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Methyl Methacrylate

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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 publish annually 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. 30 entitled "Existing Chemicals: Literature Reviews and Evaluations".

This document presents a critical assessment of the toxicology and ecotoxicology of methyl methacrylate (CAS No. 80-62-6). The report forms part of a series of similar reports on acrylates and methacrylates.

Methyl Methacrylate
CAS No. 80-62-6

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SECTION 1. SUMMARY AND CONCLUSIONS

Methyl methacrylate (MMA) is a clear, colourless, highly flammable liquid with a pungent fruity odour. It is used extensively as a monomer in the production of high molecular weight polymers.

The majority of MMA released to the environment is expected to enter the atmosphere. Its atmospheric half-life is estimated to be *circa* 3 hours. Although MMA cannot be considered as readily biodegradable according to EEC criteria, MMA will rapidly biodegrade in the aquatic environment under aerobic conditions, abiotic hydrolysis playing only a minor role. In soils, MMA is expected either to rapidly evaporate or to biodegrade. It is not expected to bioaccumulate.

The acute toxicity of MMA to bacteria and aquatic organisms (protozoa, microcrustacea, algae and fish) is low. There is no evidence of long-term adverse effects.

On the basis of its low aquatic toxicity, low bioaccumulation potential, volatility and biodegradability in the aquatic environment under aerobic conditions, MMA is considered not to present a risk to the environment.

MMA is rapidly absorbed and distributed in experimental animals following oral and inhalation exposure. *In vitro* absorption studies with human skin indicate that MMA may be absorbed through the skin and that absorption may be enhanced by occlusion. However, the small amount of the applied dose absorbed under non-occluded conditions suggests that under normal exposure conditions, the contribution of dermal absorption to the overall body burden will be small, inhalation being the major exposure route. Metabolism appears similar in man and experimental animals, and the elimination of MMA is dependant on the route of exposure. Following inhalation exposure of rats, 10 to 20% of the compound is deposited in the upper respiratory tract where it is metabolised by local tissue esterases and, to a minor extent, by conjugation with tissue non-protein sulphhydryl (NPSH) groups. Activities of local tissue esterases of the nasal epithelial cells may be lower in man than in rodents. After oral or parenteral administration, rapid hydrolysis to methacrylic acid and methanol is observed, both of the hydrolysis products being further metabolised by physiological pathways. The methacrylic acid is metabolised via methylmalonyl-coenzyme and the tricarboxylic acid pathway. Conjugation with glutathione (GSH) or NPSH plays only a minor role, occurring when the tissue concentrations of MMA are high and the hydrolytic pathway reaches saturation. In common with the other esters of acrylic and methacrylic acid, both metabolic pathways are detoxifying.

MMA has a low order of acute toxicity via the oral, dermal and inhalation routes of exposure. It is not absorbed in lethal quantities through the skin even under occluded conditions. It is mildly irritating to the skin, eyes and mucous membranes of the respiratory tract. It is a skin sensitiser in experimental animals, however its sensitisation potency is low. Cross-reaction has been demonstrated to other esters of methacrylic acid.

Subchronic exposure of rats and mice to MMA by oral, dermal and inhalation routes produced effects consistent with its irritative properties. In inhalation toxicity studies, dose related lesions were seen in the upper respiratory tract, including rhinitis, inflammation associated with necrosis and loss of olfactory epithelium in the nasal turbinates, and lung congestion. After exposure to high atmospheric concentrations of MMA (> 1,000 ppm), the body weight gain was reduced and degenerative and necrotic changes were seen in liver, kidney, brain, spleen and bone marrow. Changes in the activities of liver enzymes were observed in animals exposed to relatively low concentrations. Inconsistent data were reported on effects of MMA on the cardiovascular system. Single studies have indicated that exposure to high doses of MMA via the oral and inhalation routes may induce behavioural and neurochemical changes. Central nervous system effects have not been reported in chronic studies with exposure levels up to 1,000 ppm.

MMA is not mutagenic to bacteria even at cytotoxic concentrations. In *in vitro* systems MMA shows clastogenic activity, but it is not clastogenic *in vivo* when animals are exposed via an appropriate route.

Chronic oral exposure to rats and dogs produced no histopathological changes and no treatment-related lesions, neither neoplastic nor non-neoplastic. Following chronic exposure of mice, rats and hamsters to atmospheres containing MMA no neoplastic or pre-neoplastic changes were produced. Non-neoplastic changes were essentially restricted to the upper respiratory tract and included rhinitis, serous and suppurative inflammation, epithelial hyperplasia and degeneration of the olfactory epithelium. These changes are consistent with the hydrolytic cleavage of the MMA giving rise to methacrylic acid which is deposited in the upper respiratory tract. The primary involvement of the olfactory rather than the respiratory epithelium is also consistent with the tissue distribution of esterases and flow parameters in the rodent respiratory system. Due to the differences in anatomy and probably local tissue esterase activities between human and rodent respiratory system, it is expected that human beings are less sensitive to the observed changes in the upper respiratory tract than rodents.

MMA shows no carcinogenic potential in experimental animals.

MMA is not expected to have an adverse effect on fertility and is not teratogenic in rats and mice exposed by the inhalation route.

No deaths or serious adverse health effects have been reported in man exposed to acute doses of MMA, the pungent, characteristic odour acting as a warning of exposure. MMA is a dermal irritant after prolonged or repeated contact. In certain individuals it may induce contact allergic dermatitis, with possible cross-reactions to other esters of methacrylic acid. Mild eye and respiratory tract irritation have been reported but there is no convincing evidence that MMA causes respiratory sensitisation. Epidemiological studies of workers exposed to MMA show no evidence of excess of respiratory disease or any evidence of respiratory sensitisation.

Several publications in the literature have inferred that MMA has neurotoxic/central nervous system effects in occupationally exposed human beings. These effects are, however, non-specific and it cannot be concluded that they represent neurotoxicity. In most cases it is not possible to draw conclusions on the contribution, if any, of MMA to the symptoms.

There is no evidence to suggest that MMA is genotoxic to man. No reproductive or teratogenic effects of MMA in exposed populations have been reported.

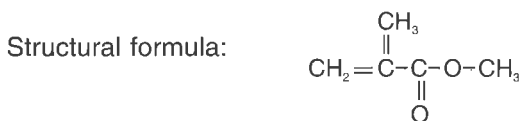
Epidemiological studies showed no evidence for any carcinogenic effects causally related to MMA exposure which is in agreement with the lack of genotoxic or carcinogenic activity in experimental animals. It is concluded that MMA does not present a carcinogenic hazard to man.

SECTION 2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 IDENTITY

Name:	Methyl methacrylate (MMA)
IUPAC name:	2-Methyl-2-propenoic acid, methyl ester
Synonyms:	Methacrylic acid, methyl ester Methyl- α -methacrylate Methyl 2-methylpropenoate Methyl 2-methyl-2-propenoate Methylpropylene-2-carboxylate D Methylmethacrylat 2-Propensäure, 2-Methyl-, Methylester DK Methylmethacrylat EL Μεθακρυλικός μεθυλεστέρας ES Metacrilato de metilo F Méthacrylate de méthyle I Metacrilato di metile Metilmetacrilato NL Methylmethacrylaat P Metacrilato de metilo
CAS name:	2-Methyl-2-propenoic acid, methyl ester

CAS Registry No:	80-62-6
EEC No:	607-035-00-6
EINECS No:	201-297-1
Formula:	$C_5H_8O_2$
Molecular mass:	100.12



2.2 PHYSICAL AND CHEMICAL PROPERTIES

Methyl methacrylate (MMA) is a clear, colourless, flammable liquid with a pungent, fruity odour. It is partially soluble in water and completely miscible with most organic solvents at any ratio. Data on the physical and chemical properties are given in Table 1.

Table 1 Physical and Chemical Properties

Parameter, units	Value	Reference
Melting temperature, °C	-48 (approx.)	Weast <i>et al</i> , 1988
Boiling temperature, °C at 1,013 hPa	100-101	Bartholomé <i>et al</i> , 1978; Weast <i>et al</i> , 1988
Heat of polymerisation, kJ/kg	544-555	Company datasheets (typical values)
Relative density, D_4^{20} (density of water at 4°C is 1,000 kg/m ³)	0.9440	Weast <i>et al</i> , 1988
Viscosity, mPa•s at 20°C	0.58-0.63	Company datasheets (typical values)
Refractive index, n_D at 20°C	1.4142	Weast <i>et al</i> , 1988
Vapour pressure, hPa at 20°C	36-47	Kirk-Othmer, 1984; Weast <i>et al</i> , 1988
Vapour density at 20°C (air = 1)	3.5	Company datasheets (typical value)
Threshold odour concentration, ppm (odour: pungent, fruity)	0.083 0.21 0.05-0.29 0.05-0.34	Amoore and Hautala, 1983 Leonardos <i>et al</i> , 1969; Stahl, 1973 in DFG, 1984 Filatova, 1962 Hellman and Small, 1974
Surface tension, mN/m at 20°C	No data	
Solubility in water, g/kg at 20°C	16 (approx.)	Company datasheets (typical value)
Solubility of water in MMA, g/kg at 20°C	12	Company datasheets (typical value)
Miscible with alcohol, ether, acetone	Yes	Weast <i>et al</i> , 1988
Fat solubility, mg/100 g at 37°C	No data	
Partition coefficient, log P_{ow} (octanol/water) at 20°C	0.67-0.7 1.38	Fujisawa and Masuhara, 1981 (measured) ^a Tanii and Hashimoto, 1982 (measured) ^b
Partition coefficient, log K_{oc} (organic carbon/water) at 20°C	1.34 1.33 1.53	SRC, 1988 Lyman <i>et al</i> , 1982 Hardies, 1991
Henry's Law constant, Pa•m ³ /mol at 20°C	22.5-29.4	Elf Atochem, 1994 (calculated)
Flash point, °C, closed cup	2	Elf Atochem, 1971
DIN 51755	10	BASF, 1989a,b; Degussa, 1989; Röhm, 1990a,b
Explosion limits, % at 10.5-45°C	lower 2.1 upper 12.5	Company datasheets (typical value)
Auto-flammability, ignition temperature, °C	421-430	Company datasheets (typical values)

a Temperature 20°C not specified

b Flash shaking method

A typical commercial sample of MMA has a specified purity of $\geq 99.8\%$ (w/w) and may contain the following impurities: water ($\leq 0.05\%$ w/w) and acid ($\leq 0.005\%$ w/w, calculated as methacrylic acid).

Light fractions (typically 800 ppm maximum) may include: acetone, methyl acetate, methanol, methacrylonitrile, methyl isobutyrate and methyl propionate. Heavy fractions (400 ppm maximum) may include ethyl acrylate, butanols, methylhydroxy-isobutyrate and succinic acid methyl ester (at ppm levels); diacetyl may be present at < 1 ppm (company data sheets).

MMA polymerises readily under the influence of heat, light or by catalysis (e.g. metals and radical forming substances such as peroxides), this being a strongly exothermic reaction. To prevent polymer formation, the monomer is stabilised by the addition of inhibitors such as 2,4-dimethyl-6-*tert*-butylphenol (10-30 ppm), hydroquinone (HQ) (25-100 ppm) and the monomethylether of hydroquinone (MeHQ, synonym *p*-methoxy phenol) (2-100 ppm).

2.3 CONVERSION FACTORS

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

- 1 ppm = 4.16 mg/m³
- 1 mg/m³ = 0.240 ppm

2.4 ANALYTICAL METHODS

2.4.1 Products

MMA may be assayed for purity by gas chromatography (GC) using a flame ionisation detector (FID) (ICI, 1993a).

To determine residual MMA levels in polymer dispersions and solid polymers, Grob closed-phase extraction (Melton *et al*, 1981), and liquid/liquid- and solid-phase extraction (Miller and Harper, 1983; Horna and Churáček, 1987; Stoev and Angelova, 1987) are used.

2.4.1 Environmental Media

The presence of MMA in environmental media can be determined down to ppb levels by capillary gas chromatography (GC) combined with mass spectrometry (MS) or a flame ionisation detector (FID) using suitable isolation and concentration procedures. The on column detection limit is 0.1 ng for GC/FID and 0.6 ng for GC/MS (James *et al*, 1985).

MMA can be trapped from gaseous samples using tubes packed with graphitised carbon black or macroreticular resins which release the analyte by heating (Krost *et al*, 1982; Darre *et al*, 1988; Morgan and Bradley, 1989), or solvent extraction (Harper, 1992). After cryofocustion the sample may be analysed by GC/MS (Krost *et al*, 1982).

A combined sorption-derivation procedure for the determination of acrylates and methacrylates in air down to ng/l levels was described by Churáček *et al* (1991). *n*-Butylthiol was used as derivation agent and the butylthioethers were subsequently analysed by GC/FID.

Dmitrieva and Kotok (1976) and Dmitrieva *et al* (1976) describe a polarographic method for the determination of airborne MMA after sorption on silica gel and solution with ethanol at high temperature. The method consists of trapping the substance with DMF and subsequent polarography in the presence of tetraethyl ammonium iodide (no further information available). The detection limit was 0.1 mg/m³ (0.024 ppm).

Liquid and solid samples can be isolated and concentrated by the purge and trap technique (Spingarn *et al*, 1982; Venema, 1986).

2.4.2 Biological Media

Tissues

Small amounts of MMA can be detected in bone tissues by extracting homogenised fine sections with normal saline and subsequent analysis of the samples by GC with a packed column. The detection limit was reported to be 50 ppm (Petty, 1980).

MMA concentrations in blood, brain and lungs were determined after extraction of tissue homogenates with acetonitrile and headspace GC analysis of the extracts using isobutylacetate as internal standard (Raje *et al*, 1985).

Blood

MMA blood levels in human patients were determined by directly injecting blood samples into a gas chromatography with FID detection. Blood levels between 0.016 and 200 mg/100 ml were determined (Pahuja *et al*, 1974; Modig *et al*, 1975; Derks *et al*, 1977; Rijke *et al*, 1977).

A headspace GC method using a packed column and FID detection for the determination of MMA in human blood samples with *n*-butylacetate as internal standard was described by Ruhnke *et al* (1974). A headspace GC method was also described by Streete *et al* (1992). Headspace GC was also used to determine MMA blood levels after treatment of the samples with NaCl and HQ solution to reduce the solubility of MMA and prevent ester hydrolysis and polymerisation (Pfäffli and Svartling, 1985; Svartling *et al*, 1986a,b).

Liquid chromatography, liquid scintillation counting and NMR spectroscopy were used to determine MMA and methacrylic acid blood levels *in vitro* (Corkill and Crout, 1982; Corkill *et al*, 1976; Crout *et al*, 1979).

Urine

Urinary metabolites have been determined after extraction and evaporation procedures using thin layer chromatography (TLC). Additionally, derivation (methylation with diazomethane, or silylation with trimethylsilan) was performed, followed by TLC, GC or GC/MS analysis. MMA itself has not been detected in the urine of exposed animals using TLC or GC analysis of urinary extracts (Bratt and Hathway, 1977; ICI, 1977b; Delbressine *et al*, 1981).

Streete *et al* (1992) described a headspace GC method for the determination of MMA in body fluids including urine. Urinary methanol levels determined by head space GC were used in biomonitoring studies of MMA (Mizunuma *et al*, 1993).

SECTION 3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 PRODUCTION

MMA is produced commercially via the acetone cyanohydrin (methacrylamide sulphate) route or through oxidation of isobutene or *tert*-butanol (C_4 route); the former route is more important. A third, minor method uses ethylene as feed stock (C_2 route). Methacrylic acid produced by other routes also serves as a key intermediate to MMA (Bauer, 1993).

Worldwide production figures on MMA are given in Table 2.

Table 2 Production Capacities 1991-1992

Region	Year	Quantity (kt)	Reference
World	1992	1,534.5	Chemical Market Research, 1988 as quoted by CSCHEM database, 1992
Western Europe	1992	550	CEFIC, 1993a
Japan	1992	448.7	Japanese Methacrylate Resin Association, 1992 as quoted by Plastics Industry News, 1992
USA	1991	499.0	US Chemical Industry Handbook, 1992 as quoted by CSCHEM database, 1992

3.2 STORAGE

To prevent polymer formation, the MMA 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 30°C. During long term storage, stabiliser levels should be checked routinely.

MMA can be stored or shipped in containers made of mild or stainless steel, or aluminium. MMA may polymerise in sealed containers with explosive force.

MMA can be stored without chemical inhibitors at a low temperature (<0°C) and transported by refrigerated road tankers.

3.3 TRANSPORT

Stabilised MMA is transported by road, rail and sea in bulk tanks and drums. Quantities up to 1 kt are regularly transported by sea.

3.4 USE

MMA is used as monomer or polymer in a large number of applications including cast sheet production, homo- and copolymers for injection moulding and extrusion compounds, surface coatings (solvent and emulsion based), adhesives, dental and medical polymers/cements, production of other methacrylates, polymer concrete, and embedding materials.

In 1992, MMA consumption was distributed among the manufacturing of acrylic sheets and moulding powders (31%), surface coating and emulsion polymers (50%) other methacrylates (13%) and miscellaneous uses (6%) (CEFIC, 1993b).

SECTION 4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 EMISSIONS

4.1.1 Natural sources

MMA is not known to occur naturally (IARC, 1979).

4.1.2 Emissions During Production and Use

MMA is produced in closed systems and hence emissions during MMA production are extremely low.

MMA is released into the environment during the manufacture of plastics and resins/preparations. Emissions during these processes are well characterised although most are not in the public domain. Data registered with National Authorities indicate emissions are within legally acceptable limits.

Consistent with environmental policy, companies and authorities have reduced emissions. The limited published data are as follows: the concentrations of MMA in the air exhaust stack of a European plant ranged from 20-81 mg/m³ (5-19 ppm) (Schulz and Günther, 1972 as quoted in IARC, 1979).

Emissions of MMA from a European plant to the ambient air were estimated to range from 139-563 g/h during the drying of acrylic resin based paints (Schulz and Günther, 1972 as quoted in IARC, 1979).

For US-production, emission was estimated to be 1% of the total production based on data for similar processes. Approximately 0.5% was lost from the manufacturing operations, mainly from vents, condensers, valves and reactors, and the other 0.5% from manufacture of other MMA products (Patterson *et al*, 1976).

Other sources of release include emissions during transport and bulk storage operations (Patterson *et al*, 1976), and spills.

Other Sources

MMA has been found in the gaseous decomposition and incomplete combustion products of polymethyl methacrylate (polyMMA) (Forestier, 1975 as quoted in IARC, 1979).

Residual Levels in Polymers and Polymer Dispersions

The typical residual monomer content in commercial plastics is between $< 0.01\%$ and about 1% depending on the applications and manufacturing process (CEFIC, 1994). Inoue *et al* (1981) measured the migration of unpolymerised MMA from polyMMA based articles containing $0.03\text{--}1\%$ residual MMA into food simulants. Migration to water and acetic acid was not detected (detection limit 0.05 ppm). Migration of MMA into 20% ethanol (solvent extraction) was 1 ppm after 1 day and 10 ppm after 90 days.

The residual monomer content in an acrylonitrile-butadiene-MMA based lattice was reported to be $0.012\text{ }\mu\text{g MMA/g lattice}$ (Bollini *et al*, 1974). Residual MMA monomer has been reported to migrate from polyMMA hip transplants, with the highest concentrations of MMA being detected in the fatty components of bone marrow (Willert *et al*, 1973 as quoted in IARC, 1979).

Residual MMA levels in polymer dispersions are $< 0.1\%$ (Druschke, 1993).

4.2 ENVIRONMENTAL DISTRIBUTION

The relatively high value of Henry's law constant (Table 1) indicates that MMA is volatile and should evaporate from surface waters to the atmosphere.

On the basis of its vapour pressure and its low absorption to soil ($K_{oc} = 21.3, 22, 34$, see Table 1: Partition coefficient $\log K_{oc}$), MMA is expected to volatilise relatively rapidly from soil.

Using the fugacity model of Mackay and Patterson (1981), a theoretical distribution can be calculated indicating that the majority (89%) of MMA released into the environment will enter the atmosphere. Most of the remainder will be found in the water-phase, and negligible amounts in soil and sediments (Table 3).

Table 3 Estimated Distribution Between Environmental Compartments at 25°C

Compartment	%
Air	89.01
Water	10.95
Soil	0.02
Sediment	0.02
Suspended matter, aquatic	0.00
Biota	0.00

4.3 ENVIRONMENTAL FATE AND BIOTRANSFORMATION

4.3.1 Atmospheric fate

Howard *et al* (1991) calculated an atmospheric half-life of 1.1 - 9.7 hours for MMA, based on an estimated rate constant for vapour phase reactions with hydroxyl radicals and ozone in air (Atkinson, 1987).

4.3.2 Aquatic fate

From the Henry's Law constant, an average half-life of 6.3 hours can be estimated for evaporation of MMA from a water body of 1 m depth, with a 1 m/s current and 3 m/s wind speed (Lyman *et al*, 1982).

Hydrolysis is not significant at neutral or acid pH (Mabey and Mill, 1978). The hydrolysis half-life was estimated to be 3.9 years at pH 7, and 14 days at pH 9 (Ellington *et al*, 1987). These data were confirmed by Archer (1990) who found a hydrolysis half-life of 143 min at pH 11 and 1,600 days at pH 7.

The absorption maximum for MMA is 231 nm (IARC, 1979), so it cannot therefore be photolysed by radiation >290 nm. Free radicals formed in natural waters by the action of light might react with MMA, but there are no estimates of the rates of these reactions.

Adsorption to sediment or particulate matter is not expected to occur to any significant extent.

4.3.3 Terrestrial Fate

Due to its physico-chemical properties, MMA spilled onto soil will volatilise rapidly to air, and contamination of ground-water is expected to be low. Some biodegradation would be expected to occur, especially where acclimatised microorganisms exist.

Experimental work has been conducted on the metabolism of ^{14}C -MMA in soil after application at rates of 100 or 1,000 mg/kg. Sixty to 70% of the radioactivity was lost by evaporation of the parent ^{14}C -MMA at both dose levels, while 28% of the low dose and 16% of the high dose appeared to have been degraded to $^{14}\text{CO}_2$. The estimated half-life for MMA in soil was less than 1 day (Hawkins *et al*, 1993).

The adsorption of MMA to soil was investigated in 5 different types of soil, using six concentrations of ^{14}C -MMA from 0.5 to 8.9 $\mu\text{g/ml}$. The study included an adsorption cycle followed by 3 desorption cycles. Soil adsorption constants (K_{oc}) ranged from 8.7 to 72 with an average of 34. On the basis of this relatively low K_{oc} value a high mobility of MMA in soil can be expected. Once adsorbed, MMA was less readily desorbed from soil. Desorption constants ranged from 14.8 to 263 (Hardies, 1991).

4.3.4 Biodegradation

Aerobic

MMA has been reported to be significantly (>30%) degraded in the MITI-I test, which uses a mixed inoculum of soil, surface water and sewage (Sasaki, 1978). Biodegradation of MMA was up to 94% within 14 days based on the BOD (Biological Oxygen Demand) test (CITI, 1992).

The maximum biodegradation of MMA was found to be 32% after 28 days, in a Modified MITI-I test. The study was performed with a modified apparatus for volatile substances as described in Annex V part C 5.2 of Council directive 79/831/EEC (EEC, 1980), but some degree of volatilisation could not be excluded (Röhm, 1989).

In a closed-bottle test based on the consumption of oxygen, a biodegradation of 88% was achieved within 28 days (Douglas, 1992). Since 60% of the biodegradation was not reached within 10 days of passing the 10% level, MMA cannot be considered as readily biodegradable according to EEC criteria.

MMA was completely degraded by adapted soil microflora in approximately 20 hours (Slave *et al*, 1974).

In a 42-day screening study using a sewage inoculum, 42% of the theoretical BOD was consumed in 19 days, including a 3-4 day lag period; with acclimated seed inoculum, 66% of the theoretical BOD was consumed in 22 days (Pahren and Bloodgood, 1961).

The rate of biodegradation was found to be >95% in both a standard and modified Zahn-Wellens test (BASF, 1988).

A biodegradation test using immobilised microorganisms was performed by Jung *et al* (1991). The maximum rate of biodegradation was 8.2 mg/l/h for MMA. The pH decreased from 6.9 to 5.5.

In a biodegradation study using acclimated immobilised sludge in a recirculation flow reactor an initial concentration of 75 mg MMA/l was removed completely after 8 hours, while 11% of the MMA had volatilised. Biodegradation accounted for the removal of the remaining 89% of MMA. The biodegradation rate was 9.3 mg/l/h at initial MMA concentrations between 75 and 550 mg/l. Oxygen uptake was increased in the presence of MMA as compared to controls without substrate indicating oxidative biodegradation. The pH dropped from 6.95 to 6.1. The authors conclude that MMA can be biodegraded relatively easily (Jung and Sofer, 1993).

4.3.5 Bioaccumulation

No bioaccumulation potential is predicted from the *n*-octanol/water partition coefficient ($\log P_{ow} = 0.7$ to 1.38, Table 1). Using the equation $\log BCF = 0.76 \times \log P_{ow} - 0.23$ (Lyman *et al*, 1982), a theoretical bioaccumulation factor ranging from 2 to 6.59 has been estimated.

4.3.6 Evaluation

The majority of MMA released to the environment is expected to enter the atmosphere. Its atmospheric half-life is estimated to be *circa* 3 hours. Although MMA cannot be considered as readily biodegradable according to EEC criteria, it will rapidly biodegrade in the aquatic environment under aerobic conditions, abiotic hydrolysis playing only a minor role. In soils, MMA is expected either to rapidly evaporate or to biodegrade. MMA is not expected to bioaccumulate.

SECTION 5. ENVIRONMENTAL LEVELS

5.1 ENVIRONMENTAL LEVELS

5.1.1 Air

No data are available.

5.1.2 Water

Data on present levels of MMA in surface water are not available.

Historical data show that MMA has been detected in river water in the USA (concentration not stated) (Schakelford and Keith, 1976 as quoted in IARC, 1979). A concentration of 10 µg/l MMA was found in surface waters in the Chicago area and around Illinois (31 sites) from August 1975 to September 1976 (Ewing *et al*, 1977). In 9 sites at Lake Michigan, a concentration of 10 µg MMA/l was found in 1975-1976 (Konasewich *et al*, 1978). MMA has been detected in 2 water samples of the river Rhine at Maasluis in concentrations up to 0.3 µg/l (Morra *et al*, 1979).

5.1.3 Soil

No data are available.

5.2 EXPOSURE LEVELS AND HYGIENE STANDARDS

5.2.1 Non-occupational Exposure

MMA was detected in the air above surfaces freshly painted with commercial acrylic latices at levels of 0.004-0.29 mg/m³ (0.001-0.070 ppm) (Kravchenko and Chemer, 1977 as quoted in IARC, 1979) and in the indoor air of an experimental plastic dwelling (levels not specified) (Ekimova *et al*, 1969 as quoted in IARC, 1979).

5.2.2 Occupational Exposure

In a detailed study of exposure at 5 plants manufacturing polyMMA sheet, the mean 8-h TWA (time-weighted average) concentration airborne of MMA ranged from 16-360 mg/m³ (3.8-86 ppm). The highest worker exposure was 100-200 mg MMA/m³ (24-48 ppm) (Cromer and Kronoveter, 1976).

In a preliminary screen of 27 "establishments", 8-h TWA exposure levels were as follows (Table 4).

Table 4 Exposure Levels in 27 "Establishments".
(Cromer and Kronoveter, 1976)

Establishment	Concentration (8-h TWA, ppm)
Monomer production	< 5
Refining	10
Resin manufacturing	< 5
Sheet manufacturing	10-130
Reinforced sheet manufacturing	2-40
Lens manufacturing	< 1.0-10
Ornament manufacturing	20-90
Acrylic contact product	< 50
Dental laboratory	< 5-10

Popler *et al* (1985) reported workplace concentrations in block polymerisation of 150-300 mg/m³ (36-72 ppm) during prepolymerisation and mould filling and 30-80 mg/m³ (7.2-19 ppm) during other operations.

Vedel and Schwarz-Lausten (1981) have reported work place concentrations during hip replacement operations. Concentrations of 47 mg/m³ (11 ppm) were reported for mixing operations in the open air. These concentrations were reduced to 20 mg/m³ (4.8 ppm) using a special mixing box. The surgeon was exposed to 6-9 mg/m³ (1.4-2.2 ppm), the anaesthiologist to 2 mg/m³ (0.5 ppm).

Darre *et al* (1992) reported work place concentrations between 50 and 100 ppm of MMA during hip and knee replacement operations in conventional operating theatres without laminar air flow. Measurements were made in the breathing zone of the surgeons. The concentrations remained at the measured levels for a maximum of 10 minutes.

In a Japanese acrylic sheet production plant 8-h TWA work place concentrations determined by personal exposure monitoring were reported to range between 0.4 ppm and 112 ppm (Mizunuma *et al*, 1993).

The most recently available data from European industry show workplace air concentrations of < 0.2-24 mg/m³ (0.05-5.8 ppm) during MMA production, unloading, loading and processing, 0.2-260 mg/m³ (0.05-62 ppm) during maintenance, 2-320 mg/m³ (0.5-77 ppm) during polyMMA sheet production, and 2-260 mg/m³ (0.5-62 ppm) during composite production (CEFIC, 1993c).

5.2.3 Hygiene Standards

A review of current occupational exposure limit values is given at Table 5.

Table 5 Occupational Exposure Limits

Country	8-h TWA		STEL		Reference
	(ppm)	(mg/m ³) ^a	(ppm)	(mg/m ³) ^a	
Australia	100	410	-	-	ILO, 1991
Austria	50	210	-	-	DFG, 1992
Belgium	100	410	-	-	ILO, 1991
Canada	100	410	-	-	ACGIH, 1992
Denmark	75	307	-	-	ILO, 1991
Finland	100	410	150	615	ILO, 1991
Fance	100	410	200	820	INRS, 1993
Germany	50	210	-	-	DFG, 1992
Hungary	-	50 ^b	-	150 ^b	ILO, 1991
Italy	100	410	125	510	ACGIH, 1992
Netherlands	100	410	-	-	Arbeidsinspectie, 1993
Norway	25	100	-	-	Arbeidstilsynet, 1990
Poland	50	-	-	-	Pemberton, 1993
Portugal	100	410	-	-	ACGIH, 1992
Sweden	50	200	150	600	AFS, 1990
Switzerland	50	210	100	420	ILO, 1991
UK	100	410 ^c	125	510 ^c	UK-HSE, 1992
USA, ACGIH	100	410	-	-	ACGIH, 1992
USA, NIOSH	-	410	-	-	ILO, 1991
USSR	-	-	-	10	ILO, 1991

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 Ceiling value

c 10min

SECTION 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 MICRO-ORGANISMS

The threshold level for inhibition of bacterial growth (EC_3) for *Microsystis aeruginosa* was 120 mg/l after exposure for 8 days (Bringman and Kühn, 1976, 1978a,b) and for *Pseudomonas putida* 100 mg MMA/l after exposure for 16 hours (Bringmann and Kühn, 1976, 1977a, 1980b,c).

6.2 AQUATIC ORGANISMS

Single-cell organisms are not sensitive to MMA, displaying a threshold level from 178 to 556 mg/l (Table 6).

Table 6 Aquatic Toxicity to Single-Cell Organisms

Organism	Effect/parameter	Time (h)	Concentration (mg/l)	Reference
	Growth inhibition			
<i>Chilonomas paramaecium</i>	EC_3	48	178	Bringmann and Kühn, 1981
<i>Entosiphon sulcatum</i>	EC_3	72	447-450	Bringmann, 1978; Bringmann and Kühn, 1980b
<i>Uronema parduczi</i>	EC_3	20	556	Bringmann and Kühn, 1980a

The lowest toxicity value (48 h EC_{50}) for *Daphnia magna* was 69 mg/l in a flow-through acute toxicity test (Table 7).

For higher organisms, acute tests with fish show LC_{50} concentrations from 130 to 560 mg/l (Table 8).

In a fish diseases survey over a 2 year period (1988 and 1989), there was no evidence of neoplastic and chronic degeneration in livers of dab (*Limanda limanda*), either from a MMA waste disposal ground in the North Sea or from a relatively uncontaminated control site at Lyme Bay in the English Channel (ICI, 1990).

Table 7 Acute Effect Concentrations for *Daphnia magna*

Organism	Effect/parameter	Time (h)	Concentration (mg/l)	Reference
<i>Daphnia magna</i>	Immobility			
	EC ₀	24	875	Bringmann and Kühn, 1977b
	EC ₅₀	24	1,760	
	EC ₁₀₀	24	2,500	
	EC ₀	24	502	Bringmann and Kühn, 1982
	EC ₅₀	24	720	
	EC ₁₀₀	24	1,042	
	EC ₀	48	48	Burgess, 1990
	EC ₅₀	48	69	

Table 8 Toxicity to Fish

Organism	Effect/parameter	Time (h)	Concentration (mg/l)	Reference
Lethality				
<i>Leuciscus idus melanotus</i>	LC ₀	48	320	Juhnke and Lüdemann, 1978
	LC ₅₀		350	
	LC ₁₀₀		380	
<i>Carassius auratus</i>	LC ₅₀	72	550	Paulet and Vidal, 1975
<i>Carassius auratus</i>	LC ₅₀ soft water	24-96	277-423	Pickering and Henderson, 1966
<i>Carassius auratus</i>	LC ₅₀	24	420	Jensen, 1978
<i>Poecilia reticulata</i>	LC ₅₀ soft water	24-96	368	Pickering and Henderson, 1966
<i>Lepomis macrochirus</i>	LC ₅₀	96	232-357	Pickering and Henderson, 1966
<i>Lepomis macrochirus</i>	LC ₅₀ static	24-96	283	Bailey <i>et al</i> , 1985
<i>Lepomis macrochirus</i>	LC ₅₀ flow-through	24-72	264	Bailey <i>et al</i> , 1985
<i>Lepomis macrochirus</i>	LC ₅₀	96	191	Bailey <i>et al</i> , 1985
<i>Pimephales promelas</i>	LC ₅₀ soft water	24-96	130-480	Pickering and Henderson, 1966
<i>Pimephales promelas</i>	LC ₅₀ hard water	24-96	311-560	Pickering and Henderson, 1966
<i>Oncorhynchus mykiss</i>	LC ₅₀	96	>79 ^a	Bowman, 1990

a An LC₅₀ could not be calculated

The 96-h static EC₅₀ of MMA for the algae *Selenastrum capricornutum* Printz was 170 mg/l (Forbis, 1990).

Long-term data for algae are shown in Table 9. *Scenedesmus quadricauda* shows growth retardation from 37 mg MMA/l when tested during an 8 day period. The blue-green algae *Microcystis aeruginosa* is less sensitive, exhibiting an EC₃ for growth-inhibition of 120 mg MMA/l after 8 days.

Table 9 Toxicity to Algae

Organism	Effect/parameter	Time (d)	Concentration (mg/l)	Reference
Growth inhibition				
<i>Scenedesmus quadricauda</i>	EC ₃	8	37	Bringmann and Kühn, 1978a,b, 1980c
<i>Microcystis aeruginosa</i>	EC ₃	8	120	Bringmann and Kühn, 1976, 1978a,b
<i>Selenastrum capricornutum</i>	EC ₅₀ NOEL	4	170 100	Forbis, 1990

6.3 SOIL ORGANISMS

In a study on the effect of MMA on the soil carbon cycle, it was shown that MMA might have some inhibitory effect on the respiration of soil microflora in the presence of ethanol, but this effect would be "small and of no biological significance" (Hossack and Thomas, 1992).

6.4 EVALUATION

The acute toxicity of MMA to bacteria and aquatic organisms (protozoa, microcrustaceans, algae and fish) is low. There is no evidence of long-term adverse effects.

On the basis of its low aquatic toxicity, low bioaccumulation potential, volatility and biodegradability in soil and the aquatic environment under aerobic conditions, MMA is considered not to present a risk to the environment.

SECTION 7. KINETICS AND METABOLISM

7.1 HUMAN

7.1.1 Metabolism After Oral Administration

Oral administration of an aqueous solution of 94 mg of sodium (Me^2H_3) methacrylate to a human volunteer with a vitamin- B_{12} deficiency, resulted in an excretion of about 1% of the dose as (Me^2H_3)methylmalonic acid. The authors suggest that MMA metabolism in man follows the same metabolic pathway as in the rat (Crout *et al*, 1982). It should be noted that this is a very limited study.

7.1.2 Dermal Absorption

After dermal exposure of 11 dental technicians to MMA for 30 to 240 minutes (dose levels not reported), 19-200 nmoles methacrylate were excreted in the urine within 24 hours of exposure (Rajaniemi *et al*, 1989). Since there was no measurement of the exposure concentration in this study, it was impossible to make a correlation between exposure and urinary levels. Excreted methacrylate concentrations showed a wide interindividual variability and were not consistently related to exposure time. The authors state that inhalation exposure would not give the observed methacrylate urine levels, due to the usually low workplace concentrations in dental laboratories.

7.1.3 Inhalation

Methanol concentrations in blood, serum and urine samples were determined by headspace GC in samples from workers exposed to concentrations of 0.4 to 112 ppm MMA (8-h TWA). Methanol concentrations in all these biological media collected at the end of the workshift were lineary related to MMA vapour concentrations. Only 1.5% of the inhaled MMA was excreted as methanol in the urine (Mizunuma *et al*, 1993).

7.1.4 Kinetics After Arthroplasty Using MMA-Based Bone Cements

MMA was determined in blood samples of 7 patients during knee arthroplasty with polyMMA cements. Samples were collected after 0.25, 2, 10, 20 and 60 minutes. Highest blood MMA concentrations (approximately 0.2-1.6 μg MMA/ml) were observed 2-10 minutes after application of the half-cured bone cement (approximately 40 g). The levels then decreased to approximately 0.05 to 0.9 μg /ml after 60 minutes (Pfäffli and Svartling, 1985).

Maximum venous MMA blood levels in 9 patients 2 to 10 minutes after tourniquet release during knee arthroplasty ranged between 0.1 and 1.44 μg MMA/ml, with one outlier of 119.8 μg /ml (determined by headspace GC). Blood samples were taken from the inferior vena cava through a catheter. The half-life of MMA in blood was reported to be 47 - 55 minutes (Svartling *et al*, 1986a,b).

Blood samples of 69 patients, with a hip arthroplasty, receiving about 48 g of a half-cured methacrylate bone cement, were taken 10, 30, 60 and 120 seconds, 3, 4, 5, 6, 8 and 10 minutes after the implantation. Concentrations of the monomer varied widely between the patients. Maximum blood levels were obtained between 30 and 60 seconds after implantation, with mean concentrations of 0.8-1.2 μg MMA/ml. The highest concentration obtained was 16 μg /ml. In samples taken after 3 and 6 minutes no MMA could be detected (Eggert *et al*, 1974).

Samples of venous and arterial blood of 11 patients receiving joint prostheses using MMA based bone cement were taken 0.5, 1, 2.5, 2, 3, 4, 5, 6 and 7 minutes after introduction of the bone cement either into the cotyloid cavity or into the femur. The samples were analysed for MMA content by GC. After introducing the bone cement into the cotyloid cavity, venous blood levels were higher than when the bone cement was applied to the femur. Arterial blood levels were significantly lower than venous blood levels. The highest MMA concentrations in venous blood (> 1 μg /ml) were reached 1.4 minutes after exposure. The elimination of MMA followed biexponential kinetics with an initial half-life of 0.3 minutes and a terminal half-life of 3 minutes (Gentil *et al*, 1991).

Blood samples were taken from the pulmonary artery, the superior vena cava and the radial artery of 15 patients receiving MMA based bone cements during total hip arthroplasties. Samples were taken 1, 2, 3, 5 and 10 minutes after application of the cement and analysed for MMA by headspace GC. Interindividual variation of the maximum MMA concentrations was high. Maximum values were found between 1 and 2 minutes after application of the bone cement with levels ranging from 0.02 to 59.4 μg MMA/ml. Mean maximum values were 7.8 μg MMA/ml in the pulmonary artery, 4.6 μg /ml in the radial artery and 1.75 μg /ml in the superior vena cava. MMA concentrations were higher after application of the cement into the femoral cavity than after application into the acetabulum. A fall in blood pressure was noted in the first 3 minutes following the application of the bone cement and an increase in pulmonary artery pressure was noted during the first 10 minutes. There was no correlation between the concentration of MMA and either of the reported effects. Blood concentrations of MMA decreased rapidly and the differences in MMA levels of the radial and pulmonary arteries can be explained by rapid elimination of MMA via the lungs (Wenda *et al*, 1988).

MMA concentrations in the venous blood obtained from the radial artery and the superior vena cava of 4 patients undergoing hip replacement, and MMA and methacrylic acid concentrations in a further 4 patients, were determined using an isotopic dilution analysis for MMA alone or a double isotope derivative dilution analysis for both MMA and MAA. Maximum concentrations determined at 5 minutes after the application of the bone cement into the acetabular cavity ranged from 0.24 to 8.05 μg MMA/ml. Similarly, maximum concentrations, 5 minutes after the insertion of the bone cement into the femoral cavity, ranged from 0.40 to 15.1 μg MMA/ml. The mean concentrations for these 2 steps were 2.07 and 3.10 μg MMA/ml respectively. MAA, the hydrolytic demethylation product of MMA was detected with maximum concentrations of 0.04 to 3.10 and 0.7 to 6.1 μg MAA/ml respectively, the mean concentrations were 1.10 and 2.40 μg MAA/ml. Both MMA and MAA were therefore detected in significant quantities. The concentrations of MAA tended to lag behind those of MMA. The authors therefore conclude that the initial step of MMA metabolism *in vivo* is hydrolysis to MAA catalysed by nonspecific serum esterases. Neither MMA nor MAA concentrations could be correlated with intermediate reduction in arterial blood pressure during the surgery (Crout *et al*, 1979).

Between 0.9 and 11.5 mg MMA was exhaled in the expired air of patients treated with methacrylate bone cements. The authors concluded that MMA absorbed onto the blood was excreted unchanged via the lungs (Eggert *et al*, 1977).

MMA concentrations were continuously monitored in the expired air of patients receiving hip prostheses using bone cement containing MMA. The amount of exhaled MMA was dependent on the surgery technique and could be reduced by measures such as femoral shaft drainage. Exhalation rapidly followed the appearance of the monomer in the blood of the inferior vena cava within about 60 seconds, with a maximum concentration after 2 to 5 minutes. The amounts of MMA exhaled within 20 minutes varied between 0.01 mg and 5.8 mg. The authors postulate that because MMA is bound to bone marrow lipid, which is then drawn into the venous blood by the surgery, the amount of MMA cleared by the lungs during hip arthroplasty is higher than the amount detected in animal experiments after intravenous (i.v.) application (Eggert *et al*, 1980).

Other Routes

Residual MMA monomer has been reported to migrate from polyMMA hip transplants. The highest concentrations of MMA were detected in the fatty components of bone marrow (Willert *et al*, 1973 as quoted in IARC, 1979).

7.2 EXPERIMENTAL

7.2.1 Absorption, Distribution and Excretion

The tissue distribution of radioactivity after i.v. administration of 1,3- ^{14}C MMA (10 mg/kgbw, 50 $\mu\text{Ci/kg}$ in polyethyleneglycol 2,000/ethanol 1:1) to 3 male Alderley Park rats was studied by whole body autoradiography. The rats were killed at 2, 5 and 15 minutes after dosing. Irrespective of the killing time the greatest concentrations of radioactivity were determined in blood, heart, lungs, liver kidneys and salivary glands. Other tissues containing smaller amounts of radioactivity included the testes, where some of the radioactivity was located in the seminal vesicles. In this study it was not possible to determine whether the radioactivity in any of the tissues was due to the presence of MMA or its metabolites (ICI, 1983).

Oral

^{14}C -labelled MMA was readily absorbed and metabolised after gavage of 5.7 mg MMA/kgbw or 120 mg/kgbw in corn oil to male Wistar rats. Elimination of 76 - 88% of the dose as $^{14}\text{CO}_2$ was recorded within 10 days, 4.7 - 6.0% was excreted in the urine, and 2.7 - 3.0% in the faeces. The rest of the radioactivity associated with the MMA dose was retained by adipose and liver tissues, the ^{14}C being associated with the corresponding hydrolysis products and unsaponifiables (Bratt and Hathway, 1977; ICI, 1977b).

Inhalation

Tissue concentrations of MMA in blood, brain, and lungs were determined in male Sprague-Dawley rats after inhalation exposure (head/nose) with 100 ppm MMA for 1, 2, 3, and 4 hours. Independent of the exposure time, concentrations were 11.14 mg MMA/100 ml blood, 20.6 $\mu\text{g/g}$ lung and 25.24 $\mu\text{g/g}$ brain (Raje *et al*, 1985).

Parenteral Administration

After i.v. application to rabbits, MMA distribution followed the one compartment open model. MMA was rapidly absorbed, distributed and eliminated. Elimination was mainly due to its metabolism in liver and blood. No further data are available in this publication (Shi *et al*, 1988).

The MMA content of expired air was determined after i.v. administration of 1-10 mg undiluted MMA/kgbw to cats. The MMA concentration in the exhaled air increased with increasing doses of

MMA (amounts not stated). MMA first occurred in the expired air a few seconds after the administration of the monomer (Eggert *et al*, 1977).

Pulmonary excretion of MMA was studied after i.v. infusion to 7 dogs at a total dose of 0.05 ml/kgbw over a 4 minutes period. MMA levels were determined in blood and expired air. Pulmonary excretion of MMA accounted only for a maximum of 3% of the administered dose. MMA levels in the expired air were maximal within 2-4 minutes of the start of the infusion and became negligible after 7 minutes. Free MMA levels in the arterial blood, taken from the femoral artery 4 minutes after the beginning of the infusion, were similar to those in expired air. After 9 minutes no MMA could be detected in the blood (Derks *et al*, 1977).

Elimination of MMA from rabbit and dog blood, after infusion of 33 mg MMA/kgbw/min in a polyethyleneglycol-400 solution for 3 minutes, was very rapid. The half-life was less than 30 seconds in rabbit and 41 seconds in dog. The authors suggested that the fast elimination of MMA was due to hydrolysis (Paulet *et al*, 1979).

Clearance of methyl ^{14}C -methacrylate monomer from blood was determined in beagle dogs after simulated hip arthroplasty and after subsequent i.v. administration of 25, 50 or 75 mg/kgbw (vehicle not specified). Samples of arterial and venous blood were taken 30 seconds and 1, 2, 3, 4, 5, 15, 30 and 45 minutes after both applications of the radiolabelled MMA. Following hip arthroplasty, venous blood concentrations of ^{14}C -label reached a maximum of 3.5 mg/100 ml after 3 minutes and decreased to 0.7 mg/100 ml over the next 16 minutes. Only 0.5% of the total amount of implanted monomer was detected in the venous circulation and no radioactivity could be detected in the arterial blood. After i.v. administration of 25 or 50 mg/kgbw maximum arterial levels of radiolabel were found at 30 seconds, but were below the limit of detection after 3 minutes. When 75 mg/kgbw was administered, the radiolabel persisted for 5 minutes after the injection. Following administration of the 75 mg/kgbw dose, a decrease was observed in pH and arterial pO_2 and an increase in arterial pCO_2 , base deficit and haematocrit which, according to the authors, indicated disturbances such as acidosis, atriovenous shunting and respiratory depression. Additionally, pulmonary oedema developed in most dogs after administration of the 75 mg/kgbw dose. According to the authors, the clearance of MMA from blood can be attributed to pulmonary excretion and other processes involving the peripheral capillary filters (McLaughlin *et al*, 1973).

After intraperitoneal (i.p.) administration of methyl ^{14}C -methacrylate in ethanol to female Wistar rats, 80% of the radiolabel was exhaled as $^{14}\text{CO}_2$, 7-14% was excreted within 24 hours in the urine and approximately 3% was retained in tissues at this time (Crout *et al*, 1982).

Dermal Administration

After percutaneous or subcutaneous (s.c.) application to rabbits at unspecified dose levels, MMA could not be detected in the blood (Shi *et al*, 1988).

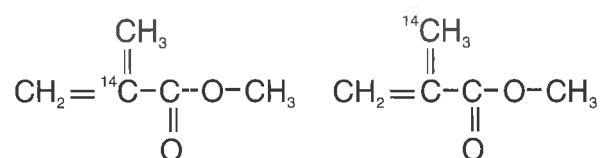
Verkkala *et al* (1983) tried to determine dermal absorption of MMA in rats by wrapping a cotton wool pad with liquid monomer on 12 cm² of proximal tail skin with an adhesive paper label. The amount of absorbed monomer was determined by weighing the pad before and after exposure and was reported to be 0.78 g after 3 hours. According to the authors, weight losses in control pads wrapped around glass rods of 0.5 cm diameter were negligible after 3 hours. However the authors did not take into consideration skin surface contamination and the elevated temperatures of the rat tails (reported to be between 28.9 and 30.5°C) which may have contributed to evaporation. The method and results seem to be highly questionable.

7.2.2 Metabolism

Oral Route

The metabolism of MMA was studied in male Wistar rats after oral gavage of MMA in corn-oil; the MMA was radiolabelled on the C₂ position or the methyl group attached to the C₂ (Figure 1) (Bratt and Hathway, 1977; ICI, 1977b).

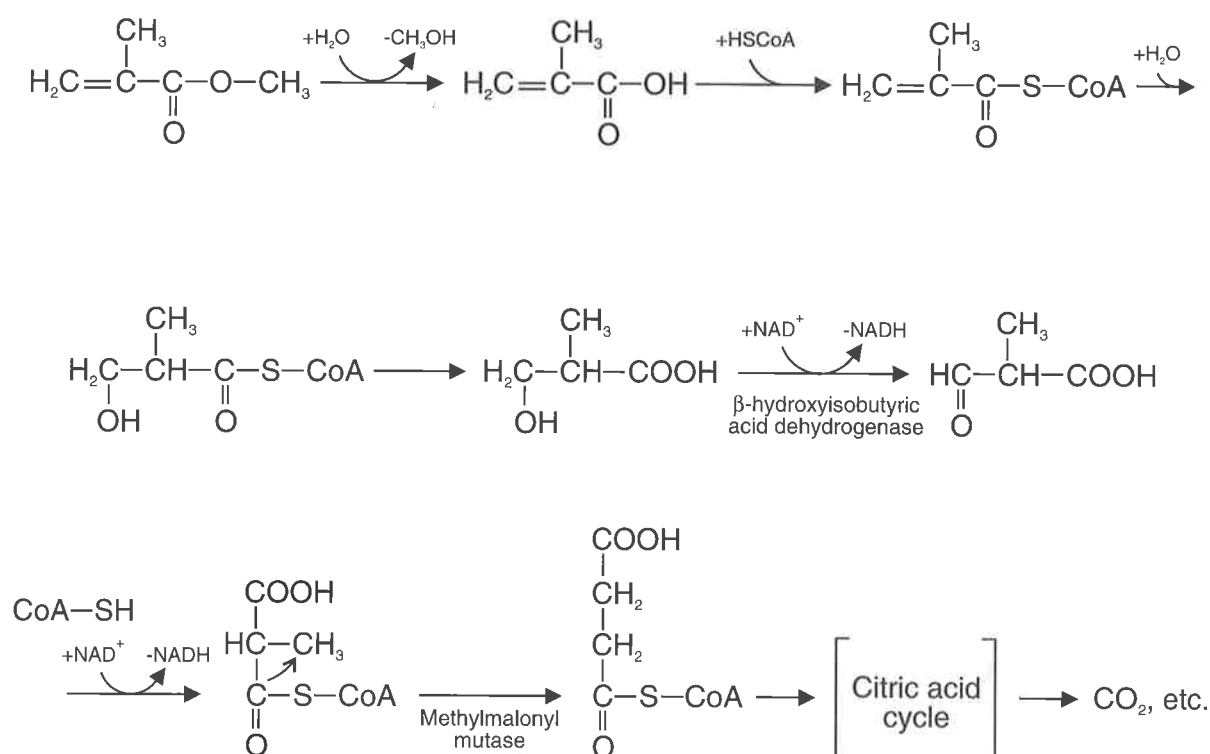
Figure 1 Position of Radiolabel in the MMA Molecule



A total of 65% of a single dose (57 mg/kgbw) of methyl(1,3-¹⁴C)propylene-2-carboxylate or a single dose (120 mg/kgbw) methyl(2-¹⁴C)propylene-2-carboxylate was exhaled as ¹⁴CO₂ within 2 hours of administration and 76-88% was exhaled within 10 days. Pulmonary excretion of unchanged MMA accounted for less than 1% of the dose in the case of methyl(1,3-¹⁴C)propylene-2-carboxylate and for 1.4% of the dose of methyl(2-¹⁴C)-propylene-2-carboxylate. Approximately 50% of the remaining dose was excreted in urine the remainder being retained in body tissues after 10 days. The elimination pattern did not differ significantly with the dose, but MMA was metabolised more slowly at the higher dose.

The following ^{14}C -containing metabolites were identified in the urine of rats treated with methyl(1,3- ^{14}C)propylene-2-carboxylate: methacrylic acid (0.8% of the dose), methylmalonic acid (1.1%), succinic acid (0.2%), 2 minor metabolites co-eluting with β -hydroxyisobutyric acid and formyl-2-propionic acid (methylmalonic semialdehyde). ^{14}C -urea (2%) and $\text{H}^{14}\text{CO}_3^-$ were assumed to be derived from $^{14}\text{CO}_2$. The authors conclude that MMA is metabolised via physiological pathways and enters into the citric acid cycle via methylmalonyl-CoA and succinyl-CoA which is a part of the valine pathway (Figure 2).

Figure 2 Main Metabolic Pathway of MMA (after ICI, 1977b; Bratt and Hathway, 1977)



Parenteral

After a single i.v. administration to male Wistar rats of methyl(1,3- ^{14}C)propylene-2-carboxylate (5.7 mg/kgbw) or methyl(2- ^{14}C)-propylene-2-carboxylate (6.8 mg/kgbw) in ethanol, the metabolism and excretion of ^{14}C -labelled MMA were qualitatively the same as after oral administration (Bratt and Hathway, 1977; ICI, 1977b).

These results were corroborated by the studies of Crout *et al* (1982), who found similar distribution patterns after i.p. administration of ^{14}C -labelled MMA in ethanol to female Wistar rats. The authors showed, that specifically labelled MMA was converted into methylmalonic acid labelled in the

corresponding position and that 97% of the radioactivity retained in adipose tissue was contained in the fatty acid fraction.

Intraperitoneal application of a bolus of 730 mg MMA/kgbw to female Chester Beaty rats resulted in a decrease of liver glutathione (GSH) levels of 8% after 30 minutes and 32% after 2 hours (Boyland and Chasseaud, 1970). Delbressine *et al* (1980; 1981) studied the formation of thioether conjugates after i.p. administration of MMA to female Wistar rats with and without pretreatment with tri- α -tolyl phosphate (TOTP), an inhibitor of tissue esterases. After a single dose of 0.14 mmol/kgbw in arachis oil, thioether excretion did not differ significantly from that of controls. After pretreatment with TOTP (0.34 mmol/kgbw in arachis oil) 18 hours prior to MMA application, 11% of the administered dose was excreted as thioether within 24 hours. The excreted metabolite was identified as N-acetyl-S-(2-carboxypropyl)cysteine. The authors concluded that there may be a competition between detoxification by esterase reaction and GSH conjugation.

These results are corroborated by studies of Elovaara *et al* (1983). Following i.p. administration of 1,000 mg MMA/kgbw in olive oil on 3 consecutive days to male Wistar rats no significant effects were seen on liver and kidney GSH levels 1, 5 or 12 days after the last injection. After i.p. administration of a single dose of 2,000 mg MMA/kgbw, a decrease in GSH levels was reported 3 hours after administration (20% of control in liver and 48% of control in kidney). Thereafter, GSH gradually increased to levels of 1.2 to 1.3 fold of controls after 12 and 24 hours. At both dose levels, transient effects on other liver enzymes (reduced activities of NADPH cytochrome-c reductase and monooxygenases), but no changes in total cytochrome P-450 levels or viability of liver cells were observed. In kidneys, after repeated administration of 1,000 mg MMA/kgbw an initial decrease of cytochrome P-450 levels was followed by increased levels at day 12.

The influence of different i.p. doses of MMA on the distribution of cytochrome P-450 isoenzymes in mouse liver microsomes was studied by Nilsen *et al* (1978). In mice receiving a low dose of MMA (60 mg/kgbw in corn oil on 4 consecutive days), a cytochrome P-450 form with a molecular mass (MW) of 47,000 (MLvMcP-450₄₇), identified by SDS-polyacrylamide gel electrophoresis, was increased, while it was totally depressed in animals receiving 4 doses of 600 mg MMA/kgbw. The same cytochrome P-450 was decreased after administration of 80 mg phenobarbital/kgbw. Corn oil controls containing the stabiliser hydroquinone showed a significant decrease in cytochrome P-450 concentration in comparison to saline treated controls. Thus the effect of the solvent was more marked than that of MMA and the study seems to be of limited relevance. MMA treatment did not alter the overall cytochrome P-450 content of mouse liver microsomes.

Inhalation

The effect of inhaled MMA vapours on pentobarbital induced sleeping time in male ICR mice was studied by Lawrence and Autian (1972). After inhalation of 164.2 mg MMA/l (39,400 ppm) for 2.7, 5.4, and 13.5 minutes (0.1, 0.2, 0.5 of the LT_{50}) for 3 days the mice were treated with a standard dose of sodium pentobarbital 24 hours after the last exposure. Control animals were treated similarly receiving air exposures prior to sodium pentobarbital treatment. MMA treatment resulted in a dose related increase in pentobarbital sleeping time compared to the controls. From this, the authors concluded that MMA may interact with drug metabolising enzymes.

Deposition of MMA vapours in the surgically isolated upper respiratory tract (URT) of urethane anaesthetised male F344 rats was studied after inhalation of 90, 437 or 2,262 mg MMA/m³ (22, 105 or 543 ppm) for 60 minutes. Two inspiratory flow conditions were used: constant velocity unidirectional flow or cyclic flow. Uptake of MMA by the URT was determined in rats without pretreatment and with bis-nitrophenylphosphate (BNPP, an carboxylesterase inhibitor) pretreatment, to determine the influence of metabolic ester hydrolysis by the nasal carboxylesterases. Tissue non-protein sulphhydryl (NPSH) levels, albumin and total protein concentrations after nasal lavage, indicative of mucous hypersecretion, cytotoxicity with leakage of intracellular materials and/or increased transudation of blood proteins, were determined after the exposure period. URT deposition efficiencies of the rats without pretreatment averaged 10-20% under both flow conditions suggesting that MMA deposits with 10-20% efficiency in normally breathing rats. Deposition of MMA was less efficient at the high than at the low and mid exposure concentrations. BNPP-pretreatment significantly reduced URT MMA deposition by 2-8% under both flow regimens suggesting that MMA is hydrolysed by carboxylesterase in nasal tissues and such metabolism serves to enhance its deposition efficiency. Significantly reduced nasal tissue NPSH content (approximately 30%) was observed only in the high concentration group, both with and without BNPP pretreatment under both flow conditions. In a similar study with methacrylic acid at a concentration of 1,385 µg/l (387 ppm), no reduction of NPSH levels was observed. Therefore it may be concluded that the intact ester rather than the acid metabolite reacts with NPSH at high concentrations. MMA inspiration had no significant effect on nasal lavage total protein and a slight increase in nasal lavage albumin content was regarded by the authors as a by chance finding (Morris, 1992).

7.3 IN VITRO STUDIES

7.3.1 Studies in Human Tissue Preparations

Ward and Heylings (1993) conducted a skin absorption study with MMA using heat separated human epidermis and a static diffusion cell model. Integrity of the skin samples was assessed by measurement of the permeability for tritiated water with abnormally permeable skin samples being discarded prior to the experiment. For the experiments, samples of $10 \mu\text{l}/\text{cm}^2$ ($9,430 \mu\text{g}/\text{cm}^2$) undiluted MMA (purity 99.93% w/w) were directly applied to the epidermal membranes. Half of the membranes were kept under occlusion for the duration of the exposure (30 hours), the other half being unoccluded. Ethanol 50% (v/v) in water was used as receptor vehicle and the temperature was maintained at 30°C . Penetration of MMA through the skin samples was assessed by determining MMA concentration (using GLC analysis) in samples taken from the receptor chamber at recorded time intervals. Absorption of MMA under both the occluded and unoccluded conditions was detected 10 minutes after application. During this period the amounts of MMA absorbed from both applications were similar (0.047% from the occluded application and 0.036% from the unoccluded application). Linear absorption versus time plots were obtained between 20 minutes and 1 hour under occluded conditions and between 10 and 30 minutes under unoccluded conditions. Absorption rates during these periods were calculated to be $274 \mu\text{g}/\text{cm}^2/\text{h}$ under occluded and $107 \mu\text{g}/\text{cm}^2/\text{h}$ under unoccluded conditions. After these periods, the rates of absorption slowed to give average absorption rates of $152 \mu\text{g}/\text{cm}^2/\text{h}$ and $3.48 \mu\text{g}/\text{cm}^2/\text{h}$ over the 0-10 hour period under occluded and unoccluded conditions respectively. After 1 hour, 2.41% of the dose had been absorbed under occluded conditions and 0.48% of the dose had been absorbed under unoccluded conditions. After 10 hours absorption was 15% of the dose under occluded conditions and only 0.56% of the dose under unoccluded conditions. The data obtained in the study indicate that MMA can be absorbed through human skin, absorption being enhanced under occluded conditions. Under unoccluded conditions only a small amount of the applied dose penetrated the skin suggesting that evaporation from the surface of the skin is a significant factor when assessing the amount of MMA that could be absorbed in any given human exposure scenario.

Following addition of MMA ($0.184 \mu\text{l}/\text{ml}$) to human blood, concentrations in blood cells were twice as high as plasma concentrations. Disappearance from plasma was very rapid, while the rate constant in the cells was about 10 times lower. The half-life of MMA in whole blood was determined to be 3 hours at 20°C (Rijke *et al*, 1977).

MMA was quantitatively hydrolysed to methanol within 4 hours after incubation of 471 µg MMA with 2 ml of human whole blood or serum at 37°C (Mizunuma *et al*, 1993).

Blood samples from 10 individuals were incubated with 10 µg ¹⁴C-labelled MMA/ml at 37°C for 90 minutes. The disappearance of MMA from human blood followed pseudo first-order kinetics. Half-lives varied from 18 to 40 minutes. No correlation between the value of the half-life and the age or sex of the blood donor could be discerned from these results. After 90 minutes the amount of ¹⁴C-MMA accounted for 40% of the initial dose. The authors suggested that the disappearance of MMA from human blood was due to enzymatic hydrolysis to MAA and methanol (Corkill *et al*, 1976).

Distribution of ¹⁴C-MMA between plasma and erythrocytes in human blood was determined by Eggert *et al* (1974) and the ratio was calculated to be 1:1.4.

7.3.2 Studies in Animal Tissue Preparations

Pantuček (1969) studied the *in vitro* metabolism of MMA using liver slices of male Wistar rats. Some of the preparations were preincubated with inhibitors of certain steps of the citric acid cycle, arsenite (1 mM) or malonate (10 mM). Metabolism of MMA was compared to that of the natural intermediate of the citric acid cycle, fumarate and found to be very similar. As malonate was not found to inhibit MMA metabolism, but arsenite inhibited it very effectively the authors concluded that MMA is metabolised via pyruvate, rather than succinyl-CoA.

Cytochrome P-450 binding spectra of MMA in rat liver microsomal preparations revealed a type I spectrum. Furthermore, the binding of dimethylaniline, a typical type I substrate to cytochrome P-450, was inhibited by prior addition of MMA to the incubation medium. Substances yielding type I binding spectra are probably bound to a substrate binding site in a hydrophobic region of the cytochrome protein. Binding of a type I substrate results in a change of the equilibrium between the high spin and low spin state of the porphyrin iron complex, by favouring the high spin state and thus facilitating the oxidation of the substrate. Therefore substances leading to type I spectra are normally considered to be substrates of the cytochrome P-450 dependent monooxygenases (Kotlovskii *et al*, 1985).

MMA was incubated with rat liver microsomes containing a standard cofactor solution with a NADPH generating system for 5 minutes. Methanol was determined in the supernatant by GC and formaldehyde content was determined photometrically after reaction with NASH-reagent. After the incubation, methanol and formaldehyde concentrations were higher than in controls incubated with

inactivated microsomes. The authors concluded that formaldehyde formation was due to methanol oxidation as the incubation of butylmethacrylate and MAA under the same conditions did not yield formaldehyde (Kotlovskii *et al*, 1988).

Following the addition of 0, 2, 5, and 10 mM MMA to isolated rat hepatocyte preparations and incubation for 2 hours at 37°C, a concentration and time dependent depletion of reduced glutathione (GSH) in the cells was observed. A minimum GSH content was reached after 30 minutes incubation. GSH levels then returned to normal, the time required being a function of the MMA concentration. After 2 hours the concentration-related GSH depletion was still observable. The viability of the hepatocytes, monitored by the integrity of the plasma membrane, was not impaired by MMA treatment. MMA had no effect on the content of cytochrome P-450 haemoprotein of the cells (Elovaara *et al*, 1983).

In contrast, MMA (1 mM or 5 mM) did not react with GSH (2 mM) in phosphate buffer (pH 6.5) when incubated with 25% rat liver supernatant for 1 or 3 hours. The enzyme glutathione-S-epoxide transferase was not active in the presence of MMA as determined by GSH loss. Although a separate enzyme in rat-liver supernatant, catalysing the reaction of α,β -unsaturated compounds with GSH could be identified, this enzyme did not catalyse the reaction of MMA with GSH (Boyland and Williams, 1965; Boyland and Chasseaud, 1967).

Rate constants for the reaction of MMA with GSH (pH 7.4, 37°C), with cellular GSH in rat red blood cells (pH 7.4, 37°C, 1 h) and for the enzymatic hydrolysis with porcine liver esterase (pH 8.0, 37°C, 20 min) were determined by McCarthy and Witz (1991). The second order rate constant for the spontaneous reaction of MMA with GSH was determined to be 0.325 l/mol/min. The rate constant for methylacrylate was 52.0 l/mol/min, i.e. methyl acrylate reacted 160 times faster than MMA. The ester concentration required to deplete 20% of rat red blood cell GSH (EC_{20}) was 2.5 mM for MMA and 0.063 mM for methyl acrylate. Rate constants for the enzymatic hydrolysis of MMA and methyl acrylate did not differ significantly (values not given in the paper). Thus α -methyl substitution does not seem to significantly affect enzymatic hydrolysis.

The second order rate constant for the reaction of MMA with GSH at pH 7.3 and 37°C was 0.17 l/mol/min (Hashimoto and Aldridge, 1970).

Rate constants of the reaction of acrylates and methacrylates with GSH were also determined by Tanii and Hashimoto (1982). The rate constant for MMA was 0.21 l/mol/min and for methyl acrylate 40 l/mol/min.

Binding constants of methacrylates and acrylates to bovine serum albumin (BSA) increased with increasing esters lipophilicity, $\log K$ versus $\log P_{ow}$ following a parabolic relationship. The $\log K$ for MMA was approximately 2.02 (Fujisawa and Masuhara, 1980).

7.4 SUMMARY

After oral or inhalation administration, MMA is rapidly absorbed and distributed. *In vitro* skin absorption studies in human skin indicate that MMA can be absorbed through human skin, absorption being enhanced under occluded conditions. However, only a very small amount of the applied dose (0.56%) penetrated the skin under unoccluded conditions. Furthermore in the light of low acute systemic toxicity after dermal exposure of rabbits (Table 12: Spealman *et al*, 1945), dermal absorption seems to be of minor importance when considering possible toxic effects.

Kinetics and metabolism seem to be similar in man and experimental animals. The elimination of MMA was found to be dependent on the route of administration. During arthroplasty, using MMA-based cements, pulmonary exhalation of the unchanged ester seems to be a major elimination pathway, while after i.v, i.p. or oral administration metabolism plays a far more important role. After inhalation exposure to rats, 10 to 20% of the compound is deposited in the upper respiratory tract where it is metabolised by local tissue esterases and, to a minor extent, by conjugation with tissue NPSH. Nevertheless, activities of local tissue esterases of the nasal epithelial cells may be lower in man than in rodents (Section 8.5.5). After oral or parenteral administration, rapid hydrolysis to methacrylic acid and methanol has been observed. The hydrolysis products are further metabolised by physiological pathways. Methacrylic acid is metabolised via methylmalonyl-CoA and succinyl-CoA, which are substrates of the citric acid cycle, with the majority of the administered dose being exhaled as CO₂. Methanol appears to be further metabolised by liver cytochrome P-450 dependent pathways. Conjugation with GSH or NPSH plays a minor role in MMA metabolism and only occurs at high tissue concentrations. Because of the steric influence of the α -methyl-group rate constants for conjugation and reactions with cellular nucleophiles are very low. Both metabolic pathways lead to a rapid detoxification of the compound.

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

8.1 ACUTE TOXICITY

8.1.1 Oral

MMA is of very low toxicity when administered via the oral route with LD₅₀ values of well above 5 g MMA/kgbw (Table 10).

Table 10 Acute Oral Toxicity

Species	LD ₅₀ (g/kgbw)	Reference
Rat	9.4	Spealman <i>et al</i> , 1945
	7.9	Deichmann, 1941
	8.0	Litchfield, 1978 as quoted by ACGIH, 1986
	8.5	Ouyang <i>et al</i> , 1988
Mouse	5.3	Lawrence <i>et al</i> , 1974
	5.2	Tanii and Hashimoto, 1982
	5.2	Schwach and Hofer, 1978
Rabbit	6.0	ACGIH, 1986
Guinea pig	5.9	Spealman <i>et al</i> , 1945
	5.9	Blagodatin <i>et al</i> , 1970 as quoted by DFG, 1984
Dog	4.7	Spealman <i>et al</i> , 1945

Following oral administration of MMA to rats and rabbits, Deichmann (1941) reported irregular and laboured respiration, increased defecation and urination, and a loss of reflex activity prior to death; blood was reported in the urine of some of the animals. Mallory *et al* (1973) investigated the effect of a single direct oesophageal installation of MMA to groups of Swiss white mice and reported mild to moderate hepatotoxic changes. No gross liver changes were observed in mice treated with MMA at 6% in olive oil although in a small percentage of the animals, minor changes in liver cell size and structure were noted. Mice treated with MMA at 11% in olive oil demonstrated evidence of central and mid-zonal fatty changes with central lobular alteration while those mice treated with MMA at 15-20% in olive oil exhibited massive fatty infiltration with alteration and disruption of the liver nuclei.

In groups of 3 male rats dosed with MMA at 0, 0.05, 0.5 or 5 g/kgbw no deaths were observed over a 14 day observation period. No adverse clinical signs were recorded in the control animals or those dosed with MMA at 0.05 or 0.5 g/kgbw. Some of the rats dosed with MMA at 5 g/kgbw were

observed to the exhibiting passiveness, scant faeces, alopecia and red stained muzzle (Rohm and Haas, 1982).

Acute oral toxicity data from which LD₅₀ values could not be calculated are detailed in Table 11.

Table 11 Acute Oral Toxicity

Species	Dose (g/kgbw)	Lethality	Reference
Rat	7.5-15.0	Yes	Lawrence <i>et al</i> , 1974
	0.5-5.0	None	Rohm and Haas, 1982
Rat	8.5-9.4	Yes	Du Pont, 1937 ^a
Mouse	0.3	20%	Mallory <i>et al</i> , 1973
Rabbit	<6.5	None	Deichmann, 1941

a Reported as 9-10 ml/kgbw

8.1.2 Dermal

No mortality was reported following dermal exposure to high doses of MMA (Table 12).

Table 12 Acute Dermal Toxicity in the Rabbit

Application	Dose (g/kgbw)	Lethality	Reference
Unoccluded	37.5	None	Spealman <i>et al</i> , 1945
	18.8	None	Spealman <i>et al</i> , 1945
Occluded	7.5	None	Lawrence <i>et al</i> , 1974
	5.0	None	Rohm and Haas, 1982
Not stated	>9.4	None	Autian, 1975

Spealman *et al* (1945) reported no lethality in rabbits dermally exposed to MMA at 18.8 or 37.5 g/kgbw although skin irritation and signs of temporary central nervous system depression were observed. As this appeared to have been conducted under unoccluded conditions, the latter effect may have been due to inhalation exposure to MMA. Lawrence *et al* (1974) reported no lethality in rabbits after occluded application of 7.5 g MMA/kgbw to rabbits.

Groups of 2 male rabbits were treated dermally with MMA at dose levels of 0.2, 2 and 5 g/kgbw under occluded conditions for 24 hours. No signs of systemic toxicity were observed during a

subsequent 14 day observation period and no gross changes were observed at necropsy (Rohm and Haas, 1982).

8.1.3 Inhalation

Details of acute inhalation studies in a variety of species are in Tables 13 and 14. Additional observations are given below.

Table 13 Acute Inhalation Toxicity (LC₅₀ Values)

Species	Time (h)	LC ₅₀ (ppm)	Reference
Rat	2	10,800-16,800 ^a	Rohm and Haas, 1958
	4	7,093	Tansy <i>et al</i> , 1980c; Oberly and Tansy, 1985
Rat	<8	3,760	Deichmann, 1941
	Unknown	10,910	Ouyang <i>et al</i> , 1988
	2	11,250-12,500	Borzelleca <i>et al</i> , 1964
Mouse	3	13,200	Spealman, 1945
	Unknown	7,416	Ouyang <i>et al</i> , 1988

a Reported as 45-70 mg/l

Deichmann (1941) reported that all rats, rabbits and guinea pigs died after a 5 hours exposure to 4,600 ppm MMA. The effects observed were the same as those following oral administration of MMA. In addition, there was marked irritation of the mucous membranes. Spealman *et al* (1945) reported that in all mice, guinea pigs and 2 dogs that died when exposed to a sufficiently high concentration of MMA, the clinical signs observed were respiratory system depression preceded by ataxia. Pathological changes manifest by swelling and degeneration in the liver and kidneys as well as congestion, haemorrhages, oedema and emphysema in the respiratory tract were observed following exposure to lethal MMA concentrations. No haematological effects were seen (Deichmann, 1941; Spealman *et al*, 1945).

Kessler *et al* (1977) reported that accidental inhalation of MMA (at an unknown concentration) by a rhesus monkey (*Macaca mulatta*) for a period of 22 hours resulted in a comatose condition followed by death. At necropsy, mottled liver, pulmonary oedema and atelectasis and a clear yellow liquid in the thoracic cavities were observed.

Exposure of rats at 11.2 mg MMA/l (2,700 ppm) for a period of 8 hours resulted in slight upper respiratory tract irritation, whereas following exposure at 16 mg/l (3,800 ppm), gastro-intestinal irritation, slight dyspnoea and increased excretion were observed (Du Pont, 1937).

Table 14 Acute Inhalation Toxicity Data

Species	Time (h)	Concentration (ppm)	Lethality (%) or parameter	Reference
Rat	1	9,800-17,800 ^a	0	Kelly, 1993
	1	400	0	Innes, 1979
	4	4,632	0	NTP, 1986
	4	16,000	100 (♂)	NTP, 1986
	4	16,000	80 (♀)	NTP, 1986
	5	4,600	100	Deichmann, 1941
	8	1,200	0	Deichmann, 1941
	8	7,200-7,900 ^b	70	Du Pont, 1937
Mouse	3	6,290 ^c	5	Spealman <i>et al</i> , 1945
	3	11,450 ^d	13	Spealman <i>et al</i> , 1945
	3	14,830 ^e	100	Spealman <i>et al</i> , 1945
	5	11,450 ^d	60	Spealman <i>et al</i> , 1945
	4	4,632	0	NTP, 1986
	4	16,000	100	NTP, 1986
	2	3,600-4,800	Min LC	Karpov, 1954a,b
Mouse	N/A	27,650	56 min LT ₅₀	Lawrence <i>et al</i> , 1974
Guinea pig	4.25	17,300 ^f	100	Spealman <i>et al</i> , 1945
	5	4,600	100	Deichmann, 1941
	8	4,200	0	Deichmann, 1941
Rabbit	3.5	4,560	100	Deichmann, 1941
	4.5	4,200	100	Deichmann, 1941
	5	4,600	100	Deichmann, 1941
Cat	N/A	3,600-4,800	0	Karpov, 1954a,b
Dog	1.5	17,300 ^f	100	Spealman <i>et al</i> , 1945
	3	9,890 ^g	100	Spealman <i>et al</i> , 1945

a-g Reported as: a, 41-74 mg/l; b, 30-33 mg/l; c, 26.2 mg/l; d, 47.7 mg/l; e, 61.8 mg/l; f, 72.1 mg/l; g, 41.2 mg/l

The NTP (1986) reported clinical signs including hypoactivity, dyspnoea and anaesthetic effects in mice and rats exposed to MMA at 16,000 ppm. No effects on body weight or gross necropsy were observed.

Raje *et al* (1985) reported lung damage including interalveolar congestion, haemorrhage, pulmonary vasodilation and oedema in rats following exposure to MMA at 100 ppm for 2, 3 or 4 hours but not following exposure to MMA at 100 ppm for 1 hour. The lung damage reported at 100 ppm in this study was not seen in other studies including repeated exposure to MMA at higher concentrations, such as those described by Tansy (1980a, b) (Section 8.3.3).

Castellino and Colicchio (1969) reported that mice exposed to MMA for 60 minutes at concentrations of 20 g/m³ (4,800 ppm) survived the period of exposure and did not exhibit any toxic effects over a 15 days period following exposure. Mice exposed to MMA at 30 g/m³ (7,200 ppm) for a period of 60 minutes survived, but soon after exposure adynamia, muscular hypotonia and moderate hyporeflexivity occurred and then subsided within 2-3 hours post-exposure. At

40 g MMA/m³ (9,600 ppm), 1 mouse died within 24 hours and a further 2 died on the 4th and 7th day respectively, after exhibiting similar clinical signs to the animals exposed at the lower concentrations.

Other Inhalation Studies

A number of other studies on MMA resulted in a range of non-lethal effects including biochemical changes.

Dipietro *et al* (1976) reported that exposure of rats up to 23,000 ppm MMA for 1 hour resulted in a decrease in serum lipids. Dorofeeva *et al* (1978b) reported an increase in arterial blood pressure and an adrenalin like substance in the blood of rats following exposure to 1/5 and 1/20 of the LD₅₀ (unspecified).

A decrease in gastrointestinal motor activities was reported in rats exposed to nominal concentrations of 93.6 mg MMA/l (22,500 ppm) for 15 minutes, 9.4 mg/l (2,260 ppm) for 15 minutes and 1 mg/l (240 ppm) for 60 minutes by Tansy *et al* (1973, 1974). Tansy *et al* (1975) observed a transient drop in arterial pressure and a marked inhibition of ongoing gastrointestinal motor activities in a dog exposed to 2,000 ppm MMA for an unspecified period of time. Tansy *et al* (1977) exposed 12 dogs to 2,000 ppm MMA and reported a decrease in tonus and contractile activity of the gastric antrum and the small bowel within 10 minutes of exposure. Innes *et al* (1979) and Innes and Tansy (1981) reported a reversible decrease in brain activity in rats exposed by inhalation to 400 ppm MMA for 1 hour. In later experiments, multi-unit electrical activity of the lateral hypothalamus and ventral hippocampus decreased at concentrations of 100 ppm MMA and above in rats exposed to 50, 100, 200, 400 or 800 ppm MMA for 60 min (Innes and Tansy, 1980; Innes, 1988). MMA inhibited conditioned reflexes in mice exposed to more than 1,200 ppm MMA for 2 hours (Karpov, 1955a,b).

Moderate weight loss and signs of respiratory tract irritation were seen in rats exposed to 41 or 74 mg MMA/l (9,800-17,800 ppm) for 1 hour (Kelly, 1993).

8.1.4 Other Routes

Acute toxicity studies have been conducted on MMA using the s.c., i.p. and i.v. routes of administration. These data have been reviewed but it is considered that the routes of exposure are not relevant to the assessment of the acute toxicity of MMA and therefore these studies are not used in this report.

8.1.5 Summary

MMA has been studied extensively in acute toxicity tests. It is of low oral, dermal and inhalation toxicity and is not absorbed in lethal quantities through the skin, even under occluded conditions which overpredict human occupational exposure. A number of inhalation studies have shown a range of non-lethal effects involving irritation of the upper respiratory tract, the nervous system and some biochemical effects, the latter appearing to be of minor relevance.

8.2 SKIN, RESPIRATORY TRACT AND EYE IRRITATION, SENSITISATION

8.2.1 Skin Irritation

MMA has been reported to be a mild skin irritant. Spealman *et al* (1945) reported skin irritation in rabbits dermally exposed at 18.8 or 37.5 g MMA/kgbw under apparently unoccluded conditions. Deichmann (1941) reported only temporary local irritation following treatment of rabbits with a cutaneous dose of 9.4 g MMA/kgbw.

Groups of 2 male rabbits were treated dermally with MMA at doses of 0.2, 2 or 5 g/kgbw under occluded conditions for 24 hours. Well-defined to severe erythema with blanching and moderate to severe oedema with pocketing were observed at 24 hours. The skin irritation was still present at day 14 in the animals treated at 2 or 5 g MMA/kgbw but was not present after day 3 in the animals treated at 0.2 g/kgbw. Eschar was observed at day 2 in animals treated at the 2 or 5 mg/kgbw dose levels and some eschar was observed to be sloughing off with new hair growth on the underlying skin at day 12 in animals dosed at 2 or 5 g/kgbw. Desiccation was also observed after day 4 in animals treated at all 3 dose levels (Rohm and Haas, 1982).

A group of 2 male rabbits were treated with 0.5 ml of undiluted MMA on closely clipped intact skin under occluded conditions for a 4 hour period and observed for 7 days. One of the rabbits exhibited erythema 72 hours after treatment and dessication at the 7 day observation time. The other rabbit exhibited erythema and oedema from 0.5 hours to 7 days. At the 24 and 72 hours and 7 days observation time the erythema was accompanied by blanching and eschar. Based on these observations the authors concluded that MMA was "moderately irritating" to the skin of rabbits (Rohm and Haas, 1982).

Ouyang *et al* (1988) reported MMA as moderately irritating to rabbit skin but experimental details were not provided in the abstract.

Castellino and Colicchio (1969) reported that daily painting of areas of shaved rabbit skin with 5 ml MMA for a total of 15 applications did not produce any phlogistic reaction. It was also reported

that the shaved skin had superficial small abrasions at the edges prior to treatment with MMA and subsequently light exudative and reactive phenomena (erythema, desquamation) with successive hyperkeratosis reactions were observed which generally subsided within 3-4 days after the last application.

In a Draize test in rabbits with a 24 hour occlusive application of 0.5ml undiluted MMA to scarified or non-scarified skin, no irritation was reported (Röhm, 1977; also cited by Cavelier *et al*, 1981). The Draize index was 0.29 out of 8. Only slight, reversible erythema was observed in rabbits with scarified skin.

Rats (number not specified) were treated dermally with MMA at a dose level of 1 ml/d for a period of 10 weeks (occluded or unoccluded not specified). Oedema was observed from weeks 6-9 but there was no effect on hair growth (Du Pont, 1937).

Kanerva and Verkkala (1986) reported that prolonged exposure of rat tail skin to MMA caused effects on epidermal cells as shown by electron microscopy (EM). Wistar rat tails were exposed to MMA 3 hours daily over a period of 8 weeks. EM showed enlargement of the intracellular spaces (spongiosis) with fine granular substance, keratinocytes with vacuoles, oedema, distorted cristae in mitochondria and pycnotic nuclei. Focal cytolysis and oedema were observed in all layers of the epidermis. The results showed that MMA caused a local irritant effect.

Kanerva and Lauharanta (1986), in an abstract, reported that MMA caused spongiosis of the epidermis of rodent (unspecified) skin.

The reaction of oral mucous membranes to MMA was studied in 11 adult mongrel dogs. The material was applied bilaterally to a specific area of the ventral surface of the tongue of the anaesthetised dogs for 5 minutes. The area was observed after 30 minutes. and microsections were examined histologically after 24 hours. Application of MMA resulted in an immediate surface dehydration and mild erythema. In some animals, the histological examination of the tissue revealed mild local inflammatory infiltration (Lilly *et al*, 1972).

8.2.2 Respiratory Tract Irritation

Spealman *et al* (1945) reported ataxia and respiratory system depression prior to death in mice, guinea pigs and dogs exposed to MMA at 11,600, 17,600 and 10,000 ppm respectively for 1.5 to 5 hours. Oedema and emphysema in the respiratory tract were also observed following exposure to these lethal concentrations of MMA.

Exposure of rats to 11.2 mg/l (2,690 ppm) MMA for a period of 8 hours resulted in very slight upper respiratory tract irritation and dyspnoea (Du Pont, 1937).

Raje *et al* (1985) reported lung damage including interalveolar congestion, haemorrhage, pulmonary vasodilation and oedema in rats following exposure to MMA at 100 ppm for 2, 3 or 4 hours but not for 1 hour. The lung damage reported at 100 ppm in this study was not seen in other studies including repeated exposure to MMA at higher concentrations, such as those described by Tansy *et al* (1980a,b) (Section 8.3.3).

An inhalation sensory irritation study (RD_{50}) in mice was reported by Stadler (1993). Exposures of groups of 4 male Swiss Webster mice with 740 to 33,000 ppm MMA did not decrease respiratory frequency below 25% of the controls. Respiratory irritation only occurred briefly at the beginning of exposure in some of the animals. No RD_{50} value could be calculated. MMA was therefore considered not to be a respiratory irritant in this study.

8.2.3 Gastro-intestinal Tract Irritation

Exposure of rats to 16 mg/l (3,800 ppm) MMA for a period of 8 hours resulted in symptoms of gastrointestinal irritation (increased bowel movement) (Du Pont, 1937).

8.2.4 Eye Irritation

Spealman *et al* (1945) showed that irritation of the rabbit eye, caused by the installation of MMA, resolved within 72 hours.

Undiluted MMA (0.1 ml) was instilled into the cornea of 2 male rabbits which were observed over a 7 day period. Only slight eye irritation, described as conjunctivitis, was noted in both rabbits 24 hours after the installation of the MMA. No validated effects were observed after 48, 72 hours or 7 days. On the basis of these data the authors concluded that MMA was "slightly irritating" to the eyes of rabbits (Rohm and Haas, 1982).

Rohm and Haas (1958) did not observe any eye irritation in 3 rabbits exposed to 57-60 mg/l (13.7-14.4 ppm) MMA for a period of 2 hours.

In a Draize study in rabbits, no irritation was observed 1 - 7 days after installation of 0.1 ml undiluted MMA. During the first 24 hours after installation, slight conjunctival irritation was observed (Röhms, 1978; also cited by Cavalier *et al*, 1981).

Ouyang *et al* (1988) reported MMA as moderately irritating to rabbits eyes but experimental details were not provided in the abstract.

Moderate hyperaemia of the conjunctiva and lacrimation were observed in rabbits after 7 repeated applications of MMA (0.5 ml) to the eyes on alternate days (Castellino and Colicchio, 1969).

8.2.5 Sensitisation (Table 15)

8.2.5.1 *In Vitro*

Santavirta *et al* (1991) tried to analyse the immunological response to MMA in human lymphocyte cultures. Peripheral blood mononuclear cells from 4 healthy volunteers were cultured with finely pulverised MMA containing bone cement. MMA did not cause an increase in lymphocyte DNA synthesis as assessed by ³H-thymidine incorporation. The stimulation of cell proliferation after 1, 3, and 5 days did not differ significantly from that of the culture medium alone, and was less than the proliferation induced by the antigen purified protein derivative of tuberculin or the mitogen phythemagglutinin. However MMA induced MHC (major histocompatibility) locus II (Ia) antigen expression on the surface of monocytes on day 1, the number of Ia positive cells decreased on days 3 and 5. The activated monocytes did not appear to induce subsequent lymphocyte activation. The authors conclude that "MMA is essentially an immunologically inert material" and the monocyte activation is non-specific due to the presence of phagocytosable particles in the medium.

8.2.5.2 *In Vivo*

Sensitisation has not been tested in experimental animals following either oral or inhalation exposure to MMA. There is currently no validated animal model available for the prediction of such respiratory sensitisation hazard.

MMA has been extensively tested in various skin sensitisation assays in experimental animals. The data are summarised in Table 15. Positive reactions were obtained in tests using adjuvants, especially when high induction and challenge concentrations were used and evaporation of the substance from the skin was avoided either by using a highly viscous solvent or occluded application. The purity of the MMA used and its stabiliser content were not specified in most of the studies.

Cross reactions of MMA with other methacrylates and acrylates were studied by Clemmensen (1984). Guinea pigs sensitised to ethyleneglycol dimethacrylate, triethyleneglycol dimethacrylate, and trimethylolpropane trimethacrylate did not cross react with MMA. Animals sensitised to MMA showed cross reactions with hydroxyethyl methacrylate, ethyleneglycol dimethacrylate, and

Table 15 Skin Sensitisation Studies

Species (strain, sex)	MMA purity	Stabiliser	Test method	Induction	Challenge	Result ^d	Reference
Guinea pig	Unknown	Unknown	Maximisation	Unknown	Unknown	-ve	Lawrence <i>et al</i> , 1974
Guinea pig (Dunkin-Hartley ♀)	>99%	Unknown	Maximisation	d 0: 0.5 M in arachis oil, i.d. ^a d 7: 1 M in 80% ethanol, 24 h, occlusive	d 21,35: 100% (maximum non-irritating concentration)	-ve (3/10)	Van der Walle <i>et al</i> , 1982a (also quoted by Wahlberg and Boman, 1985)
Guinea pig (Dunkin-Hartley ♀)	>99%	Unknown	Maximisation	d 0: 0.5 M in arachis oil, i.d. d 7: 1 M in 80% ethanol, 24 h, occlusive	d 21,35: 3 M in Aramek ^b (maximum non-irritating concentration)	-ve (2/10)	Van der Walle <i>et al</i> , 1982a (also quoted by Wahlberg and Boman, 1985)
Guinea pig (Hartley-Dunkin ♀)	Unknown	Unknown	Maximisation, modified	1. 0.1 ml 5-25% MMA in propylene glycol, i.d. 2. 0.05 ml FCA ^c + 0.05 ml 5- 25% MMA in propylene glycol, i.d. 3. 0.1 ml FCA 4. d 7: 5-25% MMA in petrolatum 48 h, occluded	d 21: maximum non- irritant concentration (value not stated) 24 h occluded	5%: -ve (0/5) 10%: +ve (2/5) 15%: +ve (2/5) 25%: +ve (4/5)	Nethercott <i>et al</i> , 1983
Guinea pig (Hartley ♀)	Unknown	Unknown	Maximisation	1. FCA in dist. water 0.1 ml, i.d. 2. 5% MMA in saline 0.1 ml, i.d. 3. 10% MMA in saline and equal volume of FCA 0.1 ml, i.d. 4. d 7: 10% MMA in ethanol 0.5 ml, 24 h, occluded	d 21: 0.5 ml 10% MMA in ethanol 24 h occluded	-ve (0/30)	Marzulli and Maguire, 1982, 1983
Guinea pig	Unknown	Unknown	Maximisation (Magnusson and Kligman)	d 0: 5% MMA in FCA and saline (amount not stated) d 7: 100% MMA, occluded (time not indicated)	1% MMA in vaseline and 5% MMA in vaseline	1%: -ve (10% of the animals 5%: +ve (50% of the animals; number of animals not indicated)	Cavelier <i>et al</i> , 1981

Table 15 Skin Sensitisation Studies (cont.)

Species (strain, sex)	MMA purity	Stabiliser	Test method	Induction	Challenge	Result ^d	Reference
Guinea pig (SSc: AL ♀)	Unknown	Unknown	Maximisation	d 0: 2 x 50 µl FCA in sterile water 1:1, 2x50 µl MMA 5% in soybean oil, 2 x 50 µl MMA 5% in FCA and water 1:1 (all i.d.) d 7: 250 mg SDS, 10% in petrolatum massaged onto test area (open) d 8: 400 µl MMA 100%, 48 h, occluded	d 21: 25 µl MMA 3% in petrolatum, 24 h occluded	+ve (9/10)	Clemmensen, 1984
Guinea pig (Hartley ♀, ♂)	Unknown	Unknown	Maximisation	d 0: 0.1 ml FCA, 0.1 ml 1% MMA in saline and FCA	From d 14: 1 x/wk for 12 wk, 5% MMA in acetone/olive oil (4:1) unoccluded	-ve (0/6)	Parker and Turk, 1983
Guinea pig	Unknown	Unknown	Maximisation	d 0: 5% MMA in water i.d. 10% MMA in FCA i.d. d 7: 100% MMA 48h epicutaneous	d 21: 5% MMA occluded 24 h	-ve (4/26)	Nyquist <i>et al</i> , 1972
Guinea pig	Unknown	Unknown	Maximisation	d 0: 0.15% MMA, in water i.d. 0.3% MMA in FCA i.d. d 7: 0.15% MMA 48h epicutaneous	d 21: 100% occluded 24h	-ve (0/13)	Nyquist <i>et al</i> , 1972
Guinea pig	Unknown	Unknown	Maximisation	d 0: 0.001% MMA in water, i.d. 0.002% MMA in FCA d 7: 0.001% 48h epicutaneous	d 21: 100% occluded 24h	-ve (0/12)	Nyquist <i>et al</i> , 1972
Guinea pig	Unknown	Unknown	Maximisation	d 0: 5% MMA, in water i.d. 10% MMA in FCA i.d. d 7: 100% MMA epicutaneous	d 21: 100% occluded 24h	+ve (20/26)	Nyquist <i>et al</i> , 1972

Table 15 Skin Sensitisation Studies (cont.)

Species (strain, sex)	MMA purity	Stabiliser	Test method	Induction	Challenge	Result ^d	Reference
Guinea pig	Unknown	Unknown	Maximisation	d 0: 0.05 ml FCA, 0.05 ml MMA 5% in dibutylphthalate i.d., MMA in FCA d 7: 5% in acetone, 49 h, occluded, irritating concentration	d 14: 5% in acetone occluded 24 h	-ve (0/10)	Du Pont, 1978
Guinea pig (Hartley albino ♂, or English short-hair ♂ and ♀)	Unknown	Unknown	Polak FCA (100 µg into footpad)	3 x MMA in 95% ethanol, topically (cumulative amounts 0.12, 0.03 or 0.06 ml)	0.05 ml 2% or 5% in ethanol 95%, topically	-ve (0/24 or 0/25)	Chung and Giles, 1977
Guinea pig (Hartley albino ♂, or English short-hair ♂ and ♀)	Unknown	Unknown	Polak FCA (100 µg into footpad)	3 x MMA in 95% ethanol topically (cumulative amount: 0.03 ml) and 1 x 0.005 ml in saline, i.d.	1 x 0.05 ml in ethanol	-ve (0/10)	Chung and Giles, 1977
Guinea pig (Hartley albino ♂, or English short-hair ♂ and ♀)	Unknown	Unknown	Polak FCA (100 µg into footpad)	3 x MMA in 95% ethanol topically (cumulative amount: 0.0077 ml)	d 25: 1 x 0.05 ml in ethanol, topically d 60: 1 x 0.05 ml in olive oil	+ve (13/13)	Chung and Giles, 1977
Guinea pig (Hartley albino ♂, or English short-hair ♂ and ♀)	Unknown	Unknown	Polak FCA (100 µg into footpad)	3 x 2 or 5% MMA in 95% ethanol topically (cumulative amount: 0.000324 ml)	d 25: 1 x 0.1 ml in saline, i.d. d 60: 1 x 0.05 ml in olive oil	+ve (8/8)	Chung and Giles, 1977
Guinea pig (Hartley ♂, ♀)	Unknown	Unknown	Polak	0.1 ml MMA in ethanol/saline (1:4) in FCA in each footpad and neck (total dose: 11.5 µmol/animal)	0.02 ml 1 and 5% (max. non-irritant conc.) in acetone/olive oil 4:1	-ve (none of the animals reacted; number of animals not indicated)	Parker <i>et al</i> , 1985
Guinea pig (Hartley ♂, ♀)	Unknown	Unknown	Polak	0.1 ml of 2 mg MMA/ml ethanol/saline (1:4) in FCA in 4 footpads, i.d.; 1 ml in neck region, i.d.	From d 7: 1 x/wk, 12 wk 5% MMA in acetone/ olive oil 4:1 unoccluded	-ve (0/6)	Parker and Turk, 1983
Guinea pig (Hartley)	Unknown	Unknown	Polak FCA (0.15 ml into footpad)	3 x 0.2 ml MMA 5% in olive oil topically	d 35: 0.05 ml 5% in olive oil	-ve (0/10)	Du Pont, 1977

Table 15 Skin Sensitisation Studies (cont.)

Species (strain, sex)	MMA purity	Stabiliser	Test method	Induction	Challenge	Result ^d	Reference
Guinea pig (Hartley)	Unknown	Unknown	Polak FCA (0.1 ml into 2 hind footpads)	d 10: 0.2 ml MMA 5% in ethanol topically	d 35: 0.05 ml 5% in olive oil	-ve (0/5)	Du Pont, 1977
Guinea pig (Hartley)	Unknown	Unknown	Polak FCA (0.1 ml into 2 hind footpads)	d 10: 0.2 ml MMA 5% in olive oil topically	d 35: 0.05 ml 5% in olive oil	-ve (0/5)	Du Pont, 1977
Guinea pig (Hartley)	Unknown	Unknown	Polak FCA (0.1 ml into 2 hind footpads)	d 25: 0.2 ml MMA 5% in ethanol topically	d 60: 0.05 ml 5% in olive oil	-ve (0/5)	Du Pont, 1977
Guinea pig (Hartley)	Unknown	Unknown	Polak FCA (0.1 ml into 2 hind footpads)	d 25: 0.2 ml MMA 5% in olive oil topically	d 60: 0.05 ml 5% in olive oil	-ve (0/5)	Du Pont, 1977
Guinea pig (Hartley)	Unknown	Unknown	Polak FCA (0.1 ml into 2 hind footpads)	d 25: 0.1 ml MMA 2% in saline i.d.	d 60: 0.05 ml 5% in olive oil	-ve (0/5)	Du Pont, 1977
Guinea pig (albino Himalayan white-spotted and Dunkin-Hartley ♀)	99%	1,2% Dimethyl-p-toluidine	FCA	d 0-9: 5 x 0.5 M in water, i.d.	d 21: 3 M in Aramek d 35: 3 M in Aramek (maximum non-irritant concentration)	-ve (2/8; after first and second challenge)	Van der Walle <i>et al</i> , 1982a
Guinea pig (Hartley)	Unknown	Unknown	Cyclophosphamide/FCA assay; animals pretreated with cyclophosphamide 3 d prior to induction (i.p. 150 mg/kgbw)	d: 0-4: 5 x 0.2 ml 10% MMA in ethanol, 24 h, occluded d 4: 2 x 0.075 ml FCA, i.d. d 9: 0.2 ml 10% MMA, 6 h, occluded	d 22: 0.5 ml 10% MMA in ethanol, 24 h occluded	-ve (0/30)	Marzulli and Maguire 1982, 1983 (also quoted in Wahlberg and Boman, 1985)
Guinea pig (Hartley ♂, ♀)	Unknown	Unknown	Split adjuvant	d 0: 0.05 ml FCA, i.d. to 5 application sites d 1: 0.1 ml of 100 µg MMA in ethanol saline (1:100), i.d. at the same sites	From d 14 1 x/wk, 12 wk, 5% in acetone/olive oil (4:1) unoccluded	-ve (0/6)	Parker and Turk, 1983

Table 15 Skin Sensitisation Studies (cont.)

Species (strain, sex)	MMA purity	Stabiliser	Test method	Induction	Challenge	Result ^d	Reference
Guinea pig (Hartley ♀)	Unknown	Unknown	Split adjuvant technique	d 0, d 3: 0.2 ml 10% MMA in ethanol, 48 h, occluded d 4: 2 injections of FCA, 0.075 ml 0.2 ml 10% MMA in ethanol, 72 h, occluded d 7: 0.2 ml 10% MMA, 48 h, occluded	d 22: 0.5 ml 10% MMA in ethanol, 24 h occluded	-ve (0/30)	Marzulli and Maguire, 1982, 1983
Guinea pig (Hartley ♀)	Unknown	Unknown	Buehler	d 0,7,14: 0.5 ml 100% MMA, 6 h, occluded	d 28: 0.5 ml 10% MMA in ethanol 24 h occluded d 28	-ve (0/30)	Marzulli and Maguire, 1982, 1983
Guinea pig (Hartley ♀)	Unknown	Unknown	Draize	3 x/wk: 10 x 0.5% in saline, i.d., 0.1 ml	14 d after last induction: 0.1 ml 10% MMA in ethanol, occluded 24 h	-ve (2/30)	Marzulli and Maguire, 1982, 1983
Guinea pig (Hartley ♀)	Unknown	Unknown	Open epicutaneous	d 0,2,4,7,9,11: 0.1 ml 3 M MMA in 95% ethanol/ methoxyethanol/Tween 80 (9:9:2), unoccluded	From d 28, 1 x/wk, 12 wk: 5% MMA in acetone/olive oil (4:1), unoccluded	-ve (0/6)	Parker and Turk, 1983
Guinea pig (Hartley ♀)	Unknown	Unknown	Epicutaneous	d 0-11: 0.1 ml 10% MMA in acetone/olive oil (4:1), unoccluded	From d 21, 1 x/wk, 12 wk: 5% MMA in acetone/olive oil (4:1), unoccluded	-ve (0/6)	Parker and Turk, 1983
Other tests							
Mouse (CF-1 ♀)	98%	Unknown	Ear swelling	d 0: 2 x 0.05 ml FCA, i.d. d 0-3: 50% MMA in ethanol 70% to the abdomen	d 10: 50% MMA in ethanol (70%) to the ear	44% of animals: 118% increase in ear thickness	Gad <i>et al</i> , 1986
Mouse (Balbc ♀)	Unknown	Unknown	Ear sensitisation (ear thickness before and 24 h after challenge)	d 0,2: 50% MMA in ethanol topically to both sides of the right ear	d 9: 50% MMA in ethanol, topically to both sides of the left ear	Significant increase in ear thickness (114%, N=15)	Descotes, 1988

Table 15 Skin Sensitisation Studies (cont.)

Species (strain, sex)	MMA Purity	Stabiliser	Test method	Induction	Challenge	Result ^d	Reference
Guinea pig (Hartley σ^7 , φ)	Unknown	Unknown	Lymph node weight after immunisation according to Polak. Preparation of monolateral and contralateral auricular and monolateral and contralateral cervical lymph nodes 4 to 6 d after epicutaneous application	0.1 ml MMA in ethanol/ saline (1:4) in FCA in 4 footpads and neck, s.c. (total dose 11.5 μ mol/ animal)	d 7, 14: 0.02 ml of 1% and 5% MMA in acetone/olive oil (4:1) unoccluded 50 μ l of a 1 M solution of MMA in acetone/ olive oil (1:1) epicutaneous unoccluded, to dorsal site of the ear	-ve (lymph node weight unaffected; number of animals not indicated)	Bull <i>et al</i> , 1985

a i.d., intradermally

b Aramek, arachis oil/methyl ethyl ketone (1:2)

c FCA, Freund's complete adjuvant

d +ve, positive; -ve, negative

triethyleneglycol dimethacrylate, but not with trimethylolpropane dimethacrylate, hexanediol diacrylate, pentaerythritol tetraacrylate or trimethylolpropane triacrylate.

No cross reactions were observed after a challenge with 1% MMA in acetone in animals sensitised to epoxyacrylate or bisphenol-A dimethacrylate (Björkner, 1981).

MMA was shown to cross react to ethyl- and *n*-butyl methacrylate (Chung and Giles, 1977). Van der Walle and Bensink (1982) reported that only some of the animals sensitised to MMA cross reacted to *n*-butyl methacrylate.

Hegggers *et al* (1978) reported that MMA elicited a cellular immune response in guinea pigs sensitised to MMA.

Nyquist *et al* (1972) reported that guinea pigs did not become sensitised to MMA when exposed at very low concentrations (0.15%) found in polyMMA particles used in a dentifrice. Guinea pigs became sensitised to higher concentrations of MMA in 24-h occluded patch tests. No cross reactions were observed when these sensitised animals were challenged with acrylate particles.

Van der Walle *et al* (1982b) studied the concomitant sensitisation to MMA stabilised with hydroquinone (HQ) and MeHQ, which are known sensitising compounds (Van der Walle, 1982b), in both the GPM-Test and Freund's complete adjuvant test (FCAT). Five of 10 animals (albino female Dunkin-Hartley guinea pigs) reacted positively after induction with 0.5 M of either stabiliser intradermally (i.d.) at day 0 and 1.0 M dermally at day 7 and then challenged with 1 M solutions dermally at day 21 and 35. Both stabilisers cross reacted with each other. HQ and MeHQ also showed a positive reaction (4 of 5 animals) in the FCAT (induction 5 x 0.5 M, challenge at day 21 and 35). Even when induction concentrations as low as 0.45 µM were used in the FCAT, positive results were obtained with the stabilisers. The latter concentration is equivalent to that normally used to stabilise MMA. Concomitant sensitisation to MMA and HQ in the FCAT was observed in some animals. When HQ was replaced by thymol, which did not induce sensitisation in this test, the animals still reacted to MMA. Therefore, sensitisation to the stabiliser does not seem to contribute to observed cross reactions with other methacrylates. Thus it may be concluded that the stabiliser may contribute to sensitisation reactions observed with MMA, but is not likely to be the sole cause of the observed skin reactions to MMA or cross reactivity between methacrylate esters.

8.2.6 Summary

MMA is mildly irritating to the skin and eyes, and to the mucosa of the respiratory tract. Sensitisation has not been reported in experimental animals following either oral or inhalation exposure to MMA. It is a skin sensitizer in experimental animals, but is not particularly potent.

Cross reactions may occur with other methacrylic acid esters. Sensitisation to stabilisers such as HQ or MeHQ can also occur and may contribute to the observed sensitisation reactions with MMA.

8.3 REPEATED DOSE TOXICITY

Numerous subacute and subchronic studies have been conducted in rats, mice, rabbits and dogs with MMA administered by various routes, mainly by inhalation. Details of the methods used are frequently not well described and therefore certain studies are only summarised in Table 16-19.

8.3.1 Oral

The data are summarised in Table 16.

Male F344 rats were administered MMA in corn oil (0, 100 and 200 mg/kgbw, 5 d/wk) for 2 weeks. Histopathologic examination of the forestomach (the only organ examined) showed that there was no significant increase of mucosal cell proliferation or hyperkeratosis (Ghanayem *et al*, 1986).

MMA induced behavioral and neurochemical changes in male Wistar rats, following daily administration of 500 mg MMA/kgbw for 21 consecutive days. Three animals (10%) died, while no deaths occurred in the control group. Locomotor activity and learning ability were markedly impaired, while foot-shock-induced aggressive behaviour was significantly increased in treated rats compared to controls. Biogenic amine levels were increased overall in the pons-medulla and hippocampus, noradrenaline was increased in the cerebral cortex and corpus striatum, dopamine was slightly decreased in the corpus stratum and 5-hydroxytryptamine was increased in the midbrain and hypothalamus. Doses of 100 and 200 mg MMA/kgbw had no effect on behaviour (Husain *et al*, 1985).

8.3.2 Dermal

The data are summarised in Table 17.

Male Wistar rats were exposed (3 h/d) to undiluted MMA on 12 cm² of proximal tail skin 1 cm distal to the anus for 8 weeks. Keratolysis without ulceration of the exposed skin and a decrease of primary muscle response to stimulation of rat tail motor nerve was observed after 4 weeks exposure. The thickness of the myelinated nerves was not significantly affected. On electron microscopic examination myelin figures, a sign of degeneration, were found in less than 10% of the axons in the upper dermis. In the epidermis, enlarged intracellular spaces and abnormal keratinocytes were found (Verkkala *et al*, 1983; Kanerva and Verkkala, 1986).

Table 16 Repeated Oral Toxicity

Species (strain, number and sex)	Dose (mg/kgbw)	Duration	Results	Reference
Rat (F344, 8 ♂)	100 or 200	5 d/wk, 2 wk	No statistically significant increase in mucosal cell proliferation or hyperkeratosis, NOEL 200 mg/kgbw	Ghanayem <i>et al</i> , 1986
Rat (Wistar, 30 ♂)	0, 100, 200, 500	21 d	Behavioral effects and changes in brain neurotransmitter cells (biogenic amines)	Husain <i>et al</i> , 1985
Rat (Porton, 4 ♂)	18,800 mg/kg in diet (410 mg/rat)	5 wk	No neurotoxic effects, no enhancement of acrylamide neurotoxicity	Edwards, 1975
Rat (unknown, 50)	25	2x/wk, 12, 20 or 32 wk	Dystrophy in liver, inflammatory changes in the stomach, reversible kidney damage, changes in clinical chemistry (data incomplete)	Motoc <i>et al</i> , 1971

Table 17 Repeated Dermal Toxicity

Species (strain, number and sex)	Dose (mg/kgbw)	Duration	Results	Reference
Rat (Wistar)	Unknown	3 h/d, 8 wk	Mild neurological changes and keratolysis (no ulcer) in the skin (rat tail)	Verkkala <i>et al</i> , 1983; Kanerva and Verkkala, 1986

8.3.3 Inhalation

The data are summarised in Table 18.

In an NTP study (1986) F344/N rats were exposed to MMA concentrations (500-5,000 ppm, 6 h/d) 10 times in a period of 11 days. All rats exposed to 5,000 ppm and 2/5 of the females exposed to 3,000 ppm died before the end of the study. Significantly reduced body weight gain and ruffled fur was reported for the 2,000 and 3,000 ppm groups. In a subsequent study, the exposure concentrations were 0, 75, 125, 250, 500 and 1,000 ppm MMA for 6 h/d for 9 days over a 10 day period (NTP, 1986). No treatment related clinical signs or effects in gross pathology were noted.

Table 18 Repeated Inhalation Toxicity

Species (strain, number and sex)	Concentration (ppm)	Duration	Results	Reference
Rat (Sprague-Dawley, 19 ♂)	0, 1,000	7 d, 8 h/d	Lung damage, slight liver and lung effects, decrease in biochemical parameters	Tansy <i>et al</i> , 1980b
Rat (F344/N, 30 ♂, 30 ♀)	0, 75, 125, 250, 500, 1,000	6 h/d, 9 d	No clinical signs, no changes in the examined parameters	NTP, 1986
Rat (F344/N, 30 ♂, 30 ♀)	0, 500, 1,000, 2,000, 3,000 or 5,000	6 h/d, 10 d	Mortality >3,000 ppm, decrease in body-weight gain, ruffled fur	NTP, 1986
Rat	100	7 h/d, 5 d/wk, 2 wk	Increased intestinal motor activity (abstract) only	Tansy <i>et al</i> , 1986
Rat (32)	0 or 116	300 h	Decrease in body weight gain, adiposity (abstract only)	Hohenleitner and Tansy, 1978
Rat (Sprague-Dawley)	1,200	6 or 8 h/d, 5 d/wk, 3 wk	Mortality and kidney injury (no other data reported)	Du Pont, 1937
Rat (42)	12 (approximately)	1-3 months, interval not indicated	Hypotonia, changes in the ECG, disturbance of liver function	Blagodatin <i>et al</i> , 1976 as quoted in DFG, 1984
Rat (Sprague-Dawley, 19 ♂)	0, 1,000	7 d, 8 h/d	Lung damage, slight liver and lung effects, decrease in biochemical parameters	Tansy <i>et al</i> , 1980b
Rat (F344/N, 5 ♂, 5 ♀)	0, 75, 125, 250, 500, 1,000	6 h/d, 9 d	No clinical signs, no changes in the examined parameters	NTP, 1986
Rat (F344/N, 30 ♂, 30 ♀)	0, 500, 1,000, 2,000, 3,000 or 5,000	6 h/d, 10 d	Mortality >3,000 ppm, decrease in body-weight gain, ruffled fur	NTP, 1986
Rat	100	7 h/d, 5 d/wk, 2 wk	Increased intestinal motor activity (abstract) only	Tansy <i>et al</i> , 1986
Rat (8)	0 or 116	300 h	Decrease in body weight gain, adiposity (abstract only)	Hohenleitner and Tansy, 1978
Rat (Sprague-Dawley)	1,200	6 or 8 h/d, 5 d/wk, 3 wk	Mortality and kidney injury (no other data reported)	Du Pont, 1937
Rat (42)	12 (approximately)	1-3 months, interval not indicated	Hypotonia, changes in the ECG, disturbance of liver function	Blagodatin <i>et al</i> , 1976 as quoted in DFG, 1984
Rat (42)	132 (approximately)	1-4 months, interval not indicated	Increased body weight, disturbance of liver function	Blagodatin <i>et al</i> , 1976 as quoted in DFG, 1984
Rat	1,200 (approximately)	1 month, interval not indicated	No mortality, changes in liver function, cardiovascular disturbances, changes in blood biochemistry	Blagodatin <i>et al</i> , 1976 as quoted in DFG, 1984
Rat (Sprague-Dawley 13 ♀)	76,000 (approximately)	20 min/d, 21 or 42 d	Increase of the systolic blood pressure, abnormal respiratory patterns, ECG-changes and a heart block pattern	Blanchet <i>et al</i> , 1982a,b
Rat (60 ♂)	0, 0.024, 0.24, 2.4	24 h/d, 60 d	Transient changes in muscle activity, slight effects on urinary and blood biochemistry, NOEL 0.024 ppm	Filatova, 1962

Table 18 Repeated Inhalation Toxicity

Species (strain, number and sex)	Concentration (ppm)	Duration	Results	Reference
Rat (F344/N, 60 ♂, 60 ♀)	0, 500, 1,000, 2,000, 3,000 or 5,000	6 h/d, 5 d/wk, 14 wk	Mortality >2,000 ppm, decrease of body-weight gain, dose-related changes in nasal cavity, liver, kidney and brain, NOEL 500 ppm	NTP, 1986
Rat (F344/N, 60 ♂, 60 ♀)	0, 500, 1,000, 2,000, 3,000 or 5,000	6 h/d, 5 d/wk, 97 d	NOEL 1,000 ppm	NTP, 1986
Rat (F344/N, 60 ♂, 60 ♀)	0, 63, 125, 250, 500 or 1,000	6 h/d, 5 d/wk, 97 d	No mortality, no compound-related gross or microscopic pathological effects, NOEL 1,000 ppm	NTP, 1986
Rat (F344, 60 ♂, 60 ♀)	0, 500, 1,000, 2,000, 3,000 or 5,000	6 h/d, 5 d/wk, 97 d	Reduced body-weight gain, CNS effects, mortality (> 2,000 ppm), rhinitis, laryngitis, pulmonary congestion, histopathological findings in nasal cavity, lung congestion	Battelle, 1980; NTP, 1986
Rat, Sprague-Dawley (46 ♂)	0, 116	7 h/d, 5 d/wk, 3 months (542 h)	Slight changes in liver and biochemical parameters	Tansy <i>et al</i> , 1980a,b
Rat (albino, 90)	17.3 or 28	6 h/d, 3 d/wk, 3 months	Behavioural changes in liver, behaviour, redox potential and catecholamines increased	Lomonova <i>et al</i> , 1980
Rat (albino, 90)	17.3 or 28	3 h/d, 6 d/wk	Liver, kidney and heart effects, no behavioural changes	Lomonova <i>et al</i> , 1980
Rat (158 ♀)	12	4 months, intervals not indicated	Time dependent reactions on the cardiovascular system, increased relative heart weight, dystrophic changes of myocard and blood vessels	Dorofeeva <i>et al</i> , 1978b
Rat	12.6, 126	4 months	Decreased weight of ovaries, decreased levels of progesterone, GSH, increased secretion of FSH, LH	Stepanov <i>et al</i> , 1991
Rat (total 51)	400	7 h/d, 5 d/wk, 2-10 wk	Neurological changes only during the first week	Innes <i>et al</i> , 1988
Rat (albino, 18 ♀)	3 or 13	Unknown, 4 months	Changes in CNS, liver enzymes (data incomplete)	Smirnova and Blagodatin, 1977
Rat (Sprague-Dawley, 100 ♂)	0, 116	8 h/d, 5 d/wk, 3 or 6 months (542 and 1,105 h)	'Shaggy appearance', after 3 months: decrease in body weight, body fat, lung- and spleen weights. Serum alkaline phosphatase elevated. After 6 months: Decrease in body weight and popliteal fat pad weights, serum protein levels. Serum alkaline phosphatase elevated. Intestinal transit rate decreased	Tansy <i>et al</i> , 1976; Kendall <i>et al</i> , 1976
Rat (10 ♂)	2,900	2x/wk, 3.5 or 8 months	Increased β -glucuronidase level, nongranular diffuse (predominant) and granular localisation of the enzyme in the hepatocytes	Constantinescu, 1972
Rat (30)	2.5 or 5	2 h/d, 7 d/wk 32 wk	Decrease of some liver enzymes and thiolgroups, NOEL < 2.5 ppm	Gabor <i>et al</i> , 1965

Table 18 Repeated Inhalation Toxicity

Species (strain, number and sex)	Concentration (ppm)	Duration	Results	Reference
Rat (50)	2, 900	2x/d, 2 d/wk, 12, 20 or 32 wk	Changes in the lungs, mild effects in the liver (data incomplete)	Motoc <i>et al</i> , 1971
Mouse (B6C3F ₁ , 30 ♂, 30 ♀)	0, 75, 125, 250, 500, 1,000	6 h/d, 9 d	No clinical signs, no changes in the examined parameters	NTP, 1986
Mouse (B6C3F ₁ , 30 ♂, 30 ♀)	0, 500, 1,000, 2,000, 3,000 or 5,000	6 h/d, 10 d	Mortality in all dose groups, redness and swelling in nasal regions, dyspnoea, possibly histopathological changes	NTP, 1986
Mouse (Swiss Webster 60 ♂)	0, 100 or 400	1 x/d, total of 160 h, number of days not stated	Reduced sleep time at 400 ppm, reduced induction time at 100 ppm	Tansy <i>et al</i> , 1980b
Mouse	39,300 or 65,500 mg/m ³ (9,430 or 15,700 ppm)	0.5 h/d, 15 d	Mortality	Spealman <i>et al</i> , 1945
Mouse, ICR (8 ♀, 8 ♂)	1,500	2 x 2 h/d, 10 d	No treatment-related effects	McLaughlin <i>et al</i> , 1979
Mouse (30)	12 (approximately)	1-3 months, interval not indicated	Hypotonia, changes in the ECG, disturbance of liver function	Blagodatin <i>et al</i> , 1976 as quoted in DFG, 1984
Mouse (30)	132 (approximately)	1-4 months, interval not indicated	Increased body weight, disturbance of liver function	Blagodatin <i>et al</i> , 1976 as quoted in DFG, 1984
Mouse	1,200 (approximately)	1 month, interval not indicated	No mortality	Blagodatin <i>et al</i> , 1976 as quoted in DFG, 1984
Mouse (B6C3F ₁ , 60 ♂, 60 ♀)	0, 500, 1,000, 2,000, 3,000 or 5,000	6 h/d, 5 d/wk, 96 d	Reduced body-weight gain, CNS effects, mortality > 2,000 ppm, rhinitis, laryngitis. Histopathological findings: dose-related changes in nasal cavity, liver kidney and brain, lung congestion. NOEL 1,000 ppm	Battelle, 1980; NTP, 1986
Mouse (B6C3F ₁ , 60 ♂, 60 ♀)	0, 63, 125, 250, 500 or 1,000	6 h/d, 5 d/wk, 96 d	NOEL 1,000 ppm	NTP, 1986
Guinea pig	39,300 or 65,500 mg/m ³ (9,430 or 15,700 ppm)	1.5 h/d, 15 d	Mortality	Spealman <i>et al</i> , 1945
Dog	39,300 or 65,500 mg/m ³ (9,430 or 15,700 ppm)	3 h/d, 15 d	Mortality, degeneration of liver and kidney	Spealman <i>et al</i> , 1945
Dog (beagle, 18 ♂)	0, 100 or 400	6 h/d, 5 d/wk, 3 months, observed 1 month	No significant differences in blood pressure, ECG, heart and respiratory rates, NOEL 400 ppm	Drees <i>et al</i> , 1979; Tansy and Drees, 1979; Smith <i>et al</i> , 1979

In the corresponding mouse (B6C3F₁) study (NTP, 1986) deaths occurred in all dose groups of males and in all females exposed to 5,000 ppm. Signs of toxicity were dyspnoea, redness and swelling of the nasal regions. In the 10 day exposure study (0 to 1,000 ppm) neither clinical signs nor macro- or microscopical changes were observed in mice.

In F344 rats and B6C3F₁ mice exposed (6 h/d 5 d/wk) to MMA at concentrations of 0, 500, 1,000, 2,000, 3,000 and 5,000 ppm for 14 weeks the most prominent effects observed were nasal lesions including inflammation of the nasal cavities, necrosis and loss of olfactory epithelium. The changes were clearly dose related. NOEL levels were reported to be 1,000 ppm for male rats and for male and female mice. Slight effects on the nasal turbinates were observed in female rats at 1,000 ppm. Other lesions such as pulmonary congestion, hepatic necrosis and vacuolation, and congestion of the brain were observed mainly at the higher concentrations of 3,000 and 5,000 ppm in both rats and mice and were more severe in animals dying spontaneously. Milder changes were observed infrequently at the lower concentrations (Battelle, 1980).

Studies have been performed by Industrial Biotest Laboratories (quoted in NTP, 1986), but the reports were not available for review.

Groups of mice, guinea pigs and dogs (sex and strain unspecified) were exposed by inhalation (30, 90 or 180 min/d) to concentrations between 39.3 and 65.5 mg MMA/l (9,430 and 15,700 ppm) for 15 days. Deaths occurred at the higher exposure levels, but in mice, the mortality was not correlated with exposure. Liver degeneration was found in guinea pigs and dogs, with degenerative changes in the tubular cells of the kidney, only in dogs. These changes were observed in a milder form also in apparently healthy, untreated laboratory animals (Spealman *et al*, 1945).

Young adult male Sprague-Dawley rats received interrupted exposures for 56 hours over a 7 day period. The exposure concentrations were 0 or 1,000 ppm MMA. Blood albumin, glucose, urea nitrogen, GOT and GPT activity and the albumin-glucose rate were significantly lower than those of the control group. No remarkable abnormalities were observed in growth or upon gross post-mortem examination. Microscopic examination showed that lung edema, fibrosis and changes suggestive of emphysema were more pronounced in exposed animals than in controls. Using scanning electron microscopy, the epithelium of the trachea showed a loss of cilia and the cellular covering of microvilli was reduced (Tansy *et al*, 1980b).

Mature, female mice (ICR, Institute Cancer Research) were exposed (2x2 h/d, 5 d/wk) to 1,520 ppm MMA for 2 weeks. Animals in the treatment group lost 4.9% body weight and the control animals 3%. Microscopical examination of the lungs, liver, heart and kidney showed no evidence of an effect (McLaughlin *et al*, 1979).

Groups of 20 male Swiss Webster mice were exposed (intermittent daily) to 0, 100 or 400 ppm MMA vapour in air for 160 hours (< 7 days). Twenty-four hours after the last exposure, 50 mg/kgbw sodium pentobarbital was injected i.p. into each mouse to determine the induction and sleeping times. The mean induction time was significantly shorter for the 100 ppm animals. The mean sleeping time was significantly decreased for mice exposed to 400 ppm MMA but was not altered statistically significant in the 100 ppm MMA group. Histopathological examination of the liver showed small areas of focal necrosis in exposed animals and also in the controls (Tansy *et al*, 1980b).

Two groups of female rats were exposed (21 min/d) to MMA vapour (air concentration of approximately 7.6%) for 21 or 42 days respectively. Five minutes prior to exposure, and then during the treatment, blood pressure, heart rate, respiration and ECG were monitored. Systolic blood pressure increased with time of exposure to MMA. Abnormal respiratory patterns, ECG changes and an increase in systolic blood pressure with increased heart rate were recorded (Blanchet *et al*, 1982a, b).

Groups of 6 Beagle dogs were exposed (6 h/d, 5d/wk) to 0, 100 and 400 ppm MMA for 3 months followed by a 1 month recovery period. For the whole period the animals were catheterised via the external iliac artery and a total of 36 variables including systolic and diastolic blood pressure, ECG, heart and respiratory rates, haematology and clinical chemistry parameters and urinalysis were recorded monthly. None of these parameters was significantly different from the control group and no changes in organ weights and bone marrow differentials were observed. Histopathological examination of the major organs was unremarkable. The NOEL was 400 ppm (Drees *et al*, 1979; Smith *et al*, 1979; Tansy and Drees, 1979).

F344/N rats and B6C3F₁ mice were exposed (6 h/d, 5 d/wk) to MMA concentrations of 0, 500, 1,000, 2,000, 3,000 and 5,000 ppm for 14 weeks. Deaths occurred at concentrations of 2,000 ppm and above and body weight gain showed a dose-related reduction in these groups. During the first 2 days, listlessness, serous ocular discharge, nasal discharge and prostration were observed. Inflammation in the nasal cavity, associated with necrosis and loss of olfactory epithelium occurred in both sexes. No changes were found in nerve bundles in the submucosa. Malacia and gliosis of

the brain were dose-related at levels above 1,000 ppm, whereas other brain lesions, follicular atrophy of the spleen and bone marrow atrophy were seen only in the high dose groups. In mice, microscopic findings included renal cortical necrosis, cortical tubular degeneration and/or focal mineralisation, inflammation with necrosis, loss of olfactory epithelium in the nasal cavity, extensive liver necrosis in males and inflammation of the nasal turbinates in female mice. All mice exposed to MMA had metaplasia of the nasal epithelium (NTP, 1986; Battelle, 1980).

In a 14-week study male and female B6C3F₁ mice were exposed (6 h/d, 5 d/wk) to 0, 63, 125, 250, 500 and 1,000 ppm MMA. No compound related deaths occurred, except for 1 male in the 500 ppm group. Body-weight gain in the highest dose group was decreased (7%) in comparison with the controls. No treatment-related macroscopic or microscopic changes were found. In a corresponding study with F344/N rats no compound-related effects were observed (NTP, 1986).

Mature male Sprague-Dawley rats exposed (7 h/d, 5 d/wk) to 116 ppm MMA vapour for 542 hours (3 months), showed no significant effect on food or water intake or body weight gain. At necropsy, no visual evidence of reduced visceral or s.c. fat or significant differences in organ weights in comparison to the control animals were observed. Serum analysis showed a significant decrease in total bilirubin and an increase in total cholesterol. Histological examination showed occasional lung damage (fibrosis, edema, changes suggestive of emphysema) which was also observed to a lesser degree in the control animals. Findings in the liver, such as small focal necrosis or swelling of individual cells, appeared to be subtle and were considered as possible liver damage by the authors (Tansy *et al*, 1980a,b).

Male Sprague-Dawley rats were exposed (8 h/d, 5 d/wk) to 116 ppm MMA vapours for 3 or 6 months respectively. The exposed animals had less body fat than the controls and serum alkaline phosphatase activity was elevated. Additionally, in the 6 months group inorganic phosphate was increased and total protein, cholesterol and serum GOT activity was decreased (Kendall *et al*, 1976). The same authors (Hohenleitner and Tansy, 1978) observed an increase in body fat when rats were exposed by inhalation of 100 ppm MMA for a total exposure time of about 300 hours. When feeding was restricted, body weight gain was reduced compared with the corresponding control group.

After exposure (regime not reported) of rats to 12 ppm MMA for 4 months time-dependent reactions on the sympathetic nerve system, effects on blood pressure, elevated enzymatic activities (ALAT, ASAT, fructosediphosphate aldolase), changes in ECG, reduced heart automatism and myocardial strength were observed. The relative heart weight was increased. Histopathological examination

showed destructive and dystrophic changes of the myocard and blood vessels (Dorofeeva *et al*, 1978b).

Smirnova and Bladogatin (1977) exposed (regime not specified) female rats to 3 or 13 ppm MMA for up to 4 months. Several biochemical parameters, a summation threshold index for cerebral activity, ECG and changes in the oestrous cycle were determined but no details were given of the methods used. The authors reported a change in the oestrous cycle at 13 ppm after 2 months and "toxic effects" in the lower exposure group. The conclusions quoted cannot be derived from the results given in the paper and the data are therefore questionable.

Rats (strain, sex and numbers not reported) were exposed (either 3 h/d, 6 d/wk or 6 h/d, 3 d/wk) to MMA vapour (0, 17.3 and 28 ppm) for 4 months. In both studies, the blood peroxidase, GSH levels and the activity of mixed function oxidase level was decreased. Additionally in the first study the cardiovascular system was affected and the liver and kidney weights were increased, whereas in the second study behavioral changes were seen (Lomonova *et al*, 1980).

Continuous exposure (24 h/d, 7 d/wk) to 0.24 or 2.4 ppm MMA for 60 days produced changes in muscle activity in rats. Coproporphyrin levels in urine and blood cholinesterase activity were decreased. Pneumonia, oxygen permeability in the alveoles, dystrophic changes in the kidney and plethora in the spleen were observed in the high dose group. Behaviour and body weight were not affected. No changes were seen at the lowest concentration of 0.024 ppm MMA (Filatova, 1962).

8.3.4 Other routes

The data are summarised in Table 19.

Repeated dose toxicity studies have been conducted on MMA using the s.c. and i.p. routes of administration. These data have been reviewed but it is considered that the routes of exposure are not relevant to the assessment of the repeated dose toxicity and therefore these studies are not used in this report (Lawrence *et al*, 1974; Nilsen *et al*, 1978; Smith *et al*, 1979; Tansy and Drees, 1979; Miller *et al*, 1982; Elovaara *et al*, 1983).

8.3.5 Summary

Following repeated oral exposure of rats and mice to MMA there was some evidence of inflammatory changes in the stomach, but no evidence of mucosal cell proliferation or hyperkeratosis. Neurochemical changes have also been reported following oral administration of

Table 19 Repeated Dose Toxicity - Other Routes of Administration

Species (strain, number and sex)	Dose	Duration	Results	Reference
Intraperitoneal (mg/kgbw)				
Rat (Wistar, 12-15 ♂)	1,000	3 d, recovery period of 1, 5 or 12 d	Reversible biochemical changes in liver and kidney	Elovaara <i>et al</i> , 1983
Rat (Sprague-Dawley, 48 ♂)	0, 125, 250 or 623	3 d/wk, 12 wk	1 animal in mid-dose group died, other data recorded but not reported	Lawrence <i>et al</i> , 1974
Mouse (NMRI, 12 ♂)	0, 60 or 600	4 d	Decrease in body-weight gain and liver to body-weight ratio, NOEL 60 mg/kgbw	Nilsen <i>et al</i> , 1978
Subcutaneous (µl)				
Rat (Sprague - Dawley, 42)	0, 200	1 x/d, 3, 7, 14 d	Elevated blood urea nitrogen (BUN) levels compared to control	Miller <i>et al</i> , 1982
Rat (Sprague-Dawley, 30)	0, 100, 200	1 x/d, 14 d	Elevated BUN, chronic inflammation of kidneys	Miller <i>et al</i> , 1982
Conjunctival (µl)				
Rabbit	500	7 x on alternate days	Reddening and lacrimation	Castellino and Colicchio, 1969

MMA to rats at 500 mg/kgbw for 21 consecutive days, a dose level which was lethal for 10% of the treated animals, including behavioural effects and changes in neurotransmitter levels. The NOEL for the behavioural effects was 200 mg/kgbw.

Following repeated dermal exposure (15 daily exposures of 5 ml MMA), slight skin reactions were observed. Prolonged exposure of the tail skin of the rat produced keratolysis but no ulceration. Decreased muscle response was observed following stimulation of the tail motor nerve. Electron microscopy of the skin showed slight degenerative changes in less than 10% of the axons in the upper dermis.

Inhalation exposure of rats and mice to atmospheres containing up to 5,000 ppm for 96 days have shown that the respiratory tract is the predominant target organ. The effects, which were dose related, included rhinitis and laryngitis, inflammation and swelling of the nasal cavities, and necrosis and loss of olfactory epithelium. Effects on the lung included oedema, fibrosis and emphysema like changes. These effects are consistent with the irritative properties of MMA.

Some liver effects have also been reported, these include changes in clinical chemistry profile, focal necrosis and vacuolation. There is also some evidence based on reduced phenobarbital sleeping times that MMA can induce certain of the liver drug metabolising enzymes.

After repeated exposure to air concentrations of or in excess of 1,000 ppm, malacia and gliosis of the brain, atrophy of the renal cortex and bone marrow have also been reported.

8.4 GENETIC TOXICOLOGY

In vitro genetic toxicology assays are used routinely as the first screen for assessing the genotoxic activity of chemicals. These assays, however, provide information only on the intrinsic potential of these chemicals to cause damage to the DNA. To determine whether or not this potential is expressed in whole animals it is necessary to conduct *in vivo* genetic toxicology assays which take account of absorption, distribution, metabolism and excretion of the chemical and its metabolites. The results of *in vivo* assays therefore often overrule results obtained *in vitro*.

8.4.1 *In Vitro* Bacterial Gene Mutation Assays

MMA has been tested in a number of bacterial gene mutation assays using standard plate incorporation or liquid pre-incubation protocols in the presence and absence of auxillary metabolic activation (S9-mix) which have reproducibly shown that it is not mutagenic to bacteria even when tested up to cytotoxic concentrations.

ICI (1976a) tested MMA in a series of standard plate incorporation assays using *Salmonella typhimurium* strains TA1535, TA1538, TA98 and TA100 and concentrations from 4 to 2,500 µg MMA/plate in the presence and absence of Aroclor-1254 induced rat liver S9-mix. The plates were sealed to minimise evaporation of MMA and although small increases in the numbers of revertant colonies were observed in some experiments, these were not dose-related or reproducible. Negative (i.e. non-mutagenic) responses were also reported by ICI (1976a) in an experiment involving the exposure of *S. typhimurium* strains TA1535, TA1538, TA98 and TA100 to MMA in the gaseous phase. Nominal concentrations of 100, 1,000 and 9,000 ppm MMA were tested in the presence and absence of Aroclor 1254-induced rat liver S9-mix and the plates were sealed in air-tight glass exposure vessels. No significant increases in revertant colonies were observed. These data are also discussed in Anderson *et al* (1979).

MMA was tested in *Salmonella typhimurium* strains TA1535, TA1537 and TA1538 at concentrations up to 10 mg MMA/plate in the presence and absence of rat liver S9-mix. No increases in the numbers of revertant colonies were reported (Du Pont, 1975).

ICI (1980) tested MMA in a bacterial gene mutation assay using *S. typhimurium* strains TA1535 and TA100 and *E. coli* strains WP2 and WP2 *uvrA* in the presence of Aroclor 1254-induced rat liver S9-mix. No significant increases in the numbers of revertant colonies were reported.

Lijinsky and Andrews (1980) tested MMA in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 using a range of concentrations up to 1,000 µg MMA/plate in both standard plate incorporation and liquid pre-incubation assays. Both assays were conducted in the presence and absence of Aroclor 1254-induced rat and hamster liver S9-mix. Although negative responses were reported in all strains, no cytotoxicity was observed at the concentrations tested thus bringing into question the selection of the maximum concentration tested.

Waegemaekers and Bensink (1984) reported negative results when MMA was tested at a range of concentrations from 40-10,000 µg MMA/plate in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 in the presence and absence of Aroclor 1254-induced or phenobarbital-induced rat liver S9-mix in a standard plate incorporation assay. To minimise the evaporation of volatile materials the treated plates were sealed in glass air-tight exposure jars. The same authors also reported MMA to be negative when tested in TA100 in a liquid pre-incubation assay at concentrations of 100, 1,000 and 10,000 µg/2ml incubation volume in the presence and absence of Aroclor 1254-induced S9-mix.

Zeiger *et al* (1987) reported MMA as non-mutagenic in 2 pre-incubation assays using *S. typhimurium* strains TA1535, TA1537 or TA97, TA98 and TA100. MMA was tested over ranges of concentrations from 10 to 10,000 µg MMA/plate in the presence and absence of Aroclor-1254 induced rat and Syrian hamster liver S9-mix. No significant increases in the numbers of revertant colonies were observed at concentrations which also resulted in cytotoxicity. These results were also discussed by the NTP (1986) and Zeiger (1990).

Hachiya *et al* (1981) reported data on a series of bacterial mutation assays in which MMA was tested in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 in the presence and absence of S9-mix at a range of concentrations from 150-4,700 µg MMA/plate. No significant increases in revertant colonies were recorded.

Querens *et al* (1981) and Ouyang *et al* (1989) have also reported negative bacterial mutation assays on MMA although the publications are only in abstract form and therefore very few details are available.

MMA was also tested in a bacterial gene mutation assay by Jensen *et al* (1991) as part of a methacrylate bone cement extract mixture. The mixture was tested twice in a standard plate incorporation assay using *S. typhimurium* strains TA 1535, TA1537, TA98 and TA100 in the presence and absence of Aroclor 1254-induced rat liver S9-mix. No increases in the numbers of revertant colonies were reported.

Poss *et al* (1979), however, reported a mutagenic effect of MMA in an unusual strain of *S. typhimurium* TM 677 when tested up to cytotoxic concentrations in the presence of metabolic activation. This strain of *S. typhimurium* is however an 8-azaguanine resistant forward mutant and therefore this result is expected in light of the responses seen in the mammalian cell forward mutation assays detailed in Section 8.4.2. A negative result was reported when MMA was tested in the absence of the metabolic activation system in this strain of *S. typhimurium*.

8.4.2 In Vitro Mammalian Cell Gene Mutation Assays

MMA has been tested extensively in L5178Y TK^{+/−} mammalian cell gene mutation assays and has been shown to induce increases in mutant numbers and frequencies.

Cifone (1981) tested MMA in 3 mouse lymphoma L5178Y gene mutation assays at ranges of concentrations up to the cytotoxic concentration of 300 nl/ml in the presence of metabolic activation. Statistically and biologically significant increases in mutant frequency were reported. MMA was also tested twice in the absence of S9-mix at concentrations up to the cytotoxic concentration of 100 nl/ml and no significant increases in mutant frequency were observed.

Moore *et al* (1988) reported small but dose-dependent increases in mutant numbers and mutant frequencies when MMA was tested over a range of concentrations up to 3,100 µg/ml (31 mM) in the mouse lymphoma L5178Y TK^{+/−} assay in the absence of S9-mix. Dose-related cytotoxicity was observed and the majority of induced mutant colonies were classified as small colonies which are considered to be indicative of a clastogenic (chromosome breakage) mechanism of action. These data were confirmed in a repeat experiment and are also presented in abstract form by Amtower *et al* (1986), in a publication by Doerr *et al* (1989) and discussed by Dearfield *et al* (1989) and Moore and Doerr (1990).

Comparable results have been reported by the NTP (1986) in 2 independent experiments, with MMA inducing dose related increases in mutant numbers and mutant frequencies when tested over a range of concentrations from 0.125 to 1 µl MMA/ml in mouse lymphoma L5178Y cells in the absence of S9-mix. The NTP (1986) also reported positive results in this assay when MMA was tested over a concentration range of 0.125 µl/ml to 1.5 µl/ml in the presence of Aroclor 1254-induced rat liver S9-mix in 2 independent experiments.

Dearfield *et al* (1991) expanded the work of Moore *et al* (1988) and have reported MMA as positive in the mouse lymphoma L5178Y assay when tested over concentration ranges of 500 to 1,000 µg/ml (5 to 10 mM) and 500 to 3,000 µg/ml (5 to 30 mM) in the presence and absence of Aroclor 1254-induced rat liver S9-mix respectively; the addition of the S9-mix was reported to increase the mutagenicity of the MMA.

Myhr *et al* (1990) have also reported MMA as positive in the mouse lymphoma L5178Y gene mutation assay when tested once over a concentration range of 125 to 1,500 nl/ml (1.25 to 15 mM) in the presence of S9-mix and when tested twice over concentration ranges of 125 to 1,500 nl/ml (1.25 to 15 mM) in the absence of S9-mix.

8.4.3 In Vitro Chromosome Damage Assays

A series of *in vitro* chromosomal aberrations assays have been conducted which have reproducibly shown MMA to have *in vitro* clastogenic activity.

Moore *et al* (1988) have reported MMA as positive in an *in vitro* cytogenetic assay in mouse lymphoma L5178Y cells following a 4 hour treatment period in the absence of S9-mix. MMA was tested over a concentration range of 1,000-3,000 µg/ml (10-30 mM) and although increases in chromosomal aberrations were observed, these were small, not clearly dose-related and observed only at concentrations above the recommended limit concentration of 10 mM (Galloway *et al*, 1993). In addition, the chromosomal aberration frequencies in the control cultures were higher than would be expected for this cell line. These data are also presented in abstract form by Amtower *et al* (1986), in a publication by Doerr *et al* (1989) and discussed by Moore and Doerr (1990).

Anderson *et al* (1990) have reported MMA to be clastogenic in an *in vitro* assay with Chinese Hamster Ovary (CHO) cells at concentrations of 5,000 µg/ml (50 mM) in the presence of Aroclor 1254 induced rat liver S9-mix. Small but statistically significant increases in the percentage of aberrant cells were also observed in cultures treated with MMA at concentrations of 1,600 and 3,000 µg/ml (16 and 30 mM) in the absence of S9-mix. Again these concentrations are in excess

of the recommended limit concentration of 10 mM. These data have also been reported by the NTP (1986).

Doerr *et al* (1989) have also reported MMA as positive for the induction of micronuclei in binucleate L5178Y cells following treatment at a range of concentrations from 1,000 to 3,000 µg/ml (10 to 30 mM) in the absence of S9-mix. The increases in the frequencies of micronucleated cells were small and not clearly dose related.

The increases in chromosomal aberrations and micronuclei in these 3 assays were all small and were observed at concentrations in excess of the recommended limit concentration for these *in vitro* assays of 10 mM. The use of concentrations above 10 mM can result in the production of artefactual increases in chromosomal aberrations as a result of physiological disturbances in the cells (Scott *et al*, 1991). However, in the case of MMA, which is a volatile material, it is unlikely that such high concentrations were actually achieved under the culture conditions employed in these assays. Evaporation of the MMA into the headspaces of the culture vessels would have been expected and this would presumably have resulted in significantly lower achieved concentrations than the high nominal concentrations quoted in the publications. The increases observed in these studies are therefore likely to be real rather than due to physiological disturbances caused by high concentrations.

8.4.4 *In Vitro* Sister Chromatid Exchange Assays

Cannas *et al* (1987) tested MMA and polyMMA at a series of concentrations up to cytotoxic levels in human lymphocyte cultures. No significant increases in the frequencies of sister chromatid exchanges were observed for either material.

Anderson *et al* (1990) tested MMA for the induction of sister chromatid exchanges in 2 experiments conducted with CHO cells in the presence and absence of Aroclor 1254 induced rat liver S9-mix. MMA induced small increases in SCE frequency when tested over ranges of concentrations up to 1,250 and 5,000 µg/ml in the absence and presence of S9-mix. These data have also been reported by the NTP (1986).

8.4.5 Other *In Vitro* Genotoxic Endpoints

ICI (1977c) reported MMA as negative in the BHK21/C13 cell transformation assay but the significance of this assay is now considered questionable. These results are also presented in abstract form by Anderson *et al* (1979).

Kurian *et al* (1990) reported that MMA had some cytotoxic and transforming ability in human neonatal foreskin fibroblasts *in vitro* but again the significance of these results is highly questionable.

Wang *et al* (1989) and Jiang *et al* (1989) both report, in brief abstracts, that MMA causes segregation defects/chromosome loss when tested in *Saccharomyces cerevisiae* D7. However no experimental details or data are provided in either of these abstracts and therefore the significance of these results cannot be interpreted.

8.4.6 *In Vivo* Chromosome Damage Assays

Several *in vivo* chromosomal damage assays have been conducted which show no convincing evidence for an *in vivo* clastogenic activity of MMA when animals are exposed via a route relevant for human exposure.

ICI (1976c, 1979) have conducted a series of experiments to evaluate MMA for its ability to induce chromosomal aberrations in the bone marrow of rats following single or multiple inhalation exposures. In the first study (ICI, 1976c) groups of 2 - 5 male Alderley Park rats were exposed to single 2-hour MMA exposures at concentrations of 100, 1,000 or 9,000 ppm in 2 independent experiments. In addition, groups of 4 - 7 male Alderley Park rats were exposed for 5 hours to MMA at concentrations of 100, 1,000 or 9,000 ppm for 5 consecutive days. No rationale is provided for dose level selection (although this may have been based on the preliminary study described below in Section 8.4.7) and no measures of cytotoxicity in the target tissue are reported. Small increases in the percentage of cells with chromosomal aberrations were reported in animals exposed to MMA at 1,000 or 9,000 ppm in all 3 studies. However, the majority of the aberrations recorded were gap-type aberrations which are now considered to be of questionable biological significance. When the percentages of cells with chromosomal aberrations (excluding those with only gap-type aberrations) are considered, the observed increases were statistically not significant.

In a follow-up study (ICI, 1979), in which groups of 8 male Alderley Park rats were exposed to either a single 2-hour or 5-hour exposure for 5 consecutive days at concentrations of 100, 400, 700 or 1,000 ppm MMA. The maximum concentration tested caused significant reductions in mitotic activity in the bone marrow of the exposed animals following the single and multiple exposures thus justifying the top concentration selected. Small and non-dose related increases in the percentages of cells with chromosomal aberrations were again observed in the animals exposed to MMA in both studies. However, these increases were almost exclusively due to gap-type aberrations and when these were excluded from the data small increases were only observed at 400 ppm in the single

exposure study and at 100 ppm in the multiple exposure study. Such small increases, observed at the lowest concentrations tested, are not considered to be biologically significant.

Bargramyan and Babayan (1974) have reported that rats exposed to a combination of 4 mg MMA/m³ (1 ppm) and 3 mg chloroprene/m³ (0.8 ppm) for a period of 4 months showed increases in chromosomal aberrations in the bone marrow. In a similar study by the same authors (Bargramyan *et al*, 1976), rats exposed to a combination of chloroprene and MMA for periods up to 75 days are also reported to show increases in chromosomal aberrations in the bone marrow. As no experimental details or data are available for these studies it is difficult to draw any conclusions from these results. However, chloroprene is a known *in vivo* clastogen (DFG, 1980) and is therefore considered likely to be responsible for the increases in chromosomal aberrations observed in these studies.

Hachiya *et al* (1981) reported data on mouse micronucleus tests. MMA was dosed orally at up to 4.52 g/kgbw in a single dose study and at 1.13 g/kgbw in a 4 dose study to groups of 6 mice. Sampling time in the single dose study was 24 hours and in the repeated dose study 5 days after the first administration. No significant increases in the incidence of micronucleated polychromatic erythrocytes were observed in both studies.

Fedyukovich *et al* (1988) reported that MMA is negative in a rat chromosomal aberration assay following a single i.p. administration at 0.5 LD₅₀ whereas the same authors (Fedyukovich and Egorova, 1991) report MMA to be positive when tested up to the same dose level; these data are therefore contradictory. Very little information is given in the 1988 abstract but the 1991 paper shows increases in chromosomal aberrations following treatment with MMA at 1.3 g/kgbw (0.5 LD₅₀) in an acute study and following treatment with MMA at 0.65 mg/kgbw (0.25 LD₅₀) twice a week for periods of 2 and 4 weeks; no significant increases in chromosomal aberrations were observed following treatment twice a week for 6 and 8 weeks. In the absence of toxicity information there is no scientific rationale for such a pattern. In addition, no criteria for the analysis of chromosomal aberrations are provided; it is therefore not clear whether or not gap-type chromosomal aberrations, which are of questionable biological significance, have been included.

Ouyang *et al* (1988) reported a negative micronucleus test in rats, but no experimental details or data are available in the brief abstract.

Jensen *et al* (1991) reported MMA as negative in a mouse micronucleus test when tested via the i.p. route in groups of 10 B6:NMRI SPF mice as part of a methacrylate bone cement extract mixture. No effect was observed on the percentage of polychromatic erythrocytes in the bone marrow of the treated animals and the significance of this study is difficult to determine based on the use of a mixture extract and lack of rationale for dose level selection.

8.4.7 Dominant Lethal Assay

Groups of 20 male CD-1 mice were exposed via inhalation to MMA atmospheres of 100, 1,000 or 9,000 ppm for 6 h/d for a period of 5 days. These concentrations, which were based on preliminary toxicity studies, resulted in the deaths of 1/20, 1/20 and 6/20 males in the 100, 1,000 and 9,000 ppm groups respectively. Each surviving male was mated with 2 virgin females each week for a period of 8 weeks and no effects on fertility, pre-implantation egg loss or early or late post-implantation foetal deaths were observed in the female mice. The positive controls responded as expected (ICI, 1976d).

8.4.8 Summary

MMA is not mutagenic to bacteria when tested up to cytotoxic concentrations. The data from a series of *in vitro* mammalian cell gene mutation and chromosomal aberration assays clearly show MMA to be an *in vitro* clastogen as evidenced by the induction of small colony mutants and chromosomal aberrations.

There is no convincing evidence for an *in vivo* clastogenic effect of MMA when animals are exposed by inhalation, that is the route relevant for human exposure (ICI, 1976a, 1979) or by oral administration (Hachiya *et al*, 1981). MMA did not induce any dominant lethal mutations *in vivo* thus adding weight to the conclusion that MMA is not an *in vivo* clastogen.

8.5 CHRONIC TOXICITY AND CARCINOGENICITY

8.5.1 Oral

Groups of 25 male and 25 female Wistar rats were exposed to MMA in drinking water for 104 weeks. The initial concentrations were 6, 60 and 2,000 ppm MMA. At the start of the 5th month the low and mid dose levels were raised to 7 and 70 ppm (Borzelleca *et al*, 1964). Survival of the exposed rats was not significantly different from the controls. In both males and females exposed to 2,000 ppm MMA, an initial reduction in body weight gain was observed, which reverted

to control levels by week 3 (females) and week 6 (males). No other effects on body weight gain were observed during the rest of the study. During the first month of the study, a reduction in food intake was observed in both sexes. This had resolved by the second month and no further adverse effects were observed on food intake, but drinking water consumption was significantly lower than controls in both males and females exposed to 2,000 ppm MMA, although the effect was more pronounced in the females. The haematological parameters measured were within normal ranges throughout the study. There were no compound related effects on urinary protein or reducing substances. With the exception of an increased kidney/body-weight ratio in female rats exposed to 2,000 ppm MMA there were no effects on organ body weight ratios. Histopathological examination of the tissues of exposed rats showed no compound related abnormalities or lesions (Borzelleca *et al*, 1964). The change in kidney/body-weight ratio in the females treated at 2,000 ppm is considered by the Task Force to be a functional adaptation in response to the significantly reduced water intake. Therefore the NOEL is 2,000 ppm.

Groups of 2 male and 2 female dogs were fed dietary equivalent concentrations of 0, 10, 100 and, initially, 1,000 ppm MMA (1x/d in as a corn-oil solution contained in gelatine capsules) for 2 year. The concentration of MMA in the high dose group was altered to 500 ppm (day 2), 0 ppm (day 3-13) and 300 ppm (day 14) due to vomiting, and then increased stepwise to 1,500 ppm over a period of 9 weeks and maintained at this level for the remainder of the 2-year study. Slight, but statistically non-significant, reductions in body weight gains were observed in dogs of both sexes fed dietary equivalents of 1,000-1,500 ppm MMA. No adverse effects were noted on food or water consumption, haematological parameters, or on the levels of urinary protein or reducing substances. Organ body weight ratios differed from controls only with statistically significant lower spleen ratios in dogs receiving 100 ppm MMA. The effect was not seen at 1,000-1,500 ppm and its biological significance is uncertain. No histopathological changes, attributable to MMA, were seen in any of the organs and tissues examined (Borzelleca *et al*, 1964).

8.5.2 Dermal

Oppenheimer *et al* (1955) reported a skin painting study in 10 Wistar rats (sex not specified). The animals were painted with MMA (3x/wk, concentration and vehicle not indicated) for 4 months. The authors reported that no tumours were detected at the end of the exposure period. Further information was not given.

8.5.3 Inhalation

Gabor *et al* (1965) studied the chronic toxicity of MMA in white rats (strain not indicated). Groups of 30 rats were exposed (2 h/d, 7 d/wk) to 0.01 and 0.02 mg MMA/l (2.4 and 4.8 ppm) for 8 months; a control group consisted of 44 animals. No changes in body weight and haematology were observed in the exposed groups. Dose related decreases in blood cholinesterase activity cerebral cytochrome oxidase and cholinesterase levels, liver catalase levels and free SH-groups in liver and blood were reported. Due to deficiencies in the reported analytical data, the significance of these findings is difficult to interpret.

Studies in laboratory animals have shown that chronic inhalation of MMA results in inflammatory lesions in the olfactory region of nasal tissues. Several studies have been reported to date.

Groups of 70 male and 70 female F344 rats were exposed (6 h/d, 5 d/wk) to atmospheres containing MMA at 0, 25, 100 or 400 ppm (mean measured concentrations: 0, 25.00, 99.79 and 396.07 ppm) for 104 weeks (Rohm and Haas, 1979a). Mortality rates for the groups exposed to MMA were comparable to the air control group. Sporadic, statistically significant effects (elevations and depressions) were seen in body weights in male rats exposed to 100 or 400 ppm MMA and in female rats at all 3 exposure concentrations. In the females exposed to atmospheres containing 400 ppm, the body weights tended to be lower than control after week 52. This was considered to be related to MMA exposure. No clinical signs of MMA-related toxicity were observed in any of the animals exposed to MMA. The clinical signs observed during the study were restricted to cloudy eyes and bloody crust around the eyes and these observations occurred with approximately equal frequency in the exposed and control animals, and were considered not to be treatment related. Evaluation of the haematology and clinical chemistry data did not show any remarkable trends. With the exception of the appearance of occult blood in the urine of all groups at week 52, urinalyses revealed no remarkable effects. Statistically significant increases in both absolute and relative weights of lung, liver, kidney and ovary were seen at week 13 in females exposed to MMA at 400 ppm. Statistically significant lower absolute and relative thyroid and adrenal weights were observed at week 52 in both sexes exposed to MMA at 400 ppm. Other sporadic statistically significant differences were noted at week 52 and 104; however, no consistent dose-related patterns emerged. No consistent, treatment related gross pathology was noted in any of the animals. The incidence of tissue masses at necropsy showed no treatment related differences with respect to frequency of occurrence. At week 13 and 52, histopathological examination of tissues from rats, exposed to atmospheres containing 400 ppm MMA, showed no treatment related changes. At week 104 (terminal kill), compound related histomorphologic changes were restricted to a very slight increase in lesions of mild rhinitis observed in the mucosal lining of the nasal

turbinates (Table 20). These lesions were characterised by slight serous exudate overlying the mucosa which occasionally contained polymorphonuclear leucocytes and distended the submucosal glands. Occasionally there was an accompanying pleocellular infiltrate in the submucosal tissues. Focal areas of squamous metaplasia were observed in 5 males and 2 females from the 400 ppm group and in 2 control males. Inflammatory polyps were originally observed in 2 males from the 400 ppm group and in 1 male from the 100 ppm group when the slides were read by the original pathologist (Rohm and Haas, 1979a). The consultant pathologist who subsequently examined these slides observed the polyps in only 2 male rats, 1 from the 100 ppm group and 1 from the 400 ppm group (Rohm and Haas, 1979c).

Table 20 Incidence of Lesions in the Nasal Mucosa of F344 Rats Following 104 Weeks Inhalation Exposure. (Rohm and Haas, 1979a,c)

	Concentration (ppm)			
	0	25	100	400
Males				
Turbinates examined (N°)	48	49	49	48
Serous exudate	3	11	12	16
Purulent exudate	2	6	4	8
Pleocellular infiltration	1	4	6	19
Distended submucosal glands	5	21	21	12
Squamous metaplasia, focal	2	3	1	5
Inflammatory polyp	0	0	1	2 ^a
Females				
Turbinates examined (N°)	44	48	44	44
Serous exudate	15	8	17	23
Purulent exudate	2	9	6	6
Pleocellular infiltration	3	14	9	11
Distended submucosal glands	3	14	12	9
Squamous metaplasia, focal	0	5	1	2
Inflammatory polyp	0	0	0	0

^a Polyps were observed in 2 animals by the original pathologist. Subsequent review by 2 pathologists have failed to confirm the presence of one of the polyps in one of the high-dose animals (Rohm and Haas, 1979c; Lomax *et al*, 1994)

None of these lesions revealed a consistent trend with exposure, but the lesions of mild rhinitis were observed more frequently in rats exposed to MMA, than in control rats. As slight irritant

effects were observed at 25 ppm, a NOEL could not be established. It is not possible, on the strength of this study alone, to determine if the rhinitis was a direct consequence of exposure to MMA or whether exposure to MMA predisposed the animals to an increased incidence of spontaneous disease. The authors concluded that the latter was likely. Based on the high incidence of rhinitis in the control animals (Lomax, 1992), the Task Force concurs with this view. Neoplasms were observed with essentially the same frequency in all groups and none were specifically correlated with exposure to MMA (Rohm and Haas, 1979a).

In a similar study, groups of 56 male and 56 female Lakeview Golden Hamsters (due to incorrect sexing, the low exposure group comprised 53 males and 59 females; the high exposure group 55 males and 57 females), were exposed (6 h/d, 5 d/wk) to atmospheres containing 0, 25, 100 or 400 ppm MMA for 78 weeks. Mean measured atmosphere concentrations were 0, 24.77, 100.06 and 398.68 ppm MMA. At week 78, cumulative mortality in the mid-exposure group males was similar to the controls. Mortality in the low- and high-dose males was significantly higher than the controls. In females, mortality in the control group was high (72.7% compared with 34.5% in the male controls). There was no dose-related mortality in females exposed to MMA. Sporadic fluctuations in body weight were observed during the study, affecting both high and low exposure males and females, but there was no treatment relationship. With the exception of statistically significant lower mean haemoglobin values at week 78 in high exposure males and a slight decrease in high exposure females, all haematological parameters were within normal limits. At post-mortem, no gross pathological effects attributable to MMA exposure were observed. The incidence of nodules and masses was not significantly different between the control and MMA exposed groups. Only the control and high exposure group was examined histopathologically, and no treatment related changes were observed (Rohm and Haas, 1979b). Nasal tissue sections of the high dose group were examined and found to be largely free of irritation or associated lesions. However, it should be noted that the olfactory regions of the nasal cavities were not examined in this study.

In order to fully establish the lack of carcinogenic potential of MMA the NTP, as part of the National Toxicology Programme, conducted a 2-year inhalation study in F344/N rats and B6C3F₁ mice in 1986 using higher concentrations than had been previously used in the Rohm and Haas (1979a) study detailed above.

Groups of F344/N rats were exposed (6 h/d, 5 d/wk) to atmospheres containing 0, 500 or 1,000 ppm MMA (males) and 0, 250 or 500 ppm MMA (females) for 102 wk. There was no significant effect on the survival of the animals to the end of the study. Body weights of males at

1,000 ppm MMA were 5-10% lower than the controls from week 81; body weights of females at 500 ppm MMA were 6-11% lower than the controls from week 73. An increase in the incidence of mononuclear cell leukaemia was observed in the 500 ppm MMA exposure group [controls, 11/50; 250 ppm, 13/50; 500 ppm, 20/50]. When analysed using life table analysis, the most appropriate test for life threatening lesions, these differences were not significant. Significant negative trends were observed for pituitary tumours (adenomas and carcinomas combined) in male rats and the incidence in rats exposed to 1,000 ppm MMA was significantly lower than the controls. Preputial gland adenomas and carcinomas occurred with a negative trend in exposed males and the incidence in male rats exposed to 1,000 ppm was significantly lower than controls. Serous and suppurative irritation of the nasal cavity and degeneration of the olfactory epithelium was observed at increasing incidences in exposed rats of both sexes, relative to the controls (Table 21). In the high exposure groups, 44/50 males and 32/50 females showed serous irritation; 30/50 males and 12/50 females showed suppurative inflammation; olfactory degeneration being observed in 42/50 males and 44/50 females. Alveolar macrophages were increased in a dose related manner, but even at the high dose the severity was considered minimal. A NOEL for nasal lesions in rats could not be established. No preneoplastic or neoplastic lesions related to MMA exposure were found in the rats exposed to MMA in this study (NTP, 1986; Chan *et al*, 1988).

Groups of 50 male and 50 female B6C3F₁ mice were exposed (6 h/d, 5 d/wk) to atmospheres containing 0, 500 or 1,000 ppm MMA for 102 weeks. There was no significant effect on the survival of the animals to the end of the study. Body weights of male and female mice exposed to atmospheres containing MMA were lower (5-8%) than controls at terminal kill. For most of the second year of the study the body weights of dosed males and high dose females were 4-9% lower than controls. Acute and chronic inflammation, epithelial hyperplasia, cytoplasmic inclusions in the epithelial cells and degeneration of the olfactory epithelium in the nasal cavity occurred at greater incidences in exposed mice of both sexes (Table 22). A NOEL for nasal lesions in mice could not be established. No preneoplastic or neoplastic lesions related to MMA exposure were found in the mice in this study (NTP, 1986; Chan *et al*, 1988).

Recently, the US Methacrylate Producers Association (MPA) commissioned a review of the histopathology of the nasal tissues from the rats in the Rohm and Haas (1979a) study. The review was conducted in response to increased awareness in the 1980's of the importance of the nasal cavity as a target organ in inhalation studies in rodents which had led to a general refinement of histological techniques and greater consistency in histopathological diagnostic nomenclature (Lomax, 1992). The review was conducted by Dr LG Lomax, pathologist at Rohm and Haas Company, USA, and included taking sections deeper into the tissue blocks than was done in the original study. The results of Dr Lomax's examination were subsequently peer reviewed by

Table 21 Incidence of Non-neoplastic Lesions in F344/N Rats Following Inhalation Exposure for 102 Weeks. (NTP, 1986; adapted from Chan *et al*, 1988)

	Concentration (ppm)		
	0	500	1,000
Males			
Nasal cavity			
Serous inflammation	0/50	37/50 ^a	44/50 ^a
Suppurative inflammation	11/50	21/50 ^b	30/50 ^a
Olfactory sensory epithelium degeneration	7/50	39/50 ^a	42/50 ^a
Lung			
Alveolar macrophages	6/49	20/49 ^a	16/50 ^b
Focal or multifocal fibrosis	6/49	6/49	5/50
Females			
	0	250	500
Nasal cavity			
Serous inflammation	4/50	17/50 ^a	32/50 ^a
Suppurative inflammation	7/50	12/50	12/50
Olfactory sensory epithelium degeneration	2/50	39/50 ^a	44/50 ^a
Lung			
Alveolar macrophages	9/50	14/50	16/50
Focal or multifocal fibrosis	1/50	2/50	7/50 ^a

a P <0.01 vs. controls

b P <0.05 vs. controls

Dr S. R. Frame, a pathologist at the DuPont Haskell Laboratory, USA. Of particular importance in this reanalysis was the differentiation between lesions of the olfactory epithelium and the respiratory epithelium, which had not been performed in the original histopathological examination (Tables 23 and 24). Fresh sections were cut from the preserved tissue blocks and assessed for nasal irritation. The nasal cavities of both males and females rats exposed to 25 ppm MMA were morphologically similar to the controls. Rats exposed to 100 or 400 ppm MMA had exposure related, concentration dependent histopathological changes to the olfactory portion of the dorsal meatus in the anterior portions of the nasal cavity; these portions of the nasal cavity contain squamous, respiratory and olfactory epithelium. Chronic exposure to MMA did not appear to affect the squamous epithelium. The olfactory region lining the dorsal meatus in the anterior region of the nasal cavity was primarily affected by the exposure to MMA and showed exposure related microscopic changes characterised by degeneration and/or atrophy of the neurogenic epithelium and submucosal glands lining the dorsal meatus, basal cell hypoplasia, replacement of olfactory epithelium with ciliate (respiratory-like) epithelium, and inflammation of mucosa and/or submucosa. These changes were generally bilateral in distribution and the severity of the lesions varied from minimal to slight at 100 ppm to slight to moderate at 400 ppm. One male rat from the 400 ppm exposure group showed severe effects (Lomax, 1992).

Table 22 Incidence of Non-neoplastic Lesions of B6C3F₁ Mice Following Inhalation Exposure for 102 Weeks. (NTP, 1986; adapted from Chan *et al*, 1988)

	Concentration (ppm)		
	0	500	1,000
Males			
Nasal cavity			
Acute/chronic inflammation	1/50	37/50 ^a	42/50 ^a
Epithelial hyperplasia	2/50	44/50 ^a	46/50 ^a
Nasal mucosa			
Cytoplasmic inclusions	14/50	46/50 ^a	46/50 ^a
Olfactory sensory epithelium degeneration	0/50	48/50 ^a	48/50 ^a
Lung			
Interstitial inflammation	1/50	0/50	8/50 ^b
Females			
Nasal cavity			
Acute/chronic inflammation	2/50	42/49 ^a	45/50 ^a
Epithelial hyperplasia	1/50	43/49 ^a	47/50 ^a
Nasal mucosa			
Cytoplasmic inclusions	24/50	44/49 ^a	46/50 ^a
Olfactory sensory epithelium degeneration	2/50	44/49 ^a	47/50 ^a
Lung			
Interstitial inflammation	0/49	0/49	1/50

a P <0.01 vs. controls

b P <0.05 vs. controls

Exposure-related microscopic changes in the respiratory epithelium occurred in rats, primarily males, exposed to 400 ppm MMA and were characterised as hyperplasia of submucosal glands and/or goblet cells in the anterior regions of the nasal cavity, especially around the dorsal meati and along the nasal septa. Inflammation of the mucosa and/or submucosa was also observed. These changes to the respiratory epithelium were primarily bilateral and were slight to moderate in severity. The 400 ppm group males had a higher incidence of chronic inflammation in the respiratory epithelial region of the nasal cavity than the 400 ppm group females. One male rat from each of the 100 and 400 ppm exposure groups had a small solitary polypoid mass attached to the lateral wall of one side of the anterior nasal cavity. These small masses were morphologically similar and were composed of well differentiated pseudoglandular structures arising from the respiratory epithelium. These were diagnosed as adenomas due to a recognised change in histopathological nomenclature (inflammatory polyps in the original study). The male rat from the 100 ppm group with the adenoma had concurrent moderate chronic inflammation of the respiratory epithelium on the same side of the nasal cavity. Two male rats exposed to 400 ppm MMA had squamous metaplasia of the respiratory epithelium in anterior region of the nasal cavity. Based on

Table 23 Summary of Histopathology of Rats Exposed to MMA for 2 Years. (Lomax, 1992)

	Concentration (ppm): No./group:	Males Affected ^a				Females Affected ^a			
		0	25	100	400	0	25	100	400
		40	49	49	47	45	48	48	44
Olfactory Epithelium	No. examined:	39	47	40	38	44	45	41	41
Degeneration/atrophy, dorsal meatus, bilateral		0	0	39	36	0	0	23	33
Degeneration/atrophy, dorsal meatus, unilateral		0	0	3	2	0	0	1	6
Basal cell hyperplasia, unilateral		4	3	1	0	0	1	1	2
Basal cell hyperplasia, bilateral		1	0	32	33	0	0	17	29
Replaced by ciliated epithelium, bilateral		0	0	0	9	0	0	7	16
Replaced by ciliated epithelium, unilateral		0	0	1	6	0	0	0	5
Inflammation chronic/active, mucosa/submucosa, bilateral		0	0	16	25	0	0	1	24
Inflammation chronic/active, mucosa/submucosa, unilateral		0	0	1	4	0	0	4	1
Exudate, lumen, dorsal meatus, unilateral		1	0	0	1	1	0	0	1
Mononuclear cell infiltrate		0	1	0	0	0	1	0	0
Thrombosis, blood vessels, submucosa		0	0	0	0	0	0	1	0
Respiratory Epithelium	No. examined:	44	47	48	42	45	45	41	42
Inflammation chronic/active, mucosa/submucosa, bilateral		0	0	1	26	1	0	0	8
Inflammation chronic/active, mucosa/submucosa, unilateral		4	0	1	0	1	0	0	1
Hyperplasia, submucosal gland/goblet cell, bilateral		0	0	1	25	0	0	0	8
Hyperplasia, submucosal gland/goblet cell, unilateral		1	0	0	0	0	0	1	1
Hyperplasia, unilateral		0	0	0	2	0	0	0	0
Mononuclear cell infiltrate		0	1	0	0	0	1	0	0
Foreign body, inflammation, ventral meatus, unilateral		3	0	1	0	4	1	3	0
Thrombosis, blood vessels, submucosa		0	0	0	0	1	0	1	0
B-adenoma		0	0	1	1	0	0	0	0
Squamous metaplasia, unilateral		1	0	0	1	0	0	0	0
Squamous metaplasia, bilateral		0	0	0	1	0	0	0	0

a Death status - all animals; controls from group(s): 1

Table 24 Severity Grade of Selected Nasal Cavity Microscopic Tissue Changes from Rats Exposed to MMA for 2 Years. (Lomax, 1992)

		Males				Females			
		Concentration (ppm)							
	Severity Grade	0	25	100	400	0	25	100	400
Olfactory Epithelium									
Degeneration/atrophy, dorsal meatus, unilateral or bilateral	Minimal	0	0	7	0	0	0	0	0
	Slight	0	0	33	11	0	0	24	10
	Moderate	0	0	2	28	0	0	0	29
	Severe	0	0	0	1	0	0	0	0
Basal cell hyperplasia, unilateral or bilateral	Minimal	5	3	5	0	0	1	0	0
	Slight	0	0	27	14	0	0	18	23
	Moderate	0	0	1	19	0	0	0	8
Replaced by ciliated epithelium, uniliteral or bilateral	Slight	0	0	2	12	0	0	7	16
	Moderate	0	0	0	3	0	0	0	5
Inflammation, mucosa/submucosa, unilateral or bilateral	Slight	0	0	16	21	0	0	5	17
	Moderate	0	0	1	7	0	0	0	8
	Severe	0	0	0	1	0	0	0	0
Respiratory Epithelium									
Hyperplasia, submucosal gland/goblet cell, unilateral or bilateral	Slight	0	0	1	13	0	0	0	6
	Moderate	1	0	0	12	0	0	1	3
Inflammation, mucosa/submucosa, unilateral or bilateral	Slight	3	0	2	20	2	0	0	8
	Moderate	1	0	0	6	0	0	0	1

this re-assessment of the study the author concluded that the nasal cavity is the target organ for MMA following exposure by the inhalation route and that the olfactory epithelium is the primary target tissue. The NOEL for nasal lesions was 25 ppm (Lomax, 1992).

8.5.4 Summary

Oral exposure via drinking water or the diet, for 2 years produced no histopathological changes and no neoplasms in dogs or rats. Inhalation exposure of mice, rats and hamsters to atmospheres containing MMA did not produce neoplastic or preneoplastic lesions in the target tissue (olfactory epithelium). The number of polypoid adenomas observed in the respiratory epithelium in the Rohm and Haas rat study is very low and may be considered to have resulted from an enhancement of the low background level of a naturally occurring lesion by the irritant effect of MMA on the nasal cavity. This view is supported by the lack of polypoid adenomas observed in the NTP rat and mouse studies which used much higher concentrations of MMA than the Rohm and Haas study. Non-neoplastic changes were restricted to the upper respiratory tract and included rhinitis, serous

and suppurative irritation, epithelial hyperplasia and degeneration of the olfactory epithelium. MMA therefore shows no carcinogenic activity following exposure via the inhalation or oral routes.

8.5.5 Evaluation

The lead effect of MMA in chronic inhalation studies in rodents is the nasal lesion characterised by inflammatory degeneration of the nasal epithelium, the target tissue at low concentrations being the olfactory epithelium; only at 400 ppm were effects seen in the anterior regions of the nose. A NOEL in the rat of 25 ppm has been established with very slight nasal lesions being observed at 100 ppm. This histological picture and the pattern of effect (ie. olfactory tissue affected at the lower concentration) is consistent with toxicity arising from metabolism of the inhaled material by the olfactory tissue. Olfactory tissue in many species, including man, is known to have a considerable capacity to metabolise inhaled materials (Lewis *et al*, 1993). A purely irritant effect of the inhaled material would have given a reversed effect pattern, ie. the anterior, respiratory epithelium lined regions would have been affected at the lower concentration with a progression with increasing concentration to the posterior olfactory regions (Hotchkiss *et al*, 1993; Morris *et al*, 1993).

These effects are therefore probably related to the deposition of MMA in the upper respiratory tract and its subsequent hydrolysis by carboxylesterase enzymes to methacrylic acid in the nasal mucosa as demonstrated by Morris (1992) (Section 7.2.2). Localisation and severity of the lesion in the olfactory epithelium is consistent with the greater esterase activity reported in the olfactory epithelium as compared with respiratory epithelium in rodents (Dahl *et al*, 1987; Bogdanffy *et al*, 1987; Bogdanffy, 1990; Frederick *et al*, 1994). Release of methacrylic acid in this tissue is likely to cause severe local irritation leading ultimately to the observed histopathological effects. This is not an unexpected observation, similar toxicity arising from acids released by the same metabolic route has been seen with ethyl acrylate (Miller *et al*, 1985), methyl and butyl acrylate (Klimisch, 1984), dibasic esters (Keenan *et al*, 1990) and glycol ether acetates (Miller *et al*, 1984). An additional factor governing tissue specificity may be due to differing sensitivities to the acid metabolite or even further metabolism of the acid. This is suggested by inhalation studies conducted on acrylic and acetic acids, both inducing olfactory epithelium lesions (Miller *et al*, 1981; Stott and McKenna, 1985).

There is currently considerable interest amongst the toxicological community in nasal toxicity and species sensitivity differences (CIIT, 1993) and this has highlighted the need to consider the relevance of rodent nasal epithelium lesions to human risk assessment. There are significant morphological differences between species in the structure of the nasal cavity and this is reflected in the differences in surface area normalised to minute ventilation reported between rodents

(9 mm²/ml/min) and human beings (2 mm²/ml/min) (Morris, 1989) which will result in differences in concentration of inhaled materials at the nasal tissue. In addition, rodents are obligate nose breathers whereas man can also breathe through the mouth, the latter method of breathing being expected to reduce exposure of the nasal epithelium. Differing nasal flow patterns also influence the proportion of inhaled air passing over specific regions of the nasal cavity (De Sesso, 1993) and hence the quantity of MMA vapour that might be absorbed. In the rat, work by Morgan *et al* (1989) suggests that a small but significant proportion of inhaled air is directed onto the regions containing olfactory epithelium. In contrast, in man during the inhalatory phase of respiration, a small eddy is generated in the olfactory region, considered to provide sufficient flow for olfaction while protecting against injury (Swift and Procter, 1977). The greater airflow across the human olfactory epithelium is during the expiratory phase when the vapour concentration would be considerably reduced due to absorption in the lower respiratory tract. Taken together, these factors suggest that human beings may be less sensitive than rodents to lesions of the nasal epithelium caused by MMA.

Although no data are currently available on the species differences in olfactory tissue carboxylesterase activity, there are scant data available on species differences in respiratory enzyme complements. Mattes and Mattes (1992) have demonstrated a 35-fold lower activity of α -naphthylbutyrate carboxylesterase in human nasal respiratory tissue as compared to the rat and, although this supports the view that man is less likely to develop olfactory lesions as a result of inhaling MMA vapours, it must be stressed that these data were generated from human tissue samples taken at polyp biopsy that may not have been morphologically normal.

It can therefore be concluded from the above that, while human nasal tissue will have the appropriate enzyme complement to metabolise MMA, the combination of the lower enzyme activities expected, together with differences in surface area to inspired flow and flow patterns, will result in a considerably reduced potential for the human to develop olfactory tissue lesions equivalent to those seen in the rat if exposed to similar concentrations of MMA vapour. More investigative work is required in this area as it is currently too early to understand how well rodents predict the possible effects on inhalatory exposure of man to chemicals; more work on the species sensitivity to inhaled chemicals is essential for a thorough understanding of the actions of those chemicals in man.

8.6 REPRODUCTIVE TOXICITY, EMBRYOTOXICITY AND TERATOGENICITY

8.6.1 Oral

No data are available.

8.6.2 Inhalation

In a dominant lethal assay, groups of 14-16 male CD-1 mice were exposed (6 h/d) to 100, 1,000 or 9,000 ppm MMA for 5 days. Each male was mated with 2 different unexposed female mice weekly over a period of 8 weeks. There were no significant differences in fertility of the treated males or survival rate, total implants and early or late post-implantation death in the offspring of treated males compared to controls (ICI, 1976d).

Groups of 30 female Alderley Park SPF rats were exposed (5 h/d) to MMA vapour at 0, 100 and 1,000 ppm from days 6 to 15 of gestation. In a second experiment, the same levels and an additional level of 25 ppm MMA were used. A dose of 1,000 ppm, which was slightly maternally toxic, produced an increase in the numbers of early resorptions, and possibly affected the total numbers of late resorptions in the first experiment. Foetal body weight and development was normal and an increase in foetal abnormalities was not seen. There was a slight retardation of ossification at the high concentration. The NOEL for delayed ossification in this study was 100 ppm. The authors concluded, that MMA was not teratogenic in the rat when administered by inhalation, but appeared to be weakly embryotoxic at the high dose level (ICI, 1977a).

MMA was administered by inhalation (6 h/d) to 5 groups of 27 presumed pregnant rats (CrI:CDRBR) at concentrations of 0, 99, 304, 1,178 and 2,028 ppm from days 6 to 15 of gestation. (The study was conducted in accordance with OECD guideline 414 and US EPA CFR Part 798.4350 and under GLP conditions.) The animals were exposed in whole-body inhalation chambers under dynamic conditions. On day 20, the dams were killed and examined for gross abnormalities as well as reproductive performance. Treatment-related effects on maternal body weight and food consumption were noted at all exposure levels tested. In the lower dose groups the decreases in body weight gain were only slight (days 6-8 of gestation) and returned to control values by the next weighing period (day 10 of gestation). Therefore a maternal no observed effect level could not be determined. No embryo or foetal toxicity was evident and no increase in the incidence of malformations or variations was noted at exposure levels up to and including 2,028 ppm (NOEL) (Solomon *et al*, 1993).

Luo *et al* (1986) exposed (2h/3d) rats (strain not stated) to air concentrations of 0, 0.52 and 4.48 mg MMA/l (0, 125 and 1,080 ppm) from days 6 to 18 of gestation. Data on the nature and purity of the test substance, exposure conditions and analytical determination of air concentration were not reported. The results of the study were summarised by the authors as follows "No notable signs of maternal toxicity were observed". A statistically significant increase in the incidence of resorptions was observed only in the high concentration group. Delayed ossification was found in

both exposure groups. No gross or skeletal abnormalities were observed. The NOEL for resorptions was reported to be 127 ppm MMA. The validity of this study cannot be determined as detailed data on the observations were not provided.

Groups of 22 to 27 pregnant Sprague-Dawley rats were exposed by head and nose (7.2 or 54.2 min/d, i.e. approximately 10% and 75% of the LT_{50} of 72.2 min) to air saturated with MMA vapour at 15°C (27,000 ppm) on gestation days 6-15. Control animals were exposed (head and nose) to air only or remained untreated, i.e. received no form of exposure. The maternally toxic MMA concentrations (4 pregnant rats died) caused early foetal deaths, decreased crown-rump length, delayed ossification, decreased foetal weight, and haematomas (Nicholas *et al*, 1979a,b,c).

Eighteen pregnant ICR mice were exposed (2 h/d) to average vapour concentrations of 1,330 ppm MMA from days 6 to 15 of pregnancy. In a control group, 14 mice were exposed only to air. A slight increase in the weight of the foetuses was found in the exposed group, but no evidence of foetal toxicity or teratogenic effect was observed. Toxic effects on the dams were not examined in this study (McLaughlin *et al*, 1978).

Exposure (6 h/d) of groups of 18 or 32 female Charles River CD-1 mice to air concentrations of 0, 116 and 400 ppm MMA from days 4 to 13 of pregnancy produced a slight decrease in foetal weight. There were no significant differences between control and MMA exposed groups in viability, gross abnormalities or skeletal and visceral abnormalities of the offspring. Signs of maternal toxicity were not reported (Tansy, 1978).

Smirnova *et al* (1977) reported a threshold concentration of 54 mg MMA/m³ (13 ppm), when inhaled continuously over 4 months by female rats, for an effect on the oestrogenic function of the ovary. It was claimed that MMA caused an increased oestrogen secretion of the ovary which reflected an increased follicle stimulating activity in the pituitary. The relevance of the data to human hazard assessment is questionable.

8.6.3 Other routes of exposure

Groups of 12 mated female Dutch rabbits were dosed i.p. with 0.004, 0.04 and 0.4 ml/kg/d from day 6 to 18 of pregnancy. On day 29, the animals were killed and their uteri examined for live foetuses and early and late resorptions. The foetuses were removed, weighed, sexed, and examined for viability and abnormalities. Nine animals, distributed evenly between the groups (solvent and MMA) died or were killed prematurely during the study. In addition, a high incidence of peritonitis and an increase in respiration rate were observed in the top dose level group. Significant reductions in

foetal weight and an increase in the numbers of early resorptions were observed at the top dose. There were no increases in soft tissue or skeletal abnormalities and the investigators concluded that MMA was not teratogenic in the rabbit following i.p. injection. It should be noted that this route of exposure is not a physiologically appropriate route for MMA (ICI, 1976b).

MMA was administered i.p. to groups of 5 female Sprague-Dawley rats at doses of 0, 0.1328, 0.2656 and 0.4427 ml MMA/kgbw (1/10, 1/5 and 1/3 of the acute LD₅₀ value of 1.328 ml/kgbw) on day 5, 10 and 15 of gestation. A dose-dependent increase of gross abnormalities (haemangiomas) was found in the foetuses, but there were no skeletal malformations. Maternal toxicity of the dams was not examined (Singh *et al*, 1972a,b).

The embryotoxic effects of MMA was tested in 3 day chicken embryos by Korhonen *et al* (1983a,b). The median effective dose for embryotoxic effects was 22 µmol MMA/egg. Malformations were observed, but the quantitative relationship remains obscure.

8.6.4 Summary

A series of studies with MMA have shown no teratogenic effects following inhalation exposure of rats and mice. Of these studies the most definitive study, conducted to a rigorous protocol in accordance with current OECD and EPA guidelines and under GLP conditions, is that of Solomon *et al* (1993) in which no teratogenicity, embryotoxicity or fetotoxicity has been observed at exposure levels up to 2,028 ppm.

A delayed ossification and an increase in resorptions observed in rats exposed to MMA at approximately 1,000 ppm (ICI, 1977a; Luo *et al*, 1986) may indicate first signs of embryotoxicity and developmental effects. However, these findings were not corroborated by the study of Solomon *et al* (1993). Two studies conducted using the i.p. route of administration produced contradictory results but it should be noted that this is not a relevant or appropriate route of administration for MMA and therefore the results of this study are of questionable value.

MMA did not reveal an effect on male fertility in mice exposed to up to 9,000 ppm MMA over a period of 5 days.

8.7 NEUROTOXICITY

Several publications in the literature have inferred that MMA is having neurotoxic/central nervous system effects in occupationally exposed human beings. As a result, a number of publications have

reported experiments to investigate if MMA has any *in vitro* or *in vivo* neurotoxic effects in a variety of experimental systems.

8.7.1 *In Vitro* Studies

The influence of MMA on resting and compound action potential of the isolated de-sheathed frog sciatic nerve was investigated by Böhling *et al* (1977). Isolated nerves were treated with 5, 10, 20, 25, 50 or 100 mM MMA for 15, 55 or 60 minutes. A reversible dose-dependent decrease of the compound action potential was observed over a period of 15 to 75 minutes. The action potential was completely abolished after 15 minutes exposure to 50mM MMA. Hyperpolarisation lasted for 15 minutes following exposure to 10, 20 or 50 mM MMA but for only 10 minutes following 100 mM MMA. The depolarising effects of calcium and veratridine were reversed by MMA. Voltage clamp measurements on the Node of Ranvier following treatment with 50 mM, MMA showed a decrease of sodium and potassium currents.

A study was made of the effects of MMA on the resting potential of the isolated desheathed sciatic nerve and the electroretinogram (ERG) of the isolated retina of a frog. A dose-dependant decrease in ERG was observed above 1 mM and of the action potential of the sciatic nerve at 10 mM. Hyperpolarisation of the membrane potential of the nerve started 1.5 min after MMA application. Replacement, in the bathing medium, of $[Na^+]_o$ by choline or of $[Cl^-]_o$ by nitrate, and an increase in $[Ca^{2+}]_o$, did not affect hyperpolarisation. It was reduced by increasing the $[K^+]_o$ concentration of the bathing fluid. Also, if $[NaCl]_o$ was replaced by sucrose there was no polarising effect of MMA. Depolarisation in Ca^{2+} -free solutions and with veratridine was reversed by MMA. The authors suggest that MMA has a complex effect on Cl^- and Na^+ -permeability and that the ester group is involved (Borchard, 1976; Borchard and Böhling, 1977).

8.7.2 *In Vivo* Studies

Wynkoop *et al* (1982) injected 21 male Sprague-Dawley rats s.c. with 200 μ l MMA/d. Groups of 7 rats were killed at 3, 7 and 14 days. Blood cholinesterase activity in the treated rats was lower than in controls. Average total catecholamine levels at 3, 7 and 14 days were 2,260, 3,560 and 3,780 pg/ml respectively for the controls and 5,260, 4,050 and 2,985 pg/ml for the MMA dosed animals. The effect at 3 days was statistically significant. Differential catecholamine analysis showed elevated levels of both adrenaline and noradrenaline which were significantly different from control. Dopamine levels were similar throughout the study for both the control and MMA dosed rats. The authors suggest that MMA may be a stressor for the sympathetic nervous system.

An *in vivo* investigation was also made on the afferent and efferent activity of the guinea-pig vagus nerve. After an i.v. dose of 10 mg/kgbw, MMA increased the frequency of afferent and efferent vagal activity synchronous to inspiration in mono-vagotomy but a decrease in bivagotomy. With monovagotomy, tachypnoea was observed which, according to the authors was due to a bronchospasm induced by a vagal reflectory mechanism as the tachypnoea vanished under bivagotomy. Under bivagotomy, bradypnoe and a decrease in respiratory volume was observed. The authors suggested that this indicated an effect of MMA on the breathing centre (Borchard and Bohling, 1977).

Seth and Seth (1989) dosed 2 groups of 8 male Wistar rats by gavage with 250 or 500 mg MMA/kgbw/d for 21 days. A third group, dosed only with the vehicle, olive oil, served as the control. Animals were killed 24 hours after the last dose. Significantly increased binding of ³H-spiperone to both brain striatal and blood platelet membranes were observed in both MMA dosed groups. The authors drew attention to the "close analogy" between clinical findings in hyperkinetic and mentally retarded patients, and suggested that they may have a model for the effects of MMA. Despite these claims, the toxicological significance of this model remains unclear and it is not possible to evaluate its role in human hazard assessment.

Innes and Tansy (1981) reported a study in which 4 electrode assemblies were positioned in predetermined areas of the brains of anaesthetised male Sprague-Dawley rats. The rats were then exposed to an atmosphere containing 400 ppm MMA for 60 minutes. During the exposure period continuous multiple-unit activity (MUA) neuronal recordings were made of 10 different areas of the brain (hypothalamic nuclei: anterior, dorsal, lateral, ventromedial and mamillary body; limbic nuclei: amygdaloid, dorsal hippocampal and ventral hippocampal; cerebral nuclei: parietal cortex, cerebellar cortex). Exposure to MMA caused statistically significant decreases in the firing rate of cells in the lateral hypothalamus and ventral hippocampus. Decreases were observed in the dorsal hypothalamus and cerebellar cortex but these were not statistically significant. The firing rates of cells in the remaining areas of the brain remained unchanged or increased (not statistically significant) in response to MMA exposure. Electroencephalographic recordings of the same areas gave no indication of the changes recorded by the in-dwelling electrodes. The firing rate of cells from the lateral hypothalamus and ventral hippocampus returned to normal following cessation of exposure. The authors concluded that the slowing of the firing rate in the cerebellar portion of the brain reflected decreased motor activity associated with anaesthesia rather than exposure to MMA (Innes and Tansy, 1981). Although the significance of these findings are uncertain, the authors tenuously linked them with reduced body weight gain seen in previous studies.

A group of 30 adult male Wistar rats was dosed, by oral gavage, with MMA (500 mg/kgbw/d) in olive oil for 21 days (Husain *et al*, 1985). A control group was dosed with olive oil only. Three of the MMA dosed rats died during the dosing period. No significant differences were observed in body weight or brain weight between the test and control groups. Rats dosed with MMA had a "shaggy" appearance and were sluggish. Immediately following dosing changes in gait and hind leg function were apparent, but completely resolved within 10 minutes. Behavioural tests, spontaneous motor activity, conditioned avoidance response (CAR) and aggressive behaviour, all showed adverse effects in MMA treated rats. Locomotor activity and CAR were significantly impaired, whilst aggressive behaviour was significantly increased. Measurements of noradrenaline, dopamine and 5-hydroxytryptamine in various parts of the brain were made 24 hours after the last administration of MMA. All 3 substances were elevated in the pons-medulla and hippocampus. Noradrenaline levels were increased in the cerebral cortex and corpus-striatum, dopamine was significantly reduced in the corpus striatum and 5-hydroxytryptamine was elevated in the hippocampus and mid-brain. The authors suggest that the alterations in biogenic amines may be responsible for the behavioural changes observed in this study. However, these are only preliminary results and therefore no exact mechanism can be postulated for the behavioural changes. It also has to be considered that the effects were seen at dose levels which were lethal to some of the animals and some of the neurological changes observed may have been secondary to other effects seen, such as irritation of mucous membranes of the gastro intestinal tract (Husain *et al*, 1985).

Karpov (1955a,b) studied the effects of MMA vapours inhaled during 2 hours at concentrations of 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 mg/l (120 to 1,700 ppm) on the escape and positive conditional reflexes and differentiation of sound signals of a group of 7 male white mice. At concentrations of 2 to 4 mg MMA/l (480 to 960 ppm) differentiation began to cease and escape reactions to an electric stimulus ceased at concentrations of 5-7 mg MMA/l (1,200-1,700 ppm). Disturbance of the conditional reflex response was interindividually different. The study conditions remain obscure and the small number of animals does not allow any conclusions to be drawn.

Verkkala *et al* (1983) exposed (3 h/d) 5 male Wistar rats to liquid MMA for 8 weeks. The exposed area comprised 12 cm² of proximal tail skin 1 cm distal to the anus. The MMA was applied to a cotton wool pad which was held in place with an adhesive paper label. From differences in the weight of the dressing before and after application, the amount of MMA absorbed was calculated to be 0.78 ± 0.20 g (Section 7.2.1). The exposure to MMA caused keratolysis without ulceration of the exposure site. Body weight gain of the exposed rats did not differ from controls. Motor latency did not differ between test and control groups, although it became shorter in both during the experiment. After 4 weeks exposure, the muscle response became increasingly pathological. The

mean amplitude decreased temporally as follows, 1.2 ± 0.4 mV at week 4, 1.0 ± 0.2 mV at week 5 and 0.4 ± 0.1 mV at week 8. Polyphasia appeared at week 4 and remained until the end of the study. No histopathology was performed on the nerve or muscle and it was not possible to define the toxic mechanism involved.

In a follow-up study Kanerva and Verkkala (1986) investigated the muscle response to stimulation of rat tail motor nerves by a skin electrode after 4 weeks of exposure as described by Verkkala (1983). Abnormal muscle responses were reported, but motor conduction velocities did not differ from those of controls. Light microscopic morphometry of the myelinated nerves revealed no significant changes in the thickness of the nerves. In electron microscopy of the skin, myelin figures, a sign of degeneration, were found in less than 10% of the axons in the upper dermis (control values not indicated in the paper). The local neurotoxic effect of MMA claimed by the authors still seems questionable in the light of the experiments described.

A group of 20 male Wistar rats received daily doses of 200 mg MMA/kgbw in corn oil by gavage for 21 days. A vehicle control group was dosed with olive oil alone. Body weight gain, appearance of the animals and righting reflexes were monitored during the study. Twenty four hours after the last treatment the animals were killed and whole brain and segments of the sciatic nerve were excised. Myelin and lipid fractions were isolated and analysed for different constituents. The majority of the treated rats were reported to be lethargic. Gait defects and hind limb weakness was seen 10 minutes after dosing but were completely reversible. Total brain lipid constituents remained unchanged but a significant increase of cholesterol and triglycerides and a slight decrease in phospholipids was seen in the sciatic nerves. No significant alterations were seen in the brain myelin lipids, but those of the sciatic nerves of the treated group exhibited an increase in total cholesterol content, with myelin protein unchanged. The authors suggested that an alteration of membrane fluidity, influencing the generation of action potentials, may be related to peripheral neurotoxicity (Husain *et al*, 1989).

In a study of the neurotoxic effects of acrylamide, a group of 4 male Porton strain rats were fed a diet containing 18,800 mg MMA/l (estimated daily intake 410 mg MMA/rat) for 5 weeks. There was no evidence of neurotoxicity and no enhancement of acrylamide neuropathy (Edwards, 1975). These results were also reported by O'Donoghue (1985).

Tansy *et al* (1973, 1974) examined the gastric mobility of 36 anaesthetised male Sprague-Dawley rats following exposure to atmospheres containing MMA. In the initial studies, an abrupt cessation of gastric pressure activity and a fall in gastric tonus was observed. Normal activity was observed

within 1 minute of the removal of the vapour source. However, these studies were flawed since no attempt was made to determine the exposure concentration. In subsequent studies, exposure ranged from 93.6 mg MMA/l/min (22,500 ppm/min) for 15 minutes to 1 mg MMA/l/min (240 ppm/min) for 60 minutes. At the high dose, a sharp reduction in gastric pressure, both in amplitude and frequency, was observed within minutes of exposure and persisted until the end of the exposure. Normal activity returned within 2 minutes of cessation of exposure. Exposures to 9.36 mg MMA/l/min (2,250 ppm/min) for 15 minutes produced a similar but less severe response. The most notable aspect of exposure to this lower level was that the reduction in gastric pressure persisted for up to 20 minutes after exposure ceased. The authors claimed that they could consistently produce effects at concentrations of 1 mg MMA/l/min (240 ppm/min) for 60 minutes. It is not clear, from this preliminary study, if the effect represents a reflex inhibition of gastric motor activity in response to pharmacological stimulation of cardiopulmonary receptors.

Gastrointestinal motor inhibition has also been studied in the dog (Tansy *et al*, 1977). A group of 12 mongrel dogs (male and female) were anaesthetised with chloralose-urethane and exposed to 2,000 ppm MMA. The dogs were ventilated at a fixed minute volume of 4-6 l during the exposure period and a marked inhibition of ongoing gastrointestinal motor activities was observed. This motor inhibition continued for 10-15 minutes following cessation of MMA exposure and the inhibitory response was not blocked by bilateral vagotomy, spinal transection, splanchnectomy or the i.v. administration of tetraethylammonium chloride. The administration of blood, from a dog exposed to the MMA vapour, produced GI motor inhibition in an expected dog and the authors concluded that MMA probably exerts a direct inhibitory effect on gastrointestinal smooth muscle via the cardiopulmonary systems (Tansy *et al*, 1977).

8.7.3 Summary

MMA has been shown to affect the physiology of the isolated desheathed sciatic nerve of the frog.

In vivo, a variety of effects were reported linking acute or subchronic MMA exposure to changes in behaviour, brain chemistry and the sympathetic and peripheral nervous system, as well as to direct effects on the smooth muscles of the gastrointestinal tract. In some cases the observed reactions may have been secondary reactions to local irritating effects. However, similar effects have not been observed in a number of well-conducted chronic studies and therefore the relevance of these findings for human risk assessment remains questionable.

8.8 OTHER STUDIES

A number of special studies have been reported. The majority of these data have been generated to support the small use of MMA in medical devices. They have been reviewed for the sake of completeness (Appendix A). The data are of limited toxicological value.

SECTION 9. EFFECTS ON HUMANS

9.1 ACUTE TOXICITY

9.1.1 Oral

No data are available concerning systemic effects on man following acute oral exposure to MMA.

9.1.2 Dermal

No data are available concerning systemic effects on man following acute dermal exposure to MMA.

9.1.3 Inhalation

The odour threshold of MMA is reported to be between 0.083 and 0.34 ppm (Table 1).

No deaths have been attributed to acute inhalation exposure to MMA.

Karpov (1954a,b; 1955a,b) reported irritation of the respiratory tract, weakness, fever, dizziness, nausea, headache and sleepiness after 20-90 minutes inhalation of MMA vapours at concentrations between 48-480 ppm. A threshold limit for changes in the electrical activity of the brain (EEG changes after light impulse during exposure of 5 individuals to 0.02 or 0.04 ppm MMA for 5 min) was reported to be 0.04 ppm.

Tansy *et al* (1973, 1974) measured gastric pressure in a single human volunteer by inserting an open-tip catheter, orally, into the gastric antrum. Immediately following exposure to the vapours from 20 ml MMA (atmospheric air concentrations not reported), a gradual depression of both amplitude and frequency of intragastric pressure activity was recorded; the reductions became more pronounced as exposure time increased.

No other reports have been found concerning the effects of acute exposure of man to MMA by inhalation.

9.2 SUBCHRONIC TOXICITY

There have been many reports (detailed below) in the literature of a range of effects (respiratory, neurological, cardiovascular, hormonal and behavioural responses) allegedly associated with

occupational exposure to MMA. The majority of the studies are poorly reported and lack important details concerning exposure levels, monitoring and analytical methods, exposure to other chemicals and the health status of the subjects. This information is essential for making proper judgements on the validity of such claims and therefore the results of such studies should be treated with caution.

9.2.1 Cardiovascular Effects

Dorofeeva (1974a,b) studied a number of end-points in a group of approximately 50 workers chronically exposed to MMA for 10-26 years (exposure levels not reported). The effects reported included chest pain, irregularities in heart beat, mild dilatation of the heart, labile arterial blood pressure and ECG abnormalities.

Dorofeeva (1976) studied a number of end-points in 2 groups of workers occupationally exposed to MMA for 3-26 years (exposure levels indicated to be above 2.6 ppm). The following effects were reported: pain in the heart region, irregular heartbeat, "variability" of blood pressure and changes in ECG. The frequency and severity of these effects was claimed to increase with exposure time.

Dorofeeva *et al* (1978b) claimed that 24 of a group of 50 workers, classified as having been chronically exposed to MMA (exposure levels not reported) for more than 10 years, showed abnormal ECG.

Lang *et al* (1986) reported incidences of neurasthenia, laryngitis and hypotension in a group of workers exposed to 2-49 ppm MMA at an organic glass factory in Beijing for periods between 3 months and 26 years. As these workers may have been exposed to other chemicals (not detailed), it is not possible to attribute the observed effects to MMA exposure alone.

Blagodatin *et al* (1971) reported occasional chest pain in 53 workers in a MMA production plant who were exposed at an average concentration of 4-12 ppm MMA (peak 65 ppm) for up to 6 years. The authors also reported headaches, dizziness, memory loss, changes in vascular tone and alterations in blood chemistry. These results are discussed further by Blagodatin *et al* (1976, 1981).

Lee (1984) reported a case of a female anaesthetist who had experienced headache and tightness in the chest for approximately 30 minutes following exposure to MMA for the first time during a total hip replacement operation she was attending. Six months later she experienced severe headache, dizziness, palpitation, tightness in the chest and erythema on her face, arms and neck after being exposed to MMA for the second time, again during total hip replacement surgery. She was reported to have experienced transient hypertension unlike the hypotension normally seen in

patients during implant operations involving the use of MMA. The anaesthetist recovered completely without complications.

Possible cardiovascular effects of MMA were studied in 22 workers exposed to 18.5 or 21.6 ppm MMA (8-h average) and 18 controls. Cardiac arrhythmias and paroxysmal unspecific repolarisation changes (large T waves in the ECG) were observed significantly more frequently in the exposed than in the control group. According to the authors the effects were equally distributed over the day, not correlated with exposure and few in number when compared to known data of the normal heart. The authors concluded that the results of this study did not support the hypothesis that MMA exposure is responsible for cardiomyodystrophy among occupationally exposed workers, but they could not exclude a possible effect of MMA on the heart completely (Marez *et al*, 1992).

Only in the area of the use of MMA as a bone cement for the fixation of joint prostheses have attempts been made to link MMA with cardiovascular collapse or arrest. Several authors claimed a link between MMA and cardiovascular effects (Cohen and Smith, 1971; Phillips *et al*, 1971; Adams *et al*, 1972; Anonymous, 1972; Brittain and Ryan, 1972; Kepes *et al*, 1972a,b; Newens and Volz, 1972; Nicholson, 1973; Schuh *et al*, 1973; Lipecz *et al*, 1974; Pahuja *et al*, 1974; Monteny *et al*, 1975; Wong *et al*, 1977; Seidel *et al*, 1980; Milanesi *et al*, 1982; Ciammitti *et al*, 1984; Esemenli *et al*, 1991). These reports were put into perspective by Cadle *et al* (1972) who reported that they had not experienced a single case of cardiovascular collapse or arrest in more than 1,000 total hip replacement operations. Peterson *et al* (1983) supported the view that cardiovascular complications during arthroplasty were dependent on the surgical technique and factors such as elevated temperature during curing of the bone cement rather than to direct cardiotoxic actions of MMA. Fearn *et al* (1972) related changes in blood pressure after implantation of bone cement to changes in the concentrations of anaesthetic agents used and to the state of the blood pressure before implantation. Svartling *et al* (1986b) demonstrated that the anaesthesia technique used may also strongly influence blood pressure and haemodynamic reactions. When MMA bone cement was used during spinal anaesthesia, hypotension and normal cortisol levels were observed, whereas during general anaesthesia arterial blood pressure and plasma cortisol levels were increased. According to the authors, cardiovascular reactions observed in arthroplastic surgery are a complex process influenced by many factors. Their view is supported by results of Wenda *et al* (1988) and Crout *et al* (1979) who were not able to correlate MMA blood levels with the observed cardiovascular effects.

Therefore, whilst some of these publications appear to implicate MMA in the findings, the fact that the subjects were anaesthetised and undergoing major surgery may prove to be a major confounding factor.

9.2.2 Other effects

Changes in blood biochemistry (lipids, proteins, cholinesterase activity, catalase activity, lactate dehydrogenase isoenzyme activity, haemoglobin, leucocytes) (Gabor *et al*, 1966; Blagodatin *et al*, 1971; Dorofeeva, 1976, 1978a,b; Saint-Maurice *et al*, 1977; Lang *et al*, 1986), hormones (Solov'eva, 1980; Makarov 1980, 1983, 1984; Makarov and Frigo, 1982; Makarov and Makarenko, 1983; Makarov *et al*, 1978, 1979b, 1980a,b, 1981a,b, 1984; Frigo *et al*, 1981), disturbances in carbohydrate metabolism (Makarov *et al*, 1977, 1979a), liver, stomach and intestines (Zubakova and Akinchits, 1977; Zubakova, 1978; Sharova *et al*, 1986; Sharova, 1988, 1989) of man reportedly exposed to MMA have also been claimed in a series of reports. In a questionnaire type study of 147 dental students constructing acrylic trays containing MMA several unspecific symptoms such as headache, dizziness and sinus irritation were reported. Vapour concentrations in the laboratory were 1.6-16.4 ppm, determined 6 x/5 h at 12 uniformly spaced sites (Pagniano *et al*, 1986). As stated above these reports lack critical details which are essential for judging the validity of the reported effects.

Cromer and Kronoveter (1976) reported a thorough occupational exposure study with a group of 91 exposed and 43 non-exposed workers in 5 polyMMA sheet manufacturing plants. No significant differences between the exposed and non-exposed groups were found for chronic liver and gastrointestinal effects, skin and allergic problems, blood pressure and pulse rate, pulmonary function, white blood cell count, haemoglobin values and urinalysis. The results of this comprehensive study, in which the predominant chemical exposure was MMA, cast major doubts on the effects described in the other reports detailed in this section. These results are supported by a recent publication of Mizunuma *et al* (1993) who did not observe any significant clinical symptoms or abnormal haematological or serum biochemical findings in 32 male workers exposed to 0.4-112 ppm of MMA (8 h TWA) as compared to 16 non-exposed control workers.

9.3 IRRITATION AND SENSITISATION

9.3.1 Skin irritation

Spealman *et al* (1945) reported mild erythema, limited to the area of application, in approximately one third of a group of 50 human beings following insertion of cotton pellets containing MMA under

patches on the forearm. Nyquist (1958) reported erythema and eczematous dermatitis in 16 of 18 human beings to MMA. No skin reactions were reported in a 48-hour patch test on the same individuals, with heat cured acrylic resin containing 5-6% residual MMA monomer. Axelsson and Nyquist (1962) examined a group of 44 edentulous patients who regularly wore polyMMA based acrylic dentures. Residual MMA content of the denture acrylate was determined at the end of the trial period, either 1.5 or 3 years and compared with the residual level determined at the time the dentures were fabricated. The initial monomer levels were reported to vary between 1.0 and 3.7% (by weight). At the end of the 1.5 year study they ranged from 1.5 to 2.8% (by weight) and at the end of 3 years, from 0.6 to 3.0%. Examination of the oral mucosa showed marked hyperkeratosis, which developed during the first week of denture usage and had resolved by the end of the first month. No other effects on the oral mucosa were observed during the study. The authors conclude that no causal relationship could be found between monomer leaching from the prostheses and prosthetical stomatitis. Fries *et al* (1975) reported dermatitis in 13 individuals who handled bone cement containing MMA. Kanerva and Lauharanta (1986) reported the effect of MMA on human skin following examination using electron microscopy. MMA, like terphenyls, was reported to cause spongiosis of the epidermis without specific effects. The authors regarded MMA as a classical irritant for epidermal cells.

9.3.2 Eye Irritation

A 40-year old operating theatre nurse complained of a sensation of a foreign body in her eye whilst mixing bone cement. Clinical examination revealed a pale eye without conjunctival hyperaemia and no ciliary injection. The cornea had a small well defined limbal depression, which was sharply demarcated in relation to the normal cornea. The corneal defect was so deep that only the Descementi membrane and the endothelial layer remained. No reaction was seen in the anterior chamber and ophthalmology was normal. The lesion resolved in 2 days following treatment with steroid cream. The corneal ulcer returned whenever she worked under the same conditions. The authors suggested that the reaction was due to a composite effect of MMA and hydroquinone vapours and that it was not an allergic reaction (Nissen and Corydon, 1985).

NIOSH (1981) reported that students working in a dental laboratory complained of eye irritation when exposed to MMA at concentrations between 0.01 and 0.19 ppm. NIOSH concluded that these exposures did not constitute a health hazard.

9.3.3 Skin Sensitisation

Repeated exposure to undiluted MMA may lead to skin sensitisation in susceptible persons. The incidence of sensitisation seems to vary widely and reactions to impurities, stabilisers, etc. should also be taken into consideration.

Volunteer Studies

When 20 female volunteers without reported previous contact to MMA were patch tested with 5% MMA in liquid paraffin or olive oil (purity, stabiliser content not indicated), 18 responded with skin reactions varying from erythema to delayed eczematous dermatitis. A distinct differentiation between sensitisation and irritation reactions was not made by the author. In a follow-up patch test of the same subjects with small plates of heat cured acrylic resin containing 5.2% to 6.4% of residual MMA monomer no skin reactions were observed (Nyquist, 1958).

A 48-hour occlusive patch test with undiluted MMA, containing 1% hydroquinone, was conducted with 30 volunteers. After 2 days, one case of erythema was observed, at day 10 no skin reaction were observed in the 27 volunteers who returned. At day 19, 20 of the volunteers were challenged using the same procedure at a different part of the back. In 2 cases, a positive skin reaction (irritation) was seen after 48 hours. A third case of a positive reaction was observed 10 days after the second application. In this case, lymphocyte infiltration of the skin area was observed. Two of the volunteers with skin reactions were subsequently tested with hydroquinone 1% in petrolatum, and did not show any reaction. Forty five volunteers were patch tested with 20% MMA in olive oil (stabiliser content 1%) for 48 to 72 hours (Finn Chamber) No skin reactions were observed after 2, 10, 20 and 30 days. A challenge application after 30 days did not reveal any skin reactions 2 days later (Cavelier *et al*, 1981).

Following exposure of 50 medical students to pellets of cotton saturated with MMA (purity, stabiliser content not indicated) sealed with elastic bandages for 48 hours on one forearm, 21 individuals showed a mild skin irritation after removal of the patches. After 10 days the same individuals were exposed in a similar way on the other forearm. No skin reactions were seen immediately after removal of the patches at 48 hours, but a few hours to 4 days later, skin erythema occurred in 10 of the individuals (Spealman *et al*, 1945).

Occupational

There are numerous reports in the literature of skin sensitisation in certain occupational environments, where frequent and prolonged unprotected skin contact with monomer containing preparations was common practice. Cases of skin sensitisation to MMA were also reported in the context of some medical or cosmetic applications. However, in many of the cases, skin contact may have been due to sensitisation to other chemicals.

The following examples have been reported :

Orthopaedic Surgeons

Fisher (1978) reported 2 cases of contact dermatitis of surgeons using bone cements. Paraesthesia of finger tips in the form of burning sensation, tingling and slight numbness persisting for several weeks after dermatitis had subsided were observed. The nature of the effects is not certain. Neither the exposure period nor the composition of bone cement mixture was indicated.

Fries *et al* (1975) reported a case of a surgeon with a contact dermatitis to acrylic bone cement. Positive patch test results were obtained only with MMA (purity, stabiliser content not reported). The authors reported another 13 cases of dermatitis in handlers of bone cement, 7 of them giving positive patch test results with MMA (10% in olive oil; purity and stabiliser content not reported).

Darre *et al* (1983) reported one case of contact dermatitis to bone cement in an orthopaedic nurse, with a positive patch test result to MMA (5%) (purity and stabiliser content not indicated). Contact was prevented by using butyl rubber gloves. These results are also reported by Vedel *et al*, 1983.

Kassis *et al* (1984) reported 2 cases of contact dermatitis to bone cements in orthopaedic nurses, 1 case had already been reported by Darre *et al* (1983) above. The reaction to other ingredients of the bone cement preparation was not tested in this case. The authors admit that the monomer used for the patch testing was of unknown purity. The second patient did not react to MMA or initiators and stabilisers in a patch test on the back. However, an occluded application of undiluted monomer (stabiliser, purity not indicated) to the fingers, where the patient experienced the reactions, led to a weak positive reaction after 24 hours.

One case of a surgeon experiencing contact dermatitis to acrylic bone cements was reported by Pegum and Medhurst (1971). Positive patch test results were obtained with undiluted monomer

and the initiator benzoyl peroxide (10% in petroleum jelly). Patch tests with the stabilisers, dimethyl-*p*-toluidine (2% in petroleum jelly) and ascorbic acid (2% in water) gave negative results.

Dentists and Dental Technicians

Of 106 dental technicians responding to a questionnaire designed to investigate the incidence of hand dermatitis in dental technicians, 19% reported irritant reactions of the hand, the incidence of atopic dermatitis was 15%. Half of the cases with hand dermatitis related the problem to handling acrylic monomer liquids without using protective gloves. The skin problems were considered to be mild. Four technicians reported allergic contact hand eczema due to MMA. Seven patients with eczema of the irritant type participated in a clinical investigation. None of them showed a positive patch test reaction to acrylic monomers. The authors concluded that the frequency of contact allergy to MMA among dental technicians handling monomers is relatively low, presumably below 10%. Other ingredients of the acrylic preparations may contribute to the observed skin reactions and the problems may be resolved by using adequate hand protection (Estlander *et al*, 1984).

Forty six dental technicians or dentists with hand dermatitis were tested for contact sensitisation to MMA and other (meth)acrylates (no indication of stabiliser content, purity). Patch testing was conducted with 10% or 2% MMA in petrolatum. Four of the patients reacted positively to MMA. Concomitant sensitisation to other (meth)acrylates was observed; in 2 cases to *n*-butyl acrylate, ethyl acrylate and hydroxypropyl methacrylate; in one case to ethyl acrylate, butyl acrylate, hydroxypropyl methacrylate and *tert*-butylacrylate; one to ethyl acrylate, butyl acrylate, 2-hydroxyethyl acrylate, hydroxypropyl acrylate, ethyl methacrylate, butyl methacrylate, 2-hydroxyethyl methacrylate, hydroxypropyl methacrylate, butanediol dimethacrylate, diethyleneglycol diacrylate, triethyleneglycol diacrylate, triethyleneglycol dimethacrylate and ethyleneglycol dimethacrylate (Kanerva *et al*, 1988).

A group of 293 dental technicians, technical assistants and students handling preparations containing acrylic monomers, including MMA were surveyed in a questionnaire study. Eighty one percent were handling acrylic monomers daily without skin protection. Current hand dermatitis or previous local dermatological problems were reported by 17%. Other finger symptoms, numbness, whitening, feeling of coldness and pain were reported by 25%. Frequency of symptoms increased with the frequency of handling acrylic monomers and the duration of occupation. Only 2% reported a previously diagnosed allergy against acrylates. Persons with current dermatitis reported atopic skin disease during childhood or allergic rhinitis and conjunctivitis more often than the others. The role of MMA with respect to the skin reactions remains unclear (Rajaniemi and Tola 1985).

One hundred and seventy five dental technicians or students, with and without previous experience of handling MMA containing dental materials, were patch tested with MMA (2%). No positive reactions were observed (Marx *et al*, 1982).

Four cases of occupational hand contact dermatitis caused by working with dental prostheses observed between 1974 and 1992 were described by Kanerva *et al* (1993). Three of them revealed a positive patch test reaction with MMA (1-10% in petrolatum). Concomitant sensitisation with butyl acrylate, ethyl acrylate and hydroxypropyl methacrylate was also observed.

Fisher (1954, 1956) reported 4 cases of dentists or dental technicians with hand dermatitis due to handling of self-curing methacrylate preparations. The same cases were reported in both publications. All 4 showed positive patch test reactions with the monomer (purity, stabiliser content not indicated), the self-curing monomer preparation and to a self-cured disk. No reactions were observed with heat-cured polymers or polymer powder.

A case of a dentist is reported who used new materials containing mono- and di-methacrylates and benzoyl peroxide. A patch test with 1% MMA, 0.5% benzoyl peroxide and the original resins showed only positive reactions to the resins, but not to MMA or benzoyl peroxide. The patient also reacted to triethylene glycol dimethacrylate, a constituent of both tested resins (Riva *et al*, 1984).

Six dental nurses and 1 dentist with an allergic contact dermatitis to dental composite resins containing a variety of (meth)acrylate and other components were patch tested with several (meth)acrylates. Two of the 7 reacted positively with MMA (purity 99.5%, stabiliser content not indicated, 2-10% in petrolatum) and also showed positive reactions to some of the other test substances (Kanerva *et al*, 1989).

Van Ketel (1977) reported a case of contact dermatitis of a dentist who reacted positively to a catalyst used for the preparation of dental resins (chemical nature not mentioned), but who did not give a positive patch test reaction with MMA (10% in petrolatum).

Two dental technicians with chronic hand eczema revealed positive patch test reactions to MMA (5% in petrolatum), and ethyleneglycol dimethacrylate (2% in petrolatum). One of the patients also reacted to the catalyst p-toyldiethanol amine and the cross linking agents triethyleneglycol dimethacrylate and tetraethyleneglycol dimethacrylate. Neither of them reacted to the stabiliser hydroquinone monobenzylether (1% in petrolatum) (Farli *et al*, 1990).

Kanerva *et al* (1992) reported a case of a dentist exposed to acrylic denture materials who experienced pharyngitis but no asthmatic symptoms or symptoms of rhinitis or conjunctivitis at work. Patch tests with 18 of 30 acrylates or methacrylates, including MMA (2% in petrolatum) were positive.

Among 82 patients suspected of occupational sensitisation to acrylates from either exposure to dental materials or anaerobic sealants, 11 were identified as having been sensitised to acrylates over a 5 year period. One patient reacted positively in a patch test with MMA (5% in petrolatum) (Guerra *et al*, 1993).

Other Occupational Exposures

Seven workers exposed to a self hardening acrylic sealant of unknown composition developed a hand dermatitis. All 7 showed a positive patch test reaction to the unpolymerised sealant (undiluted), 2 of them showed a positive patch test reaction with MMA (1% in methylethyl ketone) (Magnusson and Mobacken, 1972; Mobacken, 1983).

Six patients with skin dermatitis after occupational use of anaerobic sealants without skin protection, were investigated for contact allergic reactions to monomers. Three of them showed positive patch test results to MMA (10% in petrolatum) and hydroxyethyl methacrylate (2% in petrolatum) and 2 also to ethyleneglycol dimethacrylate (1% in petrolatum). The purity and stabiliser content of the monomers was not reported. Reactions to stabilisers or initiators have not been investigated (Condé-Salazar *et al*, 1988).

Clinical examinations of 20 employees handling 2 industrial sealing agents based on MMA for 1 month to 5 years and 56 volunteers assessed for allergic contact dermatitis did not reveal any evidence of contact dermatitis. Occluded and unoccluded patch tests were conducted with the sealing agents. No further details concerning the composition of the preparations is given in the article (Pasricha and Gupta 1985).

Mikulecký *et al* (1962) described 4 cases of slight skin reactions of occupationally exposed patients to MMA (1 or 5%, purity, stabiliser content not indicated). It is not clear if the reactions were of an irritant or allergic nature.

Patients with Limb Prothesis

In patients with limb prothesis, sensitisation to MMA seems to be a very rare event compared to the widespread use of MMA containing bone cements in arthroplastic surgery. This is understandable because this way of administration bypasses antigen presenting cells in the skin.

Fisher (1986) stated that patients receiving prosthesis very rarely, if ever, become sensitised.

Monteny *et al* (1978a) tried to link cardiovascular reactions observed in patients undergoing hip arthroplasty to possible immunological reactions involving the complement system. He monitored 25 patients for changes in serum concentrations of the haemolytic complement components 3 and 4. The introduction of the bone cement did not induce activation of the complement. Only anaesthesia with flunitrazepam, fentanyl or pancuronium induced significant activation of the complement system prior to the induction of the bone cement.

Monteny *et al* (1978b) reported one case of a positive patch test reaction to 20 or 40% MMA in olive oil out of 42 patients with hip arthroplasty. No reaction was observed when a 2-5% solution of MMA was used for the patch test. (Stabiliser content and purity not indicated).

Foussereau *et al* (1989) reported a positive patch test reaction to MMA (2% in petrolatum) in a patient with a knee prothesis. No reactions occurred to stabilisers, initiators and other constituents of the prothesis or to antibiotics.

A positive patch test result with MMA (2% in petrolatum) and several acrylates and methacrylates was reported in a patient with an incompatibility reaction to a surgical prothesis (Romaguera, 1985). Another case of eczematous allergic contact dermatitis to a limb prothesis was reported by Romaguera *et al*, 1990. Positive patch test reactions were obtained with potassium dichromate and cobalt salts as well as with MMA (2% in petrolatum) and some other methacrylates.

Casati *et al* (1986) claim that an anaphylactic systemic reaction with sudden fall in blood pressure and a bronchospasm in an asthmatic patient undergoing arthroplastic surgery and receiving different medications and blood transfusions was due to the methacrylate containing blood cement used. The authors admitted that this was a very rare event in their experience.

Romaguera *et al* (1985) reported appositive patch test result with 2% MMA in petrolether in and individual with an osteomyelitis from a hip prosthesis.

Dental Patients

Bradford and Sheff (1948) described a case of a inflammation of the mucoperisteum due to a methacrylate containing denture. A skin test with the denture material resulted in a skin rash 48 hours after application. The reaction cannot clearly be attributed to MMA and may be due to a mechanical effect as Fisher (1954) obtained similar skin reactions by stripping other inert materials to the forearms of patients.

Fisher (1954) examined 20 patients with a stomatitis which had been attributed to acrylic dentures. One case of allergic hypersensitivity to MMA (purity, stabiliser content not indicated) was identified by a positive patch test reaction.

Kanzaki *et al* (1989) reported a case of contact stomatitis resulting from a large amount of residual MMA in a denture. A positive patch test reaction to MMA (0.1-5% in acetone) was observed in the patient.

Four cases of a burning mouth syndrome following the use of denture materials were reported. In 2 patients, the allergens could not be identified, 1 patient reacted positively to MMA (25% in petrolatum, no indication of stabiliser content, purity) in a patch test and one reacted to epoxy resin (Van Joost *et al*, 1988).

Positive patch test reactions to MMA (10% in olive oil, purity not indicated) were obtained in four patients who reported discomfort due to dental prostheses. Clinical findings did not reveal any changes of the mucous membranes of the mouth (Bäuerle, 1982).

Nealey and Del Rio (1969) described one case of allergic contact stomatitis to a self curing acrylic resin used for the preparation of a partial denture. A patch test revealed a positive reaction to MMA monomer or to one of its additives. (No indication was given of the exact nature and concentration of the monomer used for the testing).

Four cases of positive patch test results to MMA (purity, stabiliser not indicated) were reported in patients with stomatitis from denture materials (Crissey, 1965).

Fifty three denture wearing patients with a burning mouth syndrome were investigated for potential allergic reactions to compounds of the denture materials. Two of the patients showed positive patch test reactions to MMA (30% in petrolatum, no indication of purity, stabiliser content). These 2

patients did not react to hydroquinone (1% in petrolatum), *p*-phenylene diamine (1% in petrolatum), dimethyl-*p*-toluidine (30% in petrolatum) or other test substances, such as metal salts, possibly present in the dentures (Kaaber *et al*, 1979).

Of 131 patients with stomatitis from dentures who underwent a skin patch test 1 reacted positively to an undiluted monomer (chemical nature not indicated) and 10 reacted positively to benzoyl peroxide (10%). According to the authors, both reactions could be of an irritant rather than of an allergic type (Marx *et al*, 1982).

Corazza *et al* (1992) reported a case of a positive patch test reaction with MMA monomer (25% and 2% in petrolether) persisting up to 30 days in a patient suffering from a stomatitis due to a dental prothesis.

Use of Artificial Nails

Fisher *et al* (1957) reported 4 cases of onychia, paronychia and dermatitis following the use of monomer/polymer preparations as sculptured artificial nails. Positive patch test reactions were seen in all patients with the liquid monomer. The nature of the monomer used for the patch testing is not clear from the article and it may well have been the liquid part of the preparation containing initiators, and other substances.

Another case of a severe reaction following the application of a artificial nail preparation containing MMA (composition of the preparation not specified) was reported by the same author. The patient experienced swelling, redness, pain, paraesthesia of the fingers and a loss of the fingernails. A patch test with MMA (5% in olive oil) was positive. After 6 years the nails had not regrown and the patient still suffered from oedema of the paronychial tissues and paraesthesia of the finger tips (Fisher, 1980a).

Marks *et al* (1979) reported the case of a 50 year old woman with dermatitis after using an artificial nail preparation containing monomers. Positive patch test results were obtained with MMA, ethyl methacrylate, and *n*-butyl methacrylate (5% monomer in petrolatum). Stabiliser content, purity were not indicated.

A patient developing contact dermatitis to self curing denture materials was reported to have used artificial nail preparations before suffering from similar skin reactions (Nealey and Del Rio, 1969).

Four dermatitis patients using artificial nail preparations showed a positive skin patch test reaction to MMA (1% in petrolatum, purity, stabiliser content not indicated). No cross reactions to *n*-butyl methacrylate or ethyl methacrylate were observed in these patients (Maibach *et al*, 1978).

Condé-Salazar *et al* (1986) reported the case of a woman who had been working in manufacture and application of artificial nails for 6 months. She experienced skin dryness and fissures at the hands. Patch tests with some of the ingredients of the preparation showed severe reactions with the primer and minor reactions with MMA in 10% petrolatum.

Other Cases

Meding and Ringdahl (1990) reported 4 positive patch test reactions to MMA (2% in petrolatum, stabiliser content, purity not indicated) out of 22 patients with dermatitis from hearing aids containing residual monomeric MMA.

Guill and Odom (1978) reported a case of an allergic contact dermatitis in an hearing aid containing large amounts of residual MMA. Patch test results with 10% MMA in olive oil were positive (purity and stabiliser content not indicated).

Three of 45 patients with a shoe dermatitis gave positive patch test reactions with MMA (purity, stabiliser content, concentration and vehicle not indicated) (Grimalt and Romaguera, 1975).

Kuželová *et al* (1985) reported 3 cases of allergic eczema in people occupationally exposed to 30-300 mg MMA/m³ (7.2-72 ppm) for an average of 10 years (no further data, abstract only).

Kanerva and Verkkala (1986) developed an immuno-histochemical profile on 2 individuals who were allergic to MMA. The immunological changes were similar to those of other allergens but there were few details of the study.

Cross Reactivities

Cross reactivity to MMA was reported in 1 patient handling anaerobic sealants without skin protection and being sensitised to polyurethane dimethacrylate. The patient also reacted to glycidyl methacrylate and ethyl methacrylate (Dempsey, 1982). Cross reactivity has also been demonstrated in a laboratory technician sensitised to hydroxyethyl methacrylate (Mathias *et al*, 1979) and in patients sensitised by artificial nail preparations to hydroxyethyl methacrylate, ethyl

methacrylate, propyl and isopropyl methacrylate (Fisher, 1980b). However no cross reactivity with MMA was demonstrated in patients sensitised to 2-ethylhexyl acrylate or N-*tert*-butyl maleamic acid from commercial adhesive tape (Jordan, 1975) or polyethyleneglycol dimethacrylate from acrylic sealants (Mathias and Maibach, 1984). Similarly, no cross reaction to MMA was observed in workers sensitised to printing inks containing urethane acrylate and pentaerythritol triacrylate (Nethercott, 1978; Nethercott *et al*, 1983) or trimethylolpropane triacrylate, pentaerythritol triacrylate, and epoxydiacrylate (Björkner and Dahlquist, 1979).

9.3.4 Respiratory Effects and Sensitisation

MMA is a volatile liquid and is classified under Annex 1 of the Dangerous Substances Directive (67/548/EEC) as irritating to the respiratory system (EEC, 1992). This irritating property of MMA has been reported in several publications on either case reports or populations of workers exposed to MMA although in some cases, due to mixed exposures, it is not possible to attribute the observations to MMA alone.

Burchman and Wheeler (1976) reported dizzy spells, difficulty in breathing, nausea and vomiting in staff in an operating theatre where MMA was used. No details were provided on atmospheric concentrations of MMA, work practices or potential exposure to other chemicals.

Cromer and Kronoveter (1976) studied a group of 91 workers exposed to 4-49 ppm MMA (mean 8-h TWA) in 5 plants manufacturing polyMMA sheet and a group of 43 non-exposed individuals. Investigations of pulmonary function (forced vital capacity [FVC], forced expiratory volume in 1 s [FEV₁], FEV₁/FVC ratio and maximal mid-expiratory flow) showed no differences between the individuals exposed to MMA and the controls.

Andrews *et al* (1979) reported that a small percentage of dental students experienced undefined acute respiratory symptoms following exposure (concentrations not reported) to MMA or during drilling of teeth. Most of the individuals with symptoms had prior histories of asthma or allergic rhinitis. Spirometry before and after controlled exposure to MMA in 77 individuals with histories of symptoms during normal uses of MMA, showed no significant changes.

Six of 32 male workers exposed to 0.4-112 ppm of MMA (8-h TWA) complained of frequent cough and sputa and 4 of throat irritation. All cases were related to the high exposure group (exposures between 5 and 112 ppm) (Mizunuma *et al*, 1993). It is however not reported in this paper, if short-term high exposure levels beyond 100 ppm were observed in this work force.

Jedrychowski (1982) and Jedrychowski *et al* (1982) studied respiratory symptoms in an industrial population consisting of 454 males exposed to MMA (up to 95 ppm) and styrene, and 683 control males who were not exposed to either material. The workers were evaluated by standardised interviews on chest symptoms and by lung function testing (measurement of FEV₁). The authors reported no difference in the prevalence of chronic chest symptoms between the 2 groups of workers, but did observe that the frequency of lung obstruction was twice as high in the group of workers exposed to MMA and styrene compared to the control group. Surprisingly, a large proportion of the cases of lung obstruction did not show any chronic chest symptoms, however, because of the mixed exposure, it is considered that the effects cannot be attributed to any single chemical.

A standardised questionnaire and spirometry study was conducted on a group of 4,717 male chemical industry workers in Poland. The prevalence of chronic bronchitis, bronchial asthma and obstructive syndrome was evaluated in relation to the variety of chemicals used on the chemical plants. As expected, increased levels of chronic bronchitis, asthma and obstructive syndrome were found in groups of subjects of advanced age and amongst smokers. The frequency on asthma and obstructive syndrome was higher in the chemical industry workers than in the general Polish population, but the frequency of chronic bronchitis was comparable in the 2 groups. The authors concluded that exposure of 1 group of the workers to styrene, benzene and MMA was responsible for the increased prevalence of the pulmonary symptoms observed (Jedrychowski and Fonte, 1984). Due to the mixed nature of the exposures to these agents, it is not possible to attribute the effects observed to any single chemical.

Marez *et al* (1993) have reported an investigation of the pulmonary effects of MMA in a group of 40 occupationally exposed workers compared to a group of 45 controls. The 40 workers occupationally exposed to MMA consisted of 8 workers with greater than 5 but less than 10 years exposure to MMA and 32 workers with more than 10 years exposure to MMA. The exposed individuals worked in 2 French factories with reported mean atmospheric concentrations of 18.5 (range 9 to 32) and 21.6 (range 11.9 to 38.5) ppm MMA. Peak exposure values were not reported. The study included a health based questionnaire and spirometry measurements of FVC, FEV₁, maximum expiratory flow volume (MEFV) and expiratory flow volume when 50% of the forced vital capacity remained to be exhaled (MEFV₅₀). Spirometric values at the beginning of the work shift were similar in both the controls and the exposed group. MEFV₅₀ and MEFV₅₀/MEFV were the only parameters which showed a small but significant reduction in the exposed group as compared to the control group following an 8-hour work shift. These changes may be indicative of a mild airways obstruction. The exposed group also showed an increased incidence of chronic cough

compared to the control group. The authors reported no case of asthma in either the control or exposed groups. The Task Force considers that the observations in this study are consistent with the irritant effect of MMA. However, the effects cannot be related to the reported exposure concentrations as the atmospheric concentrations given in the paper were not related to the individual exposures of the studied population on the day of the measurement of the pulmonary function. The results are obtained from a single investigation on peak exposures of single individuals leading to acute airways irritation could well have been the cause for the reduced average values of $MEFV_{50}$. Furthermore the exposure concentrations reported in the paper are put into perspective by a recent review of the exposure data of this workforce indicating 8 h TWA exposures of 50 ppm (Elf Atochem, 1994).

No change of lung function was observed in 10 floor layers regularly exposed to MMA concentrations between 62 and 601 ppm for intervals of approximately 20 minutes followed by a period of no exposure between 30 and 60 minutes. Three of the persons experienced irritation of the nose or throat (Lindberg *et al*, 1991).

A 24-year old male paint sprayer was reported to have developed respiratory symptoms including sneezing, rhinorrhea, nasal obstruction, dry cough and variable dyspnoea with wheezing and chest tightness which became progressively worse during occupational exposure to a specific type of spray paint. The individual, who was a smoker but had no previous history of asthma, respiratory illness, rhinitis or allergy, developed the symptoms 1 month after starting work. Monitoring of exposure at work indicated that these respiratory symptoms were associated with exposure to a specific paint spray which contained a water based emulsion of polyMMA (98%), a cross-linking agent (2% [dimethyl ethanolamine with 1,4-dioxane 7:3 ratio]) and occasionally a pigment. Simulated occupational exposures conducted in the laboratory clearly indicated that the asthmatic responses and rhinitis were due to exposure to dimethyl ethanolamine. Exposure to polyMMA emulsion alone elicited no reaction in the individual (Vallieres *et al*, 1977). This case report has been included for completeness but it is believed that it relates to the use of polyMMA and not MMA as reported by the authors.

In addition to the recognised respiratory irritation caused by exposure to MMA, a small number of case studies have attempted to link MMA exposure with occupational asthma.

A 40-year old male dental technician, who had worked with polyMMA powder and MMA liquid in the preparation of dental prosthetic pastes for several years, developed chest tightness, dyspnoea and cough which persisted for several hours after exposure to even small quantities of MMA. Controlled

inhalation exposure to both polyMMA and MMA was conducted in hospital under simulated occupational exposure conditions and resulted in a maximal fall in PEF of 24%, which resolved within 2 hours. A similar acute asthmatic attack was also observed in a second controlled challenge 1 week later. However, no control tests were performed and no attempt was made to measure specific IgE antibodies by either skin prick tests or RAST assay. Although the authors pointed out that there was a strong association in this case between the occupational exposure to MMA and the respiratory symptoms observed, they concluded that they could not exclude the possibility that MMA was acting as a non-specific provocative stimulus to a patient with hyperactive airways (Lozewicz *et al*, 1985).

A 56-year old female orthopaedic theatre nurse, with at least 7 years experience of working with bone cements consisting of polyMMA and MMA liquid, developed respiratory symptoms characterised by a persistent cough, wheeziness and breathlessness. These symptoms were associated with periods at work and resolved on rest days or on leave. Despite smoking 10-20 cigarettes per day, her pulmonary function tests were normal when she was not working. Controlled exposure to the cements and MMA, under simulated working conditions, resulted in delayed asthmatic type reaction occurring 6 hours after exposure with a maximum fall in FEV₁ of 25% 13 hours after the challenge. A controlled exposure, in which the polyMMA based cement was mixed with water, was reported not to produce a fall in FEV₁ but due to the colour and odour of MMA it was not possible to perform the challenge under blind conditions (Pickering *et al*, 1986). No skin prick tests or RAST assays were performed and, although it appears that MMA caused the observed delayed respiratory symptoms, it cannot be concluded that the symptoms resulted from allergic sensitisation.

A 39-year old orthopaedic theatre nurse developed breathing difficulties during the course of mixing cement to seal prostheses. She had previously complained of rhinitis, conjunctivitis and a spasmodic "cold". Spirometry and chest X-rays were normal. Provocative exposure to the MMA-containing cement resulted in a fall of 25% in VEMS within 30 minutes of exposure. Respiration returned to normal following the application of β -2-mimetics. Bronchial reaction to acetylcholine was positive, typical of an asthmatic subject (Reynaud-Gaubert *et al*, 1991). It is therefore considered that it cannot be concluded that MMA was acting other than in an irritant and non-specific manner.

Savonius *et al* (1993a) reported 3 cases of respiratory sensitisation that they have linked with exposure to MMA. The nomenclature used in the original publication was confusing and indicated that the individuals in question were exposed to methyl cyanoacrylates rather than to MMA. The authors have, however, recently published an erratum (Savonius *et al*, 1993b) in which they specify

that 3 of the individuals were exposed to MMA. The Task Force has considered these cases and has discussed them with the authors; although some evidence of hyperactive airways disease is evident in the 3 individuals, information critical to the interpretation of these cases is still not available. Patient M1, a 48 year old female, is alleged to have been exposed to MMA during the use of a glue (composition unspecified) during plate engraving and is reported to have developed respiratory distress at work, strain, sneezing, rhinorrhoea and stuffiness. Challenge to the implicated glue caused a maximal 24% fall in PEF values and her symptoms persisted on transfer to the use of a cyanoacrylate glue. The Task Force considers that while there is some evidence for respiratory sensitisation it is not possible to define the causative agent. Patient M2, a 32 year old male involved in the assembly of hearing devices, showed a small maximal 15% decrease in PEF values following the grinding of "a piece of methacrylate" in an exposure chamber. The Task Force consider that it is likely that this individual was exposed to polymeric material and not MMA. The third patient, M3, was a 46 year old female who had worked for about 20 years as a dental technician. She developed paraesthesia on the unular side of both hands but not dermatitis. She subsequently experienced a feeling of tickling in her throat, yawning, cough, tiredness and chest tightness; the symptoms subsided on sick leave and vacations but recurred within a week at work. Simulated occupational exposed to "methacrylate powder and methacrylate liquid" for 30 minutes resulted in a maximal fall of 26% in PEF value. Skin prick test to "methacrylate" was negative. Although this case report appears to show an association between occupational exposure to "methacrylate liquid" and the respiratory symptoms observed it is not possible from the data provided to conclude that the symptoms resulted from exposure to MMA. Therefore consideration of the available data from the 3 cases reported by Savonius *et al* (1993a,b) shows no convincing evidence of respiratory sensitisation by MMA.

Summarising 6 case reports (Lozewicz *et al*, 1985; Pickering *et al* 1986; Reynaud-Gaubert *et al*, 1991; Savonius *et al*, 1993a,b) have implicated MMA as a respiratory sensitiser. Both the Lozewicz and Reynaud-Gaubert publications reported only immediate responses which may have been simply due to irritant provocation of the airways by MMA. Information critical to the interpretation of the 3 cases reported by Savonius (1993a,b) is not available and it is not possible to conclude that the symptoms observed resulted from exposure to MMA. Pickering *et al* (1986) reported a delayed asthmatic response in 1 individual which would not normally be associated solely with an irritant provocation. The Task Force believes, however, that because of the uncertainties associated with the challenge to MMA, this study cannot be taken as a definitive case report of respiratory sensitisation. In addition, these case reports must be placed in context opposite the lack of evidence of a respiratory sensitisation effect of MMA in studies of large groups of workers occupationally exposed to MMA.

The respiratory health of workers at the Rohm and Haas Knoxville facility in the USA was examined by Rohm and Haas (1981a). The protocol included a self administered questionnaire on respiratory symptoms and smoking history, pulmonary function tests and a chest X-ray. Of the 826 workers at this facility, 780 volunteered to participate. Of these, 68 had been exposed to MMA. In this small sub-cohort there was no evidence of clinically abnormal pulmonary function.

In a follow-up study of a subcohort (workers exposed to MMA that had never smoked) 11 of the original 17 were still employed at the US Knoxville facility and their pulmonary tests were repeated. The results confirmed that these workers exposed to MMA showed normal lung function (Monroe *et al*, 1981).

In a study of olfactory function, Schwartz *et al* (1989) examined 731 workers from a Rohm and Haas plant manufacturing acrylates and methacrylates. The testing involved the administration of the University of Pennsylvania smell identification test (UPSIT) and a questionnaire concerning shift and job profile. In the original cross-sectional (prevalence) study no association was found between chemical exposure and olfactory test scores. A nested case control study was then performed on 77 of the workers who scored at or below the tenth percentile (for their age) on the UPSIT and 77 control workers (matched for age, gender and ethnic group) to assess the cumulative effect of exposure. An association was found between cumulative exposure and olfactory dysfunction, the association appeared to be dose-related. Exposure odds ratios of 2.8 and 13.5 were calculated, by logistic regression analysis, for all workers and those that had never smoked, respectively. A decreasing odds ratio was observed between olfactory dysfunction and time since last exposure, indicating reversibility of the effect. Although the study indicates a reverse association between acrylate-methacrylate exposure and decreased olfactory function, the changes were physiological rather than clinical. The full significance of this study is unclear.

A review conducted by the Dutch Expert Committee for Occupational Standards (DECOS) and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG) concluded that no allergic respiratory reactions have been described in groups of workers exposed to MMA (MacLaine Pont, 1991).

Since that review was published 2 significant and well conducted studies of workers occupationally exposed to MMA have been conducted and reported. Although both studies confirmed the recognised respiratory irritant effects of MMA, neither study showed any evidence of respiratory sensitisation in large populations of workers exposed to MMA over a significant number of years occupational exposure.

Röhm (1994) have reported results of an ongoing medical survey of 211 male workers exposed to MMA in 2 German polyMMA production plants. The report period was May 1991 to 1993. The workers spent an average of 8.8 years in acrylic sheet production (16% of the workers had been exposed to MMA for more than 20 years, 34% for more than 10 years). Present exposures to MMA varied between < 3 and 40 ppm (8 h TWA). Past exposures were between 10 and 70 ppm MMA. Occasional short term peak concentrations of 100 - 680 ppm had also been recorded. The medical examination of the workers consisted of a self-administered questionnaire about lifestyle, occupation and medical history with emphasis on complaints of nose, throat and respiratory system failures, and allergic reactions including skin and asthmatic reactions. The questionnaire was supplemented by a detailed anamnesis and anterior rhinoscopy using a speculum. In the exposed group no case of MMA exposure related respiratory or skin sensitisation were observed. Observation of irritation of the eyes and the upper respiratory tract was limited to acute and reversible reactions after short term peak exposures at concentration levels exceeding 100 ppm. There were no indications for symptoms of a work related rhinopathy or any substance related abnormalities in the nasal cavity in the exposed group.

Pickering *et al* (1993) of the North West Lung Centre, Manchester, UK conducted 2 studies on workers involved in the manufacture of polyMMA acrylic sheet and liquid MMA composites at the ICI Acrylics sites at Darwen in the UK. Worker turnover at the sites was reported by ICI to be low and exposure to MMA as high as 100 ppm (8 h TWA) in the past years. The first study was a cross-sectional study involving 384 (89.1%) of a total workforce of 412 and consisted of an assessment of lung function (using simple spirometry to measure FEV₁ and FVC) and a health questionnaire. The second study was a follow-up on the those individuals not available for the first study, a population of past leavers and those workers identified as having 2 or more work related respiratory symptoms in the first study.

In the first study 1 individual was identified by the authors to have a medical history and peak expiratory flow measurements which are suggestive of occupational asthma. As no challenges to MMA, skin prick tests or other corroborative data are available to support this judgement the Task Force consider that this does not represent a conclusive case report of respiratory sensitisation and can be adequately explained by a constitutional asthmatic being exposed to a respiratory irritant. A number of individuals in the study reported symptoms of irritation to the eyes and respiratory system particularly following high, transient exposure to MMA.

In the second study (Pickering *et al*, 1993) no evidence of respiratory sensitisation was observed in the remainder of the current workforce. From a total past leaver population of 140 individuals, 83

(59.3%) participated in the follow-up which represented 80% of the available target population. These individuals were investigated by means of a respiratory health questionnaire and spirometry measurements. Based on these data the past leavers population showed work related respiratory symptoms similar to those observed for the current working population in the first study. One individual in the population of leavers was judged by the authors to have been respiratory sensitised to MMA. However, the clinical symptoms reported for this individual indicate the development of pneumonia followed by exposure to a respiratory irritant which could have acted as a provocation to a predisposed condition. In addition, as no challenges to MMA, skin prick tests or other corroborative data are available to support the authors conclusion the Task Force consider that this does not represent a conclusive case report of respiratory sensitisation.

From these studies there is no convincing evidence that MMA is acting as a respiratory sensitiser, however, there is clear evidence of acute respiratory irritation, at high exposure levels.

9.3.5 Summary

Acute occupational exposure to MMA at high concentrations is recognised to result in respiratory irritation in a proportion of exposed workers and this has been confirmed by the studies and case reports reviewed above. One case report (Pickering *et al*, 1986) reported a delayed asthmatic response following challenge with MMA which would implicate MMA as a potential respiratory sensitiser. It is believed, however, that because of the uncertainties associated with the challenge to MMA this study cannot be taken as a definitive case report of respiratory sensitisation. This isolated case report must be placed in context opposite the lack of any evidence of a respiratory sensitisation effect of MMA in recent well conducted studies on large groups of workers occupationally exposed to MMA. It is concluded therefore that there is no convincing evidence of respiratory sensitisation in man occupationally exposed to MMA.

This conclusion is consistent with a recent review by the Danish Health and Safety Executive (Miljøstyrelsen, 1992) in which they could find no evidence that MMA was acting as a respiratory sensitiser in human beings.

9.4 GENETIC TOXICOLOGY

Two studies have been conducted in human populations exposed to MMA; neither study provides any evidence for a genotoxic effect of MMA in man.

Bargramyan *et al* (1976) reported a small increase in chromosomal aberrations in a group of workers exposed to MMA and chloroprene, the latter being a known *in vivo* clastogen (DFG, 1980). Because of this, and the lack of detail on the experimental protocol and data, no conclusions can be drawn concerning possible effects of MMA.

No increase in sister chromatid exchanges (SCE), compared to a control population, was reported in the lymphocytes of 31 workers exposed to MMA in 4 factories (mean 8-h exposure values between 0.70 and 21.6 ppm) (Marez *et al*, 1991). A very small (less than 1.4 fold) increase in SCE was observed in a subset of workers reported to be exposed to peak concentrations of MMA (114 to 400 ppm); the increase was reported to be due to a very small number of high (SCE) frequency cells (HFC).

There are several important factors which must be considered when interpreting these data.

- The biological significance of the SCE assay as an indicator for genotoxicity is still questionable (Tucker *et al*, 1993).
- The MMA monitoring method used is not accurate and it cannot be concluded that the small subset of workers were actually exposed to higher concentrations of MMA than the rest of the exposed population.
- There was no exclusion for recent vaccinations, virus infections, white blood counts, alcohol consumption, smoking habit or type of diet, all of which can affect SCE (Bender *et al*, 1988; Tucker *et al*, 1988; Marzin, 1994).
- The slides do not appear to have been scored blind as required in cytogenetic assays in order to ensure that there is no subjectivity. The number of cells analysed and the criteria for SCE are not defined.
- The use of HFC may only improve the sensitivity of the SCE assay if a large number of cell populations and an appropriate statistical analysis (e.g. dispersion analysis) is used (Tucker *et al*, 1993). The definition of an HFC and the cutoff point of 6 HFCs used by the authors are completely arbitrary and without scientific foundation. In addition, in contradiction to the authors, the number of individuals with greater than 6 HFC is not statistically significantly different from the controls when appropriate statistical tests are used. The biological significance of the reported data is therefore highly questionable.

Consideration of these factors, together with the lack of increase in SCE in the total exposed population, clearly indicates that the small increase in a small subset of workers is not indicative of a genotoxic effect.

9.5 CANCER EPIDEMIOLOGY

A series of mortality studies have been conducted on workers exposed to MMA.

The earliest studies were performed in North America by the Rohm and Haas Company on Workers from their 2 acrylic sheet manufacturing sites at Bristol and Knoxville (Rohm and Haas, 1981a; 1984; 1986; 1987). These studies were subsequently included in a publication of Walker *et al* (1991). The total cohort of these studies consisted of 13,863 workers from the 2 sites. The Bristol plant was represented by 2 cohorts, the so-called Early Bristol cohort of 3,934 white males employed between 1st January 1933 and 31st December 1945 (of which 2,904 were hired between 1941 and 1945) and the later Bristol cohort of 6,548 white males (3,916 hourly paid and 2,632 salaried workers) hired between 1st January 1946 and 31st December 1986. The Knoxville plant was represented by 1 cohort of 3,381 white males employed between 1st January 1943 and 31st December 1982. All groups were followed from the 1st day of employment or the 1st January 1933, whichever came later. Assessment of exposure to ethyl acrylate and/or MMA was based on job history and on a job specific exposure scale. The total dose for each job held by every worker was estimated by multiplying exposure intensity by the interval in days from the start to end of employment in the job, divided by 365.25. In the Early Bristol cohort there was an excess of colon cancer in workers exposed to ethyl acrylate and/or MMA when compared to the local rates (Table 25). The authors noted that it was not possible to separate exposure to ethyl acrylate from exposure to MMA for most employees.

The excess mortality appeared at least 20 years after the equivalent of 3 years employment in jobs producing the highest exposure to ethyl acrylate and/or MMA vapour and to the volatile by-products of polymerisation. Cancer of the rectum was also elevated in the Early Bristol cohort (10 deaths observed; 5.23 expected: ratio 1.9) although, due to the paucity of data this observation is less robust than the colon cancer data. A deficit of colorectal cancer was observed in the Later Bristol cohort. In the cohort (including workers who were not exposed to ethyl acrylate/MMA) the SMR for colon cancer was 0.91 (17 observed deaths versus 18.73 expected) and the SMR for rectal cancer was zero (0.00 observed; 5.06 expected deaths) both based on US mortality rates. The Knoxville cohort also showed a deficit of colorectal cancer. In the whole cohort the SMR for colon cancer was 0.96 (20 observed versus 20.74 expected) and the SMR was 0.16 for rectal cancer (1

Table 25 Mortality from Cancer of the Colon in the Early Bristol Cohort (adapted from Walker *et al*, 1991)

Achieved dose ^a	Observed deaths	Expected deaths	Fitted rate ratio ^b
None (not exposed)	12	9.66	1.24
0-4 units	13	9.39	1.39
5-9 units	6	5.17	1.16
10-14 units	1	2.24	0.45
≥ 15 units	11	4.58	2.4

a Mutually exclusive doses of ethyl acrylate/MMA at least 20 years since first achieving dose among those employed >10 months

b Fitted mortality ratio of cohort mortality rate and the combined Bucks county and Burlington County white male mortality rate for the same age and calendar period

observed death versus 6.34 expected) both based on US mortality rates. At 20 years after exposure, the SMR for colon cancer was 1.52 for all exposure categories combined. However, there were deficits at the higher exposure levels and an excess at the lowest level. In the Early Bristol cohort, all cause mortality was less than would be expected on the basis of US mortality rates (1,992 observed; 2,202.94 expected: SMR = 0.90). Mortality from all malignant neoplasms was lower than expected (433 observed; 448.91 expected: SMR = 0.96) and cancer of the respiratory system was close to expected (121 observed; 155.44 expected: SMR = 0.99). Mortality from non-malignant respiratory disease was much lower than expected (SMR = 0.78).

The mortality of the Later Bristol cohort was similar to that of the Early Bristol cohort. All cause mortality was lower than expected (981 observed; 1011.18 expected: SMR = 0.97) but mortality from all malignant neoplasms was slightly higher than expected (230 observed; 225.78 expected: SMR = 1.02). Mortality from cancer of the respiratory system was slightly elevated (90 observed; 85.64 expected: SMR = 1.05) whilst non-malignant respiratory disease mortality was reduced (46 observed; 53.29 expected: SMR = 0.86).

In the Knoxville cohort, all cause mortality marginally exceeded US rates (1,133 observed; 1,072.51 expected: SMR = 1.06) as did mortality from all malignant neoplasms (261 observed; 231.25 expected: SMR = 1.13). The increase in mortality from malignant neoplasms was due to an increase in cancer of the respiratory system (119 observed; 82.64 expected: SMR = 1.44). There was also a marginal excess mortality from non-malignant respiratory disease (76 observed; 63.37 expected: SMR = 1.10). The authors concluded that "a causal role for protracted, extremely high exposure to ethyl acrylate, MMA or the volatile by-products of the ethyl acrylate/MMA polymerisation process in the genesis of colon and rectum cancer [observed in the Early Bristol Cohort] is a

tenable explanation of the available epidemiological data". Despite the "statistical association" between exposure to ethyl acrylate and/or MMA and deaths from colorectal cancer in the Early Bristol cohort, the data are not consistent with the animal carcinogenicity data on ethyl acrylate and MMA nor with the mechanistic data indicating activity of ethyl acrylate only at or close to the point of contact. In addition, the absence of a clear dose response relationship and the lack of supporting data from the other 2 cohorts leads the Task Force to the conclusion that the correlation between the exposure to ethyl acrylate and/or MMA and death from colorectal cancer is unconvincing.

A nested case-control study of the early Bristol cohort extended to include employees who had worked in production jobs for at least 1 year by the end of 1949 was performed by Rohm and Haas (1986). The study included 54 cases of colorectal cancer who were each age-matched to 5 controls. Exposure was categorised according to work area and by department. Employment in jobs involving exposure to acrylates and methacrylates either as the monomer, the polymer, or as polymer dust was not associated with significantly increased risk of colon or rectal cancer.

A further mortality study was conducted at the Rohm and Haas facility at Deer Park, Texas, on a group of 1,849 white male workers (477 salaried and 1,372 hourly paid). Cohorts were constructed based on date of hiring and were observed until 31 December 1978. Cancers of the buccal cavity and pharynx (0 observed; 0.8 expected: SMR = 0.00), digestive tract (3 observed; 6.65 expected: SMR = 0.85), respiratory system (7 observed; 8.28 expected: SMR = 0.85), urinary system (1 observed; 1.09 expected: SMR = 0.92) and genital system (0.00 observed; 0.96 expected: SMR = 0.00) showed no statistically significant excess (Rohm and Haas, 1981b).

In a study of 2 American Cyanamid plants, Collins *et al* (1989) examined a cohort of 2,671 men (1,302 from the Fortier, Louisiana plant and 1,361 from the Santa Rosa, Florida plant; 8 had worked at both plants). The study population consisted of all men who worked at either plant from start-up (1,951 for Fortier and 1,957 for Santa Rosa) until the beginning of 1974 and they were followed-up until the end of 1983. A total of 1,561 employees had been exposed to MMA in the manufacture of acrylic fibre and the following results relate to that group. Average levels of exposure were at worst 1 ppm which occurred during the earliest years of production. Exposure estimates were developed for all jobs and smoking histories obtained for all workers. The observed deaths for both exposed (123 observed; 156.5 expected: SMR = 0.79) and unexposed (114 observed; 169.7 expected: SMR = 0.67) populations for all causes of death were less than expected. Mortality from malignant neoplasms in the exposed group was almost exactly as expected compared to the US population (SMR = 1.04) and no different from unexposed men in the same plant (SMR = 1.01). In the exposed population cancers of both digestive organs and peritoneum (6 observed; 8.1 expected:

SMR = 0.74) and large intestine (1 observed; 2.6 expected: SMR = 0.39) were less than expected. There was 1 colon cancer death compared to 2.6 expected (SMR = 0.39) and no rectal cancer deaths were observed. In the exposed population there was a small excess of both respiratory cancer deaths (15 observed deaths versus 12.5 expected: SMR = 1.20) and deaths from non-malignant respiratory disease (4 observed deaths versus 1.9 expected: SMR = 2.16). This study is currently in the process of being updated.

A study is currently in progress of employees at 2 ICI plants in the UK (because of the fact that this study is in progress and not fully reported, not all data was available to the Task Force, and that which is cited may be subject to revision). One plant is an active facility at Darwen, Lancashire which produces acrylic products. Production of acrylic products at this plant commenced in 1940 but records of the workforce prior to 1949 could not be located. The cohort consists of all weekly paid, male employees who were employed at any time between 1949 and 1989. The other cohort consists of workers who were employed at a similar facility located at Wilton, Teesside which operated between 1949 and its closure in 1969. No results are available yet for this latter cohort, but preliminary results have been supplied for the Darwen cohort (Tomenson and Bonner, 1994). The cohort consisted of 2,178 employees and the production processes and exposures were stated to have been similar to those at the Rohm and Haas, Bristol plant. The SMR for all cause mortality was 0.93. In addition to this evidence of a healthy worker effect, there was also a reduction in death due to malignant neoplasms (SMR = 0.98). The SMR for colon cancer was very slightly elevated at 1.05 (11 observed deaths versus 10.5 expected), the SMR for rectal cancer was 0.82 (6 observed deaths versus 7.4 expected) and the SMR for colorectal cancer was 0.95. Cancer of the bladder was slightly elevated (10 observed; 6.3 expected: SMR = 1.6), this is currently attributed to previous exposure to chemicals other than MMA. Cancer of the respiratory system was lower than expected (SMR = 0.89). There were no statistically significant increased SMR's for malignancies at any other sites. Small elevations in the SMR were observed for deaths due to cancer of the biliary passages and liver, cancer of the liver, and other urinary organs, cancer of the central nervous system and stomach cancer. Although not statistically significant these small increases will be reviewed when more comprehensive analyses of latency and exposure are available. The results for other causes of death besides malignancies did not demonstrate any evidence of an adverse effect of work on health. Indeed the SMR for all heart disease was statistically significantly lower than expected at 0.89 and 2 other major causes of death, cerebrovascular and non-malignant respiratory disease had SMR's of 1.05 and 0.88 respectively. Therefore, the preliminary results of this study suggest that employment in the manufacture of acrylic sheet has not adversely affected the health of the workforce and in particular, there is no evidence of an association between

exposure to MMA and death due to colorectal cancer. (The analysis of the Wilton cohort will be reported in 1996.)

The Task Force is also aware of a multisite, multiexposure, population based case-control study conducted in the area of Montreal, Canada (Siemiatycki, 1991). Exposure to 293 chemicals, including MMA and poly-acrylates were assessed in this study. However, the results of the investigation are difficult to interpret due to the large number of odds ratios calculated by the authors for exposure-cancer site combinations, each representing a different control population, or degrees of exposure.

9.5.1 Summary and Evaluation

In a retrospective mortality study of workers employed in a North American ethyl acrylate/MMA plant (early Bristol cohort) prior to 1946 an increase in mortality from colorectal cancer was observed. However, in a similar population at a separate site and in subsequent evaluations of the original site no such increases were observed. In addition, more recent studies have shown no significant increases in the incidences of deaths due to colorectal cancer.

When interpreting the results from the Early Bristol cohort, it is important to remember that the plant was located in an area with very high colorectal cancer rates. Collins *et al* (1989) noted that during the 1970s, the county in which the plant was located had colon rates at the 75th percentile for the USA. Maher and DeFonso (Rohm and Haas, 1984) reported an SMR of 2.22 (33 observed deaths versus 14.9 expected) for colon cancer in workers exposed to ethyl acrylate/MMA and employed for at least a year. This SMR was based on US mortality rates and the authors noted that the excess fell when local rates were used, but did not disappear. For the extended follow-up period reported by Walker *et al* (1991), the number of deaths from colon cancer had risen to 38 but the expected number of deaths based on local mortality rates was 25.39 giving a substantially lower SMR of 1.50.

Walker *et al* (1991) noted that the excess of deaths from colon cancer in the Early Bristol cohort among men who had worked with ethyl acrylate and MMA appeared to be largely restricted to those who worked extensively in the early 1940s in jobs entailing high exposure to ethyl acrylate and MMA monomer vapour and that the excess mortality did not occur until some 2 decades later. The Task Force considers that this is an oversimplification as a similar excess of colon cancer deaths was seen in the lowest cumulative exposure group. Such an excess substantially weakens the arguments for a causal relationship between MMA exposure and colorectal cancer. The large excess of colon cancer deaths in the lowest cumulative exposure group is important not only

because it indicates a lack of dose response, but also because many workers in the Later Bristol, Knoxville and ICI studies will have experienced exposures to MMA comparable to Early Bristol workers in this group. However, there was no excess of colorectal cancer in these studies or the study of Collins *et al* (1989).

Walker *et al* (1991) when reviewing the available data (all the studies described here with the exception of the ICI study), stated that the colorectal cancer excess "appears to be restricted to a single locale, and a stage now decades past in the historical development of the process of acrylic sheet manufacture. The origin of the present finding might be ascribed to chance by many reasonable persons, except that the class of person-time within which the excess mortality from cancers of the colon and rectum appeared is, by best accounts, that one in which exposure to ethyl acrylate/MMA was the greatest". Given that the excess of colorectal cancer was not confined to the class of person-time described above, the evidence, in reality, points more strongly to a chance explanation. In the case of MMA, this explanation is considerably strengthened by the results of the ICI study. Exposures to MMA in the early years of the Darwen plant have been estimated to be similar to the exposures experienced by workers in the Early Bristol cohort. However, the preliminary analysis of this cohort shows no evidence of an excess of colorectal cancer.

Furthermore, studies on experimental animals indicate that MMA is not an animal carcinogen. Therefore a causal relationship between exposure to MMA by inhalation and deaths due to colorectal cancer is not supported.

Some evidence of an increased death rate from respiratory cancer or non-malignant respiratory disease is provided by the American Cyanamid and Knoxville cohorts. However, in both of these cohorts especially the American Cyanamid cohort, exposure to MMA was considerably lower than in the Early Bristol cohort which showed no such excess. In addition, the recently reported ICI study showed lower than expected incidences of deaths due to respiratory cancer or non-malignant respiratory disease. It therefore does not seem plausible that the effects observed in the American Cyanamid and Knoxville cohorts were associated with MMA exposure and it raises the possibility that they may have been lifestyle related.

An overview of the epidemiological studies shows no convincing evidence for any carcinogenic effects causally related to MMA exposure and it can therefore be concluded that MMA does not represent a carcinogenic hazard to man.

9.6 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

No reproductive or developmental effects have been reported.

9.7 NEUROTOXICITY

A number of reports have alleged neurotoxic effects in humans exposed to MMA.

The majority of authors refer to unspecific symptoms which they try to relate to central nervous effects.

Karpov (1954a,b, 1955a,b) reported complaints of sleepiness, fatigue, loss of appetite and headaches in workers in a polyMMA plant. The workers were exposed for periods of 4-9 years but the MMA concentrations were not reported.

Raines and Kharkov (1957) reported that the majority of workers in a dental supply manufacturing plant suffered from hypotonia, nervousness, poor appetite, dizziness and headaches following exposure to MMA (at concentrations up to 60 ppm) in an unspecified mixture of chemicals for periods from several months to 9 years.

Christiansen (1986) reported irritation, headaches, fatigue and memory effects in dental technicians exposed to an undefined concentration of MMA.

Della Torre *et al* (1982) examined the health of a group of 18 workers (10 male and 8 female) exposed to MMA in a plant recycling MMA from scrap polyMMA by thermal depolymerisation. The factory studied was described as obsolete, poorly maintained and with poor ventilation. For the study the workforce was divided into 2 sub-groups depending on their exposure profile to MMA. Group A comprised 8 workers (4 male and 4 female, average age 35.2 years and with an average 14 years experience in the job) exposed to MMA at levels up to 736 mg/m³ (177 ppm). Group B comprised 10 workers (6 male and 4 female, average age 36.6 years and with an average 10 years experience in the job) exposed to MMA levels of ≤ 342 mg/m³ (≤ 82.1 ppm). The results of the clinical examination indicated a moderate incidence of irritation to the skin, eyes and respiratory tract. However no "serious" respiratory tract effects were found in either group. No adverse effects of occupational origin were found for the cardio-circulatory system or on hepatic function. Seven workers, 4 from group A and 3 from group B, reported paraesthesia and tingling in the upper limbs. Two others (group not specified) complained of paraesthesia of the lower limbs. Examination of this

group found changes in only 2 of the 9 workers. One was a case of carpal tunnel syndrome and the other damage to the medial and ulna nerves (exact nature of the damage unspecified). The authors concluded that the peripheral nervous system effects were the result of the mechanical tasks the subjects were performing. A significant incidence of psychonervous effects were reported in both groups with approximately equal frequency. The effects included anxiety, insomnia, cephalaea and vertigo.

Kuželová *et al* (1985) reported that 32 individuals of a group of 63 workers exposed to MMA at 7-70 ppm, and other unspecified chemicals, for an average of 10 years, complained of nervousness and headaches; 10 individuals of the group had abnormal EEGs.

Froines and Garabrant (1986a) reported complaints of nausea and headaches in manicurists in 8 shops. The 8 h TWA and peak exposures to MMA during fingernail application were 5.3 and 20.3 ppm respectively. No assessment of dermal exposure was made and ethyl and isobutyl methacrylate were also present at levels below 20 ppm. However, the lack of details provided for the sampling and analytical procedures in this study has been criticised (Crable *et al*, 1986) and further discussed (Froines and Garabrant, 1986b).

Dorofeeva (1976) reported claims of headaches, dizziness, decline in memory, and "irritability" in workers exposed for 3 to 26 years to MMA. These findings were put into perspective by Flodin *et al* (1984) who could not find a link between psycho-organic syndromes of 128 patients and occupational solvent or MMA exposure for more than 9 years.

Mizunuma *et al* (1993) emphasised the lack of CNS suppressing effects in 32 workers exposed to 0.4-112 ppm MMA (8 h TWA).

A few authors report peripheral neurotoxic effects in persons occupationally exposed with preparations containing MMA, but also with a number of other chemicals. Thus the effects cannot be clearly related to MMA exposure.

A 58-year old dental prosthetic technician complained of sensory motor disturbance which started with paraesthesia in the tips of the fingers and progressed to bilateral wasting and weakness of the ankle dorsiflexors with the absence of ankle reflexes. Neurophysiological examination revealed a neuropathy of an axonal degenerative type. Biopsy of the sural nerve showed moderately severe, chronic axonopathy with loss of large myelinated fibres and unmyelinated axons, and with evidence of regeneration. The authors likened the effects to acrylamide-induced neuropathy and suggested

that they were induced by chronic occupational exposure to MMA from dental resins. The patient had been making dentures for over 30 years. Materials used in addition to MMA in recent years contained ethyleneglycol dimethacrylate, benzoic acid, benzoyl peroxide, N,N-dimethyl-*p*-toluidine and 2-hydroxy-4-methoxy benzophenone (Donaghy *et al*, 1991). Thus it remains questionable if the observed effects can be related to MMA exposure alone.

Seppäläinen and Rajaniemi (1984) reported that there was a significant decrease in distal sensory conduction velocities on digits 1, 2 and 3 of the right hand and also from radial aspects of digits 2 and 3 on the left hand of 5 of a group of 20 dental technicians who claimed to be suffering from numbness or dermatitis. The dermal exposure data however are incomplete.

Shopov (1962) reported claims of impaired sensitivity and coordination, paraesthesia, myoclonic contractions and neuro-asthenic syndrome complex in 5 dental technicians exposed (primarily via the dermal route) to an unknown level of MMA.

A "tendency towards neuropathy" was reported in the upper extremities of a group of 10 floor layers exposed to MMA concentrations between 62 and 601 ppm for intervals of approximately 20 minutes followed by a period of no exposure between 30 and 60 minutes. Measured reaction time in these individuals was normal. Peripheral nerve function measured by ENeG was reported to be slightly reduced in arms and legs, the effects being more severe in the arms, but the variation of the measurements was high. (Of a total of 120 measurements in the exposed subjects 11 values were outside the normal range, 2 above and 9 below). The authors discuss a possible relationship between peripheral effects and dermal exposure to MMA (Lindberg *et al*, 1991). The effects described in the report seem to be very weak and close to the limit of detection. Furthermore preparations used in floor laying are a mixture of different components and it would be difficult to attribute the observed effects to MMA exposure alone. They may as well be related to the mechanical burden of the working situation.

9.8 MISCELLANEOUS

Baker *et al* (1988) reported an investigation of MMA in the saliva of healthy human beings who had recently worn autopolymerised or heat-polymerised polyMMA palatal appliances. MMA released into the saliva was detected for up to 1 week after insertion of autopolymerised appliances, most of the MMA being released within the first 24 hours. The maximum concentration recorded was 45 µg MMA/ml in whole saliva or 180 µg MMA/ml on the salivary film of the fitting surface. MMA was not detected in the blood or urine. MMA was also detected in the saliva of individuals wearing

appliances which had been heat polymerised at 70°C for 1 hour but was not detected following insertion of appliances that had been heat polymerised at 70°C for 3 hours.

Filatova (1962) studied the effect on the dark adaptation of the eye in 3 individuals by exposing them at the 15th minute with 0.04, 0.05 and 0.06 ppm MMA for 4.5 minutes. Ocular light sensitivity was measured with an ADM adoptometer. A decrease in ocular light sensitivity was reported for all 3 persons immediately after exposure with 0.06 ppm MMA and to a minor extent at 0.05 ppm MMA.

9.9 SUMMARY AND EVALUATION

Many of the studies in the published literature that claim effects on man exposed to MMA are poorly reported and lack important details concerning exposure levels, monitoring and analytical methods, exposure to other chemicals and the health status of the subjects. Such information is essential to allow a full judgement of the validity of such claims and therefore the results of such studies should be treated with caution.

No deaths or serious adverse effects have been reported in human beings exposed to acute doses of MMA. The pungent, characteristic odour of MMA combined with its low odour threshold, serves as a warning well before exposure to significant levels of MMA.

MMA is a dermal irritant after prolonged or repeated exposure and may cause contact sensitisation in certain individuals and dermal exposure should be minimised. Mild eye and respiratory irritation have also been reported but there is no convincing evidence that MMA causes sensitisation via the inhalation route of exposure. Epidemiology studies of workers exposed to MMA show no excess of respiratory disease.

Several publications in the literature have inferred that MMA is having neurotoxic/central nervous system effects in occupationally exposed human beings. These effects are, however, non-specific and it cannot be concluded that they represent neurotoxicity. In most cases it is not possible to draw conclusions on the contribution, if any, of MMA to the symptoms.

Repeated exposure to MMA has resulted in a variety of reported effects on man, such as cardiovascular effects. The majority of these effects, which are mild and reversible, remain unsubstantiated. No such effects were reported by Cromer and Kronoveter (1976) in a well documented study.

There is no evidence to suggest that MMA is genotoxic or carcinogenic in man. No reproductive or teratogenic effects have been reported in exposed populations. These data agree well with the lack of genotoxic, carcinogenic, reproductive or teratogenic effects observed in animal studies on MMA.

SECTION 10. FIRST AID AND SAFE HANDLING ADVICE

10.1 FIRST AID AND MEDICAL TREATMENT

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

10.1.1 Skin and Eye Injuries

Clothing contaminated with MMA should be removed. Affected areas of skin must be washed with copious quantities of water. The skin must be rinsed for at least 10 minutes. 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 minutes. A physician should then be consulted.

10.1.2 Inhalation

The patient must be taken into fresh air, kept warm and at rest if he experiences difficulty in breathing after inhaling MMA 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.

10.1.3 Ingestion

If MMA has been swallowed, do not induce vomiting. Never give anything by mouth to an unconscious person. A physician should be consulted.

10.2 SAFE HANDLING

10.2.1 Safety at Work

The main risk of injury stems from MMA'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 MMA vapour. MMA should be used only in well ventilated areas. MMA vapour is denser than air; pits and confined spaces should be avoided.

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

The following protective clothing must be worn when handling MMA: 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 of MMA.

10.2.2 Storage Safety

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

- MMA must be stored under air as the stabiliser (for example hydroquinone monomethylether) is only effective in the presence of oxygen
- Heat and direct sunlight must be excluded, as these promote polymerisation
- MMA must be stored at temperatures preferably not exceeding 30°C; MMA can be stored without chemical inhibitor at low temperatures (<0°C)
- Care should be taken to prevent contamination, as contaminants can render the stabiliser ineffective or can react with MMA and promote polymerisation.

10.2.3 Fire Safety and Extinguishants

MMA is classified as a highly flammable liquid. It can form an explosive mixture in air and adequate ventilation should be provided and smoking prohibited. Precautions should be maintained to eliminate all sources of ignition of MMA when in contact with air. MMA may polymerise on heating. Sealed containers may rupture if hot. Heat, UV-light, peroxide, azo-compounds, alkalis and oxidising agents may cause polymerisation resulting in explosion. Fires can be extinguished with water, alcohol-resistant foam, dry powder or CO₂.

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.

10.2.4 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;
- if work has to be done in an atmosphere enriched with MMA, bronze-beryllium alloy tools should be used to reduce the risk of sparking to a minimum;
- no welding should be done until all tanks and pipelines have been drained and thoroughly flushed with water or hot caustic soda.

10.3 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 sand, earth or suitable absorbent materials such as sand or earth. MMA 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.

Surfaces contaminated with MMA 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.

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

When aqueous waste containing MMA 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 MMA is properly diluted.

Waste quantities of MMA can be incinerated in accordance with local, state or national regulations. Empty storage drums must be decontaminated before recycling.

Polymers based on MMA can be depolymerised and the MMA recovered by specialist companies. The resulting product may be used in place of virgin monomer, subject to purity considerations. Fully polymerised MMA does not depolymerise spontaneously and can be disposed of by landfill.

APPENDIX A. OTHER STUDIES

A number of special studies have been reported. The majority of these data have been generated to support the small use of MMA in medical devices. They have been reviewed for the sake of completeness. The data are of limited toxicological value.

A.1 *IN VITRO*

MMA has been shown to be cytotoxic in various *in vitro* test systems.

Danilewicz-Stysiak (1980) compared the cytotoxicity of pure MMA (99%) with that of the liquid monomer used for the preparation of dentures to chicken embryo fibroblasts. The latter was reported to have a greater cytotoxicity than the pure monomer suggesting that additional substances of the preparation increased MMA cytotoxicity.

Turkish and Galin (1980) showed MMA (purity 99%), at a concentration of 1%, to be lethal to rabbit kidney cells after 24 hours of exposure. No cytotoxicity was observed in this assay at or below a concentration of 0.1% MMA.

The influence of MMA on protein and DNA synthesis, amino acid uptake and cell division was studied in a culture of mouse L-929 fibroblasts. After a 12 hours incubation DNA synthesis was inhibited, after 24 hours protein synthesis decreased. A growth inhibition of 50% was observed at a concentration of 3.9×10^{-2} mol MMA/l (Von Schmalz, 1979).

The ability of macrophages obtained from the peritoneal cavity of mice to phagocytise *Staphylococcus aureus* was inhibited by 0.5% MMA in the culture medium. Human heparinised blood was incubated with concentrations of 0.5%, 1.25%, and 2.5% MMA for 15 minutes. The number of leucocytes was reduced at a concentration of 2.5% MMA, no viable cells were detected by the trypan blue method, at 1.25% the number of viable leucocytes was reduced to about 50%. Phagocytic polymorphonuclear neutrophils were damaged to a greater extent than lymphocytes. Erythrocytes and platelets were completely lysed at 2.5% MMA (Welch, 1978).

Böhnke *et al* (1985) studied the effect of MMA on porcine corneal endothelial cells *in vitro* to evaluate the local effects of residual monomer in intraocular lenses. Cultures of endothelial cells were exposed for up to 6 days to various concentrations of MMA. Cell damage ranging from vacuolic degenerative changes to necrosis of endothelial cell layers was observed. The severity of

the damage increased with increasing incubation time and increasing monomer concentration. Pedersen *et al* (1983) examined the effect of the liquid MMA preparation of a commercial preparation of bone cement (composition not indicated) on the bone turnover in the isolated parietal bones of mice *in vitro* using radioactive calcium and proline release, and histochemical estimation of alkaline and acid phosphatase activity. The authors reported a concentration dependent reduction in calcium and proline release. Addition of 1 ml monomer preparation/ μ l increased significantly the initial time for alkaline and acid phosphatase activity. The authors concluded that the monomer affected osteoclast and osteoblast activity *in vitro*. This effect could be related to the observed loosening of prostheses when Methacrylate bone cements were used.

Denervated and innervated guinea pig ileum was exposed to 775 ppm MMA via the tissue bath air supply and a series of neuromuscular parameters were monitored. An inhibitory effect on the contractile mechanisms of the muscle and neurons associated with the muscle was reported. The authors concluded that the persistence of the inhibitory response of the denervated tissue indicates that the inhibitory effect is partly due to a direct action on the smooth muscles (Martin and Tansy, 1981). Spontaneous contraction of isolated guinea pig ileum was inhibited by MMA at concentration levels between 0.05 and 0.2% in the perfusion medium and antagonised the stimulant actions of acetylcholine and barium chloride, thus affecting the neuromuscular as well as the muscular stimulation (Mir *et al*, 1973b).

At concentrations between 0.001% and 0.1% MMA reduced cardiac rate, force of contraction and cardiac flow of the isolated and perfused heart (Mir *et al*, 1973a). In an isolated dog heart MMA was reported to have a direct negative inotropic effect on the myocardium (Yasuda and Iwatsuki, 1975).

Willis *et al* (1986) studied the chronotropic response to isopronterol in isolated atria of rats prior exposed to unknown concentrations of MMA vapour in a hypoxic perfusion medium. Atria from MMA exposed rats were completely refractory to isopronterol under hypoxic conditions while control atria of unexposed rats responded to isopronterol under the same conditions.

The effect of inhalation of MMA at a concentration of 2,000 ppm for 30 minutes was studied on electrically stimulated *in situ* amphibian skeletal muscle preparations. A significant fall in maximal twitch tension, a depression in elicited responses to a train of tetanising stimuli and an upward and rightward shift in the strength-duration curve were observed and did not fully return to the control level during a 30 minutes post-exposure recovery period. The authors concluded that inhalation of MMA at 2,000 ppm for 30 minutes can result in a blood concentration sufficient to significantly

reduce the mechanical responses of amphibian skeletal muscle to direct electrical stimulation (Martin *et al*, 1981).

Popinigis (1978) reported an irreversible inhibition of epinephrine stimulated transport of sodium in isolated frog skin at a concentration of 0.003% MMA.

Born *et al* (1988) studied the ability of MMA to block receptor-mediated contraction of isolated rat uteri. MMA in concentrations of 1-20 mM was added to a calcium free 45 mM potassium depolarised uterine preparation for 15 minutes prior to addition of calcium (9.4 mM). MMA produced a dose-related depression of the slope and the maximum response to calcium ions similar to nifedipine, a known calcium antagonistic drug. The EC_{50} for MMA was reported to be 2.5 mM. The authors suggested that this effect indicates that MMA blocks contraction induced by calcium, but not by directly competing with Ca^{2+} , and might block the voltage operating calcium channel of smooth muscle. In further experiments the influence of MMA (5 mM, for 5 min) on several agonists which act through stimulation of membrane receptors on concentrations normally inducing a 1.5 g contraction in the medium used in the experiments was studied. The response to acetylcholine was completely abolished by MMA and the response to angiotensin II and oxytocin was reduced by 90%. The phasic and tonic portion of the potassium induced contraction were dose-dependently decreased by MMA, with an EC_{50} of 12.20 mM for the phasic contraction and an EC_{50} for the tonic contraction of 6.09 mM. The depression of the phasic response could be reversed by increasing the calcium ion concentration. According to the authors antagonism to several receptor agonists may indicate that receptor-operated ion channels may be more susceptible to MMA than voltage operated ones. The lower EC_{50} value for the decreased tonic response to potassium with respect to the phasic response indicates that MMA acts like a slow channel-blocking agent as the tonic contraction is believed to be due to a calcium influx by slow channels.

Petty (1979) studied the influence of MMA on human immunoglobulins *in vitro* using a quantitative gel diffusion technique. MMA added to serum samples did not change the concentration of Ig G, Ig A or Ig M.

A.2 IN VIVO

McLaughlin *et al* (1973) studied blood clearance of ^{14}C -labelled MMA after simulated hip arthroplasty or i.v. injection of the monomer in beagle dogs. Pulmonary function was also studied after administration of the monomer into the femoral vein. Blood concentrations of ^{14}C labelled monomer in the inferior vena cava reached a maximum of 3.5 mg/100 ml 3 minutes after

implantation of the cement and then decreased gradually to 0.7 mg/100 ml over the next 16 minutes. After i.v. administration maximum blood levels were reached within 30 seconds. Monomer levels decreased to not detectable levels 3 minutes after administration of 25 and 50 mg MMA/kgbw and 5 minutes after administration of 75 mg/kgbw. An i.v. dose of 10 mg MMA/kgbw representing 5 times the dose reaching the blood during arthroplasty did not have any effect on the pulmonary function of the animals. Dogs receiving successive doses of 25, 50 and 75 mg MMA/kgbw revealed significant decreases in blood pH and arterial PO_2 and an increase in arterial PCO_2 and haematocrit and developed pulmonary edema. The alterations only occurred after administration of the last dose. According to the authors the amount of MMA causing pulmonary effects in the dogs was 30 to 40 times greater than the amount which probably reaches the blood during human total hip replacement.

Holland *et al* (1973) exposed dogs to 3 doses of 50 mg MMA/kgbw and noted histopathological changes of the liver and lungs characterised by haemorrhage and necrosis. In the kidneys glomerular damage was observed after injections of MMA into the thoracic aorta.

Effects of MMA on the cardiovascular system have been well studied in animals. Hypovolemic animals appeared to be more sensitive to the cardiovascular effects of MMA compared to normovolemic animals. Peebles *et al* (1972) injected dogs i.v. with 10 or 20 mg MMA/kgbw and observed a significant decrease in mean arterial blood pressure and a significant increase in heart rate at both dose levels. The mean duration of hypotension was less than 17 seconds. A significant increase in cardiac output was present in the low dose group only.

Modig *et al* (1975) reported a depression of arterial blood pressure, both systolic and diastolic, after graded infusions of MMA volumes of 0.3 ml corresponding to estimated blood concentrations of about 38 mg/100 ml and to measured concentrations of 0.7 to 1 mg/100 ml about 30 seconds after infusion. Decrease in blood pressure correlated with the infused volume. MMA did not reveal any thromboplastic activity or cause trapping of platelets and fibrin in the lung, and did not give rise to fat embolism. Blood gases and pH were not influenced.

Dogs receiving i.v. doses of 14.9-59.9 μ l MMA/kgbw showed an initial dose-related decrease in blood pressure followed by a slight increase of blood pressure above the initial level before dosing. A decrease in heart rate and an increase in respiratory rate were also observed (Mir *et al*, 1974).

Similar results were reported by Baran *et al* (1982 and 1983) and McMaster *et al* (1974), the latter also reporting no changes in electrocardiogrammes.

Ellis and Mulvein (1974) report a decrease in arterial blood pressure, but an increase in heart rate and cardiac output after i.v. injections of 1 ml MMA to greyhound dogs. The effects were reversible within 5 minutes. Similar results were reported by Brown and Parmley (1984).

D'Hollander *et al* (1976, 1979) administered 50 or 100 mg MMA/kgbw i.v. to dogs. A concentration of 11.4 mg MMA/100 ml blood was detected 4 minutes following injection of 100 mg MMA/kgbw and was associated with significant decrease in systemic diastolic pressure and an increase in cardiac output and pulmonary pressure. No significant cardiovascular effects were seen at an MMA dose of 50 mg/kgbw.

Berman *et al* (1974) infused hypovolemic and normovolemic dogs at 2 mg/100% bw. Hypotension was seen in all dogs although its duration was twice as long in the hypovolemic dogs. The cardiac output of the normovolemic dogs increased following injection while the cardiac output of the hypovolemic dogs decreased. Atropine pretreatment reduced decreases in heart rate and arterial systolic pressure and prevented all other cardiovascular effects (Baran, 1983).

Fairman *et al* (1984) exposed sheep to 2 or 12 mg MMA/kgbw by i.v. injection. A statistically significant decrease in mean systemic blood pressure and an increase in pulmonary arterial pressure were reported at 12 mg MMA/kgbw. A dose dependent increase in baseline lymph flow and pulmonary oedema were also reported. Polymorphonuclear trapping in the pulmonary parenchyma was not detected at either dose.

Several infusion experiments have been conducted. Dogs were infused with MMA solutions resulting in blood levels of 5 mg/100 ml-125 mg/100 ml for 30 minutes. At 30 minutes, a slight decrease in blood pressure was seen in the low dose group while death by respiratory arrest occurred at 125 mg/100 ml (Homsy *et al*, 1972).

Infusion of mongrel dogs with 62.4 mg MMA/kgbw for 10 minutes resulted in sustained hypotension, bradycardia, depression of cardiac output and stroke volume, and an increase in total peripheral resistance. Respiratory rate, minute volume, and oxygen uptake increased, tidal volume decreased. Other symptoms included hypercapnia, hypoxemia and acidosis. After MMA infusion animals were treated for 25 minutes with, epinephrine (1-3 μ g/kgbw/min), isopronterol (1 μ g/kgbw/min), atropine (0.1-0.2 mg/kgbw i.v.), or calcium chloride (0.105 mg/kgbw/min). While atropine antagonised all cardiovascular reactions, isopronterol reversed bradycardia, but not hypotension and epinephrine reversed hypotension, but not bradycardia. Calcium chloride reversed all cardiovascular reactions except hypotension. Bilateral cervical vagotomy prior to MMA treatment prevented acidosis,

hypercapnia, respiratory changes, and bradycardia, but not the other circulatory responses. The authors conclude that MMA appears to enhance parasympathetic influences on the cardiovascular system but may also act directly on cardiac tissue (Waters *et al*, 1992).

Surgical studies were also conducted on animals to examine the effect of MMA based bone cement. Homsy *et al* (1972) examined the effect of 4 plug implants in each of 2 long bones of dogs. MMA migration resulted in a peak blood concentration of 1.2 mg/100 ml during the first 3 minutes post implant. Fat and coagulative necrosis were immediately present at the implant site.

Butterworth and Pelling (1973) inserted based MMA bone cement into rabbit femur and observed an immediate fall in arterial blood pressure post-implant which returned to normal within 40 seconds. No changes in central venous pressure, respiratory rate and the electrocardiogram were observed in the majority of the animals.

MMA caused a variety of effects when injected undiluted into rabbit eye to achieve final concentrations from 0.05 to 5% (v/v) in the anterior chamber of the eye. Corneal oedema, neo-vascularisation, iris engorgement, inflammation and cataracts were observed in a dose related manner. The doses producing these effects were much higher than the small amount of MMA that leaches out implanted ocular lenses (Holyk and Eifrig, 1979).

Guichardière (1952) implanted small plates of MMA based resin in the eyes of rats. A slight fibroblastic conjunctival fasciculi was observed on the 15th day and had regressed by the 30th day. No other information is available from the abstract.

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