ECETOC

Joint Assessment of Commodity Chemicals No. 37

Methyl Acrylate

CAS No. 96-33-3

September 1998

European Centre for Ecotoxicology and Toxicology of Chemicals

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THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

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

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

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced, and are continuing to write, reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a producer, government official or consumer can be informed on the up-to-date position with regard to safety information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed. To assist ourselves and others working in this field we have published a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to our Technical Report No. 71 entitled "Inventory of Critical Reviews on Chemicals".

This document presents a critical evaluation of the toxicology and ecotoxicology of methyl acrylate (CAS No. 96-33-3).

Methyl Acrylate

CAS No. 96-33-3

CONTENTS

1. SUMMARY AND CONCLUSIONS

At room temperature, methyl acrylate (MA) is a clear, colourless, flammable, corrosive liquid with a pungent acrid odour. It is soluble in water and completely miscible with most organic solvents.

In western Europe approximately 57 kt were produced in 1996. Its major use is as a monomer for the production of polyacrylic fibres, plastic additives, coatings and varnishes. MA is also used as a raw material for the synthesis of other organic molecules.

Environmental releases during production and major industrial uses are low. When released into the environment, the majority (85%) of MA is expected to partition into the atmosphere. The atmospheric half-life of MA has been estimated to be 14.5 h.

In water, MA is inherently biodegradable, but fails the ready biodegradability test because it does not pass the 10-day window. In a model pond, the half-life of volatilisation has been calculated to be 3.2 days.

In soil, based on the calculated K_{oc} of 9.5, MA exhibits a high mobility and may leach into ground water. It is expected to biodegrade and to hydrolyse under alkaline conditions.

Based on a calculated bioconcentration factor of 2.4, MA is not expected to bioaccumulate in aquatic organisms.

MA is moderately toxic to fish (EC_{50}: 1.1 - 7.5 mg/l), *Daphnia* (EC_{50}: 2.2 - 2.6 mg/l) and algae (EC_{50}: 6.9 - 15.0 mg/l). In *Selenastrum capricornutum*, MA is algistatic at a concentration of 19 mg/l. It is of low acute toxicity to bacteria and protozoa.

MA and/or its metabolites are rapidly absorbed by the oral, dermal and inhalation routes and distributed throughout the body as judged by the distribution of radioactivity when radiolabelled MA was administered orally or by intraperitoneal injection. This is followed by rapid excretion of the radioactivity in urine or expired air as carbon dioxide. However, some radioactivity associated with the administered dose is retained in the mucous membranes such as those lining the mouth and stomach. Dermal absorption is slower than that occuring via the gut or the lungs and appears to follow an initial toxic response on the skin. This may reflect the de-esterification of MA with the subsequent absorption of acrylic acid.

The predominant pathway of metabolism of MA, by many tissues, appears to be hydrolysis to acrylic acid and methanol, which is catalysed by carboxyl esterase enzymes. The subsequent metabolism will follow that for acrylic acid, which is detailed fully in ECETOC (1995), and Winter and Sipes (1993),

and involves metabolism to carbon dioxide via the propionate degradation pathway. Metabolism of methanol proceeds via a catalase peroxidative pathway or alcohol dehydrogenase pathway. MA also undergoes conjugation with glutathione (GSH) to form thioethers, the main urinary conjugate being identified as N-acetyl-S-(2-carboxyethyl)cysteine. Inhibition of the hydrolytic pathway with a carboxylase inhibitor results in increased metabolism via the GSH conjugation route. Metabolism is detoxifying and there is no evidence to suggest that the vinyl moiety undergoes epoxidation.

Acute toxicity studies in experimental animals showed that the toxicity of MA is moderate by the oral, dermal, inhalation and intraperitoneal routes. MA is severely irritating to the skin and eyes of rabbits. It is irritating to the respiratory tract and mucous membranes of a wide range of mammalian species. The main toxic effect is irritation and/or corrosion at the site of contact.

Based on the results of the majority of the animal studies, MA has the potential to cause allergic contact dermatitis.

In repeated-dosing and subchronic studies the main effects observed, following oral or dermal administration or inhalation exposure, were irritation/corrosion of the gastric mucosa, and mucous membranes of the eyes and nose. No systemic effects were observed. The No Observed Adverse Effect Level (NOAEL) following a 3-month oral administration of MA to the rat with the drinking water was 5 mg/kgbw/d. The No Observed Adverse Effect Concentration (NOAEC) in a 12-week inhalation study with rats was 23 ppm (82 mg/m^3).

Irritative changes, atrophy and basal cell hyperplasia in the nasal passage, accompanied by loss of olfactory and ciliated cells of the nasal turbinates, were observed when rats were exposed to atmospheres containing MA at up to 135 ppm (483 mg/m^3) for 2 years. Opacification and vascularisation of the cornea were observed in all exposed animals. There was no evidence of systemic toxicity and no treatment related increase in tumours. The Lowest Observed Adverse Effect Concentration (LOAEC) for nasal and ocular effects was 15 ppm (54 mg/m^3). The No Observed Effect Concentration (NOEC) for systemic toxicity was 135 ppm (483 mg/m^3), the highest concentration tested.

MA is clastogenic *in vitro* but this effect is not expressed *in vivo* which suggests that genotoxicity does not represent a hazard in humans.

MA was not carcinogenic in a 2-year inhalation study in rats.

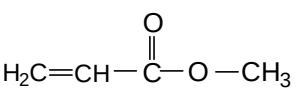
Based on data on structurally-related acrylic acid esters and on the products of hydrolysis (methanol and acrylic acid), MA is unlikely to pose a reproductive risk to humans at currently-accepted occupational exposure levels.

In humans, MA is highly irritating to the skin, eyes and mucous membranes of the respiratory and gastrointestinal tract. There is no evidence linking occupational exposure of MA with bronchial hyper-reactivity.

In the absence of dermal protection, MA may also cause skin sensitisation in repeatedly-exposed workers. The low frequency of new cases reported in the literature could be explained by the fact that MA is not a strong sensitiser and by the fact that today's occupational exposure levels are low due to observance of high safety standards. As cross-reactivity to other acrylates is known to occur, any exposure to acrylates should be avoided by persons sensitised to one or more acrylates.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 IDENTITY

Name:	Methyl acrylate
IUPAC name:	Methyl acrylate
Synonyms:	Acrylic acid methyl ester (6CI, 8CI) Methoxycarbonylethylene Methyl acrylic ester Methyl propenoate Methyl prop-2-enoate Methyl 2-propenoate Methylacrylat 2-Propenoic acid methyl ester 2-Propenoic acid, methyl ester (9CI)
Danish:	Methylacrylat
Dutch:	Methylacrylaat
Finnish:	Metyyliakrylaatti
French:	Acrylate de méthyle
German:	Methylacrylat
Greek:	Ακρυλικος μεθυλεστερας
Italian:	Acrilato di metile; metile acrilato
Norwegian:	Metylakrylat
Portuguese:	Acrilato de metilo
Spanish:	Acrilato de metilo
Swedish:	Metylakrylat
CAS name:	2-Propenoic acid, methyl ester
CAS registry No:	96-33-3
EEC No:	607-034-00-0
EINECS No:	202-500-6
Formula:	$C_4H_6O_2$
Molecular mass:	86.09
Structural formula:	

2.2 PHYSICAL AND CHEMICAL PROPERTIES

At room temperature, methyl acrylate (MA) is a clear, colourless, flammable, corrosive liquid with a pungent acrid odour. It is soluble in water and completely miscible with most organic solvents. Data on the physical and chemical properties of MA are given in Table 1.

Table 1: Physical and Chemical Properties

Parameter, units	Value	Reference
Melting temperature, °C	-75	Weast *et al*, 1989; BASF, 1995a,b
Boiling temperature, °C at 1,013 hPa	80	Weast *et al*, 1989; BASF, 1995a,b
Heat of polymerisation, kJ/kg	950	BASF, 1995a
Relative density D_4^{20} (density of water at 4°C is 1,000 kg/m^3)	0.956 0.9535	BASF, 1995a,b Weast *et al*, 1989
Viscosity, mPa·s at 25°C (DIN 51562)	0.49	BASF, 1995a; Elf Atochem, 1991
Refractive index n_D at 20°C	1.4040	Weast *et al*, 1989; BASF, 1995a
Vapour pressure, hPa at 20°C	89.1[a] 70	BASF, 1995a Weast *et al*, 1989
Vapour density at 20°C (air = 1)	3.58 kg/m^3	Elf Atochem, 1991
Threshold odour concentration, ppm (mg/m^3)	2.1 (7.5)	Amoore and Hautala, 1983
Surface tension, mN/m at 20°C	No data	
Solubility in water, g/kg at 25°C	52	BASF, 1995a,b
Solubility of water in MA, g/kg at 25°C	No data	
Miscibility with most organic solvents	Yes	Weast *et al*, 1989
Fat solubility, mg/100 g at 37°C	No data	
Partition coefficient, log K_{OW} (octanol/water) at 25°C	0.739[b] 0.797[c] 0.80[b]	BASF, 1988a BASF, 1996 Tanii and Hashimoto, 1982; Sangster, 1989
Partition coefficient, log K_{oc} (soil-sediment/water) at 20°C	9.5	Calculated [d]
Henry's Law constant, Pa·m^3/mol at 20-25°C	1.5	Calculated
Flash point, °C	-2.7	BASF, 1995b
Auto-flammability, ignition temperature, °C	393	BASF, 1995b
Explosion limits, % (v/v) at -6 to 30°C	2.1 - 14.5	BASF, 1995b

[a] Reported as 89.1 mbar

[b] Measured, shake flask method (OECD guideline 107)

[c] Calculated according to the method of Hansch and Leo with Daylight software 4.41, CLOGP3, Pomona College and BioByte, Claremont CA

[d] See Section 4.3.3

A typical commercial sample of MA has a purity of > 99.8% (w/w) and may contain the following specified impurities: water (< 0.05% w/w) and acrylic acid (< 0.01%).

MA polymerises readily under the influence of heat, light or by catalysis (e.g. metals), in a strongly exothermic reaction. To prevent polymer formation, the monomer is stabilised by the addition of an inhibitor such as the monomethyl ether of hydroquinone (MeHQ, synonym *p*-methoxy phenol) at levels of 15 ± 5 ppm.

2.3 CONVERSION FACTORS

Conversion factors for MA concentrations in air, calculated at 20°C and 1,013 hPa are:

- 1 ppm = 3.579 mg/m^3
- 1 mg/m^3 = 0.279 ppm

In this report, converted values are given in parentheses.

2.4 ANALYTICAL METHODS

2.4.1 Environmental Media

Air

MA in air is usually collected by absorption onto charcoal and, following desorption with carbon disulphide, analysed by GC with flame ionisation detection (FID) following NIOSH method S38. It is valid for concentrations ranging from 13.9 to 58.4 mg/m^3 (3.88 to 16.29 ppm) (NIOSH Manual of analytical methods, 2nd edition, 1977-present, as quoted in HSDB, 1996). The detection limit is 5 ng/sample or 0.2 to 0.35 mg/m^3 (0.06 to 0.098 ppm) in 25 litres of air (collected over 8 h) (Elf Atochem, 1997).

Alternate GC column packing may improve separation from low-molecular weight esters (Langvardt and Ramstand, 1981 as quoted in IARC, 1986). Sampling efficiency can be improved by using Tenax or purge-and-trap preconcentration. A combination of GC with mass spectrometry (MS) will increase the analytical sensitivity (Krost *et al*, 1982 as quoted in IARC, 1986).

GC can be used for detecting MA in air by direct sampling. This method makes it possible to detect MA in a small volume (> 5 ml) of workplace air. Using FID, the detection limit was 4 mg/m^3 (1.1 ppm) (Podkovyrina *et al*, 1981).

Water

MA in water can be detected and quantified using high-pressure liquid chromatography (HPLC) equipped with Keystone Deltabond ODS column and a UV diode array detector. A limit of quantification of 0.1 to 0.5 mg/l was reported (Drottar and Swigert, 1995a,b,c).

Soil and Sediments

No methods are available for the determination of MA in soil. For sediments, see Section 5.1.2.

2.4.2 Biological Media

No methods are available for the determination of MA in biological samples.

2.4.3 Methyl Acrylate in Products

Mass spectrometry (MS) has been used to identify MA, and other acrylic monomers in resin-based dental materials (Gjoes *et al*, 1983). The materials were injected, either dissolved in dichloromethane or directly, into separate solid filler materials. Mass spectra were determined for most components of dental resins.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 PRODUCTION

MA is produced commercially by oxidation of propylene (to acrolein and then to acrylic acid, which is reacted with methanol) or by a modification of the Reppe process from acetylene (reacting with methanol in the presence of acid and nickel carbonyl to yield MA directly).

Two other methods for producing MA involve the use of organic carbonates as esterifying agents and isolating 2-halo-1-alkenes from hydrocarbon feedstocks to produce MA (Haggin, 1985).

MA is also produced by reacting formaldehyde with ketene to β-propiolactone, which is then reacted with methanol (BASF method quoted in ECDIN, 1993).

In western Europe approximately 57 kt were produced in 1996 (EBAM, 1997).

3.2 STORAGE

To prevent polymer formation, the MA monomer is stabilised by the addition of an inhibitor such as MeHQ (Section 2.2). The effectiveness of phenolic inhibitors depends on the presence of oxygen. To prevent polymer formation, the monomer must therefore be stored under air (not under inert gases), in the dark at a temperature below 25°C. During long-term storage, stabiliser levels should be checked routinely.

MA dimerises slowly during storage. This reaction is promoted by elevated storage temperatures and the presence of water, and cannot be prevented by stabilisers.

MA is normally stored and shipped in containers made of stainless steel. Containers of mild steel are unsuitable.

3.3 USE

The major uses of MA in western Europe are in the manufacture of acrylic fibres (38% of production), plastics additives (15%), and coatings and varnishes (12%); production of adhesives, detergents, flocculants, dispersion aids and use as raw material for organic synthesis account for 25% and miscellaneous other uses for 10% (EBAM, 1997).

Acrylic fibres (MA polymers) are used in the manufacture of clothing, blankets, carpets and curtains. MA also forms copolymers with acrylonitrile; these acrylic fibres usually contain 85% acrylonitrile.

Other uses of MA polymers include the production of thermoplastic coatings, textile backcoatings, elastomers and plastics. MA is used as a monomer in ionic exchange resins and barrier films. Examples of organic synthesis using MA are the production of antioxidants and 2-ethylhexyl acrylate (ECDIN, 1993).

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 EMISSIONS

4.1.1 Natural Sources

MA is an extractable volatile component of pineapple purée (Näf-Müller and Wilhalm, 1971 as quoted in IARC, 1986).

4.1.2 Emissions during Production and Use

Emissions to water from the productions of MA averaged 70 g/t produced, and are below 1g/t for some units. Average emissions to air were 30 g/t produced (range: 1.5 to 90 g/t) (EBAM, 1997).

Plants manufacturing MA polymer reported emissions to water of up to 1 g/t; emissions to air are around 5 g/t. Emissions from an organic intermediates manufacturing plant were reported as 0 g/t to water and 9 g/t to air (EBAM, 1997).

Residual Levels in Polymers and Polymer Dispersions

No data are available on residual levels in end-use application, but the level of free MA is expected to be very low (EBAM, 1997).

4.2 ENVIRONMENTAL DISTRIBUTION

The theoretical distribution of MA has been estimated using the fugacity model of Mackay, Level 1 (Mackay and Paterson, 1981). According to this model, the majority of MA (84.63%) released into the environment enters the atmosphere. Most of the remainder is found in the water phase (15.36%) and negligible amounts in soil and sediment (Table 2).

Table 2: Distribution of MA between Environmental Compartments at 20°C (Pedersen *et al*, 1994)

Compartment	**%**
Air	84.63
Water	15.36
Soil	0.01
Sediment	0.01

4.3 ENVIRONMENTAL FATE AND BIOTRANSFORMATION

4.3.1 Atmospheric Fate

If released to the atmosphere, MA is expected, based upon a reported vapour pressure of 86 mm Hg at 25°C (115 hPa), to partition almost entirely into the air (Eisenreich *et al*, 1981).

MA does not directly photolyse (Brunn *et al*, 1976) however, it is susceptible to photo-oxidation via vapour phase reaction with photochemically-produced hydroxyl radicals and ozone.

An atmospheric half-life of 14.5 h has been estimated, based upon atmospheric concentrations of 5×10^5 ·OH/cm^3 and 7×10^{11} O_3/cm^3 (Atkinson, 1987).

4.3.2 Aquatic Fate

If released into water, MA is not expected to directly photolyse (Brunn *et al*, 1976).

MA will significantly volatilise from water with an estimated half-life of 6.8 h from a model river of 1 m depth, flowing 1 m/s with a wind speed of 3 m/s (Lyman *et al*, 1982).

The half-life of volatilisation from a model pond, which takes into account the effect of adsorption, has been estimated to be 3.2 d according to the Exposure Analysis Modelling System (EXAMS II) of the US EPA (1987 as quoted in HSDB, 1996).

No hydrolysis data are available for MA. Hydrolysis may be a significant process based upon the hydrolytic half-lives for the structurally similar compound ethyl acrylate: 3.5 y at pH 7, 100 d at pH 8 and 10 d at pH 9 (Mabey and Mill, 1978).

In water, MA is inherently biodegradable (Section 4.3.4). It is not expected to adsorb on sediments or suspended particulate matter.

4.3.3 Terrestrial Fate

Using the highest reported log K_{ow} of 0.8 (Table 1), a K_{oc} of 9.5 has been calculated using the regression equation log K_{oc} = 0.524 log K_{ow} + 0.8550 (Lyman *et al*, 1990). Based upon this K_{oc}, MA exhibits a high mobility in soil (Hansch and Leo, 1985; Lyman *et al*, 1982).

Based on the hydrolysis data on ethyl acrylate presented by Mabey and Mills (1978), it is anticipated that MA hydrolyses in soil. The level of hydrolysis may be greater in alkaline soils.

Given its biodegradability in aqueous screening tests, MA is anticipated to biodegrade in soil (Sasaki, 1978; BASF, 1987) and may volatilise from near surface soil.

4.3.4 Biodegradation

MA has been reported to be significantly degraded (> 30% within 14 d) in the modified MITI test which uses a mixed inoculum of soil, surface water and sewage (Sasaki, 1978).

The BOD_5 of MA was determined to be 875 mg O_2/g. The ratio BOD/COD was estimated to be 65% (BASF, 1987). In another study, the BOD_5 could not be calculated because the dissolved oxygen depletion was insufficient during the test and the latency period exceeded 5 days (Schaeffer and Swigert, 1995). In a closed-bottle test based on oxygen consumption, a biodegradation of 60% was achieved within 28 days. The authors stated that the 10-day window was not reached. The test itself did not meet OECD validity criteria for determination of a 10-day window as too few points were analysed (Wu *et al*, 1996).

Based on data available at the time, Thom and Agg (1975) placed MA in the class of synthetic organic compounds that "should be degradable by biological sewage treatment provided that suitable acclimatisation can be achieved". MA is also expected to undergo anaerobic biodegradation by industrial wastewater treatment (Speece, 1983).

4.3.5 Bioaccumulation

Using the reported log K_{ow} of 0.8 (Table 1), a bioconcentration factor (BCF) of 2.4 has been calculated using the regression equation log BCF = 0.76 x log K_{ow} – 0.23 (Lyman *et al*, 1990). In the light of this BFC value, no bioaccumulation is expected in aquatic organisms.

4.3.6 Evaluation

Environmental releases during production and major industrial uses are low.

When released into the environment, the majority (85%) of MA is expected to partition into the atmosphere. The atmospheric half-life of MA has been estimated to be 14.5 h.

In water, MA is inherently biodegradable, but fails the ready biodegradability test because it does not pass the 10-day window. In a model pond, the half-life of volatalisation has been calculated to be 3.2 d.

In soil, based on the calculated K_{oc} of 9.5, MA exhibits a high mobility and may leach into ground water. It is expected to biodegrade and to hydrolyse under alkaline conditions.

Based on the calculated bioaccumulation factor of 2.4, MA is not expected to bioaccumulate in aquatic organisms.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 ENVIRONMENTAL LEVELS

5.1.1 Air

Traces of MA were detected in ambient air samples from 2 of 8 locations near industrial sites in New Jersey and Staten Island, NY; the samples were taken in March and May 1976. The ambient air concentration near an industrial site in Newark, NJ was 4.545 mg/m^3 (1.27 ppm) and trace amounts were detected near an industrial site in Bound Brook, NJ (Pellizari, 1977 as quoted in HSDB, 1996).

5.1.2 Water

MA was not detected in surface water and sediment in Japan in 1980. The respective detection limits were 0.6 µg/l and 8.3 ng/kg (Department of Environmental Health, Japan, 1985 as quoted in ECDIN, 1993). No details of the measurement method are available.

5.1.3 Soil

No monitoring data are available.

5.1.4 Biota

No monitoring data are available (cf. Section 4.1.1).

5.2 HUMAN EXPOSURE LEVELS AND HYGIENE STANDARDS

5.2.1 Non-occupational Exposure

No information is available.

Using animal data, an Immediately Dangerous to Life or Health concentration (IDLH) at 250 ppm (895 mg/m^3) for MA has been established by the US National Institute for Occupational Safety and Health (NIOSH, 1994).

5.2.2 Occupational Exposure

During typical industrial production, average exposure to MA was 2 ppm (7 mg/m^3), with peak exposures, of 2 to 5 minutes duration, in the range 30 to 126 ppm (107 to 451 mg/m^3) (Milton *et al*, 1996).

5.2.3 Hygiene Standards

A summary of occupational exposure limit values is given in Table 3. All of the OEL values have a notation indicating that skin absorption is possible.

Table 3: Occupational Exposure Limit Values

Country	TWA		STEL		Reference
	(ppm)	(mg/m^3)[a]	(ppm)	(mg/m^3)[a]	
Australia	10	35	-		ACGIH, 1996
Belgium	10	35	-	-	ACGIH, 1996
Finland	10	35	-	-	ACGIH, 1996
France	15	50	-	-	INRS, 1993
Germany	5	18	10[b]	36[b]	DFG, 1995; TRGS, 1995
Italy	10	35			ACGIH, 1996
Netherlands	5	18	-	-	Arbeidsinpectie, 1995
Norway	10	35	20	70	Arbeidstilsynet, 1995
Sweden	10	35	15	50	AFS, 1996
Switzerland	10	35	-	-	ACGIH, 1996
UK	10	35	-	-	HSE, 1995
USA	10[c]	35[c]	-	-	ACGIH, 1996[d]
	1	3.58			NIOSH, 1994
	200	610	-	-	OSHA, 1988

TWA Time-weighted average concentration (8-h working period)

STEL Short-term exposure limit (15 min, unless specified otherwise)

[a] Official values; some countries use different conversion factors and/or other ambient temperature

[b] 5 min, max 8 x/shift)

[c] A proposal of 2 ppm (7 mg/m^3) has been adopted by ACGIH in 1997

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 MICRO-ORGANISMS

In an investigation of the influence of MA on the growth of *Pseudomonas putida,* the EC_{10} was 130 mg/l and the EC_{50} 260 mg/l after 17 hours of exposure (BASF, 1988b).

Another study reported an EC_3 value of 46 mg/l for growth inhibition of *P. putida* after an exposure of 16 hours (Bringmann and Kühn, 1977).

6.2 AQUATIC ORGANISMS

A threshold level ranging from 10 to 64 mg MA/l was reported for single-cell organisms (Table 4).

Table 4: Aquatic Toxicity to Single-cell Organisms

Organism	Parameter	Time (h)	Concentration (mg/l)	Reference
Entosiphon sulcatum	EC_3	72	11	Bringmann and Kühn, 1978a
Uronema parduczi	EC_3	20	64	Bringmann and Kühn, 1980a
Chilomonas paramaecium	EC_3	48	10	Bringmann and Kühn, 1980b

Acute toxicity tests with fish and microcrustacea show LC_{50} and EC_{50} values ranging from 0.31 to 7.5 mg MA/l (Table 5).

Table 5: Effect/Acute Toxicity to Fish And Crustaceans

Organism	Effect/ parameter	Time (h)	Concentration (mg/l)	Method	Reference
Fish	**Lethality**				
Oncorhynchus mykiss	LC_0 LC_{50}	96	2.8[a] 3.4[a]	OECD 203, flow-through	Drottar and Swigert, 1995a
Carassius auratus	LC_{50}	72	4.95		Paulet and Vidal, 1975
Leuciscus idus melanotus	LC_{50}	48	7.5		Junke and Lüdemann, 1978
Cyprinodon variegatus	LC_0 LC_{50}	96	< 0.89[a] 1.1[a]	Flow-through	Drottar and Swigert, 1995b
Crustaceans					
Moina macropa (*Cladocera*)	LC_{50}	96	0.31	Static	D'Angelo and Signorile, 1978
Cyclops sp. (*Copepoda*)		96	1.84	Static	D'Angelo and Signorile, 1978
Cypria opthalmica (*Ostracoda*)		96	1.73	Static	D'Angelo and Signorile, 1978
Mysidopsis bahia	LC_{50}	96	1.6	EPA 40 CFR § 179.130, flow-through	Drottar and Swigert, 1996
	Immobility				
Daphnia magna (Cladocera)	EC_0 EC_{50} EC_{100}	48	1.56 2.2 3.12	OECD 202, static	BASF, 1988c
Daphnia magna	EC_0 EC_{50} EC_{100}	48	0.88[a] 2.6[a] 6.4[a]	OECD 202, flow-through	Drottar and Swigert, 1995c

[a] Measured concentration

The 72-h EC_{50} (based on biomass) for the freshwater alga *Selenastrum capricornutum* was 6.9 mg MA/l and for *Scenedesmus subspicatus* 15 mg/l (BASF, 1989; Thompson and Swigert, 1995). MA was algistatic to *Selenastrum capricornutum* at 19 mg/l and algicidal at 34 mg/l (Thompson, 1995). Respective EC_3 values of 1.3 and 7 mg MA/l were reported for *Microcystis aeruginosa* and *Scenedesmus quadricauda* after an 8-day exposure (Bringmann and Kühn, 1977, 1978b).

6.3 TERRESTRIAL ORGANISMS

When MA was evaluated as a fumigant against larvae of the Caribbean fruit fly *Anastrepha suspensa*, 85.5% mortality was obtained after exposure to 10.7 mg/l (10,700 mg/m^3; 2,990 ppm) for 24 hours (Carroll *et al* , 1982).

6.4 SUMMARY

MA is moderately toxic to fish (LC_{50} 1.1 - 7.5 mg/l), crustaceans (LC_{50}/EC_{50} 0.31 - 2.6 mg/l) and algae (EC_{50} 6.9 - 15.0 mg/l). In *Selenastrum capricornutum,* MA is algistatic at a concentration of 19 mg/l. It is of low acute toxicity to bacteria and protozoa.

7. KINETICS AND METABOLISM

7.1 ABSORPTION

Although no specific absorption studies were reported, it can be inferred that MA is absorbed by the oral, dermal and inhalation routes, based on the acute LD_{50} and LC_{50} values obtained with several animal species (Section 8.1). Further supporting evidence may be deduced from the autoradiography studies in guinea pigs (which show that the radioactivity associated with MA is absorbed by oral and dermal routes), and from the excretion of thioethers following oral, dermal and intraperitoneal (i.p.) exposure (Seutter and Rijntjes, 1981).

7.2 BODY DISTRIBUTION

Whole-body autoradiography was conducted on guinea pigs following administration of methyl (2,3-^{14}C)-acrylate (specific radioactivity 0.76 mCi/mmol) by the oral, i.p. and dermal routes (the latter using a closed polystyrene cup glued to the skin). Doses administered were 0.4 mmol/kgbw (oral and i.p.) and 0.53 mmol/kgbw (dermal). Following oral dosing, radioactivity was distributed throughout the internal organs and brain within 2 hours, followed by rapid clearance over the subsequent 16 hours; radioactivity being retained longest in the liver and bladder. After 16 hours, radioactivity remained only in the mucous lining, e.g. the stomach, intestines and buccal cavity epithelium.

Within 1 hour of i.p. injection, radioactivity was distributed to all organs, this was followed by a rapid clearance from most organs, with the exception of the liver and bladder where most of the radioactivity was cleared after 24 and 48 hours respectively. A similar retention in mucous linings was observed to that seen after oral administration.

Following dermal application, the toxic response (mainly oedema) preceded penetration of the greater proportion of the radioactivity into the dermis and subcutaneous (s.c.) tissues [Task Force comment: the toxic response on the skin may reflect the de-esterification of MA to acrylic acid (Section 7.3)]. After 4 hours, the bulk of the radioactivity was associated with the site of application with small amounts associated with the kidney and bladder. After 8 hours the greater part of the radioactivity had penetrated the dermis and by 16 hours had begun distributing in the s.c. tissue and to the rest of the body (Seutter and Rijntjes, 1981).

Occlusive application of radiolabelled MA (specific activity and dose not quoted) to shaved guinea pig skin showed that metabolism of a locally administered dose was limited to the skin in the first 24 hours. Radioactivity was transported to the kidneys via the blood and concentrated in the bladder whereas other organs showed a slow rise in radioactivity. After i.p. injection of 0.29 mmol/kgbw MA most of the radioactivity was found in the liver (Delbressine *et al,* 1980).

7.3 METABOLISM AND EXCRETION

7.3.1 Metabolism *In Vitro*

Miller *et al* (1981) investigated the metabolism of MA by measuring the appearance of acrylic acid in rat tissue homogenates and blood. MA rapidly disappeared when added at final concentration of 1 mmol/ml to homogenates of liver (1 mg/ml wet tissue weight), kidney and lung (each 20 mg/ml wet tissue weight). The rate of disappearance was equal to the rate of generation of acrylic acid. Rates of hydrolysis to acrylic acid were 13, 1.2 and 0.2 nmol/min/mg wet tissue for liver, kidney and lung homogenates respectively. MA disappeared rapidly and in a biphasic manner when added to heparinised rat blood diluted 1:10 with 0.1 M phosphate buffer, pH 7.4. The $t_{½}$ for these phases were 2.7 and 20.9 minutes respectively. However, acrylic acid was not detected, indicating a different mechanism for the disappearance of MA from blood..

Silver and Murphy (1981) also demonstrated de-esterification of MA by homogenates from the rat lung, liver and kidney, prepared in bicarbonate buffer. Rates quoted (all for 20-minute periods) were for the liver 8.88 ± 0.31 mmol per 40 mg tissue, kidney 7.77 ± 0.49 mmol per 100 mg tissue and lung 9.78 ± 0.71 mmol per 150 mg tissue. Hydrolysis by plasma was quoted as 5.67 ± 0.31 mmol per 0.5 ml. These authors investigated the inhibition of metabolism of MA by tri-orthotolyl phosphate (TOTP, an inhibitor of the carboxylesterases). TOTP was administered to rats at doses ranging from 5 to 125 mg/kgbw 18 hours before sacrifice. The *in vitro* esterase metabolism of MA by lung, liver and kidney homogenates was markedly inhibited in all homogenates at 5 mg/kgbw (40-58% inhibition) and this inhibition increased with increasing dose of TOTP.

MA undergoes rapid carboxylesterase hydrolysis by nasal tissue. Stott and McKenna (1985) investigated the kinetics of hydrolysis of MA by the 5,000xg supernatants of the nasal mucosa of mice. The apparent K_m and V_{max} values were 3.14 mM and 0.241 mmol/min respectively.

Incubation of 5 mM MA with 5 mM GSH (in phosphate buffer pH 7.3 containing 0.15 mM KCN) for 5 min at 37°C resulted in a 54% decrease in MA concentration (Silver and Murphy, 1981). The measured half-life for disappearance of GSH in an incubation mixture composed of 10 mM GSH and 10 mM MA in phosphate buffer pH 7.3 was 18.4 min (Vodicka *et al*, 1990).

The absence of epoxide intermediates in the metabolic pathway of MA was demonstrated by Oesch (1977). An epoxide hydrolase inhibitor (1,1,1-trichloropropen-2,3-oxide) was incorporated into an Ames *Salmonella* microsome assay. No mutagenic effects were observed, demonstrating that MA was not a direct-acting mutagen and that mutagenic epoxide intermediates were not formed during the *in vitro* metabolism of MA by Aroclor 1254 induced rat liver S-9 enzymes.

7.3.2 Metabolism *In Vivo*

A single i.p. administration of 0.14 mmol/kgbw MA to adult female Wistar rats resulted in excretion in the urine of the thioether metabolite N-acetyl-S-(2-carboxyethyl)cysteine at a rate of 19.3 ± 0.8 mmol SH equivalents over a 24-h period (Delbressine *et al*, 1981). This represented 6.6 ± 0.6% of the dose administered and was considered to have arisen from GSH conjugation reactions. The thioethers, N-acetyl-S-(2-carboxyethyl)cysteine and the corresponding monomethyl ester were present in the urine in the ratio of 20:1. In the same study, administration of 0.34 mmol/kgbw TOTP 18 hours prior to administration of MA resulted in an increase in thioether excretion of 68.4 ± 2.9, representing 40.6 ± 2.1% of the dose with a reduction in the dicarboxylic acid: monomethyl ester ratio to 1:2. These results demonstrate, as suggested by the work of Silver and Murphy (1981), that carboxyl esterase mediated hydrolysis is a major route of metabolism of MA.

Further support for this conclusion comes from the work of Kopecky *et al* (1985). They showed that following i.p. injection of 0.14 and 0.5 mmol/kgbw MA, rats excrete two types of mercapturic acids in the urine. They were identified as N-acetyl-S-(2-carboxy-ethyl)cysteine and the corresponding monomethyl ester. TOTP pre-treatment resulted in the urinary excretion of thioethers increasing by between 2.3 and 23.8 times .

Urinary excretion of thioethers was measured in guinea pigs dosed with MA via the oral, i.p. and dermal routes (Seutter and Rijntjes, 1981). The results are tabulated below in Table 6.

Table 6: Urinary Excretion of Thioethers (% of Administered Dose) in Groups of 2 Guinea Pigs Following Oral, I.p. and Dermal Administration of MA
(Seutter and Rijntjes, 1981)

Dose (mmol/kgbw), route:	0.4, oral		0.4, i.p.		0.53, dermal	
Animal No:	1	2	1	2	1	2
Day 1	10.8	11.8	18.1	14.9	1.2	-
Day 2	2.4	2.6	11.2	10.2	2.3	0.9
Day 3	0.3	-	2.5	3.1	1.3	-

I.p. injection of 0.26 mmol/kgbw methyl (2,3-^{14}C)-acrylate (specific activity 0.2 mCi/mmol) resulted in urinary excretion of 21 ± 4; 1.3 ± 0.4 and 0.3 ± 0.2% of the administered dose as radiolabelled metabolites over the 1st, 2nd and 3rd 24-h periods, respectively (Seutter and Rijntjes, 1981). Approximately 19% of the dose was excreted as $^{14}CO_2$ within 8 hours of administration rising to a total of 35.4% of the dose by 72 hours.

After i.p. administration of 0.29 mmol/kgbw radiolabelled MA (nature of isotope and specific activity not given) to guinea pigs, 35% of the dose (based on radioactivity) was excreted as $^{14}CO_2$ in the first 8 hours after injection and 40% in the first 72 hours (Delbressine *et al*, 1980).

Following the dermal application of radiolabelled MA (nature of isotope and specific radioactivity not given) to guinea pigs (dose not stated), no thioether excretion was detected in the urine in the first 24 hours. However, 2% of the dose was detected as thioether metabolite during the second 24-h period. Systemic administration resulted in urinary thioether excretion of 6% of the administered dose in the first 24-h period and 1% in the second (Delbressine *et al*, 1980). Co-administration of TOTP resulted in an increase of thioether excretion from 4.2 to 27.4% of the dose.

Exposure of male Holtzman rats to atmospheres containing 135, 370, 490 or 720 ppm (483, 1,320, 1,750 or 2,580 mg/m^3) MA for 4 hours resulted in a concentration-related depletion of tissue non-protein sulphydryl (NPSH) in lung, liver and blood, with the greatest reduction being in the lungs (Silver and Murphy, 1981). This depletion was enhanced further by prior administration of TOTP, which resulted also in a similar depletion in the kidney. Pre-treatment with TOTP enhanced both the acute toxicity of inhaled MA (Silver and Murphy, 1981) and the respiration rate depression induced by exposure to MA vapour (concentrations ranging from 100 to 300 ppm; 360 to 1,070 mg/m^3) (Silver *et al*, 1981).

Exposure of adult male Wistar rats to 0, 500, 1,000 and 2,000 mg MA/m^3 (0, 140, 280, 540 ppm) for 6 hours resulted in thioether excretion rates of 18.9 ± 0.6, 29.3 ± 1.7 and 50.2 ± 3.0 mmol SH/kgbw respectively. This represented 2 - 3% of the assessed inhaled dose. Of the total thioether excreted in the first 24 hours, 48 - 60% was excreted during the 6-h exposure period. Statistically significant increases in blood glucose levels were seen at the end of the exposure period (Vodicka *et al*, 1990)

7.4 SUMMARY

MA and/or its metabolites are rapidly absorbed by the oral, dermal and inhalation routes and distributed throughout the body, as judged by the distribution of radioactivity when radiolabelled MA was administered orally or by i.p. injection. This is followed by rapid excretion of radioactivity in urine or expired air as carbon dioxide, however, some radiolabel associated with the administered dose was retained in the mucous membranes such as those lining the mouth and stomach. Dermal absorption is slower than that occuring via the gut or the lungs and appears to follow an initial toxic response on the skin, possibly reflecting an initial de-esterification, with subsequent absorption of the acrylic acid formed.

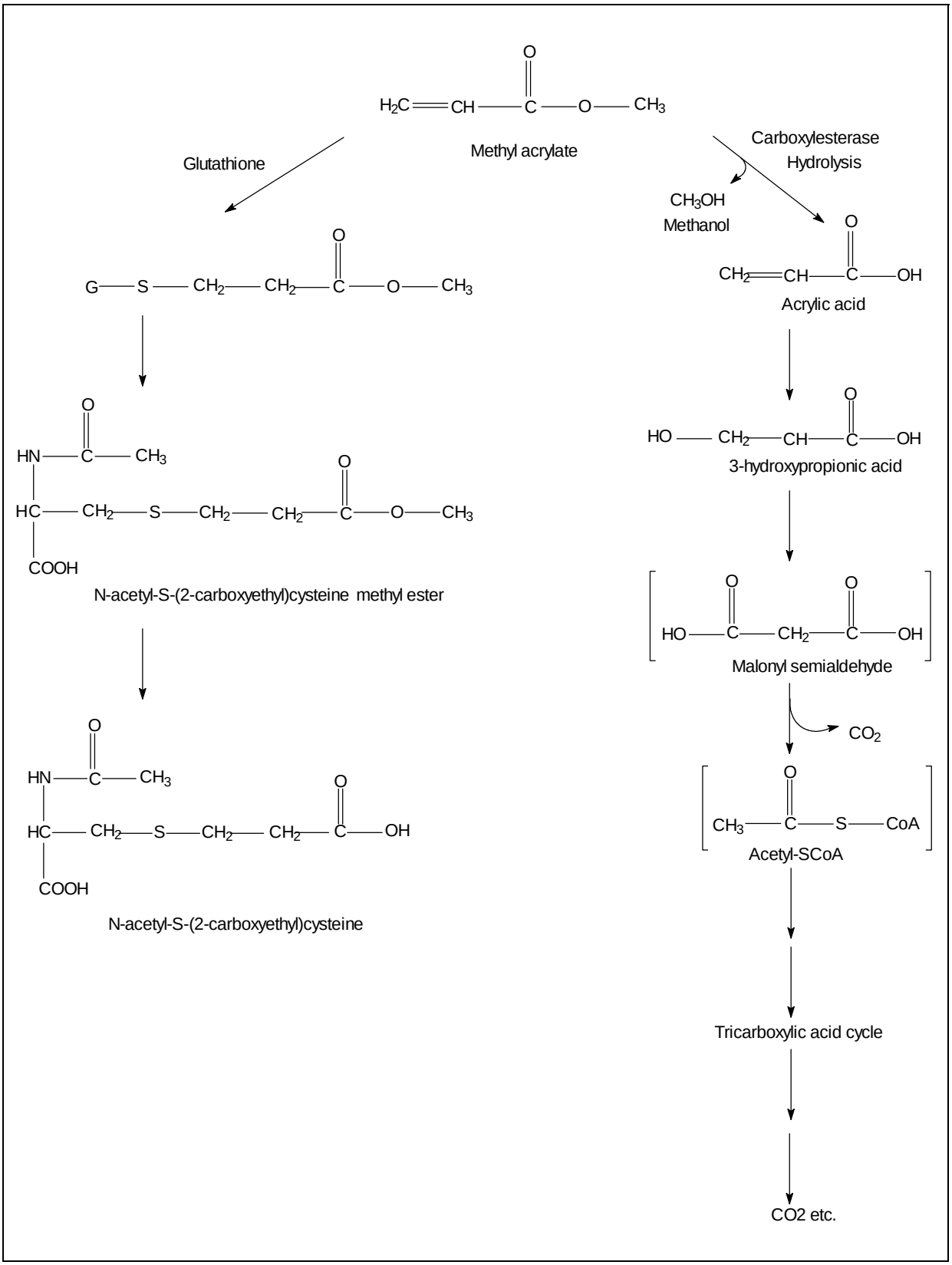
The predominant route of metabolism of MA by many tissues is carboxylesterase-catalysed hydrolysis to acrylic acid and methanol (Figure 1). The subsequent metabolism is expected to follow that for

acrylic acid, which is detailed fully in Winter and Sipes (1993) and reviewed in ECETOC (1995). This involves metabolism to carbon dioxide via the propionate degradation pathway. The methanol is metabolised via either a catalase peroxidative pathway or an alcohol dehydrogenase pathway.

MA may also undergo conjugation with GSH to form thioethers, the main urinary conjugate being identified as N-acetyl-S-(2-carboxyethyl)cysteine (Figure 1). Inhibition of the hydrolytic pathway with a carboxylase inhibitor results in increased metabolism via the GSH conjugation route.

Metabolism is detoxifying and there is no evidence to suggest that the vinyl moiety undergoes epoxidation.

Figure 1: Proposed Metabolic Pathways in Rats



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

8.1 ACUTE TOXICITY

8.1.1 Oral

LD_{50} values following oral administration of MA to mice, rats, rabbits and cats are detailed in Table 7.

Table 7: Acute Oral Toxicity

Species	LD_{50} (mg/kgbw)	Reference
Mouse	826	Tanii and Hashimoto, 1982
Mouse	840	Rohm and Haas, 1950
Rat	277	Paulet and Vidal, 1975
Rat	300	Smyth and Carpenter, 1948
Rat	765[a]	BASF, 1958a
Rabbit	180 - 280[b]	Treon *et al*, 1949
Rabbit	380 - 765	BASF AG, 1960
Cat	> 768[a,c]	BASF, 1960

[a] Approximate value calculated on the basis of the relative density

[b] Lethargy, distension of ear veins, tremor, difficulties in breathing, cyanosis, haemorrhages in the digestive tract, degenerative secondary alterations in heart, liver, kidney, spleen, hyperaemia in the lung

[c] Vomiting, no mortality

8.1.2 Dermal

The dermal LD_{50} value in rabbits was approximately 1,250 mg/kgbw (Smyth and Carpenter, 1948).

Following a 4-h application of undiluted MA to the ventral skin of rats (covering approximately 10% of the body surface), 4 out of 5 rats died during the night following the administration period. Convulsions and disturbance of equilibrium were reported 2 hours after the administration period (BASF, 1958b).

Approximately 0.19 g/kgbw of undiluted MA was applied once under semi-occluded patch to a 50 cm^2 area of the shaved dorsal skin of 3 white rabbits for 20 hours. All rabbits survived the exposure; local damage to the skin was observed in all three rabbits (BASF, 1958b).

MA was applied to the skin of the inner side of both ears of 2 rabbits under semi-occluded patch for 24 hours. At 1.9 g MA/animal there were no signs of systemic toxicity, but severe inflammatory degenerative alterations with encrustation and scar formation were present at the treated site. One animal died 15 days after administration. At 3.84 g MA/animal death occurred within 4 to 5 hours after the beginning of the administration with breathing difficulties and convulsions (BASF, 1958b).

8.1.3 Inhalation

The various LC_{50} values are summarised in Table 8. The acute (4-h) LC_{50} values for MA range from 750 to 1,810 ppm in the rat, 1,420 to 1,590 ppm in the mouse and 700 to 890 ppm in the hamster. Fasting of the animals did not significantly affect the toxicity values. A 1-h LC_{50} value of 2,430 ppm for the rabbit has also been reported.

Table 8: Acute Inhalation LC_{50} Values

Species	Exposure time (h)	Concentration[a] (ppm)	(mg/m^3)	Reference
Rat	Not specified	(2,040)[c]	7,300[b]	Lomonova and Klimova, 1979
Rat	4	1,000	(3,580)	Smyth and Carpenter, 1948
Rat	4	750-1,000	(2,680-3,580)	Silver and Murphy, 1981
Rat (fasted)	4	(1,590)	5,700[b]	BASF, 1979a
Rat	4	(1,810)	6,500[b]	BASF, 1979b
Rat	4	1,350	(4,830)	Oberly and Tansy, 1985
Mouse	Not specified[c]	(3,570)[c]	12,800[b]	Lomonova and Klimova, 1979
Mouse (fasted)	4	(1,590)	5,700[b]	BASF AG, 1979c
Mouse	4	(1,420)	5,100[b]	BASF AG, 1979d
Hamster (fasted)	4	(890)	3,200[b]	BASF AG, 1979e
Hamster	4	(700)	2,500[b]	BASF AG, 1979f
Rabbit	1	(2,430)	8,700[b]	Treon *et al*, 1949

[a] Converted values in parentheses

[b] Originally reported in mg/l

[c] Value questionable because duration of exposure not specified

Silver and Murphy (1981) have demonstrated that pretreatment with TOTP (Section 7.3.1) causes the LC_{50} for MA to decrease from 750-1,000 ppm to < 500 ppm (2,680-3,580 to < 1,790 mg/m^3). This indicates the apparent importance of the initial ester cleavage, to form acrylic acid, to the toxicity of MA.

In addition to the reported LC_{50} values given above, a 5-h LCLo value of 5.4 mg MA/l (5,400 mg/m^3; 1,510 ppm) has been reported for the rat (Velling and Arkhangel'skaya, 1957) and an LCLo, after unspecified exposure duration, of 9.7 mg/l (9,700 mg/m^3; 2,710 ppm) for the mouse (Karpov, 1955).

In a static system, following a 1-h exposure to a saturated atmospheric concentration (33,000 to 34,000 ppm; 118,000 to 157,000 mg/m^3) of MA, 1/5 male and 3/5 female rats died (Vernot *et al*, 1977).

In a flow-through system, groups of 6 rats were exposed to saturated atmospheric concentrations of MA vapour for 2, 4 or 8 minutes. Following the 2-min exposure, mucous membrane irritation was observed but no deaths; 4-min exposure resulted in convulsions with 2 deaths out of 6 animals 2 hours post exposure; all animals died within 30 minutes after the 8-min exposure (BASF, 1958a).

Two out of 4 rabbits died after exposure to 8.7 mg MA/l (8,700 mg/m^3; 2,430 ppm) for 1 hour, while all animals died after exposure to 9.04 mg/l (9,040 mg/m^3; 2,520 ppm) for 1 hour. Sensory irritation (ocular and respiratory) and cyanosis were observed (Treon *et al*, 1949).

The Task Force noted that the atmosphere concentrations claimed for the inhalation studies were derived from calculation and not atmosphere analysis. Therefore these values should be interpreted and used with caution.

8.1.4 Intraperitoneal

LD_{50} values following i.p. administration of MA to mice and rats are shown in Table 9.

Table 9: Acute I.p. Toxicity

Species	LD_{50} (mg/kgbw)	Reference
Mouse	382	BASF, 1958a
Mouse	253	Lawrence and Autian, 1972
Rat	325	Paulet and Vidal, 1975

8.1.5 Summary

Acute toxicity studies in experimental animals showed that the toxicity of MA is moderate by the oral, dermal, inhalation and i.p. routes. No clear signs of systemic toxicity were described. The main toxic effect is irritation and/or corrosion at the site of contact.

8.2 SKIN, EYE AND RESPIRATORY IRRITATION, SENSITISATION

8.2.1 Skin Irritation

Undiluted MA (0.5 ml) was applied, for 24 hours under an occlusive patch, both to the abraded and intact skin of New Zealand white albino rabbits (6/group). After 24 hours intact skin showed erythema (graded very slight to severe), haemorrhages and oedema (graded very slight to moderate). By 72 hours there was well-defined erythema, distinct encrustation and oedema (graded very slight to slight). At 24 hours the abraded skin showed erythema (graded as well-defined to severe), haemorrhages and oedema (graded very slight to moderate). By 72 hours there was distinct encrustation and oedema (graded slight to moderate). In-depth injury was observed in most of the test animals. After three to five weeks all wounds had healed but in some rabbits hair growth was absent on the new skin. The Primary Irritation Index was 5.5, thus MA is severely irritating to the skin (BASF, 1978).

Potokar (1985) applied 0.5 ml of undiluted MA to the skin of rabbits for 1 hour and 4 hours, under both occluded and semi-occluded conditions. Skin irritation, characterised by erythema and oedema (severity not reported) was observed in the semi-occluded group following both 1-h and 4-h exposure and in the occluded group after the 1-h exposure. In the group exposed under occluded conditions for 4 hours, corrosion of the application site was observed.

Occluded application of MA to rabbit skin produced erythema and oedema within 1 hour and blistering of the skin after 2 hours (Karpov, 1954).

Delbressine *et al* (1980) reported a bullous erythema, characterised histologically by a spongiosis deep within the dermis, following the occluded application of MA (dose and duration not specified) to the skin of the guinea pig.

8.2.2 Eye Irritation

Two specific eye irritation studies are available.

Undiluted MA (0.1 ml) was instilled into one eye of one New Zealand white rabbit. During the first 24 hours after instillation, the eye showed moderate corneal damage, slight iritis and moderate to severe lesions of the conjunctivae. At the end of the 7-day recovery period, there was no obvious recovery. The cornea showed moderate to severe opacity with no details of the iris visible. In addition slight iritis and moderate to severe lesions of the conjunctivae were present. The eye irritation score for the test rabbit was 66 out of a maximum of 110, thus the authors considered MA as severely irritating to the eyes (BASF, 1978b).

Instillation of 0.5 ml MA into the rabbit eye produced severe eye injury (eye injury score of > 5 out of a maximum of 20; actual score not specified), whereas 0.02 ml gave less-severe eye injury (actual score not specified) (Carpenter and Smyth, 1946).

8.2.3 Respiratory Tract Irritation

Ocular, nasal, and respiratory tract irritation have been reported in rats, rabbits, guinea pigs, and a monkey exposed (7 h/d) for 2 to 130 days to a wide range of MA concentrations from 0.107 to 9.04 mg/l (107 to 9,040 mg/m^3; 30 to 2,520 ppm) (Treon *et al* , 1949).

Mice exposed to atmospheric concentrations ranging from 3 to 33 mg MA/l (3,000 to 33,000 mg/m^3; 840 to 9,210 ppm) for an unspecified duration showed signs of irritation in the lungs (Karpov, 1954).

Exposure of cats to an atmosphere containing 0.13 mg MA/l (130 mg/m^3; 36 ppm) for 15 minutes did not produce any signs of irritation (Karpov, 1954). However, concentrations of 0.25 to 0.5 mg/l (250 to 500 mg/m^3; 70 to 140 ppm) produced ocular irritation and concentrations of 1.5 to 3 mg/l (1,500 to 3,000 mg/m^3; 420 to 840 ppm) produced salivation (Karpov, 1954, 1955).

Mucous membrane irritation was reported when groups of rats were exposed to saturated MA vapour for 2, 4 or 8 minutes (BASF, 1958a).

Rats exposed to atmospheric concentrations of MA ranging from 100 to 500 ppm (360 to 1,790 mg/m^3) showed a concentration dependent reduction in respiratory frequency, tidal and minute volumes (Silver *et al*, 1981).

Acute exposures of rats to atmospheric concentrations of MA ranging from 1,086 to 2,715 ppm (3,890 to 9,720 mg/m^3) for 4 hours produced irritation of the eyes, nose, and respiratory tract (Oberly and Tansey, 1985).

Exposure of rats (6 h/d, 5 d/wk) for 12 weeks to an atmosphere containing 626 ppm (2,240 mg/m^3) MA produced mucosal irritation, sanguinous ocular and nasal discharges, and dyspnoea. Histological changes in the respiratory tract indicative of irritation such as epithelial cornification, rhinitis, and tracheitis were seen. Exposure to 242 ppm (870 mg/m^3) produced similar clinical effects as those seen at 626 ppm, but were observed only at the start of the study. No irritation effects were seen in animals exposed to 23 ppm (82 mg/m^3) (BASF, 1978a, 1980).

Exposure of rats to atmospheres containing 15, 45 and 135 ppm (54, 161 and 483 mg/m^3) MA for 2 years did not produce any significant clinical signs of irritation, however, histological examination of the nose and eyes showed lesions consistent with an irritant effect (Reininghaus *et al*, 1991).

8.2.4 Gastrointestinal Tract Irritation

No acute data are available. However, based on the effects on the skin, it is reasonable to assume that high doses of MA would be irritant to the gastrointestinal tract on acute exposure. This conclusion is supported by the repeat-dose studies (Section 8.3.1) which show thickening of the gastric mucosa and focal haemorrhage following two oral doses of 0.4 ml/kgbw (380 mg/kgbw) (BASF, 1960).

8.2.5 Skin Sensitisation

A number of skin sensitisation studies have been conducted in various guinea pig assays, summarised in Table 10. Positive reactions were observed in most of the studies.

Table 10: Sensitisation Studies in Guinea Pigs

Test method	Induction	Challenge	Result	Reference
Skin painting	20 consecutive applications by cross painting on a shaved flank of 10 guinea pigs with increasing concentrations of MA (starting at 20% in ethanol to full strength application), an additional patch with MA (50% in chloroform) was applied on the same flank	9 d after the last treatment the other flank was challenged by an application of 5% MA in chloroform	**-ve**, no skin reaction in all the tested animals	BASF, 1958b
Polak	Day 1: 1 mg MA per animal by 4 x 0.1 ml injections, 1 x 0.1 ml of 0.2 mg/ml MA in an emulsion of ethanol/saline (1:4) and CFA[a], injected in the nape of the neck	Day 7 and weekly thereafter for up to week 12: application on the shaved skin of the flanks of 0.02 ml MA at concentrations of 0.5, 1, and 5% in acetone and olive oil (4:1)	**+ve** at day 7 and thereafter at all tested concentrations	Parker and Turk, 1983
Split Adjuvant	Day 0: 0.05 ml CFA[a] by intradermal injections on 5 sites of the dorsolateral flanks Day 1: Intradermal injection of 100 µmol MA in ethanol/saline (1:100)	Day 14 and weekly thereafter for up to week 12: application of 0.02 ml MA at a concentration of 5% in acetone and olive oil (4:1)	**+ve** at day 14 and thereafter in 4/6 animals	Parker and Turk, 1983
Maximisation (modified Magnusson and Kligman)	Day 0: double intradermal injection into the shaved back of the neck: 2 x 0.1 ml CFA[a] and 0.1 ml MA 1% in saline, 2 x 0.1 ml of an emulsion of 1% MA in CFA[a]	Day 14 and weekly thereafter for up to week 12: application of 0.02 ml MA at a concentration of 5% in acetone and olive oil (4:1)	**+ve** at day 21 and thereafter in 2/6 animals	Parker and Turk, 1983
Epicutaneous A (Levene)	Days 0, 2, 4, 7, 9, 11: application of 0.1 ml of a 0.3 M MA solution in 95% ethanol/ 2-methoxy-ethanol/Tween 80 (9:9:20) onto a marked area of the shaved flank	Day 28 and weekly thereafter for up to week 12: application of 0.02 ml MA at a concentration of 5% in acetone and olive oil (4:1)	**+ve**	Parker and Turk, 1983
Epicutaneous B (Draize)	Day 0, 1, 2, 3, 4, 7, 8, 9, 10, 11: application of 0.1 ml MA 10% in acetone/olive oil (1:1) onto a marked area of the shaved flank	Day 21 and weekly thereafter for up to week 12: application of 0.02 ml MA at a concentration of 5% in acetone and olive oil (4:1)	**+ve** at day 21 and thereafter in 4/6 animals	Parker and Turk, 1983

Table 10: Sensitisation Studies in Guinea Pigs (continued)

Test method	Induction	Challenge	Result	Reference
Polak	Day 1: 1 mg MA per animal by 4 x 0.1 ml injections, 1 x 0.1 ml of 0.2 mg/ml MA in an emulsion of ethanol/saline (1:4) and CFA[a], injected in the nape of the neck	Day 7 and weekly thereafter for up to week 12: application on the shaved skin of the flanks of 0.02 ml MA at concentrations of 0.5, 1, and 5% in acetone and olive oil (4:1) 4-6 d after the challenge the auricular and contralateral cervical lymph nodes were weighed and by histopathologically examined for LPC[b]	**+ve** Increase of LPC[b], no increase of the weight of the lymph node MA was considered a strong sensitiser	Bull *et al,* 1985
Open epicutaneous	Day 0: 50 µmol MA in acetone : olive oil, 1:1 applied on the dorsal surface of the right ear	Day 7 and 14: challenge on the shaved flank with 50 µmol MA in acetone: olive oil (1:1) 4-6 d after the challenge the auricular and contralateral cervical lymph nodes were weighed and histopathologically examined for LPC[b]	**+ve** Increase of LPC[b], no increase of the weight of the lymph node MA was considered as medium potential sensitiser	Bull *et al,* 1985

[a] Complete Freund Adjuvant

[b] Large Pyroninophilic Cells

Overall, the available data indicate that MA is a potential skin sensitiser, although it does not appear to be of high potency.

8.2.6 Summary

MA is severely irritating to the skin and eyes of rabbits. It is irritating to the respiratory tract and mucous membranes of a wide range of mammalian species.

Based on the results of the majority of the animal studies, MA has the potential to cause allergic contact dermatitis.

8.3 REPEATED-DOSE TOXICITY

8.3.1 Oral

MA was administered in the drinking water *ad libitum* to 15 male and 15 female CDF-F344 rats at target doses of 0, 1, 5 or 20 mg/kgbw/d for 13 weeks. In the 20 mg/kgbw dose group, slight decreases in body weight gain and water consumption were observed in both sexes, and an increase in urinary specific gravity was observed in the females, probably as a result of decreased water intake. Both sexes showed an increased incidence of the spontaneous renal disease that occurs normally in this strain of rats and is characterised histopathologically by dilated renal tubules and eosinophilic cast formation. The authors concluded that doses of MA up to 20 mg/kgbw/d did not produce evident toxicity on any organ upon ingestion by rats for 13 wk, even though concentrations providing the highest dose were less palatable. Based on the effects seen at the 20 mg/kgbw/d dose the No Observed Adverse Effect Level (NOAEL) was determined to be 5 mg/kgbw/d for male and female CDF-F344 rats (Wade *et al*, 1981).

An aqueous solution (up to 5%, i.e. saturated) of MA was administered by gavage (5 x/wk) to rabbits for 5 weeks. Two administrations of 0.4 ml/kgbw (380 mg/kgbw) caused the death of 4/4 animals. Upon examination substantial damage to the gastric mucosa (increased thickness of the mucosa and focal haemorrhage) were observed. Ten administrations of 0.2 ml/kgbw (190 mg/kgbw) to 2 males and 10 administrations of 0.1 ml/kgbw (95 mg/kgbw) to 2 males and 2 females did not cause any mortality. Furthermore, no irritation of the mucosa of the stomach was observed (BASF, 1960).

In an oral gavage study MA was administered to 2 female rabbits at a dose of 23 mg/kgbw on each of 5d/wk until 24 doses had been given over a period of 33 days, followed by a post-treatment period of 2 months. Retardation of growth or small losses of weight were reported during the administration period; these were the only signs of toxicity. Two months after the last administration the

macroscopic pathological evaluation indicated no significant pathological alterations. The authors concluded that MA has "no cumulative effects" (Treon *et al*, 1949).

8.3.2 Dermal

MA, 1 to 5 ml/rabbit (4.3 - 32.6 g/kgbw) applied (every 10 min for 1 to 3 h) dermally under occlusive dressing for 1 to 2 days caused local oedema, haemorrhage and inflammation. There were no deaths during the study (Treon *et al*, 1949).

A single dose of 1 ml undiluted MA applied to the skin of rabbits (number and sex of animals and frequency of treatment were not specified) resulted in depression of the γ-globulin and an increase of the α- and β-globulin in the blood. Sixty applications of 4 ml of a 1% MA solution (solvent not specified) led to an increase of the α- and β-globulin; the albumin-globulin quotient was decreased (Suvorov, 1969).

Undiluted MA (1 ml) was applied (2 x 5 h within 24 h) to the skin of rabbits (sex and number of animals not specified). A decrease of blood ascorbic acid and glutathione and a lesion described by the authors as “deep dystrophic and necrobiotic alteration in the skin” were observed. Following a post-treatment period of 30 days the findings had normalised (Suvorov and Kudin, 1971; abstract only available).

Sixty administrations of 4 ml of a 1% MA solution (number and sex of animals, solvent and frequency of treatment not specified) induced necrotic alterations of the skin (necroses of epidermis and adventitia) with increase of the acid and alkaline phosphatase and a local concentration of mast cells and lymphocytes in the corium (true skin under the epidermis) (Suvorov, 1973; abstract only available).

8.3.3 Inhalation

In a 12-week repeat-exposure inhalation study, Sprague-Dawley rats (groups of 10 males and 10 females) were exposed (6 h/d, 5 d/wk) to atmospheres containing 0, 23, 124, 242 and 626 ppm (0, 82, 444, 866 and 2,240 mg/m^3) MA. All rats exposed at 626 ppm died between weeks 2 and 27 of exposure. Clinical signs included severe irritation and haemorrhagic discharge from the eyes and nose, and severe dyspnoea. Morphological findings included atrophy of the nasal mucosa, keratinisation of the transition zone between respiratory and olfactory epithelium, rhinitis, tracheitis, hyperaemia of the lungs and bronchopneumonia. In animals of the 242 ppm group, these clinical alterations were only seen at the beginning of the study; only the irritation of the nasal epithelium persisted throughout the duration of the study. Other signs included reduced body weight gain and an increase in relative lung (male and female) and liver (only females) weights. The effects seen in

animals of the 124 ppm group were reduced body weight gain and increased relative lung and liver weights in the females without detectable alterations in the organs. In animals exposed at 242, 124 and 23 ppm, no morphological alterations in the nasal epithelium could be detected. At a concentration of 23 ppm no degeneration of the nasal epithelium or clinical signs was observed. Thus, the No Observed Effect Concentration (NOEC) was 23 ppm (82 mg/m^3) (BASF, 1978a, 1980).

In addition, a substantial number of repeat-exposure, short-term inhalation studies have been conducted in which a range of experimental animals were exposed to MA vapours for different durations. These studies are reviewed in Table 11.

Table 11: Repeat-Exposure Inhalation Studies

Species	Number of animals	Number of exposures, duration	Exposure regime (h/d, d/wk)	Atmospheric concentration[a] (ppm)	(mg/m^3)	Result[b], signs of toxicity	Reference
Rabbit Guinea Pig Rat	4 2 2	2 3 7	7, 2 7, 3 7, 7	578	(2,069)	All animals died. Symptoms prior to death included excitation, ear vein distension, sensory irritation (ocular and respiratory), cyanosis, lethargy and convulsions.	Treon *et al* , 1949
Rats Guinea pig Rat	5 2 2	11 12 12	7, 5 7, 5 7, 5	237	(848)	Weight loss, sensory irritation and lethargy. All rabbits and guinea pigs died, all rats survived.	Treon *et al* , 1949
Rabbit Guinea pig Rat	4 2 2	50 50 50	7, 5 7, 5 7, 5	95	(340)	Slight ocular and nasal irritation in rabbits, no remarkable signs of toxicity in guinea pigs and rats. No pathological changes seen in any animal.	Treon *et al* , 1949
Rabbit Guinea pig Rat Monkey	4 2 2 1	130 130 130 130	7, 5 7, 5 7, 5 7, 5	31	(111)	Weight loss in all species except rat. No remarkable signs of toxicity and no pathological changes seen in any animal.	Treon *et al* , 1949
Rat Rat Rat	15 15 15	Continuous for 100 d Continuous for 100 d Continuous for 100 d	24, 7 24, 7 24, 7	(0.0028) (0.028) (0.28)	0.01 0.1 1	No major effects. A number of minor changes were reported. However, based on the translation of the paper it is not possible to assess their biological relevance.	Osintseva *et al* , 1970

Table 11: Repeat-Exposure Inhalation Studies (continued)

Species	Number of animals	Number of exposures, duration	Exposure regime (h/d, d/wk)	Atmospheric concentration[a] (ppm)	(mg/m^3)	Result, signs of toxicity	Reference
Rat Rat	Not stated	Continuous for 100 d	24, 7 24, 7	(0.028) (0.28)	0.1 1	The exposure led to chromaxia of the muscles, increased serum urea, reduced coproporphyrin excretion in the urine and reduced concentration of ascorbic acid in the brain, kidneys, liver, spleen and adrenals. The biological relevance cannot be evaluated.	Bezpal'ko, 1967
Rat	Not stated	3 months 3 months	3, 6 6, 3	(19.8) (19.8)	71 71	A decrease of the peroxidase activity in the blood and a reduction of the glutathione level, compared to the control group, is described as well as the activity of the mixed functional oxidases in the liver.	Lomonova *et al*, 1980
Rabbit	Not stated	10-29	2.5, 5	(159)	570	Animals died within 10 to 29 days. Red blood cell counts and haemoglobin concentrations increased after 3 to 4 exposures and then decreased. Necropsy revealed hyperaemia and haemorrhage in the visceral organs. In the lungs pulmonary emphysema, atelectasis, oedema, and signs of pneumonia were seen. Necrosis of the liver, fatty degeneration of the various organs and cerebral haemorrhage were also observed.	Lomonova *et al*, 1980
Rat (male)	4	32	4, 5	110	(394)	No significant body or tissue weight changes were observed. Blood chemistries, gross metabolic performance and spontaneous small intestine motor activities showed no significant discernible difference between the MA exposed animals and the controls. No overt signs of respiratory distress or central nervous system effects were seen.	Oberly and Tansy, 1985

[a] Converted values in parentheses

8.3.4 Summary

In repeated dosing and subchronic studies, the main effects observed in laboratory animals by the oral, dermal and inhalation routes were irritation/corrosion of the gastric membranes, mucous membranes, eyes and nose. This may be result from the generation of acrylic acid by de-esterification of MA.

The NOAEL for a 3-months oral administration of MA to the rat via the drinking water was 5 mg/kgbw/d and the NOEC in a 12-week inhalation study was 23 ppm (82 mg/m^3).

8.4 GENETIC TOXICOLOGY

8.4.1 *In Vitro*

Bacterial Gene Mutation

MA has been tested in a number of bacterial gene mutation assays, using both the standard Ames test and variations thereof. In all of the studies, MA showed no genotoxic potential. All tests were performed with and without auxiliary metabolic activation (S9-mix) (Table 12).

Table 12: Bacterial Gene Mutation Assays With and Without Metabolic Activation

Salmonella typhimurium strain	Induction of metabolic activation (S9-mix)[a]	Concentration	Result[b]	Reference
TA 98 TA 100 TA 1535 TA 1537	Aroclor 1254	3.15 - 1,000 nl/plate	**–ve**	BASF, 1977
TA 98 TA 100 TA 1535 TA 1537	Not stated	3 µmol/plate	**–ve**	Florin *et al*, 1980
TA 98 TA 100 TA 1535 TA 1537 TA 1538	PCB KC500	0.15 - 4.7 mg/plate	**–ve**	Hachiya *et al*, 1982
TA 98 TA 100 TA 1537	PCB KC400	Not specified	**–ve**	Ishidate *et al*, 1981
TA 98 TA 100 TA 1535 TA 1537 TA 1538 C 3076 D 3052 GA 46 LT-2 *Escherichia coli* WP2 WP2 uvrA$^-$	Aroclor 1254	0.1 - 1,000 µg/ml	**–ve**	McMahon *et al*, 1979
TA 98 TA 100 TA 1535 TA 1537 TA 1538	Aroclor 1254 and phenobarbital	40 - 2,500 µg/plate	**–ve**	Waegemakers and Bensink, 1984
TA 100	Aroclor 1254	60 - 6,000 µg/2 ml incubation volume	**–ve**	Waegemakers and Bensink, 1984

[a] Rat liver only, no liver homogenates from other animals were used

[b] +ve, positive; –ve, negative

Only in a publication by Zhang *et al* (1988) is MA reported to be positive in the Ames assay. This study was only available to the Task Force as a short abstract and as no methodological details are given, a critical evaluation of the study was not possible.

Mammalian Cell Gene Mutation

MA did not induce significant increases in mutant frequency in two Chinese hamster ovary (CHO) *hpgrt* locus mutation studies conducted in the absence of S9 (Moore *et al*, 1989; 1991).

Oberly *et al* (1993) examined the mutagenicity of MA towards AS52/XPRT Chinese hamster ovary cells in the absence of S9, over the concentration range of 10 to 25 μg/ml. No mutagenic activity was demonstrated. AS52/XPRT cells are Chinese hamster cells in which the hprt gene has been largely deleted and replaced by a single copy of the functional xanthine-guanine phosphoribosyl transferase (XPRT) gene (gpt) from *Eschericia coli*; see Aaron and Stankowski (1989).

In contrast, MA has been shown to be active in the Mouse lymphoma $TK^{+/-}$ mutation assay using L5178Y cells in the absence of S9 (Table 13).

Table 13: Mouse Lymphoma $TK^{+/-}$ Mutation Assays

+S9 mix	-S9 mix	Concentration	Result	Reference
No	Yes	22 μg/plate	**+ve**	Amtower *et al*, 1986[a]
Not specified	Not specified	Not specified	**+ve**	Doerr *et al,* 1988[a]
Not specified	Not specified	Not specified	**+ve**	Millis *et al*, 1988[a]
No	Yes	16 - 24 μg/ml	**+ve**	Moore *et al,* 1989

[a] Abstract only

The majority of the mutant colonies induced by MA were reported to be small colonies (Amtower *et al*, 1986; Doerr *et al*, 1988; Moore *et al*, 1989), indicating that the mutants induced by MA are the result of a clastogenic activity.

Chromosomal Damage

Exposure of Chinese hamster lung (CHL) cells to MA, in the absence of metabolic activation and over the dose range 7.5 to 15.0 μg/ml, resulted in a dose-related increase in chromosome aberrations (Ishidate *et al*, 1981).

8.4.2 *In Vivo*

Chromosomal Damage

Three micronucleus assays have been reported.

Sofuni *et al* (1984) exposed groups (group size not specified) of male ddY strain mice to atmospheres containing 1,300 or 2,100 ppm (4,650 or 7,520 mg/m^3) MA in air for 3 hours. Bone marrow was sampled at 18, 24, 30, 48 or 72 hours after exposure. No increase in micronuclei was observed, at either dose level, at any of the sample times.

Groups of 6 male ddY mice were exposed to MA via a single oral dose of 62.5, 125 or 250 mg/kgbw. In addition, a further group of 4 male ddY mice was dosed with 125 mg/kgbw on 4 consecutive days. Bone marrow was sampled 24 hours after the last dose. No increase in bone marrow micronucleated cells was observed at any dose level, by either treatment regimens (Hachiya *et al*, 1982).

In contrast, exposure of groups of 4 male Balb/C mice to 37.5, 75, 150 or 300 mg MA/kgbw by the i.p. route (2 injections, 24 h apart) produced a threefold increase in micronuclei (Przybojewska *et al,* 1984). However, the increase was not clearly dose-dependant and significant reductions in the ratio of polychromatic to normochromatic erythrocytes was observed indicating a cytotoxic effect of MA and/or its metabolites on the bone marrow. No cytotoxicity was observed in rat bone marrow with acrylic acid (ECETOC, 1995). One possible mechanism for the observed cytotoxicity relates to the i.p. exposure route, which may have allowed MA to avoid the de-esterification associated with the more relevant absorption routes. This would, potentially, allow exposure of the bone marrow to MA and the in situ formation of both acrylic acid and methanol.

In the same study the authors reported that ethyl acrylate (EA) was also positive (see ECETOC 1994a). These results could not be reproduced with EA (purity 98.5%) in 4 micronucleus tests in C57BL6 mice (5 or 10 males/group and 10 females/group) and Balb/c mice (10 males/group) utilising single or double i.p. dosing regimens at levels up to 85% of the LD_{50} (738 mg EA/kgbw for single dose or 812 mg/kgbw for double doses) (Ashby *et al*, 1989). (See ECETOC, 1994a for a full critique.) The inability of other investigators to reproduce the findings of Przybojewska *et al* for EA also casts some doubt on the validity of the results obtained with MA.

In a micronucleus study by Zhang *et al* (1988), MA is reported to be negative. This study is available only in an abstract form and no methodological details are available.

Drosophila Sex-Linked Recessive Lethal Test

MA was tested for mutagenic potential in the Drosophila sex linked recessive lethal (SLRL) assay (Zimmering *et al*, 1989). *Drosophila melanogaster* larvae were fed on a corn meal diet containing 500 ppm (1,790 mg/m^3) MA. No increase in SLRL mutations was observed. Thus under the conditions of this study MA was not mutagenic.

8.4.3 Summary and evaluation

Genotoxicity tests *in vitro* have demonstrated that MA is not a gene point mutagen in *Salmonella typhimurium* or *Escherichia coli*. MA does not induce mutations in CHO cells (HGPRT locus). However, positive results have been obtained in mouse lymphoma cells (L5178Y). MA has also been shown to be clastogenic in CHL cells.

In vivo, micronucleus studies in the mouse have given mixed results. In a study of which the validity has been questioned, MA by the i.p. route gave positive results. However, by the oral and inhalation routes, which are more appropriate to potential human exposure, it was negative. An SLRL assay in *Drosophila* was negative. Based on these data, MA is clastogenic *in vitro* but this effect is not expressed *in vivo* which suggests that genotoxicity does not represent a hazard in humans.

8.5 CHRONIC TOXICITY AND CARCINOGENICITY

In a 2-year inhalation study with a 6-month recovery subgroup, Sprague-Dawley rats (86 males and 86 females/group, 35-d old at the start of the study) were exposed (6 h/d, 5 d/wk) to 0, 5, 15 and 45 ppm (0, 18, 54 and 161 mg/m^3) MA during the first 3 weeks and thereafter to 0, 15, 45 and 135 ppm (0, 54, 161 and 483 mg/m^3) MA. The exposure regime was maintained for 24 months. After 12, 18, and 24 months, 10 or 15 male and female rats per treatment group were killed for interim examination. All rats that were killed or died were subjected to necropsy and organ weights were determined. Clinical signs, mortality, food consumption, body weight gain, and results of blood tests in the exposed animals were similar to control. A slight decrease in body weight gain was observed in the animals of the 135 ppm group, which the authors attributed to irritating properties of MA. Mild atrophy and slight basal cell hyperplasia was observed in the nasal passages of some animals ($\leq$ 6%) in the 15 ppm group, hyperplasia was accompanied by loss of olfactory and ciliated cells of the nasal turbinates in the females of the 45 and 135 ppm groups and in the males of all exposure groups. Chronic tissue damage (opacification and vascularisation) of the cornea was observed in all exposed groups. All these changes were secondary to the irritating properties of MA. There was no indication of effects on longevity or systemic toxicity by urine analysis and haematological parameter determination or gross histological examination. No treatment-related tumours were observed after 2 years of exposure to MA at concentrations up to 135 ppm (Reininghaus *et al*, 1991). The NOEC for systemic toxicity was 135 ppm (483 mg/m^3). The Lowest Observed Adverse Effect Concentration (LOAEC) for nose and eye irritation effects was 15 ppm (54 mg/m^3).

8.6 REPRODUCTIVE TOXICITY

There are no specific data available on the reproductive toxicity of MA. However, as MA is expected to rapidly degrade to acrylic acid and the corresponding alcohol (methanol), data on these latter two

compounds, and data on other acrylate esters should be considered when assessing the reproductive toxicity of MA.

In multi-generation reproduction studies where rats received acrylic acid in their drinking water, dose-dependent signs of general toxicity were observed including reduced food and water intake and lower mean body weight gain in the F_0 generation at 5,000 mg/l (460 mg/kgbw/d) and in the F_1 parental generation at 5,000 and 2,500 mg/l. Retarded growth was exhibited in the F_1 and F_2 pups of the parental group at 5,000 mg/l but not pronounced at 2,500 mg/l. The NOAEL for reproductive function was 5,000 mg/l (460 mg/kgbw/d) in 2 successive generations. The NOAEL concerning general toxicity was 2,500 mg/l (240 mg/kgbw/d) for the F_0 generation and 500 mg/l (53 mg/kgbw/d) for the F_1 parental generation and F_1 and F_2 offspring.

Inhalation exposure to acrylic acid did not result in embryotoxicity even at maternally toxic dose levels. No major effects were observed in a one-generation study at doses toxic to the parents (ECETOC, 1995).

Exposure (7 h/d) of rats to atmospheres containing methanol at 0, 5,000 or 10,000 ppm (0, 7,270 or 14,530 mg/m^3) during gestational days 1 to 19, and to 20,000 ppm (29,060 mg/m^3) during gestational days 7 to 15, produced slight maternal toxicity (unsteady gait) at 20,000 ppm. At 10,000 and 20,000 ppm, decreased foetal weight and malformations were observed. The malformations were predominantly extra or rudimentary cervical ribs and urinary or cardiovascular defects. In this study, the No Observed Adverse Effect Concentration (NOAEC) for both maternal toxicity and developmental effects was 5,000 ppm (7,270 mg/m^3) (Nelson *et al*, 1985).

Exposure (7 h/d) of CD-1 mice to atmospheres containing methanol at 0, 2,000, 5,000 or 15,000 ppm (0, 2,910, 7,270 or 21,800 mg/m^3) during gestational days 6 to 15 resulted in resorptions of most litters in the 15,000 ppm exposure group. Of the litters surviving to day 17, 38% showed exencephaly. Exencephaly was observed in a third of the litters and 5 to 10% of the foetuses from the 5,000 ppm exposure group, and in 1 of 220 foetuses in the 2,000 ppm exposure group. A NOAEC could not be established in this study (Rogers *et al*, 1991 as quoted by Lington and Bevan, 1994).

Butyl acrylate was maternally toxic and embryotoxic, following inhalation, at concentrations of 135 ppm (720 mg/m^3) and above in the rat; the NOEC was 25 ppm. By the oral route, butyl acrylate was maternally toxic and embryotoxic in mice at doses of 1,000 mg/kgbw/d and above; the NOEL was 100 mg/kgbw/d. At the currently accepted occupational exposure levels, butyl acrylate represents no reproductive risk to humans (ECETOC, 1994b).

Ethyl acrylate was not teratogenic in rats at inhalation exposure concentrations up to 150 ppm (620 mg/m^3), the maximum level examined, which was toxic to the dams. There was no evidence for specific embryotoxicity or foetotoxicity at non-maternally toxic concentrations (ECETOC, 1994a)

At the currently accepted occupational exposure levels of MA, the amount of methanol generated *in situ* will not approach the levels employed in the above studies. The Task Force concludes that, at the currently accepted occupational exposure levels, MA is not likely to pose a reproductive risk to humans.

9. EFFECTS ON HUMANS

Limited data are available on the effects of human exposure to MA. These data are confined to the effects of MA that might be encountered in industrial handling situations and much of it is derived from short abstracts of Russian publications. Insufficient information is provided on the conduct of these studies to evaluate the significance of the effects reported.

9.1 ACUTE AND SUBCHRONIC TOXICITY

Although there have been no reported deaths, in humans, associated with exposure to atmospheres containing MA, animal experiments suggest that exposure to saturated vapours may pose a risk for man and that the toxic effects (including death) may be delayed in onset (BASF, 1958a).

The “fatal dose” following inhalation has been estimated at 1,000 ppm (Dreisbach, 1974).

9.2 IRRITATION AND SENSITISATION

The lowest concentration to have an irritant effect on humans has been reported as 75 ppm (Sandmeyer *et al* , 1981).

9.2.1 Eye and Respiratory Tract Irritation

Irritation of the upper respiratory tract and the conjunctivae was observed in humans exposed (duration not specified) to 0.25 and 0.5 mg MA/l (250 and 500 mg/m^3; 70 to 140 ppm). The odour threshold was given as 0.13 mg/l (130 mg/m^3; 36 ppm) (Karpov, 1955).

Burns of the cornea have occurred with MA in the eyes (Lefaux, 1968).

A short-term epidemiological follow-up study was conducted by the Hoechst Celanese Corporation (Milton *et al*, 1996; unpublished study). The study was an extended medical surveillance project conducted to determine whether an OEL of 5 ppm (18 mg/m^3) adequately protects against acute irritation to the eyes and respiratory tract. MA was produced intermittently in campaigns lasting approximately 8 weeks. Therefore, this study applied only to the potential for acute effects of intermittent exposure. A total of 15 production workers and an industrial hygienist were studied using a case-crossover design. Measurements of irritation included spirometry, peak expiratory flow (PEF), ophthhalmologic examinations, and self-reporting of symptoms. In addition to 12-h TWA personal samples, area and task specific peak-exposure samples were analysed for MA. In the highest-exposed job category, the average exposure was 2.0 ppm (7.2 mg/m^3) and peak exposures during tasks of 2 to 5 min duration averaged 30 to 126 ppm (107 to 451 mg/m^3). This short-term prospective

study of MA production workers found little evidence of acute effects at the exposure levels encountered during a normal production campaign. There were no changes in the finding of ophthalmologic examinations from before to after exposure. Eye symptoms were rare and although more frequent in the most exposed group, they were of low intensity and not significantly increased. Respiratory health monitoring also found no significant changes among the workers, although the subjects had a relatively high rate of bronchial responsiveness prior to the start of MA production.

9.2.2 Skin Irritation and Sensitisation

Application of MA (20% dissolved in olive oil) to the skin of human subjects for 2 days in a Finn chamber produced local skin irritation in 10 out of 30 subjects. In 2 out of 22 subjects challenged with MA at 2%, an allergic skin reaction was elicited. No cross-reaction occurred with methyl methacrylate (Cavelier *et al*, 1981).

From the available abstract of the Karpov (1955) paper, epicutaneous tests from employees of the fibre industry showed a higher than normal prevalence of weakly positive skin responses (Karpov, 1955). It is not possible to judge from the abstract whether this is indicative of skin irritation or sensitisation.

Skin irritation, hyperkeratosis and dermatitis were observed in workers of a Russian plant producing “Nitron”, a fibre composed of acrylonitrile and methyl acrylate. Epicutaneous drop challenge tests were performed on 187 workers; 20% of them exhibited positive reactions with MA (Dovzhanskij, 1976).

Intradermal samples showed positive haemagglutination reactions when a group of 105 workers who had been in contact with acrylonitrile, MA, and sodium cyanide were examined. Respectively, 86.5, 76.1, and 65.6% of the workers showed a positive response. Clinical presence of dermatitis, eczema, and urticaria was observed in 53.7% of the workers (Khromov, 1974).

Allergic contact dermatitis to MA has been observed in a worker whose foot was accidentally contaminated when his rubber boot filled with undiluted technical MA. Eight days later, the exposed skin developed a bullous lesion that resolved with topical treatment. Approximately 17 days after the first exposure, the worker was re-exposed to MA (in the atmosphere) during his normal work profile. On the following day eczema developed on his neck and upper forehead and a bullous flare-up reaction appeared on the previously exposed ankle. Because of the temporal relationships between skin reaction and exposure and the fact that the worker had been employed in the same factory for 15 years, with MA only being introduced three months before he developed dermatitis, these results suggest that MA might be able to induce an allergic response after a single high exposure. Cross-sensitisation with ethyl acrylate, butyl acrylate, 2-hydroxyethyl acrylate, 2-hydroxypropyl acrylate,

methyl methacrylate 1,6-hexanediol diacrylate and diethylene glycol diacrylate was also reported in this patient (Kanerva *et al*, 1993).

9.3 REPRODUCTIVE FUNCTION

No data specific to MA are available.

10. ASSESSMENT OF HAZARD TO HUMAN HEALTH

The main population likely to be exposed to MA is workers involved in production and in industrial manufacture of polymers used in products such as fibres, coatings, and adhesives. Consumer exposure and indirect exposure to the monomer via the environment are considered negligible.

The primary toxic effect of MA, by exposure routes relevant to workers, is irritation/corrosion at the site of contact. MA also has the potential to produce allergic contact dermatitis. Experiments in animals suggest that exposure to saturated vapours may pose a risk for man and that the toxic effects (including death) may be delayed in onset.

Repeated-dose cumulative toxicity studies through both oral, dermal, and inhalation routes show a similar pattern of toxicity seen with acute exposure. MA produces irritation effects at the site of contact with no systemic toxicity effects being observed. Chronic inhalation exposure to MA also shows contact site irritation to the upper respiratory tract and the eyes as the lead toxic effect. No systemic toxicity or increases in the treatment-related tumour incidence occur.

The lack of treatment-related tumours in the chronic study is consistent with the MA genetic toxicity profile. The results of the *in vivo* genotoxicity assays by exposure routes relevant to humans demonstrate that MA does not pose a genotoxic risk to humans.

No data are available on the reproductive toxicity of MA itself. As MA is rapidly de-esterified to acrylic acid and methanol, information concerning potential reproductive hazards of MA can be inferred from animal studies with these metabolic products. Reproductive studies with both acrylic acid and methanol suggest that MA is unlikely to cause significant adverse effects to the reproductive organs or to the developing embryo or foetus at currently accepted occupational exposure levels.

Therefore, the overall toxicity profile for MA from acute, subchronic and chronic animal studies shows that the lead effect is local irritation at the site of contact with the inhalation route as the major route of occupational exposure. From the available studies, it can be concluded that sensory and respiratory tract irritation are the most common effects to arise from inhalation exposure to MA. It is generally accepted that the rat is more sensitive to nasal irritants than man due to physiological and anatomical differences. The rat is an obligate nose breather with significantly more complex nasal passages than man. The relative surface area per unit volume in the nose of the rat is 8 times that of man (DeSesso, 1993). Therefore, as a model for inhalation hazard of irritant chemicals, the rat provides an additional safety factor when evaluating the risk to man. It is concluded that the LOAEC of 15 ppm (54 mg/m^3) observed in the 2-year inhalation study can be used as the basis for a risk evaluation in man.

11. FIRST AID AND SAFE HANDLING ADVICE

11.1 FIRST AID AND MEDICAL TREATMENT

There is no specific treatment or antidote for over-exposure to MA. Supportive medical treatment as indicated by the patient's condition is recommended.

11.1.1 Skin and Eye Injuries

Clothing contaminated with MA should be removed (and either discarded or laundered before reuse). Affected areas of skin must be washed with copious quantities of water. The skin must be rinsed for at least 10 min. If the eyes are splashed, they should be irrigated immediately with eye-wash solution or clean water, holding the eyelids apart for at least 10 min. A physician should then be consulted.

11.1.2 Inhalation

The patient must be taken into fresh air, kept warm and at rest if he experiences difficulty in breathing after inhaling MA fumes. If the patient stops breathing, artificial respiration should be administered until qualified medical personnel is able to take over. Medical aid should be summoned immediately.

11.1.3 Ingestion

If MA has been swallowed, vomiting is not to be induced. (Never give anything by mouth to an unconscious person.) A physician should be consulted immediately.

11.2 SAFE HANDLING

11.2.1 Safety at Work

The main risk of injury stems from MA's irritating action on the skin and mucous membranes. Contact with the skin and eyes should therefore be avoided as should inhalation of high concentrations of MA vapour. MA should be used only in well-ventilated areas. MA vapour is denser than air; pits and confined spaces should be avoided.

Suitable respiratory equipment must be worn on occasions when exposure to MA vapour above the recommended exposure limit is likely.

The following protective clothing must be worn when handling MA: eye-face protection and rubber gloves (preferably nitrile) which should be changed regularly to avoid permeation. Rubber boots should also be worn when handling large quantities.

11.2.2 Storage Safety

MA is stable in the presence of a polymerisation inhibitor. It is susceptible to polymerisation initiated by prolonged heating or catalyst. Therefore, the following precautions must always be observed when storing MA.

- MA must be stored under air as the stabiliser (hydroquinone monomethylether) is only effective in the presence of oxygen
- Heat and direct sunlight must be excluded, as these promote polymerisation
- MA must be stored at temperatures preferably not exceeding 25°C
- Care should be taken to prevent contamination, as contaminants can render the stabiliser ineffective or can react with MA and promote polymerisation.

11.2.3 Fire Safety and Extinguishants

MA is classified as a highly flammable liquid. It can form an explosive mixture in air; adequate ventilation should be provided and smoking prohibited. Precautions should be maintained to eliminate all sources of ignition of MA when in contact with air. MA may polymerise on heating. Sealed containers may rupture if hot. Heat, UV-light, peroxide, azo-compounds, alkalis and oxidising agents may cause rapid polymerisation resulting in explosion. Fires can be extinguished with water, alcohol-resistant foam, dry powder or CO_2.

If fire does break out, neighbouring tanks and pipelines must be kept cool with plenty of water, otherwise the heat generated by the fire will cause their contents to polymerise.

11.2.4 Protection against Fire and Explosion

To avoid ignition, the following precautions are recommended.

- All plant and equipment should be explosion-proof as laid down in national standards
- All containers must be earthed
- All sources of ignition must be excluded
- No smoking is allowed
- No welding should be done until all tanks and pipelines have been drained and thoroughly flushed with water or hot caustic soda.

11.3 MANAGEMENT OF SPILLAGE AND WASTE

In all cases of spillage, naked flames should be extinguished. Smoking and sparks must be avoided. Small spills of a few litres can be soaked up with suitable absorbent materials such as sand or earth. MA should not be absorbed onto sawdust or other combustible materials. Larger spills must be prevented from spreading by the use of earth or sand and the material should be pumped into containers, using explosion proof-pumps.

Surfaces contaminated with MA should be washed well, first with alcohol and then with soap and water. All wastes should be sealed in vapour-tight plastic bags for eventual disposal.

MA should not be allowed to drain into domestic sewers as serious explosion hazards could result. Local authorities should be informed immediately if spilt liquid MA has entered surface water drains.

Waste quantities of MA can be incinerated in accordance with local, state or national regulations. Empty storage drums must be thoroughly rinsed and washed before recycling.

When aqueous waste containing MA is discharged to adapted biological waste-water treatment plants, it is expected to be mineralised. No disturbance of the bacterial activity of sewage treatment plants is expected if MA is properly diluted.

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