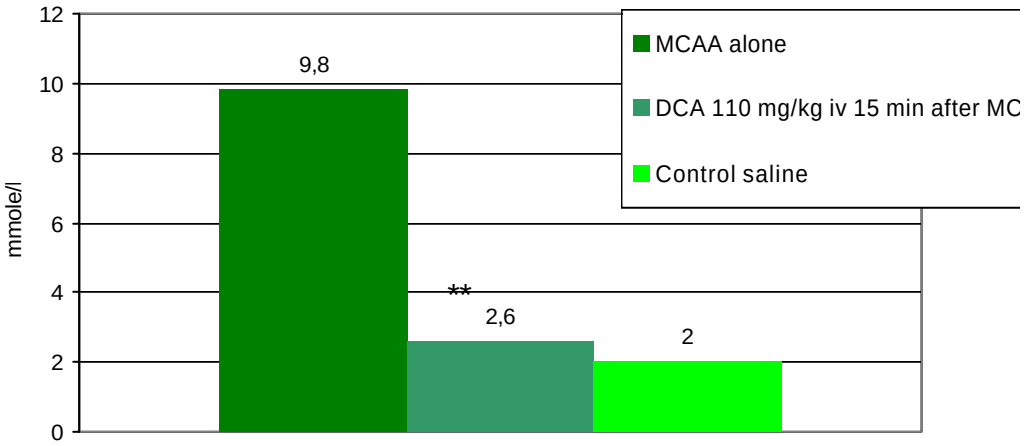
Figure 4c: Effect of DCA administered 45 min after MCAA intoxication on blood lactate levels measured 90 min after MCAA dosing (Elf Atochem, 1998b)



** p? 0.01 (Dunnett test, n=5)/MCAA alone

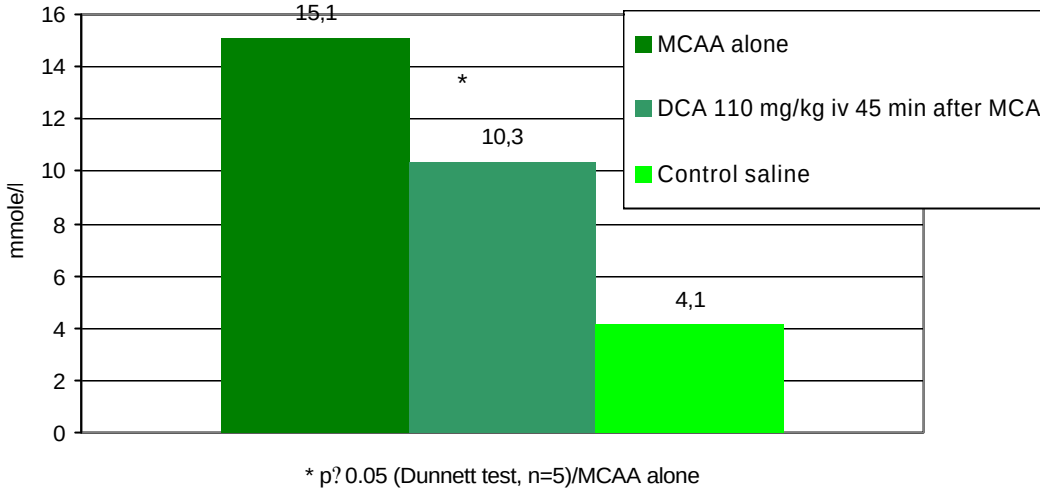
Figure 5: CSF lactate levels in rats after MCAA intoxication (80 mg/kg iv) and DCA treatment

Figure 5a : Effect of DCA administered 15 min after MCAA intoxication on CSF lactate levels measured 75 min after MCAA dosing (adapted from Mitroka, 1989)



** p? 0.01 (Bonferroni's test, n=5-7)/MCAA alone

Figure 5b: Effect of DCA administered 45 min after MCAA intoxication on CSF lactate levels measured 90 min after MCAA dosing (Elf Atochem, 1998b)



7.3 Clinical Safety of DCA for Short-term Administration

The clinical pharmacology, pharmacokinetics, metabolism and toxicology of DCA were reviewed by Stacpoole et al (1998a, b). The following focuses on the elements relevant for the assessment of the clinical safety of short-term administration of DCA in the treatment of severe MCAA intoxication.

DCA has been used for almost 50 years as a drug for the treatment of several metabolic, cardiovascular and cerebrovascular disorders. Oral and iv doses of the sodium salt have ranged from 25-100 mg/kg/day in short-term or chronic treatment. Courses of treatment exceeding one per week have been confined so far to infants, children or young adults with homozygous familial hypercholesterolaemia (Moore *et al*, 1979) or with congenital forms of lactic acidosis (Stacpoole *et al*, 1997).

7.3.1 Pharmacokinetics

The kinetic profile of DCA seems to be independent of the route of administration and sex (Stacpoole *et al*, 1998b). Studies in animals (Lin *et al*, 1993) and in human volunteers (Curry *et al*, 1985, 1991) have shown that orally-administered DCA is rapidly and virtually completely absorbed.

Activation of cellular PDH can be detected within 60 minutes of a single oral dose, which indicates good tissue distribution and easy uptake by the cells (Chu, 1987). The mechanism has not yet been clarified, but the initial dose is cleared from plasma more rapidly than subsequent doses. The plasma elimination half life for the first dose is about one hour, increasing to about eight hours after five days of administration (Stacpoole *et al*, 1998b). Elimination is through exhalation of CO_2 or excretion in the urine.

There are two main pathways for DCA metabolism: namely by reduction to MCAA or by cytochrome-P450 oxidation to glyoxylate. The latter pathway is quantitatively more important. The bulk of glyoxylic acid is converted to oxalate and CO2, either directly by lactate oxidase/glycolate oxidase or via glycolate with involvement of the enzymes lactate dehydrogenase/glycolate oxidase/glycolate dehydrogenase (Stacpoole *et al*, 1998b). The MCAA formed is conjugated with glutathione to form thiodiacetic acid and is eliminated by the kidneys (Larson and Bull, 1992). Plasma levels of MCAA have been found to be about one tenth those of DCA (Stacpoole *et al*, 1998a).

7.3.2 Toxicology of DCA

Human data

It is not uncommon for healthy adults, receiving single or repeated oral or iv doses of DCA at 25 or 50 mg/kg, to experience a sedative or anxiolytic effect (Stacpoole *et al*, 1998b).

A reversible peripheral neuropathy has been observed after several months of treatment with 50-100 mg/kg/day DCA (Moore et al, 1979; Kurlemann *et al*, 1995). Pre-treatment neurological status, confirmed both clinically and by nerve conduction velocity testing, was reached within six months of discontinuation of treatment with DCA. In these patients, DCA treatment was then re-instituted at 10-25 mg/kg/day without subjective or objective reappearance of the neuropathy (Stacpoole et al, 1992, 1998a).

Mild (two-fold), dose-dependent and asymptomatic elevation of serum transaminase has been reported in at least two children when doses of 25-75 mg/kg/day were given for several months. Reducing the DCA dose resulted in these parameters returning to normal in one subject (Stacpoole *et al*, 1998a).

Urinary oxalate excretion and serum ketone levels are increased by DCA (Curry *et al*, 1985); no clinical problems have so far been associated with this increase (Stacpoole *et al*, 1998a).

Animal data

DCA is of low acute toxicity by the oral (LD50/rat = 4.5 g/kg), and iv (LD50/rat > 2.2 g/kg) route (Woodard *et al*, 1941; Katz *et al*, 1981).

Depending on the dose level, 90-day oral administration of DCA to rats and dogs induced neurotoxicity, ocular anomalies, hepatotoxicity, nephrotoxicity and testicular toxicity. Most of these effects were reversible or improved following cessation of treatment. No NOAELs can be derived from these studies; the lowest-observed-adverse effect level (LOAEL) was 12.5mg/kg/day in dogs (Mather *et al*, 1990; Bhat *et al*, 1991; Katz *et al*, 1981; Yount *et al*, 1982; Cicmanec *et al*, 1991).

DCA was hepatocarcinogenic on long-term administration to mice (DeAngelo *et al*, 1991; Daniel *et al*, 1992; Pereira, 1996), and male rats (DeAngelo and Daniel, 1992; DeAngelo *et al*, 1996). The NOAEL was 3-8 mg/kg/d. Possible primary mechanisms for the hepatocarcinogenicity in rodents are either the induction of peroxisome proliferation

or the repeated induction of necrosis and healing of affected areas; the latter would act to stimulate the growth of previously-initiated cells, and if this continued it would increase the probability of spontaneous progression to a malignant state (Potter *et al*, 1990; Sanchez and Bull, 1990; Bull *et al*, 1990; Carter *et al*, 1995; DeAngelo and McFadden, 1995; Richmond *et al*, 1995; Bruschi and Bull, 1993). In 1995, IARC considered that overall DCA was "not classifiable as to carcinogenicity to humans" (Group 3). The US Environmental Protection Agency (1996) categorised the compound as a "probable human carcinogen" (Class 2B).

Some early *in vitro* genotoxicity assays for gene mutations (Herbert *et al*, 1980; Harrington-Brock *et al*, 1992) and primary DNA damage (Waskell, 1978; Meier and Blazak, 1985; Ono *et al*, 1991) gave equivocal results. Recent *in vitro* assays, with purified DCA in some studies, have been consistently negative (Chang *et al*, 1992; CWFG, 1994a; Watanabe et al, 1996; Fox *et al*, 1996). *In vivo* induction of DNA strand breaks in mouse liver was described initially (Nelson and Bull, 1988; Nelson *et al*, 1989), but did not receive further confirmation (Chang *et al*, 1992). Micronucleus (Fox *et al*, 1996; Fuscoe et al, 1996) and sister chromatid exchange (DeAngelo *et al*, 1989) assays in bone marrow and/or blood of mice or rats, as well as chromosomal aberrations in V79 (CWFG, 1994b) and Chinese hamster ovary cells (Fox *et al*, 1996) were reported as negative. Overall there is no consistent evidence that would suggest that DCA is genotoxic.

DCA treatment induced adverse effects on the male rat reproductive system and, at high doses (125 mg/kg/d) affected fertility; no NOAEL could be derived (Toth *et al*, 1992). DCA induced foetal malformations of the cardiovascular system. The NOAEL for the developmental toxicity of DCA in the pregnant rat was 14 mg/kg/day (Smith *et al*, 1992; Randall *et al*, 1991; Epstein *et al*, 1992; Epstein *et al*, 1990).

7.3.3 Conclusions for the short-term therapeutic use of DCA

Apart from a mild sedative effect, the side effects expected in man on the bases of animal and clinical evidence would occur only if therapeutic doses of DCA were given over many weeks; there is no clinical evidence that in short-term use these effects are manifest in man.

Although DCA has been shown to be carcinogenic in rodent lifetime studies, it does not appear to be genotoxic. The proposed mechanisms of hepatocarcinogenicity, which include peroxisome proliferation, require prolonged and sustained administration and are of little relevance to man. In view of these factors a short-term and possibly lifesaving regime of DCA should not be considered to carry a significant risk of cancer.

The acceptability of a developmental hazard should be balanced against the benefits expected from DCA treatment for potentially lethal MCAA intoxication, bearing in mind that the lactic acidosis induced by MCAA is in itself embryotoxic (Powell and Brace, 1991; Bocking *et al*, 1991).

7.4 Conclusion

Short-term treatment with DCA is potentially valuable for the management of acute systemic MCAA intoxication, with the probable benefits for this life-threatening condition far outweighing the risks.

8. EFFICACY AND SAFETY OF PHENOBARBITONE FOR TREATMENT OF MCAA INTOXICATION

8.1 Mode of Action and Pharmacodynamics

The mode of action of phenobarbitone (PB) in the treatment of MCAA intoxication has not been established. At therapeutic dosages, PB enhances the inhibition of nerve synapses by the GABA-ergic receptor system through allosteric modification of elements (probably the chlorine channel) of the receptor complex. There is no specific receptor site for PB, so the mechanism is thought to be due to accumulation of PB in lipid membranes. At higher dosages there is a general impairment of both CNS and peripheral excitable tissue activity (e.g cardiovascular tissue) by a generalised blocking of active and passive membrane processes (e.g. those regulating the sodium and calcium fluxes involved in excitation processes), as well as the activity of various intracellular enzyme systems (Martin and Haefele, 1995). Electrical activity and energy consumption in the brain may thus be reduced to low levels. The doses used in the animal experiments described below, are probably sufficient for such a sub-total blocking. Thus, the blocking of intracellular energy production by MCAA would not have deleterious effects on hibernating cells. In the meantime MCAA would be removed from the brain cells by passive diffusion in the course of normal metabolism and elimination (van Hinsbergh and Vermeer, 1994).

8.2 Experimental Basis for Recommendation as Antidote

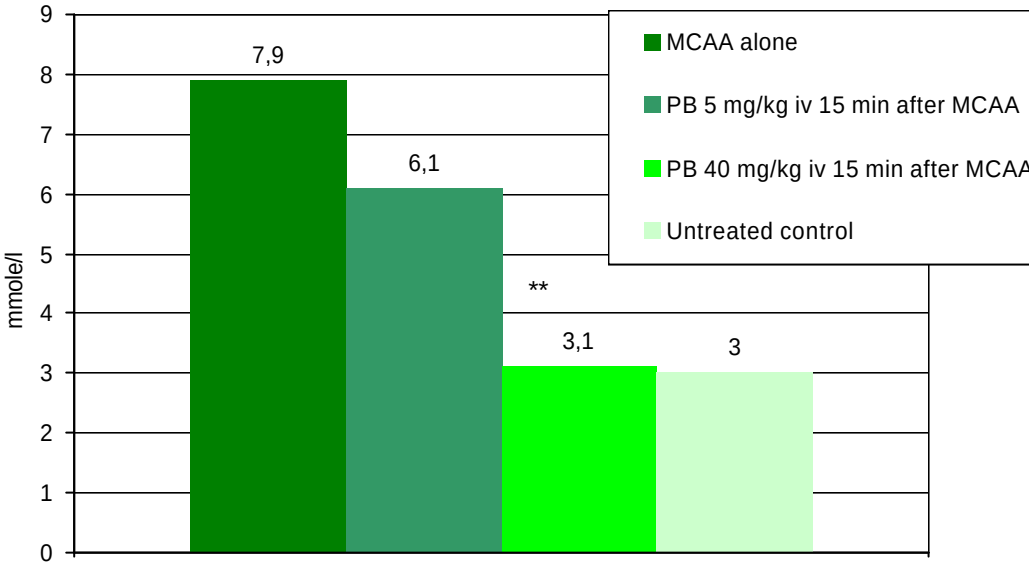
In order to explore the effects of a decrease in basal metabolism on MCAA-induced lethality, PB was administered iv to rats (Mitroka, 1989; Elf Atochem, 1998a, b) and to mice (Mitroka, 1989) before or after intoxication with a dose of MCAA giving a high level of lethality (Table 12). In all cases a high dose of PB (40 mg/kg) significantly increased survival rate (Table 12), and significantly decreased lactate levels in blood (Figure 6) and CSF (Figure 7).

Table 12: Experimental studies with PB as potential antidote for MCAA intoxication

Species/MCAA dose	PB dose/mode of administration	Effect on MCAA lethality and toxicity	Reference
Sprague-Dawley rats 80 mg/kg iv	5 mg/kg iv 15 min after MCAA	3/6 rats survived on day 8, all rats presented early clinical signs and 2/3 surviving rats presented in addition delayed clinical signs (versus 1/12 survival with delayed clinical signs n MCAA controls)	Elf Atochem, 1998a
	40 mg/kg iv 15 min after MCAA	5/6 rats survived on day 8, one rat was sacrificed *in extremis* on day 8, all rats presented early clinical signs and 2 rats presented in addition delayed clinical signs (versus 1/12 survival with delayed clinical signs in MCAA controls)	
Sprague-Dawley rats 80 mg/kg iv (LD_{80})	40 mg/kg ip 15 min after MCAA (2 independent experiments)	7/8 and 8/8 rats survived on day 1 (versus 1/8 and 3/8 survivals in MCAA controls, respectively)	Mitroka, 1989
	40 mg/kg ip 15 min before MCAA	13/15 rats survived on day 1 (versus 8/15 survivals in MCAA controls)	
Sprague-Dawley rats 80 mg/kg iv	40 mg/kg iv 45 min after MCAA	7/10 rats survived on day 15, all rats presented early clinical signs, 1/7 surviving rats presented delayed clinical signs and was in a poor clinical condition on day 15 (versus 2/10 survival without persistent clinical signs in MCAA controls)	Elf Atochem, 1998b
Swiss-Webster mice 160 mg/kg iv (LD_{80})	80 mg/kg ip 30 min after MCAA	5/10 mice survived on day 1 (versus 0/10 in MCAA controls)	Mitroka, 1989

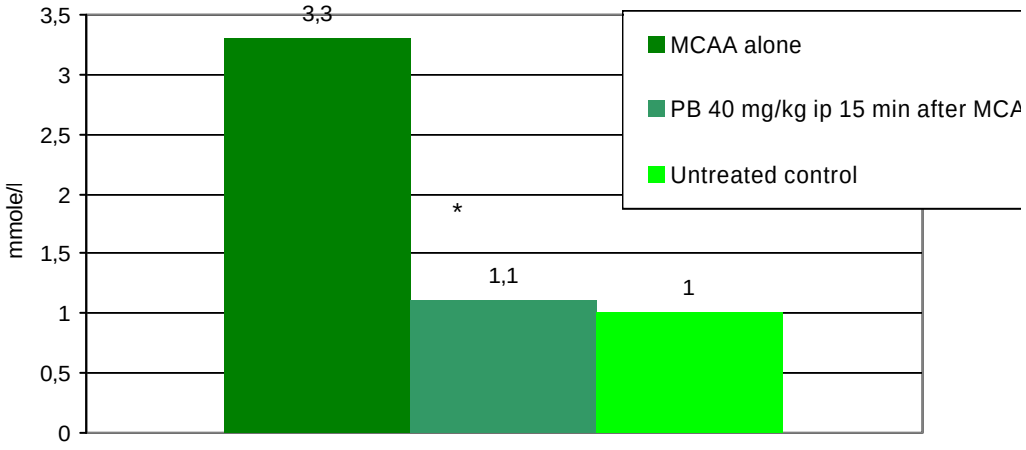
Figure 6: Blood lactate levels in rats after MCAA intoxication (80 mg/kg iv) and PB treatment

Figure 6a : Effect of PB administered 15 min after MCAA intoxication on blood lactate levels measured 90 min after MCAA dosing (Elf Atochem, 1995a, 1998a)



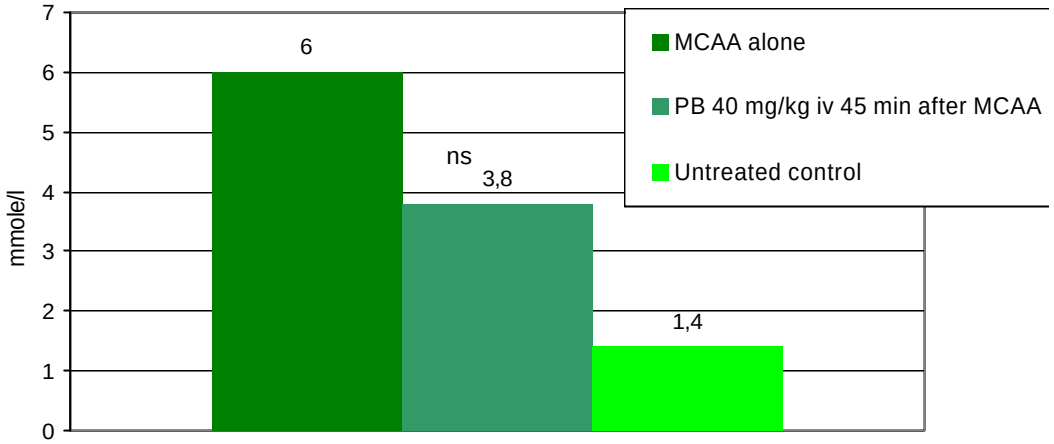
** p? 0.01 (Dunnett test, n=5-12)/MCAA alone

Figure 6b : Effect of PB administered 15 min after MCAA intoxication on blood lactate levels measured 75 min after MCAA dosing (adapted from Mitroka, 1989)



* p? 0.05 (Bonferroni's test, n=5-8)/MCAA alone

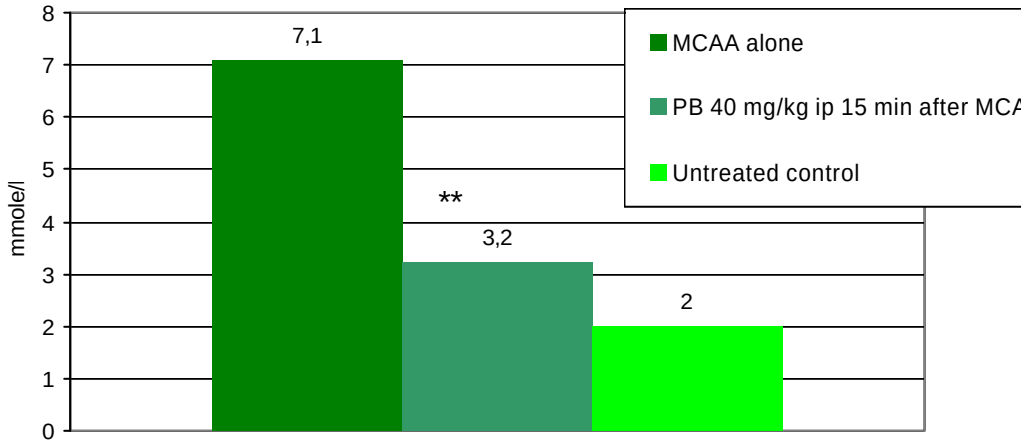
Figure 6c : Effect of PB administered 45 min after MCAA intoxication on blood lactate levels measured 90 min after MCAA dosing (Elf Atochem, 1998b)



ns: not significant (Dunnett test, n=5)/MCAA alone

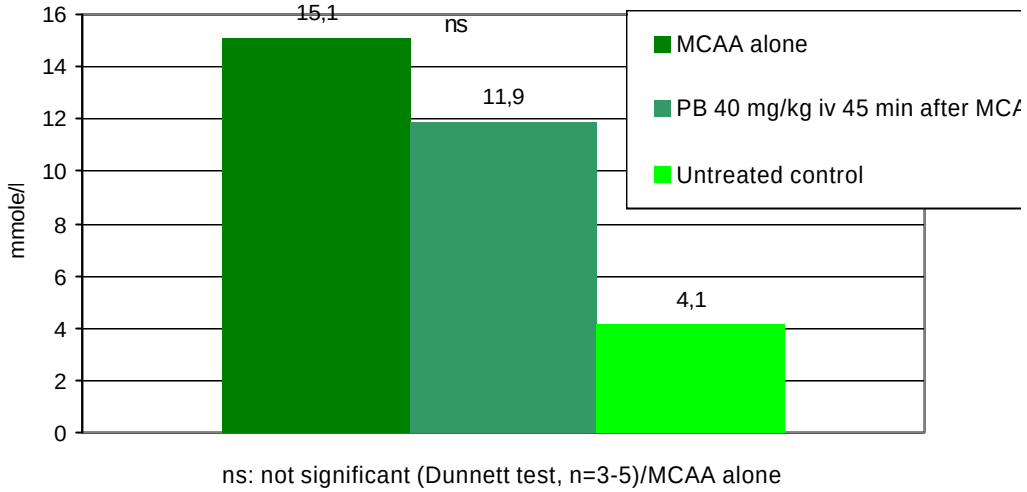
Figure 7: CSF lactate levels in rats after MCAA intoxication and PB treatment

Figure 7a: Effects of PB administered 15 min. after MCAA intoxication on CSF lactate levels measured 75 min. after MCAA dosing (adapted from Mitroka, 1989)



** p?0.01 (Bonferroni's test, n=5-8)/MCAA alone

Figure 7b : Effects of PB administered 45 min after MCAA intoxication on CSF lactate levels measured 90 min after MCAA dosing (Elf Atochem, 1998b)



ns: not significant (Dunnett test, n=3-5)/MCAA alone

8.3 Clinical Safety of Phenobarbitone for Short-term Administration

8.3.1 Pharmacokinetics

Phenobarbitone is rapidly and completely absorbed following oral and im administration; total bioavailability by both routes is approximately equal to iv administration. In adults, the average plasma half-life is 85 hours (60-140 hours). In adults not chronically treated with PB, less than 3% of PB is excreted in an unchanged form in the urine. PB is initially distributed over all well-perfused organs with the exception of the brain. Penetration into the brain is relatively slow, but after 60-90 minutes, high concentrations of PB are found in brain tissue. Elimination is mainly through transformation into the p-hydroxy moiety with subsequent glucuronidation and by the formation of an N-glucoside metabolite. Since these two routes account for only 50% of total PB, a faecal excretion pathway and/or as yet undetected metabolites are thought to exist (Levy et al, 1986).

8.3.2 Clinical toxicology

Phenobarbitone is a long-acting barbiturate, used for many decades as a sedative, as an hypnotic and anaesthetic and as an anti-epileptic agent. With the exception of its use as an anti-epileptic agent, it has been replaced largely since the 1960s by benzodiazepines, as the margin between desired and adverse effects is narrow. The main effect of PB is on the nervous system. Drowsiness, somnolence, sleep, stupor and coma may be induced, depending on the dose. If the coma is so deep that the patient does not respond to painful stimuli, there is a serious risk of central respiratory depression and death by asphyxiation. Cardiovascular collapse may occur. This is probably not due to a direct toxic action on the heart, since there is generally a response when the circulating volume

is supplemented. Hypothermia, due to suppression of the thermo-regulatory centre in the brainstem, should be prevented by adequate covering. In PB-intoxicated patients, bullae may appear on pressure areas of the skin (Moeschlin, 1971).

The dose of PB that would be effective as an antidote in man for MCAA intoxication is not known. The dose levels found to be effective in animals (40 - 80 mg/kg) would cause serious side effects in humans[1]. Given the probable mechanism of action (Section 8.1), induction of unconsciousness might be inevitable or even desirable. Such a degree of CNS depression would certainly require permanent observation in an intensive care setting, and life-supporting measures to combat the risk of respiratory and cardiovascular depression and failure. The long duration of action of PB (half-life for elimination 2-6 days depending on dose) would make it dangerous to use the required high doses, since an overdose could not be corrected. Also, as with all barbiturates, there is little correlation between doses (or plasma concentration) and CNS effects. All barbiturates have an identical mode of action as far as acute effects are concerned, with only the speed of onset and duration being different. Short-acting barbiturates, such as sodium methohexital or sodium thiopentabarbitone (thiopental) might therefore be preferable, since their effect can be titrated by electroencephalography and they are eliminated rapidly on ceasing administration (Shubin and Weil, 1971). However, supervision and support of vital functions by an anaesthetist experienced in the use of these substances would be essential.

8.3.3 Animal and *in vitro* toxicology

The results of *in vitro* mutagenicity and genotoxicity testing are ambiguous and conflicting. However *in vivo* assays are consistently negative (IARC, 1987). Thus, PB does not appear to be genotoxic.

According to IARC (1987), PB produced and promoted benign and malignant hepatocellular tumours in mice and hepatocellular tumours in rats after chronic oral administration. IARC classified PB overall in group 2B (possibly carcinogenic to humans). However, despite its widespread use, there is no evidence of carcinogenicity in man. In one cohort, an association was found between the incidence of brain tumours and the use of PB in epileptic patients. However, the incidence of brain tumours decreased when the duration of use of PB was longer, suggesting that the tumours were related to the primary disease rather than to PB *per se*. A non-significant excess of lung cancer was found in various cohorts, but could at least be partly accounted for by the effects of smoking. An excess of liver cancer in another cohort was likely to be due to the use of thorotrast (a carcinogenic Röntgen contrast medium) for diagnostic purposes (IARC, 1987).

[1] The estimated mean lethal dose (i.e. the mean dose taken in fatal intoxications) is 1.5 g (or 21 mg/kg) for an average adult (Dreisbach, 1966). Without treatment, more patients having taken a lower dose would also die, thus decreasing the potentially fatal dose even further. Lethality from clinically-treated PB intoxications ranges from about 1-8%, depending on the sophistication of the care provided. Upper estimates for a fatal dose range from 3-6 g for an adult i.e. 42-84 mg/kg.

PB is a potent enzyme inducer, especially of the CYP2 family from the cytochrome P-450 complex. Initially, it was believed that this induction led to carcinogenesis through metabolic activation of other compounds. However, despite the reasonable correlation between enzyme induction and carcinogenicity of various barbiturates, no definite mechanistic explanation has been found for the role of enzyme induction in PB liver carcinogenicity (Williams, 1997).

PB is also known to be a strong promoter of liver tumours in rodents, either spontaneous, initiated by other genotoxic compounds, or by proliferation-inducing events. Various PB-induced non-genotoxic phenomena have been described that help explain the role of PB in tumour promotion (Rundhaug *et al*, 1997; Cohen, 1997). The tumours found in the rodent bio-assays are now thought to be due to promotion of spontaneously arisen foci. Tumour promotion requires prolonged administration of the agent. So far, no rodent liver tumour promoter has been associated with cancer in humans. Therefore, it is concluded that the carcinogenic findings in animals are of no concern in considering the short-term use of PB as an antidote in man.

8.4 Conclusion

Based on animal data, PB may be useful for the short-term treatment of acute systemic MCAA intoxication, a life-threatening condition. However, the potential serious side effects at the required dose levels would limit its use to intensive care conditions.

9. PROPOSAL FOR CLINICAL MANAGEMENT OF MCAA SYSTEMIC INTOXICATION

9.1 Comparison of DCA with PB

In comparing DCA with PB for the management of MCAA intoxication, DCA seems to be the drug of choice for the following reasons.

DCA rapidly reaches the target organ and acts directly on the enzyme system involved in the toxic action of MCAA. It is well tolerated at doses required to reduce or eliminate cerebral lactic acidosis. Thus, it may be given before clinical symptoms are manifest. It is the most effective antidote in animal experiments, and has been successfully used in man for other disorders in which cerebral lactic acidosis plays a major role. At present its major drawback is its lack of availability. Currently, the only known officially-approved application is as a research drug in the USA. Formal registration for use in MCAA intoxication is prohibitively expensive, and European (e.g. Dutch) drug registration authorities are reluctant to allow an "orphan" drug registration for such a limited use. Prescription by the treating physician is possible in most European countries despite lack of registration, but this is hampered by the low probability that DCA is stocked in local pharmacies. In Sweden, the national Medical Products Agency has recently given permission for the use of DCA used as an antidote in cases of life-threatening MCAA intoxications.

In contrast to DCA, PB reaches the brain cells relatively slowly and probably works through a non-specific mechanism that requires doses that may induce life-threatening side effects in humans. A beneficial effect is thus solely dependent on metabolism and elimination of MCAA elsewhere. Coma-inducing doses of PB would probably not be acceptable to most clinicians unless there was clear evidence of the life-threatening complications of MCAA contamination. However, treatment at that stage might be too late, since the clinical management of fully-developed metabolic acidosis is very difficult and often unsuccessful. PB is also less effective than DCA in the animal experiments. The main point in favour of PB is its availability, although this may vary considerably from country to country. Other short-acting barbiturates might be as effective as PB and less dangerous to use, but would still require highly-skilled supervision.

9.2 Clinical Protocol

Intensive-care physicians from four European national poison control centres, participating in a workshop on the use of DCA and PB in the treatment of MCAA intoxication, concluded that, if available, DCA was the preferred antidote (Akzo Nobel, 1997) and proposed a treatment regimen (Kulling, 1997). Since knowledge of the toxicokinetics and toxicodynamics of MCAA in man is still limited, the protocol included recommendations for data collection. The protocol proposed by Kulling (1997) was submitted to IPCS-INTOX and subsequently incorporated into their Poison Information Monograph on MCAA (IPCS-INTOX, 2001). This protocol is summarised below, with additional comments and proposals (in italics) from the Task Force in consultation with external specialists (see Acknowledgements).

First-aid measures and management principles

- Following MCAA ingestion, urgently apply gastric decontamination.

  A careful evaluation of the situation is necessary as views on gastric decontamination differ between countries. However, induction of vomiting is contra-indicated because of existing oesophageal burns and the potential for additional acidic injury. Activated charcoal is not recommended as it may induce vomiting and obscure endoscopic findings. Immediate dilution with water might be beneficial.
- Following MCAA skin exposure, 1) apply immediate (in the following seconds) and prolonged flushing with copious amounts of water even under the clothes, 2) remove contaminated clothing without discontinuing the flushing, 3) continue flushing for at least 15 minutes.

  Some producers have installed heated baths filled with saturated sodium bicarbonate solution. Submersion is the fastest way to guarantee dilution, and the reaction between bicarbonate and MCAA may help to prevent further corrosive action, if not skin absorption.
- Following MCAA eye exposure, immediately flush with water for 15 minutes.

  If irritation, pain, swelling, lacrimation or photophobia persist after 15 minutes of irrigation, an ophthalmologist should be consulted.
- Following MCAA vapour inhalation, remove the victim to uncontaminated fresh air, administer oxygen and other treatments as for irritant gases.

Medical Treatment

- Apply symptomatic therapy in systemic poisoning (fluid replacement, correction of metabolic acidosis and hypokalaemia, adequate urine production and alkalinisation of urine to avoid myoglobin precipitation in renal tubules, inotropic therapy in cardiac failure, cerebral oedema treatment).

  Alkalinisation of urine is not routinely recommended according to the Poisindex scheme for treatment of rhabdomyolysis (Poisindex, 2001).
- If available, 50 mg/kg DCA (buffered to pH 7.2) should be given as a slow iv injection or infusion, preferably prior to the onset of lactic acidosis and in all cases where more than 6% body surface is contaminated. The treatment to be repeated after two hours. It is recommended that the study protocol given below is followed.
- If no DCA is available, PB in high dosages, sufficient to cause deep pre-coma, might be attempted provided respiratory support can be given.
- Additionally or alternatively, haemodialysis should be performed.

  Treatment with N-acetylecysteine and/or ethanol, as mentioned earlier (Sections 6.1 and 6.2) is unlikely to be effective for the treatment of the MCAA intoxication as such. However the mechanisms described in Section 7.3.1 may lead to a depletion of liver glutathione. Therefore the use of N-acetylcysteine should be considered as adjuvant therapy.

- Plasmapheresis may be considered in severe rhabdomyolysis.

  Plasmapheresis is not recommended for the treatment of rhabdomyolysis in the Poisindex scheme for the treatment of rhabdomyolysis (Poisindex, 2001).

Protocol for DCA treatment in MCAA poisoning

1. Adequately document the skin damage (including drawing on the skin and photographs).

2. Monitor haemodynamics (blood pressure, heart rate, and if possible including e.g. central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output) at regular intervals (hourly) for 24 hours (or longer).

3. Take blood samples (minimum 2 ml) for further analyses of MCAA and DCA (if appropriate) concentrations in plasma (EDTA/heparin tubes) blood. Separate and freeze the plasma.

   MCAA: Begin sampling as soon as possible and continue after 5, 10, 20, 40, 60, 120, 240 minutes and then after another 2, 6, 10 and 22 hours.

   DCA: Begin sampling five minutes before administration, at administration and thereafter as for MCAA after 5, 10, 20, 40, 60, 120, 240 minutes and then after another 2, 6, 10 and 22 hours.

Table 13: Blood analyses

Time	Acid/base lactate	Electrolytes (K+, Na+, Cl-)	B- Glucose	S-Creatinine S-Urea	S-Creatine kinase	S-AST, S-ALT, S-Bilirubin	S-Myoglobin	Coagulation parameters
Entry	x	x	x	x	x	x	x	x
1 h	x							
2 h	x	x	x	x				
3 h	x							
4 h	x	x	x	x				
5 h	x							
6 h	x	x	x	x				
7 h	x							
8 h	x	x	x	x	x	x	x	x
12 h	x	x	x	x				
16 h	x	x	x	x	x	x	x	x
20 h	x	x	x	x				
24 h	x	x	x	x	x	x	x	x
36 h	x	x	x	x	x	x	x	x
48 h	x	x	x	x	x	x	x	x

9.3 Availability of DCA

So far attempts to register DCA as an "orphan" drug have failed and distribution as a therapeutic drug is prohibited. MCAA suppliers are currently considering providing customers with pharmaceutical-grade DCA and instructions on how to prepare an iv drip solution. The intention is that this "package" would then be sent to the hospital with the MCAA-accident victim. From this the hospital dispensary could prepare the necessary solution, but only if and when prescribed by the physician responsible for the patient. This would avoid the complexities of providing a registered drug, while still enabling a medical prescription to be legally fulfilled. Similar measures are adopted by organisations producing cyanides. In Sweden, the national Medical Products Agency has recently given permission for the use of DCA as an antidote in cases of life-threatening MCAA intoxications.

Since accidents occur mainly during cargo handling and maintenance work, the above actions should cover most instances of accidental exposure to MCAA. In relation to accidents during transportation, the accompanying documents should specify the relevant telephone numbers of the MCAA supplier and of the concerned customer, where adequate information and (possibly) the antidote would be available.

10. CONCLUSION

- The Task Force considers that the available data support the recommendation of the MCAA/DCA Workshop to use DCA at an early stage in the management of MCAA intoxication.
- The availability of DCA should be improved in order to give effective treatment to future victims of exposure to MCAA.
- If no DCA is available, PB (or short-acting barbiturates) in high doses, sufficient to cause a deep stupor or coma, might be attempted, provided that respiratory and cardiovascular support can be given.

BIBLIOGRAPHY

Akzo Nobel. 1997. Minutes of workshop on use of DCA and/or phenobarbitone in the treatment of MCA intoxications. Hengelo.

Berardi MR. 1986. Monochloroacetic acid toxicity in the mouse associated with blood-brain barrier damage. Dissertation submitted to the Graduate School New Brinswick Rutgers, State University of New Jersey; excerpt published as Berardi MR, Snyder R, Waritz RS and Cooper KR, 1987. Monochloroacetic acid toxicity in the mouse associated with blood-brain barrier damage. *Fund Appl Toxicol* 9: 469-479.

Bersin RM, Stacpoole PW. 1997. Dichloroacetate as metabolic therapy for myocardial ischemia and failure. *Am Heart J* 134: 841-855.

Bhat HK, Kanz MF, Campbell GA, Ansari GAS. 1991. Ninety day toxicity study of chloroacetic acids in rats. *Fund Appl Toxicol* 17: 240-253.

Bocking AD, Challis JR, White SE. 1991. Effect of acutely-induced lactic acidemia on fetal breathing movements, heart rate, blood pressure, ACTH and cortisol in sheep. *J Dev Physiol* 16: 45- 50.

Bruijnzeel PLB, De Lange J, Braun CLJ, Elliott GR. 1998. Reducing systemic absorption from monochloroacetic acid exposure through dermal decomtanimation: use of the pig ear organ culture system. *J Toxicol Cutan Oc Toxicol* 17: 111-126.

Bruschi SA, Bull RJ. 1993. In vitro cytotoxicity of mono-, di-, and trichloroacetate and its modulation by hepatic peroxisome proliferation. *Fund Appl Toxicol* 21: 366-375.

Bull RJ, Sanchez IM, Nelson MA, Larson JL, Lansing AJ. 1990. Liver tumor induction in B6C3F1 mice by dichloroacetate and trichloroacetate. *Toxicol* 63: 341-359.

Carter JH, Carter HW, DeAngelo AB. 1995. Biochemical, pathologic and morphometric alterations induced in male B6C3F1 mouse liver by short-term exposure to dichloroacetic acid. *Toxicol Lett* 81: 55-71.

Chang LW, Daniel FB, DeAngelo AB. 1992. Analysis of DNA strand breaks induced in rodent liver in vivo, hepatocytes in primary culture, and a human cell line by chlorinated acetic acids and chlorinated acetaldehydes. *Environ Mol Mutagen* 20: 277-88.

Chenoweth MB, Kandel A, Johnson LB, Benett DR. 1951. Factors influencing fluoroacetate poisoning. Practical treatment with glycerol monoacetate. *J Pharm Exp Ther* 102: 31-49.

Christofano EE, Frawley JR, Reed HL, Keplinger ML. 1970. Skin exposure to monochloroacetic acid. *Am Ind Hyg Assoc* J 7: 35.

Chu P-I, 1987. Pharmacokinetics of sodium dichloroacetate. PhD Dissertation. Gainesville, FL, University of Florida.

Cicmanec JL, Condie LW, Olson GR, Wang SR. 1991. 90-Day toxicity study of dichloroacetate in dogs. *Fund Appl Toxicol* 17: 376-389.

Cohen SM. 1997. The role of cell proliferation in the etiology of neoplasia - cell proliferation and non-genotoxic carinogens: nongenotoxic liver carcinogens. In: *Comprehensive toxicology,* Sipes IG, McQueen CM and Gandolfi AF (eds), Pergamon.

Contassot JC, Ruty J, Millischer RJ, Vincenti M, Jouglard J. 1987. Monochloroacetic acid : systemic poisoning from transcutaneous transfer. A report of a recent accident. International Congress on Occupational Health (ICOH), Sydney, Australia.

Curry SH, Chu PI, Baumgartner TG, Stacpoole PW. 1985. Plasma concentrations and metabolic effects of intravenous sodium dichloroacetate. *Clin Pharmacol Ther* 37: 89-93.

Curry SH, Lorenz A, Chu P-I, Limacher M, Stacpoole PW. 1991. Disposition and pharmacodynamics of dichloroacetate (DCA) and oxalate following oral DCA doses. *Biopharm Drug Disp* 12, 375-390.

CWFG (Chemie-Wirtschaftsförderungs-Gesellschaft). 1994a. Study of the capacity of dichloroacetic acid to induce gene mutation in V79 Chinese hamster lung cells, RBM no. 930589.

CWFG (Chemie-Wirtschaftsförderungs-Gesellschaft. 1994b. Study of the capacity of dichloroacetic acid to induce chromosome aberrations in V79 Chinese hamster lung cells, RBM no. 930590.

Daniel FB, DeAngelo AB, Stober JA, Olson GR, Page NP. 1992. Hepatocarcinogenicity of chloral hydrate, 2-chloroacetaldehyde, and dichloroacetic acid in the male B6C3F1 mouse. *Fund Appl Toxicol* 19: 159-168.

Dartsch PC, Wolburg H, Al Makdessi S, Schiek, D, Sweidan H, Kimmel R, Schmahl FW. 2000. Sodium monochloroacetate causes cytotoxic effects, an increased lactate and pyruvate level and induces ultra structural and cytoskeletal alterations in cultured kidney and liver epithelial cells. *Human Exptl Toxicol* 19: 138-148.

DeAngelo AB, Daniel FB. 1992. An evaluation of the carcinogenicity of the chloroacetic acids in the male f344 rat. *Toxicologist* 12: 206.

DeAngelo AB, McFadden AL. 1995. Dichloroacetic acid (DCA) alterations of hepatic glucocorticoid receptor binding activity (GR) in male B6C3F1 mice. *Toxicologist* 15: 314.

DeAngelo AB, Daniel FB, McMillan L, Wernsing P, Savage RE. 1989. Species and strain sensitivity to the induction of peroxisome proliferation by chloroacetic acids. *Toxicol* Appl Pharmacol 101: 285-298.

DeAngelo AB, Daniel FB, Most BM, Olson GR. 1996. The carcinogenicity of dichloroacetic acid in the male fischer 344 rat. *Toxicol* 114: 207-221.

DeAngelo AB, Daniel FB, Stober JA, Olson GR. 1991. The carcinogenicity of dichloroacetic acid in the male B6C3F1 mouse. Fund Appl *Toxicol* 16: 337-347.

DKK (Denka Kagaku Koyo Company). 1984. Personal communication.

Dreisbach RH. 1966. In: Handbook of poisoning diagnosis and treatment. Lange Medical Publications, California.

ECETOC. 1999. Monochloroacetic acid and its sodium salt. Joint Assessment of Commodity Chemicals No. 38.

Elf Atochem. 1987. Test pour la recherche de l'effet antidote de l'ethanol administré par voie veineuse dans l'intoxication par l'acide monochloroacetique appliqué par voie cutanée chez le lapin. Hazleton-IFT report no. 707340.

Elf Atochem. 1989. Recherche d'un effet antidote éventuel de l'ethanol contre le monochloroacetate de sodium chez le chien beagle. Sanofi Recherche study no. RS 860890620/JV1.

Elf Atochem. 1995a. Acute intravenous toxicity in male rats with monochloroacetic acid. CIT report no. 12052 TAR.

Elf Atochem. 1995b. Determination of lactate levels after intoxication by intravenous route in male rats. CIT report no. 12102 PAR.

Elf Atochem. 1998a. Monochloroacetic acid. Comparison of three antidote treatments after intoxication by intravenous route in male rats. CIT report no.13486 PAR.

Elf Atochem. 1998b. Monochloroacetic acid. Comparison of two effective antidote treatments after intoxication by intravenous route in male rats. CIT report no. 13787 PAR.

EPA (Environmental Protection Agency). 1996. Integrated risk information system on dichloroacetic acid (79-43-6). National library of Medicine's TOXNET system.

Epstein DL, Nolen GA, Randall JL, Christ SA, Read EJ, Stober JA, Smith MK. 1990. The effects of dichloroacetic acid (DCA) on cardiogenesis in the Long-Evans rat foetus. *Teratology* 41: 553.

Epstein DL, Nolen GA, Randall JL, Christ SA, Read EJ, Stober JA, Smith MK. 1992. Cardiopathic effects of dichloroacetate in the foetal Long-Evans rat. *Teratology* 46: 225-235.

Feldhaus K, Hudson D, Rogers D, Horowitz RS, Brent J, Dart RC, Gomez H. 1993. Pediatric fatality associated with accidental oral administration of monochloroacetic acid (MCA). *Vet Hum Toxico*l 35: 344.

Fox AW, Yang X, Murli H, Lawlor TE, Cifone MA, Reno FE. 1996. Absence of mutagenic effects of sodium dichloroacetate. *Fund Applied Toxicol* 32: 87-95.

Fuscoe JC, Afshari AJ, George MH, De Angelo AB, Tice RR, Salman T, James WA. 1996. In vivo genotoxicity of dichloroacetic acid: evaluation with the mouse peripheral blood micronucleus assay and the single cell gel assay. *Environ Mol Mutagen* 27: 1-9.

Gibson JE. 1973. Studies on the antidotal treatment and acute toxicity of monochloroacetic acid in rats. Report to Hercules.

Gibson JE, Hayes FD. 1971. Studies on the mechanism of monochloroacetic acid toxicity in rats. Report to Hercules.

Harrington-Brock K, Smith TW, Parker LM, Moore MM. 1992. Genotoxic effects of by-products of the chlorination of drinking water. *Env Mol Mutagen* 19: suppl. 20-24.

Hayes FD, Short RD, Gibson JE. 1973. Differential toxicity of monochloroacetate, monofluoroacetate and monoiodoacetate in rats. Toxicol Appl Pharmacol 26: 93-102.

Herbert V, Gardner A, Colman N. 1980. Mutagenicity of dichloroacetate, an ingredient of some formulations of pangamic acid (trade-named "vitamin B_{15}"). *Am J Clin Nutr* 33: 1179-1182.

Hercules. 1969a. Letter to Occupational Health Committee Microfiche EPA-OTS 0537559.

Hercules. 1969b. Acute dermal toxicity study on monochloracetic acid in the molten (liquid) state in male albino rabbits and a mongrel dog. IBT report no. A7447

Hercules. 1971. Effect of sodium bicarbonate in rabbits exposed to a topical lethal dose of monochloroacetic acid. IBT report no. T9855.

Huismans JS. 1998. MCA intoxication case reports. Personal communication.

Hutchens JO, Wagner H, Podolsky B, McMahon TM. 1949. The effects of ethanol and various metabolites on fluoroacetate poisoning. *J Pharm Exp* Ther 95: 62-70.

IARC (International Agency for Research on Cancer). 1987. IARC monographs on evaluation of carcinogenic risks to humans. *Supplement 7. Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 - 42.*

IARC (International Agency for Research on Cancer). 1995. IARC monographs on evaluation of carcinogenic risks to humans. Volume 63. *Dry cleaning, some chlorinated solvents and other industrial chemicals*.

IPCS-INTOX. 2001. IPCS INTOX SYSTEM and IPCS INTOX CD-ROM, WHO/ILO/UNEP International Programme on Chemical Safety. http://www.intox.org.

Jackson VN, Halestrap AP. 1996. The kinetics, substrate, and inhibitor specificity of the monocarboxylate (lactate) transporter of rat liver cells determined using the fluorescent intracellular pH indicator, 2I,7I-bis(carboxyethyl)-5(6)-carboxyfluorescein. *J Biol Chem* 271: 861-868.

Katz R, Tai CN, Diener RM, McConnell RF, Semonick DE. 1981. Dichloroacetate, sodium : 3- month oral toxicity studies in rats and dogs. *Toxicol Appl Pharmacol* 57: 273-287.

Kulling P. 1997. Monochloroacetic acid monograph. Swedish Poisons Information Centre, Stockholm (Unpublished).

Kulling P, Andersson H, Bostrôm K, Johansson LA, Lindstrôm B, Nystrôm B. 1992. Fatal systemic poisoning after skin exposure to monochloroacetic acid. *Clin Toxicol* 30: 643-652.

Kurlemann G, Paetzke I, Mohler H, Masur H, Schluierer G, Weglage J, Koch HG. 1995. Therapy of complex I deficiency: peripheral neuropathy during dichloroacetate therapy. *Eur J Pediat* 154:928-932.

Kusch GD, Mc Carty LP, Lanham JM. 1990. Monochloroacetic acid exposure. A case report. *Polish J Occup Med* 3: 409-414.

Larson JL, Bull RJ. 1992. Metabolism and lipoperoxidative activity of trichloroacetate and dichloroacetate in rats and mice. *Toxicol Appl Pharmacol* 115: 273-287.

Leroux JP, Demaugre F, Buc HA , Saudubray JM. 1980. Effects of dichloroacetate and 2-chloropropionate on carbohydrate metabolism of isolated hepatocytes. Therapeutic applications. CR Sean Soc Biol Fil 174, 506-516.

Levy RH, Wilensky AJ, Friel PN. 1986. Applied pharmacokinetics In: *Applied therapeutics* Evan WR, Schentag JJ and Jusko WJ (eds).

Lin ELC, Mattox JK, Daniel FB. 1993. Tissue distribution, excretion, and urinary metabolites of dichloroacetic acid in the male fischer 344 rat. *J Toxicol Environ Hlth* 38, 19-32.

Mann GT. 1969. Report of autopsy. Commonwealth of Virginia. Office of the Chief Medical Examiner.

Martin JR, Haefele WE. 1995. In: Munson's *Principles of pharmacology*. Chapman and Hall, 378- 380.

Mather GG, Exon JH, Koller LD. 1990. Subchronic 90 day toxicity of dichloroacetic and trichloroacetic acid in rats. *Toxicol* 64: 71-80.

Meier JR, Blazak WF. 1985. Evaluation of genotoxicity of dichloroacetic acid and trichloroacetic acid. Presented at the 2nd international symposium on health effects of drinking water disinfectants and disinfectant by-products, Cincinnati, OH. (Cited in DeAngelo *et al*, 1989).

Millischer RJ, Jouglard J, Vincenti M, Ruty J, Contassot JC. 1987. Monochloroacetic acid : seven worldwide cases of systemic poisoning resulting from accidental skin contact. Occupational Health in the Chemical Industry, 22nd Congress, Sydney.

Mitroka JG. 1989. Monochloroacetic acid lethality in the rat in relation to lactic acid accumulation in the cerebrospinal fluid. Dissertation, Rutgers State University of New Jersey, no. 9008948.

Moeschlin S. 1971. In: *Acute barbiturate poisoning*. Ed. Mattew H. Exerpta Medica, Amsterdam, 117-128.

Moore GW, Swift LL, Rabinowitz D, Crofford OB, Oates JA, Stacpoole PW. 1979. Reduction of serum cholesterol in two patients with homozygous familial hypercholesterolemia by dichloroacetate. Atherosclerosis 33, 285-293.

Nelson MA, Bull RJ. 1988. Induction of strand breaks in DNA by trichloroethylene and metabolites in rat and mouse liver *in vivo. Toxicol Appl Pharmacol* 94: 45-54.

Nelson MA, Lansing AJ, Sanchez IM, Bull RJ, Springer DL. 1989. Dichloroacetic acid and trichloroacetic acid-induced DNA strand breaks are independent of peroxisome proliferation. *Toxicol* 58: 239-248.

Ono Y, Somiya I, Kawamura M. 1991. The evaluation of genotoxicity using DNA repairing test for chemicals produced in chlorination and ozonation processes. *Wat Sci Tech* 23: 329-338.

Pereira MA. 1996. Carcinogenic activity of dichloroacetic acid and trichloroacetic acid in the liver of female B6C3F1 mice. *Fund Appl Toxicol* 31: 192-199.

Poisindex. 2001. Poisindex database. Micromedex, Thomson Healthcare (http://www.micromedex.com).

Potter CL, DeAngelo AB, Daniel FB. 1990. Effects of dichloroacetic acid on hepatic growth and ornithine decarboxylase activity in B6C3F1 mice. *Toxicologist* 10: 182.

Powell TL, Brace RA. 1991. Elevated fetal plasma lactate produces polyhydramnics in the sheep. *Am J Obstet Gynecol* 165: 1595-1607.

Randall JL, Crist SA, Nolen GA, Read EJ, Smith MK. 1991. Developmental effects of dichloroacetic acid in Long-Evans rats. II. Establishment of no adverse effect level. *Teratol* 43: 454.

Régnier JF. 1997. Experimental evaluation of potential antidotes for monochloroacetic acid acute intoxication. Workshop on use of DCA and/or phenobarbitone in the treatment of MCAA intoxications, Hengelo.

Richmond RE, Carter JH, Carter HW, Daniel FB, DeAngelo AB. 1995. Immunohistochemical analysis of dichloroacetic acid induced hepatocarcinogenesis in male Fischer (F344) rats. *Cancer Letters* 92: 67-76.

Rogers DR. 1995. Accidental fatal monochloroacetic acid poisoning. *Am J Forens Med Pathol* 16: 115-116.

Rundhaug JE, Fisher SM, Bowden T. 1997. Tumor promoters and models of promotions: barbiturates. In: *Comprehensive toxicology*, Sipes IG, McQueen CM and Gandolfi AF (eds), Pergamon.

Ruty J. 1985. Rapport d'accident de Monsieur T. Elf Atochem Saint-Auban Med Dept. Personal communication.

Sanchez IM, Bull RJ. 1990. Early induction of reparative hyperplasia in the liver of B6C3F1 mice treated with dichloroacetate and trichloroacetate. *Toxicol* 64: 33-43.

Shubin H, Weil S. 1971. In: *Acute barbiturate poisoning*. Ed. Mattew H, Exerpta Medica, 135.

Smith MK, Randall JL, Read EJ, Stober JA. 1992. Developmental toxicity of dichloroacetate in the rat. *Teratol* 46: 217-223.

Stacpoole PW. 1989. The pharmacology of dichloroacetate. *Metabolism* 38: 1124-1144.

Stacpoole PW, Barnes CL, Hurbanis MD, Cannon SL, Kerr DS. 1997. Treatment of congenital lactic acidosis with dichloroacetate: a review. *Arch Dis Child* 77: 535-541.

Stacpoole PW, Henderson GN, Yan Z, Cornett R, James MO. 1998a. Pharmacokinetics, metabolism and toxicology of dichloroacetate. *Drug Metab Rev* 30: 499-539.

Stacpoole PW, Henderson GN, Yan Z, James MO. 1998b. Clinical pharmacology and toxicology of dichloroacetate. *Environ Hlth Persp* 106(suppl.4): 989-994.

Stacpoole PW, et al and the Dichloroacetate-lactic Acidosis Study Group. 1992. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. *N Engl J Med* 327: 1564-1569.

Toth GP, Kelty KC, George EL, Read EJ, Smith MK. 1992. Adverse male reproductive effects following subchronic exposure of rats to sodium dichloroacetate. *Fund Appl Toxicol* 19: 57-63.

Toyama G. 1999. Personal communication to AkzoNobel.

van Hinsbergh VWM. 1991. Toxicity of monochloroacetic acid on human endothelial cells. Interim Report and Second Research Proposal Gaubius Laboratory, TNO-IVVO Leiden.

van Hinsbergh VWM, Vermeeer M. 1994. Toxicity of monochloroacetic acid on human endothelial cells and rat heart mitochondria. Third Interim Report, Gaubius Laboratory TNO-PG, Leiden.

Vincenti M. 1987. A propos d'un cas d'intoxication percutanée par l'acide monochloroacétique. Thèse médecine, Université de Marseille, France.

Wang Kongfu, Na Tyanyun, Zhang Guang, Gong Guanlong, Cao Ruan. 1997. Report on an accident leading to 14 victims (1 fatal) of burns and intoxication from monochloroacetic acid. *Occup Hlth Emerg Rescue* (Abs)15, 103.

Waskell L. 1978. A study of the mutagenicity of anesthetics and their metabolites. *Mutation Res* 57:141-153.

Watanabe K, Sakamoto K, Sasaki T. 1996. Comparisons on chemically-induced mutagenicity among four bacterial strains, *Salmonella typhimurium* TA102 and TA2638, and *Escherichia coli* WP2/pKM101 and WP2 *uvrA*/pKM101: Collaborative study I. *Mutation Res* 361: 143-155.

Whitehouse S, Cooper RH, Randle PJ. 1974. Mechanism of activation of pyruvate dehydrogenase by dichloroacetate and other halogenated carboxylic acids. *Biochem J* 141: 761-774.

Williams GM. 1997. Carcinogenic responses to toxic liver injury in rodents - epigenetic hepatocarcinogens: promoters. In: *Comprehensive toxicology*, Sipes IG, McQueen CM and Gandolfi AF (eds), Pergamon.

Woodard G, Lange SW, Nelson KW, Calvery HO. 1941. The acute oral toxicity of acetic, chloracetic, dichloracetic and trichloracetic (sic) acids. *J Ind Hyg Toxicol* 23: 78-82.

Yount EA, Felten SY, O'Connor BL, Peterson RG, Powell RS, Yum MN, Harris RA. 1982. Comparison of the metabolic and toxic effects of 2-chloropropionate and dichloroacetate. *J Pharmacol Expt Therap* 222: 501-502.

Zeldenrust J. 1951. Over een geval van peracute vergifting door monochloroazijnzuur. *Arch Belg Méd Soc* 9: 19-22.

APPENDIX 1

Participants in a workshop on use of DCA and/or PB in treatment of MCAA intoxications, Hengelo, 1997

Besson JC	Elf Atochem
van Berkum F	Hospital "Streekziekenhuis Midden Twente
Braun C	Akzo Nobel Nederland
Brockstedt M	Berlin Poison Center
Bury D.	Hoechst, acting on behalf of Clariant
Flückiger A	Hoffmann-La Roche
Gerrits CJH	Hospital "Streekziekenhuis Midden Twente"
Huisman H	Hospital "Streekziekenhuis Midden Twente"
Huismans JS	Akzo Nobel Chemicals Hengelo
Kuitonen T	Helsinki Poison Center
Kulling P	Swedish Poison Center
Mattson B	Akzo Nobel Chemicals Skoghall
Régnier J-F	Elf Atochem
Stacpoole P	University of Florida
de Vries I	Dutch Poison Information Center
Wettstrom R	Akzo Nobel Chemicals Skoghall

APPENDIX 2

Table 14: Clinical signs, biochemistry and autopsy outcomes of systemic MCAA intoxication (modified from ECETOC, 1999)

		Number of cases	Case Reports †
Clinical signs			
GI tract:	nausea	4	5,6,9,11
	vomiting	22	2,4,5,6,8,9,10,11
	diarrhoea	1	5
respiratory tract	cough	2	1,6
	pulmonary oedema	2	1,12
cardiovascular system	arhythmia	4	2,5,6,8
	tachycardia	5	5,6,8,9,11
	cardiovascular shock	7	2,4,5,7,8,9,11
	ECG alterations	2	5,7
CNS	convulsions	4	1,2,4,7
	excitation	3	5,6,8
	depression	14	2,4,5,9
	alternating excitation/depression	2	7,5
	coma	10	1,2,3,4,5,7,8,9,11
	intracranial hypertension	1	7
kidneys	anuria	2	4,7

Table 14 (continued): Clinical signs, biochemistry and autopsy outcomes of systemic MCAA intoxication modified from ECETOC, 1999)

	Number of cases	Case Reports †
Biochemistry/haematology		
(metabolic) acidosis	3	5,7,8
hypokalaemia	4	2,5,6,7
hypocalcaemia	1	7
hyperglycaemia -	1	5
creatine kinase -	2	5,7
ALAT -	1	7
ASAT	1	7
myglobinaemia	1	7
leucocytosis	1	2
coagulation disturbances	1	5

Table 14 (continued): Clinical signs, biochemistry and autopsy outcomes of systemic MCAA intoxication (modified from ECETOC, 1999)

		Number of cases	Case Reports †
Autopsy results (from 4 autopsies)			
Skin	first degree burns	1	1
	first and second degree burns, 30%	1	7
	third degree burns, 20%, petechia on unburned skin	1	2
GI tract	congested liver	3	1,2,7
	gastritis	1	3
respiratory system	pulmonary haemorrhagic congestion consolidation, no mucosal damage	3	1,2,7
	pulmonary oedema	1	2
	haemorrhagic congestion, mucosal hyperaemia, alveolar necrosis	1	1
cardiovascular system	cardiac haemorrhagic congestion, dilation	3	1,2,7
CNS	cerebral congestion and oedema infarction, uncal and cerebellar	2	7,8
	herniation	1	7
	haemorrhagic congestion, petaechia	1	1
kidneys	swollen; acute tubular necrosis, hyaline and myoglobulin casts	1	7
	congestion	1	1
muscles	segmental necrosis	1	7

† References To Case Reports (reports describing the same case are given together)

1 Zeldenrust ,1951
2 Hercules, 1969a, b; Mann, 1969
3 Christofano *et al*, 1970
4 DKK, 1984
5 Ruty, 1985; Contassot *et al*, 1987; Vincenti, 1987
6 Kusch *et al*, 1990
7 Kulling *et al*, 1992
8 Feldhaus *et al*, 1993
9 Wang Kongfu *et al*, 1997
10 Huismans, 1998
11 Toyama, 1999

LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
CNS	central nervous system
2-CP	2-chloropropionic acid
CSF	cerebrospinal fluid
DCA	dichloroacetate
GABAergic	c amino butyric acid
im	intramuscular
ip	intraperitoneal
iv	intravenous
LOAEL	lowest-observed-adverse effect level
MCAA	monochloroacetic acid
NOAEL	no-observed-adverse effect level
p-a	post-accident
PB	phenobarbitone
PDHc	pyruvate dehydrogenase complex
PIM	Poison Information Monograph
sc	subcutaneous
SMCA	monochloroacetic acid, sodium salt
TDA	thiodiacetic acid

MEMBERS OF THE TASK FORCE

* J-F. Régnier (Chairman)	Atofina F-Paris
* J-C. Besson	Atofina F-Saint-Auban
* C. Braun	Akzo Nobel NL-Arnhem
* R. Jung	Clariant D-Sulzbach
* A. Flückiger	F.Hoffmann-La Roche CH-Basel
F. Kinoshita‡	Hercules USA-Wilmington
P. Thomas	Atofina F-Paris
D. van Wijk	Akzo Nobel NL-Arnhem
M. Butler (Secretary)	ECETOC B-Brussels

* Members of the Toxicology/medical Sub-group.

‡ Corresponding member.

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MEMBERS OF THE SCIENTIFIC COMMITTEE

(Peer Review Committee)

C. Braun Occupational Toxicologist	Akzo Nobel NL-Arnhem
N. Carmichael, (Co-Chairman), Head of Toxicology	Aventis Crop Science F-Sophia Antipolis
C. D'Hondt, Head, Environmental Safety Department	Novartis CH-Basel
T. Feitel, Manager, Professional and Regulatory Services	Procter & Gamble B-Brussels
B. Hildebrand, Director Experimental Toxicology and Ecotoxicology	BASF D-Ludwigshafen
J. Jackson, Senior Associate, Medical Adviser	Monsanto B-Brussels
E. Löser, Institute of Industrial Toxicology	Bayer D-Wuppertal
R. Millischer, Head, Industrial Toxicology Department	Atofina F-Paris
G. Randall, (Co-Chairman), Director Environmental Laboratory	AstraZeneca UK-Brixham
A. Sarrif, Director, Toxicology Affairs, Europe	Dupont D-Bad Homburg
J. Solbé, Head, SEAC Environment	Unilever UK-Bebington
L. Smith, Director, Central Toxicology Laboratory	Syngenta UK-Macclesfield
H-J. Wiegand, Head, Product Safety Department	Degussa D-Marl