Canadian Environmental Protection Act

Priority Substances List
Supporting Document

Methyl Methacrylate

Government of Canada
Environment Canada
Health and Welfare Canada

Gouvernement du Canada
Environnement Canada
Santé et Bien-être social Canada

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1.0 SUMMARY

For the summary of this report, please refer to the Assessment Report.

2.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of National Health and Welfare to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances to determine whether they are "toxic" as defined in Section 11 of the Act which states:

> "...a substance is toxic if it is entering or may enter the environment in a quantity or concentration, or under conditions:
>
> (a) having or that may have an immediate or long-term harmful effect on the environment;
>
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed to be "toxic" according to this Section may be placed on Schedule 1 of the Act. Consideration can then be given to developing regulations, guidelines or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

To identify the toxicological and environmental data relevant to the preparation of the Supporting Document, literature searches were conducted on the following computerized databases: Hazardous Substance Data Bank (HSDB), Registry of Toxic Effects of Chemical Substances (RTECS), Chemical Carcinogenesis Research Information System (CCRIS) (1991), Toxline (1981 to 1991), Toxlit (1989 to 1991, only), Chemistry Abstracts (1967-1991), Biological Abstracts (1969-1991), National Technical Information Service (NTIS) (1964-1989), Pollution and Toxicology Database (POLTOX) (1987-1992), Pollution Abstracts (1978-1989), and International Registry of Potentially Toxic Chemicals (IRPTC), DIALOG, and Environmental Bibliography (to 1989). Other sources of information were identified through FATERATE (1989) and Chemical Evaluation Search

and Retrieval System (CESARS) (1988). For toxicological data, searches were also conducted of the three most recent monthly editions of CURRENT CONTENTS were conducted.

To identify data relevant to the estimation of exposure of the general population to methyl methacrylate, the following databases were searched: Environment Canada Departmental Library Catalogue (Elias) (1991), AQUAREF (1970 to 1991), Canadian Research Index (MICROLOG) (1979 to 1991), Cooperative Documents Project (CODOC) (1991).

For assessment of data other than those considered to be critical for determination of whether methyl methacrylate (MMA) is "toxic" to the environment or human health under the Act, existing evaluations, such as those of the U.S. Environmental Protection Agency (U.S. EPA, 1985) and the International Agency for Research on Cancer (IARC, 1979) have been consulted where considered appropriate. The Methacrylate Producers Association also provided a report entitled "Methyl Methacrylate: A Toxicology Review" (MPA, 1991) for consideration in the preparation of the Supporting Document. Unvalidated studies of Industrial Biotest (IBT) Laboratories have been cited but not used directly in the assessment of "toxic" under CEPA.

Information was also sought from the following agencies:

- World Health Organization, Geneva, Switzerland;
- Dutch Expert Committee for Occupational Standards, Netherlands;
- Department of Toxic Substances, Ministry of Social Affairs and Employment, Netherlands;
- International Agency for Research on Cancer, Lyon, France;
- European Chemicals Industry Ecology and Toxicology Centre, Brussels, Belgium;
- Norwegian State Pollution Control Authority, Oslo, Norway;
- United States Environmental Protection Agency (U.S. EPA).

Data relevant to assessment of whether MMA is "toxic" to human health obtained after the completion of these sections of the assessment report (i.e., September 1992) were not considered for inclusion. Similarly data relevant to assessment of whether MMA is "toxic" to the environment obtained after the completion of these sections of the assessment report (i.e., March 1992) were not considered for inclusion.

Although review articles were consulted where considered appropriate, all original studies relevant to the assessment of whether or not MMA is "toxic" under Section 11 of CEPA have been critically evaluated by the following staff of Environment Canada

(entry, and environmental exposure and effects) and Health and Welfare Canada (human exposure and effects on human health):

Environment Canada	Health and Welfare Canada
K.M. Lloyd	P.K.L. Chan M.E. Meek F. Wandelmaier

The human health-related sections of this document were reviewed externally by Dr. J. Siemiatycki, University of Quebec; Dr. N.D. Krivanek, E.I. du Pont de Nemours, Delaware and British Industrial Biological Research Association (BIBRA) Toxicology International. These sections were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health and Welfare Canada. The environmental portions of this document were reviewed internally by Dr. Brian Brownlee, National Water Research Institute, Canada Centre for Inland Waters, and externally by Dr. N. Bunce, University of Waterloo and Dr. N.D. Krivanek, E.I. du Pont de Nemours.

In this report, the technical information is presented in greater detail than in the published Assessment Report, which contains an extended summary of technical information critical to the assessment, as well as the assessment of whether methyl methacrylate is "toxic" under CEPA.

Copies of this unpublished Supporting Document and the published Assessment Report are available upon request from:

Commercial Chemicals Branch
Environment Canada
14th Floor
Place Vincent Massey
351 St. Joseph Boulevard
Hull, Quebec
K1A 0H3

Environmental Health Centre
Health and Welfare Canada
Room 104
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

3.0 Identity of Substance

3.1 Name of Substance

The name of the substance as given on the Priority Substances List is methyl methacrylate, with CAS number 80-62-6. The IUPAC name of the substance is methacrylic acid methyl ester. Other names used are: methyl 2-methyl-2-propenoate; 2-methyl-2-propenoic acid methyl ester; methacrylic acid methyl ester; methyl 2-methylpropenoate; and ethacrylic acid methyl ester. Trade names are Pegalan and Diakon.

The empirical formula is $C_5H_8O_2$. The structural formula is given below.

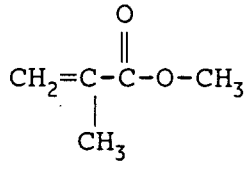


Figure 3-1. Structure of MMA

3.2 Analytical Methodology

Because of the extensive use of acrylic compounds in the manufacturing industry, the literature documents their qualitative and quantitative characterization with a number of laboratory benchmark techniques, including gas chromatography (GC) (Shen *et al.*, 1988; Raynor *et al.*, 1987), mass spectrometry (MS) (Gjos *et al.*, 1983), GC/MS (Horna *et al.*, 1986), nuclear magnetic resonance (Shen *et al.*, 1988) and infrared spectroscopy (O'Neill and Christensen, 1975). Investigations that have included MS in the analysis of acrylic monomers and polymers have relied on either electron ionization (EI) (Gjos *et al.*, 1983) or chemical ionization (CI) (Horna *et al.*, 1986) methods. A recent paper (Snyder, 1990) described the use of oxidative pyrolysis, atmospheric pressure chemical ionization in conjunction with tandem quadrupole mass spectrometry (MS/MS) to characterize methacrylate compounds.

Levels of MMA in blood and in contact lenses have been analyzed by high performance liquid chromatography (HPLC) (Larroque and Brun, 1990; Aitzetmuller and Eckert, 1978).

4.0 Physical and Chemical Properties

MMA is a colourless, volatile liquid at ambient temperature, with an acrid fruity odour. A summary of the physical and chemical properties of methyl methacrylate is presented in Table 4-1. MMA has a relatively high vapour pressure (4000 Pa at 20°C), moderate water solubility (15 800 mg/L), and a low log octanol:water partition coefficient (log K_{ow}) (1.38). MMA has a UV/visible absorption maximum of 231 nm.

For several physical and chemical properties, different values were presented in the literature. For example, there are three groups of data on the octanol:water partition coefficient; those determined experimentally, which ranged from 0.67 - 1.38; those calculated based on the "group contribution method: the substituent or fragment method" by Hansch and Leo (1979) or the "fragment constant method" by Rekker (1977), which ranged from 1.36 - 1.38; and a third group which ranged from 0.79 to 1.03 and appeared to be derived from the averaged value of the experimental and calculated values. Given that a value of 1.38 was measured experimentally and that the calculated value of both Hansch and Leo (1979) and Rekker (1977) is known to be accurate within 0.12 log unit for log K_{ow} values between 1 and 5 (Lyman *et al.*, 1982), the preferred value for log K_{ow} is 1.38. This value is also the one recommended by Sangster (1989), and by Hansch and Leo (Log P Database), who critically reviewed the available measured values in the literature. Professional judgement by Mackay *et al.* (1992b) was used to select the most appropriate value for use in the environmental fate model (Section 6.3.6).

The variation in values presented in the literature for the adsorption coefficient (log K_{oc}) and bioconcentration factor (log BCF) is due to the use of different values of log K_{ow}. The values presented in Howard (1989) are questionable, as he states that the log K_{ow} is 1.38, however he has used a value of 1.03 in equations to calculate both the K_{oc} and bioconcentration factors. The preferred value for log K_{oc} based on a log K_{ow} of 1.38 is 2.1 using the equation of Kenaga and Goring (1978) and for log BCF is 0.82, calculated using the equation in Veith *et al.* (1979).

Table 4-1. Physical and chemical properties of methyl methacrylate.

Property	Value	Reference
Physical State	colourless liquid	
Melting Point (°C)	-48	Perry and Chilton 1973; Weast 1982-83;
Boiling Point (°C)	100.3 100-101	Perry and Chilton 1973; Weast 1982-83;
Flash Point (°C)	13	EPA 1985
Density (g/cm^3 at 20°C)	0.9433 0.9440 0.936	Dean 1985; Weast 1982-83; Verschueren 1983
Molar Volume (cm^3/mol)	106.6 (25°C)	Stephenson and Malanowski 1987
Molecular Weight	100.13	Deichmann 1941
Vapour Pressure ($\times 10^3$ Pa)	4.9 (37 mm Hg at 20°C) 3.9 (29.3 mm Hg at 20°C) 4.0 (30 mm Hg at 20°C) 3.7 (28 mm Hg at 20°C) 5.3 (40 mm Hg at 26°C) 5.3 (40 mm Hg at 25.5°C) 4.6 (38.4 torr) 4.8 (extrapolated, Antoine equation) 5.1 (interpolated, Antoine equation)	Envirofate " ACGIH, 1986 Verschueren 1983 " Weast 1982-83 Howard 1989 Dean 1985 Stephenson and Malanowski 1987
Water Solubility (mg/L)	16000 15000 15900 15600	Dean 1985 EPA 1985; Envirofate; ISHOW Yalkowsky *et al.* 1989 Riddick *et al.* 1986
Henry's Law Constant ($Pa\ m^3/mol$)	24.31 32.823 (calculated from water sol. and vapour pressure)	EPA 1985 Howard 1989
($mol/L \cdot atm$)	3 (calculated from 30 $Pa\ m^3/mol$)	

continued...

Table 4-1. Physical and chemical properties of methyl methacrylate (continued)

Property	Value	Reference
Octanol:Water Partition Coefficient log K_{ow}	0.70 (shake flask)	Fujisawa and Masuhara 1981
	0.67 (HPLC)	Fujisawa and Masuhara 1981
	1.38 (shake flask-GLC)	Tanii and Hashimoto 1982
	1.36 (fragment constant)	Hansch and Leo 1982
	1.38 (fragment constant)	Rekker 1977
	0.79[a] (fragmentation)	EPA 1985
	1.03	Hazardous Sub. Databank
	0.95	ISHOW
Sorption Partition Coefficient, log K_{oc}	1.80[b]	EPA 1985
	1.94[c]	Howard 1989
	1.17 - 2.13[d]	
Bioconcentration Factor, log BCF	-0.03[e]	EPA 1985
	0.55[f]	Howard 1989
Spectroscopy (absorption max.)	231 nm	IARC 1979
Refractive index	n_d^{20} 1.4142	

[a] Calculated using a fragmentation method presented in Lyman *et al.* (1982), but specific method not stated.

[b] Calculated using a log K_{ow} of 0.79, and the equation of Kenaga and Goring (1978), log K_{oc} = 0.544 log K_{ow} + 1.377.

[c] Presented in Howard (1989) and calculated based on K_{ow} (equation not specified).

[d] Calculated range using a log K_{ow} of 1.38 and 6 equations presented in Lyman *et al.* (1982).

[e] Calculated using a log K_{ow} of 0.79, and the equation of Veith *et al.* (1979), log BCF = 0.85 log K_{ow} - 0.7.

[f] Calculated using a log K_{ow} of 1.03, using the equation of Veith *et al.* (1979).

5.0 Production, Use and Release to the Environment

5.1 Natural Sources

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

5.2 Man-made Sources

5.2.1 *Production*

There is no production of methyl methacrylate in Canada.

5.2.2 *Canadian Imports*

The Canadian market is supplied primarily by imports from the United States. In 1988, Canada imported 20.11 kilotonnes from the United States and minor amounts from the United Kingdom (0.14 kilotonnes) and West Germany (0.04 kilotonnes). Imports of 24 kilotonnes are forecast for 1993 (CPI, 1989).

The major importers are Rohm and Haas Canada and Chemacryl Plastics. Rohm and Haas Canada uses the product captively for production of cast acrylic sheet and oil additives, but also sells methyl methacrylate on the merchant market. Chemacryl Plastics uses all the methyl methacrylate it imports captively at its Niagara Falls, Ontario moulding-powder operation. Imports rose sharply in 1987 to meet increased demand by Chemacryl who introduced new processes for production of moulding and extrusion resins. Rohm and Haas has expanded and automated its Morrisburg, Ontario plant, improving its mold assembly operation in the cell-cast acrylic sheet process. In addition, the capacity for cell-cast acrylic sheet has more than doubled. Most of the extra output is sold to the USA.

5.2.3 *Manufacturing Process*

MMA is prepared based on the cyanohydrin process, in which acetone and hydrogen cyanide are reacted to produce acetone cyanohydrin, which is treated with concentrated sulphuric acid. The resulting methacrylamide sulphate is reacted directly with methanol to form crude methyl methacrylate which is purified by distillation. The products obtained from this process and commercially available in the United States contain 99.8% methyl methacrylate, 0.003% methacrylic acid, 0.03% water and 10-15 ppm of hydroquinone and monomethyl hydroquinone as inhibitors.

5.2.4 *Uses and Canadian Demand*

MMA polymerizes easily, especially when heated or in the presence of hydrochloric acid. The polymer forms clear, ceramic-like resins and plastics, commonly known as Plexiglas and Lucite. In Canada, methyl methacrylate is used in the production of coatings, waxes and glazing compounds. Demand for these products increased sharply in the early 1980s before moderating more recently. The outlook calls for a growth rate of 3-4% to 1993.

The monomer and polymers are widely used in medical technology as bone cement, spray adhesive or nonirritant bandage solvent and in dental technology as a ceramic filler or cement (Clayton and Clayton, 1981). The demand pattern is presented in Table 5-1.

5.2.5 *Releases*

MMA can enter the environment during its transport, bulk storage and use in Canada. No data were found on releases of MMA into the Canadian environment.

In Table 5-2, examples provided from the United States Toxic Release Inventory (1989) of the estimated emissions to air, water and soil from plants in the United States are presented. This random sample of 66 out of 245 listings suggests that there are five locations in the USA at which over 100,000 lb/y are released, the total for these five being 1,300,000 lb with only 20,000 lb being to water (i.e. 1.5%) and 750 lb to soil (i.e. <0.1%) (Table 5-2). The other 65 records amount to an additional 300,000 lb/y. From this sample of 27% of the sources in the USA, the total releases in the USA probably lie within a range of 1.54 to 1.76 million lb or about 0.46% of total USA production, assuming production was about 1300 million lb in 1989. This is a likely level of containment for a captive product. Howard (1989) suggested that in the United States, the total emissions in 1974 were about 1% of production.

Applying the figure of 0.46% to Canadian imports of 22 million kg, total emissions are estimated to be 100,000 kg/y or 11.4 kg/h. Given that MMA is not manufactured in Canada, and the plants therefore differ from some of those cited in TRI, it is unknown whether this estimate for Canada is realistic. This may represent a worst-case estimate given that the nature of MMA use is such that no MMA is deliberately discharged.

5.2.6 *Transportation and Storage*

MMA is stored in 440 lb drums, and is transported by tank cars and trucks. An emission factor of 0.071 lb/truck during tank truck cleaning has been measured (Pope *et al.*, 1988).

Table 5-1. Demand pattern in Canada for methyl methacrylate.

Use	Demand (kilotonne)	
	1989	1993 forecast
acrylic emulsions	4.2	5.0
acrylic solution	0.9	1.0
molding and extrusion	8.0	10.0
acrylic sheet	5.0	6.0
miscellaneous	2.0	2.0
total domestic demand	24.0	
imports and total supply	24.0	

Table 5-2. Releases of methyl methacrylate to air, water, soil and underground as reported to the Toxic Chemical Release Inventory (TRI 1989).

Max. amt on-site[1]	State	Release (lbs/y)				
		Air	Water	Under-ground	Soil	Total
C	TX	1,981	0	0	0	1981
D	NY	466,568	0	0	0	466,568
B	LA	8	0	13	0	21
B	NJ	1,765	1,130	0	0	2,895
D	WV	47,505	2,523	0	0	50,028
E	TN	389,000	20,000	0	0	409,000
C	NJ	4,535	0	0	0	4,535
D	MI	803	0	0	0	803
B	MI	247	0	0	0	247
C	OH	2,490	0	0	0	2,490
B	MS	5,843	0	0	0	5,843
f*	OR	3,291	0	0	0	3,291
B	CA	1,500	0	0	0	1,500
A	PR	4,000	0	0	0	4,000
f*	TX	1,770	0	0	0	1,770
C	CT	129,000	0	0	0	129,000
B	VA	5,100	0	0	0	5,100
C	OH	34,180	0	0	0	34,180
B	MO	68	0	0	0	68
D	AR	15,100	0	0	0	15,100
B	NJ	0	0	0	0	0
B	OH	225	0	0	0	225
B	AL	2,950	0	0	0	2,950
B	IL	1,086	0	0	0	1,086
B	CA	750	0	0	0	750
B	KS	2,218	0	0	0	2,218
B	NC	747	0	0	0	747
B	NJ	102	0	0	0	102
C	KY	50	0	0	0	50
D	WI	500	0	0	0	500
B	IL	1,650	0	0	0	1,650
C	PA	681	0	0	0	681
B	AR	2,050	250	0	0	2,300
B	OH	654	0	0	0	654
B	VA	274	0	0	0	274
B	CA	5,700	12	0	0	5,712
B	PA	27,500	0	0	0	27,500
B	MA	500	0	0	0	500
B	MO	1,350	0	0	0	1,350
B	PA	1,000	0	0	0	1,000
C	VA	1,075	0	0	0	1,075

continued

Table 5-2. continued

Max. amt on-site[1]	State	Release (lbs/y)				
		Air	Water	Under-ground	Soil	Total
B	KY	150	0	0	0	150
C	OH	25,800	0	0	0	25,800
C	NJ	36,200	750	0	0	36,950
B	CA	2,751	0	0	0	2,751
B	PA	1,500	0	0	0	1,500
B	GA	3,066	0	0	0	3,066
B	OH	500	0	0	0	500
C	CA	15,800	0	0	0	15,800
C	NC	123	0	0	0	123
B	SC	1,950	0	0	0	1,950
C	MA	153	0	0	0	153
D	PA	157,831	250	0	750	158,831
B	IL	500	0	0	0	500
C	KY	290	0	0	0	290
B	MA	890	0	0	0	890
C	IL	668	0	0	0	680
C	CA	552	0	0	0	552
C	AR	900	0	0	0	900
C	OH	500	0	0	0	500
D	WV	128,000	0	0	0	128,000
B	NJ	531	0	0	0	531
C	VA	1,000	0	0	0	1,000
C	MS	6,037	0	0	0	6,037
B	IL	3,590	0	0	0	3,590
C	MI	151	1	0	0	152

[1] Maximum amount on site -

A	1,000 -	9,999 lbs
B	10,000 -	99,999 lbs
C	100,000 -	999,999 lbs
D	1,000,000 -	9,999,999 lbs
E	10,000,000 -	49,999,999 lbs

f* - used as a formulation component
all other uses are as a reactant

The above data represent a random sample of 66 records of a total of 245. Most releases are estimated by mass balance calculations.

6.0 Environmental Transport, Transformation and Levels

6.1 *Transport and Distribution Between Media*

Transport between media as a result of volatilization and adsorption are discussed in this Section. In Section 6.2, degradation processes such as hydrolysis, photolysis and biodegradation are discussed.

6.1.1 *Water*

When released into water, methyl methacrylate will be lost primarily through volatilization. Using the simple volatilization model of Lyman *et al.* (1982), (based on the Henry's law constant and the molecular weight of the substance) assuming a river 1 metre deep, 20°C, with a flow of 1 m/s and a wind velocity of 3 m/s, Howard (1989) estimated a half-life for volatilization from water of 6.3 hours. The half-life in lakes and ponds will be longer, due to differences primarily in depth and current. No appreciable adsorption to sediment or particulate matter occurs.

6.1.2 *Air*

MMA is highly reactive to hydroxyl radicals, thus its lifetime in the atmosphere will be short. Because the concentration of hydroxyl radicals depends on the intensity of sunlight, the half-life of MMA in the troposphere will vary geographically, seasonally and diurnally. The half-life of MMA in the troposphere at a latitude such as that of Toronto will vary from <5 hours in summer to a few days in winter (Bunce, 1992). These estimates agree with those of Howard (1989, 1991).

When released to air, due to the high vapour pressure of MMA, and the low tendency to partition into water, soil or sediment, MMA will remain in the air compartment.

6.1.3 *Soil*

When discharged to soil, most of the methyl methacrylate remains in the soil due to lack of removal processes. The main removal process is evaporation to air and subsequent rapid degradation. Given the relatively low octanol:water partition coefficient, MMA will not be tightly bound to soil particles. Small amounts may leach into groundwater. Biodegradation could occur where acclimated organisms exist (Howard, 1989).

6.1.4 *Biota*

Although no studies have been done to estimate bioconcentration factors (BCF) for MMA, based on the equation by Veith *et al.* (1979), which estimates BCF from log K_{ow}, the BCF is estimated to be about 3. MMA is thus not expected to bioconcentrate or biomagnify in food chains.

6.2 *Transformation*

The estimated half-lives in various environmental compartments are presented in Table 6-1. These half-lives were selected based on the reactivity class suggested by Mackay *et al.* (1992a), the degradation half-lives given by Howard *et al.* (1991), and degradation rates reported for other processes as indicated in the following sections.

6.2.1 *Biodegradation*

Several studies have shown the potential for biodegradation of MMA. Methyl methacrylate was completely degraded by activated sludge in 20 hours (Slave *et al.*, 1974). Methyl methacrylate was significantly degraded (i.e. >30% after 2 weeks) in the biodegradability test of the Japanese Ministry of International Trade and Industry, which uses a mixed inoculum of soil, surface water and sewage at pH 7 and 25°C (Sasaki, 1978).

In a standard biodegradability test using sewage seed, 42% of the theoretical BOD was consumed in 19 days, including a 3- to 4-day lag period. With acclimated seed, 66% of the theoretical BOD was consumed in 22 days (Pahren and Bloodgood, 1961).

Methyl methacrylate was biodegraded by calcium alginate immobilized activated sludge in a batch recirculation bioreactor. The maximum rate of biodegradation was 8.2 ppm/hour (Jung *et al.*, 1991).

Expert systems survey found that both aerobic ultimate degradation in receiving waters and anaerobic ultimate degradation were within a month and aerobic primary degradation in receiving waters was within a few days. The aqueous aerobic degradation half-life is estimated to be 1 to 4 weeks (based on the acclimated screening from above) and the anaerobic degradation half-life is 4 to 16 weeks (Howard *et al.*, 1991; Syracuse Research Corporation, 1989).

Table 6-1. Estimated half-lives of methyl methacrylate in various environmental compartments with estimated 95% limits.

Compartment	Half-life (h)
air[a]	6 (2 to 18)
water[b]	300 (100 to 900)
soil[c]	550 (200 to 2,000)
sediment[c]	1700 (300 to 10,000)

[a] The half-life in air is 1.1 to 9.7 hours (Howard *et al.*, 1991), based upon the estimated hydroxyl radical reaction in air according to the method of Atkinson (1989).

[b] The half-life in surface and ground water of 168 to 672 hours is based upon estimated aqueous unacclimated aerobic biodegradation (Howard *et al.*, 1991).

[c] The half-life in soil of 168 to 672 hours is based upon estimated aqueous unacclimated aerobic biodegradation (Howard *et al.*, 1991). The soil and sediment values are selected on the basis that degradation in these media will be slower than in water and photolysis will be absent.

6.2.2 *Abiotic Transformation*

Abiotic transformation routes consist of photolysis and hydrolysis. The rate of these processes can be affected by adsorption to sediment or suspended solids.

No data were available on photolysis rates of MMA. The ozone layer prevents radiations of less than 290 nm from penetrating the stratosphere and limits to >290 nm range the wavelengths available for photolysis at the earth's surface. The UV/visible absorption maximum of MMA is 231 nm (IARC, 1979), thus photolysis is a minor route of transformation. Free radicals formed in natural waters by the action of light might react with methyl methacrylate, but environmentally pertinent data in this area are lacking.

Methyl methacrylate was moderately reactive in a smog chamber. With methyl methacrylate and NO_x concentration ratios typical of urban areas (i.e., 2:1), the half-life for photodegradation was 2.7 hours; the half-life exceeded 3 hours when the concentration ratios were typical of rural areas (i.e., 20:1). At the 2:1 ratio, MMA was reactive in terms of ozone formation. The ozone maximum at this ratio was 0.73 ppm, whereas at the higher ratio of 20:1, the ozone maximum was 0.20 ppm (Joshi *et al.*, 1982). The photooxidation half-life is 1.1 to 9.7 hours based upon estimated rate constants for vapour phase reaction with hydroxyl radicals and ozone in air (Atkinson, 1987; Howard *et al.*, 1991).

Hydrolysis, which is base catalyzed, is not significant at neutral and acidic pH. Based on the measured second order hydrolysis rate constant of 200/(M·h) at 25°C and pH 11 (Ellington *et al.*, 1987), the hydrolysis half-life is estimated to be 3.9 years at pH 7 and 14.4 days at pH 9 (Howard, 1989).

No experimental data on the adsorption of methyl methacrylate could be found. From the log K_{ow}, the log K_{oc} is 1.17 to 2.13 (depending on the method used; see Table 4-1), indicating that little adsorption to soil, sediment or suspended solids should occur.

6.3 Environmental Levels

6.3.1 *Surface water*

In a database containing 5700 entries on the frequency of organic compounds identified in water in the United States, MMA was listed four times, once in river water and three times in finished drinking water (Shackelford and Keith, 1976). One of the drinking water listings was a result of analyses of 204 water samples collected from 14 heavily industrialized river basins in the United

States (Ewing and Chian, 1977). Methyl methacrylate was detected (D.L. = 1 μg/L) only once in the survey (10 μg/L in final tap water after chlorination in Chicago in 1976). As no additional information was provided, the validity of this number is not known.

Methyl methacrylate has been detected in deionized charcoal-filtered water, perhaps as a result of preparation or storage of ion exchange resins or charcoal (Dowty *et al.*, 1975).

6.3.2 *Groundwater*

Data on levels in groundwater have not been identified.

6.3.3 *Air*

Data on concentrations of MMA in ambient or indoor air have not been identified.

6.3.4 *Soil/Sediment*

Data on levels in soil or sediment have not been identified.

6.3.5 *Biota/Tissues*

In a study carried out in Atlantic Canada aimed at detecting organic and inorganic contaminants in shellfish, MMA was not detected (detection limit = 0.01 μg/g) in any of the assayed samples from 28 locations (Environment Canada, 1989).

Given the low bioconcentration factor, and the low levels in water, levels in aquatic animals are expected to be very low.

Residual MMA in commercial acrylic bone cements has also been reported to migrate into a prepared tissue medium. The concentrations detected in the fatty components of bone marrow were as high as 0.7 to 5.1% by weight (IARC, 1979). No information on the protocol of this study was provided.

6.3.6 *Food*

The MMA monomer may be present in food as a result of migration from food wrap made from polymethyl methacrylate. The migration of MMA from commercial plastic wrap into 20% ethanol at 25°C was 1 ppm in 1 day and 10 ppm in 90 days. The amount of migration into water at 70°C was 2 ppm in 24 hours (Inoue *et al.*, 1981, in U.S. EPA, 1985). Quantitative data on concentrations of MMA in food have not been identified.

6.3.7 *Prediction of Environmental Fate Using Computer Modelling*

Due to the lack of data on the environmental fate or levels of methyl methacrylate, a modelling technique was used to predict the environmental fate and concentrations based on the substance's physical and chemical properties (Table 4-1), its transformation half-lives (Section 6.2) and emission rates (Section 5.2). As the environmental reaction rates vary greatly from region to region, with season, intensity of sunlight, pH, oxygen concentration and the nature of the prevailing microbial community, the confidence limits on the reaction rates achieved are fairly wide.

The model used was the Level III Fugacity Model (Mackay *et al.*, 1992a; Mackay and Paterson, 1991, 1981, 1982; and Mackay *et al.*, 1985). The following assumptions were made in the modelling exercise:

1. All of the use and emissions of MMA in Canada are in southern Ontario. Although there are 15 buyers of MMA in Canada, there are two main importers: Chemacryl Plastics of Niagara Falls, Ontario and Rohm and Haas of Morrisburg, Ontario. The southern Ontario model encompasses an area of about 170,000 km^2 as shown in Figure 6-1.

2. As stated in Section 5.2.5, from the TRI (1989) output, more than 98% of the emissions were estimated to be released to the air. This may be an over estimate, although data are lacking. To allow for increased release to other compartments, input to the model was 95, 4.5 and 0.5% to air, water and soil, respectively.

3. Total emissions in Canada, based on release of 0.46% of Canadian imports of 22 million kg, are 100,000 kg/y or 11.4 kg/h (see Section 5.2.5).

The estimated concentrations and amounts in each compartment at steady state following input of 11.4 kg/h in the southern Ontario regional model are presented in Table 6-2. The predicted overall persistence is 27 hours or 1.1 days. The mass balance is depicted in Figure 6-2.

When MMA is discharged into the air, most of it remains in the air, with little entering water, soil or sediment. The persistence in air is about 8 hours.

When MMA is discharged into the water, most of the chemical is found in water, with little partitioning into sediment or suspended solids. The principal fate processes are evaporation, reaction and advection. The persistence is increased (relative to the air compartment) to about 9 days, because of slower reaction and

advection from water. When MMA is discharged to soil, most of the substance remains in the soil. The major removal process is evaporation to air followed by reaction.

Thus the fate or behaviour of MMA depends on how it enters the environment. When discharged to air or water it will tend to remain in the media of emission due to its high vapour pressure (favouring evaporation) and high water solubility and low air:water partition coefficient. When emitted to soil, the high vapour pressure results in volatilization to air and subsequent rapid degradation. The relatively short overall persistence is controlled by reaction resulting in only local contamination problems.

Table 6-2. Estimated concentrations and amounts predicted by the Fugacity Level III model for the southern Ontario region.

Phase	Concentration	Amount (kg)	Percent Amount in each Phase
Air	2.4×10^{-4} $\mu g/m^3$	82.3	26.6
Water	0.13 ng/L	188.0	60.8
Soil	1.2×10^{-6} $\mu g/g$	38.8	12.6
Sediment	8.7×10^{-8} $\mu g/g$	0.091	0.03
Fish	1.5×10^{-7} $\mu g/g$	negligible	
Total		309.3	100.0

Figure 6.1 Illustration of the Southern Ontario Region (7)

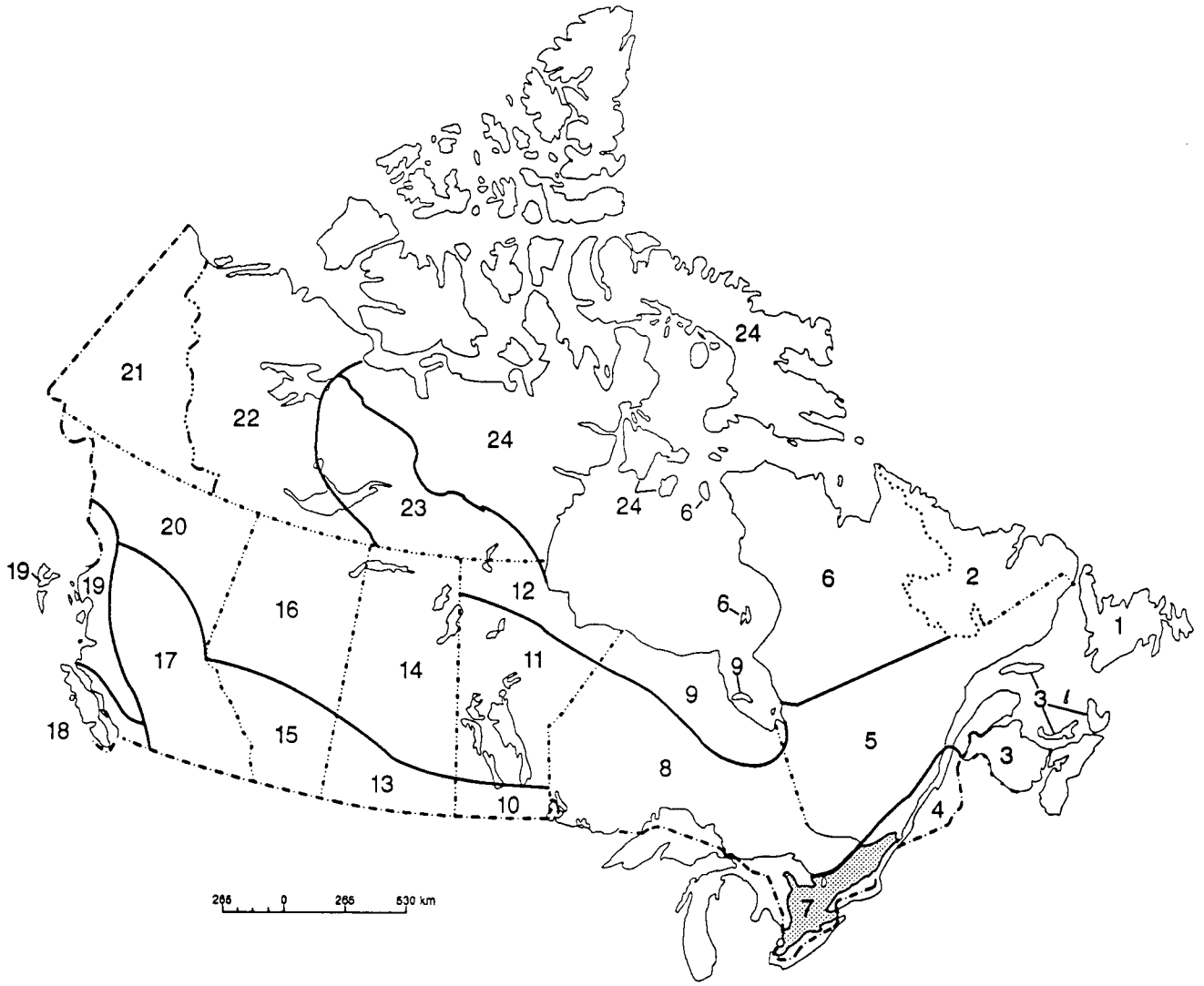
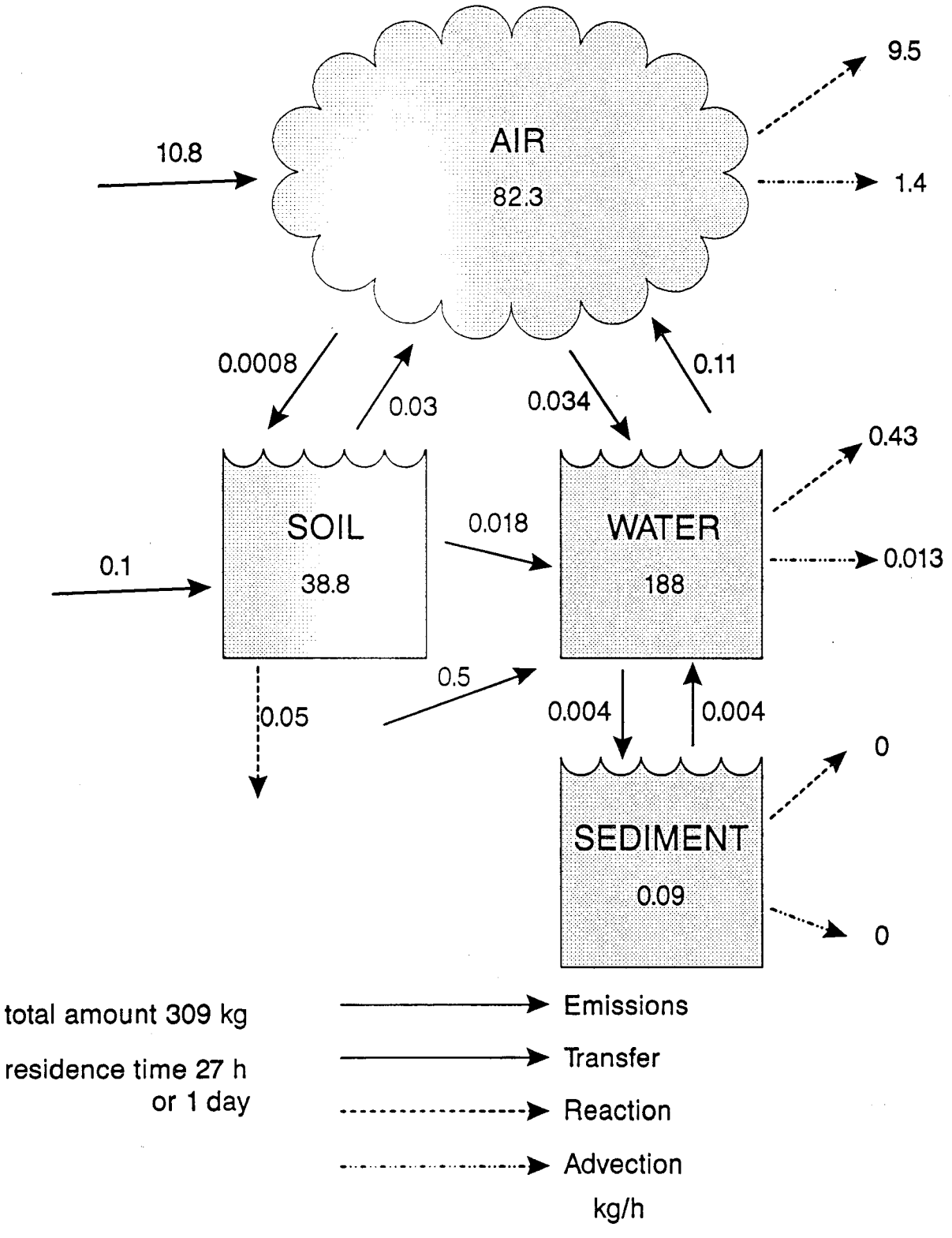


Figure 6.2 Mass balance diagram for 11.4 kg/h of MMA discharged in the Southern Ontario region



7.0 Population Exposures

Available data on concentrations of MMA in environmental media to which humans and other biota are exposed are inadequate to serve as a basis for quantitative estimation of exposure of the general population in Canada or to other populations, such as wildlife. Levels have, therefore, been predicted by fugacity modelling (estimated concentrations of 2.44×10^{-4} $\mu g/m^3$ in air, 0.13 ng/L in water, 1.2×10^{-6} $\mu g/g$ in soil and 1.5×10^{-7} $\mu g/g$ in fish, as presented in Section 6.3.7).

7.1 Wildlife Population Exposure

In general, three routes of exposure to environmental contaminants may be of concern for wildlife: oral, inhalation and dermal. Oral exposures might occur via ingestion of contaminated food (e.g., aquatic prey) or water or incidental ingestion of contaminated media (soil, sediment). Inhalation of vapours or particulates might be a significant route of exposure for animals active near point sources. Dermal exposures are likely to be most significant for burrowing mammals (i.e., via contact with contaminated soils) and animals that spend considerable amounts of time partially submerged in contaminated surface waters.

In order to estimate wildlife exposure to MMA, mink (*Mustela vison*) was chosen as the model species. Mink are opportunistic carnivores with aquatic organisms comprising up to 100% of their diet, depending on the season. Based on the data presented in Table 7-1, total daily intake of MMA by mink in southern Ontario is estimated to be 0.17 ng/kg-bw·d, with approximately 80% of the exposure being attributable to inhalation.

Table 7-1. Estimated total daily intake of MMA for 1 kg adult mink.

MEDIUM	CONCENTRATION[a]	RATE OF CONSUMPTION[b] (per kg-bw·d)	DAILY INTAKE (ng/kg-bw·d)
Air	0.24 ng/m^3	0.55 m^3	0.132
Water	0.13 ng/L	0.1 L	0.013
Fish	1.5×10^{-4} ng/g	158 g	0.024
TOTAL	---	---	0.169

[a] predicted using the Fugacity Model Level III

[b] rate of consumption data for air from Stahl (1967), for water from Calder and Braun (1983) and for fish from Nagy (1987), with the assumption that fish comprise 75% of the mink diet

7.2 General Human Population Exposure

On the basis of the concentrations predicted by the fugacity model, it is estimated that inhalation would be the principal route of exposure (for example, 5.5×10^{-4} µg/day for adults based on the predicted background concentration of 2.4×10^{-5} µg/m^3 and assumed inhalation volume of 23 m^3 of air daily) (EHD, 1992a). Estimated intake from drinking water would be slightly less, (for adults, 2.0×10^{-4} µg/day based on a predicted concentration of 0.13 ng/L and assumed ingested volume of 1.5 litres daily) (EHD, 1992a). Based on the predicted concentrations in fish and soil, estimated intake from food and soil are expected to be negligible compared to that inhaled, though it should be noted that migration from food wrap into foodstuffs may contribute to total daily intake of MMA.

It is estimated, therefore, that the average daily intake of MMA for Canadian adults would not exceed 8.2×10^{-5} µg/kg b.w./day for a 70 kg human (EHD, 1992a). For 5 to 11 year olds, the age group with greatest predicted exposure on a body weight basis, the estimated intake is 11.3×10^{-5} µg/kg b.w./day, assuming an average body weight of 27 kg, daily inhalation volume of 12 m^3 of air, ingestion of 0.9 L of water daily, ingestion of 35 mg/day of soil per day and consumption of 4.8 g of fish daily (EHD, 1992a).

8.0 Toxicokinetics and Metabolism

8.1 Absorption

MMA is rapidly and extensively absorbed following oral administration (Bratt and Hathway, 1977). Following intravenous (i.v.) or oral (gavage) administration to adult male Wistar rats, the pattern and amount of recovery of radioactivity was nearly identical, which indicated that absorption from the GI tract was probably complete (100%).

In 11 dental technicians who had dermal contact with liquid methyl methacrylate (Rajaniemi et al., 1989), there was a large variation in levels of MMA (19 to 200 nmol) in 24 hour urine samples. This variation probably reflected differences in exposure or absorption and excretion since concentrations of MMA in urine samples of the volunteers before work were low (ND to 30 nmol/mmol creatinine, detection limit 0.5 nmol/L).

8.2 Distribution and Retention

The clearance of radioactivity from the blood of beagle dogs was examined following injection into the external jugular vein of single doses of 25, 50 and 75 mg/kg b.w. of ^{14}C-MMA administered successively at one hour intervals (McLaughlin et al., 1973). Following administration, peak levels of radioactivity in arterial blood of approximately 4, 30 and 50 mg/100 mL were reached within 30 seconds, and declined rapidly to $\leq$ 2 mg % at 1, 3 and 5 min, respectively.

Bratt and Hathway (1977) reported that 10 days after oral or i.v. administration of 5.7 mg/kg b.w. ^{14}C-MMA to Wistar rats, radioactivity was detectable only in the liver and adipose tissue.

Based on the rapid metabolism and excretion of metabolites of methyl methacrylate in the rat and dog, there appears to be little potential for accumulation of the parent compound within tissues (U.S. EPA, 1985).

8.3 Metabolism

In a study conducted by Bratt and Hathway (1977), 5.7 mg/kg b.w. ^{14}C-MMA, labelled as methyl-[1,3-^{14}C]-propylene-carboxylate, or as methyl-(2-^{14}C)-propylene-2-carboxylate, was administered to adult male Wistar rats either intravenously or intragastrically. In a ten day period, 84 to 88% of the radioactivity was found in the expired air as $^{14}CO_2$, regardless of the route of administration or the position of the specific labelling. The urinary metabolites included ^{14}C-methacrylic acid, ^{14}C-methylmalonic acid and

^{14}C-succinic acid. Small amounts of ^{14}C-methylmalonate, ^{14}C-succinate, possibly, ^{14}C-β- hydroxyisobutyrate and ^{14}C-2-formylpropionate were also excreted. It was hypothesized on the basis of these results, that all four carbon atoms from methacrylic acid enter the TCA cycle simultaneously, accounting for the rapid expiration of identical amounts of $^{14}CO_2$, regardless of the position of the label. It was further proposed that MMA is hydrolyzed to methacrylic acid, which was converted enzymatically into its coenzyme A ester, which in turn entered the tricarboxylic acid cycle.

In order to test the above hypothesis, Crout et al. (1982) conducted a study in which two female Wistar rats were administered 7 or 9 mg methyl-[^{14}C]methacrylate by intraperitoneal injection. The results indicated that ^{14}C-methyl methacrylate was directly converted to ^{14}C-methylmalonic acid labelled in the same carbon atom. Of the administered dose, 80% was exhaled as $^{14}CO_2$ similar to the results described above, while an average of 0.22% of the administered dose was excreted as methylmalonic acid, specifically labelled with ^{14}C in a manner consistent with the proposed pathway of metabolism. In addition, it appeared that the same metabolic pathways occurred in a human subject administered 94 mg sodium [methyl-$^{2}H_3$]methacrylate orally in aqueous solution, based on the detection of [methyl-$^{2}H_3$]methylmalonic acid in the urine at a level of 170 times greater than the normal levels.

Thus, methyl methacrylate appears to be rapidly metabolized to methacrylic acid, which is subsequently converted to carbon dioxide via the tricarboxylic acid (TCA) cycle.

8.4 Elimination

Following oral or intravenous administration of 5.7 mg/kg b.w. ^{14}C-MMA to adult male Wistar rats, approximately 65% of the dose was exhaled in the expired air as $^{14}CO_2$ in 2 hours. Ten days following oral administration, recovery of radioactivity was 4.7% in the urine, 2.7% in feces, 88.0% as $^{14}CO_2$, 0.1% as unchanged ^{14}C-MMA in the expired air and 4.1% in the carcass and skin. Following i.v. administration, recovery of radioactivity was 6.6% in urine, 1.7% in feces, 84% as $^{14}CO_2$, 0.7% as unchanged ^{14}C-MMA in the expired air and 6.6% in the carcass and skin (Bratt and Hathway, 1977).

8.5 Induction of Metabolizing Enzymes

When mice (NMRI strain) were administered 60 or 600 mg/kg b.w./day of MMA in corn oil for 4 days by intraperitoneal injection, there was no effect on the total concentration of cytochrome P-450 in the hepatic microsomes (Nilsen *et al.*, 1978). Four forms of cytochrome P-450 were identified which included those

with molecular weights (m.w.) of 47,000, 50,000, 54,000 and 56,000. Only the form with m.w. of 47,000 was induced by the lower dose, but was totally suppressed by the higher dose.

In another study, on the fifth day after male Wistar rats were administered intraperitoneally 1.0 g/kg b.w. MMA for 3 successive days, there were decreases in the activity of hepatic NADPH-cytochrome c reductase, 7-ethoxycoumarin O- deethylase and 2,5-diphenyloxazole hydroxylase without any coincident effect on the total amount of cytochrome P-450 hemoprotein itself. One week later, activities of these enzymes were similar to those in the controls (Elovaara *et al.*, 1983).

In a study designed to investigate the effects of MMA on hepatic function (Tansy et al., 1980b), male Swiss Webster mice were administered by inhalation intermittent daily concentrations of 0 (n = 17), 100 (n = 20), or 400 ppm (n = 22) (0, 410 or 1640 mg/m^3) MMA vapour respectively, for a total exposure period of 160 hours. Twenty-four hours after the final period of exposure, 50 mg/kg b.w. sodium pentobarbital was intraperitoneally administered to each mouse. The mean induction time was significantly shorter for animals exposed to 100 ppm, but this may have been due to chance, since there was no exposure-response relationship for this effect. The sleeping times of the animals exposed to 400 ppm were significantly less than ($p<0.05$) those of controls, although the decrease for the other exposed group was not statistically significant. Indications of a reduced barbiturate sleeping time (enzyme induction) were found in both exposed groups.

9.0 Mammalian Toxicology

9.1 Acute Toxicity

In all species studied, the acute toxicity of MMA was low, though in some cases, effects at the site of entry (i.e., lungs following inhalation) have been observed after short periods of exposure to relatively low concentrations. [Indeed, intraalveolar congestion/haemorrhage, pulmonary vasodilation and oedema were observed in rats (male SID, n=4 per group) exposed to concentrations as low as 100 ppm MMA for 2, 3, or 4 hours (Raje *et al.*, 1985)]. Inhalation of high concentrations of MMA for brief periods resulted in significant decreases in pulmonary function, emphysema, edema, hemorrhage, and congestion in the lung, irritation of the eye and mucous membranes, prostration and narcosis with death (Deichmann, 1941; Spealman *et al.*, 1945; Tansy *et al.*, 1980c; Raje *et al.*, 1985; NTP, 1986). The 4-hour LC_{50}s for MMA in rats ranged from 3750 to 7093 ppm (15375 to 29080 mg/m^3) (Kennedy and Graepel, 1991; Tansy *et al.*, 1980c) and 8-hour LC_{50}s were 4634 ppm (19000 mg/m^3) in rats, rabbits and guinea pigs (U.S. EPA, 1985). Doses administered orally which have caused death in experimental animals are relatively high. Acute oral LD_{50}s of 8.4 g/kg b.w. (Deichmann, 1941), 8 g/kg b.w. (Kennedy and Graepel, 1991) and 10.0 mL/kg b.w. (9.4 g/kg b.w.) (Spealman *et al.*, 1945) have been reported for rats. Oral LD_{50}s of 6.3 and 5.0 mL/kg b.w. (5.9 and 4.7 g/kg b.w., respectively) have been estimated for guinea pigs and dogs, respectively (Spealman, 1945). LD_{50}s of 5.5 mL/kg b.w. (5.2 g/kg b.w.) and 6 g/kg b.w. have been reported in mice and rabbits, respectively (Kennedy and Graepel, 1991; U.S. EPA, 1985). The signs of toxicity following oral administration included decreased respiration, loss of reflexes and coma; corrosion of the stomach walls and degeneration of the liver and kidney were also observed (Deichmann, 1941; Spealman *et al.*, 1945).

The LD_{50}s following subcutaneous injection of MMA in rats, mice, guinea pigs and dogs were 7.5, 6.3, 6.3 and 4.5 c.c./kg b.w. (7.08, 5.9, 5.9 and 4.2 g/kg b.w.), respectively (Spealman *et al.*, 1945). The LD_{50} following intraperitoneal (i.p.) injection was 1/5 to 1/10 of the oral LD_{50}. Effects on the nervous system, loss of orientation and paralysis of the respiratory apparatus were seen prior to death following i.p. injection (Spealman *et al.*, 1945). In rats administered up to 2 g/kg i.p. and sacrificed within 24 hours, there were no changes in body or liver weights although impaired respiration, decreased activity and decreased glutathione levels were noted (Elovaara *et al.*, 1983).

Pulmonary edema was observed in dogs after intravenous (i.v.) injections of 75 mg/kg b.w. (McLaughlin *et al.*, 1973) and a decreased heart rate was reported at a dose of 5% v/v following

i.v. injection (Mir *et al.*, 1974).

9.2 Short-term repeated dose toxicity

In short-term repeated dose studies, death, decreases in body weight, cardiovascular effects, changes in respiration rate, increases in level of blood urea nitrogen, and pulmonary damage were observed after exposure to high concentrations of MMA with mice being more susceptible than rats; effects on the respiratory tract of mice were observed at the lowest tested concentration of 500 mg/m^3 (2050 mg/m^3) (Table 9-1). Histopathological effects were limited to those at the site of entry (i.e., the lung in inhalation studies). Renal effects were also reported in rats administered MMA by subcutaneous injection though available data in the published account of this study are inadequate for evaluation. Neurotoxic effects had also been observed in short-term studies but these are addressed in a separate section (Section 9.7).

In an inhalation study conducted at Industrial Biotest (IBT) Laboratories (NTP, 1986), groups of five male and female F344/N rats were exposed to 0, 75, 125, 250, 500, or 1000 ppm (0, 308, 512, 1025, 2050 or 4100 mg/m^3) MMA for 6 hours/day for 10 days. Final mean body weights of the exposed rats were within 6% of those of the controls. No clinical signs or gross pathological effects were observed (NOEL = 1000 ppm or 4100 mg/m^3). However, in a separate study when rats were exposed to 0, 500, 1000, 2000, 3000 or 5000 ppm (0, 2050, 4100, 8200, 12300, 20500 mg/m^3) MMA for 6 hours/day for a total of 11 days, all rats exposed to 5000 ppm and 2/5 females exposed to 3000 ppm died before the end of the studies. Ruffled fur was the only compound-related effect observed in animals that survived. Final mean body weights of rats exposed to 2000 or 3000 ppm were 10% and 19% lower than those of the controls, respectively (NOEL = 1000 ppm or 4100 mg/m^3). No compound-related clinical signs or gross pathological effects were observed.

In the same study conducted at IBT Laboratories, similarly sized groups of mice were exposed to 0, 500, 1000, 2000, 3000 or 5000 ppm (0, 2050, 4100, 8200, 12300, 20500 mg/m^3) MMA for 6 hours/day for a total of 11 days or to 0, 75, 125, 250, 500, or 1000 ppm (0, 308, 512, 1025, 2050 or 4100 mg/m^3) MMA for 6 hours/day for 10 days. In the former study, deaths occurred in all groups of male mice; all animals exposed to 5000 ppm died (LOAEL = 500 ppm or 2050 mg/m^3). Dyspnea and redness and swelling of the nasal region but no histopathological effects were observed (histopathological examinations were restricted to 1 or 2 animals from each dose group). In the latter study in which animals were exposed to 75 to 1000 ppm, all mice survived and there were no adverse effects (NOEL = 1000 ppm or 4100 mg/m^3). Histopathological examinations were restricted to high dose and control groups, 5

males in 125 ppm group and 1 of each sex in 500 ppm group.

In a study reported in the form of an abstract (Miller *et al.*, 1982), groups of 10 Sprague-Dawley rats (sex not specified) were injected subcutaneously for 34 days with either 100 or 200 μL MMA. The average levels of blood urea nitrogen (BUN) for the exposed rats were significantly higher than the BUN values for the control rats. Histological examination of the kidneys of the experimental animals revealed a chronic inflammatory process which tended to correlate with the elevated BUN levels found in the exposed animals. The results suggested that MMA has an adverse effect on renal function, though data presented in the published account of this study were inadequate for evaluation.

Table 9-1 Short-Term Toxicity

Species	Protocol	Results	Effect Levels	References
Rat (female Sprague- Dawley, albino, 3 groups of 4)	Inhalation of unspecified concentration of MMA: the first group was exposed daily for 20 minutes to vapourized MMA for 21 days; the second group was exposed daily for 20 minutes for 42 days; a third unexposed group served as control. All of the rats were monitored during and for 5 minutes prior to, the first and last exposure period, for systolic blood pressure, heart rate, respiration, and electrocardiographic abnormalities (ECG).	One rat in the first group had laboured breathing, an irregular ECG 14 minutes into the first exposure and died later. Upon initial exposure to MMA vapours, five of the eight rats had marked changes in respiratory pattern. Three of the rats had altered ECG patterns. There was an initial drop in systolic blood pressure in the first 2 min., followed by a rise after continued exposure in two of the rats. When the first group was tested on the 21st day, 3 of the 4 rats had breathing irregularities during the period in which they were not exposed. All four had abnormal respiratory patterns ranging from a modified Cheyne-Stokes type to periods of very shallow breathing followed by deep breathing, while two rats had ECG changes during the exposure. The initial blood pressure had decreased from the control value in one animal. Later, all rats had higher blood pressures, heart rates and respiratory rates. At the end of the 42 day period, the second group exhibited similar respiratory patterns to the first group.	unspecified concentration; small group sizes; no statistical analysis	Blanchet et al., 1982
Mouse (female ICR white, groups of 6 to 8)	Inhalation of 1500 ppm (6150 mg/m^3) MMA vapour 2 h/d, twice daily, 5 d/wk, for two weeks. Between the two exposure periods, the mice were removed and provided with food and water, for one hour. Control mice were exposed to air on the same schedule.	Body weight decrease in exposed mice (average of 2.2 g of weight vs. 1.1 g for the control). No histopathological effects in the lung, heart, liver and kidney tissue of all of the animals upon examination.	One dose group only; small group sizes; effects observed at 1500 ppm (6150 mg/m^3)	McLaughlin et al. 1979
Rat (male Sprague-Dawley, groups of 9 to 10)	Inhalation for a total of 56 h over a 7-day period of 1000 ppm (4100 mg/m^3) MMA vapour. Controls were sham-exposed. Histopathological examination of certain visceral organs (heart, kidney, spleen, stomach, and adrenals) and blood chemistries at necropsy.	The mean values for six of the 14 blood parameters (albumin, glucose, blood urea nitrogen, serum glutamate-oxaloacetate transaminase, serum glutamate-pyruvate transaminase and albumin/glucose ratio) examined for the exposed group were significantly lower than the control group ($p \leq 0.05$). Some lung damage was evident, such as fibrosis, edema and emphysema, but this was also seen in some sham exposed animals, although qualitatively less severe. No remarkable abnormalities were found upon gross postmortem examination.	One dose group only; effects observed at 1000 ppm (4100 mg/m^3)	Tansy et al. 1980b
Rat (F344/N, groups of 5 per sex)	Inhalation of 0, 500, 1000, 2000, 3000, or 5000 ppm (0, 2050, 4100, 8200, 12300, 20500 mg/m^3) MMA vapour for 6 h/d for a total of 10 exposures over 11 days. The rats were observed daily and weighed on days 0, 4, 8 and 12. All surviving rats were necropsied at the end of exposure.	All 10 of the high dose rats died on days 1 - 3. In the 3000 ppm group, 1 female died on day 4, and another on day 6. MMA caused only ruffled fur in the survivors. The final mean body weights of the animals in the 2000 and 3000 ppm groups were 10 - 19% lower than controls.	NOEL = 1000 ppm (4100 mg/m^3) LOEL = 2000 ppm (8200 mg/m^3) Small group sizes	NTP, 1986 (conducted at Industrial Biotest Laboratories)

Table 9-1 (Continued)

Species	Protocol	Results	Effect Levels	References
Mouse ($B6C3F_1$, groups of 5 per sex)	Inhalation of 0, 500, 1000, 2000, 3000, or 5000 ppm (0, 2050, 4100, 8200, 12300, 20500 mg/m^3) MMA vapour for 6 h/d for a total of 10 exposures over 11 days. The mice were observed daily and weighed on days 0, 4, 8 and 12. Histological examination of the tissues from the lung, heart, kidney, salivary gland, mammary gland and nose of 1 or 2 males from all exposed groups.	Deaths occurred in all groups of exposed males after 1 - 10 days. All of the mice in the highest dose group died (females day 1, males days 1 and 2). MMA caused dypsnea and redness and swelling of the nasal region. Necropsy revealed no MMA-related effects.	LOAEL = 500 ppm (2050 mg/m^3) Small group sizes	NTP, 1986 (conducted at Industrial Biotest Laboratories)
Rat (F344/N, groups of 5 per sex)	Inhalation of 0, 75, 125, 250, 500, or 1000 ppm (0, 308, 512, 1025, 2050 or 4100 mg/m^3) MMA for 6 h/d (except only 1 h/d on day 5), for 9 exposures over 10 days. The rats were observed daily and weighed on days 0, 4, 8, and 11. Necropsies for all rats at end of exposure.	All of the rats survived the 10 day study. The final mean body weights of the exposed rats were within 6% of the controls. MMA caused no clinical or gross pathologic effects.	NOEL = 1000 ppm (4100 mg/m^3) Small group sizes	NTP, 1986 (conducted at Industrial Biotest Laboratories)
Mouse ($B6C3F_1$, groups of 5 per sex)	Inhalation of 0, 75, 125, 250, 500, or 1000 ppm (0, 308, 512, 1025, 2050 or 4100 mg/m^3) MMA for 6 h/d (except only 1 h/d on day 5), for 9 exposures over 10 days. The mice were observed daily and weighed on days 0, 4, 8, and 11. Histopathological examinations of the tissues from the lung, heart, kidney, salivary gland, mammary gland and nose of 5 mice of each sex in the highest exposure and control groups, 5 males in the 125 ppm group, and on 1 of each sex in the 500 ppm group.	All of the mice survived the 10 day study. MMA caused no gross or microscopic pathologic effects.	NOEL = 1000 ppm (4100 mg/m^3) Small group sizes	NTP, 1986 (conducted at Industrial Biotest Laboratories)
Rat (Sprague-Dawley, groups of 10; sex unspecified)	Subcutaneous injection of 0, 100, or 200 uL/day (94.4 or 188 mg/day, respectively) of MMA for 34 days. Biochemical analysis of blood and histopathological examination of kidney.	Blood urea nitrogen (BUN) levels in the low and high dose groups were significantly higher than in the control group. Chronic inflammation in the kidneys which correlated with these BUN levels.	LOEL = 100 uL/day (94.4 mg/kg/day)	Miller et al., 1982 (Abstract)

9.3 Long-term repeated dose toxicity

Gross or microscopic pathological effects reported in long-term repeated dose studies in rats, mice and dogs are limited (Table 9-2). In most studies conducted to date, animals have been exposed to MMA by inhalation; effects observed most commonly in these investigations were decreases in body weight gain and irritation of the skin, nasal cavity and eye at high concentrations, [generally greater than or equal to 500 ppm (2050 mg/m^3)] (IBT for Rohm and Haas, 1977a; IBT and Batelle Northwest for NTP, 1986). Other effects on the kidney such as renal cortical necrosis and tubular degeneration and liver necrosis have also been reported (Tansy *et al.*, 1980a; NTP, 1986; Deichmann-Gruebler and Read, date not specified). On the basis of decreases in final mean body weight and squamous metaplasia at the site of entry (i.e., the lung), the lowest reported NOELs and LOELs in a subchronic inhalation bioassay in which several dose levels were administered were 250 and 500 ppm (1025 and 2050 mg/m^3) in mice, respectively (IBT for Rohm and Haas, 1977a; IBT and Batelle Northwest for NTP, 1986). With the exception of effects at the site of entry, histopathological effects have not been observed in the two most extensive bioassays in rats at concentrations less than or equal to 1000 ppm (4100 mg/m^3) (IBT for Rohm and Haas, 1977a; IBT and Batelle Northwest for NTP, 1986). In less extensive and well documented studies conducted by Tansy (1976, 1980a, 1980b), effects on the trachea and some indications of liver damage in mice were recorded at the lowest tested concentration of 116 ppm, administered for 7 hours/day for 6 months (though the statistical significance of the pulmonary changes was not specified and similar effects were observed in some of the sham-exposed control animals). In a supplementary study, there was weak evidence of an effect on liver function (barbiturate sleeping time) in groups of 20 male mice administered "intermittent daily exposures" of 100 ppm for a total of 160 hours (Tansy, 1980b). Initial reports of reduced fat deposits after exposure for 3 months were not confirmed in repeat studies (Tansy, 1980a,b).

In a study conducted for Rohm and Haas by IBT Laboratories (Rohm and Haas, 1977a), groups of 10 F344/N rats of each sex were exposed to 0, 63, 125, 250, 500 or 1000 ppm (0, 258, 512, 1025, 2050 or 4100 mg/m^3) of MMA, 6 hours/day for 65 days. There were no statistically significant differences in body weights between the control and exposed groups for both male and female rats. No gross or histopathologic alterations attributable to the effects of MMA were observed in any of the exposed rats (NOEL = 1000 ppm or 4100 mg/m^3).

In another IBT study in mice described in the same report (Rohm and Haas, 1977a), groups of 10 $B6C3F_1$ mice of each sex were

exposed to the same concentrations of MMA as the rats, 6 hours/day for 64 days. The body weights in male mice exposed to 500 or 1000 ppm (2050 or 4100 mg/m^3) were statistically significantly lower at weeks 12 and 13 ($P<0.05$ and $P<0.01$, respectively) than in controls. No gross or histopathologic alterations were observed in any of the exposed mice (NOEL = 250 ppm or 1025 mg/m^3).

In separate studies conducted by two different laboratories under the auspices of the National Toxicology Program (NTP, 1986) in F344/N rats and B6C3F$_1$ mice, groups of 10 males and 10 females of each species were exposed to 0, 63, 125, 250, 500 or 1000 ppm (0, 258, 512, 1025, 2050 or 4100 mg/m^3) in the first study conducted at the IBT Laboratories or to 0, 500, 1000, 2000, 3000 or 5000 ppm (0, 2050, 4100, 8200, 12300, 20500 mg/m^3) in the second study conducted at Batelle Pacific Northwest Laboratories (BNW), 6 hours/day, 5 days/week for 14 weeks. In the first study in rats, no compound-related effects were reported upon histological examination of an unspecified range of tissues (NOEL = 1000 ppm or 4100 mg/m^3). In the second study, there were deaths, effects on body weight, and lesions of nasal turbinates and brain at 2000 to 5000 ppm. Changes in the spleen occurred at 3000 ppm or more. At 1000 ppm, there was some indication of a low incidence of mild effects on the brain and nasal turbinates in females. No toxicity was reported at 500 ppm (2050 mg/m^3). Although there was no detailed histological examination of the brain and nasal turbinates at 500 ppm, the minimal severity and incidence of the pathology at 1000 ppm would suggest that the lowest tested dose of 500 ppm (2050 mg/m^3) was unlikely to induce pathological effects. Other compound-related pathological effects included follicular atrophy of the spleen in 4/10 males, bone marrow atrophy in 8/10 males in the group exposed to 5000 ppm and cerebellar congestion and penducle hemorrhage in the females exposed to 3000 and 5000 ppm which died early (NOEL = 500 ppm or 2050 mg/m^3).

In the study conducted at IBT Laboratories, there were no compound-related gross or microscopic pathologic effects observed in mice (NOEL = 500 ppm). In the study conducted by BNW Laboratories, 8 male and 8 female mice exposed to 5000 ppm, 4 male mice exposed to 3000 ppm, and 2 male and 1 female mouse exposed to 2000 ppm, died. Reduced mean body weights were seen in all MMA exposed groups. Compound-related lesions included renal cortical necrosis, renal cortical tubular degeneration and renal focal mineralization in male mice exposed to 2000 ppm and above, and liver necrosis in male mice exposed to 5000 ppm. There was inflammation of the nasal turbinates in mice exposed to 2000 ppm and above and nasal epithelial metaplasia in all exposed male and female mice (LOEL = 500 ppm or 2050 mg/m^3).

In a less extensive study conducted by Tansy *et al.* (1976),

male Sprague-Dawley rats exposed to 116 ppm (476 mg/m^3) MMA, 5 days/week for 3 or 6 months by inhalation had significantly lower visceral and subcutaneous fat content, mean body weight, and popliteal fat pad weights. For the 6 month study, there was no difference in visceral fat deposits between the exposed and control groups, whereas the differences in the amount of subcutaneous fat were still apparent upon visual inspection. No explanation for the difference in visceral fat deposits between the 3- month and the 6-month exposure periods was provided by the authors. Mean body weights, popliteal fat pad weights and mean intestinal transit time were significantly lower, and mean alkaline phosphatase and inorganic phosphate concentrations were significantly higher in the exposed versus control groups. However, these effects were not confirmed in later studies by the same authors in which rats were exposed to the same concentration (Tansy *et al.*, 1980a; 1980b). Mild lung damage was observed in some rats exposed to 116 ppm MMA by inhalation but the statistical significance of the increase between the exposed and control groups was not specified. (Similar changes were observed in sham-exposed controls) (Tansy et al., 1980b). There were no exposure-related effects in beagle dogs exposed to 100 (410 mg/m^3) or 400 ppm (640 mg/m^3), 5 days/week for 3 months in a study reported by the same authors (Tansy and Drees, 1979).

In an unpublished 70 day study (Deichmann-Gruebler and Read, date not specified) in small groups of rats of an unspecified strain exposed by gavage, the NOAEL was considered to be 3 c.c./kg b.w. (2.8 mg/kg b.w.). At the higher dose, rats had distended bladders filled with blood, and exhibited liver change and kidney damage. The range of tissues examined was not reported.

Table 9-2 Long-Term Toxicity

Species	Protocol	Results	Effect Levels	Reference
Rat (male Sprague-Dawley, groups of 50)	Inhalation of 0 or 116 ppm (476 mg/m^3) MMA 8 h/d for 5 d/wk. Approximately half of the rats in each group were sacrificed after 3 months; blood and tissue samples were taken immediately. The remainder of the rats were exposed for 6 months. Intestinal transit-time was examined in 8 rats from the six month control and exposed group. The remainder of the rats were killed and organ weights and blood were taken.	All of the rats exposed for 3 months noticeably lacked visceral and subcutaneous fat deposits. They also had significantly lower body, lung and spleen weights. Significantly higher mean serum alkaline phosphatase concentration in the exposed than in the control rats. For the 6 month exposure period, there was no difference in visceral fat deposits between the exposed and control rats, whereas the exposed group had less subcutaneous fat. Significantly lower mean body weights, popliteal fat pad weights, mean intestinal transit time, and significantly higher mean alkaline phosphatase and inorganic phosphate concentrations in the exposed vs. control groups.	One dose group only; effects observed at 116 ppm (476 mg/m^3)	Tansy et al. 1976
Rat (male Sprague-Dawley, groups of 23)	Inhalation of 0 or 116 ppm (476 mg/m^3) MMA 5 d/wk., averaging 7 h/d, for 542 h (3 months). Excretion studies in nine rats from each group. Rats received food and water ad libitum, except during the exposure period, when they received only water. Histopathological examinations of heart, lung, kidneys, spleen, stomach, small bowel, liver and adrenal.	There was no difference in visceral or subcutaneous fat deposits between the two groups. The exposed rats had significantly lower total bilirubin and higher total cholesterol levels than the control rats. No significant difference in final mean body, adrenal, epididymal fat pad, and popliteal fat pad weights. There were signs of possible liver damage in the exposed group but details were not reported. The amount of food and water intake and water excretion did not change significantly in either the exposed or control rats, neither during the week nor during the two days of no exposure. During the exposure period, the exposed rats excreted less feces than did the controls, but there were no differences in average values for weekends (periods of no exposure).	One dose group only; effects observed at 116 ppm (476 mg/m^3)	Tansy et al. 1980a
Rat (male Sprague-Dawley, groups of 23 for 3 months and unspecified number for 6 months)	Inhalation of 0 or 116 ppm (476 mg/m^3) MMA 7 h/d, 5 d/wk, for 3 or 6 months. Histopathological examinations of heart, lung, kidneys, spleen, stomach, small bowel, liver and adrenal.	Mild lung damage in some of the rats exposed for 3 and 6 months and sham exposed (no statistical analysis). No deaths, tumor growth, or other abnormalities were noted. All six of the rats sampled from the group exposed for 6 months had damaged tracheal mucosa, compared to none in controls. The epithelium was denuded of cilia, and the cellular covering of microvilli was reduced in rats exposed to 116 ppm for 3 months.	One dose group only; effects observed at 116 ppm (476 mg/m^3)	Tansy et al. 1980b

Table 9-2 (Continued)

Species	Protocol	Results	Effect Levels	Reference
Dog (Beagles, groups of 6, sex unspecified)	Inhalation of 0, 100, or 400 ppm (0, 410 or 1640 mg/m^3) MMA vapour 6 h/d, 5 d/wk., for 3 months. Each dog had an external iliac artery catheter. 2 dogs from each group were sacrificed at the end of the 3 month period. The remaining dogs were observed for an extra month before sacrifice and necropsy.	A control and a low dose dog died prematurely following complete thrombosis of the distal aorta and iliac branches, and tissue degeneration and infection. The food consumption of all 3 groups, and the mean body weight of the control group decreased significantly over the course of the exposure; this was attributed to problems with the chronic catheterization. No significant differences in systolic and diastolic blood pressure, ECG, heart and respiratory rates, hematology, clinical chemistries and urinalyses between the exposed and control groups. Histopathological examination of the major organs was unremarkable.	NOEL = 400 ppm (1640 mg/m^3)	Tansy and Drees, 1979
Rat (F344, groups of 10 of each sex)	Inhalation of 0, 63, 125, 250, 500, or 1000 ppm (0, 258, 512, 1025, 2050 or 4100 mg/m^3) MMA, 6 h/d for 65 days. All survivors were killed one day after the final exposure, complete gross pathological and histopathological examinations.	Some clinical signs and one death each in groups exposed to 63 ppm and controls but not dose-related. No statistical differences in body weights between the control and the exposed groups for both male and female rats. There were no gross or histopathological alterations.	NOEL = 1000 ppm (4100 mg/m^3)	Rohm and Haas, 1977a (conducted at Industrial Biotest Laboratories)
Mouse (B6C3F$_1$, groups of 10 of each sex)	Inhalation of 0, 63, 125, 250, 500 or 1000 ppm (0, 258, 512, 1025, 2050 or 4100 mg/m^3) MMA, 6 h/day for 64 days. One day after the final exposure, all survivors were killed for complete gross pathological and histopathological examinations.	Some clinical signs and one death in the group exposed to 500 ppm but not dose-related. The body weights of the males receiving the two highest doses were significantly decreased during weeks 11 - 13 (500 ppm) and weeks 6, 11 and 12 (1000 ppm). The decrease in body weight of the highest dose group was significant. In female mice, the total body weight changes were statistically significantly lower in animals exposed to 500 ppm (2050 mg/m^3) but not to 1000 ppm (4100 mg/m^3). No gross or histopathological alterations (any seen were similar to those in the control mice).	NOEL = 250 ppm (1025 mg/m^3) LOEL = 500 ppm (2050 mg/m^3)	Rohm and Haas, 1977a (conducted at Industrial Biotest Laboratories)
Rat (F344/N, groups of 10 of each sex)	Inhalation of 0, 63, 125, 250, 500 or 1000 ppm (0, 258, 512, 1025, 2050 or 4100 mg/m^3) MMA 6 h/d, 5 d/wk. for 14 weeks (65 exposures). Rats were observed daily and weighed weekly; moribund animals were killed. Survivors were killed after 97 days. Necropsies were performed. Histologic examinations were conducted of an unspecified range of tissues from all high dose and control rats, those that died before the end of the study, and on some of the rats from the other groups.	No MMA-related deaths (1 male control, and 1 female in the lowest dose group, both at week 3). No treatment-related effects on the mean body weights or gross or microscopic pathology.	NOEL = 1000 ppm (4100 mg/m^3)	NTP, 1986 (conducted at Industrial Biotest Laboratories)

Table 9-2 (Continued)

Species	Protocol	Results	Effect Levels	Reference
Rat (F344/N, groups of 10 of each sex)	Inhalation of 0, 500, 1000, 2000, 3000, or 5000 ppm (0, 2050, 4100, 8200, 12300, 20500 mg/m^3) MMA 6 h/d, 5 d/wk. for 14 weeks (65 exposures). Histological examinations were performed on the controls, the 2 highest dose groups, the rats that died before the end of the study. Tissues from the nasal turbinates, larynx, trachea, lungs, and brain for all rats exposed at 1000 ppm and survivors of the 2000 ppm groups were also histopathologically examined.	In the 2000 ppm group, 1 male (week 11) and 3 females (week 2 - 5) died. In the 3000 ppm group, 1 male died in week 3, and 8 females died in week 2 and 1 in week 3. All rats died in the first week of exposure to the highest dose. The final mean body weights of rats in the 2000 and 3000 ppm groups were less than the controls: males 7% and 20%, respectively; females 11% and 20%, respectively. Other compound-related pathological effects included follicular atrophy of the spleen in 4/10 males, bone marrow atrophy in 8/10 males in the group exposed to 5000 ppm and cerebellar congestion and penducle hemorrhage in the females exposed to 3000 and 5000 ppm which died early. At the highest exposure concentration, MMA caused listlessness, nasal and serous ocular discharge, and prostration during the first 2 days, nasal cavity inflammation with necrosis and loss of epithelium, follicular atrophy of the spleen and bone marrow atrophy in the males. Cerebellar congestion and penducle hemorrhage in the early death females exposed to 3000 and 5000 ppm, and malacia and gliosis in 5/9 females exposed to 2000 ppm and 1/8 females exposed to 1000 ppm.	NOEL = 500 ppm (2050 mg/m^3)	NTP, 1986 (conducted at Battelle Pacific Northwest Laboratories)
Mouse (B6C3F$_1$, groups of 10 of each sex)	Inhalation of 0, 63, 125, 250, 500, or 1000 ppm (0, 258, 512, 1025, 2050 or 4100 mg/m^3) MMA 6 h/d, 5 d/wk. for 14 weeks (64 exposures). The mice were observed daily and weighed weekly. Survivors were killed after 96 days and necropsies were performed on all mice. Histologic examinations of an unspecified range of tissues of all mice in the highest dose and control groups, all animals that died before the end of the study, and some mice in the other groups.	No compound-related deaths occurred (1 male in the 500 ppm group died during week one). The final mean body weight of the highest dose males was 7% lower than controls. No compound-related gross or microscopic pathological effects.	NOEL = 500 ppm (2050 mg/m^3) LOEL = 1000 ppm (4100 mg/m^3)	NTP, 1986 (conducted at Industrial Biotest Laboratories)

Table 9-2 (Continued)

Species	Protocol	Results	Effect Levels	Reference
Mouse ($B6C3F_1$, groups of 10 of each sex)	Inhalation of 0, 500, 1000, 2000, 3000, and 5000 ppm (0, 2050, 4100, 8200, 12300, 20500 mg/m^3) MMA 6 h/d, 5 d/wk. for 14 weeks. Histologic examinations of tissues from the major organs of all mice in the highest dose and the control groups and mice that died before the end of the study. At 2000 and 3000 ppm, the lung and nasal turbinates of the males and the nasal membranes of all females were histologically examined as was the liver of the males of the 2000 ppm group. At 1000 ppm, the nasal turbinates from both sexes and brain from the males were also histologically examined.	The final mean body weights of all groups of exposed mice were lower than controls (males 13% - 27%, females 6% - 18%). In the 2000 ppm group, 2 males died (weeks 1 and 2) and 1 female died (week 2). In the 3000 ppm group, 4 males died in week 2. In the highest dose group, 6 males died in weeks 1 and 2, and 2 males died in week 10; in this group, 8 females died (weeks 1 - 5). Compound-related effects in the males included renal cortical necrosis, cortical tubular degeneration and/or focal mineralization, nasal cavity inflammation with necrosis and loss of olfactory epithelium at 2000 to 5000 ppm and extensive liver necrosis in males exposed to 5000 ppm. Inflammation of the nasal turbinates in females exposed to 2000 ppm and above. All exposed mice had metaplasia of the nasal epithelium.	LOEL = 500 ppm (2050 mg/m^3)	NTP, 1986 (conducted at Battelle Pacific Northwest Laboratories)
Rat (white male, strain and number unspecified)	Ingestion of 940 mg (total dose) MMA dissolved in edible oil by gavage, biweekly for 2, 3 or 4 months. The liver mitochondria were examined with an electron microscope.	Significantly decreased mitochondrial respiration and oxidative phosphorylation. There were irreversible changes in the structure of the mitochondria and dystrophic changes especially in the pericentrilobular region of the liver.	One dose group only; effects observed at 940 mg (total dose)	Constantinescu and Filipescu, 1971
Rat (sex and strain unspecified, groups of 5)	Ingestion of 0, 1, 3 or 5 c.c./kg b.w. (0, 0.9, 2.8 or 4.7 mg/kg b.w.) orally by gavage, every second day for 70 days. Urine samples from rats of all groups were periodically collected and examined for blood. Histopathological examinations unspecified.	Rats in mid-dose group did not gain as much weight as those in low-dose and animals in high-dose group died before the 4th treatment. No blood was found in the urine from the animals receiving 1 or 3 c.c./kg b.w. All high-dose rats had distended bladders filled with blood. At the high dose, there was a moderate degree of cellular degeneration in the liver, but without necrosis or fibrosis; in the kidney, there were hemorrhages in the tubules, marked hyperemia, and degeneration of the tubular epithelium.	NOAEL = 3 c.c./kg b.w. (2832 mg/kg b.w.) Small group sizes.	Deichmann-Gruebler et al. (undated)
Rat (sex and strain unspecified, number as specified in Protocol)	1 c.c./d of MMA was dropped onto the shaved backs of 5 rats for 10 weeks. 3 other rats served as controls. The experiment was repeated with 12 experimental and 10 control rats, for 7 weeks. At the end of the experiment the rats were killed for pathological studies (not specified).	In the first trial, the treated animals appeared edematous after 6 to 9 weeks of administration, especially at the head and back. MMA did not retard the regrowth of hair. Weight gain in exposed animals was rapid throughout the 8 weeks. In the second trial, the only toxic effect was temporary local irritation. The blood porphyrin content did not rise and there were no distinct pathological changes (not specified).	One dose group only; transient local irritation observed at 1 c.c./d (944 mg/d)	Deichmann-Gruebler et al. (undated)

Table 9-2 (Continued)

Species	Protocol	Results	Effect Levels	Reference
Rat (Wistar, sex and number not specified)	Rat tails were exposed to liquid MMA (>99% purity) for 3 h/d over a period of 8 weeks. Biopsies were taken from the treated area for light and electron microscopy.	The intercellular spaces of the epidermal cells were enlarged with fine granular substance. There were vacuoles, oedema, distorted cristae in mitochondria, and pyknotic nuclei in the keratinocytes. Focal cytolysis and oedema were observed in all layers of the epidermis. Myelin figures as a sign of degeneration were found in less than 10% of the axons in the upper dermis.	One dose group only; effects observed (pure liquid)	Kanerva and Verkkala, 1986

In studies reported by Verkkala *et al.* (1983) and Kanerva and Verkkala (1986) in which Wistar rat tail skin was exposed to liquid MMA, 3 hours/day over a period of 8 weeks, there was keratolysis without ulcerations in the exposed skin. Based on examination by light and electron microscopy, the intercellular spaces of the epidermal cells were enlarged with fine granular substance. There were vacuoles, oedema, distorted cristae in mitochondria, and pyknotic nuclei in the keratinocytes. Focal cytolysis and oedema were observed in all layers of the epidermis. Myelin figures as a sign of degeneration were found in less than 10% of the axons in the upper dermis. In an unpublished study (Deichmann-Gruebler and Read, date not specified) in which 1 c.c./day of MMA was dropped onto the shaved backs of rats (strain not specified) for 7 or 10 weeks, the exposed animals appeared edematous after 6 to 9 weeks of exposure. The only effect observed was temporary local irritation.

9.4 Chronic toxicity/Carcinogenicity

In the few studies identified in which the chronic toxicity and carcinogenicity of MMA were investigated, the observed effects were, in general, similar to those reported in short-term and long-term studies, including inflammation and epithelial hyperplasia of the nasal cavity and degeneration of the olfactory sensory epithelium. In these studies, there has been no evidence that MMA is carcinogenic.

In a well documented inhalation study conducted at BNW Laboratories as reported in NTP (1986) and Chan *et al.* (1988), groups of 50 male F344/N rats were exposed to 0, 500 or 1000 ppm (0, 2050 or 4100 mg/m^3) MMA and groups of 50 females, to 0, 250 or 500 ppm (0, 1025, 2050 mg/m^3) MMA, 6 hours/day, 5 days/week for 102 weeks. Clinical signs, body weight, mortality and gross observations at necropsy were recorded and histological examination of a comprehensive range of tissues of all animals was undertaken. The mean body weights of male rats exposed to 1,000 ppm (4100 mg/m^3) were 5 to 10% lower than those in controls after 81 weeks, while those of the female rats exposed to 500 ppm (2050 mg/m^3) MMA were 6 to 11% less after 73 weeks. Minimal increases in the numbers of alveolar macrophages were observed in exposed male and female rats at all concentrations. The incidence of focal or multifocal fibrosis of the lung was increased in female rats exposed to 500 ppm (2050 mg/m^3). The incidence of serous and suppurative inflammation and degeneration of the olfactory epithelium in the nasal cavity was increased in exposed male and female rats at all concentrations relative to controls. The incidence of mononuclear cell leukemia occurred with a significant positive trend in female F344/N rats (control, 11/50; 250 ppm, 13/50; 500 ppm, 20/50). While the incidence at 500 ppm (2050 mg/m^3) was significantly greater than that in the control group by

the incidental tumour test, it was not significant by life-table analysis, which is considered more appropriate for life threatening lesions. Moreover, there were no differences in severity (three stages defined) between the treated and control groups. Furthermore, the incidence of mononuclear cell leukemia in previous untreated groups of female F344/N rats at the same laboratory has ranged from 22 to 36%, just slightly less than the incidence observed in the high dose group exposed to MMA. The incidence of adenomas or carcinomas of the pituitary and preputial glands in male rats was significantly lower than that in the controls. On the basis of inflammation and degeneration of the olfactory epithelium and minimal increases in the numbers of alveolar macrophages in the nasal cavity at all dose levels, the LOEL was considered to be 250 ppm (1025 mg/m^3).

In the same study (NTP, 1986; Chan *et al.*, 1988), groups of 50 B6C3F$_1$ mice of each sex were exposed to 0, 500 or 1000 ppm (0, 2050, 4100 mg/m^3) MMA 6 hours/day, 5 days/week for 102 weeks. Similar to the study in rats, clinical signs, body weight, mortality and gross observations at necropsy were recorded and histological examination of a comprehensive range of tissues of all animals conducted. The mean body weights of male and female mice exposed to both concentrations were lower than those of the controls throughout most of the study. The incidence of acute and chronic inflammation, epithelial hyperplasia, cytoplasmic inclusions in the epithelial cells, and degeneration of the olfactory epithelium in the nasal cavity was greater in exposed male and female mice at both concentrations relative to controls. The incidence of interstitial inflammation was increased in male mice exposed to 1000 ppm (4100 mg/m^3). Significant dose related decreases in tumour incidence were observed in the pituitary and preputial glands, lung and liver and possibly the uterus. The LOEL was considered to be 500 ppm (2050 mg/m^3) on the basis of lower mean body weights in exposed mice and localized damage at the site of entry.

It was concluded that under the conditions of these 2-year studies, "there was no evidence of carcinogenicity of MMA for male F344/N rats exposed at 500 or 1000 ppm, for female rats exposed at 250 or 500 ppm, or for male and female B6C3F$_1$ mice exposed at 500 or 1000 ppm" (NTP, 1986).

In an unpublished 18-month inhalation study conducted by Hazleton Laboratories (Rohm and Haas, 1977b), groups of 56 male and 56 female golden hamsters were exposed to 0, 25, 100 or 400 ppm (0, 102.5, 410 or 1640 mg/m^3) MMA 6 hours/day, 5 days/week for 18 months. Clinical signs, mortality and body weights were recorded and hematological and gross and microscopic examination of a comprehensive range of tissues of all animals were conducted. From

approximately week 60 of exposure, the body weights of both male and female hamsters exposed to the high concentration were consistently lower than that of control hamsters. In addition, the cumulative mortality of male hamsters in this group at week 78 was substantially higher than the mortality in the control group. There were no compound-related increases in the incidences of gross pathological and histopathological findings by sex and group. Thus, it was concluded by the authors that 100 ppm (410 mg/m^3) was the NOEL and that 400 ppm (1640 mg/m^3) was the LOEL based on the observed decreased in body weight.

In another unpublished report study by Hazleton Laboratories (Rohm and Haas, 1979), groups of 70 albino F344 rats per sex per group were exposed to 0, 25, 100 or 400 ppm (0, 102.5, 410 or 1640 mg/m^3) of MMA vapour 6 hours/day, 5 days/week, with interim kills of groups of 10 each at 13 and 52 weeks and the remainder exposed for 104 weeks. Endpoints examined included clinical signs, mortality, body and organ weights, biochemical effects, absolute and relative body weights. A wide range of tissues from all animals in the control and high dose groups (brain, spinal cord, pituitary, thyroid, adrenal, heart, lung, spleen, liver, and kidney) was examined histopathologically as well as selected tissues from animals in the other dose groups (the ovaries or the testes from ten males and ten females and the nasal turbinates of all animals in the low- and mid-dose groups). Statistically significantly lower body weights were noted in the females exposed to the highest concentration, which was considered to be compound-related by the authors. Compound-related histomorphological alterations were limited to a very slight increase in the incidence of mild rhinitis in the nasal mucosal lining of the turbinates at the highest concentration. Inflammatory polyps were observed in two males exposed to the highest concentrations, but no exposure-response relationship was observed. Focal areas of squamous metaplasia were observed in seven rats exposed to the highest concentration and in two controls. However, the lesions were very mild, the total number of rats affected was small and no exposure-response relationship was observed. No other effects attributable to the exposure to MMA vapour were noted for any of the other parameters evaluated. The NOEL and LOEL were considered to be 100 ppm and 400 ppm (410 and 1640 mg/m^3), respectively, based on the observed effects on body weights and respiratory tract in the group exposed to the highest concentration.

In an early study designed to examine the effects of chronic ingestion of MMA (Borzelleca *et al.*, 1964), groups of 25 male and 25 female Wistar rats were administered 0, 6, 60 or 2000 ppm (equivalent to 0, 0.4, 4 or 121 mg/kg b.w./day for males and 0, 0.5, 5, or 146 mg/kg b.w./day for females based on intakes and body

weights presented by the authors) MMA in drinking water for 2 years. One group ingested drinking water containing 2000 ppm for the entire 2-year period and other groups received water with 6 and 60 ppm for 5 months, when the concentrations were increased to 7 and 70 ppm, respectively, for the remainder of the two year period. At the end of the studies, organ to body weight ratios were determined for heart, spleen, kidney, liver, and testes and a wide range of tissues were examined histopathologically, except those from rats exposed to the lowest concentration of MMA (for which the extent of histopathological examination was not specified). At 3 monthly intervals during the study, a limited haematological examination and urine analysis were conducted on groups of 5 rats of each sex. The only effect noted was an increase in the ratio of kidney:body weight in females exposed to 2000 ppm MMA. The NOEL was, therefore, 60 ppm (about 5 mg/kg b.w./day for females and about 4 mg/kg b.w./day for males) and the LOEL, 2000 ppm (about 146 mg/kg b.w./day for females and 121 mg/kg b.w./day for males), though there was considerable variation between the administered doses in this study. In the same study, groups of 2 male and 2 female beagle dogs ingested dietary equivalents of 0, 10, 100 or 1000 ppm of MMA in corn oil (the high dose was gradually increased to 1500 ppm at week 9), for two years. At sacrifice, organ to body weight ratios were determined and histopathological examination of a wide range of tissues was conducted. Limited analysis of the haematology and urine was undertaken at 3 monthly intervals throughout the study. Body weight gains of dogs at the highest concentration were slightly, but not statistically significantly, lower than those of the controls. No other treatment-related effects were noted upon gross or histopathological examination, urinalysis or hematology (NOAEL = 1500 ppm in the diet, about 38 mg/kg b.w./day; very small group sizes).

9.5 Mutagenicity and related end-points

MMA was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with or without S9 activation by plate incorporation or liquid preincubation (Lijinsky and Andrews, 1980; Waegemaekers and Bensink, 1984; U.S. EPA, 1985; NTP, 1986). Poss *et al.* (1979) reported that MMA was mutagenic in *Salmonella* in the presence of an S9 metabolising fraction; however the protocol was unusual (strain TM677 and azaguanine resistance). Moreover, the activity was observed only at concentrations for which survival of the bacteria was only about 20%.

Methyl methacrylate induced chromosomal aberrations in a cell line of lung fibroblasts from Chinese hamsters exposed to 0.0065 mg/mL *in vitro* (Ishidate *et al.*, 1981). In cultured Chinese hamster ovary (CHO) cells, a slight dose-related increase in chromosomal aberrations was induced in the absence of S9; an

increase in the frequency of aberrations was seen only at a near-lethal dose of 5 mg/mL in the presence of S9 (Galloway *et al.*, 1985, NTP, 1986). MMA also produced a dose-related increase in the frequency of sister-chromatid exchanges with or without S9 from the livers of rats in cultured CHO cells (NTP, 1986). (The positive results in these studies were observed throughout the range of tested concentrations and cell survival for most of the range was quite acceptable).

At doses of 0.125 to 1.000 μL/mL (118 to 944 μg/mL) or greater, MMA was mutagenic in L5178Y/TK+/- mouse lymphoma cells in the presence or absence of S9 activation (NTP, 1986). In another study in L5178Y mouse lymphoma cells (Moore *et al.*, 1988; Doerr *et al.*, 1989), MMA induced concentration-dependent increases in mutant frequency at concentrations from 2200 to 3000 μg/mL. There was a significant increase in chromatid breaks and rearrangements with no change in the number of chromosomal aberrations in cells exposed to high concentrations of MMA. Micronucleus responses were also variable with weakly positive results recorded for this same range of concentrations.

When male Alderley Park rats were exposed by inhalation to concentrations of 0, 100, 1000 or 9000 ppm (0, 410, 4100 or 36900 mg/m^3) for a single exposure period of 2 hours or for 5 hours/day for 5 successive days, increases in the frequencies of chromosomal aberrations in the bone marrow cells were observed at 9000 ppm. MMA also caused chromosomal damage following a single exposure to 1000 ppm, but not after multiple exposures to this concentration (Anderson and Richardson, 1976 in U.S. EPA, 1985). There was no increase in micronucleated erythrocytes following administration of 125 or 250 mg/kg/b.w./day MMA to male CD-1 mice (number unspecified) by gavage for 4 days (Hachitani *et al.*, 1981).

In a dominant lethal assay conducted by Anderson and Hodge (1976), groups of 14 to 16 male CD-1 mice were exposed to 0, 100, 1000 or 9000 ppm (0, 410, 4100 or 36900 mg/m^3) for 6 hours a day for 5 days. MMA was not mutagenic to the germ cells of mice.

Based on the limited available information, MMA has not been mutagenic in a number of standard *in vitro* studies in *Salmonella typhimurium*. It was mutagenic and produced chromosomal effects in mammalian cells in culture. At high atmospheric concentrations, MMA induced chromosome damage in mice; however, results of a dominant lethal study in male mice administered similarly high concentrations were negative.

9.6 Reproductive and developmental toxicity

The available studies on reproductive and developmental toxicity are summarized in Table 9-3. Based on these studies in different species, no significant differences were found in the number of dead or live fetuses, and litter size after inhalation or intraperitoneal exposure to MMA. Gross abnormalities in rats were observed only following intraperitoneal injection or inhalation during pregnancy of doses only slightly less than acute lethal doses [0.1328 mL/kg b.w. (125 mg/kg b.w.) by i.p. injection in Singh et al. (1972) or 110 mg/L (110,000 mg/^{3}) by inhalation in Nicholas et al. (1979)] in Sprague-Dawley rats. In the former study, a dose dependent increase in hemangiomas was reported; effects observed in the mothers were not addressed. The group sizes in this study were small. In the latter investigation, there were decreases in maternal body weight gain associated with decreases in food consumption. Ossification was delayed, and there were early deaths, hematomas and a decrease in fetal weight in the offspring of rats exposed to the doses at which decreases in body weight gain in the mothers were observed (probably associated with decreases in food consumption). No reason for the unusual exposure conditions was presented other than that the administered concentration was related to the maximum airborne level at the saturated vapour pressure.

In a well documented developmental toxicity study conducted by Solomon *et al.* (1991) in which groups of 27 Crl:CDBR rats were exposed to 0, 99, 304, 1178 or 2028 ppm (0, 406, 1246, 4830 or 8315 mg/m^3) for 6 hours/day on days 6 to 15 of gestation by whole body inhalation exposure, there was no reproductive toxicity even at the highest test concentration of 2028 ppm (8315 mg/m^3). In a study reported in the form of an abstract in which pregnant rats (strain unspecified) were exposed to 0, 0.52 or 4.48 mg/L (0, 520 or 4480 mg/m^3) MMA by inhalation for 2 hours once every three days from the 6th to the 18th day of gestation, no maternal toxicity was noted; however, delayed ossification was observed at both concentrations and there was a significant increase of the incidence of resorptions in the group exposed to the highest concentration (Luo *et al.*, 1986). Slight decreases in maternal weight gain and increased incidence of early resorptions were reported in rats (strain unspecified) inhaling 1000 ppm (4100 mg/m^3) for 5 hours/day from days 6 to 15 of gestation (Hodge and Palmer, 1977).

A small but significant decrease in mean fetal weights of the offspring of CD-1 mice exposed to 116 or 400 ppm (476 or 1640 mg/m^3) MMA on days 1 to 13 of gestation was observed, in the absence of overt maternal toxicity (Tansy, 1975). Similarly, in a study reported by McLaughlin et al. (1978) in which ICR mice were exposed during days 6 to 15 of gestation to 1330 ppm (5450 mg/m^3)

MMA, there were no significant differences between exposed and control groups in the numbers of live fetuses, resorptions or defects. (Maternal toxicity was not addressed in the published report of this investigation).

In a group of 12 rabbits receiving i.p. injections of 40 mg/kg b.w. MMA during days 6 to 18 of pregnancy, no reduction in fetal weight, delayed ossification, early resorptions or maternally toxic effects were reported. Higher doses (400 mg/kg b.w.) were embryo- and feto-toxic and overtly toxic to the mothers, but the nature of the effects was not specified (Hodge, 1976).

In the only study of reproductive performance, Anderson and Hodge (1976) exposed male mice to 100, 1000 or 9000 ppm (410, 4100 or 36900 mg/m^3) MMA by inhalation, 6 hours/day for 5 days, and mated each male mouse with two different female mice each week for 8 weeks. There was no reduction in fertility as measured by the percentage of male mice that mated successfully/week, or the percentage of female mice which became pregnant, one of the males in the F_0 generation exposed to 100 ppm, died.

9.7 Neurotoxicity

Very few studies on the neurotoxicity of MMA have been identified. The most notable effect when chloralose-urethanized mature male Sprague-Dawley rats (n = 5 to 19) were exposed to 400 ppm (1640 mg/m^3) MMA for 60 minutes was the depression of multiple-unit electrical activity in the lateral hypothalamus and ventral hippocampus. In marked contrast, there were insignificant changes in multiple-unit electrical activity in the parietal cortex, cerebellum, dorsal hippocampus, medial amygdala, ventral medial hypothalamus, anterior hypothalamus, septum, and mammillary body. The authors concluded that the observed effects on the cerebellar portion of the brain reflected the decreased motor activity associated with anesthesia and not exposure to the MMA vapour (Innes and Tansy, 1981).

In a study in which six male Wistar rats were administered 500 mg/kg b.w./day MMA by gavage in olive oil for 21 days, locomotor activity and learning were markedly impaired, while aggressive behaviour significantly increased (Husain *et al.*, 1985). There was an overall increase in levels of biogenic amine in the pons-medulla and hippocampus. Levels of noradrenaline in the cerebral cortex, and 5-hydroxytryptamine in the mid-brain and the hypothalamus were increased while there was a slight decrease of dopamine in the corpus striatum. In a separate study conducted under the same experimental conditions (Husain *et al.*, 1989), the total lipid content or levels of constituents such as phospholipids, cholesterol and triglycerides remained unchanged in the whole

brain. However, a significant increase in cholesterol (26%) and triglycerides (65%) and a slight decrease in the total phospholipid content of the sciatic nerve were reported. The authors concluded that the peripheral neurotoxic effects of MMA might be related to the alteration in the content of cholesterol and/or phospholipids in the sciatic nerve.

In a study reported only in the form of an abstract (Wynkoop *et al.*, 1982), groups of 7 male Sprague-Dawley rats were administered 200 µL/day of liquid MMA by subcutaneous injection for 3, 7 and 14 days and sacrificed immediately thereafter. There were significant decreases in the cholinesterase levels in the blood in exposed versus the control animals. The average total catecholamine levels were significantly higher in exposed animals as compared with the controls at 3 days. Levels of both epinephrine and norepinephrine in the blood were elevated in exposed animals, but only the norepinephrine level was significantly different from that of the controls. Dopamine levels of both the control and exposed animals were similar throughout the experiment. Based on the results of this study, the authors suggested that MMA acts as a stressor upon the sympathetic nervous system of the rat.

Abnormal muscle responses to stimulation of the motor nerves by a skin electrode through the tail after 4 weeks of application for 3 hours/day of liquid MMA (> 99%) to the tail of Wistar rats were reported; however, the motor conduction time did not differ from that of the controls (Verkkala *et al.*, 1983). Under the same experimental conditions (Kanerva and Verkkala, 1986), myelin figures considered to be a sign of degeneration of nerve processes were observed in the dermis.

9.8 Immunotoxicity

In a study in which the leukocyte-migration inhibition method was employed to determine if MMA was potentially a causative agent in denture stomatitis, three groups of 5 albino rabbits of both sexes were injected intramuscularly with 1 mL of MMA (99.9%) on days 1, 5 and 15 (Zafiropoulos *et al.*, 1985). On the 36th day, blood was drawn to test the inhibition of leukocyte migration. The results indicated that MMA was a specific antigen which was capable of inducing cellular immune reaction.

Table 9-3 Developmental and Reproductive Toxicity

Species	Protocol	Results	Effect Levels	Reference
Developmental Toxicity Rat (Crl:CDBR, groups of 27)	Inhalation of 0, 99, 304, 1178 or 2028 ppm (0, 406, 1246, 4830 or 8315 mg/m^3) for 6 h/d on days 6 to 15 of gestation.	No exposure-related deaths were noted at any concentration. The only clinical sign was a minimal increase in the incidence of scant feces at 2028 ppm in the mother. Exposure-related decreased maternal body weight gain at all concentrations. These decreases were slight and transient since body weight gain returned to control values by days 8 to 10 of gestation. Exposure-related decreases in feed consumption of mother at all concentrations but returned to the control values during the post-treatment period. No exposure-related changes among dams during the gross postmortem examination. There were no exposure-related changes in the number of litters produced or in the mean number per litter of corpora lutea, implantations, resorptions, live or dead fetuses or sex ratio. There were no exposure-related increases in the type or incidence of external or visceral effects or variations due to retarded development. Fetal body weights were similar between the control and treated groups.	NOEL = 2028 ppm (8315 mg/m^3) (offspring) LOEL = 99 ppm (406 mg/m^3) (mothers, transient decrease in body weight possibly related to decrease in food consumption)	Solomon et al., 1991
Mouse (ICR white, groups of 14 to 18)	Inhalation of 0 or 1330 ppm (5450 mg/m^3) 2 h, twice daily from days 6 to 15 of gestation, killed on day 18. The mice were deprived of food and water during exposure periods.	No significant difference between exposed and control groups in number of live fetuses, resorptions or defects. In the exposed group, 96% of the fetuses were alive (2 deaths) and normal versus 95% (one death) in the control group. There were 7 fetal resorptions in each group: exposed (2.9%), and control (3.9%). There were no abnormal fetuses in the exposed group while one in the control group had a typical club foot. While there was no significant difference between the mean litter size of the two groups, the fetuses of the exposed mice were significantly heavier than those from the control group (0.90 g +/- 0.10 vs. 0.84 g +/- 0.01). Maternal toxicity was not addressed.	One dose group only; no effects observed at 1330 ppm (5450 mg/m^3); maternal toxicity not addressed	McLaughlin et al., 1978

Table 9-3 (Continued)

Species	Protocol	Results	Effect Levels	Reference
Rat (Sprague-Dawley, number as specified in Protocol)	2 groups of pregnant rats exposed by inhalation (head and nose only) to 110 mg/L (110,000 mg/m^3) MMA for 17.2 min (22 rats) or 54.2 min (27 rats) daily, on days 6 to 15 of gestation. These exposure times represent approx 1/4 and 3/4 of the LT_{50} (the time required to kill 50% of rats at the specified dose). A control group of 26 pregnant rats was exposed to air only. 22 pregnant rats served as untreated controls. The rats were killed on the 20th day of gestation.	The average maternal body weight in the group exposed for longer periods was significantly less than that in the controls on days 11, 15 and 20. Similarily the mean maternal body weight in the group exposed for shorter periods was significantly less than that in the unexposed control group on day 15, and than that in both control groups on day 20. The food consumption in the group exposed for the longer periods was less than all other groups on days 7, 11, and 15. The group exposed for shorter periods consumed significantly less food than all of the groups on days 7 and 11, and than all but the air only exposed group on day 15. There were no significant differences in food consumption between the four groups on the 20th day. When compared to the 3 other groups, the 54.2 min/day exposure to MMA resulted in a significant increase of early fetal deaths (8.8% vs. 0-1.6%), and decrease in fetal weights (~3 g vs. ~4 g) and lengths (~3.1 cm vs. ~ 3.5 cm). As compared to the controls, the number of fetuses with hematomas was significantly increased in the group exposed for longer periods; similarly, the occurrence of delayed vertebral ossification was increased for this group. The occurrence of delayed sternal ossification in the groups exposed for shorter (60.1%) and longer (94.6%) periods was significantly increased. A low incidence of a number of other skeletal abnormalities were noted in the long exposure group.	One dose group only, though for two different periods of exposure. No reason provided for the unusal exposure conditions other than the concentration was related to the maximum airborne level at the saturated vapour pressure; effects in offspring observed following both long and short periods of exposure at 110,000 mg/m^3. Decrease in body weight gain of mothers probably related to decrease in food consumption	Nicholas et al., 1979
Rat (strain unspecified, groups of 30)	Inhalation of 0, 100 or 1000 ppm (0, 410 or 4100 mg/m^3) of MMA vapour, 5 h/d, on days 6 to 15 of gestation. The experiment was repeated with a 25 ppm exposure group added. Food and water were withheld only during the exposure periods. The rats were examined daily and were killed on day 20.	Maternal weight gain was slightly reduced at 1000 ppm but not at 100 ppm in the first study and at both 25 and 1000 ppm in the second study. There was slight (insignificant) retardation of ossification at 1000 ppm. The observed increase in numbers of early resorptions at 1000 ppm indicated that MMA was weakly embryotoxic at that concentration. MMA had no effect on embryonic or foetal development at 100 ppm.	NOEL = 100 ppm (410 mg/m^3) (offspring) LOEL = 1000 ppm (4100 mg/m^3) (offspring) NOEL = 100 ppm (410 mg/m^3) (mothers)	Hodge and Palmer, 1977

Table 9-3 (Continued)

Species	Protocol	Results	Effect Levels	Reference
Mouse (CD-1, number as specified in Protocol)	Inhalation of 0 (n = 38), 116 (n = 32) or 400 (n = 18) ppm (0, 456 or 1640 mg/m^3) of MMA, 6 h/d on days 4 to 13 of gestation. There was a 1 hour break half way through the daily exposure periods; food was withheld only during exposure. Mice were killed on day 18 of gestation.	No difference between groups in maternal body-weight gain. Small but significant decrease in mean fetal weights of all the exposed groups. The proportion of non-viable fetuses in the exposed and control groups did not differ significantly.	LOEL = 116 ppm (476 mg/m^3)	Tansy, 1975
Rat (strain and number unspecified)	Inhalation of 0, 0.52 or 4.48 mg/L (0, 520 or 4480 mg/m^3) for 2 hours once every three days from days 6 to 18 of gestation.	No acute toxic effects on pregnant rats in the exposed groups. Delayed ossification observed in both exposed groups. A statistically significant increase in the incidence of resorptions in the high dose group. No differences in maternal weight, fetal weight, and crown-rump length among the three groups. No gross skeletal anomalies in any groups.	LOEL = 0.52 mg/L (520 mg/m^3) (offspring); no maternal toxicity reported	Luo et al., 1986 (abstract)
Rat (Sprague-Dawley, groups of 5)	Intraperitoneal injection of 0, 1/10 (0.1328 mL/kg b.w. or 125 mg/kg b.w.), 1/5 (0.2656 mL/kg b.w. or 251 mg/kg b.w.), or 1/3 (0.4427 mL/kg b.w. or 418 mg/kg b.w.) of the LD_{50} for MMA (1.3280 mL/kg b.w.) on days 5, 10 and 15 of gestation. Control groups received 0.8222 mL injections of distilled water, normal saline or cottonseed oil. The rats were killed on the 20th day of gestation.	There were no statistically significant differences in the percent resorptions, the percentages of live fetuses or in the number of fetuses with skeletal abnormalities. There was a dose-related increase in the frequencies of gross abnormalities whereby hemangiomas were most commonly seen. Maternal toxicity was not addressed. There was a significant increase in the incidence of gross abnormalities at the two highest dose levels (16.7 and 8%, respectively). The 2% incidence found in the lowest dose group, was the same as that recorded in 2 of the vehicle control groups.	NOEL = 0.1328 mL/kg b.w. (125 mg/kg b.w.) (offspring); maternal toxicity not addressed	Singh et al., 1972
Rabbit (Dutch, groups of 12)	Intraperitoneal injection of 0, 4, 40, or 400 mg/kg b.w. on days 6 to 18 of pregnancy. The rabbits were killed on day 29 and the fetuses were examined.	The highest dose was fetotoxic (reduced fetal weight and ossification) and embryotoxic (increased early resorptions); it was also reported to be severely toxic to the pregnant rabbits but the effects were not reported. No teratogenic effects were observed.	NOEL = 40 mg/kg b.w. (offspring and mothers) LOAEL = 400 mg/kg b.w. (offspring and mothers)	Hodge, 1976

Table 9-3 (Continued)

Species	Protocol	Results	Effect Levels	Reference
Reproductive Toxicity Mouse (CD-1, groups of 20)	Fertile male mice were exposed to 0, 100, 1000 or 9000 ppm (0, 410, 4100 or 36900 mg/m^3) MMA vapour 6 h/d for 5 days. They were then mated weekly for 8 weeks. The maturation stages of spermatogenesis were observed for mutagenic effects. The female mice were separated from the males after 5 days, and were killed 10 days later. The (unexposed but mated) female mice were examined for: pregnancy; number of implants; and post-implantational foetal deaths.	14/20 exposed to 9000 ppm and 19/20 exposed to 1000 ppm survived. One death in the 100 ppm group in the week after exposure. No mutagenic effects on any maturation stages of spermatogenesis. No significant increases in the number of post-implantational early foetal deaths; no evidence of pre-implantational egg loss as indicated by the total implants per pregnant female. There was no reduction in fertility as measured by % of male mice that mated successfully/week, or % of female mice which became pregnant.	LOEL = 100 ppm (410 mg/m^3); no adverse reproductive effects at 9000 ppm (36900 mg/m^3)	Anderson and Hodge, 1976

10.0 Effects on Humans

10.1 Case reports

Several case reports of adverse effects following exposure to, or contact with, MMA have been identified. A small number of cases of dermatitis have been reported among surgeons or nurses exposed to MMA from its use in bone cement and in dentists or laboratory technicians exposed in the production of dentures or other orthopaedic devices (Rajaniemi, 1986; Pegum and Medhurst, 1971; Kassis *et al.*, 1984; Farli *et al.*, 1990). A beautician also developed dermatitis from the use of an MMA-containing formulation used to make artificial nails (Conde-Salazar *et al.*, 1986).

Methyl methacrylate induced asthma has been recorded in a dental laboratory technician (Lozewicz *et al.*, 1985). In orthopaedic theatre nurses, one case of MMA induced asthma (Pickering *et al.*, 1986) and one of episodes of hypertension, dyspnea and generalised erythroderma (Scolnick and Collins, 1986) have been reported. Various mild neurological symptoms in the hands of a number of dental technicians have also been reported (Rajaniemi, 1986) and there is one report of a more severe case of peripheral neuropathy which started in the dominant fingers but then progressed to involve all four limbs (Donaghy *et al.*, 1991). Other reported effects included increases in blood pressure and a decrease in arterial oxygen tension after total hip replacement surgery (Svartling *et al.*, 1986; Svartling, 1988), cardiac arrest following the experimental use of acrylic bone cement (Cohen and Smith, 1971), burning mouth sensation and contact stomatitis from wearing dentures made from methyl methacrylate (Kaaber *et al.*, 1979; Ali *et al.*, 1986; van Joost *et al.*, 1988; Kanzaki *et al.*, 1989), and occlusion of the artery after total hip replacement (Hirsch *et al.*, 1976; Crispin and Boghemans, 1980; Brentlinger *et al.*, 1987; Rutsaert *et al.*, 1988). In one case report (Fiore *et al.*, 1986), upper ureteral obstruction caused by methylmethacrylate cement following orthopedic fixation of a pathologic fracture was noted.

10.2 Clinical studies in human volunteers

In one of the few identified clinical studies, pellets of cotton saturated with one of two different batches of MMA were applied to each forearm of fifty medical students (49 males and 1 female) (Spealman *et al.*, 1945). Forty eight hours later, these patches were removed. Fifteen volunteers had a reaction to batch "A" and six to batch "B". Four individuals reacted to both batches. These reactions were mild in nature consisting chiefly of an area of mild erythema limited to the site of application of the pellet. When reapplied 10 days later on these same individuals,

there was no immediate sign of reaction in any of the subjects. However, at intervals varying from a few hours to four days later, dermal reactions characterized by erythematous, itching areas occurred in 10 subjects and persisted for periods up to a week and longer.

No local irritant effects were reported in other limited clinical study reported by van Joost *et al.* (1988) and Kaaber *et al.* (1979). In the former investigation, 8 volunteers were patch tested with 25% MMA in petrolatum while the latter study involved 20 volunteers patch tested with 30% MMA in olive oil. Both studies involved covered contact for 24 or 48 hours.

10.3 Epidemiological studies

10.3.1 *Effects on the skin, lungs, nervous system and blood*

Results of principally cross-sectional studies of populations exposed occupationally to MMA are presented in Table 10-1. Effects investigated in these studies include those on the skin, lungs, nervous system and blood.

Dermatitis and symptoms such as whitening and feelings of numbness, coldness and pain in 102 dental technicians have been reported after daily contact of the skin with MMA, with the rate increasing with frequency of contact and time in the occupation (Rajaniemi and Tola, 1985). However, in a study of 31 men (14 students and 17 instructors, average age of 30.8 years) at a Japanese dental school, there were no positive allergic skin reactions to patch tests with 40 compounds (principally components of dental alloys and plastics, including MMA) (Oshima *et al.*, 1991).

Mild axonal degeneration in areas of the hand with the closest and most frequent contact with MMA as indicated by slower distal sensory conduction velocities was noted in 20 dental technicians who handled MMA daily (Seppalainen and Rajaniemi, 1984). In a cross-sectional analysis of 731 workers at a chemical facility (Schwartz *et al.*, 1989), there was no association between olfactory test scores and exposure to acrylate and methacrylate vapours. However, in a nested case-control study, there was a dose-response relationship between olfactory dysfunction and cumulative exposure scores. Based on logistic regression analysis controlling for multiple confounders including chemical exposure, smoking status, ethnic group, medications, age, history of olfactory dysfunction, history of medical problems, level of education, gender, and work shift tested, the odds ratios for the association between exposure to MMA and olfactory dysfunction was 2.8 for all workers and 13.5 for workers who never smoked cigarettes. The odds ratios decreased

with increasing time lapsed since last exposure to these chemicals, which suggested that these effects may be reversible.

The pulmonary effects of exposure to MMA have been investigated in two studies. In one study (Jedrychowski, 1982), interviews, clinical examinations and lung function tests were conducted for 454 men working in a plant which producted MMA and styrene and 683 workers from the control group who were never occupationally exposed to MMA or styrene. The mean concentration of MMA and styrene in the production facility was 11.06 mg/m^3 (ranged from 0.20 to 382.2 mg/m^3) and 2.66 mg/m^3 (ranged from 0.06 to 31.8 mg/m^3), respectively. There was no significant difference in the prevalence of chronic symptoms in the chest in both groups, but the frequency of lung obstruction appeared to be more than twice as high among the exposed workers than in the controls. The investigator noted that it was not possible to separate the effects of MMA and styrene. In another study reported only as an abstract (Andrews *et al.*, 1979), the past histories and symptoms associated with usual laboratory activities of 502 dental students were determined based on a multiple-choice questionnaire. Of those students exposed, 6% reported respiratory symptoms associated with exposure to MMA and 5% while working with high speed drills. Eighty-eight percent of students reporting MMA sensitivity had histories of either asthma or allergic rhinitis. In addition, spirometry was performed before and after a controlled exposure to MMA (concentration unspecified) in subsets of individuals representing normals, asthmatics, those with allergic rhinitis, smokers, and those students who reported symptoms on usual exposure. There were no significant differences in spirometry or pulmonary symptoms among the 77 students examined.

In a study reported by Lang *et al.*, (1986), 46 to 77 workers at the Beijing Organic Glass Factory were clinically examined. The duration of employment ranged from 3 months to 36 years and the age varied from 21 to 60 years. The concentration of MMA was 100 to 200 mg/m^3 in the air of the polymerization processes and 11 to 33 mg/m^3 in other processes. There was a dose-dependent increase of hemoglobin, cholinesterase activity, leukocytopenia, neurasthenia, laryngitis and hypotension and a decrease in serum cholesterol. However, there was no reference to a comparison population in the English abstract of this study.

In a study conducted by the National Institute for Occupational Safety and Health (NIOSH), 91 workers exposed to monomeric MMA vapour, and 43 nonexposed workers at five plants manufacturing polymethyl methacrylate sheets were clinically examined (NIOSH, 1976). Based on extensive air sampling, mean 8-hour time-weighted average concentrations by job category ranged from 4 to 49 ppm (16.4 to 200.9 mg/m^3). There were no significant

acute effects over the work shift as measured by symptomatology, blood pressure, and pulse rate. The results indicated that there were chronic effects on serum glucose, and blood urea nitrogen, cholesterol, albumin, and total bilirubin at the higher concentrations but this was likely due to different age distributions of exposed and control groups.

Table 10-1 Cross Sectional Studies

Protocol	Results	Reference
89 dental technicians, 116 technical aids and 91 students, in Finland during a single academic year were surveyed for their use of the acrylic ester monomer and subjective symptoms in a self-administered multiple choice questionnaire. Dental technicians and technical aids handled MMA very frequently: 41% less than 1 h/d, 48% for 1 - 3 h/d, and 9% more than 3 h/d. 72% of the aids handled acrylic articles more than 1 h/d.	34% of the respondents reported previous dermatitis on their hands, and 17% reported dermatitis at the time of study. The number of reported episodes of dermatitis increased among dental technicians as the length of time in the current occupation increased. This relationship was not apparent for technical aids with generally shorter professional experience. The rate of the self-reported dermatitis was increased in those with frequent contact with the acrylic monomer; the symptoms were spontaneously reported to be associated with MMA by 42% of the respondents. 25% of the respondents had experienced at least one of the remaining symptoms such as whitening and feelings of numbness, coldness and pain (more frequent among women) of hands. Senior year students had significantly more symptoms than the other students, especially dermatitis of the hand. They reported the same frequency of occurrence as the qualified dental technicians.	Rajaniemi and Tola, 1985
31 men, including 14 students and 17 instructors at the same Japanese dental school, average age 30 8 years (range 20 to 49 years), were patch tested with 40 substances including MMA. None had any history of allergy, including to dental materials. The vehicles and concentrations of all substances tested were not reported.	No positive allergic skin reactions to the 13 components of dental alloys, the 18 components of dental plastics, or to any of the other dental components including MMA.	Oshima et al., 1991
Examination of maximal motor conduction velocity (MCV), motor distal latency (DL), orthodromic sensory conduction velocity (SCV), distal sensory conduction velocity (dSCV) and nerve conduction velocities in the fingers of 20 right handed dental technicians (6 women and 14 men) who had reported paresthesia, numbness or dermatitis in their fingers and a control group of 5 women and 13 men. The mean age of the 38 people tested was 42 years (ranged from 30 to 61 years).	The results for the first three tests listed were similar in the exposed and control groups. Exposed subjects had significantly slower dSCVs of the right median nerve. The same was true for dSCV measured from the thumb and from the radial aspect of the left forefinger. The dSCVs of the median nerve were significantly slower on the right (exposed) side than on the left side of the exposed group; also, that on the radial side of the fingers was slower than the ulnar side when intraindividual NCV measures were compared. Results were normal in ten subjects who had neurological complaints. Among those subjects who had had both symptoms of irritation and neurological complaints, 3/5 had slight abnormalities in NCVs, while only 1/5 with both dermatitis and neurological complaints had neurophysiological abnormalities as well. Abnormal nerve conduction velocities were found in those who had been in the field since the 1950s or 1960s, and in one woman who had prolonged daily contact (3 h).	Seppalainen and Rajaniemi, 1984

Table 10-1 (Continued)

Protocol	Results	Reference
618 males and 113 females (mean age of 42.9 years) of the total number of 909 short and long term employees of the Rohm and Haas Co. (manufactures acrylic acid, acrylates and methacrylates). The employees were asked to complete a University of Pennsylvania Smell Identification Test (UPSIT), and questionnaires on job histories as well as personal and medical information. Employees were grouped into 4 exposure categories: no significant chemical exposures (n = 319), exposure to other chemicals (n = 193), exposure to low levels of acrylate/methacrylate (n = 164) and exposure to higher levels (n = 55). Nested case-control study of 77 workers who scored below the 10th percentile in their age group on the UPSIT; they were matched with controls (scored at or above 50th percentile). Exposure was classified in terms of whether workers had been exposed to MMA for at least six weeks, the total time of employment at the plant, and a cumulative exposure score - a semi-quantitative index of lifetime exposure to the acrylates - for each worker.	Upon cross-sectional analysis, when the age, ethnic group and smoking status were considered, the mean UPSIT scores in the four exposure groups did not differ. For the "no significant chemical exposures", "exposure to other chemicals", "exposure to low levels of acrylate/methacrylate", and "exposure to higher levels", the scores were 37.8, 37.4, 37.0, and 37.6, respectively. Based on logistic regression analysis, adjusting for multiple confounders, in the nested case-control study, the odds ratios for the association of UPSIT score with exposure to MMA for all workers was 2.8 (95% CI 1.1 - 7.0)) and for those who never smoked was 13.5 (95% CI 2.1 - 87.6); the crude odds ratios were 2.0 and 6.0 respectively. There was a dose response relationship between olfactory dysfunction and the cumulative exposure. The odds ratios increased with the cumulative exposure scores, except for a decrease in the highest exposure category. The olfactory dysfunction may be reversible, since the odds ratios decreased with the length of time since the last exposure.	Schwartz et al., 1989
454 males from a plant (Plant A) producing styrene and MMA, while 683 males from a plant producing carbon derivatives served as controls (in both plants, jobs were similar, but in the latter case, no exposure to styrene or MMA). Standardized interviews on chest symptoms, measured heights, lung function tests and examinations for chronic bronchitis and asthmatic syndrome were conducted. The workers were divided into the following groups: non-smokers, ex-smokers and current smokers. Styrene and MMA concentrations were determined in 18 work places in Plant A. For MMA, the mean concentration in Plant A was 11.06 mg/m^3	There was a nonsignificantly lower occurrence of bronchitis and/or asthma in the exposed (17.8%) compared to the control group (19.5%). There was no significant difference in the incidence of chronic chest symptoms between the two groups. However, the frequency of lung obstruction was over twice as high in the exposed workers (45.4% vs 18.0%); this percentage was higher for smokers than for non-smokers (20.9% vs 13.6%). Within the exposed group, the occurrence of lung obstruction in smokers and in non-smokers did not differ significantly. 56% of the controls and 76% of the exposed workers with lung obstruction did not have any chronic chest symptoms. The lung function of the exposed group was significantly poorer than that of the controls; the effects were slightly worse among smokers in both groups. The relative risk of lung obstruction (compared to non-exposed ex- and non-smokers) was 1.7 for non-exposed smokers, while for exposed ex- and non-smokers, it was 4.7, and for exposed smokers it was 5.5.	Jedrychowsi, 1982
502 dental students (who handled MMA in their labs) completed self-administered multiple-choice questionnaires concerning their past histories and any symptoms (not specified) associated with activities in the lab. Spirometric tests were performed before and after exposure to unreported amounts of MMA for 77 students who had allergic rhinitis, smoked, or had symptoms upon usual exposure.	In exposed students, 6% reported respiratory symptoms (88% had histories of asthma or allergic rhinitis), and 5% when using high speed drills. Among the 77 students that underwent spirometric tests, there was no significant change in symptoms or spirometry.	Andrews et al. 1979 (Abstract)
Clinical examination of 46, 66 and 77 workers in a Beijing glass factory in 1976, 1977 and 1978, respectively. The age of these workers (51.6 to 63% female) ranged from 21 to 60 years, with employment durations of 3 months to 26 years. These workers were exposed to 100 to 200 mg/m^3 MMA in the prepolymerized processes or 11 to 33 mg/m^3 in other processes.	The incidence of neurasthenia was 20 to 30%, of laryngitis was 50 to 60% and of hypotension was 9.2 to 26.3% among exposed workers. There was a dose-dependent increase in hemoglobin, activity of cholinesterase and leukocytopenia, and a decrease in serum cholesterol. There was no mention of a control population in this abstract.	Lang et al., 1986 (English abstract)

Table 10-1 (Continued)

Protocol	Results	Reference
A study of 91 exposed and 43 non-exposed workers, from 5 MMA cast sheet manufacturing plants in the USA. The survey included: a medical questionnaire, measurement of clinical symptoms, blood pressure and pulse rate, testing of pulmonary function and blood chemistry, urinalysis, and white blood cell counts. Based on 8 hour time weighted average exposures to MMA, workers were divided into 5 categories: less than 5 ppm (n = 13), 5 - 25 ppm (n = 20), 25 to 50 ppm (n = 33), no current exposure but past exposure >1 year (n = 25) and the control group with no exposure (n = 43). The ages and smoking histories of exposure groups were not matched very well because of the low number of volunteers.	Some significant differences in terms of coughing and expectoration, but these were likely due to differences in smoking habits. When smoking histories were taken into consideration, there was no significant change in pulmonary function among the exposure groups. No significant differences in blood pressure, or in white blood cell count were found. There were several significant differences in the blood chemistry tests of the "not current" group, but this was likely due to the fact that they were significantly older than the controls.	NIOSH, 1976

10.3.2 *Carcinogenicity*

Available cohort and case-control studies of cancer mortality on workers exposed occupationally to methyl methacrylate are presented in Table 10-2.

In a study conducted in 1984, there was no excess of respiratory cancer among ethyl acrylate/MMA workers at the largest acrylic sheet manufacturing facility of Rohm and Haas at Bristol, Pennsylvania. However, there was an excess of mortality due to colon cancer in the exposed workers (cited in Walker *et al.*, 1990). Since then, several historical cohort studies have been conducted to examine the mortality rate from cancer of the colon or rectum among male workers employed at two plastics manufacturing plants in Bristol, Pennsylvania and Knoxville, Tennessee (DeFonso and Maher, 1986; Maher and Defonso, 1987a; 1987b) (Table 10-2). In these studies, there has been no evidence a relationship between occupational exposure to ethyl acrylate/methyl methacrylate and mortality from any type of cancer including colorectal cancer in workers employed for ≥ 1 year between the late 1940's and the early 1980's. Mortality from cancer of the colon and rectum among men exposed to high concentrations of MMA (estimated on the basis of workers' job histories and job-specific exposure rating scales) was similar to that of men not exposed to EA/MMA in the workplace. It should be noted, however, that trace rates in two of these cohort studies (Maher and Defonso, 1987a; Maher and Defonso, 1987b) were poor and observed rates were compared, with the exception of one study (Maher and Defonso, 1987b), to national rates, only. In addition, the study carried out by Walker *et al.* (1990; 1991), subsumed these earlier ones and their report provides the basis of the following presentation.

In this study by Walker *et al.* (1990; 1991), the data for these cohorts were analyzed based on the period of employment of the workers. Because of the small numbers of nonwhite workers in the cohorts, the reanalyses were restricted to the white population. The Bristol plant began operation in 1917 while the Knoxville plant began production in 1943. By 1946, Rohm and Haas had instituted production and other changes (not specified) that resulted in reduced exposure to ethyl acrylate (EA) and MMA in both of these plants. The production and finishing of acrylic sheet entailed exposure to EA and MMA monomers and polymers, as well as to a variety of other agents, including lead, ethylene dichloride, methylene chloride, and acrylonitrile (quantities of these were not reported). The exposed population was subdivided into three cohorts: those employed at Bristol before 1946, those employed at Bristol after 1946 and those employed at Knoxville. The early Bristol cohort comprised 3934 men employed as hourly workers at any time between January 1, 1933 and December 31, 1945. Of these men,

2906 (73.9%) were hired between 1941 and 1945. The later Bristol cohort comprised all men hired between January 1, 1946 and December 31, 1982 and consisted of a total of 6548 men: 3916 hourly employees and 2632 salaried employees. The Knoxville cohort comprised the 3381 white men employed at this facility from January 1, 1943 to December 31, 1982.

These cohorts were followed from the first day of employment to death or December 31, 1986. The percentages of the cohorts known to be alive, known dead and with unknown vital status were 39.1, 50.6 and 10.3, respectively, for the early Bristol cohort, 75.6, 15.0 and 8.6, respectively, for the later Bristol cohort and 58.3, 33.5 and 8.2, respectively, for the Knoxville cohort. For each cohort, the minimum period of employment for inclusion in the study was the shortest duration of completed employment for which there was at least 85% successful follow-up. For the early Bristol cohort, this resulted in the exclusion of 1410 men, with 2524 included, while there were no exclusions in the other two cohorts.

The exposures of members of the three cohorts to methyl methacrylate/ethyl acrylate (MMA/EA) were estimated on the basis of job histories and job-specific exposure rating scales. The only available monitoring data for EA/MMA were from the Bristol plant beginning in 1972. Attempts were made to reconstruct earlier levels of exposure from production records and interviews with plant personnel. The authors cautioned that the resulting scales were semiquantitative, relied on recollection of long-term employees, pertained to vapour exposure only, did not distinguish between EA and MMA, were not verifiable and did not take into account the presence of other possibly carcinogenic substances in the workplace. In addition, the separate ordinal scales for each cohort are not comparable. In the early Bristol study, each job was assigned a score from zero to five. A score of 5 corresponded to work in the "boil-out" phase of acrylic sheet production, where exposure to EA/MMA vapor was judged to have been the greatest. Level 2 was designed to represent "minimal" exposure, and level 1 included jobs in which there may have been no exposure. Level zero was assigned to jobs for which it was believed that there was no exposure. In the later Bristol study, exposures were classified as "no routine exposure", less than 5 ppm (20.5 mg/m^3), 5 to 24 ppm (20.5 to 98.4 mg/m^3) and 25 ppm (102.5 mg/m^3) or greater. In the Knoxville cohort, jobs were classified into one of four levels, based on a reconstruction of past production practices. A score of 3 denoted "major exposure" and a score of zero denoted "no exposure". An index of total exposure for each job held by each worker was derived by multiplying the exposure intensity (i.e., the number of the level in which the job was included) by the interval in days from start to end of employment in the job, divided by 365.25. One unit of accumulated dose could, therefore, represent

exposure for one year in a job with a dose rating of one, six months in a job with a rating of two, or three months in a job with a rating of four.

The association between elapsed time and cancer mortality was examined, taking as the starting point for time measurements the dates at which workers accumulated various reference levels of cumulative exposure. Mortality due to cancer of the colon and rectum was also considered in relation to cumulative levels of acrylate exposure attained 20 years earlier, maximum exposure intensity and date of hire. In the early Bristol cohort, there was excess mortality due to colon cancer (O:E for all categories = 38:25.4) with elapsed time since accumulation of reference cumulative exposures for all categories, except those that were not exposed (Observed:Expected deaths for <5, 5 to 19 and ≥ 20 years since achievement of reference cumulative exposure (> 0 units) were 2:0.46, 5:3.54 and 31:21.39, respectively). Excess mortality was largely confined to the period 20 or more years since the achievement of a reference level of cumulative exposure; moreover, the greatest relative increase was observed in the highest category of cumulative exposure [i.e., ≥ 15 units of exposure accumulated 20 years prior to observation (O:E = 11:4.58)]. One of the largest excesses was observed, therefore, in workers with ≥20 years of employment employed extensively in the early 1940s in jobs with the highest exposures to vapor-phase MMA/EA monomer and volatile by-products of the MMA/EA polymerization process such as lead, ethylene dichloride, methylene chloride, and acrylonitrile. There was no convincing indication of a gradual increase in risk with increasing cumulative dose. There was no association between mortality due to colon cancer and maximum exposure intensity.

The authors further examined the possibility that the elevated mortality due to colon cancer associated with high (unspecified) cumulative exposure may have been an artifact of hiring practices during the Second World War. In a comparison of men hired before 1940 [Standardized Mortality Ratio (SMR) = 3.1, on the basis of five observed deaths] to those hired later (SMR = 2.1, on the basis of six observed deaths), there was no evidence that the elevated mortality due to cancer of the colon observed in the men 20 years or more after the accumulation of 15 units of exposure was restricted to those hired during the war years. Among the exposed persons, mortality due to rectal cancer was elevated in the same categories for which mortality due to colon cancer was elevated. There was a paucity of data for the observed person-time, largely as a result of the much lower rate for rectal than for colon cancer. There were elevations in mortality due to rectal cancer in the 0-4, 10-14 and ≥ 15 unit dose categories (O:E = 6:2.39, 1:0.54 and 3:1.06, respectively), but there were deficits in the unexposed (0:E = 2:2.78) and in the 5-9 unit dose category (O:E = 0:1.24).

Among all exposed persons, there were 10 deaths observed and 5.23 expected, for an observed-to-expected ratio for rectal cancer of 1.9 (95% CI 0.92-3.4). However, it should be noted that the numbers of observed and expected deaths in each of the categories was extremely small owing to the low rates of rectal cancer.

In the later Bristol cohort, there were very few person-years in the high exposure categories. There was no indication of an elevated risk at lower levels of exposure, for which the accumulated person years were substantial. There were no deaths due to rectal cancer more than 20 years after hire in the later Bristol cohort. In the Knoxville cohort, there was no relationship between mortality due to colon cancer 20 years following achievement of a reference cumulative exposure, as the number of deaths due to this cancer was lower than expected at high levels (observed deaths = 1, expected deaths = 1.6 for 15 units) and higher than expected at the lowest level (observed deaths = 17, expected deaths = 9.19 for 0 to 4 units). There were no deaths due to colon cancer among the unexposed (expected deaths = 0.80). However, there was only a very small number of men at Knoxville who had had no exposure at all. There was only a single death due to rectal cancer in the lowest exposure group (expected deaths = 2.30).

In summary, in the two cohorts with later dates of first hire, there was no excess mortality due to cancer of the colon or rectum. In the early cohort, there was an apparent excess of deaths due to colon cancer. This cohort worked in conditions which are thought to have involved high exposures to the vapor phase of EA and MMA monomer, as well as to a variety of volatile by-products of the EA/MMA polymerization process. Although the focus of this research was on colon and rectal cancers, Walker *et al.* also reported cause-specific SMR's for other causes of death in each cohort. There was no systematic pattern of excess risk of any other site of cancer. For respiratory cancer however, there was a significantly high SMR (1.44) in the Knoxville cohort, with no excess in either of the Bristol cohorts.

The mortality of a cohort of 2,671 white and nonwhite men, 1561 of whom were exposed to MMA, employed at two American Cyanamid Company plants (the Fortier plant and the Santa Rosa plant), between 1951 and 1983 has also been examined (Collins *et al.*, 1989). The cohort was subdivided based on four categories of cumulative exposure: none, 0.0 to 0.19, 0.20 to 2.0, and more than 2.0 ppm-yr. There were no statistically significant excesses in deaths due to all causes (SMR = 0.79 and 0.67 for unexposed and exposed, respectively). Mortality from all malignant neoplasms (SMR = 1.04) was similar to that of the US population (SMR = 1.01). There was no relationship between mortality due to several types of

cancer (including colon and rectal cancer) and concentration of MMA. Men exposed to high concentrations of MMA had cancer rates similar to those for men not exposed in the workplace, as well as for the male US population. Although these findings provided no support for the hypothesis that MMA was a human carcinogen, the power of this study was limited. Based on a two-tailed 5% significance level, the study had an 80% power of detecting a six fold increase of cancer of the large intestine.

A population-based case-control study of cancer was carried out in Montreal to investigate the associations between hundreds of occupational exposures and many types of cancer. Interviews were carried out with 3730 cancer patients and 533 population controls. For each site of cancer analyzed, two control groups were used, cancer controls and population controls. The probing interview elicited detailed lifetime job histories, and information on potential confounders. Each job in each subject's job history was reviewed by a specially-trained team of chemists and hygienists who translated it into a list of occupational exposures, using a checklist of 294 occupational exposures. Each occupational substance was then analyzed as a potential risk factor in relation to each site of cancer included in the study. Among the substances on the checklist was methyl methacrylate, to which only 21 of the entire study population of 4263 had been exposed at some time (i.e. lifetime exposure prevalence = 0.5%). With so few subjects exposed to MMA, the statistical power to detect elevated risks was very low. There were no cases of colon cancer among workers exposed to MMA, nor were there any apparent excesses for most other sites of cancer. For lung cancer, however, there were a total of 5 observed cases and this produced highly significant relative risk estimates in the region of 4.0 to 5.0. The risk estimates were somewhat higher using cancer controls than using population controls. The lung cancer excess may be due to statistical fluctuation or to confounding by other occupational carcinogens. The negative finding for colon cancer must be interpreted in the light of the limited sample sizes, possibly low exposure levels, and possible misclassification error in exposure assessment.

10.3.3 *Genotoxicity*

In the only identified genotoxicity study in human populations exposed to MMA alone, the presence of SCE in the peripheral lymphocytes of thirty one French men occupationally exposed to MMA [mean values for 8 hrs ranged from 0.70 to 21.6 ppm (2.9 to 88.5 mg/m^3)] in four factories in France was examined (Marez *et al.*, 1991). The control group was composed of 31 healthy male workers with similar mean age and smoking habits (none had smoked during the past year). The mean number of SCE in exposed workers (7.85 $\pm$ 2.66) was not higher than that in the control group (7.49 $\pm$ 2.33).

However, the distribution of SCE was significantly higher in the group exposed to MMA at peak concentrations ranging from 114 to 400 ppm (467 to 1640 mg/m^3) although the number of individuals in this exposure subgroup was small (n = 6) (Table 10-2).

10.3.4 *Developmental and Reproductive Toxicity*

Studies of developmental or reproductive effects in epidemiological studies of populations exposed to MMA alone, were not identified.

Table 10-2 Epidemiological Studies - Cancer Mortality and Genotoxicity

Protocol	Results	Reference
Cancer Mortality 1849 male workers (Caucasian and Hispanic) employed for any length of time between 1948 and 1978 in a plant in Texas manufacturing acrylate and methacrylate esters followed to the end of 1978 (96.1% traced; 117 deaths). The employees were divided into six 5-year groups based on the year of hire (1948 - 1977). Employees contributed person-years of risk according to their years of experience at the plant (meant to reflect exposure levels). Analyses for all employees whether hourly or salaried as well as hourly employees only. Mortality rates were compared to those for U.S. white males.	There was no significant increase, and a general decrease in the total deaths from all causes, ischaemic heart disease and cerebrovascular lesions compared to that expected. Death rates from the following cancers were similar to that expected: buccal cavity and pharynx, digestive tract, respiratory system and urinary and genital systems. Deaths from malignant neoplasms for all employees combined, and for various subgroups, were lower than expected. For the group hired from 1958 - 1962, there was a significant increase in total cancer deaths due to the elevated occurrence of lymphatic cancer and of "other and unspecified malignant neoplasms". Three deaths were due to brain cancer (2 in 1955 and 1 in 1963); durations of employment for these workers who died within 4 years of commencement of work at the plant were 1.0, 2.2, and 2.8 years (unlikely caused by occupational exposures). Two workers died from lymphatic cancer (1976 and 1977); both had started work in 1958, and durations of employment were 16.6 and 18.0 years.	DeFonso and Maher, 1981
A nested case control study in which the cases and controls were selected based on death certificates of men who had worked at a Bristol plant manufacturing and polymerizing acrylate and methyl methacrylate for at least a year between 1933 and 1945. 54 cases of colorectal cancer were identified (this was declared the primary cause of death in 52 cases) and compared with 5 controls each, matched for age (varied by less than 5 years), and who died at approximately the same age. Odds ratios were determined for three durations of employment in two areas of the plant (any amount, > 6 months, and > one year). 15 cases and 79 controls were employed in the "monomer area" (manufacture and polymerization of methacrylate and acrylate esters) and 34 cases and 161 controls were employed in the "plexiglass area" (production, finishing and shipping of sheets of copolymerized MMA).	For the "monomer area" group, the odds ratios for colorectal cancer were 0.93 - 0.98 for the 3 periods of duration (not significant, $p > 0.897$). For the "plexiglass area" group, the odds ratios were 1.15 - 1.23 (not significant, $p > 0.609$). When these two groups were considered together, the odds ratios were 1.45 - 1.62 (not significant, $p > 0.237$). Because none of the odds ratios was significantly different from one, colorectal cancer was not associated with MMA exposure.	DeFonso and Maher, 1986 (DRAFT)

Table 10-2 (continued)

Protocol	Results	Reference
6667 white men (4035 were hourly employees and foremen, and 2632 received salaries) employed for any length of time between 1946 and 1982 at a Bristol plant producing ethyl acrylate (EA) monomer and polymerization of MMA to produce acrylic sheet followed to December 31, 1988 (91% traced; 701 deaths). The cohort was subdivided into several categories of exposure: no routine exposure (0), regular exposure to less than 5 ppm (1), 5 - 24 ppm (2) and > 25 ppm (3). Mortality rates were compared to those of U.S. white males.	The 701 deaths identified among the males of the entire plant (hourly and salaried) were significantly fewer than the 821 deaths predicted based on the U.S. rates (O/E = 0.85, $p<0.01$), due in part to the low mortality due to accidents, suicides and homicides (73 observed; 139.3 expected). There were also significantly fewer (than expected) deaths from pneumonia and from diseases of the digestive system and the genito-urinary system. Mortality from arteriosclerotic heart disease and from cancer (for any site) was similar to that of the U.S. population. In the cohort, there were 2.35 times the expected number of deaths in the "symptoms, senility and ill-defined" category. In nearly all cases, the individual was 50 years of age or older and cause of death was listed as "natural causes". When the salaried workers were excluded, the number of deaths due to arteriosclerotic heart disease was elevated for men who had worked less than one year (O/E = 1.25, $p<0.05$). There were no significant excesses of mortality due to cancer at any site. Deaths due to symptoms and ill-defined conditions were significantly elevated (20 observed vs. 7.6 expected; 13 of these deaths occurred among men who had worked less than 1 year). When only the hourly employees and foremen with routine exposure (n = 2644) were considered, the only elevated cause of death was the "ill-defined" category. There were no excesses of deaths due to cancer of the large intestine and rectum among those hired after 1945, nor among those exposed to MMA in particular.	Maher and DeFonso, 1987a
All males (3381 whites and 476 non-whites) employed for any length of time between 1943 and 1982 at a Knoxville plant manufacturing plexiglass acrylate sheet followed to December 31, 1982 (91% traced; 858 deaths and 81% traced; 152 deaths, respectively). Ranking of each job in terms of qualitative measures of EA/MMA exposure based on individual work histories: no (remote operations in which equipment is isolated from the work area), minor (closed system with equipment vented outside the work area, instrument control in the equipment area and mechanical handling of materials in bulk, moderate (non-continuous operations usually provided local exhaust ventilation) and major (hand operations performed without local exhaust ventilation). The jobs were similarly ranked for exposure to polymer particulates. Mortality rates were compared to those of U.S. (white and non-white) males and for the Knoxville County region. The critical p-value was set at 0.05.	Overall mortality among plant employees was lower than that of U.S. males due primarily to significant deficits in deaths from diseases of the circulatory system. The mortality from digestive system diseases for white males compared to U.S. rates was also significantly lower. Excess respiratory cancer among white male employees and cancers of the lymphatic and hematopoietic tissues among non-white males (but 5 of the 6 were short term employees) compared to the U.S. rates but not based on comparison with local rates. Mortality due to leukemia was significantly less in the white males compared to U.S. rate. Mortality due to cancers of the digestive tract including colorectal cancers and prostrate cancers was significantly less frequent than expected based on comparison with the U.S. rates and local rates. Over 90% of the employees had jobs with potential for EA/MMA exposure; there were no associations between measure of exposure and increased risk of cancer at any site. In both white and non-white males, the only elevated cause of deaths was the "ill-defined" category.	Maher and Defonso, 1987b

Table 10-2 (continued)

Protocol	Results	Reference
Reexamination of mortality from cancer of the colon and rectum of the white male employees (due to small number of nonwhites in the cohort) of the Bristol and Knoxville MMA production plants. The employees at the Bristol plant were considered during 2 time periods: early, 1933 - 1945 (3934 hourly workers; of these men, 2906 were hired between 1941 to 1945; follow-up began on the first day of employment until death or December 31, 1986) and late, 1946 - 1982 (3916 hourly and 2632 salaried, same follow-up period as above). The 3381 hourly Knoxville plant workers were employed between 1943 and 1982 (same follow-up period as above). There was no minimum employment duration for the workers included in the studies of the Knoxville and the late Bristol cohorts. In order to obtain at least 85% successful follow-up, the minimum duration of employment for the early period in the Bristol cohort was 10 months (i.e. leaving 2524 of the initial 3934). Cumulative total MMA exposures for each job of each worker were estimated semi-quantitatively. Mortality due to cancers of the colon and rectum was examined in relation to elapsed time since achieving several values of cumulative exposure, cumulative level of exposure reached 20 years earlier, maximum exposure intensity experienced and the date of hire. Expected deaths were based on local mortality rates.	Excess colon cancer mortality was largely restricted to men who worked extensively in jobs in the early 1940's that entailed very high (but unspecified) exposure to vapour phase EA/MMA monomer and volatile byproducts 20 or more years after first exposure. In the early Bristol cohort, rectal cancer mortality was elevated in most of the same subgroups for which there was excess mortality from colon cancer, but the rates were much lower. Among the exposed persons overall, there was a total of 38 cases of colon cancer (compared with an expected number of 25.4). Rectal cancer was elevated in most of th esame subgroups for which there was excess mortality from colon cancer, but hte rates were lower. Among the exposed persons overall the 10 deaths from rectal cancer compares with an expected number of 5.32. No excess mortality from colon or rectal cancer in the Knoxville and late Bristol cohorts. The highly exposed workers may also have been exposed to other, possibly harmful chemicals such as lead, ethylene dichloride, methylene chloride and acrylonitrile.	Walker et al., 1991
2,671 male workers (2473 whites and 198 non-whites) employed for any length of time between the start up of two plants (1951 in Fortier and 1957 in Santa Rosa) and 1974 were followed to the end of 1983 (traced 98%; causes of death ascertained for 224 of 237 deaths). In these plants which manufactured or used MMA in other product manufacture, 1561 of these men were exposed to MMA, at various levels. Exposure was estimated for each job. Profiles for each member of the cohort including smoking habits, and duration of each type of work were established. Subdivision into three groups based on cumulative exposure: none, 0 - 0.19, 0.20 - 2.0, and more than 2.0 ppm-years. Comparison with a group of men who were not exposed to MMA at the two plants and men in the U.S. population.	For the non-exposed group, the standardized mortality ratio (SMR) for all causes was 0.79, while for all malignant neoplasms, it was 1.01. For the exposed group, the SMR for all causes of death was 0.67; this was significantly less than expected ($p < 0.05$). The SMR for all malignant neoplasms of the exposed men at 1.04 based on 35 cancer deaths, was the same as that of the unexposed men, and was similar to that of the US population (1.04). There was no excess mortality from colon, rectal or other cancers in the exposed group though there has been one cancer of th elarge intestine (2.6 expected). The percentage of workers who smoked was similar in the exposed (73.8% for the group with greatest cumulative exposure) and non-exposed (72.2%) groups.	Collins et al., 1989

Table 10-2 (continued)

Protocol	Results	Reference
A population-based case-control study of cancer was carried out in Montreal, Canada to investigate the associations between hundreds of occupational exposures and many types of cancer. Case ascertainment covered all large Montreal area hospitals. The study was limited to males, aged 35-70 and resident in Montreal. A total of 3730 cancer patients (response rate of 82%) and an age-stratified sample of the general population of 533 (response rate of 72%) were successfully interviewed. For each site of cancer analyzed, two control groups were used, giving rise to two separate sets of analyses and results, one control group selected from among the other sites in the study (cancer controls) and the other from the population controls. Each subject's job history was reviewed by a specially-trained team of chemists and hygienists who translated it into a list of occupational exposures, using a checklist of 294 of the most common occupational exposures in the Montreal area. For each agent thought to have been present in the subject's job environment, the team of chemists and hygienists also noted, using three-point ordinal scales, the concentration of exposure, frequency of exposure, and degree of certainty (i.e., possible, probable, or definite) in the exposure assessment. The exposures were analyzed at two levels: "any" and "substantial". In fact, what was called "any exposure" in these analyses excluded exposures characterised by the coders as "possible", as opposed to probable and definite, and it excluded exposures occurring within the 5 years preceding disease onset. "Substantial" exposure was a subset of "any", based on a minimum exposure duration of 10 years and at least medium scores for both concentration and frequency of exposure. For each site, each type of control group and each exposure level, a Mantel-Haenszel estimate was made of the odds ratio, including as confounders a number of established non-occupational risk factors (age, smoking, ethnic group, and socioeconomic status). Only 21 of the entire study population of 4263 had been exposed at some time (i.e. lifetime exposure prevalence = 0.5%) to MMA. Four subjects had their first exposure before 1940, another 8 between 1940 and 1950, and the rest since 1950. Two-thirds of those exposed to MMA had been dentists or dental technicians, while most of the rest were exposed in construction trades. No study subjects had been in MMA manufacturing; all were in user industries. The authors did not indicate what absolute exposure levels correspond to the three-point ordinal scale of concentration. It is likely that exposures were lower in this study population than those in the cohort studied by Walker et al.	With so few subjects exposed to MMA, the statistical power to detect elevated risks was very low. There were no cases of colon cancer in those exposed to MMA nor were there any apparent excesses for most other sites of cancer. There were 2 cases of rectal cancer in the exposed workers and the expected number was much less than 1.0. While this excess was technically significant, it is difficult to give much credence to an excess based on only 2 observed cases. For lung cancer, however, there were a total of 5 observed cases (of which 4 were at the substantial level), and this produced highly significant relative risk estimates in the region of 4.0 to 5.0. The risk estimates were somewhat higher using cancer controls than using population controls. The positive associations for lung cancer must be interpreted in the light of the multiple testing context and the fact that mutual confounding by occupational exposures was not controlled in these analyses. The null result for colon cancer must be interpreted in the light of the limited sample sizes, possibly low exposure levels, and possible misclassification error in the exposure assessment.	Siemiatycki, 1991

Table 10-2 (continued)

Protocol	Results	* Reference
Genotoxicity 31 males occupationally exposed to MMA in four French factories and 31 healthy male workers, matched for age and smoking habits (no one had smoked during the past year), were examined for the presence of sister chromatid exchanges (SCE) in peripheral lymphocytes. The mean ages of the exposed and control groups were 40.5 and 40.6, respectively. Subjects in the exposed and control groups had not been exposed to ionizing radiation either professionally or for diagnostic purposes or to mutagens professionally or to mutagenic drugs for at least three months. The mean MMA concentration (8 h average) ranged from 0.70 to 21.6 ppm.	The number of SCE in exposed workers (7.85 $\pm$ 2.66) was not higher than in the control group (7.49 $\pm$ 2.33). However, the distribution frequency of SCE was significantly higher in the group exposed to MMA at peak concentrations ranging from 114 to 400 ppm. This increase was attributable to a few cells with a large number of SCE.	Marez et al., 1991

11.0 Effects on the Ecosystem

11.1 Toxicity to Aquatic Organisms

The only information on aquatic toxicity of MMA is acute toxicity tests on fish, *Daphnia magna* and algae and one chronic toxicity study on frogs. Because MMA is a volatile compound, it requires aquatic testing procedures which eliminate losses through volatilization. Maintenance of closed, flow-through systems with measured concentrations throughout the test period are necessary to ensure minimal loss of the chemical and to ensure that the concentration of the test substance is close to the nominal value during the exposure period. Few of the studies described below meet these criteria and thus their conclusions are potentially suspect.

11.1.1 *Fish*

Bailey *et al.* (1985) studied the toxicity of methyl methacrylate to juvenile bluegill sunfish (*Lepomis macrochirus*) (0.9 g wet weight) at 22°C under static and flow-through conditions of various durations (i.e., 1 - 96 hours). LC_{50} estimates were based on actual concentrations. In the static assay, the 24, 48, 72 and 96-hour LC_{50}s were all 283 mg/L. In the flow-through assay, the 24, 48 and 72-hour LC_{50}s were 264 mg/L and the 96 hour LC_{50} was 191 mg/L. In shorter exposure flow-through assays, the LC_{50}s were: 420, 373, 367, 360, 360 and 356 for 1, 2, 4, 8, 16 and 24 hours exposure, respectively.

The 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) under flow-through conditions was > 79 mg/L. Sublethal/behavioural responses were noted among the fish in the 40 and 79 mg/L dose groups (Bowman, 1990).

Pickering and Henderson (1966) reported the median tolerance limit (or LC_{50}) using a static test at 25°C for four species of fish: fathead minnows (*Pimephales promelas*), bluegills (*Lepomis macrochirus*), goldfish (*Carassius auratus*), and guppies (*Lebistes reticulatus*) (Table 11-1). Initial concentrations only were reported. The pH and dissolved oxygen decreased during the experiment although the authors did not state the magnitude of the changes. Initial pH for soft water was 7.5 and for hard water was 8.2. For the fathead minnow, the 96 hour TL_m was significantly lower in soft water than in hard water. For the fathead and bluegill, the 24 hour TL_m was significantly higher than the 96 hour TL_m.

The 48-hour LC_0, LC_{50} and LC_{100} for the golden orfe (*Leuciscus idus melanotus*) were 320, 350 and 380 mg/L (Juhnke and Ludemann,

1978).

Reinert (1987) in studying the quantitative structure activity relationships based on K_{ow} and LC_{50} values, used a 96-hour LC_{50} value for fathead minnow of 660 mg/L and a 72 hour-LC_{50} value for goldfish of 180 mg/L.

11.1.2 *Invertebrates*

Using MMA, the 24-hour EC_{50} for immobilization of *Daphnia magna* was 720 mg/L, with the extrapolated EC_0 and EC_{100} being 502 and 1042 mg/L, respectively (Bringmann and Kuhn, 1982). The 24-hour LC_{50} for *Daphnia magna* was 1760 mg/L and for the LC_0 and LC_{100} was 875 and 2500 mg/L, respectively (Bringmann and Kuhn, 1977). These studies on *Daphnia* were static, open studies, thus the actual concentrations may have been less than the nominal at the end of the study period.

In a similar study, the toxicity threshold for onset of inhibition of cell multiplication was 447 mg/L for the flagellate protozoan *Entosiphon sulcatum* after a 72-hour exposure period (Bringmann, 1978).

Table 11-1. Acute toxicity of methyl methacrylate to fish (from Pickering and Henderson, 1966).

Species	Water Type	Duration	LC_{50} (mg/L)
Fathead minnow	soft	24 h	421, 455
		48 h	338, 455
		96 h	159, 160
	hard	24 h	498, 391
		48 h	338, 368
		96 h	311, 320
Bluegill	soft	24 h	368
		48 h	357
		96 h	232
Goldfish	soft	24 h	423
		48 h	423
		96 h	277
Guppy	soft	24 h	368
		48 h	368
		96 h	368

11.1.3 *Plants*

Toxicity thresholds for onset of inhibition of cell multiplication by methyl methacrylate for the blue green alga *Microcystis aeruginosa* was 120 mg/L and for the green alga *Scenedesmus quadricauda*, 37 mg/L, at pH 7 (Bringmann and Kuhn, 1976, 1978a, 1978b). Organisms were exposed for 8 days. The 96-hour LC_{50} for *Selenastrum capricornutum* was 170 mg/L with a NOEL of 100 mg/L (Forbis, 1990). No studies were identified on higher plants.

11.1.4 *Amphibians*

The significance of chronic exposure to MMA upon the function of respiratory ciliated epithelium was studied using adult northern grass frogs exposed to 116 ppm and 400 ppm methyl methacrylate in air. No significant effect was demonstrated at the 116 ppm dose, but transit capability degraded rapidly in the 400 ppm dose group due to altered ciliary morphology (Tansy and Kendall, 1979).

11.2 Toxicity to Terrestrial Organisms

11.2.1 *Wild Mammals*

No field data on effects on wild mammals were identified, thus laboratory toxicity studies on mammals are used to extrapolate to effects on wild mammals (see Section 9).

11.2.2 *Birds*

No field or laboratory data on effects on birds were identified.

11.2.3 *Invertebrates*

No field or laboratory studies on terrestrial invertebrates were identified.

11.2.4 *Plants*

No field or laboratory studies on terrestrial plants were identified.

11.2.5 *Bacteria*

Only one study was identified on the effects of MMA on bacteria. The toxicity threshold of MMA for onset of inhibition of cell multiplication of the bacterium *Pseudomonas putida* was 100 mg/L (Bringmann and Kuhn, 1976).

12.0 Current Regulations, Guidelines and Standards

12.1 Canada

No objectives, guidelines or standards for MMA in Canada were identified.

12.2 International

MMA has been classified in Group 3 by IARC (i.e. not classifiable as to its carcinogenicity to humans) (IARC, 1987) and in Group D (not classifiable as to human carcinogenicity) by the U.S. EPA (U.S. EPA, 1985).

The Scientific Committee for Food of the European Commission have recently assigned a temporary group ADI for methacrylic acid esters (including MMA) of 0.1 mg/kg b.w. (BIBRA, personal communication).

The American Conference of Governmental Industrial Hygienists (ACGIH, 1988) has a Time Weighted Average value of 100 ppm (410 mg/m^3) for this compound, a level considered to be protective against the irritating and acute systemic effects (ACGIH, 1980). NIOSH (1985) lists the same level of 100 ppm (410 mg/m^3) as a recommended exposure limit. The level considered Immediately Dangerous to Life or Health (IDLH) by the ACGIH was 4000 ppm (16400 mg/m^3). This level defined only for the purpose of respirator selection, represents a maximum concentration from which, in the event of respirator failure, one could escape within 30 minutes without experiencing any escape-impairing or irreversible health effects.

Under the U.S. EPA RCRA, MMA is listed as a hazardous constituent of waste (Code of Federal Regulations, Title 40, Section 261) and as a water pollutant (Code of Federal Regulations, Title 40, Section 116.4). Methyl methacrylate is subject to notification under the Toxic Substances Control Act (TSCA) inventory.

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