METHYL METHACRYLATE

This substance was considered by a previous Working Group, in February 1978 (IARC, 1979). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

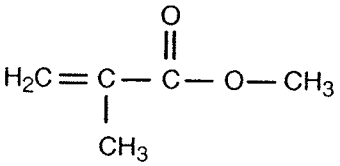
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 80-62-6
Chem. Abstr. Name: 2-Methyl-2-propenoic acid, methyl ester
IUPAC Systematic Name: Methacrylic acid, methyl ester
Synonyms: 2-(Methoxycarbonyl)-1-propene; methyl 2-methylacrylate; methyl 2-methyl-2-propenoate; MMA

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_5H_8O_2$ Relative molecular mass: 100.12

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (CYRO Industries, 1987), with a fruity, pungent odour (American Conference of Governmental Industrial Hygienists, 1991)
(*b*) *Boiling-point*: 100–101 °C (Lide, 1991)
(*c*) *Melting-point*: –48 °C (Lide, 1991)
(*d*) *Density*: 0.9440 at 20 °C/4 °C (Lide, 1991)
(*e*) *Spectroscopy data*: Infrared [2226], ultraviolet, nuclear magnetic resonance and mass spectral data have been reported (Sadtler Research Laboratories, 1991; US National Library of Medicine, 1993a).
(*f*) *Solubility*: Slightly soluble in water (1.6 g/100 ml at 20 °C), glycerine and ethylene glycol (CYRO Industries, 1987; Bauer, 1990); soluble in acetone, diethyl ether and ethanol (Lide, 1991)

(*g*) *Volatility*: Vapour pressure, 3.87 kPa at 20 °C (Bauer, 1990; Rohm & Haas Co., 1993); relative vapour density (air = 1), 3.45 (Verschueren, 1983)

(*h*) *Stability*: Highly inflammable vapours (Mannsville Chemical Products Corp., 1987); lower explosive limit, 2.1 vol. % in air (CYRO Industries, 1987)

(*i*) *Reactivity*: Monomer can be polymerized by light, heat, oxygen or ionizing radiation and by benzoyl peroxide (American Conference of Governmental Industrial Hygienists, 1991)

(*j*) *Octanol–water partition coefficient (P)*: log P, 1.38 (Sangster, 1989)

(*k*) *Conversion factor*: $mg/m^3 = 4.1 \times ppm$[a]

1.1.4 *Technical products and impurities*

The purity of commercial methyl methacrylate is typically 99.9% [specification, 99.8% min.]; it contains traces of acidity as methacrylic acid (0.003% max.; specification, 0.005% max.) and water (0.03% max.; specification, 0.05% max.). Inhibitors added for storage and transportation are usually 10–50 ppm [specification, 9–55 ppm] methyl ether of hydroquinone and 25–60 ppm hydroquinone, although other phenolic inhibitors, such as dimethyl *tert*-butyl phenol, can also be used (Degussa AG, 1988; Bauer, 1990; CYRO Industries, 1992; Rohm & Haas Co., 1993). Phenothiazine has been used for this purpose because it acts both anaerobically and aerobically, but it is not commonly used in products intended for use as polymer intermediates (Bauer, 1990).

1.1.5 *Analysis*

Methyl methacrylate can be determined in air by gas chromatography with flame ionization detection. The sample is adsorbed on fused silica (XAD-2 resin) or charcoal coated with 4-*tert*-butylcatechol and desorbed with carbon disulfide or toluene. The estimated limit of detection is 0.01 mg per sample (Eller, 1989; US Occupational Safety and Health Administration, 1990; Harper, 1992). A method involving desorption with 5% isopropanol in carbon disulfide from charcoal has a detection limit of 0.8 mg/m^3 (Kollár *et al.*, 1988).

1.2 Production and use

1.2.1 *Production*

Methyl methacrylate was first produced commercially in Germany in 1933. The original process was a variant of the current acetone–cyanohydrin process, in which acetone and hydrogen cyanide are reacted to produce acetone cyanohydrin; this is treated with concentrated sulfuric acid to form methacrylamide sulfate, which is reacted directly with methanol to form crude methyl methacrylate and ammonium bisulfate. The crude methyl methacrylate is purified by distillation (Mannsville Chemical Products Corp., 1987; Bauer, 1990).

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[a]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

In the isobutylene (isobutene) process, introduced in Japan in 1983, methyl methacrylate is made by oxidation of isobutylene to methacrylic acid with nitric acid and subsequent esterification with methanol. *tert*-Butanol is used as the starting material. In another process based on isobutylene used in Japan, the methacrylonitrile process, isobutylene is converted by ammoxidation to methylacrylonitrile, which is then hydrolysed with sulfuric acid and reacted with methanol to produce methyl methacrylate (Bauer, 1990).

Some methyl methacrylate monomer is recovered by 'cracking' (depolymerizing) polymethyl methacrylate scrap (Mannsville Chemical Products Corp., 1987).

Production of methyl methacrylate monomer in Japan was 403 thousand tonnes in 1990, 401 thousand tonnes in 1991 and 384 thousand tonnes in 1992 (Japan Chemical Week, 1991, 1992; Japan Petrochemical Industry Association, 1993). Production of methyl methacrylate in the USA was (thousand tonnes) 536 in 1990, 500 in 1991 and 380 in 1992 (preliminary figures) (Anon., 1993); in the years 1960, 1965, 1970, 1975, 1980 and 1981, production was 54, 113, 202, 248, 354 and 404 thousand tonnes, respectively (US International Trade Commission, 1982; Mannsville Chemical Products Corp., 1987). Capacities for the production of methyl methacrylate in 1988 in several countries are presented in Table 1. Global production was approximately 1400 thousand tonnes.

Table 1. Capacity for production of methyl methacrylate in several countries, 1988

Country	No. of facilities	Process	Capacity (thousand tonnes/year)
France	1	Acetone cyanohydrin	60
Germany	2	Acetone cyanohydrin	160
	1[a]	Ethylene	–
Italy	1	Acetone cyanohydrin	50
Japan	3	Acetone cyanohydrin	131
	3[a]	Isobutylene	135
	1	Methacrylonitrile	60
Spain	2	Acetone cyanohydrin	50
United Kingdom	1	Acetone cyanohydrin	105
USA	3	Acetone cyanohydrin	514
Other countries			about 150

From Bauer (1990)
[a]One in construction

Information available in 1991 indicated that methyl methacrylate was produced by six companies in Japan, three each in China, Mexico and the USA, two each in Germany and Spain, and one each in Argentina, Brazil, the former Czechoslovakia, France, Italy, Poland and the United Kingdom (Chemical Information Services Ltd, 1991).

1.2.2 *Use*

Methyl methacrylate, methacrylic acid and other methacrylates readily polymerize to form long-chain homopolymers and copolymers. Methyl methacrylate monomer is the most

important ester of methacrylic acid commercially. Acrylic sheeting, made by casting, moulding or extruding polymethyl methacrylate or modified polymers, is the largest application for methyl methacrylate. Cast sheeting, used, for instance, for safety glazing, panels and lighting, is the major type of sheeting produced. Polymethyl methacrylate resins are also used to make moulded and extruded products that require resins with good optical clarity and stability, such as plumbing fixtures and outdoor lighting. Methyl methacrylate–butadiene–styrene resins are being made increasingly for use as impact modifiers for clear rigid polyvinyl chloride, particularly for making bottles (Mannsville Chemical Products Corp., 1987; Bauer, 1990).

Methyl methacrylate polymers and copolymers are used in waterborne, solvent and undissolved coatings. Exterior latex paint based on emulsions containing methyl methacrylate is the surface coating in which the monomer is used most widely. Solvent reducible polymers containing methyl methacrylate are used for industrial finishes, metal and foil coatings and a variety of overlays for special purposes. Solvent and emulsion polymers containing methacrylates are also used in adhesives, sealants, leather coatings, paper coatings, inks, floor polishes and textile finishes (Mannsville Chemical Products Corp., 1987; Bauer, 1990). Engineering adhesives are undissolved, liquid, reactive, durable adhesives for bonding durable substrates, and consist primarily of methyl methacrylate monomer with polymethyl methacrylate and other polymers (Gehman, 1990).

Special methacrylate polymers are used for dental prostheses, surgical bone cements and leaded acrylic radiation shields. Polymer concretes based on methyl methacrylate and Portland cement are used to patch highways and bridges. Methyl methacrylate is also used in the production of polymers added to lubricating oils (Mannsville Chemical Products Corp., 1987; Bauer, 1990).

Dental prosthesis fabrication involves preparation of impression trays, orthodontic appliances and dentures. A powder containing small, prepolymerized, spherical acrylate particles—usually polymethyl methacrylate or mixed acrylate copolymers—is combined with a liquid, the main component of which is methyl methacrylate. The liquid also contains either a cross-linking polyfunctional monomer or a self-curing activator. The solid and liquid components are combined and handled manually while the material is moulded into plastic or metal impression trays (Ruyter & Sjøvik, 1981; Rajaniemi, 1986). Bone cements are also usually two-component mixtures prepared just before use (Darre *et al.*, 1987).

Methyl methacrylate is also used in the preparation of synthetic fingernails (IARC, 1993) and orthotic shoe inserts (Gunter & Schulenberg, 1982).

Typical use patterns for methyl methacrylate in the USA are presented in Table 2. In Europe in 1992, 31% methyl methacrylate was used in the manufacture of acrylic sheet and moulding powders, 50% for surface coating and emulsion polymers, 13% for other methacrylates and 6% for miscellaneous uses (European Chemical Industry Council, 1993).

1.3 Occurrence

1.3.1 *Natural occurrence*

Methyl methacrylate is not known to occur in nature.

Table 2. End use patterns for methyl methacrylate in the USA (%)

Use	Year			
	1981	1985	1988	1991
Cast and extruded sheet	32	30	25	24
Moulding powders and resins	25	25	25	21
Surface coatings	32	33	20	18
Exports	10	10	8	11
Impacts modifiers	–	–	10	10
Emulsion polymers	–	–	6	8
Mineral-based sheet	–	–	–	3
Higher methacrylates	–	–	2	2
Polyester modifiers	–	–	4	1
Miscellaneous[a]	1	2	–	2

From Anon. (1981, 1985, 1988, 1991); –, not reported
[a]Includes synthetic fibre modification

1.3.2 *Occupational exposure*

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 indicated that 170 082 US employees were potentially occupationally exposed to methyl methacrylate (US National Institute for Occupational Safety and Health, 1993). Of this number, 9% were estimated to be exposed to methyl methacrylate and 91% to materials containing methyl methacrylate. The estimate is based on a survey of US companies and did not involve measurements of actual exposures.

Industries in which exposures to methyl methacrylate may occur include: monomer production, polymer production and plastics manufacture, thermoplastics processing, plastics cutting, hospitals and dental clinics. Occupations in which there is potential exposure to methyl methacrylate include: chemical process operator, surgeon and surgical assistant, operating room nurse, dental technician and hygienist, and beauty technician applying synthetic fingernails. Air concentrations of methyl methacrylate in a variety of industries are given in Table 3. Most of the data on exposure are from the chemical industry during production or use of the monomer as a chemical intermediate in production of acrylic plastics and polymers, and from dental clinics and laboratories during dental prosthesis manufacture and repair.

(*a*) *Chemical industry*

In two US chemical plants, the concentrations in personal air samples in 1960–83 ranged from not detected to 7.83 ppm [32 mg/m^3] during methyl methacrylate production and from 0.05 to 11.5 ppm [0.2–47 mg/m^3] during acrylic fibre production from the monomer. Workers were also potentially exposed to acrylamide, acrylonitrile, epichlorohydrin and

Table 3. Occupational exposures to methyl methacrylate

Industry (country)	Operation/Process	Type of sample	No. of samples	Air concentration (mg/m^3)		Year of measurement	Reference
				Mean	Range		
Monomer, primary production and use							
Methyl methacrylate manufacture (USA)	Various	Personal	NR	[2.83]	[0–32]	1965–69	Collins *et al.* (1989)
	Various	Personal	NR	[1.44]	[0–26]	1975–79	
	Various	Personal	NR	[0.53]	[0–5.8]	1980–83	
Acrylic fibre manufacture (USA)	Various	Personal	NR	[3.4]	[0.2–47]	1975–79	Collins *et al.* (1989)
	Various	Personal	NR	[3.0]	[0.2–22]	1980–83	
Acrylic ester–styrene copolymer production (USA)	Solution polymer reactor (open hatch batch process)	Personal	20	[0.29]	[ND[a]–1.55]	[1981]	Samimi & Falbo (1982)
	Solution polymer reactor (closed batch reactor)	Personal	13	[0.42]	[ND[a]–1.53]		
	Polymer flake reactor (closed continuous reactor)	Personal	6	ND	ND		
	All production areas	Area	57	[~1.0]	[ND[a]–13.5]		
	Unloading docks	Personal	11	[0.074]	[ND[a]–0.38]		
Thermoplastics processing (Finland)	Injection moulding, 235 °C	Area	4	0.06	SD 0.05	NR	Vainiotalo & Pfäffli (1989)
	Thermoforming, 100 °C	Area	12	1.0	SD 0.3		
	Thermoforming, 160 °C	Area	8	4.6	SD 1.4		
	Extrusion, 220–270 °C	Area	11	1.8	SD 0.4		
Plastics processing (Denmark)	Cleaning	Personal	4	452	NR–450	1983–89	ATABAS (1994)
	Moulding	Personal	13	57	NR–195		
	Mechanical mixing	Personal	24	180	NR–453		
	Manual mixing	Personal	3	501	NR–754		
	Filling	Personal	11	164	NR–337		
Monomer production (Slovakia)	NR	Personal	6	42	20.9–133	NR	Kollár *et al.* (1988)
Polymethyl methacrylate sheet manufacture (USA) (five plants)	NR, 8-h TWA	Personal	169 workers	105	4.1–713	1975	Cromer & Kronoveter (1976)

Table 3 (contd)

Industry (country)	Operation/Process	Type of sample	No. of samples	Air concentration (mg/m^3)		Year of measurement	Reference
				Mean	Range		
Polymethyl methacrylate production (Russia)	Polymerization	Area	> 800	NR	8–60	NR	Blagodatin *et al.* (1970)
	Block glass	Area		NR	75–150		
	Ornamental	Area		NR	10–65		
Polymer production (Russia)	Process reactor	Area	NR	NR	100–600	1969	Dobrinskij (1970)
Polymethyl methacrylate production (China)	Purification	Area	75	28.2	NR	1976–78	Lang *et al.* (1986)
	Prepolymer	Area	89	95.5	NR		
	Polymerization	Area	115	62.4	NR		
	Extrusion	Area	62	33.1	NR		
	Model making	Area	61	21.3	NR		
	Pouring glass surface	Area	48	11.3	NR		
	Prepolymer	Area	265	155.5	NR	1982–83	Lang *et al.* (1986)
	Polymerization	Area	366	203.2	NR		
	Extrusion	Area	138	32.2	NR		
	Model making	Area	183	19.3	NR		
Monomer production (Poland)	Various	Area	378	11	0.2–382	NR	Jedrychowski (1982)
Dental clinics							
Dental clinic (USA)	Denture fabrication	Personal	8	2.4	ND[b]–5.3	1980	Boiano (1980a)
	Orthodontics fabrication	Personal	4	0.55	0.4–0.84		
	Grinding	Personal	2	ND[b]	–		
Dental laboratory (Norway)	Denture fabrication	Area	4	[50]	[10–140]	NR	Brune & Beltesbrekke (1981)
Dental clinic (USA)	Denture fabrication	Personal	4	[0.28]	[0.08–0.78]	1981	Lewis & Shoemaker (1981)
	Denture fabrication	Area	1		[0.08]		
Dental clinic (USA)	Denture fabrication/repair	Personal	1	16.3	–	1991	McCammon (1992)
		Area	3	17.5	[< 0.25]–50		

Table 3 (contd)

Industry (country)	Operation/Process	Type of sample	No. of samples	Air concentration (mg/m^3)		Year of measurement	Reference
				Mean	Range		
Dental laboratory (USA)	Denture fabrication	Personal	4	3.8	2.2–5.6	1982–83	Rom *et al.* (1984)
Dental clinics (Denmark)	Denture fabrication	Personal	21	30	NR–121	1983–89	ATABAS (1994)
Dental laboratories (United Kingdom)	Denture fabrication (modern laboratory)	Area	4	[11]	[0.8–25]	1986	Money *et al.* (1987)
	Denture fabrication (special laboratory)		5	[180]	[14–590]	1986	
	Denture fabrication (no ventilation)		4	[273]	[98–420]	1986	
Other uses							
Hospital (USA)	Mixing and application of surgical bone cement	Personal	11	[7.2]	[< 1.6–12.7]	1983	Apol & Helgerson (1984)
Optical lens manufacture (USA)	Acrylic lens production	Area	4	[6.3]	[3.7–8.2]	1980	Boiano (1980b)
Newspaper printing (USA)	Letter-flex platemaking	Personal	10	ND[b]	–	1982	Gunter (1982)
Orthopaedic clinic (USA)	Orthotic inserts fabrication	Personal Area	3 3	67 253	17–110 23–417	1982	Gunter & Schulenberg (1982)
Research laboratory (Finland)	Cutting acrylic with laser	Area	2	246	206–286	NR	Hietanen *et al.* (1992)
Plastic furniture manufacture (USA)	Furniture construction Band saw Joiner Gluing	Personal Area Area Area	25 2 3 4	5.6 3.8 1.8 2.95	0.3–18 2.5–5 0.8–2.7 0.4–5.3	1976	Hollett (1977)
Beauty salon (USA)	Artificial fingernail preparation	Personal Area	3 2	[87.5] [53]	[61.5–102.5] [53 and 53]1976	1976	Kronoveter (1977a)

Table 3 (contd)

Industry (country)	Operation/Process	Type of sample	No. of samples	Air concentration (mg/m^3)		Year of measurement	Reference
				Mean	Range		
Beauty salon (USA)	Artificial fingernail preparation	Personal, short-term	25	[83.2]	SD [16]	NR	Froines & Garabrant (1986)
		Personal, 8-h	59	[21.7]	SD [1.6]	NR	
Hospital (USA)	Mixing surgical bone cement	Personal	19	[114]	[8.2–316]	1977	Kronoveter (1977b)
Hospital (Denmark)	Knee replacement	Area	NR	NR	[0–205]	NR	Darre *et al.* (1992)
	Hip replacement	Area	NR	NR	[0–410]		

NR, not reported; SD, standard deviation; ND, not detected; 8-h, 8-hour time-weighted average

[a] < 0.004 mg/m^3

[b] < 0.01 mg/sample

formaldehyde during methyl methacrylate production, and to acrylonitrile and vinylidene chloride during acrylic fibre production (Collins *et al.*, 1989).

Area samples for the analysis of methyl methacrylate were collected at four Finnish plants where polymethyl methacrylate was processed (Vainiotalo & Pfäffli, 1989). The average concentrations of methyl methacrylate in air during polymethyl methacrylate degradation were 0.06–4.6 mg/m^3. Other compounds present included oligomers of methyl methacrylate of higher relative molecular mass, including free radicals.

The exposures of workers and area concentrations of styrene and several acrylates, including methyl methacrylate, were monitored in an acrylic ester–styrene copolymer production facility in the USA where solution polymers, emulsion polymers and polymer flakes were produced (Samimi & Falbo, 1982). Concentrations in personal samples ranged from not detected to 0.378 ppm [$\leq$ 1.55 mg/m^3] and those in area samples up to 3.3 ppm [13.5 mg/m^3]. The highest concentrations of methyl methacrylate were found at the batch reactors and the unloading dock. Other compounds measured included ethyl acrylate, *n*-butyl acrylate, styrene, α-methyl styrene (*ortho*-vinyltoluene, see monograph, p. 373) and 2-ethylhexyl acrylate (see monograph, p. 475).

(*b*) *Dental clinics and laboratories*

The concentrations of methyl methacrylate in the air of dental clinics vary widely depending on the facility, production volume and type of ventilation (see Table 3). The preparation of dental prostheses and orthodontic devices involves manual handling (Rajaniemi & Tola, 1985), and dermal exposure to methyl methacrylate may occur even when gloves are used because of the permeability of glove materials to methyl methacrylate (Rajaniemi, 1986). In a Finnish study of 163 dental technicians and technical assistants who reported daily dermal contact with methyl methacrylate-containing compounds, only three subjects wore protective gloves during acrylic moulding and only 15 subjects wore gloves while performing other tasks that may have involved exposure to methyl methacrylate (Rajaniemi & Tola, 1985). Methyl methacrylate comprised 3–5% of the autopolymerizing acrylic compound used for repair and less than 1% of the polymerized hot-cure acrylic denture base handled by these workers. Other exposures in dental laboratories include phenolic inhibitors, formaldehyde mercury vapour and dusts containing gold, chromium, nickel and cobalt alloys, silicon carbide, and corundum (Al_2O_3).

In a separate study of dental technicians, monitoring of methacrylate in the urine of workers exposed dermally to methyl methacrylate showed that percutaneous uptake had occurred. Urine specimens were collected from 11 dental technicians exposed to methyl methacrylate during construction and repair of dental prostheses and from 10 unexposed controls over a 24-h period which included a normal working day. The actual durations of exposure were 30–240 min. The highest urinary concentrations of methacrylate in the exposed group ranged from 16 to 373 nmol/mmol creatinine (mean, 81 [standard deviation, 102; geometric mean, 53; geometric standard deviation, 2.4]). There was no clear relationship between duration of exposure and urinary output. The primary route of uptake was presumed to be percutaneous, although the concentrations in air were not measured (Rajaniemi *et al.*, 1989).

(c) *Other occupational exposures*

During the fabrication of orthotic shoe inserts, short-term personal exposures to methyl methacrylate ranged from 17 to 110 mg/m^3; the concentrations in area samples were 23–417 mg/m^3 (Gunter & Schulenberg, 1982).

Methyl methacrylate is released as a pyrolysis product when acrylic plastics are cut with a carbon dioxide laser beam. Air concentrations of methyl methacrylate measured 20 cm from a cutting surface over a period of 15–20 min were found to be 206 and 286 mg/m^3 (Hietanen *et al.*, 1992). Other pyrolysis products measured included anthracene, fluoranthrene, pyrene, benzene, toluene, methyl acrylate and ethyl acrylate.

Operating room personnel employed in mixing and applying bone cement were exposed to concentrations of < 1.6–316 mg/m^3 (Kronoveter, 1977b; Apol & Helgerson, 1984). Other compounds to which they were exposed included nitrous oxide and halogenated anaesthetic gases.

1.3.3 *Environmental occurrence*

No data were available to the Working Group on concentrations of methyl methacrylate in ambient air or water. The annual total air emissions, water releases, underground injection releases and land releases of methyl methacrylate in the USA, reported to the US Environmental Protection Agency by industrial facilities from 1987 through 1991, are presented in Table 4.

Table 4. Annual air, water, underground injection and land releases of methyl methacrylate in the USA, 1987–91

Year	No. of locations	Releases (tonnes)			
		Air	Water	Underground injection	Land
1987	194	1650	11	103	5
1988	217	1600	13	148	4
1989	248	1430	13	89	2
1990	258	1200	12	95	< 1
1991	240	1200	3	123	2

From US National Library of Medicine (1993b)

1.3.4 *Food*

Methyl methacrylate was found at levels of 180 and 275 ppb (μg/L) in maple syrup that had been contaminated by its plastic container. The residues in the container may have resulted from incomplete polymerization of methyl methacrylate–styrene–butadiene co-polymer resin or from decomposition of the plastic when the container was formed (Hollifield *et al.*, 1980).

Migration of methyl methacrylate from polymethyl methacrylate containers to food-simulated solvents was investigated by gas chromatography with a detection limit of 0.05 ppm

[0.05 mg/L]. Residual amounts found in commercial polymethyl methacrylate wares ranged from 0.03 to 1.0%; no methyl methacrylate appeared to migrate to water or to 4% acetic acid. In a similar study, migration of methyl methacrylate into 20% ethanol was 1 ppm [1 mg/L] after one day and 10 ppm [10 mg/L] after 90 days at 25 °C (Inoue *et al.*, 1981a,b).

1.3.5 *Tissues and body fluids*

Methyl methacrylate was detected in the saliva of subjects wearing autopolymerized dental appliances at a maximum concentration of 45 μg/ml in whole saliva and 180 μg/ml in the salivary film on the fitting surface. Methyl methacrylate was detected for up to one week after insertion of the appliance. It was not detected in blood or urine and not in dental appliances made from conventionally heat-cured acrylic resins (Baker *et al.*, 1988).

Blood levels of monomeric methyl methacrylate in eight patients during knee replacement operations were 0.10–1.44 μg/ml after tourniquet release. In a ninth patient, an exceptionally high concentration (119.8 μg/ml) was seen immediately after tourniquet release (Svartling *et al.*, 1986). Methyl methacrylate was detected in the blood of patients following use of polymethyl methacrylate bone cement during hip replacement surgery at concentrations ranging from 0.24 to 15.1 μg/ml (Crout *et al.*, 1979).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for methyl methacrylate are presented in Table 5. The US Food and Drug Administration (1993) has established regulations for the use of monomers, polymers, copolymers and homopolymers of methyl methacrylate in products intended for use in contact with food. The monomer content in styrene–methyl methacrylate copolymers used as components of paper and paperboard in contact with fatty foods is limited to 0.5%.

Table 5. Occupational exposure limits and guidelines for methyl methacrylate

Country or region	Year	Concentration (mg/m^3)	Interpretation
Argentina	1991	410	TWA
Australia	1983	410	TWA; sensitizer
		510	STEL
Austria	1982	410	TWA
Belgium	1984	410	TWA
		510	STEL
Brazil	1978	320	TWA
Canada	1986	410	TWA
Chile	1983	328	TWA
Denmark	1988	307	TWA
Finland	1993	410	TWA
		615	STEL
France	1990	410	TWA
		820	STEL

Table 5 (contd)

Country or region	Year	Concentration (mg/m^3)	Interpretation
Germany	1993	210	TWA; sensitizer; local irritant; PR3
Hungary	1978	50	TWA; skin; sensitizer; irritant
		250	STEL
Indonesia	1978	410	TWA
Mexico	1989	410	TWA
Netherlands	1986	410	TWA
Poland	1982	50	TWA
Romania	1975	300	Average
		500	Maximum
Sweden	1991	200	TWA; skin; sensitizer
		600	STEL
Switzerland	After 1987	210	TWA; sensitizer; PR3
		420	STEL
Taiwan	1981	410	TWA
United Kingdom	1992	410	TWA
		510	STEL (10-min)
USA			
ACGIH (TLV)	1994	410	TWA
OSHA (PEL)	1992	410	TWA
NIOSH (REL)	1992	410	TWA
Venezuela	1978	410	TWA
		510	Ceiling

From Cook (1987); Arbejdstilsynet (1988); ILO (1991); US National Institute for Occupational Safety and Health (NIOSH) (1992); US Occupational Safety and Health Administration (OSHA) (1992); American Conference of Governmental Industrial Hygienists (ACGIH) (1993); Deutsche Forschungsgemeinschaft (1993); Institut National de Recherche et de Sécurité (1993); Työministeriö (1993); UNEP (1993)

TWA, time-weighted average; STEL, short-term exposure limit; TLV, threshold limit value; PEL, permissible exposure level; REL, recommended exposure level; PR3, there is no reason to fear a risk of damage to the developing embryo or fetus when exposure limits are adhered to (Group C); skin, absorption through the skin may be a significant source of exposure

2. Studies of Cancer in Humans

2.1 Cohort studies

Following unpublished reports that indicated a significant excess risk for colorectal cancer among employees exposed to both ethyl acrylate and methyl methacrylate, a mortality study was designed at two US plants to investigate whether exposure to methyl methacrylate was associated with an increased cancer risk (Collins *et al.*, 1989). In total, 2671 men (2473 whites and 198 non-whites) who had worked in either plant from their inception (1951 and 1957, respectively) until 1974 were included in the study; 1302 had worked in a plant

manufacturing methyl methacrylate and 1361 in a facility using methyl methacrylate for the manufacture of acrylic fibres; eight men had worked in both plants. The follow-up period was from plant inception to 31 December 1983 and was 98% complete. A job–exposure matrix was developed on the basis of environmental monitoring data and interviews of plant employees in order to characterize the exposure histories of individual workers. In the two plants, 25 and 15 job titles, respectively, were considered to have involved exposure to methyl methacrylate. In the latter plant, all 15 jobs also entailed exposure to acrylonitrile and vinylidene chloride. In the former plant, possible exposure to acrylamide, acrylonitrile, epichlorohydrin and formaldehyde was reported. In both plants, the mean 8-h time-weighted exposure to methyl methacrylate was below 1.0 ppm between 1960 and 1983; reported peak levels were 11.5 ppm in the plant for the manufacture of acrylic fibre and 7.8 ppm in the other facility. Cumulative exposure to methyl methacrylate was calculated for each worker. Information on smoking habits was available from medical records for nearly 60% of the cohort members. The cohort was divided into unexposed (cumulative exposure, < 0.1 ppm-year) and exposed (cumulative exposure, > 0.1 ppm-year). Indirectly standardized mortality ratios (SMRs) and directly standardized relative risks (SRRs) were calculated. SMRs were adjusted by age, period and ethnicity, as were SRRs, which were also adjusted for latency and smoking (smokers, nonsmokers, unknown). The exposed cohort (28 021 person-years) showed significantly decreased mortality from all causes (114 deaths; SMR, 67) and nonsignificantly increased mortality from all cancers (35 deaths; SMR, 104); six deaths from digestive cancer were observed (8.1 expected), one of which was due to cancer of the large intestine (2.6 expected). Cancer mortality was also analysed according to attained cumulative exposure (0, 0–0.19, 0.20–2.0 and > 2.0 ppm-years). For none of the cancer sites was a significantly increasing risk found in parallel with increasing dose.

Walker *et al.* (1991) reviewed and analysed (with some additional new material) all of the data in the original unpublished reports on colorectal cancer and exposure to ethyl acrylate and methyl methacrylate of three cohorts in two US plants. One cohort (I) comprised 3934 white men employed between 1933 and 1945 in a plant where ethyl acrylate production began in 1933 and use of methyl methacrylate in 1936; the second (II) comprised 6548 white men from the same plant who had been hired between 1946 and 1982; the third cohort (III) comprised 3381 white men employed between 1943 and 1982 in another, similar facility where production of acrylic sheet began in 1943. Exposure in the plants was to ethyl acrylate and methyl methacrylate simultaneously, as well as to other agents, including ethylene dichloride, methylene chloride and acrylonitrile. Methyl methacrylate was the most extensively used chemical (88–100%). Exposure of cohort members was estimated on the basis of a job-specific semi-quantitative rating scale, which did not distinguish between ethyl acrylate and methyl methacrylate. In the three cohorts combined, overall mortality for 1933–86 was below that expected on the basis of mortality rates for US white males (4106 deaths observed; SMR, 96). The ratio for deaths from all cancers was slightly increased (924 observed; SMR, 102), as was that for deaths from cancer of the large intestine (99 observed; SMR, 121). Detailed analyses of colorectal cancer mortality were performed for each of the three cohorts. Expected deaths were calculated from the mortality rates of the counties relevant to each plant. Table 6 presents results for those workers classified as having been exposed to methyl methacrylate and ethyl acrylate. Mortality from colon cancer was

significantly increased in cohort I (SMR, 150; 95% confidence interval [CI], 106–205) and nonsignificantly increased in cohort III (SMR, 152; 95% CI, 92–238). The rate for rectal cancer was increased in cohort I (SMR, 192; 95% CI, 92–340). Mortality from cancers of the colon and rectum was further analysed among exposed workers in cohort I (Table 7).

Table 6. Mortality from colon and rectal cancer among workers exposed to ethyl acrylate and methyl methacrylate in two US plants at different periods (see text for definition of cohorts)

Cohort	Colon			Rectum		
	O/E	SMR	95% CI	O/E	SMR	95% CI
I	38/25.4	150		10/5.2	192	
II	7/7.1	99		0/1.3	0	
III	19/12.5	152		1/3.1	32	
Total	64/44.9	143	110–182	11/9.6	115	57–205

From Walker *et al.* (1991); O, observed; E, expected; SMR, standardized mortality ratio; CI, confidence interval

Table 7. Dose–response analysis of risks for colon and rectal cancer among workers in cohort I

Exposure	Colon		Rectum	
	No. of deaths	SMR	No. of deaths	SMR
Achieved exposure score				
≥ 1	38	150	NR	NR
≥ 5	21	146		
≥ 10	13	159		
≥ 15	12	215		
Exposure score ≥ 20 years since first employment				
1–4	13	139	6	252
5–9	6	116	0	0
10–14	1	45	1	185
≥ 15	11	240	3	283

From Walker *et al.* (1991); SMR, standardized mortality ratio; NR, not reported

No regular increase according to years elapsed since first exposure was observed for colon cancer. Analysis by achieved exposure score showed the greatest increase in the category of highest exposure (SMR, 215; 95% CI, 111–376). Analysis by exposure score 20 or more years after first employment did not indicate a consistently increasing risk for either colon or rectal cancer. The risk for colon cancer was highest in the $\geq$ 15 category (SMR, 240; 95% CI, 133–434). Analysis by maximal intensity of exposure also did not reveal an increasing risk with increasing maximal exposure to ethyl acrylate or methyl methacrylate.

2.2 Case-control studies

In the case–control study conducted in Montréal (see the monograph on styrene, p. 258), methyl methacrylate was one of the exposures assessed. The prevalence of exposure was 0.4%. The only cancer site for which there was a significantly increased risk was lung (any exposure: odds ratio, 5.9, 90% CI, 1.7–21; five exposed cases). No significant increase in risk for colorectal cancer was observed (Siemiatycki, 1991).

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Rat: Groups of 25 male and 25 female young Wistar rats were administered 0, 6, 60 or 2000 ppm [mg/L] methyl methacrylate ([purity unspecified] containing 10 ppm monomethyl ether of *tert*-butylhydroquinone to inhibit polymerization) in the drinking-water for two years. At the start of the fifth month of treatment, the 6- and 60-mg/L dose levels were raised to 7 and 70 mg/L. Survival at two years in the control, low-, mid- and high-dose groups was: 13, 18, 15 and 13 males and 16, 18, 18 and 15 females, respectively. No treatment-related increase in the incidence of tumours was reported (Borzelleca *et al.*, 1964). [The Working Group noted the small number of animals and the inadequate reporting.]

3.2 Inhalation

3.2.1 *Mouse*

Groups of 50 male and 50 female B6C3F1 mice, eight to nine weeks of age, were exposed by inhalation to 0, 500 or 1000 ppm [2050 or 4100 mg/m^3] methyl methacrylate (purity, > 99%; containing 10 ppm monomethyl ether of hydroquinone as an inhibitor of polymerization) for 6 h a day on five days a week for 102 weeks. Animals were killed at 113–114 weeks of age. During most of the second year of the study, the mean body weights of treated male mice and high-dose female mice were 10–18% lower than those of the controls. Survival in the control, low-dose and high-dose groups at the end of the experiment was 44, 42 and 47 males and 27, 26 and 33 females. No tumour related to the treatment was found. Alveolar–bronchiolar adenomas and carcinomas (combined) occurred in a significant negative trend in males (control, 11/50; low-dose, 1/50; and high-dose, 4/50; $p = 0.017$, incidental tumour test), as did hepatocellular adenomas and carcinomas (combined) (control,

16/50; low-dose, 7/48; and high-dose, 7/49; $p = 0.043$, incidental tumour test). Pituitary adenomas and carcinomas (combined) occurred at a significant negative trend in females (control, 12/49; low-dose, 3/44; and high-dose, 2/39; $p = 0.004$, incidental tumour test). A dose-dependent increase in the incidence of nasal cavity inflammation and epithelial hyperplasia was observed (US National Toxicology Program, 1986; Chan *et al.*, 1988).

3.3.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, seven to eight weeks of age, were exposed by inhalation to 0, 500 or 1000 ppm [2050 or 4100 mg/m^3] (males) and 0, 250 or 500 ppm [1025 or 2050 mg/m^3] (females) methyl methacrylate (purity, > 99%, containing 10 ppm monomethyl ether of hydroquinone as an inhibitor of polymerization) for 6 h a day on five days a week for 102 weeks. Animals were killed at 111–112 weeks of age. Survival rates in the control, low- and high-dose groups at the end of the experiment were 26, 29 and 28 males and 30, 27 and 29 females. A marginal increase in the incidence of mononuclear-cell leukaemia was observed in female rats (control, 11/50; low-dose, 13/50; high-dose, 20/50; $p = 0.051$, life-table trend test). The historical incidence of mononuclear-cell leukaemia in females exposed by inhalation at the same laboratory was 29.3% (range, 22–36%). In males, significant, dose-related decreases were observed in the incidences of adenomas and carcinomas (combined) of the pituitary gland (control, 24/45; low-dose, 20/47; high-dose, 13/48; $p = 0.004$, incidental tumour trend test) and preputial gland (control, 5/50; low-dose, 4/50; high-dose, 0/50; $p = 0.029$, incidental tumour trend test). A dose-dependent increase in the incidence of nasal cavity inflammation was observed (US National Toxicology Program, 1986; Chan *et al.*, 1988). [The Working Group considered that the marginally increased incidence of mononuclear-cell leukaemia observed in female rats was not biologically significant, as it fell within the range of values seen in historical controls.]

4. Other Data Relevant for an Evaluation of Carcinogenicity and Its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Methyl methacrylate can be absorbed through the skin (Rajaniemi, 1986). Blood levels of monomeric methyl methacrylate were studied in 11 patients after total hip arthroplasty; its elimination was characterized by a biphasic pattern, with a half-life of 0.3 min for the initial portion and 3.0 min for the terminal phase. The peak concentration of the monomer occurred after 1.7–2.0 min (Gentil *et al.*, 1993). A widely different half-life for methyl methacrylate was reported by Svartling *et al.* (1986). The presence of methacrylic acid has been demonstrated in the blood of patients during hip replacement (Crout *et al.*, 1979); and dental technicians exposed to methyl methacrylate excreted 19–200 nmol methacrylate in urine collected over 24 h, pre-shift concentrations being about 10 times lower (Rajaniemi *et al.*, 1989).

4.1.2 *Experimental systems*

A high proportion of methyl methacrylate is fully oxidized in rats: thus, irrespective of whether administration was oral or intravenous, up to 65% of a single dose (5.7 mg/kg bw) of [1,3-^{14}C]methyl methacrylate was expired as $^{14}CO_2$ within 2 h and 84–88% within 10 days. The same pattern of excretion was seen after oral or intravenous administration of [2-^{14}C]methyl methacrylate. Less than 2% of the dose was exhaled as the parent compound and 4–7% remained in the carcass 10 days after treatment (Bratt & Hathway, 1977).

After intraperitoneal injection of methyl methacrylate into rats, a mercapturic acid and a methacrylic acid were identified as metabolites. Only after co-administration of the esterase inhibitor tri-*ortho*-tolyl phosphate was there a strong, significant increase in urinary thioether excretion over that in controls (rising from zero to 11%), showing that hydrolysis by carboxylesterase is an important metabolic route for this substance (Delbressine *et al.*, 1981). The initial rate of pulmonary excretion of $^{14}CO_2$ was the same whatever carbon was labelled, implying that the three propylene carbons are metabolized simultaneously. On this basis, it has been proposed that, following hydrolysis of the parent compound, methacrylic acid complexes with coenzyme A to enter the pathway indicated in Figure 1 in which methylmalonyl coenzyme A, which is also formed in valine catabolism, is converted to succinyl coenzyme A. Hence, all four carbons would enter the citric acid cycle (Bratt & Hathway, 1977).

Formation of formaldehyde from methyl methacrylate via methanol has been observed *in vitro* in the presence of rat liver microsomes as the metabolizing system (Kotlovskii *et al.*, 1988).

Methyl methacrylate is an α,β-unsaturated carbonyl compound which reacts in Michael-type additions with nucleophilic atoms; however, no data are available on adduct formation with proteins or DNA *in vivo*. Although formation of an epoxide metabolite from methyl methacrylate has been predicted (Boyland & Chasseaud, 1970), it has not been demonstrated.

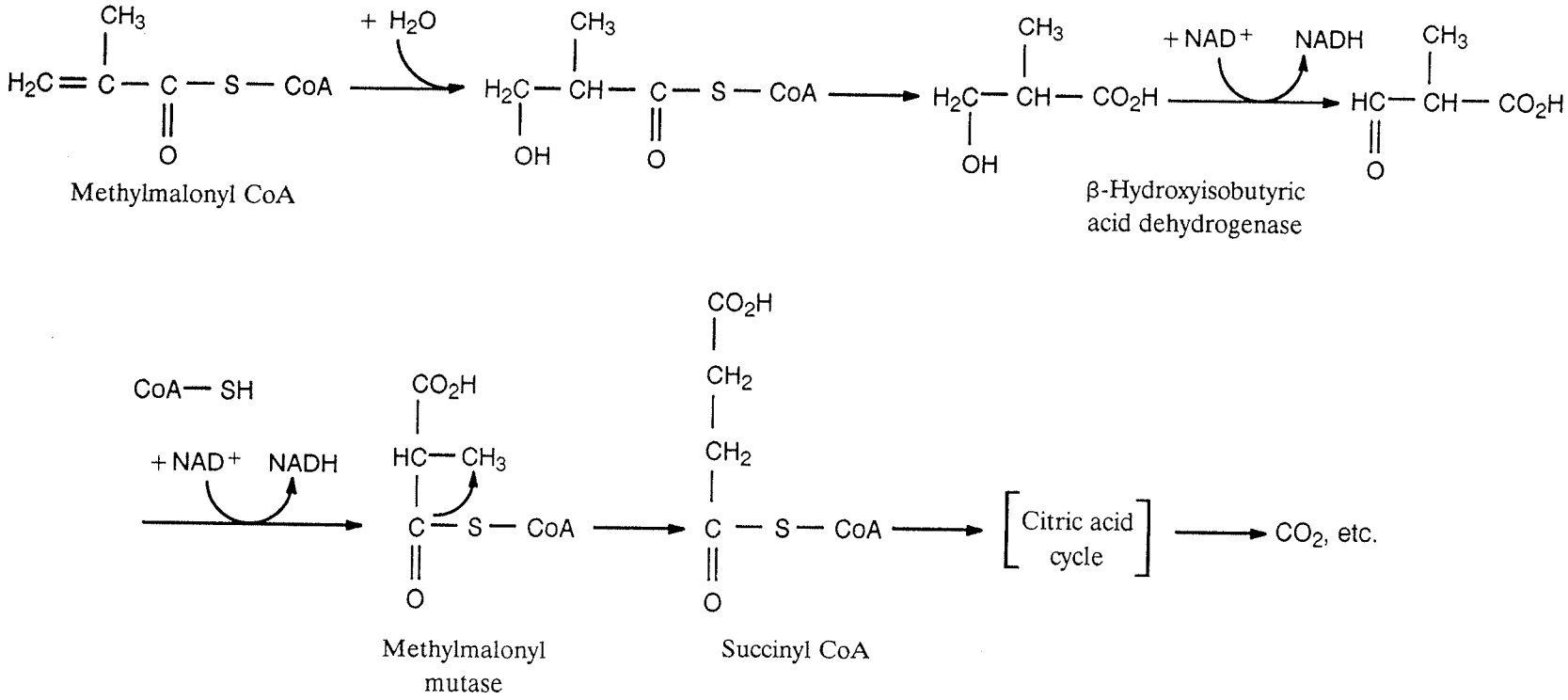
4.2 Toxic effects

4.2.1 *Humans*

Several adverse effects on health have been reported in people exposed either occupationally or during surgery to methyl methacrylate. Among the subjective neurological symptoms described by dental technicians are numbness, pain and whitening of the fingers (Rajaniemi & Tola, 1985). Several other symptoms, including intoxication and loss of appetite, memory and ability to concentrate, have also been reported (Steendahl *et al.*, 1992). Local neurotoxicity, as demonstrated by a significant decrease in distal sensory conduction velocities from the digits (Seppäläinen & Rajaniemi, 1984) and generalized peripheral neuropathy (Donaghy *et al.*, 1991), has also been diagnosed in dental technicians.

Methyl methacrylate is known to cause contact dermatitis (Farli *et al.*, 1990), asthma (Pickering *et al.*, 1986) and effects on the gastrointestinal (Sharova, 1989), cardiovascular (Schuh *et al.*, 1973; Marez *et al.*, 1992) and respiratory systems (Marez *et al.*, 1993). In two groups of workers exposed for up to 26 years to 11–33 and 100–200 mg/m^3 time-weighted

Fig. 1. Scheme for the degradation of methyl methacrylate in mammals



From Bratt & Hathway (1977)

average concentrations of methyl methacrylate, dose-dependent increases in the incidences of neurasthenia, laryngitis and hypotension were reported (Lang *et al.*, 1986).

Interactions of methyl methacrylate with the endocrine system, resulting in altered levels of insulin, somatotropic hormone and prolactin, were thought to be the cause of the adipogenicity observed in female but not male workers (Makarov *et al.*, 1981).

4.2.2 *Experimental systems*

Methyl methacrylate affects the endocrine system in rats (Stepanov *et al.*, 1991), the respiratory system in sheep (Fairman *et al.*, 1984), the cardiovascular system in dogs (Waters *et al.*, 1992) and the nervous system in rats (Husain *et al.*, 1985). Sensitization has been demonstrated in guinea-pigs (van der Walle & Bensink, 1982).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Three groups of five pregnant Sprague-Dawley rats were treated intraperitoneally with 0.13, 0.27 or 0.44 ml/kg bw (0.1, 0.2 or 0.4 g/kg bw) methyl methacrylate on days 5, 10 and 15 of gestation and 43–50 fetuses per group were examined. Significantly reduced fetal body weights were observed in all three groups, and increased numbers of haematomas were seen at various sites in the animals given the two higher doses. No increase in the incidence of skeletal defects was observed (Singh *et al.*, 1972).

McLaughlin *et al.* (1978) exposed 18 ICR mice to 1330 ppm [5453 mg/m^3] methyl methacrylate by whole-body inhalation for 2 h twice daily from days 6 to 15 of gestation, and examined the fetuses on day 18. No adverse effect on the pregnancies or on fetal development was observed. The fetal weights were increased slightly.

Nicholas *et al.* (1979) exposed groups of 22 and 27 pregnant Sprague-Dawley rats to 110 mg/L [26 800 ppm] methyl methacrylate vapour (head only), for 17 and 54 min per day (about 25 and 75% of the time to death of 50% of animals after a single exposure of 72.2 min), respectively, from days 6 to 15 of gestation. The fetuses were examined on day 20 for gross and skeletal malformations only. Both doses were toxic to the dams, as shown by loss of body weight during the first few days of treatment and decreased food intake throughout. The highest dose caused a small but significant increase in early fetal deaths and both doses reduced fetal weight and crown–rump length. The highest dose induced increased incidences of haematomas and retarded ossification.

In a well-conducted study, groups of 27 Crl:CD rats were exposed to 99, 304, 1178 or 2028 ppm [406, 1246, 4830 or 8315 mg/m^3] methyl methacrylate vapour for 6 h per day on days 6–15 of gestation and the fetuses examined on day 20. Transient reduction in body weight gain was observed in all groups of dams, which persisted at the two highest doses throughout the treatment period. No adverse effect on pregnancies, on embryofetal

development or on malformation frequency was observed at any dose level (Solomon *et al.*, 1993).

4.4 Genetic and related effects (see also Table 8 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Methyl methacrylate did not cause gene mutation in the commonly used reversion strains of *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system. A significant response for forward mutation was observed in *S. typhimurium* in the presence of an exogenous metabolic system.

Methyl methacrylate was shown to induce gene mutation, micronuclei and chromosomal aberrations in mouse lymphoma L5178Y cells, and chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells. No sister chromatid exchange was observed in human lymphocytes *in vitro*. [The Working Group noted that both tests were performed with inadequate exposure.]

In vivo, methyl methacrylate was reported to induce chromosomal aberrations in rat bone-marrow cells but not micronuclei in mouse bone marrow cells.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Methyl methacrylate is produced mainly by a process based on the reaction of acetone with hydrogen cyanide. It is an important monomer used mainly in the production of acrylic sheeting, moulding powders and resins and surface coatings. Occupational exposures have been measured during its production and during its use in polymers, as a component of surgical bone cement, in denture fabrication and during the preparation of artificial fingernails.

5.2 Human carcinogenicity data

A large mortality study was conducted of workers in acrylic sheet manufacture in two US plants. A significant increase in mortality from colon cancers was seen in one plant and a nonsignificant increase in the other; a nonsignificant increase in mortality from rectal cancer was found in the first plant. The increases were most evident among workers employed during the earliest production period and in jobs entailing the highest exposure. Exposure was predominantly to methyl methacrylate, but workers were also exposed to ethyl acrylate and to volatile by-products of the polymerization process.

Another US study examined the mortality of workers employed in methyl methacrylate manufacture and polymerization and found no significant increase in the number of cancer deaths.

Table 8. Genetic and related effects of methyl methacrylate

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAF, *Salmonella typhimurium* TM677, forward mutation (8-*aza*^{r})	–	+	5000.0000	Poss *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Lijinsky & Andrews (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000.0000	Hachitani *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2300.0000	Waegemaekers & Bensink (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Lijinsky & Andrews (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2300.0000	Hachitani *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000.0000	Waegemaekers & Bensink (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1700.0000	Zeiger *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Lijinsky & Andrews (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2300.0000	Hachitani *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000.0000	Waegemaekers & Bensink (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1987)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Lijinsky & Andrews (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2300.0000	Hachitani *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5000.0000	Waegemaekers & Bensink (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Lijinsky & Andrews (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2300.0000	Hachitani *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000.0000	Waegemaekers & Bensink (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	1700.0000	Zeiger *et al.* (1987)
G5T, Gene mutation, mouse lymphoma L5178Y cells *in vitro*, *tk* locus	+	0	2200.0000	Doerr *et al.* (1989)

Table 8 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G5T, Gene mutation, mouse lymphoma L5178Y cells *in vitro*, *tk* locus	+	0	2000.0000	Moore *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells *in vitro*, *tk* locus	+	+	250.0000	Myhr *et al.* (1990)
G5T, Gene mutation, mouse lymphoma L5178Y cells *in vitro*, *tk* locus	+	+	500.0000	Dearfield *et al.* (1991)
MIA, Micronucleus formation, mouse lymphoma L5178Y cells *in vitro*	(+)	0	2200.0000	Doerr *et al.* (1989)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	16.0000	Anderson *et al.* (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	(+)	1600.0000	Anderson *et al.* (1990)
CIM, Chromosomal aberrations, mouse lymphoma L5178Y cells *in vitro*	(+)	0	2200.0000	Doerr *et al.* (1989)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	?	0	0.1000	Cannas *et al.* (1987)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	-	0	0.0000	Bigatti *et al.* (1989)
MVM, Micronucleus formation, mouse bone-marrow cells *in vivo*	-		4500×1 ip	Hachitani *et al.* (1981)
MVM, Micronucleus formation, mouse bone-marrow cells *in vivo*	-		1100×4 ip	Hachitani *et al.* (1981)
CBA, Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		1300×1 ip	Fedyukovich & Egorova (1991)
CBA, Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		650×2/wk, up to 8 wk	Fedyukovich & Egorova (1991)

[a] +, positive; (+), weak positive; -, negative; 0, not tested; ?, inconclusive (variable response within several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

5.3 Animal carcinogenicity data

Methyl methacrylate was tested for carcinogenicity in one experiment in mice and one experiment in rats exposed by inhalation. No significant treatment-related increase in tumour incidence occurred. One study in rats by oral administration was inadequate for evaluation.

5.4 Other relevant data

Methyl methacrylate can be absorbed through the skin and is rapidly metabolized in man. In rats, it is first hydrolysed, and the dominant metabolic pathway is to fully oxidized carbons which are exhaled as carbon dioxide; a very small proportion is excreted as thioethers in the urine. Methyl methacrylate produces a number of toxic effects in man and experimental animals.

Exposure of mice and rats to methyl methacrylate by inhalation had no adverse reproductive effects.

No data were available on the genetic and related effects of methyl methacrylate in humans.

It caused chromosomal aberrations in rat bone marrow but did not induce micronuclei in mouse bone marrow *in vivo*. Gene mutation, sister chromatid exchange, micronuclei and chromosomal aberrations were induced in mammalian cells *in vitro*. Methyl methacrylate did not cause reverse gene mutation in bacteria but induced forward gene mutation in *Salmonella typhimurium* in a single study in the presence of an exogenous metabolic activation system.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of methyl methacrylate.

There is *evidence suggesting lack of carcinogenicity* of methyl methacrylate in experimental animals.

Overall evaluation

Methyl methacrylate *is not classifiable as to its carcinogenicity to humans (Group 3).*

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[1]For definition of the italicized terms, see Preamble, pp. 27–30.

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