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DEC and NEG Basis for an Occupational Health Standard:

Methyl methacrylate

M. A. Maclaine Pont

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NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

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Preface

An agreement has been signed by the Dutch Expert Committee for Occupational Standards (DEC) of the Dutch Directorate-General of Labour and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities both in the Netherlands and in the Nordic Countries.

This document on health effects of methyl methacrylate was prepared by Dr M. A. Maclaine Pont at the Wageningen Agricultural University, The Netherlands, and was reviewed by the Dutch Expert Committee as well as by the Nordic Expert Group.

J. J. Kolk
Chairman
Dutch Expert Committee

P Lundberg
Chairman
Nordic Expert Group

Contents

1. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, MONITORING

1.1 IDENTITY

(73)

Chemical name:	methylmethacrylate
Chemical substance prime name:	2-propenoic acid, 2-methyl, methylester
CAS registry number:	80-62-6
Synonyms:	acrylic acid, 2-methyl-, methylester
	methyl-alpha-methylacrylate
	methyl-2-methyl-2-propenoate
	2 methyl-2 propenoic acid methyl ester
	"monocite" methacrylate monomer

Methylmethacrylate (MMA) is a clear, colourless, flammable liquid with an unpleasant strong acrid odour (61, 65, 76).

1.2 PHYSICAL AND CHEMICAL PROPERTIES

(42, 48, 65, 73, 96, 97)

Molecular formula	: $C_5H_8O_2$
Structural formula	: $H_2C = \underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}} - \overset{\displaystyle O}{\overset{\displaystyle \|}{C}} - O - CH_3$
Molecular weight	: 100.13
Boiling point (100 kPa)	: 100 - 101° C
Melting point	: - 48° C
Vapour pressure (20° C)	: 3.87 kPa
Relative density of the saturated vapour in the air (20° C, 100 kPa, air = 1)	: 1.09
Vapour percentage in saturated air (20° C, 100 kPa)	: 3.8 %
Density of the liquid (25° C) (water = 4° C)	: 0.9440

Flash point (tag open cup)	: 13° C (48) 10° C (65)
Explosion limits in air (20° C, 101 kPa)	: 2.1% - 12.5 %
Solubility in water	: slightly soluble, 1.5 g/100 ml
in alcohol	: very soluble
in ether	: very soluble
Azeotrope	: 14% water (B.P. = 83° C)
Log $P_{oct/w}$	: 1.38 (84)
Odour threshold: detection	: between 0.2 and 0.62 mg/m^3 air
recognition	: between 0.85 and 1.9 mg/m^3 air (36, 37)
Conversion factors (20° C, 100 kPa)	: 1 ppm = 4.16 mg/m^3 1 mg/m^3 = 0.24 ppm

The chemical properties are defined by its very reactive double binding. The monomer is readily polymerized by light, heat, oxygen, ionizing radiation and catalysts (61) because of its ability to form a radical or anion. Polymerisation is an exothermic reaction and can be accelerated by the use of initiators (such as hydrochloric acid). In order to prevent polymerisation a small amount of hydroquinone or its monomethylether is added. Poly methyl methacrylate (PMMA) is inert (65).
Addition to the double bond of water, alcohol, acids, ammonium, amine, H_2S, mercaptane, etc., takes place to form iso-butyric acid-esters (96). MMA is soluble in methyl ethyl ketone, tetrahydrofuran, esters, aromatic and chlorinated hydrocarbons (98).

1.3 ANALYTICAL METHODS

1.3.1 Environmental monitoring

NIOSH (58) analytical method:
A known volume of air is drawn through a tube containing XAD-2 resin. MMA is desorbed with carbon disulfide (CS_2). An aliquot of the sample solution is injected into a gas chromatograph (GC) equipped with a flame ionization detector (FID).
This method was validated over the range of 193-725 mg/m^3 and an

atmospheric pressure of 762 mm Hg using a 3-liter sample volume.
This method was to be revised by June, 1986 (59).
In view of the advised MAC value a lower detection limit must be strived for.
An alternative GC-method for the determination of MMA in working atmosphere is presented by Kollár et al (49). Using this method, MMA can be determined with withdrawing tubes and passive dosimeters.
Both types are packed with activated carbon GA-I. As extractive agent CS_2 with 5 vol % of isopropyl alcohol is used. MMA is determined with GC/FID. The limit of detection under the recommended conditions is 0.8 mg/m^3.

Methacrylates have also been analyzed by thin-layer chromatography (TLC), polarography and colorimetry (48).
MMA can also be analyzed by high performance liquid chromatography (HPLC) and gel-permeation chromatography (GPC) (48).
Methods have been developed for determination of methacrylates in mixtures with other monomers, in solvents including water, in biological fluids and in polymers.

1.3.2 Biological monitoring

There is no validated method to analyse MMA in biological material.

2. SOURCES OF EXPOSURE

2.1 NATURAL OCCURRENCE

MMA is not known to occur as a natural product (42).

2.2 MAN-MADE SOURCES

2.2.1 Production

The most common way to synthesize MMA is by conversion of acetone cyanohydrin with concentrated sulfuric acid (H_2SO_4), methanol and water. Acetone cyanohydrin is mixed with H_2SO_4 (mol ratio 1:1.5) in a cooling reactor by intensive stirring at 80-100° C. Then the reaction product is heated to 130-150° C and the resultant methacrylamide sulfate is mixed with methanol and water at 90° C to form the crude product, which is contaminated with volatile organic compounds. The product is purified by destillation (42, 96) giving a commercial product that is at least 99.6% pure (99.8% in the United States according to (61) and 99.95% according to (96). The impurities are: methacrylic acid, 0.003% max; water 0.05% max; it may contain a small amount of hydroquinone and its monomethylether as inhibitors (42).

The monomer MMA can be recaptured from the polymer through thermal depolymerisation (cracking) at 350-400° C (96). The polymer is nontoxic (65).

In 1975, three companies in the United States produced 248 million kilograms and Japanese companies produced 114 million kilo-grams MMA. Western European countries produced 220 million kilograms in 1976 (42).
The production came to ca. 750 x 10^3 kilograms in the Western world in 1977 at a production capacity of 1.1 million ton/year (96). In 1976 the Netherlands imported 0.57 million kilograms MMA from the United States (42).

2.2.2 Uses

MMA is primarily used in the manufacturing of PMMA to fabricate crystal-clear or coloured plastics, the so-called acrylic glasses (Plexiglass, Lucite, Perspex and Altuglass), clear ceramic-like resins, and for acrylic moulding and extrusion powder (12, 65).
Western European use of MMA in 1976 was in the production of PMMA (80%), paints (9.5%), acrylic emulsions (3%) polyvinyl modifiers (3%), fibres (2%) and unsaturated polyester resins (0.5%)(42).
In the U.S. approximately 20% of the compound is used to produce copolymers that act as coating binders in acrylic surface coatings, such as latex paint and lacquer (12).
The monomer is also used in the manufacture of emulsion polymers such as floor polishes, textile backing coatings, paper coating, sealants, and adhesive cements (42).

The monomer and polymers have wide applicability in medical technology.
MMA serves as a medical spray adhesive or non-irritant bandage solvent. It is also used to coat corneal contact lenses (65) and to manufacture artificial nails (14).
In orthopaedic surgery it is used as bone cement for fixation of metal and plastic prostheses (76) and to fill space in bones (61).
MMA is also used in neurosurgery and surgery of the jaw (7).

To prepare prostheses and orthopaedic devices, a mixture of MMA with prepolymerized oligomers is used, that has to be finished with the preparer's bare hands to obtain the desired dimensions before the final hardening. This is also the case in dentistry where MMA-based material is specifically employed in removable dentures, orthodontic appliances, occlusal bite planes and splints, veneer crowns, tooth coloured fillings, and the pit and fissure sealants (77).

Dental and orthopaedic use of MMA differ from industrial applications. Generally, the latter do not require manual handling of monomer containing products (69).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 ENVIRONMENTAL LEVELS

3.1.1 Water

MMA has been detected in U.S. drinking water with minimum concentrations of <1.0 µg/l (90). In New Orleans MMA was identified in Commercial Deionized Charcoal Filtered water (26). It could have originated from the plastics used somewhere in the preparation or storage of the ion exchange resins or charcoal (42).

MMA has also been detected in plant sewers, waste water (61) and in U.S. river water (42).

3.1.2 Food

Residual MMA has been detected in commercial polystyrene plastics at a concentration of 36 mg/kg (42), but no information is available about the migration of MMA from plastics to food.

3.1.3 Air (Ambient)

(from: 42)

Total emission of MMA to the ambient air in the U.S. in 1974 was estimated by the U.S. Environmental Protection Agency to be 3.6-million kilograms.

The sources and amounts were: MMA production, 1.7 million kg; end-product manufacture, 1.7 million kg; bulk storage 0.2 million kg.

In one study in Europe, during the drying of paints based on acrylic resins emissions of MMA were estimated to range from 139-563 g/hour. In air exhaust stacks of paint plants the concentrations of MMA were estimated to range from 20-81 mg/m^3. This is only a fraction of what has been found during the drying of paints.

MMA has been detected as a gaseous product of the combustion of PMMA.

3.2 HUMAN EXPOSURE

3.2.1 General population

MMA has been found in the tissues of patients receiving "bone cement" in dental or orthopaedic surgery; concentrations as high as 0.7-5.1 wt% has been found in the fatty components of bone marrow (no further details) (cited in 12).

MMA may be set free from dental fillings even up to 6 days after polymerization (7).

3.2.2 Occupational population

Groups exposed to MMA are: workers in the plastic industry, laboratory technicians and health profession personnel, who are concerned with the manufacture of prostheses, contact lenses and cosmetic products, and with the application of coatings for cellulose and textile fibres, glass and rubber (22).

In 1974, the U.S. National Institute for Occupational Safety and Health (NIOSH) estimated that 30,000 workers in the U.S. were exposed to MMA (42). However, in 1983 a NIOSH national occupational exposure survey estimated that 128,962 workers were exposed to MMA, of which 58,565 were female (74).

In a study of exposure at five plants manufacturing PMMA sheets, the mean eight-hour TWA exposure ranged from 16-300 mg/m^3, and the TWA highest exposure for workers examined medically was 100-200 mg/m^3 (42).

Preparation of impression trays, occlusal splints and orthodontic appliances, moulding and repair of prostheses exposes dental technicians, dentists and auxiliary personnel possibly to a higher extent to MMA, because they have to handle it with their bare hands (70).

Darre et al (21) evaluated the air concentrations of MMA emitted from seven commercially available bone cements, during mixing and setting. Measuring time equalled mixing time and was 40-60 sec. The air concentrations (mean of three experiments) ranged from 1770 to 2940 mg/m^3 for the various brands. When stirred for 4 min. the MMA concentration was 3450 mg/m3.

The concentration of MMA vapour in an operating room was measured at four time intervals during three total hip-replacement procedures by McLaughlin et al (54). Acrylic cement Simplex P was used which contained MMA, 97.4%; N,N-dimethyl-p-toluidine, 2.6%; and hydroquinone (75 ± 15 ppm).

Results:

When mixing of the cement started: 832-1170 mg/m^3;

two minutes after mixing started: 230-420 mg/m^3;

six minutes after mixing begun: <42 mg/m^3.

When the cement hardened in the patient: <42 mg/m^3.

Manicurists exposure to MMA during preparation of artificial fingernails has been measured by Froines and Garabrant (32) in eight nail shops, each of which employed 2 to 17 manicurists. Results are given in Table 1.

Table 1. Exposure of manicurists to MMA during preparation of synthetic nails (32).

nail shop	number of measurem.	mean intermittent exposure (mg/m^3)[a]	number of measurements	mean continuous exposure (mg/m^3)[b]
1	2	148 ± 41[c]	2	23 ± 11
2	2	82 ± 20	5	8.7 ± 2.9
3	6	129 ± 29	7	19 ± 5
4	2	198 ± 147	5	20 ± 5
5	4	65 ± 20	4	19 ± 5
6	2	38 ± 20	7	10 ± 3
7	5	94 ± 60	23	28 ± 3
8	2	74 ± 6	6	25 ± 8
overall	25	84 ± 16	59	22 ± 2

a. Intermittent exposure corresponds to exposure to MMA during the actual periode of use of MMA.
b. Continuous exposure is the 8-hour TWA.
c. Mean exposure ± S.E.

The mean intermittent exposure to MMA ranged from 38 to 198 mg/m^3, with an average of 84 mg/m^3. Peak exposures, the highest single maximum level observed during a procedure, ranged from 64 to 570 mg/m^3 with an average of 223 mg/m^3. The 8-hour TWA-exposure to MMA ranged from 8.7 to 28 mg/m^3, with an average of 22 mg/m^3.

4. GUIDELINES AND STANDARDS

4.1 GENERAL POPULATION

No data available.

4.2 OCCUPATIONAL POPULATION

(2, 4, 16, 24, 40, 62, 72, 75, 83).

Country	concentration	interpretation
Denmark	307 mg/m^3 (75 ppm)	MAC-TWA
Finland	410 mg/m^3 (100 ppm)	MAC-TWA
Germany, Fed. Rep.	210 mg/m^3 (50 ppm)	MAK,I*, S**,C***
Great Britain	410 mg/m^3 (100 ppm)	OEL-TWA
	510 mg/m^3 (125 ppm)	STEL
Iceland	410 mg/m^3 (100 ppm)	MAC-TWA
The Netherlands	410 mg/m^3 (100 ppm)	MAC-TGG
Norway[1)]	100 mg/m^3 (25 ppm)	MAC-TWA
Sweden[1)]	200 mg/m^3 (50 ppm)	MAC-TWA
	600 mg/m^3 (150 ppm)	STEL
USA	410 mg/m^3 (100 ppm)	TLV-TWA

* peak limitation category I = local irritants
peak = 2 * MAK
duration: 5 min, momentary value
frequency per shift: 8

** danger of sensitization (S): higher than normal number of sensitivities

*** Pregnancy group (C): there is no reason to fear risk of damage to the developing embryo or foetus when MAK and BAT values are adhered to.

1) notation for skin absorption and sensitisation.

5. TOXICOKINETICS

5.1. ABSORPTION

After inhalatory exposure MMA can be absorbed through the lungs.
No study is available which explicitly deals with absorption.
After dermal exposure MMA can be absorbed through the skin.
Dermal absorption has been studied both in laboratory animals (rats) by Verkkala et al (91) and in occupationally exposed workers (dental technicians) by Rajaniemi et al (71).

Absorption through rat tail was rather high and amounted to 22 $mg/cm^2/hr$.

After human dermal absorption the urinary MMA excretion ranged from 19 to 200 nmol MMA/24 hr (1.9 - 20 µg/24 hr). Without exposure these dental technicians excreted either 6 - 30 nmol MMA/-mmol creatinine or N.D. (less than 0.5 nmol/l). Persons who were never exposed to MMA excreted less than 15 nmol MMA/mmol creatinine.
Only a limited number of volunteers (n = 11) was studied and no quantitative data on exposure were available.
Urine samples were collected after what was considered a normal working day: the estimated time that there was manual contact with the liquid monomer varied from 30 minutes to four hours. As a control a preshift sample was taken and urine was also taken from 10 unexposed persons. The manual contacts were probably scattered over the working period, as there was no consistent pattern in the highest urinary methacrylate concentration in relation to the time of the day. The highest concentration ranged from 16 to 373 nmol MMA/mmol creatinine. It is concluded that the large variation probably reflects differences in exposure rather than differences in metabolism.
Four volunteers had dermatitis, but the urinary MMA correlated poorly with it. Five volunteers used protective gels or creams, but the authors state that this provided only partial protection.

Because no exposure data are available the only quantitative

conclusion that can be drawn from the study by Rajaniemi et al (71) is that MMA excretion after human dermal exposure is two to seven times higher than before exposure.

Verkkala et al (91) measured the dermal absorption in a quantitative way.
Five male Wistar rats had 12 cm^2 of their tails exposed for 3 hr to liquid MMA (occlusive method, evaporation was negligible). After the exposure the amount absorbed was assayed by weighing the cotton wool pad before and after the test and amounted to 0.78 ± 0.20 g.
Although the method is rather crude and can lead to gross overestimation, this study gives at least an indication of the quantity of MMA absorbed.

5.2 DISTRIBUTION

MMA is distributed rapidly over the body and quantitatively excreted within 24 hr.
There is only one study which explicitly deals with distribution kinetics.
This study (from 1973, described in (7), the original publication was not available) showed that 5 min. after i.v. injection of radioactive MMA in Wistar rats the highest activity was found in blood and kidney. Low concentrations were found in liver and red bone marrow. After 2 hr the total activity had decreased and a shift from the bone marrow to the compact bone could be observed. In the period from 4 to 8 hr, activity was found only in skeletal bones, liver, intestine and salivary glands. After 24 hr, total injected MMA was eliminated. No further quantitative data are available.
However, it should be noted that the biotransformation studies referred to in the next section also indicate that MMA is rapidly distributed over the body, irrespective of the route of administration.

5.3 BIOTRANSFORMATION

MMA is readily biotransformed in the species studied sofar.

The biotransformation of MMA has been studied in detail. The most frequently reported study is the one by Bratt and Hathway (11), who demonstrated in rats that MMA is metabolised through the same pathway as the naturally occurring amino acid valine, irrespective of the route of administration (intravenously or orally by gavage).

The process is visualised in Figure 1.

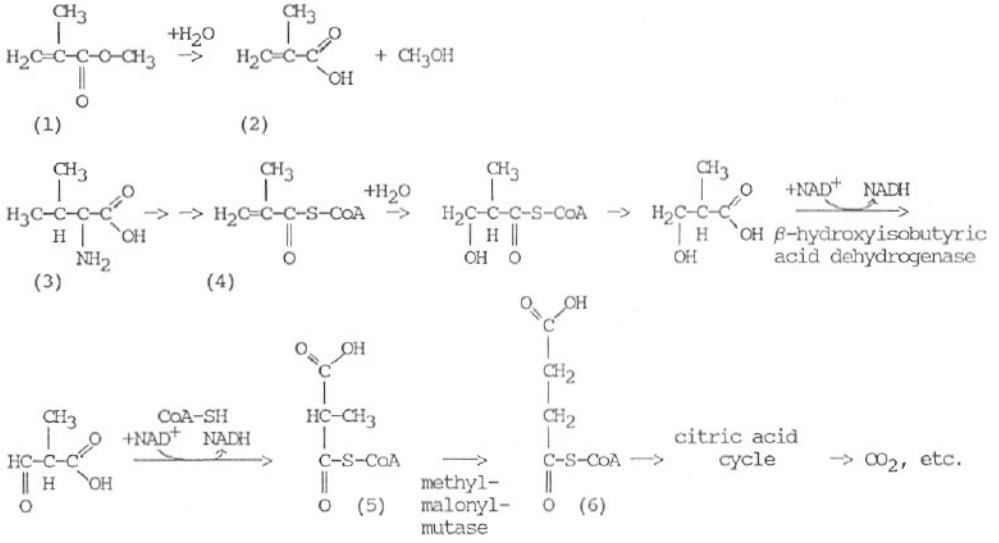

Figure 1. Scheme for the degradation of MMA in mammals (11, 19). Compound 1 = MMA, compound 2 = methacrylic acid, compound 3 = valine, compound 4 = methylacrylyl-CoA, compound 5 = methylmalonyl-CoA, compound 6 = succinyl-CoA.

The first step is hydrolysis of MMA (compound 1 in the Figure) by carboxylesterase into methacrylic acid (compound 2) and methanol. Both methacrylic acid and valine (compound 3) are metabolised into methylacrylyl-CoA (compound 4), which can be further degraded and taken up in the citric acid cycle.

The main data originate from the abovementioned study in rats, who

expired up to 88% of a single dose of ^{14}C-MMA as $^{14}CO_2$ in 10 days, irrespective of the route of administration (11). About half the remainder of the dose was excreted in the urine and the rest was retained by the body tissues. Pulmonary excretion of unchanged MMA accounted for less than 1.0% of the dose.

These results are confirmed by the study by Crout et al (19) who injected two rats i.p. with radiolabeled MMA.

Bratt and Hathway (11) also found several of the intermediates of the degradation pathway in the urine, excreted by exposed rats, among them ^{14}C-methacrylic acid (0.8% of the dose), ^{14}C-methylmalonic acid (1.4% of the dose) and ^{14}C-succinic acid (0.2% of the dose).

Crout et al (19) found a somewhat higher percentage as radioactivity in the urine: 14.5 and 7% (data of two rats).

These data in experimental animals are confirmed by studies in humans.

The formation of methacrylic acid from MMA was found **in vitro** (17) and **in vivo** (20, 82).

In vitro the half life time of MMA was 20-40 min, as was measured in serum obtained from ten volunteers (17).

In vivo the half life time of MMA was 47-55 min, as was measured in serum of nine patients who underwent total knee arthroplasty (82).

MMA does not change the hepatic cytochrome P-450 level quantitatively, however, it may induce some qualitative changes. This was found after i.p. injection in mice (57) and rats (30).

When high dosages of MMA are administered, the enzymatic route of hydrolysis of MMA is saturated and detoxification occurs via glutathione conjugation. Thioether excretion increases. Also when carboxylesterases are blocked the thioether excretion increases.

Thioether excretion after massive dosing was studied by Elovaara et al (30), thioether excretion after blocking the carboxylesterase pathway was studied by Delbressine et al (21) and depletion of GSH and GSSH after massive dosing was studied by Boyland and Chasseaud (10) and Elovaara et al (30). Further, the excretion of intermediate products was assessed in a vitamin B12-deficient individual (19).

A single i.p. dose of 2 g MMA/kg in rats increased the thioether excretion up to 11 times that of control. Urine collected from 12 to 24 hr after the injection still contained 8 times more thioethers than control. In the same experiment three i.p. injections (one per day) of 1 g/kg in the rat did not increase thioether excretion (30).

Blocking the carboxylesterase pathway with tri-o-tolyl phosphate (TOTP) increases the thioether excretion even when low dosages of MMA are administered.

Delbressine et al (22) injected rats i.p. once with 0.14 mmol MMA/kg (14 mg/kg) without and with previous adminstration of TOTP (0.34 mmol/kg). The thioether excretion increased from 11 to 27 µmol/24 hr, corresponding with 0 and 11% of the dose.

Concurrent with this excretion depletion of hepatic GSH levels was found. Two studies in rats are available. Boyland and Chasseaud (10) found a hepatic GSH level of 92% of the control 30 min after i.p. injection of 0.87 ml/kg (821 mg/kg). After 2 hr the GSH level was 68% of the control.

The second study used a higher dosage, which induced as a consequence a larger depletion: a single i.p. dose of 2 g/kg in rats decreased the hepatic GSH level to 20% of the control after 3 hr. The GSSH level was decreased to 50% of the control.

Depletion in the kidney was less dramatic: after 3 hr the renal GSH level was 48% of the control while the GSSH level did not change (30).

When other steps in the degradation pathway of MMA are blocked, intermediate products can be found in the urine. For instance,

When other steps in the degradation pathway of MMA are blocked, intermediate products can be found in the urine. For instance, patients with vitamin B12 deficiency (the conversion of methylmalonyl-CoA (compound 5) into succinyl-CoA (compound 6) is blocked) will excrete large amounts of methylmalonic acid. This was found in one vitamin B12-deficient individual, who received as a treatment 1 mg of vitamin B12 monthly. An oral dose of 94 mg [Me-$^{2}H_3$]-MMA resulted in the next 24 hr in 1029 µg [Me-$^{2}H_3$]-methylmalonic acid, detected in the urine, representing approximately 1% of the administered dose (19).

5.4 ELIMINATION

As already mentioned in section 5.3, elimination of MMA is rapid and complete. After hydrolysis of MMA and subsequent conjugation with Coenzyme A, the degradation follows the same pathway as the amino acid valine (see Figure 1).

Within 2 hr 65% of the administered dose was expired as $^{14}CO_2$ by rats, irrespective of the route of administration. After 10 days 88% of the dose was expired (11). Detailed information on the various excretion products are presented in Table 2.

Table 2. Excretion and retention of radioactivity in rats after administration of methyl-[^{14}C]methacrylate (11)

			Recovery of ^{14}C (% of dose)*					
					Exhaled gases			
Form of ^{14}C label	Route of administration	Dose (mg/kg)	Urine	Faeces	$^{14}CO_2$	Unchanged [^{14}C] MMA	Carcass plus skin	Total
Methyl[1,3-^{14}C]-propylene-2-carboxylate	By stomach tube [a]	5.7	4.7	2.7	88.0	0.1	4.1	99.6
	i.v. [a]	5.7	6.6	1.7	84.0	0.7	6.6	99.6
Methyl[2-^{14}C]-propylene-2-carboxylate	i.v. [a]	6.8	7.2	1.8	84.1	1.0	6.6	100.7
	By stomach tube	120.0	6.0	3.0	76.4	1.4	b—	

* 10 days after administration
a The data displayed are representative of that obtained in several animals.
b Unmeasured.

two rats. After 4 hr ca. 72% and after 24 hr ca. 85% of the dose was recovered as $^{14}CO_2$. The percentage of radioactivity recovered in the urine was 14.5 and 7%.

The half-life time of MMA in blood in vitro at 37° C lies in the range of 20 - 40 min (independent of age or sex, n= 10). The initial concentration was 10 µg/ml (17).
The in vivo half life time was 47 - 55 min. MMA was measured in central venous blood of nine patients undergoing total knee arthroplasty. The highest concentraton ranged from 0.10 to 1.44 µg/ml (82).
Even after high exposures, that is, when MMA polymerises into poly-MMA for the fixation of prostheses in orthopedic surgery, MMA and methacrylic acid were only detected in blood, not in urine. Concentrations MMA ranged from 0 to 15 µg/ml, for methacrylic acid it ranged from 0 to 6.1 µg/ml (20).

5.5 BIOLOGICAL MONITORING

Although MMA is rapidly metabolised, low levels can be found in the urine after exposure to relatively high concentrations. Unexposed persons excrete less than 15 nmol MMA/mmol creatinine. No quantitative data are available on the relationship between exposure and internal or excreted dose (71).
Methylmalonic acid is a degradation product of MMA. It is normally excreted in the urine in very small amounts and is often below the limit of detection. When MMA is metabolised through hydrolysis the concentration of methylmalonic acid rises, but is still very low.
In GC systems it is usually eluted with a retention time identical, or almost identical to that of 3-hydroxy-3-methylbutanoic acid (β-hydroxyisovaleric acid), with which it may easily be confused (19).

5.6 SUMMARY

MMA is absorbed through the skin by experimental animals and humans. Absorption through rat tail amounted to 22 mg/cm^2/hr, measured with a method which can easily lead to overestimation. No quantitative data are available on human absorption. In humans urinary excretion of MMA after exposure is two to seven times higher than before exposure.

Irrespective of the route of administration MMA is rapidly distributed over the body and quantitatively excreted within 24 hr.

MMA is metabolised through the same pathway as the amino acid valine.
The first step is hydrolysis by carboxylesterase into methacrylic acid and methanol.
The in vitro half-life time of MMA is 20 - 40 min (measured in human blood) and the in vivo half-life time is 47-55 min (measured in surgical patients).
High doses of MMA saturate the enzymatic hydrolysis and MMA is conjugated to glutathione. GSH depletion occurs mainly in the liver and to a lesser extent in the kidneys and thioethers are excreted in the urine. A single dose of 2 g/kg i.p. injected into rats increased the thioether excretion.
Blocking the carboxylesterases also increases the thioether excretion, even when low dosages of MMA are administered.
In the case of vitamin B12 deficiency methylmalonic acid is excreted in the urine, which amounted to approximately 1% of the administered dose in one person.

Elimination of MMA is mainly by expiration of CO_2.
In rats within 2 hr 65% of the administered dose is expired, within 10 days 88% is expired, irrespective of the route of administration.
About half the remainder of the dose is excreted in the urine and the rest is retained by the body tissues. Pulmonary excretion of unchanged MMA accounted for less than 1.0% of the dose.

6. EFFECTS

6.1. ANIMAL EXPERIMENTS

6.1.1. Irritation and sensitisation

IRRITATION

The dermal irritation potency of MMA appears to be low, as can be concluded from a number of studies with rabbits, guinea pigs and rats.

The rabbit data on skin and eyes are from Spealman et al (80). Symptoms in the eye are inflammation and oedema, returning to normal after 72 hr. On the skin MMA caused fleeting and mild irritation. In all cases 100% MMA was used.

The dermal irritation for Freund Complete Adjuvant (FCA) pretreated guinea pigs was low. The maximum non-irritating concentration was undiluted MMA (95).

Some indirect evidence for a low dermal irritation potency for guinea pigs can be derived from the high concentrations used in the sensitisation tests. The concentrations used ranged from 50% (in 70% ethanol) (33) to 100% (34).

Finally some indication for low dermal irritation for rats is found in a study which was primarily aimed as a dermal absorption experiment (see section 5.1). Three hr of occlusive exposure of 100% MMA daily for 8 weeks caused keratolysis without ulcerations in rat tail (46, 91).

A polymerising MMA product, rubbed in daily for 2 min during four weeks on the backs of 14 rabbits induced erythema (2 animals), erosions (3 animals), ulcerations (5 animals), crusts (7 animals) and desquamation (3 animals). It is not clear whether the compound was removed after the rubbing-in. Although the process of polymerisation is exothermic, this does not cause the toxic effects. A less severe testing scheme induced less toxic effects in intensity and extent. However, a possible allergic component could not be excluded (81).

SENSITISATION

There is some evidence that MMA may cause sensitisation in experimental animals.

Gad (34) induced sensitisation in guinea pigs using the Guinea Pig Maximisation Test (GPMT). The incidence was 30% when 100% MMA was used for induction and 5% for challenge.

The GPMT was also used by Van der Walle et al (95). For induction either 0.5 M (= ca. 6% w/w) and 1 M or 0.5 M and 100% MMA were used. Challenge was with 100% MMA. The incidence of sensitisation was resp. 20 and 30%. The test with FCA yielded a sensitisation percentage of 25%.

Another study failed to induce sensitisation in guinea pigs (64). Five different immunisation methods were used, among them the GPMT. In all cases 0/6 animals were sensitised, probably because of low dosages (ranging from 0.2 to 10%).

Sensitisation in mice was induced with a new type of test when using 50% MMA for induction and challenge. The incidence was 44%. This test, the Mouse Ear Swelling Test (MEST), compares the thickness of the treated ear with the untreated ear (33).

However, Dunn et al (28) evaluated the MEST again and in this case none of the 14 mice responded when 50% MMA was used both for induction and challenge. The same strain of mice was used as by Gad et al (33) and two laboratories with prior MEST experience performed the experiments. Dunn et al (28) considered their own outcome false negative and concluded that the MEST is not reliable for detecting weak to moderate contact allergens.

No sensitisation was observed in the rat, in a study on dermal absorption (46).

6.1.2 Acute toxicity

The acute toxicity of MMA is low. Only after i.v. or i.p. administration the LD50 was lower than 1000 mg/kg.

According to the classification and labelling guidelines of the E.C. (29) there is no need to label MMA as a dangerous compound.

In rats and mice death is preceded by hypoactivity, dyspnoea and anaesthesia (61). Older data also mention a fall in blood pres-

sure, irregular respiration, lacrimation, defaecation, urination, followed by respiratory failure and cardiac arrest (5).
Brain research in the rat indicated that exposure to 1664 ± 83 mg MMA/m^3 for 1 hr depressed the electrical activity in several areas of the brain. This loss of activity can be an explanation for the often heard complaints of loss of appetite by persons occupationally exposed to MMA (44).

Data on the acute toxicity of MMA are presented in Tables 3 and 4.

Table 3. Oral, i.v., s.c., dermal and i.p. toxicity of MMA

Species	Parameter	Value (mg/kg)	Reference
Mouse	oral LD 50	5296	51
	oral LD 50	5200	84
	s.c. LD 50	5950	80
	i.v. LD 50	297	23
	i.p. LD 50	940	80
	i.p. LD 50	1120	50
	i.p. LD 50	1130	51
Rat	oral LD 50	9440	80
	oral LD 50	7800	42
	oral LD 50	8000	1
	oral LD 50	8500	23
	oral LD 50	>7550 - <15100	51
	s.c. LD 50	7080	80
	s.c. LD 100	12300	7
	i.p. LD 50	1700	80
	i.p. LD 50	1250	78
	i.p. LD 50	2640	51
Rabbit	oral LD L0	6550	42
	oral LD 50	6000	1
	dermal LD 50	> 7550	51
	dermal LD 50	> 9440	5
	dermal LD 50	> 10,000	65
Guinea Pig	oral LD 50	5950	80
	s.c. LD 50	5950	50
	i.p. LD 50	1890	80
Dog	oral LD 50	4720	80
	s.c. LD 50	4250	80

Table 4. Toxicity of MMA after acute inhalatory exposure

species	exposure	parameter	effects	reference
mouse	5 hr (47700 mg/m^3)	9/15 †	Depression, liver degeneration, hepatitis and focal necrosis	80
	3 hr (96400 mg/m^3)	20/20 †	Depression, liver degeneration, hepatitis and focal necrosis	
	3 hr (61800 mg/m^3)	15/15 †	Depression, liver degeneration, hepatitis and focal necrosis	
	3 hr (26200 mg/m^3)	1/20 †		
	3 hr (55000 mg/m^3)	LC 50	Depression, liver degeneration, hepatitis and focal necrosis	
	13000 mg/m^3	LC Lo		3
	56 min (115000 mg/m^3) (by blowing)	LT 50		51
	26.95 min (164000 mg/m^3) (by bubbling)	LT 50		51
	4 hr (4955-19269 mg/m^3)	all lived (n=60)		61
	4 hr (66560 mg/m^3)	10/10 †	No compound related effects (hypoactivity, dyspnoea, anaesthesia) were observed at necropsy	61
Rat	4 hr (4955-19269 mg/m^3)	all lived (n=10)		61
	4 hr (66560 mg/m^3)	9/10 †	No compound related effects (hypoactivity, dyspnoea, anaesthesia) were observed at necropsy	61
	4 hr (29500 mg/m^3)	LC 50		86
	2 hr (50000 mg/m^3)	LC 50		23
	8 hr (15000 mg/m^3)	LC 50		65
	72.2 min (110800 mg/m^3)	LT 50		56
Rabbit	4 1/2 hr (17500 mg/m^3)	LC Lo		65
Guinea Pig	4 1/2 hr (72100 mg/m^3)	6/6 †	CNS Depression, liver degeneration	80
	5 hr (19000 mg/m^3)	LD Lo	Liver degeneration and focal necrosis	23
Dog	3 hr (41200 mg/m^3)	2/2 †	CNS Depression, excessive salivation, irritation, liver degeneration and tubular degeneration in kidney	80
	1 1/2 hr (72100 mg/m^3)	2/2 †		

6.1.3 Short-term toxicity

After inhalatory exposure to MMA local effects in nose, respiratory tract and fur and systemic effects on lung, liver, kidney and gastrointestinal tract have been observed.
After oral administration of high dosages behavioural changes have been observed.

INHALATORY EXPOSURE

MMA can exert local effects in nose and respiratory tract (mice and rats). A remarkable feature is that an effect on fur (rats) is reported. No explanation is given. MMA can exert systemic effects like dyspnoea, liver and kidney degeneration, lung damage and a reduction in gastrointestinal activity (several animal species).

Local effects

Redness and swelling of the nasal region was found in mice, when exposed to 20800 mg/m^3, 6 hr/day with 10 exposures in 11 days. Nasal effects do not occur in rats with the same exposure regimen or in mice at lower dosages.
With three months exposure MMA was able to induce nasal effects in rats. From 12480 mg/m^3 and higher for males and from 8320 mg/m^3 and higher for females, with intermittent exposure, inflammation occurred in the nasal cavity associated with necrosis and loss of olfactory epithelium.
After three months of exposure all mice had metaplasia of the nasal epithelium even at the lowest dose tested: 2080 mg/m^3 (500 ppm) (61).
Longer exposure regimens induce damage in the tracheal mucosa. Cilia and microvilli were absent in rats, when exposed to 482 mg/m^3 (116 ppm), 7 hr/day, 5 d/week for 6 months (88).

Systemic effects

The main systemic effects found are dyspnoea, liver and kidney degeneration, fibrosis and oedema in the lung and a decrease in gastrointestinal motility.

Dyspnoea was found in mice when exposed to 20800 mg/m^3, 6 hr/day with 10 exposures in 11 days (61).
Liver degeneration, described as swollen cells with altered nuclei, was found in guinea pigs, when exposed to 65500 mg/m^3, 3 hr/day for 3 days (80).
Liver and kidney degeneration was found in dogs, when exposed to 46800 mg/m^3 either ℓ hr/day for 15 days or 1ℓ hr/day for 8 days (80).
The lowest concentration inducing possible liver damage in rats was 482 mg/m^3, when exposed for 7 hr/day, 5 d/week for 3 months. However, these changes were apparently unrelated to dose or time (87).
Lung fibrosis and oedema was found in rats when exposed to 4160 mg/m^3, 8 hr/day for 7 days (88). The fibrosis is a remarkable observation since this develops only slowly. It is therefore doubtful, whether the diagnosis was correct.
Changes in blood chemistry were within the range of normal variation in rats when exposed either to a high concentration for a short period (4160 mg/m^3, 8 hr/day for 7 days) (88) or to a lower concentration for a longer period (482 mg/m^3, 7 hr/day, 5 d/week for 3 months) (87).
No systemic effects were observed in male and female rats, when exposed intermittently for 3 months to resp. 4160 mg/m^3 and 2080 mg/m^3. At 4160 mg/m^3 and higher female rats showed a dose-related increase in brain lesions (malacia (softening) and gliosis (hyperplasia of the neuroganglia)).
Both male and female mice did not show any systemic effects when exposed to 4160 mg/m^3, with the same dosing regimen. At 8320 mg/m^3 and higher male mice showed a dose-related increase in renal lesions (cortical necrosis, cortical tubular degeneration and/or focal mineralisation). Also the liver showed necrosis (61).
A reduction in gastrointestinal activity was observed in some studies in rats and dogs. However, the only studies mentioning this phenomenon are by Tansy and coworkers. This activity consists mainly of retrograde peristalsis and segmental contractions and therefore a decrease results most of the time in an increase in

faecal production.
Exposure to 480 mg MMA/m^3, 7 hr/day, 5 d/week for 3 months decreased the small intestinal transit performance, as was measured by quantifying faecal production. However, only in weeks 7, 10 and 11 faecal excretion was significantly increased compared to the control rats. Faecal production was normal during the days without exposure (87).
Also in vitro the intercontractile interval of the duodenum was increased in rats exposed to "near TLV values" (ca. 410 mg/m^3), 7 hr/day, 5 d/week for 10 days. No quantitative data are given (89).
On the other hand the NTP study (61) did not mention anomalous intestinal activity, exposing rats and mice for 1, 10 or 11 days, 3 months or 2 years.
Further consolidation of the effect on gastrointestinal activity is necessary.

ORAL EXPOSURE

Administration by gavage of MMA did not significantly increase the incidence of forestomach mucosal cell proliferation and hyperkeratosis in rats. MMA was administered at 100 and 200 mg/kg, 5 d/week for 2 weeks to groups of 8 male F344 rats (38).
Behavioural changes were observed when rats received 500 mg/kg by gavage daily for 21 days. Adult male Wistar rats showed impaired locomotor activity and increased aggressiveness. Analysis of a separate batch of rats indicated an increase in biogenic amines in several parts of the brain. The level of biogenic amines may be related to the behavioural changes observed. No effect on behaviour was observed at dosages of 100 and 200 mg/kg (41).

6.1.4 Long-term toxicity/carcinogenicity

No evidence for carcinogenicity have been found in the animal species studied sofar, after inhalatory or oral administration.

INHALATORY EXPOSURE

There is no evidence that inhalatory exposure of MMA causes an increase in neoplasms in rats, mice, Syrian Golden hamsters or

dogs.
Two studies have been reported. One (79) communicate in abstract form the negative findings in rats, hamsters and Beagle dogs. Male and female F344 rats and Syrian Golden hamsters were exposed to 0, 104, 416 or 1664 mg/m^3, 6 hr/day, 5 d/week for 24 and 18 months, resp. Male Beagle dogs were exposed to 0, 416 or 1664 mg MMA/m^3, 6 hr/day, 5 d/week for 3 months. Gross and histopathologic evaluations were made after exposures of 3 months to dogs, 18 months to hamsters and 3, 12 and 24 months to rats. With the exception of mild rhinitis in rats, no exposure-related effects were observed.
The second study was carried out within the framework of the National Toxicology Program and a detailed report has been prepared (61).
Groups of 50 male F344/N rats and 50 B6C3F1 mice of both sexes were exposed to 0, 2080 or 4160 mg/m^3, 6 hr/day, 5 d/week for 102 weeks. Groups of 50 female F344/N rats were exposed to 0, 1040 and 2080 mg/m^3 on the same schedule.
Survival rates of the treated animals were similar to those of their respective controls. After several weeks on study body weights were reduced (up to 19% reduction compared to control), but returned to normal from week 89 onward. Upon necropsy an extensive histopathological examination was performed on all animals. No compound-related neoplastic lesions were found in treated mice or rats. The increased incidence of mononuclear cell leukaemia in high dose female rats was not significant.
Treatment-related effects observed were found in the nasal region: inflammation of the nasal cavity and degeneration of the olfactory epithelium in mice and rats; in mice epithelial hyperplasia of the nasal cavity was also observed. The lesions are described in more detail by Chan et al (12). No other effects were seen.

ORAL EXPOSURE

No evidence for carcinogenic activity of MMA was found in rats and dogs after oral dosing for two years.
One study is available (8).
Groups of 25 male and female Wistar rats received 0, 6, 60 and

2000 ppm MMA in their drinking water 7 days/week. At the start of the fifth month the low and medium levels were raised to 7 and 70 ppm, resp. These levels in drinking water were calculated as equivalent to a dietary intake of ca. 14.3, 137 and 3360 ppm in the food for females and 12.2, 115 and 3210 ppm in the food for males.

Groups of 2 male and 2 female Beagle dogs received daily by gavage 0, 10, 100 and 1000 ppm MMA, calculated as dietary equivalent. The high dose was increased to 1200 ppm at 5 weeks, to 1400 ppm at 7 weeks and to 1500 ppm at 9 weeks and for the rest of the study. After two years both rats and dogs were sacrificed. In rats and dogs mortality, organ-to-body-weight ratio, haematologic values and urine concentrations of protein were within normal limits for all groups. Two exceptions: the elevated relative kidney weight in high dose female rats is not further explained and the lower relative spleen weight in middle dose dogs were not considered of biological significance.

Extensive histopathology showed no treatment-related abnormalities or lesions in both rats and dogs.

The negative findings in the dogs after oral and inhalatory exposure are equivocal because the dosing of dogs was not lifetime, neither was the moment of observation at the end of the dog's life. Moreover, the number of animals used was small.

CONCLUSION

Under the conditions of the 2-year inhalation studies by NTP, there is no evidence of carcinogenicity of MMA for male F344/N rats exposed at 2080 or 4160 mg/m^3, for female F344/N rats exposed at 1040 or 2080 mg/m^3, or for male and female B6C3F1 mice exposed at 2080 or 4160 mg/m^3.

The only treatment-related effects found were lesions in the nose, which were still present at the lowest concentration tested (1040 mg/m^3, intermittent exposure) in female rats.

Furthermore, there is no evidence of carcinogenicity of MMA for Syrian Golden hamsters, inhalatory exposed at 104, 416 or 1664 mg/m^3 for 18 months. There is no evidence of carcinogenicity of

MMA for Wistar rats after dosing 6, 60 and 2000 ppm in drinking water for two years.

6.1.5 Mutagenicity

MMA is not mutagenic for bacteria. In high dosages, MMA induces clastogenic effects and SCEs in mammalian cells **in vitro** both with and without metabolic activation.

The data are summarized in Table 5.

The positive results were only obtained at low survival rates (ca. 10%). Moreover, Moore et al (55) noted that not all cultures treated with > 2,000 µg/ml showed a positive response. For that all, the concentrations used in th test are so high, that in reality they do not constitute a hazard.

However, in most, if not all, MMA samples hydroquinone is present as an inhibitor of spontaneous polymerisation. Hydroquinone can induce SCEs in mammalian cells in vitro with and without metabolic activation. Hydroquinone induces chromosomal aberrations only after metabolic activation (35). The quantitative results are presented in Table 6.

Table 6. Mutagenic data for hydroquinone tested in Chinese hamster ovary cells (35)

	conc. tested	results	LEC[1] (µg/ml)
SCE NA	0.5-5 µg/ml	+	< 0.5[2]
RLI	50-800 µg/ml	+/+[3]	50/600[3]
ABS NA	5-20 µg/ml	-	20
RLI	150-600 µg/ml	+	450

1) Least effective concentration tested (LEC) is the lowest dose to give a statistically significant increase ($p < 0.05$) in aberrations or a 20% increase in SCEs.
2) Lowest dose tested gave a positive response
3) Individual trial results (separated by "/")
ABS = aberrations

If 100 ppm of hydroquinone, which is very much, would have been added to MMA, there would be only 0.5 µg/ml hydroquinone in a

Table 5. Mutagenic and genotoxic data

Type of test	species	conc. tested	remarks	result	ref
Ames	Salm. typh. TA1535, TA1537, TA1538, TA98, TA100 NA[1]	< 10,000 µg/plate		—	61
Ames	" NA	40-10,000 µg/plate	MMA was diluted in DMSO; addition of 2 µg hydroquinone or p-methoxyphenol to positive control plate did not influence the response of TA100	—	93
	RLI[2]			—	
Ames	Salm. typh. TA100, TA1535, TA1537, TA98 NA	10-10,000 µg/plate	Solvent: DMSO; purity of MMA > 99%	—	99
	HLI[3]			—	
	RLI			—	
Ames	Salm. typh. TA100, TA1535, TA97, TA98 NA	33-6,666 µg/plate	Solvent: DMSO; purity of MMA > 99%	—	99
	HLI			—	
	RLI			—	
Ames	NA	33-6,666 µg/plate	Solvent: DMSO; 6,666 µg/plate was slightly toxic to all species	—	61
	HLI			—	
"	RLI			—	
mutation	L5178Y TK +/- mouse lymphoma NA	118-944 µg/ml	4 hr treatment	+	61
	RLI			+	
clastogenic	L5178Y TK +/- mouse lymphoma NA	1,000-3,100 µg/ml	4 hr treatment; solvent DMSO; 10 ppm methylhydroquiwas added; small colony formation, TFT resistant mutants, gross aberrations, ≥ 2000 µg/ml induced a positive response	+	55
clastogenic	Chinese hamster ovary cells NA	750-3,000 µg/ml	there was a slight dose-related increase in chromosomal aberrations	+	61
clastogenic	Chinese hamster ovary cells RLI	160-5,000 µg/ml	Increase of frequency of aberrations only at the highest, near-lethal dose	+	61
induction of SCEs	Chinese hamster ovary cells NA	50-1500 µg/ml	there was a dose-related increase	+	61
	RLI			+	

1) NA = not activated
2) RLI = rat liver activated
3) HLI = hamster liver activated

sample of 5000 µg MMA/ml. From the study described above it can not be concluded that hydroquinone is not the causing factor of the positive results of the mutagenicity tests with MMA. On the other hand Moore et al (55) stated that NTP found a concentration of 0.62 µg/ml of hydroquinone to be negative. Additional tests have to be performed to exclude possible mutagenicity by hydroquinone.
However, in view of the negative findings in the carcinogenicity studies the genotoxic activity of MMA may be less relevant.

6.1.6 Reproduction toxicity and teratogenicity

MMA can increase the number of resorptions in rats after inhalatory exposure, and can induce gross abnormalities in rats after i.p. administration or inhalatory exposure. A decrease in foetal body weight and foetal crown-rump length and delayed ossification could also be found in rats (four studies).
In mice no effects have been found at the dosing regimens used (two studies).

Inhalatory studies in rats were performed by Nicholas et al (56), Luo et al (53) and DFG (23).
Nicholas et al (56) exposed groups of 22 - 27 pregnant Sprague Dawley rats to 112000 mg/m^3 for 17.2 min or for 54.2 min per day on Gestation Days (G.D.) 6 - 15. The dosing induced a decrease in food consumption and maternal weight. Both groups had a decreased foetal body weight and foetal crown-rump length, and delayed ossification of the sternebrae. The high dose exposure group had haematomas and delayed ossification of the vertebrae.
Luo et al (53) exposed groups of pregnant rats to 520 or 4480 mg/m^3 for 2 hr once every three days on G.D. 6 - 18. No maternal toxicity was observed. In both groups delayed ossification occurred, in the high concentration exposure group an increase in resorptions was observed.
DFG (23) describe a study in which groups of pregnant rats were exposed to 104, 416 or 4160 mg MMA/m^3, 5 hr/day on G.D. 6 - 15. The highest concentration level increased the number of resorp-

tions. No effects were found on embryos or foetuses at the middle dose.
Unfortunately the original study was not made available by the company. Therefore it is not possible to judge the data in detail.

One study with intraperitoneal exposure in rats is available (78). The dosages represented 0.1, 0.2 and 0.33 of the i.p. LD50. Groups of 5 pregnant Sprague Dawley rats were i.p. injected with 125, 250 or 418 mg/kg on G.D. 5, 10 and 15. The two highest dosages increased the number of gross abnormalities (haemangiomas) in the foetuses.

The two studies in mice are from McLaughlin et al (54) and Tansy and Kendall (85). Both use the inhalatory route.
Exposure to 464 or 1664 mg/m^3, 6 hr/day on G.D. 4-13 did not induce teratogenicity or an increase in resorptions (85, dosing regimen is described in 23).
McLaughlin et al (54) exposed a group of 18 pregnant ICR mice to 5530 mg/m^3, 2 x 2 hr/day on G.D. 6 - 15. No maternal or foetal toxicity was observed. The foetal weight in the treated group was slightly increased compared to control.

CONCLUSION

From the available data it is clear that MMA may cause reproductive effects. Mice are less sensitive to the reproductive effects of MMA than rats.
In rats, maternal toxicity can be observed at high exposures (112000 mg/m^3, with daily exposures for 17.2 or 54.2 min per day on G.D. 6-15). At lower dosages (4480 mg/m^3, for 2 hr once every three days on G.D. 6-18) an increase in resorptions and delayed ossification occur.
A NAEL can be derived from the DFG study, which used a dosing regimen compliant with intermittent exposure in the occupational setting. No effects were observed at 416 mg/m^3 (5 hr/day, G.D. 6-15). However, since the step from the middle dose to the next dose tested was very large the NAEL lies between 416 and 4160 mg/m^3.

6.2 OBSERVATIONS IN MAN

6.2.1 Irritation and sensitisation

GENERAL

MMA can be irritating to skin, eyes or mucous membranes and can cause allergic dermatitis or stomatitis. Apparently man is more sensitive in this respect than the animal species tested. The allergic dermatitis is characterised as itching, with erythema, oedema and vesiculation followed by eczema and unique and consistent paresthesia. In some cases tenderness is observed outlasting the duration of the eruption (7).

CASES OF INDIVIDUALS EXPOSED TO MMA

In total 9 cases are described in 7 studies (14, 46, 47, 52, 60, 68, 76).
The overall conclusion is that MMA can be irritating to the skin, eyes and mucous membranes; in some individuals it can cause asthmatic and sensitisation reactions.
The case studies can be summarised as follows.
With reference to the occupation:
Eight of the nine cases developed symptoms while mixing bone cement and one manufactured, applied and painted artificial nails and wore artificial nails herself. Three of the eight cases were dental technicians, three theatre sisters and two female nurses.
With reference to the symptoms:
Dermal allergy developed in the woman handling artificials nails (14), in two dental technicians (46) and two female nurses (47).
In the two dental assistants dermatotoxic and neurotoxic effects were observed in biopsies from positive patch tests.
Asthmatic reactions were observed in one dental technician (52) and one theatre sister (68).
The two remaining cases developed rather unusual symptoms which cannot be well explained: one theatre sister developed a corneal

ulcer (60) and one theatre sister developed bifrontal headache, a sensation of heaviness in arms and legs, light-headedness and a sense of extreme lethargy (76).
With reference to the exposure levels:
Only in three cases the air levels of MMA were measured. The study by Pickering et al (68) was the most elaborate one. The results are described in Table 7.

Table 7. Environmental MMA vapour concentrations (mg/m^3) resulting from mixing of polymeric cement on open trolley (68)

time (sec)	Procedure	conc. of MMA (mg/m^3)
0	Breakage of phial	0
15	Addition of liquid cement	520
30	Mixing	1140
45	Mixing	1560
60	Mixing	680
75	Spoonful of cement removed from bowl	520
105	Bowl cleaned out	330

The peak concentrations of MMA occurred during the first 90 seconds of mixing. Although the time weighted average did not exceed the TLV of 410 mg/m^3, brief but repeated exposure to high peak concentrations of MMA occurred.
Very low levels of MMA were measured in the two unusual cases (the corneal ulcer and the CNS symptoms), they were in the order of 2 to 6 mg/m^3 (60, 76).
For the cases with dermal allergy the air levels of MMA are less relevant. The handling of a polymerising MMA product with bare hands implies exposure to varying concentrations of MMA. MMA can even penetrate through one or two layers of latex gloves. It seems that only butyl rubber gloves are of value to prevent penetration of MMA (47).

SURVEYS OF GROUPS EXPOSED TO MMA

The irritative properties of MMA to the skin are well-known.

Allergic reactions are also frequently described, although the incidence varies. The description of the symptoms is not always unambiguous, hindering therefore the diagnosis.
Repeated contact with MMA, frequent hand washing and occlusive exposure enhance the skin reactions.
Six surveys on groups of persons exposed to MMA or a polymerising product have been performed: two studies used questionnaires (30, 69) and four studies used the patch test (6, 14, 67 and one is described in 7).
Further one study patch tested MMA on unexposed medical students (81).
Furthermore, the passage of MMA through gloves was studied by Pegum and Medhurst (66) and by Waegemaekers et al (93).

The frequency of the dermal allergic and irritation reactions as found in the seven studies is summarised in Table 8a and b.

dermal allergy

The larger studies show an incidence of 2 to 15%. Exposure is either occupational or non-occupational: dental technicians handle the polymerising product with their bare hands and patients with poly-MMA dentures come into contact with residual monomer.
The high incidence of allergic reactions found in the other studies is probably due to selection of the test group (7, 15) or due to the use of 100% MMA as a test solution (80).
The allergy is described as a contact dermatitis with erythema and itching.

dermal irritation

Dermal irritation varies from ca. 18% in occupationally exposed persons (31, 69) to 1 - 50% when patch tested with various solutions of MMA (6, 80). The symptoms are described as contact eczema, dermatitis or mild erythema.

Table 8a: Summary of the frequency of dermal reactions found in group surveys, materials and methods

reference; surveyed group	type of test	number of persons	occlusive exposure
31 dental technicians	questionnaire	106	no (98%)
69 dental technicians	questionnaire	202	no (81%)
7 handlers of bone cement in operation theatres	patch (10% sol.)	13	yes
15 sealants in car factory, engineering and electronic industry	patch (10% sol.)	6	no
67 suspected allergy to dentures	patch (30% sol.)	132	yes
6; suspected allergy to dentures	patch (10 and 1% sol.)	199	yes
80 medical students	patch (undil.)	50	no exposure

Table 8b, results

dermal irritation		dermal allergy	
frequency	symptoms	freqency	symptoms
19% (n = 20)	irritant contact eczema	15% (n = 16)	atopic dermatitis
17% (n = 34)	dermatitis	2% (n = 4)	not described
	not described	54% (n = 7)	contact dermatitis (itching erythema, oedema)
	not described	50% (n = 3)	contact dermatitis
		3% (n = 4)	not described
1 and 2% (n = 2 and 4)	not described	2.5 and 5% (n = 5 and 10)	not described
50% (n = 25)	mild erythema	20% (n = 10)	erythematous, itching areas

respiratory allergy

No allergic respiratory reactions have been described in groups as a result of exposure to volatile MMA. The two cases of asthmatic reactions found in (52) and (68) are described in the section on case studies.
The only remark referring to respiratory allergy is that persons with a skin disease during childhood or with previous asthma, allergic rhinitis or conjunctivitis report a higher rate of acrylate-associated dermal problems than other subjects (69).

penetration through gloves

In order to prevent dermal contact with MMA, the use of gloves is advised.
The disadvantages of the use of gloves are: hindered manual handling and, depending on the material of which the glove is made, penetration of MMA followed by occlusive exposure.
MMA penetrated disposable rubber gloves (66) and 5 latex, 1 polystyrene-butadiene and 1 polychlorobutadiene gloves (92).
A better protective material is urgently needed.

6.2.2 Acute toxicity

No data have been found.

6.2.3 Short-/long term exposure

The main effects of MMA concern the CNS (32, 63; further a Russian study, described by 42, 44, 61; several other Russian studies are described by 23).
Secondly, occupational contact to MMA decreases the nerve conduction velocity locally (70, 77).

The CNS disturbances found in the abovementioned studies are described as headache, pain in the extremities, nausea, loss of appetite, fatigue, sleep disturbances, irritability and loss of memory. Other symptoms described (summarised in 23) are changes in

blood parameters and in lipid, hormone and iodine metabolism. The dose range was either very wide (2 to 208 mg/m^3), incompletely given, or not given. Therefore, no dose-response relationship can be established. Furthermore, in most cases no control groups were included.
The only study with some information on exposure is the one by Pagniano et al (63). Vapour concentrations were measured when 147 dental students were constructing acrylic trays containing MMA. The concentrations of MMA vapour ranged from 6.7 to 68.2 mg/m^3 (environmental monitoring; 6 sampling times during 5 hr). A control group was not included. Survey results showed that the most prevalent symptoms were of transient nature and consisted of headache (53%), dizziness (51%), and sinus irritation (36%). These were followed, in decreasing order, by irritation to skin, loss of concentration, breathing difficulty, hunger, nausea, coughing, irritation to eyes and tachycardia.
Froines and Garabrant (33) measured the exposure to MMA in nailshops (see Table 1, section 3.2.2), but did not link these data with the CNS complaints of the manicurists.

The nerve conduction velocity was measured in a group of dental technicians selected from a questionnaire study by Rajaniemi and Tola (69). The results are described in two studies (70, 77). Nineteen cases had complained of neurological symptoms like coldness, numbness, whitening or pain in the finger exposed to MMA. The study group consisted either of 20 or 15 right-handed subjects. An age-matched control group was also tested.
The sensory conduction velocities of finger nerves of the dominant hand were slower both when the exposed group was compared with the control group and also when within the exposed group the dominant hand was compared with the non-dominant hand.
The decrease was correlated with the feeling of numbness. These findings are considered to represent mild axonal degeneration on the areas with the closest and most frequent contact with MMA. Frank axonal neuropathy was suspected only in two cases. The neurophysiological findings did not correlate with current der-

matitis; however, they were more common among those with a longer and/or heavier exposure.

6.2.4 Epidemiological studies

From the described epidemiological and long-term studies it can be concluded that CNS-symptoms and dermal problems are common complaints of people working with MMA. Changes in several blood parameters are also reported. However, a dose-response relationship cannot be established.

In the mortality studies no excess was found in all-cause or cause-specific mortality. Only with exposure to high levels of MMA in combination with high levels of ethylacrylate and by-products of the polymerisation process an increase in colon cancer was found.

Four studies are available: two mortality studies (13, 94), and two on CNS-symptoms and changes in blood parameters (18, 42).

IARC (42) described a report (the original is not available) on 152 workers exposed for years to 2 - 200 mg MMA/m^3. Hundrednineteen complained of headache, 45 noted pain in the extremities, 32 showed excessive fatigue, 32 had sleep disturbances, 30 had loss of memory and 25 showed irritability. A majority of workers had been employed for 10 or more years. DFG (23) report about this study that the authors also observed an increased leucocyte count and a trend towards erythrocytosis with macrocytosis, a change in K - Ca ratio and a change in cholinesterase-activity in the majority of the 152 workers. These data are from a Russian study, no more data are available.

The study by Cromer and Kronoveter (18) falls apart in two studies: a screening and a comprehensive survey.

In the screening survey employees were studied of 27 establishments (which varied from monomer production and lens manufacturing facilities to dental laboratories) for health effects potentially resulting from exposure to MMA vapours. MMA concentrations are specified from each job category, and lie between < 20 mg/m^3 and

≤540 mg/m^3 TWA 8 hr (two personal air samplers were used in 8 hr). From approximately 350 questionnaires returned (of the 552) it could be seen that the complaints, primarily referable to MMA exposure were eye and upper respiratory tract irritation, headache, light-headedness (a feeling of being high), and skin rash or burn. These symptoms usually occurred during MMA spills, when levels of MMA were likely to be high. The prevalences of complaints referable to the cutaneous (19%), respiratory (30%) and urogenital systems (25%) were noteworthy, although respiratory complaints came nearly all from individuals who had a history of smoking. No control group was present for comparison. With reference to the genitourinary complaints the authors mention that these data come from self administered questionaires, often lacking in pertinent detail. Moreover, lack of exposure data make these findings tenuous.

Subsequent evaluation focussed on these indicative complaints.

A group of 67 of these MMA exposed workers and 61 controls underwent three serial complete blood cell counts over a several years period. No differences were noted in haemoglobin levels or differential count values. A significant difference ($p < 0.002$) was noted in mean white blood cell count values: mean value of 8.44 x $10^3/mm^3$ for exposed, and 7.78 x $10^3/mm^3$ for nonexposed.

On the basis of the screening survey a comprehensive survey was carried out at five cast sheet manufacturing facilities. Although the authors suggested that effects in several blood parameters and on the CNS occur after exposure to MMA, especially in the job categories with higher exposure, the following imperfections in study design prevent the establishment of a dose-response relationship:

- In one of the sheet plants both MMA and ethylacrylate were within measurable quantities; in all plants a large variety of additives was used in small amounts. No remark was made what the effect is of combined exposure; it was stated that the predominant exposure is to MMA.
- Of a total of 169 workers in the five plants 91 cooperated in

the survey. The group with the highest exposure (four distillers, mean exposure 366 mg/m^3) did not volunteer for the study. Further, no information is given which persons in what job category withdrew from the survey.

- The 91 persons were divided into four groups, according to exposure level. In group one were combined the persons which were currently exposed to less than 21 mg/m^3 and those with less than 2 months of exposure. These two groups are in fact incomparable and therefore cannot be combined. Together with the three other exposure groups (two current and one past exposure group) the division leads to a small number of persons per exposure group, therefore the increase in effects found is not statistically significant. No mention is made what job category is represented in each exposure group.
- The control group, which was not different from the exposed groups concerning age, sex, race or smoking history, consisted in one case of 43 persons, in other cases of 41 or 35 persons. Further, in each group several persons did not volunteer for the blood tests.
- Environmental monitoring at the various work areas by means of personal air sampling (sampling time between 4.7 and 7.2 hr) revealed a large variation in exposure and a high standard deviation. Furthermore, apart from the group of four distillers, in two of the four factories the group of mold fillers was the highest exposure group, and in the other two factories the group of mix men was the highest exposure group. For the fifth plant only the total number of employees was given. Therefore, a classification into exposure groups according to job category was impossible.

Collins et al (13) studied the mortality pattern in a group of 1561 workers exposed to MMA. Exposure estimates ranged from 0 to 48 mg/m^3 (mean: 0.5 to 4 mg/m^3). Twohundredthirtyseven death certificates were evaluated: 123 from the non-exposed group and 114 from the exposed group. No statistically significant excess was found in all-cause or cause-specific mortality. However, due to

the low exposure concentrations MMA-associated deaths are not expected.

Walker et al (94) studied the mortality from cancer of the colon and rectum in three cohorts exposed to ethyl acrylate and MMA. The cohorts worked in 1933-1982 in two plants manufacturing and polymerising acrylate monomers. In the early years ethylacrylate was used in a quantity of 12% of the polymerising mixture. From 1943 on changes in the production methods resulted in a decline to zero in the use of ethylacrylate in acrylic sheet production. Therefore, it can be concluded that MMA and not ethylacrylate is the risk factor.
The three cohorts consisted of 2524, 6548 and 3381 men. The cohorts were analysed in three ways. One divided the workers in four cumulative dose groups. The other used a division in six categories of maximum achieved exposure levels. And third, the workers were separated according to the year in which they were hired.
In dividing the workers in cumulative dose groups there was no indication of an elevated risk for colon cancer at lower levels of exposure, for which the accumulated experience was substantial. In the high exposure categories there were insufficient amounts of person-time to conclude an increased risk for colon cancer. The rate of rectal cancer was much lower than for colon cancer, therefore, the results are more imprecise.
When the workers were divided according to maximum achieved exposure levels there was no indication of a regular increase in relative mortality due to colon cancer.
When the workers were divided according to date of hire it was found that the two cohorts with later dates of hire showed no excess mortality. In the earliest cohort excess colon cancer seemed restricted to men employed extensively in the early 1940s in jobs entailing the highest exposures to ethylacrylate and MMA and volatile by-products of the polymerisation process. The excess mortality appeared only some two decades after the equivalent of three years'employment in jobs with the most intense exposures.

6.3 SUMMARY

ANIMAL DATA

irritation and sensitisation

MMA is mildly irritating to the skin of rabbit, rat and guinea pig and to the rabbit eye.

MMA may cause sensitisation in mice and guinea pigs. No sensitisation was observed in rats.

acute toxicity

The acute toxicity of MMA is low. After a single oral dose the LD50 is higher than 5000 mg/kg in mice, rats, rabbits and guinea pigs. The inhalatory LC50 for rats is 29500 mg/m^3 (4 hr of exposure) and for mice even higher.

short-term exposure

inhalatory exposure, local effects

The lowest concentration tested, 482 mg/m^3 (= 116 ppm), 7 hr/day, 5 d/week for 6 months induced damage to the tracheal mucosa in rats.

The lowest concentration tested in mice, 2080 mg/m^3 (= 500 ppm), 6 hr/day, 5 d/week for 3 months, induced metaplasia of the nasal epithelium.

The ruffled fur found in rats was considered treatment-related but no further explanation was given.

inhalatory exposure, systemic effects

At high concentrations (20800 mg/m^3 = 5000 ppm) dyspnoea was observed in mice.

Lower concentrations induced liver and kidney degeneration in guinea pigs, dogs, mice and rats and lung fibrosis and oedema and brain lesions in the rat.

No systemic effects were found in male rats and male and female mice exposed for three months to 4160 mg/m^3 (= 1000 ppm), 6 hr/day, 5 d/week. In female rats no systemic effects were observed at 2080 mg/m^3 (= 500 ppm), 6 hr/day, 5 d/week for 3 months.

oral exposure, local effects

No cell proliferation was observed in the forestomach of rats after administration of 200 mg/kg, 5 d/week for 2 weeks.

oral exposure, systemic effects

Behavioural changes were observed in rats after administration of 500 mg/kg/day for 21 days. At 200 mg/kg/day behavioural changes were not observed.

long-term toxicity/carcinogenicity

No evidence for carcinogenicity of MMA was found after inhalatory exposure in rats, mice, Syrian golden hamsters and dogs.

After oral exposure there was no evidence for carcinogenicity of MMA in rats and dogs.

The lowest dose tested (1040 mg/m^3 (= 250 ppm), 6 hr/day, 5 d/week for 102 weeks) induced nasal lesions in the female rat. At this dosage no other treatment-related effects were found.

genotoxicity

MMA is not mutagenic in bacteria. In high dosages MMA induces clastogenic effects and SCEs in mammalian cells in vitro both with and without metabolic activation. The genotoxic activity of the inhibitor hydroquinone remains to be established.

reproduction toxicity

After inhalatory exposure MMA increases the number of resorptions and gross abnormalities in rats. After i.p. administration MMA induces gross abnormalities in rats. No reproductive effects have been found in mice.

A NAEL for rats lies between 416 and 4160 mg/m^3 (5 hr/day on gestation days 6 - 15).

HUMAN DATA

irritation and sensitation

MMA is irritating to skin, eyes and mucous membranes. It can cause sensitisation, the incidence varies from 2 to 15%.

short-/longterm exposure

MMA induces various effects on the central nervous system.
After dermal absorption MMA reduces the nerve conduction velocity and may cause coldness and numbness.

epidemiological studies

Effects on the central nervous system, irritation of eyes and upper respiratory tract and changes in several blood parameters are reported without a dose-response relationship.
No excess was reported in all-cause or cause-specific mortality after exposure to low MMA levels. Only with exposure to high levels of MMA in combination with high levels of ethylacrylate and by-products an increase in colon cancer was reported.

7. PREVIOUS EVALUATION BY (INTER)NATIONAL BODIES

The Working group of the IARC (43) concluded that MMA is not classifiable as to their carcinogenicity to humans (group 3), based on data in IARC monograph volume 19 (42). There was no adequate evidence for human and animal carcinogenicity.

A TLV of 100 ppm (410 mg/m^3) TWA has been recommended by the ACGIH (1) to protect workers against discomfort from irritation and against acute systemic effects based upon data available at that time. However, protection under conditions of long-term exposure is not certain at this TLV, because no information about effects of long-term exposure was available. Elimination of the STEL was recommended until additional toxicological data and industrial hygiene experience become available. References were from 1983 or earlier.

The DFG (25) lowered the MAK-value from 410 mg/m^3 (100 ppm) to 210 mg/m^3 (50 ppm). They also recommended a maximum peak value of 2*MAK with a maximum duration of 5 minutes for a frequency per shift of eight. The DFG stated that MMA causes a higher than normal number of sensitivities and that there is no reason to fear risk of damage to the developing embryo or foetus when MAK values are adhered to.
The reason for lowering the MAK value is not clear; it is not based on the 2 years study of NTP (61).
The establishment of a maximum peak value is based on local irritation.
NTP (61) concluded that there is no evidence of carcinogenicity of MMA for rats and mice, under the conditions of the two-year inhalation studies performed.

8. EVALUATION OF HUMAN HEALTH RISKS

8.1 GROUPS AT RISK

Because of the sensitising properties of MMA workers with an MMA allergy are at extra risk.

Since the metabolism of MMA involves vitamin B12, persons with a vitamin B12 deficiency are at extra risk.

8.2 ASSESSMENT OF HEALTH RISKS

systemic effects

MMA is rapidly metabolised through the same pathway as the amino acid valine. The compound is mainly excreted as CO_2, irrespective of the route of administration (11, 19).

After inhalatory exposure systemic effects in humans concern mainly the central nervous system; complaints included headache, sleep disturbances, excessive fatigue, loss of memory, irritability, loss of appetite, nausea (23, 32, 42, 44, 61, 63). No dose-response relationship can be established.

In laboratory animals MMA does not induce neoplasms, both after oral (8) and inhalatory exposure (61, 79). The lowest concentration tested (1040 mg/m^3 (250 ppm), 6 hr/day, 5 d/week for 102 weeks) induces nasal lesions in the female rat.

Probably the most important effect observed in animal studies is the effect on reproduction in rats. Reproductive effects are not found in mice (54, 85). After inhalatory exposure reproductive effects in rats include resorptions and gross abnormalities (haematomas) (23, 53, 56). The NAEL lies between 416 and 4160 mg/m^3.

local effects, animal studies

MMA is mildly irritating to rabbit skin and eyes (80). There is indirect evidence for low dermal irritation in guinea pigs, high dosages of MMA induce sensitisation in this species (33, 34).

MMA induces little dermal irritation in rat tail. No sensitisation occurs. A crude method indicates that the absorption rate through rat tail can be high (46, 91).

Low dosages of MMA do not sensitise guinea pigs (64). Mice can be

sensitised (33), but not all investigators succeed (28).

MMA does not induce cell proliferation of the forestomach of rats, after oral administration of 200 mg/kg, 5 d/week for 2 week (38).

Cilia and microvilli in the tracheal mucosa of rats disappear after inhalatory exposure to 482 mg/m^3 (116 ppm), 7 hr/day, 5 d/week for 6 months (88).

local effects, human data

In contrast to what one would expect on the basis of the animal studies dermal effects are frequently found.

The incidence of human dermal irritation varies from 1 to 50% in group surveys, depending on the extent of exposure (6, 31, 69, 80).

Also after dermal absorption local neurotoxicity occurs (70, 77).

No dose-response relationship can be established.

The incidence of human dermal allergy varies from 2 to 15% in large group surveys (6, 31, 67, 69).

To a lesser extent irritation and allergy of the upper respiratory tract occur (18, 23, 52, 68).

risk assessment

In the animal studies the most critical effect at low dose is the reproduction effect in rats, and a NAEL of 416 mg/m^3 was found, at a dosing regimen compliant with the occupational setting. As no human data were found on reproduction effects it is proposed to accept the level of 416 mg/m^3 as a starting point for the extrapolation procedure.

The critical effect at the lowest dose studied long-term (1040 mg/m^3) is a local nasal effect in the female rat. In order to obtain a virtual NAEL a safety factor of 10 is used.

At the same time the resulting figure (104 mg/m^3) is low enough to exclude effects on the tracheal mucosa and reproductive risks.

Local dermal effects can be prevented by wearing gloves which are impenetrable for MMA.

In view of the possible high absorption rate in rat skin, and assuming that human skin absorbs MMA as efficiently as the rat, human dermal absorption can add considerably to the quantity inhaled occupationally. Therefore, a skin notation is considered necessary.

9. RECOMMENDATIONS FOR RESEARCH

Since MMA can penetrate the skin and exert local neurological effects this phenomenon must be studied further. The toxic dose must be established in relation to the dose inducing dermatological effects. Its mode of action and metabolism must be studied.

SUMMARIES

10.1 Summary in English

Maclaine Pont MA. DEC and NEG Basis for an Occupational Health Standard. Methylmethacrylate. Arbete Och Hälsa 1991:36, pp 1-58.

Methylmethacrylate is a monomer which is readily polymerised. It is absorbed through the skin, and irritating to skin, eyes and mucous membranes. It can cause sensitisation. Inhalation mainly effects the central nervous system. There is no evidence for carcinogenicity in experimental animals. The critical effect is the induction of nasal lesions in the female rat (LOAEL 1040 mg/m^3 (= 250 ppm), 102 weeks). In reproduction studies methylmethacrylate increases the number of resorptions and gross abnormalities in rats (NAEL between 416 and 4160 mg/m^3). An Occupational Exposure Limit of 42 mg/m^3 (= 10 ppm) TWA 8 hr is recommended. A skin notation is advised.

Key words: methylmethacrylate, occupational standard, health assessment

10.2 Summary in Swedish

Maclaine Pont MA. DEC and NEG Basis for an Occupational Health Standard. Methylmethacrylate. Arbete och Hälsa 1991:36 , s 1-58.

Metylmetakrylat är en monomer som lätt kan polymeriseras. Hudkontakt med monomeren förekommer huvudsakligen bland manikyrister, tandtekniker, tandläkare och ortopedkirurger. Ämnet kan absorberas genom hud och verkar irriterande på hud, ögon och slemhinnor. Inandning påverkar främst centrala nervsystemet. Det föreligger inte några bevis för carcinogenicitet från djurförsök. Den kritiska effekten är induktion av skador i nosen, iakttagen hos råttor (LOAEL 1040 mg/m^3 (250 ppm), 102 veckor). Vid reproduktionsstudier har antalet resorptioner och synbara missbildningar visats öka hos råtta (NAEL mellan 416 och 4160 mg/m^3).

Nyckelord: metylmetakrylat, hygieniskt gränsvärde, bedömning av hälsoeffekter.

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