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n-Butyl Methacrylate
Isobutyl Methacrylate
OEL Criteria Document

May 1998

European Centre for Ecotoxicology
and Toxicology of Chemicals

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PREFACE

This report has been prepared by ECETOC for use by the Commission of the EU (DG V) and its standing Scientific Committee for Occupational Exposure Limits to Chemical Agents (SCOEL), in accordance with guidance provided (CEC, 1992). It contains a review and assessment of toxicological data to provide a scientific basis for an occupational exposure limit for two isomers of butyl methacrylate, *n*-butyl methacrylate (CAS No. 97-88-1; *n*-BMA) and isobutyl methacrylate (CAS No. 97-86-9; *i*-BMA). Because of the close similarity of their chemical structure, production methods and use pattern, the two isomers are considered together. The abbreviation *n*-BMA/*i*-BMA is used whenever the text is applicable to both isomers. A summary evaluation of the health significance and a recommendation for an occupational exposure limit are presented in Section 11.3 and 11.4.

Reference is made to the extensive database on methyl methacrylate because of its close structural analogy with *n*-BMA/*i*-BMA and the common metabolism to the corresponding alcohol and free methacrylic acid. A summary of the data on methyl methacrylate is contained in Appendix A.

This review has been based on an earlier report on *n*-BMA/*i*-BMA (ECETOC, 1996), supplemented by data that have since become available.

n-Butyl Methacrylate and Isobutyl Methacrylate

OEL Criteria Document

CAS No. 97-88-1 and 97-86-9

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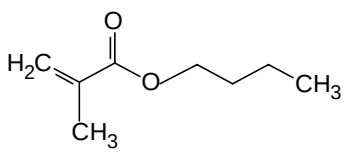
1. SUBSTANCE IDENTIFICATION

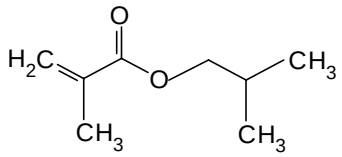
1.1 *n*-BUTYL METHACRYLATE

Common name:	*n-B*utyl methacrylate (*n*-BMA)
CAS name:	2-Propenoic acid, 2-methyl-, butyl ester
CAS registry No.	97-88-1
EEC No.	607-033-00-5
EEC classification:	Irritant
EEC labelling:	Symbol irritant (Xi), R10-36/37/38-43, nota D
RTECS No.	OZ 367 5000
IUPAC name:	Butyl 2-methyl-2-propenoate
EINECS name:	2-Propenoic acid, 2-methyl-, butyl ester
EINECS No.	202-615-1
Synonyms and trade names:	Butyl 2-methacrylate 2-Methyl-2-propenoate, butyl- Methacrylic acid, butyl ester 2-Methylbutylacrylate
Chemical group:	Organic acids and their derivatives
Formula:	$C_8H_{14}O_2$
Structure:	

Molecular mass:	142.20
Purity:	≥ 99.0 % (w/w)
Stabilisers:	2–(1,1-dimethylethyl)-4,6-dimethylphenol (10-100 ppm, maximum < 0.1 % w/w), hydroquinone (HQ) (10-100 ppm, maximum < 0.1 % w/w) and the monomethyl ether of hydroquinone (MeHQ, synonym *p*-methoxyphenol) (10-100 ppm, maximum < 0.1 % w/w)
Impurities:	The identity of impurities will vary depending on the production process and may include water (0.05 % w/w) traces of methacrylic acid and methyl methacrylate and other trace impurities.

1.2 ISOBUTYL METHACRYLATE

Common name:	Isobutyl methacrylate (*i*-BMA)
CAS name:	2-Propenoic acid, 2-methyl-, 2-methylpropyl ester
CAS registry No.	97-86-9
EEC No.	607-113-00-X
EEC classification:	Irritant
EEC labelling:	Concentration ≥ 20 %: symbol irritant (Xi), R 10-36/37/38-43; S 24-37, nota D 1 % ≤ concentration < 20 %: symbol irritant (Xi), R43
RTECS No.	OZ 490 000
IUPAC name:	Isobutyl 2-methylpropenoate
EINECS name:	2-Propenoic acid, 2-methyl-, 2-methylpropyl ester
EINECS No.	202-613-0

Synonyms and trade names:	Butyl 2-methacrylate Butyl 2-methyl-2-propenoate Methacrylic acid, butyl ester 2-Methylbutylacrylate Isobutyl 2-methylacrylate Isobutyl 2-methyl-2-propenoate Methacrylate, 2-methylpropyl ester Methacrylic acid, isobutyl ester 2-Methyl-2-propenoic acid, 2-methylpropyl ester 2-Methylpropyl methacrylate Propenoic acid, 2-methyl, isobutyl ester
Chemical group:	Organic acids and their derivatives
Formula:	$C_8H_{14}O_2$
Structure:	
Molecular mass:	142.20
Purity:	≥ 98.5 % (w/w)
Stabilisers:	2-(1,1-dimethylethyl)-4,6-dimethylphenol (10-100 ppm, maximum < 0.1 % w/w), hydroquinone (HQ) (10-100 ppm, maximum < 0.1 % w/w) and the monomethyl ether of hydroquinone (MeHQ, synonym *p*-methoxyphenol) (10-100 ppm, maximum < 0.1 % w/w)
Impurities:	The identity of impurities will vary depending on the production process and may include water (≤ 0.01-0.02 %, maximum 0.1 % w/w) traces of methacrylic acid and methyl methacrylate and other trace impurities.

2. PHYSICAL AND CHEMICAL PROPERTIES

At room temperature, *n*-BMA and *i*-BMA are clear, colourless, flammable liquids with a faint characteristic ester odour. Both compounds have a low solubility in water and are soluble in most organic solvents. Data on the physical and chemical properties of *n*-BMA/*i*-BMA are given in Table I and II.

Table I: Physical and Chemical Properties of *n*-BMA

Parameter, units	Value	Reference
Melting temperature, °C, approximately	–25	Company data sheets[a]
	–75	HSDB, 1994
Boiling temperature, °C at 1,013 hPa	160-163	Company data sheets[a]; Weast *et al*, 1989; Bauer, 1993
	163.5-170.5	Nemec and Kirch, 1981
Relative density D_4^{20}	0.896-0.8975	Company data sheets[a]
	0.895	Degussa, 1989
	0.8948	Bauer, 1993
	0.8936	HSDB, 1994; Weast *et al*, 1989[b]
Vapour pressure, hPa at 20 °C	2.6-2.7	Company data sheets[a]
	6.1-6.5	Deichman, 1981; Rohm and Haas, 1993; HSDB, 1994
Vapour density at 20 °C (air=1)	4.8	Deichman, 1981; HSDB, 1994
Threshold odour concentration, ppm	0.015-0.06	Company data sheets[a]
	0.025	Shepel'skaya, 1978
Solubility in water, g/kg at 20 °C	< 0.45	Company data sheets[a]
	0.882[c]	Lissi *et al*, 1983
Miscible with most organic solvents	Yes	Company data sheets[a]; HSDB, 1994
Fat solubility, mg/100 g at 37 °C	No data	
Partition coefficient, log P_{ow} (octanol/water), measured at 20 °C	2.6[c]	Fujisawa and Masuhara, 1981; Dillingham *et al*, 1983
	2.88[c]	Tanii and Hashimoto, 1982
	3.01[c]	Morris *et al*, 1992
	2.26[d]	Fujisawa and Masuhara, 1981
Flash point, °C, closed cup	46	Röhm, 1995a
	49	Degussa, 1968
Explosion limits, % at 65-96 °C and 1,000 hPa	2-8	Company data sheets[a]; HSDB, 1994
Auto-flammability, ignition temperature, °C	315	Degussa, 1990
	400-496	Degussa, 1968

[a] ICI Acrylics, 1994a; Degussa, 1995a; Röhm, 1995a
[b] The stated value of 0.9836 presumably contains a typing error
[c] Shake flask method
[d] High performance liquid chromatography (HPLC) method

Table II: Physical and Chemical Properties of *i*-BMA

Parameter, units	Value	Reference
Melting temperature, °C, approximately	–37 - –34	Hommel, 1994; Company data sheets[a]
Boiling temperature, °C at 1,013 hPa	155	Deichman, 1981; Weast *et al*, 1989; Richter *et al* , 1961; Company data sheets[a]
Relative density D_4^{20}	0.882-0.888	Degussa, 1989; Nemec and Kirch, 1981; Rehberg and Fisher, 1948; Richter *et al*, 1961; Weast *et al*, 1989; Company data sheets[a]
Vapour pressure, hPa at 20 °C	4 2.4-2.6	Company data sheets[a] Deichman, 1981; ICI Acrylics, 1994b
Vapour density at 20 °C (air=1)	4.9	Deichman, 1981
Threshold odour concentration, ppm	0.016-0.069	ICI Acrylics, 1994b
Solubility in water, g/kg at 20 °C	0.133	Mao, 1995
Miscible with most organic solvents	Yes	Weast *et al*, 1989; ICI Acrylics, 1994
Partition coefficient, log P_{OW} (octanol/water), measured at 20 °C	2.66[b] 2.01[c]	Tanii and Hashimoto, 1982 Fujisawa and Masuhara, 1981
Flash point, °C, closed cup (DIN 51755)	42.5-45.5	Degussa, 1968; ICI Acrylics, 1994; Röhm, 1995b; Company data sheets[a]
Explosion limits, % at 25 °C and 1,013 hPa	1-7.4 2-8	DIPPR, 1995 Degussa, 1995a,b
Auto-flammability, ignition temperature, °C	367-400	Company data sheets[a]; Degussa, 1994

[a] Elf Atochem, 1993; Degussa, 1995b,c; Röhm, 1995b
[b] Shake flask method
[c] High performance liquid chromatography (HPLC) method

2.1 CONVERSION FACTORS

Conversion factors for concentrations of *n*-BMA and/or *i*-BMA in air at 20 °C and 1.013 hPa are:

- 1 ppm = 5.91 mg/m^3
- 1 mg/m^3 = 0.169 ppm

2.2 CHEMICAL REACTIVITY

n-BMA/*i*-BMA polymerises readily under the influence of heat, light or by catalysis (e.g. metals and radical forming substances such as peroxides), this being a strongly exothermic reaction. To prevent polymer formation, the monomer is stabilised by the addition of inhibitors.

3. OCCURRENCE

3.1 SOURCES

3.1.1 Industrial Sources

n-BMA/*i*-BMA may be released into the environment via fugitive and stack emissions, and via wastewater during its production and use in the manufacture of large volume resins and polymers. Estimates of the overall quantities emitted in the EU are given in Table III.

Table III: Emissions from Monomer and Polymer Production in the EU in 1994 (CEFIC, 1996)

Emission	*n*-BMA (t/y)	*i*-BMA (t/y)
To air	< 0.3	< 0.15
To water	< 0.15	< 0.05
To soil	0	0

For *n*-BMA/*i*-BMA processing (polymerisation) only very limited data are available. These indicate losses to air of 15 g/t monomer and to water 10 g/t monomer (CEFIC, 1996).

n-BMA was detected in pottery kiln emissions at concentrations between 1.2 and 151 µg/m^3 (Bradley and Morgan, 1989).

3.1.2 Domestic Sources

Residual levels of *n*-BMA/*i*-BMA monomers in solid polymers and polymer dispersions are always < 1 %, typically in the range 0.1-0.5 % for solid polymers and ≤ 0.01-0.1 % for polymer dispersions (CEFIC, 1996). Migration of residual unpolymerised *n*-BMA/*i*-BMA from polymer articles is very low as typified by migration into food simulants. Both isomers are listed on the positive list of monomers and other starting substances for plastics and coatings intended to come into contact with foodstuffs (CEC, 1990a,b). The European Commission has suggested a group maximum total daily intake of 0.1 mg/kgbw (calculated as methacrylic acid) (CEC, 1994b).

3.1.3 Natural Sources

i-BMA was found in abundance (6.07 % or 1.85 mg/kg) in fresh beli (*Aegle marmelos*), a tropical fruit native to India but commonly grown in Sri Lanka; no *n*-BMA was found in canned, processed beli cream or puree (MacLeod and Pieris, 1981). Traces of *i*-BMA occur in the essential oil from Roman camomile (*Anthemis nobilis* L.) (Klimes and Lamparsky, 1984).

4. PRODUCTION AND USE DATA

4.1 PRODUCTION METHODS

The majority of *n*-BMA or *i*-BMA is produced in closed systems by catalytic trans-esterification of methyl methacrylate with *n*-butanol or isobutanol or via the acetone cyanohydrin (methacrylamide sulphate) route using the appropriate alcohol. Another process uses methacrylic acid and alcohol as raw materials (Richter *et al*, 1961; Bauer, 1993).

4.2 HANDLING, STORAGE AND TRANSPORT

The use of personal protective equipment is recommended to avoid *n*-BMA/*i*-BMA's irritating action on the skin and mucous membranes. The following protective clothing must be worn when handling *n*-BMA/*i*-BMA: eye-face protection and rubber gloves (preferably nitrile) which should be changed regularly to avoid permeation. Rubber boots should also be worn when handling large quantities.

n-BMA/*i*-BMA should be used only in well ventilated areas. Suitable respiratory equipment must be worn on occasions when exposure to *n*-BMA/*i*-BMA vapour above the recommended exposure limit is likely.

n-BMA/*i*-BMA vapour is denser than air and will accumulate in pits and confined spaces.

To prevent polymer formation, the *n*-BMA/*i*-BMA monomer is stabilised by the addition of an inhibitor such as MeHQ. The effectiveness of phenolic inhibitors depends on the presence of oxygen. To prevent polymer formation, the monomers must therefore be stored under air (not under inert gases), in the dark and at a temperature below 30 °C. During prolonged storage, stabiliser levels should be checked routinely.

n-BMA/*i*-BMA is stored or shipped in containers lined with polyethylene, or made of glass, stainless steel or aluminium. Both isomers are shipped in containers with pressure relief valves.

Stabilised *n*-BMA/*i*-BMA is transported by road, rail and sea in bulk tanks and drums. Quantities up to 1 kt are regularly transported by sea.

4.3 USES

4.3.1 Quantities Produced

In EU countries, 32 kt of *n*-BMA and 8 kt of *i*-BMA were produced in 1994. Production in 1995 was 12 % higher than 1994 (CEFIC, 1996).

4.3.2 Usage

n-BMA/*i*-BMA is used as a monomer or co-monomer for the industrial production of acrylic polymers.

n-BMA/*i*-BMA is used as a co-monomer in acrylic surface coatings, in the production of resins, solvent coatings, adhesives and oil additives, emulsions for textiles and leather and paper finishing. *n*-BMA/*i*-BMA is also used in the manufacture of contact lenses, in dental technology (both as a monomer and comonomer) and as copolymers, for example, in paraffin embedding media. Resins containing less than 1 % *n*-BMA/*i*-BMA as polymers are found in dental and other applications

Approximately 13 % of the Western European *n*-BMA/*i*-BMA production was exported in 1994 (CEFIC, 1996). The distribution of *n*-BMA/*i*-BMA consumption remaining in the EU in 1994 is depicted in Table IV.

Table IV: Use Pattern in the EU in 1994
(CEFIC, 1996)

Type of use	*n*-BMA (%)	*i*-BMA (%)
Solid polymers, coatings, ionomers	48	50
Dispersions (aqueous based polymers)	45	45
Sales (comanufacturers, industrial users)	4	4
Oil additives	2	-
Reactive resins/adhesives (industrial applications)	1	-

5. QUANTITATIVE INFORMATION ON EXPOSURE AND UPTAKE

5.1 EXPOSURE LEVELS AT THE WORKPLACE

As with other volatile methacrylate esters, workplace concentrations of *n*-BMA/*i*-BMA are lower in closed or semi-closed manufacturing processes than in down-stream user operations where monomer or syrup is often handled in open systems. The available workplace exposure data have almost exclusively been generated in larger companies representing the former group. The only data available on downstream user activities are those published by Froines and Garabrant in 1986 (see below) and collected at a manicure salon where short-term high exposures would have contributed to the higher background levels. It is unusual to monitor the workplace of these small industries and these data may not be typical.

***n*-BMA**

The available data on occupational exposure levels of *n*-BMA during monomer production and polymerisation are summarised in Table V.

Table V: Occupational Exposure Levels of *n*-BMA during Monomer Production and Polymerisation (CEFIC, 1996)

Work place	Year of measurement	Sample type[a]	Concentration (mg/m^3)	
			TWA[b]	Short-term level[c]
Production				
Laboratory	1992-93	Area	0.2	< 0.5-3.77
NS	1992	Area	0.9	-
Filling	1992-93	NS	-	ND[d] - 0.37
Other operations	1992-94	NS	0.09-0.16	-
Pump house	1992	NS	-	7.6
Polymerisation				
Block polymerisation	1992-94	NS	0.13	1.21
Bead polymerisation	1992-94	NS	0.05	0.45
Storage and distribution	1992-94	NS	0.04	0.99

[a] Area = background monitoring at the work place; NS = not stated; there are no data on personal monitoring in the worker's breathing zone
[b] TWA = time-weighted average exposure concentration (4 to 8-h working period)
[c] Short-term level = exposure concentration during short period (5 min - 1 h)
[d] ND = not detectable (detection limit not stated)

Workplace concentrations of *n*-BMA and other vapours during the extrusion of acrylic sheets ranged between < 0.1 and 8 ppm (< 0.6-47 mg/m^3) under normal conditions and between < 0.1 and 16.5 ppm (< 0.1-97.5 mg/m^3) under degradation conditions (600 °F or 315 °C) (Rohm and Haas, 1989).

***i*-BMA**

The available data on occupational exposure levels of *i*-BMA during production and polymerisation are summarised in Table VI.

Table VI: Occupational Exposure Levels of *i*-BMA during Monomer Production and Polymerisation (CEFIC, 1996)

Work place	Year of measurement	Sample type[a]	Concentration (mg/m^3)	
			TWA[b]	Short-term level[c]
Production				
Laboratory	1992-93	NS/Area	0.06	< 0.5 - 0.14
NS	1992	Area	0.4	-
Filling	1992-93	NS	0.05	ND[d] - < 0.11
Other operations	1992-94	NS	0.02	-
Polymerisation				
Block polymerisation	1992-94	NS	0.29	1.49
Storage and distribution	1992-94	NS	0.32	-

[a] Area = background monitoring at the work place; NS = not stated; there are no data on personal monitoring in the worker's breathing zone
[b] TWA = time-weighted average exposure concentration (4 to 8-h working period)
[c] Short-term level = exposure concentration during short period (5 min - 1 h)
[d] ND = not detectable (detection limit not stated)

Froines and Garabrant (1986a,b) have reported on workplace concentrations of *i*-BMA during the preparation of synthetic nails (Table VII).

Table VII: Exposure of Manicurists to *i*-BMA during Preparation of Synthetic Nails (Froines and Garabrant, 1986a,b)

Nail shop	Number of measurements	Exposure concentration (mg/m^3)			
		Intermittent[a]		Continuous[b]	
		Mean	Median	Mean	Median
1	3	30.7	29.6	5.3	4.7
2	2	45.5	-	16.0	-
Overall	5	36.6	29.6	9.5	7.7

[a] Exposure to *i*-BMA alone
[b] Exposure mixed with ethyl methacrylate, 8-h TWA

***n*-BMA/*i*-BMA**

Workplace concentrations between < 0.03 and 0.29 ppm (0.18 and 1.71 mg/m^3) of *n*-BMA/*i*-BMA (isomer not specified) were reported by a polymer company; no further data are available (Hi-Tek Polymers, 1989).

Median concentrations of *n*-BMA/*i*-BMA (isomer not specified) in the breathing zone of workers in shipyards (building and outfitting operations) were reported to range between 0.02 and 0.03 mg/m^3 with a maximum of 0.14 mg/m^3 (10 measurements) (Engström *et al*, 1990).

5.1.1 Biomonitoring

No methods for biological monitoring have been established, and data on levels in human tissues, secreta or excreta are not available.

5.2 LEVELS IN FOOD AND DRINKING WATER, AND EXPOSURE RELATED TO LIFESTYLE

No data are available.

5.3 ENVIRONMENTAL LEVELS

No data are available on *n*-BMA/*i*-BMA levels in air, water, soil and biota.

5.4 SUMMARY AND EVALUATION

Environmental releases during production and major industrial uses are very low.

Occupational exposure in downstream user industries is anticipated to be higher but hygiene monitoring is uncommon.

6. MEASUREMENT TECHNIQUES AND ANALYTICAL METHODS

A number of different analytical methods for the determination of *n*-BMA/*i*-BMA in various media have been described in the literature (ECETOC, 1996).

6.1 WORKPLACE AIR

n-BMA/*i*-BMA in workplace air can be determined by means of NIOSH method 1450 (esters I), involving adsorption on activated carbon by active sampling (4 l/h) followed by desorption with carbon disulphide and analysis by GC/FID. Detection limits are 0.06 mg/m^3 for an 8-hour sample and 6 mg/m^3 for short-term measurements (5 min) (NIOSH, 1984; Röhm, 1996). Using a similar method Degussa (1992) achieved a detection limit of 1 μg/sample (17 μg/m^3).

6.2 BIOLOGICAL TISSUES AND FLUIDS

No standardised method for assaying *n*-BMA/*i*-BMA and its metabolites in biological tissues, secreta or excreta is available.

Kuznetsova *et al* (1991) have described a GC method for the determination of n-BMA/i-BMA in biological fluids (blood, urine, amniotic fluid) and tissues (liver, lungs). No further details are available from the literature abstract.

GC/FID was used to quantify *n*-BMA in extracts of *in vitro* incubation mixtures with carboxylesterases (McCarthy and Witz, 1991).

Although HPLC methods have been used for the analysis of *n*-BMA/*i*-BMA in biological media, GC analysis combined with extraction or headspace pre-concentration is expected to be more useful.

7. TOXICOLOGY

7.1 TOXICOKINETICS

7.1.1 Uptake

From the physico-chemical data (Table I) and by analogy with methyl methacrylate (ECETOC, 1995a; Appendix A) it is anticipated that *n*-BMA/*i*-BMA is rapidly absorbed after oral, dermal and inhalation exposure.

7.1.2 Distribution

Male rats received 6.7 mmol/kgbw of [1-^{14}C-butyl]methacrylate (equivalent to 10 mBq/kgbw) by intraperitoneal (i.p.) injection 2, 12, 24 or 48 hours before they were killed. Radioactivity was rapidly distributed to all major organs The initial half-life of radioactivity in the blood was 10 hours. A small amount (3.5 %) of the radioactivity was tightly associated with plasma proteins after 48 hours. Maximum levels of radioactivity were observed in liver, kidney, heart, brain and plasma after 2-12 hours; the highest activity in liver and kidneys, the lowest amounts were found in the brain. The half-life of radioactivity in the kidney was 24 hours. After 48 hours 38 % of the administered radioactivity remained in these organs; the nature of this radioactivity was not determined (Svetlakov *et al*, 1989).

Due to the predicted hydrolysis of *n*-BMA to *n*-butanol and methacrylic acid it is uncertain whether the distributed radioactivity was attributable to intact *n*-BMA, *n*-butanol or its metabolites. *In vitro* data do not substantiate the authors' claim that *n*-BMA/*i*-BMA covalently binds to plasma protein. Cytochrome P_{450}-binding of *n*-BMA in rat liver microsomal preparations revealed a type I spectrum. Substances leading to type I spectra are normally considered to be substrates of the cytochrome P_{450}-dependent mono-oxygenases (Kotlovskii *et al*, 1985). The respective binding constants of *n*-BMA and *i*-BMA to bovine serum albumin were determined to be 2.16 and 1.99 (l/Avogrado No of binding) at pH 5.0 and 21 °C (Fujisawa and Masuhara, 1980).

7.1.3 Biotransformation

n-BMA

n-BMA is rapidly hydrolysed by liver esterases yielding methacrylic acid and *n*-butanol *in vitro*. *n*-BMA (at a concentration of 36 mmol/l) was incubated with rat liver microsomes at pH 7.4 and 37 °C for 5 minutes. *n-B*utanol was determined in the supernatant by GC analysis. *n*-Butanol was formed at a

rate of 55 nmol/g protein per minute of incubation. The reaction rate was greater than that of the hydrolysis of methyl methacrylate determined in the same test system (0.5 nmol/mg protein/min) and in the same range as that of *n*-butyl acrylate (50 nmol/mg protein/min). When the incubation mixture was inactivated by heating to 100 °C prior to the addition of *n*-BMA, no butanol was generated indicating that microsomal hydrolysis of the ester was enzyme catalysed (Kotlovskii *et al*, 1988).

The kinetic constants of the enzymatic hydrolysis of *n*-BMA using a porcine liver carboxyl esterase were determined to be K_m = 72 ± 28 µmol/l and V_{max} = 1.84 nmole/min (incubation for 20 min with 5-250 µmol/l *n*-BMA at 37 °C at pH 8). The constants were comparable to those of butyl acrylate. Compared with ethyl methacrylate *n*-BMA had lower K_m and V_{max} values indicating an increase in substrate affinity, but a decrease in turnover for the enzymatic hydrolysis with increasing chain length of the alcohol residue (McCarthy and Witz, 1990, 1991, 1997; McCarthy, 1995).

There are no data available on reaction kinetics *in vivo*.

Hydrolysis Data on Analogous Substances

Hydrolysis of methyl methacrylate has been extensively studied and may provide some insight into the hydrolysis of *n*-BMA/*i*-BMA.

Hydrolysis of methyl methacrylate occurs at the site of first contact, as demonstrated in the upper airways of rats when methyl methacrylate was administered by inhalation (Morris and Frederick, 1995). Ester hydrolysis of methyl methacrylate is known to occur within minutes in human peripheral blood *in vivo* with a half-life of about 5 minutes (Crout *et al*, 1979). *In vitro* studies with the *n*-butyl ester indicate that hydrolysis will occur with *n*-BMA/*i*-BMA but that the rate could be slower than that for methyl methacrylate due to the increased chain length of the alcohol (McCarthy and Witz, 1991).

Glutathione Conjugation

Conjugation with GSH does not appear to play an important role for *n*-BMA/*i*-BMA biotransformation as evidenced in *in vitro* experiments. Rate constants for the reaction of different acrylates and methacrylates with GSH (pH 7.4, 37 °C), and with cellular GSH in rat red blood cells (pH 7.4, 37 °C, 1 h) were determined by McCarthy and Witz (1994). *n*-BMA did not react with GSH to any measurable extent. Incubation of *n*-BMA with a solution of reduced GSH at 37 °C did not result in a decrease in GSH within 120 minutes, while with *n*-butyl acrylate a 50 % reduction of GSH was observed after 5 minutes (Svetlakov *et al*, 1989).

Further Metabolism of Hydrolysis Products

Bratt and Hathway (1977) and ICI (1977b) conducted studies with radiolabelled methyl methacrylate administered in corn oil by gavage to male Wistar rats. It was shown that the methacrylic acid arising from the primary hydrolysis step was metabolised via methylmalonyl-CoA and succinyl-CoA, which are substrates of the citric acid cycle, with the majority being exhaled as carbon dioxide.

*n-B*utanol is a substrate of alcohol-dehydrogenase (Von Rietbrock and Abshagen, 1971; Saito, 1975). The main metabolic pathway in rats following oral administration of radiolabelled *n*-butanol to rats was rapid oxidation to ultimately carbon dioxide. A minor part was excreted was urine as glucuronide or sulphate (Di Vincenzo and Hamilton, 1979). After repeated ingestion of *n*-butanol (saturated solution in drinking water) by rabbits small amounts of the following urinary metabolites were identified: acetaldehyde, acetic acid, *n*-butyraldehyde and unchanged *n*-butanol (Saito, 1975).

When rabbits received oral doses of 2 ml isobutanol/kgbw the blood level of isobutanol reached 0.8 mg/ml after 30 minutes. Elimination from the blood was almost complete 5 hours after administration (Saito, 1975).

7.1.4 Excretion

It can be anticipated that if hydrolysis constitutes a major pathway of *n*-BMA/*i*-BMA metabolism *in vivo* the resulting reaction products will be rapidly eliminated by the body using physiological oxidation pathways.

7.1.5 Biological Monitoring

No data are available.

7.1.6 Summary and Evaluation

From the physico-chemical data and by analogy with methyl methacrylate it is anticipated that *n*-BMA/*i*-BMA is rapidly absorbed after oral and inhalation exposure.

n-BMA is rapidly hydrolysed by carboxyl esterases yielding methacrylic acid and *n*-butanol. By analogy with methyl methacrylate it is anticipated that hydrolysis of *n*-BMA/*i*-BMA with further metabolism of the respective cleavage products (methacrylic acid and *n*-butanol or isobutanol) by normal physiological pathways (to ultimately CO_2) will be the main route of metabolism for *n*-BMA/*i*-BMA.

7.2 TOXICODYNAMICS

7.2.1 Acute Toxicity

7.2.1.1 *Inhalation*

The acute toxicity following administration of *n*-BMA/*i*-BMA vapour is low as judged by LC_{50} values available for several animal species (Tables VIII-X).

Table VIII: Acute Inhalation Toxicity of *n*-BMA/*i*-BMA[a]

Species	Duration (h)	LC_{50} (ppm)	Reference
Rat	4	> 4,901 [b]	Kelly, 1993
Rat	4	4,910[c]	Oberly and Tansey, 1985
Rat	4	> 1,014	Shepel'skaya, 1975
Rat	8	> 4,900[d]	Smyth *et al*, 1969
Mouse	4	> 1,041	Shepel'skaya, 1975
Mouse	2	4,410	Danishevskii, 1957

[a] Isomer not specified
[b] Reported as 29 mg/l
[c] Over subsequent 24-h period
[d] Saturated vapour

Table IX: Acute Inhalation Toxicity of *n*-BMA

Species	Duration (h)	LC_{50} (ppm)	Reference
Rat	4	3,330[a]	Kustova *et al* , 1979
Rat	8	> 880	Autian, 1975
Rat	8	> 845	Deichmann, 1941
Rabbit	8	> 845	Deichmann, 1941
Guinea pig	8	> 845	Deichmann, 1941
Mouse	7.6	> 2,874	Lawrence *et al*, 1974

[a] Reported as 19.7 mg/l

Table X: Acute Inhalation Toxicity of *i*-BMA

Species	Duration (h)	LC_{50} (ppm)	Reference
Rat	6	> 3,600	Autian, 1975
Mouse	4.8	> 5,026	Lawrence *et al*, 1974

Where clinical signs of exposure were reported in these studies, they are consistent with exposure to a material that is irritant to the eyes and respiratory tract, e.g. lung noise, irregular respiration, nasal and ocular discharge, eyes closed or squinted.

Inhalation of 19.7 mg *n*-BMA/l (3,330 ppm) by rats for 4 hours caused hypervolemia of organs (unspecified), emphysematous swelling and point haemorrhages of the lungs, and decreased lymphocyte levels. Circulatory disturbances in the organs persisted for 2 weeks but lung effects persisted for 1 month (Kustova *et al*, 1979). In accordance with the vapour pressure of *n*-BMA, exposures at concentrations above 1,000 ppm would have been to a mixture of vapour and aerosol.

7.2.1.2 *Oral*

The acute oral toxicity of *n*-BMA/*i*-BMA following oral administration is low as judged by LD_{50} values available for several animal species (Table XI and XII).

Table XI: Acute Oral Toxicity *n*-BMA

Species	LD_{50} (mg/kgbw)	Reference
Rat	> 2,000	Sarver, 1993a
Rat	16,000	Kustova *et al* , 1979
Rat	18,020	Shepel'Skaya, 1974
Rat	18,561	Smyth *et al* , 1969
Rat	17,900	Deichmann, 1941
Rat	> 3,200	Eastman Kodak, 1984
Mouse	> 3,200	Eastman Kodak, 1984
Mouse	15,800	Kustova *et al* , 1979
Mouse	12,900	Klimkina *et al*, 1976
Mouse	13,515	Shepel'Skaya, 1974
Mouse	14,416	Lawrence *et al*, 1974
Rabbit	25,000	Klimkina *et al* , 1976
Rabbit	> 6,300	Deichmann, 1941
Rabbit	5,370	Deichmann, 1941

Table XII: Acute Oral Toxicity *i*-BMA

Species	LD_{50} (mg/kgbw)	Reference
Rat	9,600	Röhm, 1977a
Rat	6,400-12,800	Autian, 1975
Mouse	11,824	Tanii and Hashimoto, 1982

For both *n*-BMA/*i*-BMA the clinical signs described in these studies are slight weakness, hypoactivity, inco-ordination, hypotonia, diarrhoea and cyanosis.

7.2.1.3 *Dermal*

The acute dermal toxicity of *n*-BMA/*i*-BMA is judged to be low. LD_{50} values following dermal administration of *n*-BMA in rabbits and guinea pigs are detailed in Table XIII.

Table XIII: Acute Dermal toxicity of *n*-BMA

Species	LD_{50} (mg/kgbw)	Reference
Rabbit	> 2,000	Sarver, 1993b
Rabbit	10,181	Smyth *et al*, 1969
Guinea pig	> 20 ml/kg	Eastman Kodak, 1984

There are no data on clinical signs reported in these studies.

7.2.1.4 *Evaluation*

n-BMA/*i*-BMA is of low acute toxicity via the oral, dermal or inhalation routes of exposure. Where clinical signs were reported they are consistent with exposure to an irritant material.

A skin notation (for systemic toxicity following dermal absorption) is not warranted (ECETOC, 1993).

7.2.2 Irritation, Sensitisation and Immunotoxicity

7.2.2.1 *Skin Irritation*

***n*-BMA**

Application of undiluted *n*-BMA to the skin of rabbits produces slight to strong primary irritation. Key studies are listed in Table XIV.

Table XIV: Skin Irritation Studies with *n*-BMA

Species	Contact time (h)	Method	Observations	Reference
Rabbits	24	Draize	Slight irritation, PII 1.92	Röhm, 1977b
Rabbits	24	Draize	Well-defined to moderate erythema, barely-perceptible to moderate oedema and induration of the skin (2/6), PII 3.79	Elf Atochem, 1980a
Rabbits	1, 4	Not stated	Slight erythema and slight oedema (4 h only), 4/6 animals recovered by day 7, PII 1-1.9	Degussa, 1982
Rabbits	4	Not stated	Mild to moderate erythema, slight to mild oedema (3/6), desquamation and superficial necrosis (2/6), areas of necrosis (1/6)	Sarver, 1993b

***i*-BMA**

Application of undiluted *i*-BMA to the skin of rabbits has been shown to produce slight to moderate irritation (Table XV).

Table XV: Skin Irritation Studies with *i*-BMA

Species	Contact time (h)	Method	Observation	Reference
Rabbits	24	Draize	Well defined erythema and barely perceptible to moderate oedema, PII 4.16	Elf Atochem, 1980b
Rabbits	24	Draize	Slight irritation. PII 1.83	Röhm, 1977c

7.2.2.2 *Gastric Irritation*

No data are available.

7.2.2.3 *Respiratory Tract Irritation*

Results from a number of single and repeated exposure inhalation studies demonstrate that *n*-BMA is irritant to the respiratory tract. Exposure of groups of five male and five female Crl:CDBR rats to 0, 13.8, 18.2, 23.9, 26.6, 28.6 or 36 mg/l (0, 2,332, 3,076, 4,039, 4,495, 4,833 or 6,084 ppm) *n*-BMA for 4 hours (Kelly, 1993) evoked clinical signs consistent with marked irritation to the respiratory tract (nasal discharge, gasping, irregular respiration, lung noise) and eyes (corneal opacity, one rat at 6,091 ppm).

In a 4-week vapour inhalation study in Crl:CDBR rats exposed to 0, 310, 952 and 1,891 ppm *n*-BMA, clinical signs, consistent with irritancy to the respiratory tract e.g. laboured breathing, were seen during

the first day of exposure to 1,891 ppm *n*-BMA (Hagan *et al*, 1993; Section 7.2.3.1). The NOEL was 310 ppm.

Although the above studies were conducted only with *n*-BMA, it is expected that *i*-BMA would respond in a similar manner because of its similar irritant properties and similar vapour pressure.

Sensory irritation potential of *n*-BMA was assessed using the method of Alarie by exposure of groups of 4 male Swiss Webster mice to 490, 980, 6,300 and 20,000 ppm *n*-BMA for 30 minutes. This test assesses the ability of a material to stimulate the trigeminal and other nerve endings in the nose and lung of mice by measurement of the concomitant reflex change in respiratory rate. Such findings have been used as a basis for extrapolating the irritancy potential to man. Breathing patterns of individual animals were recorded prior to, during and following exposure. An initial decrease in respiratory rate occurred in all exposed groups and remained slightly lower (15.4-19.7 %) than pre-exposure levels throughout the exposure period. No concentration-response relationship was observed. It was concluded that *n*-BMA was not a sensory or pulmonary irritant (Stadler, 1993). However, as clinical signs of irritancy were present in other inhalation studies, this would suggest that the "Alarie test" findings are, on this occasion, inappropriate for prediction of the respiratory tract irritancy of *n*-BMA/*i*-BMA in man.

7.2.2.4 *Eye Irritation*

_n_-BMA

Instillation of undiluted *n*-BMA into the eyes of rabbits resulted in slight irritation (Table XVI).

Table XVI: Eye Irritation Studies with *n*-BMA

Species	Volume (ml)	Observation	Reference
Rabbit	0.1	Slight to well defined conjunctival redness (4/6)	Elf Atochem, 1980a
Rabbit	0.1	Very slight conjunctival redness (2/3) regressed by 24 h	Röhm, 1988e
Rabbit	0.16 (drop)	Slight to mild conjunctival redness regressed by 24 h	ICI,1959
Rabbit	0.5	Slight irritation	Smyth *et al*, 1969
Rabbit	0.1	Iritis, palpebral irritation and chemosis. Grade 2 on 0-3	Powell *et al*, 1970

Eye irritation has also been observed in inhalation studies with *n*-BMA. Marked irritation of the "mucous membranes" was seen in rabbits, guinea-pigs and rats exposed to the vapour at concentrations of up to 5 g/m^3 (845 ppm) (Deichmann, 1941).

In a 4-week vapour inhalation study in rats, clinical signs consistent with irritancy to the eyes were seen. Lachrymation was observed twice during the first 3 days of exposure (once at 952 ppm and once at 1,891 ppm *n*-BMA) and squinting was observed between days 3 and 20 (excluding day 4) at 1,891 ppm *n*-BMA (Hagan *et al*, 1993).

_i_-BMA

Instillation of undiluted *i*-BMA into the rabbit eye resulted in slight irritation (Table XVII).

Table XVII: Eye Irritation Studies with *i*-BMA

Species	Volume (ml)	Observation	Reference
Rabbit	0.1	Slight conjunctival redness and chemosis in some animals	Elf Atochem, 1980b
Rabbit	0.1	Non-irritating	Röhm, 1988f
Rabbit	0.1	Slightly irritating	ICI, 1977a
Rabbit	0.016 (drop)	Slightly irritating. Transient conjunctival redness regressed by 24 h	ICI, 1977a

7.2.2.5 *Immunotoxicity (Skin Sensitisation)*

_n_-BMA

Guinea Pig Maximisation Test

n-BMA was not sensitising in a number of Guinea Pig Maximisation (GPM) tests (Table XVIII).

Freund's Complete Adjuvant Test

No evidence of sensitisation was reported in a standard Freund's Complete Adjuvant (FCA) test protocol (Van der Walle *et al*, 1982) and in a test according to the Polak method (Parker and Turk, 1983) (Table XIX).

In a study performed with 19 male guinea pigs, each animal received 100 mg of FCA in the four foot pads on day 0. On days 0, 2 and 5 each animal received topical applications of 0.038 ml *n*-BMA in 95 % ethanol (volume applied: 0.2 ml). A first challenge was made on day 25 using a topical application of 2 or 5 % *n*-BMA in 95 % ethanol (volume applied: 0.05 ml). A second challenge was made on day 60 using either a topical challenge with 10 % *n*-BMA in olive oil or an intradermal challenge with either 0.01 ml or 0.1 ml of *n*-BMA in 0.1 ml saline. A third challenge was made on day 122 using either 0.4 or 5 % *n*-BMA in olive oil (volume applied: 0.05 ml). Macroscopic skin reactions (erythema and oedema) were evaluated and scored at 24, 48, 72, 96, 144 or 168 hours after each

challenge. No reactions were seen after the first challenge which the authors attribute to the rapid evaporation of *n*-BMA from the skin surface. At the second challenge, 38 and 54 % of the animals challenged by intradermal injection with 0.01 and 0.1 ml *n*-BMA respectively gave positive reactions at 48 hours. Topical application at the second challenge resulted in positive reactions in 88 % of the animals. At the third challenge, 93 % of animals challenged with either 0.4 or 5 % *n*-BMA gave positive results at 72 hours after challenge. Nine male guinea pigs received 100 mg of FCA in the four foot pads on day 0. Each animal received also a single topical application of 0.0077 ml *n*-BMA in 0.2 ml of olive oil. On day 60 each received a topical application of 2 % or 5 % *n*-BMA in olive oil (volume applied 0.05 ml). On day 95 each received a topical application of 10 % *n*-BMA in olive oil. All animals gave positive responses at both application times (Chung and Giles, 1977). These studies are of complex design and difficult to evaluate.

Other Sensitisation Tests

In a standardised skin sensitisation test with *n*-BMA (no details available), one out of 10 guinea pigs was weakly sensitised while the other nine did not show any sensitisation response (Eastman Kodak, 1984).

n-BMA did not induce contact sensitivity in guinea pigs (referred to as strain 13) in an open epicutaneous test. The fact that for immunisation syngenetic haptenised macrophages were used instead of FCA is in this case irrelevant (Von Blomberg-Van der Flier *et al*, 1984).

Cross-sensitisation

In animals sensitised to ethyl and methyl methacrylates, ethyl, *n*-butyl, *t*-butyl, pentyl and neopentyl acrylates, *n*-BMA elicited a sensitisation response (Chung and Giles, 1977; Van der Walle and Bensink, 1982).

Table XVIII: Guinea Pig Sensitisation Tests

Test method	Induction	Challenge	Result[d]	Reference
n-BMA				
Maximisation	d 1: 2 % in liquid paraffin and FCA[a] i.d.[b] d 6: undiluted 24 h occluded	d 21: 10 % in petrolatum 24 h occluded	**–ve** (1/12)	Elf Atochem, 1980c
Maximisation	Unknown	Unknown	**–ve**	Lawrence *et al* , 1974
Maximisation	d 1: 0.5 M in liquid paraffin i.d. [b] d 6: 1 M in ethanol 24 h occluded	d 21, 35: undiluted 24 h occluded	d 21: **–ve** (0/10) d 35: **–ve** (2/10)	Van der Walle *et al* , 1982
FCA[a]	d 1-9: 5 x 0.5 M in FCA[a]	d 21, 35: undiluted 24 h occluded	**–ve** (0/8)	Van der Walle *et al* , 1982
Polak	d 0: FCA[a], 100 µg into 4 footpads d 0, 2, 5: 0.038 ml in 95 % ethanol topical	d 25: 2 or 5 % in 95 % ethanol topical	**–ve** (0/19)[e]	Chung and Giles, 1977
		d 60: 10 % in olive oil topical	**+ve** (88 %)[f]	
		d 60: i.d.[b] 0.01 µl in 0.1 ml saline	**+ve** (38 %)[f]	
		d 60: i.d.[b] 0. 1 µl in 0.1 ml saline	**+ve** (54 %)[f]	
		d 122: 0.4 or 5 % in olive oil (0.05 ml) topical	**+ve** (93 %)[e,f]	
	d 0: FCA[a], 100 µg into 4 footpads d 0: 0.0077 ml in olive oil, topical, 0.2 ml	d 60, d95: topical, 2 or 5 % in olive oil	**+ve** (9/9)[g]	
Not stated	Unknown	Unknown	**–ve** (1/10)	Eastman Kodak, 1984
Open epicutaneous (haptenised macrophages adjuvant)	Haptenised macrophages into ears, footpads and flanks	d 12-14: 28 mg in 20 µl Aramek[h]	**–ve** (0/6)	Von Blomberg-Van der Flier *et al*, 1984
Polak, FCA[a]	d 0: 0.1 ml of 2 mg/ml in ethanol/ saline (1:4) in FCA[a] into 4 footpads and neck	From d 7: 1 x/wk, 12 wk maximum non-irritant concentration in acetone/olive oil (4:1) unoccluded	**–ve** (0/6)	Parker and Turk, 1983
i-BMA				
Maximisation	d 1: 2 % in liquid paraffin i.d. [b] d 6: undiluted 24 h occluded	d 21: 10 % in petrolatum 24 h occluded	**–ve** (0/10)	Elf Atochem, 1980d
Steven's ear/flank test	10 % in DMF[c]	10 %, 1 %, 0.1 % in DMF[c]	**–ve** (0/6)	ICI, 1977a

[a] FCA, Freund's complete adjuvant
[b] i.d., intradermally
[c] DMF, dimethylformamide
[d] **+ve**, positive; **–ve**, negative
[e] both concentrations
[f] total number of animals not given
[g] both concentrations, both application times
[h] Aramek, Arachis oil/methyl ethyl ketone 1:2

***i*-BMA**

i-BMA was not found to be sensitising in a Guinea Pig Maximisation (GMP) test (Elf Atochem, 1980d) and in a Stevens ear/flank test (ICI, 1977a).

7.2.2.6 *Evaluation*

n-BMA/*i*-BMA is irritant to the skin and the eyes of rabbits; *n*-BMA, under certain test conditions, produces stronger irritation than *i*-BMA.

n-BMA/*i*-BMA is not sensitising according to the results of standard Guinea Pig Maximisation tests, whilst *n*-BMA produced weak sensitisation after an additional challenge at day 35.

The results of the FCA test showed that *n*-BMA is not sensitising at the 21 or 25 or 35 days challenges, however cutaneous reactions were observed in animals at additional challenges on day 60 and 122 when induction was made in olive oil and at day 60 with intradermal challenges. Cross-reactions with other acrylates were also recorded in animals sensitised to *n*-BMA .

Overall, these results suggest that *n*-BMA is a weak skin sensitiser. Based on a limited data base *i*-BMA does not appear to be a skin sensitiser.

7.2.3 Subchronic Toxicity

7.2.3.1 *Inhalation*

Ten young adult male rats were exposed (6 h/d, 5 d/wk) to 0 and 1,246 ppm *n*-BMA vapour for 2 weeks. Compared with the controls, rats exposed to *n*-BMA had moderately high red blood cell counts and slightly higher haemoglobin and haematocrit values. Following a 2-week recovery period values had returned to control levels. No other effects attributable to inhalation of *n*-BMA were observed (Kelly, 1977).

Three rats were exposed (6 h/d) to a nominal atmospheric concentration of *n*-BMA of 2,250 ppm for 20 days. No deaths occurred. Animals were lethargic, incontinent and gained less weight than unexposed rats. Histologically there was congestion of blood vessels in liver, lungs and kidneys but no evidence of cell injury (ICI, 1959).

Groups of 5 male and 5 female Crl:CDBR rats were exposed (6 h/d, 5 d/wk) to 0, 310, 952 and 1,891 ppm *n*-BMA for 4 weeks (Hagan *et al*, 1993). The only treatment-related signs of toxicity observed were inactivity, lachrymation, eye squinting and laboured breathing. These signs were

observed sporadically during exposure throughout the study in rats exposed to 952 or 1,891 ppm *n*-BMA. Body weights and food consumption were unaffected by exposure. No toxicologically significant effects were seen at necropsy in haematological and clinical chemistry parameters or in organ weights. The only treatment-related histopathological findings were in the olfactory epithelium of the nasal cavity. These were reported as slight and localised bilateral degeneration of olfactory epithelium lining the dorsal meati of all rats exposed to 1,891 ppm *n*-BMA, and one rat only of each sex exposed to 952 ppm. No effects were observed in the nasal passages of rats exposed to 310 ppm. The no-observable effect level (NOEL) was considered to be 310 ppm *n*-BMA.

7.2.3.2 *Oral*

Mice (numbers and sex not stated) were administered *n*-BMA orally at doses of 1,290 and 2,580 mg/kgbw/d for 30 days (Klimkina *et al*, 1976). The authors concluded from a general condition of the animals and a number of functions (histamine levels, SH groups, enzyme activities) that *n*-BMA was of relatively low toxicity and had a moderate capacity to accumulate in mammals.

7.2.3.3 *Dermal*

No data are available.

7.2.3.4 *Evaluation*

n-BMA/*i*-BMA is of low toxicity via the oral and inhalation routes in repeated exposure studies up to 28 days.

The critical health effect in a 28-day inhalation study in rats was the formation of lesions indicative of an irritant effect in the olfactory region of the nasal cavity, the NOEL being 310 ppm with no evidence for systemic toxicity. In two older, more limited, repeat-exposure inhalation studies transient increases in red blood cell values (above 1,000 ppm) and congestive effects on liver, lungs and kidneys (above 2,000 ppm) were reported.

This lesion in the olfactory region of the nose is consistent with subchronic and chronic inhalation studies with methyl methacrylate and with other volatile esters that are cleaved by non-specific tissue carboxylesterases.

7.2.4 Genotoxicity

7.2.4.1 *In Vitro*

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

_n_-BMA

Waegemaekers and Bensink (1984) reported negative results when *n*-BMA was tested at a range of doses from 40-2,500 mg *n*-BMA/plate in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 in the presence and absence of Aroclor 1254-induced or phenobarbital-induced rat liver S9-mix in a standard plate incorporation assay. To minimise the evaporation of volatile materials the treated plates were sealed in glass air-tight exposure jars. The same authors also reported *n*-BMA to be negative when tested in TA 100 in a liquid pre-incubation assay at concentrations of 100, 1,000 and 10,000 mg/2 ml incubation volume in the presence and absence of Aroclor 1254-induced S9-mix.

A pre-incubation screening assay with *S. typhimurium* strain TA 1538 at doses between 0.0028 and 10 ml *n*-BMA/plate showed a positive response at 3.1 and 10 ml/plate with metabolic activation (Aroclor-induced rat liver S9) (McGoldrick *et al*, 1990). This rapid screening test was followed by a definitive pre-incubation assay (McGoldrick *et al*, 1991). In the definitive study, doses ≥ 0.094 ml/plate produced signs of toxicity consisting of precipitation, reduced or absent background lawns and/or microcolonies in the preliminary toxicity assay with TA 1537 and TA100. At concentrations of 0.0028 to 0.3 ml/plate, *n*-BMA was found to be negative both with and without metabolic activation (Aroclor-induced rat liver S9). The investigators concluded that *n*-BMA was not a mutagen in this test system. A standard plate incorporation assay with and without metabolic activation by Aroclor-induced rat liver S9 was negative at doses between 60 and 300 mg/plate in the strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 (Du Pont, 1976).

Zeiger *et al* (1987) reported *n*-BMA as non-mutagenic in 2 pre-incubation assays using *S. typhimurium* strains TA1535, TA1537, TA98 and TA100. The compound (purity 99 %) was tested over a range of doses from 1-10,000 mg *n*-BMA/plate in the presence and absence of Aroclor-1254 induced rat and Syrian hamster liver S9-mix. No significant increases in the numbers of revertant colonies were observed at doses which also resulted in cytotoxicity.

***i*-BMA**

Zeiger *et al* (1987) reported *i*-BMA (purity 98 %) as non-mutagenic between 100 to 10,000 mg *i*-BMA/plate under otherwise similar conditions as detailed above in the presence and absence of Aroclor-1254 induced rat and Syrian hamster liver S9-mix. No significant increases in the numbers of revertant colonies were observed at doses which also resulted in cytotoxicity.

7.2.4.2 *In Vivo*

***i*-BMA**

A micronucleus test has been performed with *i*-BMA in mouse bone marrow cells according to OECD Guideline 474. Dose groups of 5 female and 5 male NMRI mice were treated by gavage with a single dose of 5,000 mg/kgbw (MTD) in carboxymethyl cellulose (1 %). The animals were sacrificed 24, 48 and 72 hours after administration. A cytotoxic effect was evidenced by a reduction in number of polychromatic erythrocytes (PCE) in relation to the normochromatic erythrocytes (NCE). A score of 1,000 PCE was determined for each animal revealing no indication for a genotoxic activity of *i*-BMA *in vivo* (Röhm, 1989).

7.2.4.3 *Evaluation*

Neither *n*-BMA nor *i*-BMA were mutagenic in a number of bacterial gene mutation assays. *i*-BMA was not clastogenic in a mouse micronucleus assay. There is no alert for genotoxicity although it must be noted that the database is limited and relies, in part, on the close structural similarity of the two isomers.

7.2.5 Chronic Toxicity and Carcinogenicity

7.2.5.1 *Chronic Toxicity*

No data are available for carcinogenicity and no reliable data are available for chronic toxicity of *n*-BMA/*i*-BMA.

A limited chronic study is available. Aqueous solutions of *n*-BMA were administered orally (5 x/wk) to groups of 10 rats (0, 0.05, 0.5 and 5.0 mg/kgbw) and 8-9 rabbits (0, 0.5 and 5.0 mg/kgbw) for 9-10 months. A number of haematological, serum chemistry, liver and brain parameters were measured in one or both species together with histopathological examination of organs (unspecified but which included the liver). The authors state that the liver is a target organ for toxicity but claim the erythrocytes become more acid resistant and that some biochemical/physiological changes occur in the brain. The minimum dose was considered to be 0.5 mg/kgbw with a no-effect level of

0.05 mg/kgbw (Klimkina *et al*, 1976). The study as reported lacks essential detail, such as nature and severity of the changes which would be required to determine the significance of the findings. Due to these limitations this study is of questionable validity and relevance.

7.2.5.2 *Evaluation*

_n_-BMA/_i_-BMA

By discounting the study of Klimkina *et al* (1976), the longest duration repeat dose study available on *n*-BMA is the 28-day inhalation toxicity study in rats (Hagan *et al*, 1993). In this study the most sensitive endpoint was irritation of the olfactory epithelium in the nasal cavity. This lesion has also been observed in acute and subchronic inhalation studies conducted with methyl methacrylate and other volatile esters, and has been confirmed in chronic inhalation studies as the critical health effect by this route of exposure (ECETOC, 1995a; see further below).

Recent subchronic studies with methyl methacrylate in rats (Zeneca, 1997) have demonstrated that the olfactory lesions arise rapidly and that by 28 days adaptation of the tissue occurs, a normal phenomenon observed following exposure to many other chemicals. Consequently, the NOEL of 110 ppm for the onset of olfactory lesions in this study is comparable to the NOEL of 25 ppm reported by Rohm and Haas (1979) and Lomax *et al* (1994) following acute and subchronic exposure to methyl methacrylate. (In the latter two studies, the next dose level of 100 ppm showed only mild effects in a proportion of the animals.) Therefore, the 28-day study for *n*-BMA is regarded as a reliable indicator of the effects of chronic exposure. It is anticipated that *i*-BMA will have similar toxicity.

Further information on the toxicity of *n*-BMA/*i*-BMA may be gained by direct analogy to methyl methacrylate, for which there are more extensive relevant data. These data have been extensively reviewed by ECETOC (1995a) and the toxicological profile provides little cause for concern (Appendix A). Perhaps the key studies worthy of further consideration in this context are a chronic drinking water study and two chronic inhalation studies.

Administration for 2 years of methyl methacrylate to male and female Wistar rats via their drinking water up to a concentration of 2,000 mg/l gave no indication of the development of treatment-related tumours. The only significant finding was a increase in relative kidney weight in the females (Borzelleca *et al*, 1964).

In a chronic inhalation study, F344/N rats and B6C3F_1 mice (male and female animals in both cases) were exposed to methyl methacrylate concentrations between 250 and 1,000 ppm for 102 weeks. The main toxic effects were inflammation in the nasal cavity and degeneration of the olfactory sensory

epithelium (NTP, 1986; Chan *et al*, 1988). These effects were probably caused by methacrylic acid, which is derived from methyl methacrylate cleavage catalysed by the carboxyl esterases in the upper respiratory tract (Morris and Frederick, 1995).

In another two-year inhalation study, F344/N rats were exposed to methyl methacrylate at concentrations between 25 and 400 ppm. A NOEL of 25 ppm for irritation of the olfactory epithelium was determined (the next dose level of 100 ppm showed only mild effects in a proportion of the animals). (Rohm and Haas, 1979; Lomax *et al*, 1994)

For further discussion of the chronic toxicity of methyl methacrylate, see ECETOC (1995a) which concluded that there is no concern with regard to carcinogenic potency. A similar judgement was reached by the International Agency for Research on Cancer in 1994 when it concluded that there is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals and inadequate evidence in humans (IARC, 1994).

Considering the likely rapid hydrolysis of *n*-BMA/*i*-BMA and the potential for exposure to the free acid and alcohol during chronic toxicity studies, toxicity data on the hydrolysis products may provide further insight into the chronic toxicity of *n*-BMA/*i*-BMA.

While repeated-exposure studies exist for methacrylic acid and isobutanol, extrapolation of their findings to the toxicity of *i*-BMA should be undertaken with circumspection owing to the uncertainties associated with the rates of hydrolysis of the ester and subsequent release of the acid and alcohol. Some concern with regard to carcinogenicity is implied by the studies of Gibel *et al* (1974, 1975) who reported carcinomas occurring in Wistar rats after chronic oral and s.c. administration of isobutanol during their lifetime (oral: single dose of 0.2 ml/kgbw, 2 x/wk, average survival time 495 days; s.c.: single dose 0.06 ml/kgbw, 2 x/wk; average survival time 544 days). Carcinomas were reported in 3 of 19 treated animals (0 of 25 controls) after oral administration, including 2 forestomach carcinomas, 1 liver carcinoma and 2 leukemias. After s.c. administration 8 of 24 animals (0 of 25 controls) had carcinomas, including 2 forestomach carcinomas, 2 liver sarcomas, 1 mesenthelioma, 1 spleen sarcoma and 2 retroperitoneal sarcomas. These studies are poorly reported, lack sufficient detail to evaluate the data and are considered not to be in accordance with current standards (IPCS, 1987). The US Environmental Protection Agency has added isobutanol to the Priority Testing List requesting an oncogenicity study (US-EPA, 1991) but no further data are presently available.

In summary, the lead health effect seen in a 28-day inhalation study with *n*-BMA was lesions in the olfactory region of the nasal passage with a NOEL of 310 ppm. This lesion is common to methyl methacrylate and other volatile esters for which localised metabolism results in the liberation of free

acid which in turn evokes tissue toxicity. As the lesion is not anticipated to progress significantly this study is judged relevant for assessment of the effects of the chronic exposure. A possible carcinogenic effect of isobutanol at present cannot be completely excluded. Therefore once reliable data on metabolism of the esters and the carcinogenicity of the alcohols are available the hazard assessment of *n*-BMA/*i*-BMA will have to be reconsidered.

7.2.6 Reproductive Toxicity

7.2.6.1 *Fertility and Effects on Reproductive Organs*

No specific data are available.

In the 28-day inhalation toxicity study (Section 7.2.3.1) there was no evidence for an effect of *n*-BMA on male or female reproductive organs of rats (Hagan *et al* ,1993).

7.2.6.2 *Teratology*

_n_-BMA/_i_-BMA

n-BMA/*i*-BMA was administered undiluted by the i.p. route. to groups of 5 female Sprague-Dawley rats at doses equating to 1/10, 1/5 and 1/3 of the acute LD_{50} value i.e., 205, 411 and 686 mg *n*-BMA/kgbw or 124, 248, 414 mg *i*-BMA/kgbw, on day 5, 10 and 15 of gestation. The following observations were reported for both esters. A significant increase of resorptions was observed in the high dose group and a dose related increase of gross abnormalities in the foetuses. No significant increases in skeletal abnormalities were observed above controls. A dose-dependent decrease in foetal weight was reported by the author, but the data does not support this claim. Maternal toxicity of the dams was not reported (Singh *et al*, 1972a,b).

The studies by Singh *et al* suggest that *n*-BMA/*i*-BMA may possess teratogenic potential in the rat by the i.p. route. However, the study design is flawed as it did not exclude recognised confounding factors such as maternal toxicity and local irritation, both of which could have been predicted as being unavoidable using this protocol. Since this study was published it has become widely accepted that the i.p. route is not an appropriate route of administration for the assessment of developmental hazard of industrial chemicals and particularly for chemicals that are contact site irritants.

7.2.6.3 *Evaluation*

Whilst the data available on *n*-BMA/*i*-BMA are limited and of dubious quality, reliable data are available for the close structural analogue methyl methacrylate and butanol.

A series of studies conducted on methyl methacrylate have shown no teratogenic effects following inhalation exposure of rats and mice (ECETOC, 1995a). Of these studies the most definitive study, conducted in accordance with current OECD and EPA guidelines, is that of Solomon *et al* (1991) in which no teratogenicity, embryotoxicity or foetotoxicity was observed in Crl:CDBR rats at exposure levels up to 2,028 ppm which were maternally toxic.

Singh *et al* (1972a,b) also conducted developmental toxicity studies on methyl methacrylate using the same protocol as reported in Section 7.2.6.2 for *n*-BMA/*i*-BMA and again reported positive findings. The study findings of Solomon *et al* demonstrated that this protocol is perhaps inappropriate for hazard assessment under relevant exposure conditions.

While no data are available for methacrylic acid, *n*-butanol did not show developmental toxicity in doses that were not maternally toxic when Sprague-Dawley rats were exposed (7 h/d) by inhalation to 0, 3,500, 6,000 and 8,000 ppm from day 1 to 19 of gestation. The NOAEL for maternal and developmental toxicity was 3,500 ppm (Nelson *et al*, 1989a, 1990).

Similarly no effects on embryo- or foetotoxicity or development of the foetus were observed in Wistar rats or Himalayan rabbits receiving oral doses (6 h/d) of 0.5, 2.5 or 10 mg/l of isobutanol from day 6 to 15 of gestation. In rats no maternal toxicity was observed; in rabbits a slightly reduced maternal body weight gain was reported in the high dose animals (BASF, 1990a,b).

Taken together, the data available for methyl methacrylate and butanol do not suggest a concern for possible developmental effects of *n*-BMA/*i*-BMA administered by inhalation at non-maternally toxic concentrations.

In the 28-day inhalation toxicity study there was no evidence for an effect of *n*-BMA on male or female reproductive organs of rats. Limited information on relative hazard can be found in the literature on methyl methacrylate, methacrylic acid and *n*-butanol.

No effects on reproductive organs were observed in two-year inhalation studies with methyl methacrylate in rats and mice (NTP, 1986; Rohm and Haas, 1979) and in 90-day inhalation studies in rats and mice with methacrylic acid (CIIT, 1984).

In a fertility study of *n*-butanol in male rats exposed (7 h/d) to 3,000 and 6,000 ppm, for 6 weeks and mated with unexposed females no influence on pregnancy rate was observed, indicating that fertility was not affected (Nelson *et al*, 1989a,b).

Taken together, the limited available data on *n*-BMA, methyl methacrylate, methacrylic acid and *n*-butanol do not suggest a concern for possible reproductive effects arising from routes of administration relevant to occupational exposure.

7.3 EFFECTS ON HUMANS

7.3.1 Short-term Exposure

No data are available.

7.3.2 Irritation, Sensitisation and Immunotoxicity

7.3.2.1 *Skin Sensitisation*

One of 542 dermatitis patients gave a positive patch test result with n-BMA (technical grade, 1 % in petrolatum) (Maibach *et al*, 1978).

One case of a positive patch test reaction to *n*-BMA (1 % solvent not mentioned) in a patient not working with acrylates was reported by Mikulecky *et al* (1962), who did not differentiate between an irritant and a contact allergic effect.

One case of contact dermatitis with a positive patch test reaction after 48 and 96 hours with *n*-BMA (1 % in ethanol) was reported from the use of artificial fingernails (Marks *et al*, 1979). The authors report that the sensitising agent in these preparations was ethyl methacrylate and the patient's reaction to *n*-BMA represents cross-sensitisation.

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

7.3.3 Long-term Exposure

No data are available.

7.3.4 Evaluation

Despite the use of *n*-BMA/*i*-BMA for many years, no adverse health effects have been reported. The sensitisation potential of *n*-BMA to humans seems to be low.

8. GROUPS AT EXTRA RISK

No groups of workers have been identified that would be at extra risk from occupational exposure to *n*-BMA/*i*-BMA.

9. GAPS IN KNOWLEDGE AND ONGOING RESEARCH

9.1 ACUTE TOXICITY

None.

9.2 IRRITATION AND SENSITISATION

None.

9.3 REPEATED EXPOSURE

The critical health effect in a 28-day inhalation study in rats is the development of lesions in the olfactory region of the nasal cavity. It is anticipated that this localised lesion would be present in chronic studies with *n*-BMA/*i*-BMA and that the NOEL would be comparable.

Following systemic absorption *n*-BMA is relatively rapidly hydrolysed to methacrylic acid and *n*-butanol. Chronic studies with methyl methacrylate, which also liberates methacrylic acid upon hydrolysis, indicate that there is little concern for chronic toxicity due to systemically derived methacrylic acid. The chronic toxicity of *n*-butanol and isobutanol is well characterised. No further studies are considered necessary.

9.4 CARCINOGENICITY

No carcinogenicity studies are available on *n*-BMA/*i*-BMA.

By analogy with methyl methacrylate there is no concern for the carcinogenicity of the parent esters *n*-BMA/*i*-BMA or for the primary metabolite methacrylic acid. Whilst there is no concern for the carcinogenicity of the *n*-butanol metabolite the same cannot be said for isobutanol. The carcinogenic potential of isobutanol is currently under investigation (US-EPA, 1991) and the outcome of these investigations will be of relevance to the hazard assessment of *i*-BMA.

9.5 GENOTOXICITY

Only bacterial mutagenicity data exist for *n*-BMA. In addition, only *i*-BMA has been assessed in a mammalian micronucleus study. Current approaches to the assessment of genotoxicity would suggest that a mammalian chromosomal aberration study is lacking for *n*-BMA. However, as *i*-BMA did not show clastogenic activity in the mouse micronucleus test, there is no immediate concern with regard to genotoxicity for *n*-BMA due to the close structural similarity of both molecules.

9.6 DEVELOPMENTAL TOXICITY AND TERATOGENICITY

No developmental toxicity or teratogenicity studies are available with *n*-BMA/*i*-BMA. A teratology study in rat is performed by INRS (1997).

As *n*-BMA/*i*-BMA is rapidly hydrolysed into methacrylic acid and the corresponding butanol it is assumed that the blood level of methacrylic acid is high and that it is methacrylic acid that predominantly reaches the placenta. It follows that the results of the studies performed with methyl methacrylate, that also liberates methacrylic acid upon hydrolysis, could be used for the assessment of the developmental toxicity hazard of *n*-BMA/*i*-BMA.

Methyl methacrylate has been shown to be not teratogenic, embryotoxic or foetotoxic in a teratology study by the inhalation route of exposure (Solomon *et al*, 1991). Furthermore, methyl methacrylate did not reveal an effect on male fertility in mice exposed up to 9,000 ppm over a period of 5 days.

The negative results in the developmental toxicity studies with *n*-butanol and isobutanol (Nelson *et al*, 1989a, 1990; BASF, 1990a,b) suggest that there is no concern with regard to the other product of *n*-BMA/*i*-BMA hydrolysis for this endpoint.

10. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Three industrialised countries have adopted occupational exposure limit values (Table XIX).

Table XIX : Occupational Exposure Limit Values for *n*-BMA/*i*-BMA

Country	TWA (ppm)	TWA (mg/m^3)[a]	STEL (15min) (ppm)	STEL (mg/m^3)[a]	Reference
Norway	50[b]	300	75	450	Arbeidstilsynet, 1995
Sweden	50[c]	300	75	450	AFS, 1996
Netherlands	10	59	-	-	Arbeidsinpectie, 1996

TWA Time-weighted average concentration (8-h working period)
STEL Short-term exposure limit (15 min, unless specified otherwise)
[a] Official values; some countries use different conversion factors and/or other ambient temperature
[b] "A" (allergenic)
[c] "S" (sensitising)

Several *n*-BMA/*i*-BMA monomer and polymer producing companies have adopted internal OEL's for *n*-BMA/*i*-BMA at or around 50 ppm with a STEL of 75 ppm.

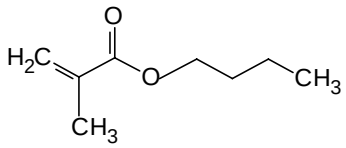
11. SUMMARY EVALUATION AND RECOMMENDATION FOR A SCIENTIFICALLY-BASED OCCUPATIONAL EXPOSURE LIMIT

11.1 SUBSTANCE IDENTIFICATION

11.1.1 *n*-Butyl Methacrylate

Common name:	*n-B*utyl methacrylate (*n*-BMA)
CAS registry No.	97-88-1
EEC No.	607-033-00-5
EEC classification:	Irritant
EEC labelling:	Symbol irritant (Xi), R10-36/37/38-43, nota D
EINECS name:	2-Propenoic acid, 2-methyl-, butyl ester
EINECS No.	202-615-1
Formula:	$C_8H_{14}O_2$

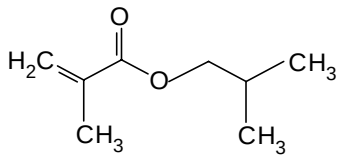
Structure:



Molecular mass:	142.20

11.1.2 Isobutyl Methacrylate

Common name:	Isobutyl methacrylate (*i*-BMA)
CAS registry No.	97-86-9
EEC No.	607-113-00-X

EEC classification:	Irritant
EEC labelling:	Concentration ≥ 20 %: symbol irritant (Xi), R 10-36/37/38-43; S 24-37, nota D 1 % ≤ concentration < 20 %: symbol irritant (Xi), R43
EINECS name:	2-Propenoic acid, 2-methyl-, 2-methylpropyl ester
EINECS No.	202-613-0
Formula:	$C_8H_{14}O_2$
Structure:	
Molecular mass:	142.20

11.2 OCCURENCE AND USE

11.2.1 Chemical and Physical Properties

At room temperature, *n*-BMA and *i*-BMA are clear, colourless, flammable liquids with a faint characteristic ester odour. Both compounds have a low solubility in water and are soluble in most organic solvents. *n*-BMA/*i*-BMA has a low vapour pressure of 2.4 and 2.4-4 hPa at 20 °C respectively.

n-BMA/*i*-BMA polymerises readily under the influence of heat, light or by catalysis (e.g. metals and radical forming substances such as peroxides), this being a strongly exothermic reaction. To prevent polymer formation, the monomer is stabilised by the addition of inhibitors such as hydroquinone.

Conversion factors for concentrations of *n*-BMA and/or *i*-BMA in air at 20 °C and 1,013 hPa are:

- 1 ppm = 5.91 mg/m^3
- 1 mg/m^3 = 0.169 ppm

11.2.2 Occurrence and Use

n-BMA/*i*-BMA is used as a monomer or co-monomer for the industrial production of acrylic polymers, acrylic surface coatings, in the production of resins, solvent coatings, adhesives and oil additives, emulsions for textile, leather and paper finishing, concrete treatment, the manufacture of contact lenses, in paraffin embedding media and dental polymers.

In EU countries, 32 kt of *n*-BMA and 8 kt of *i*-BMA were produced in 1994. Production in 1995 was 12 % higher than 1994. Approximately 13 % of the Western European *n*-BMA/*i*-BMA production was exported in 1994 (CEFIC, 1996).

11.2.3 Exposure Levels at the Workplace

Workplace concentrations of *n*-BMA/*i*-BMA during monomer production and polymerisation in the EU in 1994 were less than 1 mg/m^3 (0.2 ppm), expressed as a 4-8 hour time-weighted average (TWA). Short-term levels were higher during certain operations, e.g. during block polymerisation, in the laboratory up to 3.77 mg/m^3 (0.63 ppm) or in a pump house 7.6 mg/m^3 (1.29 ppm) (CEFIC, 1996). Workplace concentrations of *n*-BMA and other vapours during the extrusion of acrylic sheets ranged between < 0.1 and 8 ppm (< 0.6-47 mg/m^3) under normal conditions and between < 0.1 and 16.5 ppm (< 0.1-97.5 mg/m^3) under degradation conditions (600 °F or 315 °C) (Rohm and Haas, 1989). Limited data on dispersive down-stream uses suggests that workplace concentrations are appreciably higher, i.e. up to 8 ppm (45.5 mg/m^3) (Froines and Garabrant, 1986a,b).

11.2.4 Exposure Levels in the Environment

No data are available on *n*-BMA/*i*-BMA levels in air, water, soil and biota. Environmental releases during production and major industrial uses are low.

11.2.5 Measuring methods

n-BMA/*i*-BMA in workplace air can be determined by means of NIOSH method 1450 (esters I), involving adsorption on activated carbon by active sampling (4 l/h) followed by desorption with carbon disulphide and analysis by GC/FID. Detection limits are 0.06 mg/m^3 for an 8-hour sample and 6 mg/m^3 for short-term measurements (5 min) (NIOSH, 1984; Röhm, 1996). Using a similar method Degussa (1992) achieved a detection limit of 1 μg/sample (17 μg/m^3).

11.3 HEALTH SIGNIFICANCE

From the physico-chemical data and by analogy with methyl methacrylate it is anticipated that *n*-BMA/*i*-BMA is rapidly absorbed after oral and inhalation exposure.

n-BMA is rapidly hydrolysed by carboxyl esterases yielding methacrylic acid and *n*-butanol (Kotlovskii *et al*, 1988; McCarthy and Witz, 1990, 1991, 1997; McCarthy, 1995). By analogy with methyl methacrylate it is anticipated that hydrolysis of *n*-BMA/*i*-BMA with further metabolism of the respective cleavage products methacrylic acid and *n*-butanol or isobutanol by normal physiological pathways (to ultimately CO_2) will be the main route of metabolism for *n*-BMA/*i*-BMA (Von Rietbrock and Abshagen, 1971; Saito, 1975; Bratt and Hathway, 1977; ICI, 1977b; Di Vincenzo and Hamilton, 1979; McCarthy and Witz, 1991).

n-BMA/*i*-BMA possesses a low order of acute oral, dermal and inhalation toxicity in experimental animals. Where symptoms were reported they are consistent with exposure to an irritant material (for references, see Table VIII to XIII). A skin notation (for systemic toxicity following dermal absorption) is not warranted (ECETOC, 1993).

n-BMA/*i*-BMA is irritant to the rabbit skin (Röhm, 1977b,c; Elf Atochem, 1980a,b; Degussa, 1982; Sarver, 1993b) and rabbit eye (ICI, 1959, 1977a; Smyth *et al*, 1969; Powell *et al*, 1970; Elf Atochem, 1980a,b; Röhm, 1988e,f; Hagan *et al*, 1993). *n*-BMA appears to be a weak skin sensitiser whilst *i*-BMA is not (references in Table XVIII).

Neither *n*-BMA nor *i*-BMA were mutagenic in a number of bacterial gene mutation assays (Du Pont, 1976; Waegemaekers and Bensink, 1984; Zeiger *et al* ,1987; McGoldrick *et al*, 1990, 1991). *i*-BMA was not clastogenic in a mouse micronucleus assay (Röhm, 1989). The limited data on *n*-BMA/*i*-BMA indicate that neither compound is mutagenic.

No data are available for carcinogenicity and toxicity to reproduction. However, information concerning potential hazards of *n*-BMA/*i*-BMA can be inferred from studies with methyl methacrylate which is metabolised to the same metabolic product, methacrylic acid, as *n*-BMA/*i*-BMA in animals and humans. The data on methyl methacrylate have been extensively reviewed by ECETOC (1995a). In particular, a chronic drinking water study with methyl methacrylate in rats (Borzelleca *et al*, 1964), an inhalation study in rats and mice (NTP, 1986; Chan *et al*, 1988) and an inhalation study in rats (Rohm and Haas, 1979; Lomax *et al*, 1994) suggest that *n*-BMA/*i*-BMA is unlikely to possess carcinogenic potential. According to a teratogenicity study by Solomon *et al* (1991) and teratogenicity studies with *n*-butanol and isobutanol (Nelson *et al*, 1989a, 1990; BASF, 1990a,b), *n*-BMA/*i*-BMA, by relevant exposure routes, is not expected to cause adverse effects to the developing embryo or foetus.

No effects on the reproductive organs were observed in a repeated dose study with *n*-BMA (Hagan *et al*, 1993) as well as in two-year inhalation studies with methyl methacrylate in rats and mice (NTP, 1986; Rohm and Haas, 1979) and in 90-day inhalation studies with methacrylic acid in rats and mice

(CIIT, 1984). In a fertility study of *n*-butanol in male rats exposed by the inhalation route no effects on fertility were observed (Nelson *et al*, 1989a,b). Therefore *n*-BMA/*i*-BMA is not expected to cause significant adverse effects to the reproductive organs by relevant occupational exposure routes.

The lead health effect seen in a 28-day inhalation study with *n*-BMA in rats was irritation of the olfactory region of the nasal cavity with a NOEL of 310 ppm (Hagan *et al*, 1993). This lesion has also been observed in acute and subchronic inhalation studies conducted with methyl methacrylate and other volatile esters (ECETOC, 1995a), and has been confirmed in two chronic inhalation studies with MMA as the critical health effect by this route of exposure (NTP,1986 and Chan *et al*, 1988; Rohm and Haas, 1979; Lomax *et al*, 1994). Recent studies with methyl methacrylate have demonstrated that the olfactory lesions arise rapidly and do not progress significantly beyond 28 days and up to 2 years (Zeneca, 1997). Therefore, the 28-day study for *n*-BMA is regarded as a reliable indicator of the effects of chronic exposure. It is anticipated that *i*-BMA will exhibit similar toxicity to that of *n*-BMA.

11.4 FINAL EVALUATION AND RECOMMENDATION

Because of the close similarity of *n*-BMA/*i*-BMA and the comparability of their toxicity data, they will be considered jointly.

11.4.1 Hazard Identification

The major route of occupational exposure is the inhalation route, even though exposure is limited by the low vapour pressure of *n*-BMA/*i*-BMA.

The critical health effect of *n*-BMA/*i*-BMA identified in acute and subchronic inhalation studies is the development of a localised lesion in the olfactory region of the nasal passage. The NOEL for this effect is 310 ppm in the rat. The NOEL for chronic exposure is not anticipated to differ markedly.

The lesion in the olfactory tissue is believed to be the result of hydrolysis of the inhaled ester by tissue carboxyl esterase enzymes resulting in the formation of cytotoxic levels of methacrylic acid. Human olfactory tissue contains carboxyl esterase enzymes capable of hydrolysing *n*-BMA/*i*-BMA and therefore the lesion is of relevance to man. However, it is generally accepted that the rat is more sensitive than man to the effects of nasal irritants due to physiological and anatomical differences. The specific activity of carboxyl esterases responsible for the hydrolysis of methyl methacrylate in rat olfactory tissue is approximately 6-fold higher than the corresponding activity in human olfactory tissue (Zeneca, 1996). In addition, the rat is an obligate nose breather with significantly more complex nasal passages than man. The relative surface area per unit volume in the nose of the rat is 8 times that of man

(DeSesso, 1993) and this should be taken into consideration when establishing a health-based Occupational Exposure Limit value (OEL).

11.4.2 Risk Assessment

The main populations likely to be exposed to *n*-BMA/*i*-BMA are workers involved in production of the monomers and in industrial manufacture of polymers for use in products such as coatings, oil additives and adhesives, and workers in small down-stream user industries. Consumer exposure and indirect exposure to the monomer via the environment are considered negligible because of low levels of release and lack of persistence.

When deriving an OEL from the NOEL of 310 ppm observed in the 28-day rat inhalation study the following considerations may be made.

In terms of extrapolation from subchronic to chronic exposure to *n*-BMA/*i*-BMA, the adjustment factor to be used can be based on the effects observed with the closely related compound methyl methacrylate which hydrolyses to the same metabolite (methacrylic acid) and for which it has been shown that hydrolysis is a key step in the development of the nasal lesion (Zeneca, 1996). Indeed, the nasal effects observed with *n*-BMA/*i*-BMA in the 28-day inhalation study in rats are the same as those observed with methyl methacrylate, albeit at a higher exposure concentration. With both materials, the critical effect consists of localised lesion in the olfactory region of the nasal passages. Studies on methyl methacrylate (Zeneca, 1997), using the same strain of rat as used in the chronic studies, have demonstrated that the exposure level that produced olfactory lesion remained constant from acute to subchronic and to chronic exposure conditions. In these studies, the lesions developed within 6 hours of the onset of acute exposure with a LOEL of 110 ppm. After continuous exposure for 28 days the LOEL was still 100 ppm and after 2 years exposure the LOEL was 100 ppm; the NOEL was 25 ppm. Based upon what is observed with methyl methacrylate, no adjustment factor would be needed to extrapolate from short to long-term exposure to *n*-BMA/*i*-BMA. However, because there are no specific data on the kinetics and metabolism of *n*-BMA/*i*-BMA in rat nasal tissue, an adjustment factor of 3, to reflect this limitation of the database, is proposed as an overall adjustment factor for study duration (ECETOC, 1995b) .

Both toxicodynamic and toxicokinetic elements must be considered when establishing an overall factor for inter-species extrapolation, i.e. from rodents to humans.

In terms of toxicodynamic differences between rodents and humans, it is believed that as the tissue damage is caused by the localised production of MAA within the tissue and the mechanism of cellular

toxicity will be essentially the same in both species, no adjustment for toxicodynamic differences is justified.

In terms of toxicokinetic differences, the olfactory tissue was identified as the most sensitive tissue in the rat study. This is confirmed in the studies with methyl methacrylate in which histological examination in the 2-year inhalation study in the rat showed that the LOEL for lesion development in the olfactory tissue was 100 ppm, whereas the LOEL for the next most sensitive tissue, the respiratory epithelium, was 400 ppm.

Whilst it may be expected that these effects will occur in humans, it must be recognised that humans, unlike rodents, breath through the mouth as well as the nose and therefore it is not possible to judge with certainty whether the olfactory epithelium is the primary target or whether damage occurs in other regions of the respiratory system. Whilst there is no data for relative sensitivity of tissues in humans, a recent publication using acyclovir 2'-esters in rats has shown that esterase activity within the respiratory system is highest in nasal (combined olfactory and respiratory) tissue with the order of activities: nasal; pulmonary parenchymal (lower alveolar); trachea (Shao *et al*, 1994). This strongly suggests that the olfactory epithelium is the most sensitive epithelium of the respiratory tract (US-EPA, 1991) in both rats and humans and that an NOEL for effects on this tissue will protect against damage occurring in other less sensitive tissues.

Although the olfactory tissue will be the most sensitive tissue in the human respiratory system the level at which the effect will occur may vary due differences in regional dosimetry and metabolism. It is becoming increasingly recognised that physiological and morphological differences between the nasal passages of rats and humans favour significantly higher (up to 8 times) deposition in the rats than humans (DeSesso, 1993). Similarly, recent studies with methyl methacrylate and other esters indicate that there are other toxicokinetic differences between rodents and humans which also have bearing. Recent studies with methyl methacrylate indicate that there is significantly less carboxylesterase activity in human than rodent olfactory tissue (Zeneca, 1996). This would result in a lower rate of conversion of ester to free acid and a reduced "metabolic draw" (concentration gradient across the tissue as a result of removal of intracellular ester by metabolism) into the olfactory tissue of humans when compared to that of rodents. Other aspects that may also have bearing, such as partitioning of the volatile ester into mucous, absorption into the olfactory tissue and clearance, may also vary between rodents and humans but probably to a lesser extent. Hence, no adjustment factor for toxicokinetic differences is considered justified.

As the available data suggest that the rat is likely to be the more sensitive species, and therefore provides an inherent safety factor when evaluating risk to man, no additional factor for inter-species

extrapolation is considered necessary. Consequently, an overall adjustment factor of 1 is judged appropriate.

There are no data on intra-species variation in regard to the potential development of this type of lesion in humans other than it is known that carboxylesterase enzymes are ubiquitous and hypersensitivity due to the dysfunction of this family of enzymes has not been reported. Hence, intra-species variation would be expected to be low. In the absence of relevant data, a default factor of 2 has been recommended for intra-species variation in occupational situations (ECETOC, 1995b).

Thus by applying an overall assessment factor of 6 (3x1x2) to the NOEL of 310 ppm a health based OEL of approximately 50 ppm is derived.

A STEL (15 min) of approximately 150 ppm is recommended, based on the NOEL in the 28-day inhalation study in rats and the intra-species adjustment factor of 2.

Based on the physico-chemical data it is anticipated that *n*-BMA/*i*-BMA can be absorbed through the skin. However, *n*-BMA/*i*-BMA is of low systemic toxicity following single dermal exposure (and by other routes). Therefore, a skin notation is not required (ECETOC, 1993).

11.4.3 Recommendation

An OEL of 50 ppm (300 mg/m^3) (8-h TWA) is recommended for *n*-BMA/*i*-BMA.

A STEL (15 min) of approximately 150 ppm (890 mg/m^3) is recommended.

A skin notation is not warranted.

At present, no method for biological monitoring can be recommended.

In workplace air, *n*-BMA/*i*-BMA can be determined by means of NIOSH method 1450 (esters I) or similar.

11.5 KEY BIBLIOGRAPHY

BASF (1990a). Prenatal toxicity of 2-methyl-1-propanol in rats after inhalation. Project 37R 0057/ 88047. Volume I, report. Programme for the prevention of health hazards caused by industrial substances. BG Chemie, Heildelberg.

BASF (1990b). Prenatal toxicity of 2-methyl-1-propanol in rabbits after inhalation. Project 90R0057/88048. Volume I, report. Programme for the prevention of health hazards caused by industrial substances. BG Chemie, Heildelberg.

Borzelleca, J.F., Larson, P.S., Hennigar, G.R., Huf, E.G., Crawford, E.M., Blackwell Smith, R. (1964). Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. *Toxicol. Appl. Pharmacol.*, **6**, 29-36.

Bratt, H., Hathway, D.E. (1977). Fate of methyl methacrylate in rats. *Brit. J. Cancer*, **36**, 111-119.

CEFIC (European Chemical Industry Council) (1996). Data of *n*- and iso-butyl methacrylate. Letter by Thomas D. CEFIC Methacrylates Toxicology Committee, Brussels.

Chan, P.C., Eustis, S.L., Huff, J.E., Haseman, J.K., Ragan, H. (1988). Two year inhalation carcinogenesis studies of methyl methacrylate in rats and mice: inflammation and degeneration of the nasal epithelium. *Toxicol.*, **52**, 237-252.

CIIT (Chemical Industry Institute of Toxicology) (1984). 90-Day vapor inhalation toxicity study of methacrylic acid in B6C3F_1 mice, Sprague-Dawley rats and Fischer-344 rats. Toxicogenics study 420-1086, revised. CIIT, Research Triangle Park NC.

Degussa (1982). Bericht über die Prüfung der lokalen primären Reiz-/Ätzwirkung von *n*-Butylmethacrylat (Methacrylsäure-*n*-butylester, *n*-BUMA) nach einmaliger Applikation an der Haut des Kaninchens (Patch-Test). Zechel, H.J., Tox. Inst. Degussa-Asta. Degussa, Hanau.

Degussa (1992). Bericht über die Messung luftfremder Stoffe nach TRGS 402. TÜV Rheinland, Institut für Umweltschutz und Energietechniek, rep. 920-2540202. Degussa, Wesseling.

DeSesso, J.M. (1993). The relevance to humans of animal models for inhalation studies of cancer in the nose and upper airways. *Quality Assurance, Good Practice, Regulation and Law*, **2**, 213-231.

Di Vincenzo, G.D., Hamilton, M.L. (1979). Fate of *n*-butanol in rats after oral administration and its uptake by dogs after inhalation or skin application. *Toxicol. Appl. Pharmacol.*, **48**, 317-325.

Du Pont (1976). Mutagenic acitivity of methacrylic acid, *n*-butyl ester in the *Salmonella* / microsome assay. Haskell Lab rep 982-76. Du Pont, Newark DE.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1993). Strategy for assigning a skin notation. Document 31, revised. ECETOC, Brussels.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1995a). Joint assessment of commodity chemicals 30. Methyl methacrylate, CAS 80-62-6. ECETOC, Brussels.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1995b). Assessment factors in Human Health Risk Assessment. Technical report 68. ECETOC, Brussels.

Elf Atochem (1980a). Methacrylate de butyle (MABU): Irritation studies in the rabbit. Poole, L.J, Consultox, London, rep. CL80:60:2025. Norsolor, Verneuil en Halatte.

Elf Atochem (1980b). Methacrylate d'isobutyle (MAISOBU). Irritation studies in rabbit. Poole, L.J., Consultox, London, rep. CL80:63:2028. Norsolor, Verneuil en Halatte.

Froines, J.R., Garabrant, D.H. (1986a). Quantitative evaluation of manicurists exposure to methyl, ethyl and isobutyl methacrylate during production of synthetic fingernails. *Appl. Ind. Hyg.*, **1**, 70-74.

Froines, J.R., Garabrant, D.H. (1986b). Quantitative evaluation of manicurists exposure to methyl, ethyl and isobutyl methacrylate during production of synthetic fingernails. Authors' reply to comments of Crable, J *et al*. *Appl. Ind. Hyg.*, **1**, 200-201.

Hagan, J.V., Bernacki, H.J., Lomax, L.G. (1993). Butyl methacrylate: Four week vapor inhalation toxicity study in rats. Protocol 92P 143, report 92R 143. Rohm and Haas, Spring House PA, 157 p.

ICI (1959). Toxicological report, *n*-butyl methacrylate. Swan, A.A.B. Rep. CTL/TR 202. ICI, Alderley Park, Macclesfield, Cheshire.

ICI (1977a). Local irritation and skin sensitisation potential: Isobutyl methacrylate. Ball, S.E. Rep. CTL/T/1079/S. ICI, Alderley Park, Macclesfield Macclesfield, Cheshire.

ICI (1977b). The biological fate of methylmethacrylate in rats. Hathway, D.E., Bratt, H. Rep. CTL/R/396. ICI, Alderley Park, Macclesfield, Cheshire.

Kotlovskii, Y.V., Grishanova, A., Yu, Mishin, V.M., Bachmanova, G.I. (1988). [Role of rat liver microsomal fractions in the metabolism of methyl methacrylate to formaldehyde]. *Vopr. Med. Khim.*, **34**, 14-17 [Russian]

Lomax, L.G., Brown, D.W., Frederick, C.B. (1994). Regional histopathology of the mouse nasal cavity following two weeks of exposure to acrylic acid for either 6 or 22 hours per day. *Inhalation Toxicol.*, **6**, 445-449.

McCarthy, T.J., Witz, G. (1990). Structure-activity relationships and enzymatic hydrolysis of acrylate and methacrylate esters by carboxylesterase. *Toxicologist*, **10**, 187 [abstract].

McCarthy, T.J., Witz, G. (1991). Structure-activity relationships of acrylate ester reactivity towards gluthathione and hydrolysis by carboxylesterases *in vitro*. *Adv. Exp. Med. Biol.*, **293**, 333-335.

McCarthy, T.J. (1995). Carboxylesterase hydrolysis of acrylates esters *in vitro*. Letter to Mayr, W. and Jacobi, S., Degussa, Hanau. School of Hygiene and Public Health, John Hopkins University, Baltimore MD.

McCarthy, T.J., Witz, G. (1997). Structure-activity relationships in the hydrolysis of acrylate and methacrylate esters by carboxylesterase *in vitro*. *Toxicol.*, **116**, 153-158.

McGoldrick, P.B., Blackburn, G.R., Schreiner, C.A., Mackerer, C.R. (1990). An Ames *Salmonella* / mammalian microsome mutagenesis pre-incubation assay for determination of potential mutagenicity of butyl methacrylate. Study 63736ZC. Mobil, Princeton, NJ.

McGoldrick, P.B., Blackburn, G.R., Schreiner, C.A., Mackerer, C.R. (1991). An Ames *Salmonella* / mammalian microsome mutagenesis pre-incubation assay for determination of potential mutagenicity of butyl methacrylate. Study 63915. Mobil, Princeton, N.J.

Nelson, B.K., Brightwell, W.S., Robertson, S.K., Khan, A., Krieg, E.F., Massari, V.J. (1989a). Behavioral teratology investigation of 1-butanol in rats. *Neurotoxicology and Teratology*, **11**, 313-315.

Nelson, B.K., Brightwell, W.S., Khan, A., Burg, J.R., Goad, P.T. (1989b). Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fund. Appl. Toxicol.*, **12**, 469-479.

Nelson, B.K., Brightwell, W.S., Krieg, E.F. (1990). Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation to rats. *Toxicol. Ind. Health*, **6**, 373-387.

NIOSH (US National Institute of Occupational Safety and Health) (1984). NIOSH manual of analytical methods. Esters I, method 1450. US Department of Health, Education and Welfare, Cincinnati, OH, 1450,1-6.

NTP (US National Toxicology Programme) (1986). Toxicology and carcinogenesis studies of methyl methacrylate (CAS No. 80-62-6) in F344/N rats and B6C3F_1 mice (inhalation studies). NTP TR 314, NIH 87-2570. NTP, Research Triangle Park NC.

Powell, D., Lawrence, W.H., Turner, J., Autian, J. (1970). Development of a toxicity evaluation program for dental materials and products. Screening for irritant responses. *J. Biomed. Mater. Res.*, **4**, 583-596.

Rohm and Haas (1979). A two-year vapor inhalation safety evaluation study in rats, methyl methacrylate. Final report by Hazleton Lab America, with addendum. Rohm and Haas, Spring House, PA.

Rohm and Haas (1989). Vapors emitted during the extrusion [of various acrylates and methacrylates]. Letter by Kauffman, J.M. Rohm and Haas, Philadelphia PA [NTIS, OTS0520652].

Röhm (1977b). Prüfung von Butylmethacrylat auf primäre Hautreizwirkung beim Kaninchen. Sterner, W., Stiglic, A.V., International Bio-Research. Unpublished report 77-016. Röhm, Darmstadt.

Röhm (1977c). Prüfung von Isobutylmethacrylat auf primäre Hautreizwirkung beim Kaninchen. Sterner, W., Stiglic, A.V., International Bio-Research. Unpublished report 77-013. Röhm, Darmstadt.

Röhm (1988e). Test report on acute eye irritation/corrosion of *n*-butylmethacrylat. Schreiber, G., Wodtke, G., Fraunhofer-Institut. Unpublished report 88-022. Röhm, Darmstadt.

Röhm (1988f). Test report: acute eye irritation/ corrosion of isobutylmethacrylate. Schreiber, G., Fraunhofer-Institut. Unpublished report 88-023. Röhm, Darmstadt.

Röhm (1989). Micronucleus assay in bone marrow cells of the mouse with isobutylmethacrylate. Völkner, W., Cytotest Cell Research. Unpublished report 89-001. Röhm, Darmstadt.

Röhm (1996). Arbeitsvorschrift Arbeitsplatz-Messung. Allgemeine Arbeitsvorschrift 1. Röhm, Darmstadt.

Saito, M. (1975). Studies of the metabolism of lower alcohols. *Nichidai Igaku Zasshi*, **34**, 569-585 [Japanese with English abstract].

Sarver, J.W. (1993b). Acute dermal toxicity study with *n*-butyl methacrylate in rabbits. Haskell Lab. Methacrylate Producers Association, Washington DC.

Shao, Z., Hoffman, A.J., Mitra, A.K. Biodegradation characteristics of acyclovir 2'-esters by respiratory carboxylesterases: Implications in prodrug design for intranasal and pulmonary drug delivery. *Int. J. Pharmaceutics*, **112**, 181-190.

Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., Nyeun, J.S. (1969). Range-finding toxicity data VII. *Amer. Ind. Hyg. Assoc. J.*, **30**, 470-476.

Solomon, H.M., Hagan, J.V., Swenson, R.E., Wanner, F.J., O'Hara, G.P., McLaughlin, J.E., Krivanek, N.D. (1991). Methyl methacrylate: Inhalation development toxicity study in rats. Rohm and Haas, Spring House, PA.

US-EPA (US Environmental Protection Agency) (1991). Twenty-eighth report of the interagency testing committee to the administrator; receipt of report and request for comments regarding priority list of chemicals. United States Environmental Protection Agency, Washington, DC. *Fed. Regist.*, **56**, 41212-41264.

Von Rietbrock, N., Abshagen, U. (1971). Pharmakokinetik und Stoffwechsel aliphatischer Alkohole. *Arzneimittelforschung*, **9**, 1309-1319.

Waegemaekers, T.H.J.M., Bensink, M.P.M. (1984). Non-mutagenicity of 27 aliphatic acrylate esters in the *Salmonella*-microsome test. *Mutat. Res.*, **137**, 95-102.

Zeiger E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. (1987). *Salmonella* mutagenicity tests III. Results from the testing of 255 chemicals. *Environ. Mutagen.*, **9**, 1-110.

Zeneca (1996). The metabolism of methyl methacrylate in the nasal tissues of rat and human,

CAS 80-62-6. Green, T., Central Toxicology Laboratory Report CTL/P/5159. CEFIC, Brussels.

Zeneca (1997). Methyl methacrylate, 28-day subchronic inhalation study in rats, CAS 80-62-6. Pinto, P.J., Central Toxicology Laboratory Report CTL/P/5159. CEFIC, Brussels.

APPENDIX A. METHYL METHACRYLATE (ECETOC, 1995a)

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

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

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

Subchronic exposure of rats and mice to MMA by oral, dermal and inhalation routes produced effects consistent with its irritative properties. In inhalation toxicity studies, dose related lesions were seen in the upper respiratory tract, including rhinitis, inflammation associated with necrosis and loss of olfactory epithelium in the nasal turbinates, and lung congestion. After exposure to high atmospheric concentrations of MMA (> 1,000 ppm), the body weight gain was reduced and degenerative and necrotic changes were seen in liver, kidney, brain, spleen and bone marrow. Changes in the activities of liver enzymes were observed in animals exposed to relatively low concentrations. Inconsistent data were reported on effects of MMA on the cardiovascular system. Single studies have indicated that exposure to high doses of MMA via the oral and inhalation routes may induce behavioural and neurochemical

changes. Central nervous system effects have not been reported in chronic studies with exposure levels up to 1,000 ppm.

MMA is not mutagenic to bacteria even at cytotoxic concentrations. In *in vitro* systems MMA shows clastogenic activity, but it is not clastogenic *in vivo* when animals are exposed via an appropriate route. Chronic oral exposure to rats and dogs produced no histopathological changes and no treatment- related lesions, neither neoplastic nor non-neoplastic. Following chronic exposure of mice, rats and hamsters to atmospheres containing MMA no neoplastic or pre-neoplastic changes were produced. Non-neoplastic changes were essentially restricted to the upper respiratory tract and included rhinitis, serous and suppurative inflammation, epithelial hyperplasia and degeneration of the olfactory epithelium. These changes are consistent with the hydrolytic cleavage of the MMA giving rise to methacrylic acid which is deposited in the upper respiratory tract. The primary involvement of the olfactory rather than the respiratory epithelium is also consistent with the tissue distribution of esterases and flow parameters in the rodent respiratory system. Due to the differences in anatomy and probably local tissue esterase activities between human and rodent respiratory system, it is expected that human beings are less sensitive to the observed changes in the upper respiratory tract than rodents.

MMA shows no carcinogenic potential in experimental animals.

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

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

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

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

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

12. BIBLIOGRAPHY

12.1 REFERENCES QUOTED IN THE DOCUMENT

AFS (Arbetarskyddsstyrelsens författnings-samling) (1996). Hygieniska gränsvärden, AFS 1996: 2. AFS, Stockholm.

Arbeidstilsynet (1995). Administrative normer for forurensning i arbeidsatmosfære. Veiledning til arbeidsmiljøloven 361. Direktoratet for Arbeids-tilsynet, Oslo.

Arbeidsinspectie (1996). De nationale MAC-lijst 1996. P 145, Ministerie van Sociale Zaken en Werkgelegenheid. Sdu Uitgeverij, Den Haag, 24.

Autian, J. (1975). Structure-toxicity relationships of acrylic monomers. *Environ. Health Perspect.*, **11**, 141-152.

BASF (1990a). Prenatal toxicity of 2-methyl-1-propanol in rats after inhalation. Project 37R 0057/ 88047. Volume I, report. Programme for the prevention of health hazards caused by industrial substances. BG Chemie, Heildelberg.

BASF (1990b). Prenatal toxicity of 2-methyl-1-propanol in rabbits after inhalation. Project 90R0057/88048. Volume I, report. Programme for the prevention of health hazards caused by industrial substances. BG Chemie, Heildelberg.

Bauer W. (1993). Methacrylic acid and derivatives. In: Elvers, B., Hawkins, S., Schulz, G. (eds), *Ullman's encyclopedia of industrial chemistry*, 5th ed. VCH, Weinheim A16, 441-448.

Borzelleca, J.F., Larson, P.S., Hennigar, G.R., Huf, E.G., Crawford, E.M., Blackwell Smith, R. (1964). Studies on the chronic oral toxicity of monomeric ethyl acrylate and methyl methacrylate. *Toxicol. Appl. Pharmacol.*, **6**, 29-36.

Bradley, N., Morgan, E.D. (1989). Sampling and analysis of organic vapors in the flue gases from pottery kilns. *Anal. Proc.*, **6**, 6-8.

Bratt, H., Hathway, D.E. (1977). Fate of methyl methacrylate in rats. *Brit. J. Cancer*, **36**, 111-119.

CEC (Commission of the EC) (1990a). Commission directive of 23 February 1990 concerning materials and plastics intended to come into contact with foodstuffs (90/128/EEC), Off. J. EC, L 75, 19-25, 28 [German].

CEC (Commission of the EC) (1990b). Corrigendum of Commission directive 90/128/EEC of 23 February 1990 concerning materials and plastics intended to come into contact with foodstuffs, Off. J. EC L75 of 21 March 1990. Off. J. EC L349, 26-32, 35 [German].

CEC (Commission of the EC) (1994a). Technical guidance on risk assessment of existing substances in the context of Commission Regulation (EC) No. 1488/94 in accordance with Coucil regulation (EEC) No. 793/93 on the evaluation and control of existing substances. Doc. XI/919/94-EN [with calculation of K_{oc} by Degussa, 1995]. CEC DG XI, Brussels.

CEC (Commission of the EC) (1994b). Draft provisional list of monomers and aitives used in the manufacture of plastics and coatings intended to come into contact with foodstuffs (updated 15 May 1994). Synoptic document N.7. CS/PM/2356. Commission of the EC, DG III, Brussels.

CEFIC (European Chemical Industry Council) (1996). Data of *n*- and iso-butyl methacrylate. Letter by Thomas D. CEFIC Methacrylates Toxicology Committee, Brussels.

Chan, P.C., Eustis, S.L., Huff, J.E., Haseman, J.K., Ragan, H. (1988). Two year inhalation carcino-genesis studies of methyl methacrylate in rats and mice: inflammation and degeneration of the nasal epithelium. *Toxicol.*, **52**, 237-252.

Christensen KP (1995a). *i-B*utyl methacrylate, determination of the sorption and desorption properties. Springborn Lab. Rep. 94-12-5609. Methacrylate Producers Association, Washington DC.

Chung, C.W., Giles, A.L. (1977). Sensitization potentials of methyl, ethyl and *n*-butyl methacrylates and mutual gross-sensitivity in guinea pigs. *J. Invest. Dermatol.*, **68**, 187-190.

CIIT (Chemical Industry Institute of Toxicology) (1984). 90-Day vapor inhalation toxicity study of methacrylic acid in B6C3F$_1$ mice, Sprague-Dawley rats and Fischer-344 rats. Toxicogenics study 420-1086, revised. CIIT, Research Triangle Park NC.

Crout, D.H.G., Corkhill, J.A., James, M.L., Ling, R.S.M. (1979). Methyl methacrylate metabolism in man (the hydrolysis of methyl methacrylate to methacrylic acid during total hip replacement). *Clin. Orthop. Rel. Research*, **141**, 90-95.

Danishevskii, S.I. (1957). Toxicology of butyl metha-crylate. *Gig. Tr. Prof. Zabol.*, **6**, 87-91 [Russian; *Chem. Abstr*., **54** (1960), 17707f].

Degussa (1968). Flammpunktbestimmungen nach DIN 51755 (Nov. 63), Äthylmethacrylat, Butyl-methacrylat, iso-Butylmethacrylat. Degussa, Wolfgang.

Degussa (1982). Bericht über die Prüfung der lokalen primären Reiz-/Ätzwirkung von *n-B*utylmethacrylat (Methacrylsäure-*n*-butylester, *n-B*UMA) nach einmaliger Applikation an der Haut des Kaninchens (Patch-Test). Zechel, H.J., Tox. Inst. Degussa-Asta. Degussa, Hanau.

Degussa (1989). Brechungsindex und Dichte von MMA, MAS, *n*- und iso-BMA. Degussa, Hanau.

Degussa (1990). Zündtemperatur (DIN 51 794), N-Butyl-Methacrylat. Degussa, Hanau.

Degussa (1992). Bericht über die Messung luftfremder Stoffe nach TRGS 402. TÜV Rheinland, Institut für Umweltschutz und Energietechniek, rep 920-2540202. Degussa, Wesseling.

Degussa (1994). Bestimmung der Zündtemperatur nach DIN 51 794, i-Butylmethacrylat. Degussa, Hanau.

Degussa (1995a). Sicherheitsdatenblatt (93/112/EG) *n*-Butylmethacrylat unstab., stab. mit 2 ppm MEHQ. Degussa, Hanau.

Degussa (1995b). Sicherheitsdatenblatt (93/112/EG) Iso-Butylmethacrylat stab. mit 5 ppm, 100 ppm MEHQ. Degussa, Hanau.

Deichman, W.B. (1981). Acrylates and metha-crylates. In: Clayton G.D., Clayton F.E. (eds), *Patty's industrial and hygiene and toxicology,* 3rd ed. J. Wiley, New York, NY, 2291-2303.

Deichmann, W. (1941). Toxicity of methyl, ethyl and *n*-butyl methacrylate. *J. Ind. Hyg. Toxicol.*, **23**, 343-351.

DeSesso, J.M. (1993). The relevance to humans of animal models for inhalation studies of cancer in the nose and upper airways. *Quality Assurance, Good Practice, Regulation and Law*, **2**, 213-231.

Di Vincenzo, G.D., Hamilton, M.L. (1979). Fate of *n*-butanol in rats after oral administration and its uptake by dogs after inhalation or skin application. *Toxicol. and Appl. Pharmacol.*, **48**, 317-325.

Dillingham, E.O., Lawrence, W.H., Aution, J. (1983). Acrylate and methacrylate esters: Relationship of hemolytic activity and *in vivo* toxicity. *J. Biomed. Mater. Res.*, **17**, 945-947.

DIPPR (1995). DIPPR data bank, update June 1995. American Institute of Chemical Engineers, New York NY.

Du Pont (1976). Mutagenic acitivity of methacrylic acid, *n*-butyl ester in the *Salmonella* / microsome assay. Haskell Lab. Rep. 982-76. Du Pont, Newark DE.

Eastman Kodak (1984). Basic toxicity of a butyl methacrylate solution. O'Donoghue, J.L. EPA-OTS 0516721, doc. 86-890000184. Eastman Kodak, Rochester, NY.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1993). Strategy for assigning a skin notation. Document 31, revised. ECETOC, Brussels.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1995a). Joint assessment of commodity chemicals 30. Methyl methacrylate, CAS 80-62-6. ECETOC, Brussels.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1995b). Assessment factors in human health risk assessment. Technical report 68. ECETOC, Brussels.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1996). Joint assessment of commodity chemicals 36. *n*-Butyl Methacrylate, Isobutyl Methacrylate, CAS 97-88-1, 97-86-9. ECETOC, Brussels.

Elf Atochem (1980a). Methacrylate de butyle (MABU): Irritation studies in the rabbit. Poole, L.J., Consultox, London, rep CL80:60:2025. Norsolor, Verneuil en Halatte.

Elf Atochem (1980b). Methacrylate d'isobutyle (MAISOBU). Irritation studies in rabbit. Poole, L.J., Consultox, London, rep. CL80:63:2028. Norsolor, Verneuil en Halatte.

Elf Atochem (1980c). Methacrylate de butyle (MABU). Test for contact sensitisation potential in the Guinea pig (maximisation test) Consultox, London, rep. CL80:81:2046. Norsolor, Verneuil en Halatte.

Elf Atochem (1980d). Methacrylate d'isobutyl (MAISOBU). Test for contact sensitisation potential in the Guinea pig (maximisation test). Consultox, London, rep. CL80:84:2049. Norsolor, Verneuil en Halatte.

Elf Atochem (1993). Material safety data sheet isobutyl methacrylate (isoBMA). Elf Atochem, Paris.

Engström, B., Henriks-Eckerman, M.J., Ånäs, E. (1990). Exposure to paint degradation products when welding, flame cutting, or straightening painted steel. *Am. Ind. Hyg. Assoc. J.*, **51**, 561-565.

Froines, J.R., Garabrant, D.H. (1986a). Quantitative evaluation of manicurists exposure to methyl, ethyl and isobutyl methacrylate during production of synthetic fingernails. *Appl. Ind. Hyg.*, **1**, 70-74.

Froines, J.R., Garabrant, D.H. (1986b). Quantitative evaluation of manicurists exposure to methyl, ethyl and isobutyl methacrylate during production of synthetic fingernails. Authors' reply to comments of Crable, J *et al*. *Appl. Ind. Hyg.*, **1**, 200-201.

Fujisawa, S., Masuhara, E. (1980). Binding of methyl methacrylate to bovine serum albumin. *J. Dent. Res.*, **59**, 2056-2061.

Fujisawa, S., Masuhara, E. (1981). Determination of partition coefficients of acrylates, methacrylates, and vinyl monomers using high performance liquid chromatography (HPLC). *J. Biomed. Mater. Res.*, **15**, 787-793.

Gibel, W., Lohs, Kh., Wildner, G.P. (1975). Experimentelle Untersuchungen zur kanzerogenen Wirkung von Lösungsmitteln am Beispiel von Propanol-1, 2-Methylpropanol, 3-Methylbutanol-1. *Arch. Geschwulstforsch.*, **45**, 19-24.

Gibel, W., Lohs, K.H., Wildner, G.P., Schramm, T. (1974). Experimentelle Untersuchungen zur kanzerogenen Wirkung höherer Alkohole am Beispiel von 3-Methyl-1-butanol, 1-Propanol, 2-Methyl-1-Propanol. *Z. Exper. Chirurg.*, **7**, 233-239.

Hagan, J.V., Bernacki, H.J., Lomax, L.G. (1993). Butyl methacrylate: Four week vapor inhalation toxicity study in rats. Protocol 92P 143, report 92R 143. Rohm and Haas, Spring House PA, 157 p.

Hi-Tek Polymers (1989). Industrial hygiene sampling results [on methyl methacrylate, butyl methacrylate & ethyl acrylate] reported by Natslco. Personal correspondence by Lewis, K.S. to EPA TSCA Document Processing Center. Hi-Tek Polymers, Louisville KY [NTIS-OTS 0520427].

Hine, J., Mookerjee, P.K. (1975). The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. *J. Org. Chem.*, **40**, 292-298.

Hommel, G. (ed.) (1994*). Handbuch der gefährlichen Güter*, 7th ed. Merkblatt Nr. 614. Springer, Heidelberg.

HSDB (Hazardous Substances Databank) (1994). Data on *n*-butyl methacrylate. Print-out Dec 94. NLM, Washington DC.

IARC (International Agency for Research on Cancer) (1994). Methyl methacrylate. In: *IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans 60, some industrial chemicals*. IARC, Lyon, 468.

ICI Acrylics (1994a). Chemical safety datasheet, *n*-butyl methacrylate. ICI, Cleveland.

ICI Acrylics (1994b). Chemical safety datasheet, iso-butyl methacrylate. ICI, Cleveland.

ICI (1959). Toxicological report, *n*-butyl metha-crylate. Swan, A.A.B. Rep. CTL/TR 202. ICI, Alderley Park, Macclesfield, Cheshire.

ICI (1977a). Local irritation and skin sensitisation potential: Isobutyl methacrylate. Ball, S.E. Rep. CTL/T/1079/S. ICI, Alderley Park, Macclesfield, Cheshire.

ICI (1977b). The biological fate of methyl-methacrylate in rats. Hathway, D.E., Bratt, H. Rep. CTL/R/396. ICI, Alderley Park, Macclesfield, Cheshire.

Kanerva, L., Estlander, T., Jolanki, R., Pekkarinen E. (1992). Occupational pharyngitis associated with allergic patch test reactions from acrylics. *Allergy*, **47**, 571-573.

Kelly, D.P. (1977). Two-week subacute inhalation studies, *n*-butyl methacylate. Haskell Lab. Rep. 652-77. Du Pont, Newark DE.

Kelly, D.P. (1993). Inhalation median lethal concentration (LC_{50}) studies with methacrylates in rats: methacrylic acid, butyl methacrylate, ethyl methacrylate, and methyl methacrylate. Haskell lab. Methylacrylate Producers Association, Washington DC.

Kenaga, E.E., Goring, C.A.I. (1978). Relationship between water solubility, soil sorption, octanol-water partitioning, and concentration of chemicals in biota. In: Eaton, J.G., Parrish, P.R., Hendricks, A.C. *Aquatic Toxicology. Proceedings of the Third Annual Symposium on Aquatic Toxicology*. ASTM Special publication 707. American Society for Testing and Materials, Philadelphia, PA, 78-109.

Klimes, I., Lamparsky, D. (1984). Unsaturated components in the essential oil of *Anthemis nobilis* L. (Roman camomile). *Perfumer and Flavorist*, **9**, 1-13.

Klimkina, N.V., Ekhina, R.S., Sergeev, A.N. (1976). Experimental substantiation of the maximum permissible concentration of methyl methacrylate and butyl methacrylate in the water of reservoirs. *Gig. Sanit.*, **4**, 6-11. [Russian; English translation].

Kotlovskii, Y.V., Bekerev, V.E., Bachmanova, G.I., Invanov, V.V. (1985). Interaction of acrylates with the microsomal oxidation system in rat liver tissue. *Vopr. Med. Khim.*, **31**, 74-77 [Russian; *Chem. Abstr.*, **104**, 63636y]

Kotlovskii, Y.V., Grishanova, A. Yu, Mishin, V.M., Bachmanova, G.I. (1988). [Role of rat liver microsomal fractions in the metabolism of methyl methacrylate to formaldehyde]. *Vopr. Med. Khim.*, **34**, 14-17 [Russian]

Kustova, Z.R., Astapova, S.A., Gizatullina, N.S. *et al* (1979). Toxicological characteristics of butyl metha-crylate. *Toksikol. Sanit. Khim. Plastmass.*, **3**, 15-18. [*Chem. Abstr.*, **93** (1980), 38846]

Lawrence, W.H., Malik, M., Autian, J. (1974). Development of a toxicity evaluation programme for dental materials and products. II. Screening for systemic toxicity. *J. Biomed. Mater. Res.*, **8**, 11-34.

Lissi, E.A., Caceres, T., Veliz, C. (1983). Solubility of vinyl monomers and vinyl monomer mixtures in micellar solutions. *Bol. Soc. Chil. Quim.*, **28**, 13-25.

Lomax, L.G., Brown, D.W., Frederick, C.B. (1994). Regional histopathology of the mouse nasal cavity following two weeks of exposure to acrylic acid for either 6 or 22 hours per day. *Inhalation Toxicol.*, **6**, 445-449.

Lyman, W.J., Reehl, W.F., Rosenblatt, D.H. (1982). Handbook of chemical property estimation methods. Adsoprtion coefficient for soils and sediments. McGraw-Hill, New York, NY, 4.1-33.

MacLeod, A.J., Pieris, N.M. (1981). Volatile flavor components of beli fruit (*Aegle marmelos*) and a

processed product. *J. Agric. Food Chem.*, **29**, 1262-1264.

Maibach, H., Hjorth, N., Fregert, S. *et al* (1978). Butyl methacrylate monomer and ethyl methacrylate, frequency of reaction. *Contact Derm.*, **4**, 60.

Mao, J. (1995). *i-B*utyl methacrylate. Determination of water solubility. Springborn Lab. Rep. 94-12-5605. Methacrylate Producers Association, Washington DC.

Marks, J.G., Bishop, M.E., Willis, W.F. (1979). Allergic contact dermatitis to sculptured nails. *Arch. Dermatol.*, **115**, 100.

McCarthy, T.J., Witz, G. (1990). Structure-activity relationships and enzymatic hydrolysis of acrylate and methacrylate esters by carboxylesterase. *Toxicologist*, **10**, 187 [abstract].

McCarthy, T.J., Witz, G. (1991). Structure-activity relationships of acrylate ester reactivity towards gluthathione and hydrolysis by carboxylesterases *in vitro*. *Adv. Exp. Med. Biol.*, **293**, 333-335.

McCarthy, T.J. (1995). Carboxylesterase hydrolysis of acrylates esters *in vitro*. Letter to Mayr, W. and Jacobi, S., Degussa, Hanau. School of Hygiene and Public Health, John Hopkins University, Baltimore MD.

McCarthy, T.J., Witz, G. (1997). Structure-activity relationships in the hydrolysis of acrylate and methacrylate esters by carboxylesterase *in vitro*. *Toxicol.*, **116**, 153-158.

McCarthy, T.J., Hayes, E.P., Schwartz, C.S., Witz, G. (1994). The reactivity of selected acrylate esters toward glutathione and deoxyribonucleosides *in vitro*: structure-activity relationships. *Fundam. Appl. Toxicol.*, **22**, 543-548.

McGoldrick, P.B., Blackburn, G.R., Schreiner, C.A., Mackerer, C.R. (1990). An Ames *Salmonella* / mammalian microsome mutagenesis pre-incubation assay for determination of potential mutagenicity of butyl methacrylate. Study 63736ZC. Mobil, Princeton, NJ.

McGoldrick, P.B., Blackburn, G.R., Schreiner, C.A., Mackerer, C.R. (1991). An Ames *Salmonella* / mammalian microsome mutagenesis pre-incubation assay for determination of potential mutagenicity of butyl methacrylate. Study 63915. Mobil, Princeton, NJ.

Mikulecký, Z., Kolisch, P., Znojemský, S. (1962). Beitrag zur Wirkung der Akrylmonomere auf die Haut. In: Konopik, J. (ed.), *1st Symposium Dermatologorum Corpus Lectionum*, Prague, 1960.

Morris, D.S., Comber, M.H.I., Cornish, S.K. (1992). *n*-Butyl methacrylate: determination of octanol water partition coefficient. Zeneca, Brixham Env. Lab. study W1037/E. Methacrylate Producers Association, Washington DC.

Nelson, B.K., Brightwell, W.S., Robertson, S.K., Khan, A., Krieg, E.F., Massari, V.J. (1989a). Behavioral teratology investigation of 1-butanol in rats. *Neurotoxicology and Teratology*, **11**, 313-315.

Nelson, B.K., Brightwell, W.S., Khan, A., Burg, J.R., Goad, P.T. (1989b). Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fund. Appl. Toxicol.*, **12**, 469-479.

Nelson, B.K., Brightwell, W.S., Krieg, E.F. (1990). Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation to rats. *Toxicol. Ind. Health*, **6**, 373-387.

Nemec, J.W., Kirch, L.S. (1981). Methacrylic acid and derivatives. In: *Kirk Othmer Encyclopedia of Chemical Technology*. Wiley Interscience, New York, **15**, 346-376.

NIOSH (US National Institute of Occupational Safety and Health) (1984). NIOSH manual of analytical methods. Esters I, method 1450. US Department of Health, Education and Welfare, Cincinnati, OH, 1450,1-6.

NTP (US National Toxicology Programme) (1986). Toxicology and carcinogenesis studies of methyl methacrylate (CAS No. 80-62-6) in F344/N rats and B6C3F$_1$ mice (inhalation studies). NTP TR 314, NIH 87-2570. NTP, Research Triangle Park NC.

Oberly, R., Tansy, M.F. (1985). LC_{50} values for rats acutely exposed to vapours of acrylic and methacrylic acid esters. *J. Toxicol. Environ. Health*, **16**, 811-822.

Parker, D., Turk, J.L. (1983). Contact sensitivity to acrylate compounds in the guinea pig. *Contact Dermatitis*, **9**, 55-60.

Powell, D., Lawrence, W.H., Turner, J., Autian, J. (1970). Development of a toxicity evaluation program for dental materials and products. Screening for irritant responses. *J. Biomed. Mater. Res.*, **4**, 583-596.

Rehberg, C.E., Fisher, C.H. (1948). Properties of monomeric and polymeric alkyl acrylates and methacrylates. *Ind. Eng. Chem.*, **40**, 1429-1433.

Richter, F., Ostertag, R., Ammerlahn, G., Baumann, M., Behrle, E., Kobel, M. (1961). *Beilsteins Handbuch der Organischen Chemie*, 4 Aufl., 3 Erg., Bd II, Teil 2,H.

Rohm and Haas (1979). A two-year vapor inhalation safety evaluation study in rats, methyl methacrylate. Final report by Hazleton Lab. America, with addendum. Rohm and Haas, Spring House, PA.

Rohm and Haas (1989). Vapors emitted during the extrusion [of various acrylates and methacrylates]. Letter by Kauffman, J.M. Rohm and Haas, Philadelphia PA [NTIS, OTS0520652].

Röhm (1977a). Akute Toxizitätsprüfung von Isobutylmethacrylat nach oraler Applikation an der Ratte. Sterner, W., Stiglic, A.V., International Bio-Research. Unpublished report 77-012. Röhm, Darmstadt.

Röhm (1977b). Prüfung von Butylmethacrylat auf primäre Hautreizwirkung beim Kaninchen. Sterner, W., Stiglic, A.V. International Bio-Research. Unpublished report 77-016. Röhm, Darmstadt.

Röhm (1977c). Prüfung von Isobutylmethacrylat auf primäre Hautreizwirkung beim Kaninchen. Sterner W., Stiglic, A.V., International Bio-Research. Unpublished report 77-013. Röhm, Darmstadt.

Röhm (1988e). Test report on acute eye irritation/corrosion of *n*-butylmethacrylat. Schreiber G., Wodtke, G., Fraunhofer-Institut. Unpublished report 88-022. Röhm, Darmstadt.

Röhm (1988f). Test report: acute eye irritation/ corrosion of isobutylmethacrylate. Schreiber, G., Fraunhofer-Institut. Unpublished report 88-023. Röhm, Darmstadt.

Röhm (1989). Micronucleus assay in bone marrow cells of the mouse with isobutylmethacrylate. Völkner, W., Cytotest Cell Research. Unpublished report 89-001. Röhm, Darmstadt.

Röhm (1995a). Monomere *n-B*utyl Methacrylat. Datenblatt AM 003. Geschäftsführungsbereich Methacrylate, Formmassen. Röhm, Darmstadt.

Röhm (1995b). Monomere iso-Butyl Methacrylat. Datenblatt AM 004. Geschäftsführungsbereich Methacrylate, Formmassen. Röhm, Darmstadt.

Röhm (1996). Arbeitsvorschrift Arbeitsplatz-Messung. Allgemeine Arbeitsvorschrift 1. Röhm, Darmstadt.

Saito M. (1975). Studies of the metabolism of lower alcohols. *Nichidai Igaku Zasshi*, **34**, 569-585 [Japanese with English abstract].

Sarver, J.W. (1993a). Acute oral toxicity study with *n*-butyl methacrylate in male and female rats. Haskell Lab. Methacrylate Producers Association, Washington DC.

Sarver, J.W. (1993b). Acute dermal toxicity study with *n*-butyl methacrylate in rabbits. Haskell Lab. Methacrylate Producers Association, Washington DC.

Shepel' Skaya, N.R. (1975). Toxicity of the butyl methacrylate. *Gig. Tr. Prof. Zabol.*, **9**, 57-58 [Russian; *Chem. Abstr*., **84**, 13163]

Shepel' Skaya, N.R. (1978). Hygienic assessment of the escape of butyl methacrylate from polymer

building materials. *Gig. Sanit.*, **3**, 107-108. [*Chem. Abstr*., **884**, 184066].

Singh, A.R., Lawrence, W.H., Autian, J. (1972a). Embryo-fetal toxicity and teratogenic effects of a group of methacrylate esters in rats. *Toxicol. Appl. Pharmacol.*, **22**, 314-315 [abstract].

Singh, A.R., Lawrence, W.H., Autian, J. (1972b). Embryonic-fetal toxicity and teratogenic effects of a group of methacrylate esters in rats. *J. Dental Res.*, **519**, 1632-1638.

Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., Nyeun, J.S. (1969). Range-finding toxicity data VII. *Amer. Ind. Hyg. Assoc. J.*, **30**, 470-476.

Solomon, H.M., Hagan, J.V., Swenson, R.E., Wanner, F.J., O'Hara, G.P., McLaughlin, J.E., Krivanek, N.D. (1991). Methyl methacrylate: Inhalation development toxicity study in rats. Rohm and Haas, Spring House, PA.

SRC (Syracuse Research Corporation) (1994). Programme PCKOCWIN. Calculations of K_{OC}. Degussa, Hanau.

Stadler, J.C. (1993). Inhalation sensory irritation (RD_{50}) study in mice with selected methacrylates and methacrylic acid. Haskell lab. Methylacrylate Producers Association, Washington, DC.

Sugden, S. (1924). The variation of surface tension with temperature and some related functions. *J. Chem. Soc. (London, Transactions)*, **125**, 32-41.

Svetlakov, A.V., Ivanov, V.V., Fefelova, YuA, Golounin, A.V. (1989). Body distribution and interaction of rat serum proteins with butyl acrylate and methacrylate. *Gig. Tr. Prof. Zabol.*, **3**, 51-52 [English translation; *Chem. Abstr*., **111**, 110595]

Swann, R.L., Laskowski, D.A., McCall, P.J., Vander Kuy, K., Dishburger, H.J. (1983). A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. *Residue Reviews*, **85**, 17-28.

Tanii, H., Hashimoto, K. (1982). Structure-toxicity relationship of acrylates and methacrylates. *Toxicol. Lett.*, **11**, 125-129.

US-EPA (US Environmental Protection Agency) (1991). Twenty-eighth report of the interagency testing committee to the administrator; receipt of report and request for comments regarding priority list of chemicals. United States Environmental Protection Agency, Washington, DC. *Fed. Regist.*, **56**, 41212-41264.

Van der Walle, H.B., Bensink, T. (1982). Cross reaction pattern of 26 acrylic monomers on guinea pig skin. *Contact Dermatitis*, **8**, 376-382.

Van der Walle, H.B., Klecak, G., Geleick, H., Densuik, T. (1982). Sensitising potential of 14 mono(meth)acrylates in the guinea pig. *Contact Dermatitis*, **8**, 223-235.

Von Blomberg-Van der Flier, M., Scheper, R.J., Boerrigter, G., Polak, L. (1984). Induction of contact sensitivity to a broad variety of allergens with haptenized macrophages. *J. Invest. Dermatol.*, **83**, 91-95.

Von Rietbrock, N., Abshagen, U. (1971). Pharmakokinetik und Stoffwechsel aliphatischer Alkohole. *Arzneimittelforschung*, **9**, 1309-1319.

Waegemaekers, T.H.J.M., Bensink, M.P.M. (1984). Non-mutagenicity of 27 aliphatic acrylate esters in the *Salmonella*-microsome test. *Mutat. Res.*, **137**, 95-102.

Weast, R.C., Astle, M.J., Beyer, W.H. (1989*). CRC handbook of chemistry and physics*, 69th ed. CRC, Boca Raton, Florida, C-348, D-199.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. (1987). *Salmonella* mutagenicity tests III. Results from the testing of 255 chemicals. *Environ. Mutagen.*, **9**, 1-110.

Zeneca (1996). The metabolism of methyl methacrylate in the nasal tissues of rat and human, CAS 80-62-6. Green T, Central Toxicology Laboratory Report CTL/P/5159. CEFIC, Brussels.

Zeneca (1997). Methyl methacrylate, 28-day subchronic inhalation study in rats, CAS 80-62-6. Pinto, P.J. Central Toxicology Laboratory Report CTL/P/5159. CEFIC, Brussels.

12.2 REFERENCES NOT QUOTED IN THE DOCUMENT

The following references were consulted by the Task Force, but not quoted in the document for one or more of the following reasons.

- Abstract superseded by publication
- Abstract only, without further (detailed) information
- Internal report, superseded by scientific paper
- Irrelevant data reported
- No exposure data reported
- No formal protocol reported
- No new data reported
- Not obtainable
- Not translated (e.g. from Russian)
- Opinion, position, statement, testimony or comment
- Original (full) paper(s) quoted (e.g. in case of a review)
- Same data or information covered by another author

Anderson, D.G., Isakson, K.E., Snow, D.L., Tessari, D.J., Vandeberg, J.T. (1971). Analysis of acrylic polymers using combined Zeisel reaction-gas chromatography and infrared spectrometry. *Anal. Chem.*, **43**, 894-900 [*Chem. Abstr*., **75**, 37114].

Anonymous (1981). Information from the Soviet Toxicology Center. *Gig. Tr. Prof. Zabol. ISS*, **11**, 57-60 [Russian; Toxline 82-073901-TOXBIB].

Anonymous (1982). Toxicology of new chemical compounds. *Gig. Sanit.*, **8**, 89-91 [Russian; review].

Applegate, V.C., Howell, J.H., Hall, Jr. A.E., Smith, M.A. (1985). Toxicity of 4346 chemicals to larval lampreys and fishes. Spec. Sci. Rep-Fish, 207, Fish. Wildi. Serv., USDI, Washington DC, 157 [nominal concentration, only 2 fish/dose].

Avgul, T.V., Kovaleva, N.V. (1987). Preconcentration of organic substances from aqueous solutions on Carbochrom S. *Zh. Anal. Khim.*, **42**, 2037-2042 [Russian; *Chem. Abstr*., **108**, 105683].

Avgul, T.V., Gudyno, T.V., Senyavin, M.M. (1990). Sorptive preconcentration of regulated organic compounds from water prior to gas chromatography. *Probl. Anal. Khim.*, **10**, 211-20 [Russian; *Chem. Abstr*., **114**, 29811].

Bachmann, M., Dagon, R. (1972). [Determination of (meth)acryl monomers in the presence of polymers, reaction for locating the double bond in pyrrolidine]. *Chimia*, **26**, 262-264. [German; Chem. Abstr., 77, 48832].

Bartholomé, E., Biekert, E., Hellmann, H., Ley, H., Weigert, W.M., Weise, E. (eds) (1978). Höhere Methacrylsäureester. In: *Ullmans Encyklopädie der technischen Chemie*, 4th ed., vol. 16. Verlag Chemie, Weinheim, 612.

Bezuglyi, V.D., Ponomarev, Y.P. (1968). Separate determination of acrylates and methacrylates by polarography. *Zh. Anal. Khim.*, **23**, 599-605 [Russian; *Chem. Abstr*., **69**, 32850].

Bezuglyi, V.D., Voskresenskaya, I.B., Dmitrieva, V.N., Alekseeva, T.A. (1970). Separate determination of methacrylic acid and esters of acrylic and methacrylic acids in a mixture. *Zavod. Lab.*, **36**, 1040-1042 [Russian, Chem. Abstr., 73:131335; method unreliable for low concentrations].

Black, R.E. (1977). *Analysis of nail extenders Newburger's Man*. In: Senzel, A.J. (ed.), Assoc. Off. Anal. Chem., Washington DC. *Cosmet. Anal*., 70-71 [*Chem. Abstr*., **87**, 73227; *n*-BMA/*i*-BMA not mentioned].

Böhling, H.G., Borchard, U., Drouin, H. (1977). Monomeric methylmethacrylate (MMA) acts on the desheathed myelinated nerve and on the node of Ranvier. *Arch. Toxicol.*, **38**, 307-314.

Brantner, A., Vamos, J., Kertesz, P., Jozan, M., Vegh, A., Simonyi, I. (1972). Monomeric impurities of Akrinit E copolymer and of Plastubol spray I. Purity testing by thin-layer chromatography. *Gyogyszereszet*, **16**, 11-15 [Hungarian; Chem. Abstr. 77, 20536].

Brunn, J., Peters, F., Dethloff, M. (1976). Die UV-Spektren α,β-ungesättigter Ester und ihre Beeinflussung durch Lösungsmittel und Komplexbildung. *Journal f. prakt. Chemie*, **318**, 745-755.

Cederbaum, A.I., Dicker, E., Rubin, E., Cohen, G., 1978. Effect of hydroxyl radical scavengers on microsomal oxidation of alcohols and on associated microsomal reactions. *Biochemistry*, **17**, 3058-3064.

Cederbaum, A.I., Dicker, E., Rubin, E., Cohen, G. (1979). Effect of thiourea on microsomal oxidation of alcohols and associated microsomal functions. *Biochemistry*, **18**, 1187-1191.

Christiansen, M.L. (1983). Acrylater och methacrylater, Nordiska expertgruppen för gränsvärdesdokumentation. *Arbete och Hälsa*, **21**, 1-62 [review].

Cohen, B.G.F. (1984). Human aspects in office automation. Division of Biomedical and Behavioral Science. NIOSH, Cincinnati OH [NTIS PB84-240736, PB84-240738; mentions *n*-BMA/*i*-BMA emitted by telefax machines].

Czerczak, S. (1983). Gas-chromatographic determination in air of the chemical compounds present in acrylic aqueous dispersion. *Chem. Anal.*, (Warsaw) **28**, 35-41 [Chem. Abstr., 100, 38821].

Daubert, T.E., Danner, R.P. (1989). *Physical and thermodynamic properties of pure chemicals*. Hemisphere, 4.

Davy, K.W.M., Braden, M. (1991). Residual monomer in acrylic polymers. *Biomaterials*, **12**, 540-544 [Abstract excludes methacrylates].

DECOS (Dutch Expert Committee for Occupational Standards) (1994). Ethyl methacryate, *n*-butyl methacrylate and isobutyl methacrylate. Gezondheidsraad, Den Haag [review].

DECOS (Dutch Expert Committee for Occupational Standards) (1994). Methyl methacrylate. Gezondheidsraad, Den Haag [review].

Degussa (1995d). *n-B*utylmethacrylate, Calculation of half lives of photochemical oxidation reactions, Programme AOPWIN 1.60, Syracuse Research Corporation, SRC, 1995 [Superseded by Elf Atochem, 1996]

Dmitriev, M.T., Komrakova, E.A., Tikhomirov, YuP. (1987). Gas chromatography of acrylic compounds in environmental samples. From: Ref. Zh., Khim. 1988, Abstr. No 6I618. Anal. Okruzh. Prirod. Sredy. Gor'kii, 106-108 [Chem. Abstr., 109, 162683; similar method quoted].

Dmitriev, M.T., Komrakova, E.A., Tikhomirov, YuP. (1987). Gas chromatography of acrylic compounds in environmental samples. Anal. Okruzh. Prirod. Sredy. Gor'kii, 106-108 [*Ref. Zh. Khim*., **1988**, 6I618 abstract; *Chem. Abstr.*, **109**, 162683; not relevant].

Dzhandzhapanyan, A.N., Puzyan, E.A. (1988). Determination of microquantities of butyl acrylate and butyl methacrylate in air by GC using a flame ionization detector (FID) following adsorption on activated carbon. *Gig. Sanit.*, **11**, 43-45 [Russian; German translation; similar method quoted]

Ellington, J.J., Stancil, F.E., Payne, W.D., Trusty, C. (1987). Measurement of hydrolysis rate constants for evaluation of hazardous waste land disposal, Volume 1, data on 32 chemicals. Environmental Research Lab. Rep. EPA/600/3-86/043. EPA, Washington DC [NTIS PB87-140349/GAR].

Fisher, A.A. (1980). Short Communications. Cross reactions between methyl methacrylate monomer and acrylic monomers presently used in acrylic nail preparations. *Contact Dermatitis*, **6**, 345-368.

Fuller, M. (1982). Analysis of paint-on artificial nails. *J. Soc. Cosmet. Chem.*, **33**, 51-74 [*Chem. Abstr*., **97**, 11632; *n*-BMA/*i*-BMA not mentioned].

General Electric (no date). Acute inhalation toxicity in the albino rat, AR-85124. International Research and Development Corporation, report of 31 december 1975. [NTIS: EPA-OTS 0535667, 8EHQ-0292-2255; not available].

Gould, H. (1985). Comparison of biological reactivity and toxicity of acrylate and methacrylate esters. *Toxic Substances J.*, **7**, 1-15.

Greim, H., Ahlers, J., Bias, R., Broecker, B., Hollander, H., Gelbke, H-P., Jacobi, S., Klimisch, H-J., Mangelsdorf, I., Mayr, W., Schön, N., Stropp, G., Stahnecker, P., Vogel, R., Weber, C., Ziegler Skylakakis, K., Bayer, E. (1995). Assessment of structurally related chemicals: toxicity and ecotoxicity of acrylic alkyl esters (acrylates), methacrylic acid and methacrylic acid alkyl esters (methacrylates). *Chemosphere*, **31**, 2637-2659.

Gurenko, L.V., Narizhnaya, O.N. (1977). Gas chromatographic method of determining butanol and butyl methacrylate in DTB-2 hardener. *Metody Anal. Kontrolya Proizvod. Khim. Prom-sti.*, **10**, 20-21 [Russian; *Chem. Abstr*., **88**, 191978; not relevant].

Hann, R.W., Jepsen, P.A. (1977). Water quality characteristics of hazardous materials. Texas A & M Univ College Station. NOAA, Texas Engineering Experiment Station, Rockville [NTIS PB-285946].

Hansch, C., Leo, A.J. (1985). The log P datase from the Pomona College medicinal chemistry project. Technical Database Services, New York NY.

Hedlund, S.G., Kiessling, K.H. (1969). The physiological mechanism involved in hangover 1. The oxidation of some lower aliphatic fusel alcohols and aldehydes in rat liver and their effect on the mitochondrial oxidation of various substrates. *Acta. Pharmacol. Toxicol.*, **27**, 381-396.

Horna, A., Pechova, H., Kaspar, O., Churacek, J., 1991. [Analysis of acrylates and methacrylates using a derivatization technique]. *Sb. Ved. Pr*., *Vys. Sk. Chemickotechnol. Pardubice*, **55**, 7-23 [Czech; Chem. Abstr., 118, 234833].

Horna, A., Taborsky, J., Dufka, O., Matoussek, P., Churacek, J. (1985). Chromatography of monomers II. Glass capillary gas chromatography of C1-C18 alkyl esters of acrylic and methacrylic esters. *J. Chromatogr.*, **325**, 367-378.

Jones, D.W., Hall, G.C., Sutow, E.J., Langman, M.F., Robertson, K.N. (1991). Chemical and molecular weight analyses of prosthodontic soft polymers. *J. Dent. Res.*, **70**, 874-879 [*Chem. Abstr*., **115**, 78853, refers to polyethylene/methyl methacrylate].

Kalmykova, Lazaris (1990). Determination of residual monomers in copolymers of methyl methacrylate with butyl methacrylate and butyl acrylate. Metody Issled. Akril. Sopolimerov NII Khimii i Tekhnol. Polimerov Im. V. A. Kargina, M. 57-61. [*Ref. Zh. Khim*. **1991**, 16S484; Russian abstract, title only translated; does not refer to *n*-BMA/*i*-BMA].

Kanerva, L., Estlander, T., Jolanki, R., Pekkarinem, E. (1992). Occupational pharyngitis associated with allergic patch test reactions from acrylics. *Allergy*, **47**, 571-573.

Kang, F., Xue, X., Chen, M. (1982). GC determination of residual monomers in acrylic coatings. *Tuliao Gongye*, **66**, 39-42, 25 [Chem. Abstr., 97, 7839; not relevant].

Kaspar, K., Dusek, Z., Herrmann, F., Moravkova, V., Matousek, P. (1989). Determination of very low concentrations of residual low-molecular substances in polymer samples, waste waters and atmosphere by capillary gas chromatography following preconcentration on Tenax GC as a sorbent. *Plasty a Kaucuk*, **26**, 272 [similar method quoted; no translation available].

Keith, L.H., Walters, D.B. (1985). Butyl methacrylate. In: *Compendium of safety data sheets for research and industrial chemicals*. VCH Publishers, Deerfield Beach FL, 254-255, 1130-1131.

Kertesz, P., Jozan, M., Brantner, A., Vamos, J., Vegh, A., Simonyi, I. (1972). Examination of the monomeric impurities of Akrinit E copolymer and of Plastubol spray II. Bromochlorometric determination of the monomers. *Gyogyszereszet*, **16**, 169-73 [Hungarian; *Chem. Abstr*., **77**, 92917; not relevant].

Komrakova, E.A., Kuznetsova, L.V. (1981). Gas chromatographic determination of acrylic acid and methacrylic acid esters in the atmosphere. *Gig. Sanit.*, **1**, 43-45 [Russian; Chem. Abstr., 94, 213499; similar method quoted: sensitivity for *n*-BMA is 0,002 mg/m^3; no translation].

Kovacs, L., Talas-Rohonczy, E., Horkay, F. (1971). Thermal investigations of varnishes and paints with the derivatograph 1. Use of thermoanalysis in the paint industry. *Farbe Lack*, **78**, 304-309 [*Chem. Abstr*., **77**, 21649].

Kravchenko, T.I., Chemer, G.A. (1976). Determination of methyl and butyl esters of acrylic and methacrylic acids in air by a thin-layer chromatographic method. *Gigiena Primeneniya Polimer. Materialov.*, 254-256. [Russian; *Chem. Abstr*., **86**, 176168; older method; title only translated].

Kreshkov, A.P., Balyatinskaya, L.N., Chesnokova, S.M. (1972). Alkoxymercurimetric method for monitoring the degree of polymerization and polycondensation of some monomers. *Tr. Mosk. Khim-Tekhnol. Inst.*, **70**, 146-147 [Russian; Chem. Abstr. 79, 19144; refers to methacrylic acid].

Kühn-Birett (1982). Acrylsäure-*n*-butylester stabilisiert. In: *Merkblätter Gefährliche Arbeitsstoffe*. Ecomed, München, M 07.

Kukui, N.M., Fufaeu, A.A., Bushueva, T.A., Vasil'eva, V.N., Potolovskii, L.A. (1979). Calculation of the boiling points of individual *n*-alkyl esters of methacrylic acid. *Khim. Tekhnol. Topl. Masel.*, **6**, 11-13.

Lewis, R.J. (ed.) (1992). *Sax's Dangerous Properties of Industrial Materials*, 8th ed., vol. 2. Van Nostrand Reinhold, New York, 593.

Lipina, T.G. (1973). Determination of isobutyl methacrylate, heptyl acrylate and nonyl acrylate in air. *Gig. Tr. Prof. Zabol.*, **17**, 56-57 [Russian; title only translated; older method].

Lundberg, P. (ed.) (1985). Consensus report for acrylic and methacrylic acids and their esters. Scientific basis for Swedish occupational standards VI. *Arbete och Hälsa*, **32**, 6-21 [review].

Luo, S-Q., Gang, B-Q., Sun, S-Z. (1986). Study on embryotoxicity and fetoxicity in rats by maternal inhalation of low level methyl methacrylate. *Toxicol. Lett.*, **31**, 80 [Abstract]

Luskin, L.S. (1970). Acrylic Acid, Methacrylic Acid and the Related Esters. In: Leonard E.C. (ed.), *High polymers, vinyl and diene monomers*. Wiley Interscience, New York 24, 105 203.

Mackay, D., Paterson, S. (1981). Calculating fugacity. *Environ. Sci. Technol.*, **15**, 1006-1014.

Mathias, C.G.T., Cadwell, T.M., Maibach, H.I. (1979). Contact dermatitis and gastrointestinal symptoms from hydroxyethylmethacrylat. *Briti. J. Dermatol.*, **100**, 447-449.

McCammon, C.S., Radha Krishnan, E., Morelli-Schroth, P.A. (1989). Industrial hygiene walk-through survey report of Digital Equipment

Corporation, Greenville PWB facility, Greenville, SC. NIOSH, Cincinnati OH [NTIS-OTS 40518106].

Mir, G.N., Lawrence, W.H., Autian, J. (1973a). Toxicological and pharmacological actions of methacrylate monomers I: Effects on isolated, perfused rabbit heart. *J. Pharmaceutical Sciences*, **62**, 778-782.

Mir, G.N., Lawrence, W.H., Autian, J. (1973b). Toxicological and pharmacological actions of methacrylate monomers II, Effects on isolated guinea pig ileum. *J. Pharmaceutical Sciences*, **62**, 1258-1261.

Mir, G.N., Lawrence, W.H., Autian, J. (1974). Toxicological and pharmacological actions of methacrylate monomers III, Effects on respiratory and cardiovascular functions of anesthetized dogs. *J. Pharmaceutical Sciences*, **63**, 376-381.

Mitsubishi Rayon (1988). Methacrylic monomers, specifications and handling. Mitsubishi Rayon, Tokyo.

Morris, J.B. (1992). Uptake of inspired methyl methacrylate and methacrylic acid vapors in the upper respiratory tract of the F344 rat. School of Pharmacy, Univ. of Conneticut. Methacrylate Producers Association, Washington DC.

Muir, W.M., Gray, R.A., Courtney, J.M., Ritchie, P.D. (1973). Permeability selective dialysis membranes part 2 films based on acrylic-acid *n*-butyl methacrylate co-polymers, a critical comparison with cellulose films. *J. Biomed. Mater. Res.*, **7**, 3-37 [title only; not relevant].

NIOSH (US National Institute of Occupational Safety and Health) (1992). Methacrylic acid, isobutyl ester, update 92-01. US Department of Health, Education and Welfare, Cincinnati, OH [quoted in: RTECS].

NTIS (1979). Information profiles on potential occupational hazards Vol. 2, Chemical classes. Methacrylic acid and its esters. NTIS-Report PB81-148892.

OECD (1981). OECD guideline for testing of chemicals 302, adopted 12 May 1981, inherent biodegradability. 302 C, Modified MITI test (II). OECD, Paris, 1-21.

OECD (1992). OECD guideline for testing of chemicals 301, adopted by the Council on 17th July 1992, ready biodegradability. 301 D, Closed bottle test. OECD, Paris, 32-40.

Oppenheimer, B.S. *et al* (1955). Further studies of polymers as carcinogenic agents in animals. *Cancer Res.*, **15**, 333-340.

Paryjczak, T., Czerczak, S. (1981). Effect of adsorptive properties and the amount of stationary liquid phase on the separation of acrylic compounds by gas chromatography. *Chem. Anal.*, **26**, 845-851 [*Chem. Abstr*., **99**, 32559; similar method quoted].

Paryjczak, T., Czerczak, S. (1981). Effect of adsorptive properties and the amount of stationary liquid phase on the separation of acrylic compounds by gas chromatography. *Chem. Anal.*, **26**, 845-851 [*Chem. Abstr*., **99**, 32559].

Pavlenko, Sm, Klimkina, N.V. (1975). Experimental comparative study of the state of the central nervous system of white rats by the conditioned reflex and summation threshold indexes methods in a chronic toxicological experiment. *Sanit-Toksikol. Metody Issled Gig.*, **1975**, 8-15. [*Chem. Abstr*., **87**, 112624j]

Rapaport, L.I., Livyi, G.V., Lepikhova, S.V., Frenkel, S.A. (1978). Determination of trace quantities of acrylic esters by gas-liquid chromatography. *Gig. Tr. Prof. Zabol.*, **11**, 50-51 [*Chem. Abstr*., **90**, 173703].

Reinert, K.H. (1987). Aquatic toxicity of acrylates and methacrylates: Quantitative structure-activity relationships based on K_{ow} and LC_{50}. *Regul. Toxicol. Pharmacol.*, **7**, 384-389 [Review].

Rekker, R.F. (1977). The hydrophobic fragmental constant. In: Nauta WT and Rekker RF (eds), Pharmacochemistry library vol 1. Elsevier Scientific Publishing, New York [calculation method of log Pow, no data].

Rohm and Haas (1993). Report 92R-134. Butyl methacrylate: Four-week vapour inhalation toxicity study in rats. Rohm and Haas Company, Spring House, Pennsylvania, USA.

Rohm and Haas (1994). Methyl acrylate, ethyl acrylate, *n*-butyl acrylate, methyl methacrylate, and styrene. Rohm and Haas workplace exposure limits. Doc. IH9402. Rohm and Haas, Spring House, PA.

Roth (1985). Wassergefährdende Stoffe 2 Erg, 69.

Rudenko, B.M., Zelenskaya, I.A., Lebedev, V.P., Kashchavtsev, I.G., Kornil'eva, N.E. (1979). Determination of residual monomers in alkyd-acrylic resins by a gas-liquid chromatographic method. Khim Prom-st, *Metody Anal. Kontrolya Kach. ProdKhim. Prom-sti.*, **1**, 11-14 [Russian; *Chem. Abstr*., **9**, 92330].

Rygle, Kathy, J. (1980). Trace residual monomer analysis by capillary gas chromatography. *J. Coat Technol.*, **52**, 47-52 [*Chem. Abstr*., **94**, 158358].

Sandmeier, E.E., Kirmin, C.J. (1982). Esters. In: Clayton, G.D., Clayton, F.E. (1982). *Patty's Industrial Hygiene and Toxicology*, Vol 2A, Toxicology, 3rd ed. J Wiley, New York, 2292-2293, 2300-2302.

Sangster, J. (1989). Octanol-water partition coefficients of simple organic compounds. *J. Phys. Chem. Ref. Data*, **18**, 1180.

Sarver, J.W. (1993). Acute dermal irritation/corrosion study (OECD) with *n*-butyl methacrylate in rabbits. Haskell Lab. Methacrylate Producers Association, Washington DC.

Shepel' Skaya, N.R. (1976). Comparative hygienic evaluation of some polymeric material on the basis of butyl methacrylate. *Gig. Sanit.*, **1**, 93-95 [Russian; abstract; not relevant].

Sporykhina, V.S., Zavadskaya, A.I., Mirkind, L.A. (1977). Polarographic determination of monomers in acrylic resins. *Lakokras Mater. Ikh. Primen.*, **5**, 61-63. [*Chem. Abstr*., **88**, 74758; covered by Nemec and Kirch, 1981].

SRI (1984). Methacrylic acid and esters process. Economics Program SRI International, Menlo Park, California, Report 11 Suppl C.

Teschke, R., Hasumura, Y., Lieber, C.S. (1974). NADPH-dependent of methanol, ethanol, propanol and butanol by hepatic microsomes. *Biochemical and Biophysical Research Communications*, **60**, 851-857.

Tobler, M., Freiburghaus, A.U. (1990). Contact dermatitis from acrylate and methacrylate compounds in Lowicryl® embedding media for elecron microscopy. *Contact Dermatitis*, **23**, 96-102.

Tobler, M., Freiburghaus, A.U. (1990). Occupational risks of (meth)acrylate compounds in embedding media for electron microscopy. *J. Microsc.*, **160**, 291-298.

US-EPA (US Environmental Protection Agency) (1986). The health and environmental effects of acrylate and methacrylate chemicals and the acylate/methacrylate category, revised 10/15/86.. EPA, Washington, DC [NTIS- OTS0589004].

Van der Walle, H.B., Klecak, G., Geleick. H., Densuik, T. (1982a). Sensitising potential of 14 mono (meth) acrylates in the guinea pig. *Contact Dermatitis*, **8**, 223-235.

Van der Walle, H.B., Delbressine, L.P.C., Seutter, E. (1982b). Concomitant sensitization to hydroquinone and *p*-methoxyphenol in the guinea pig, inhibitors in acrylic monomers. *Contact Dermatitis*, **8**, 147-154.

Vlasov, S.M., Konov, A.S. (1970). [Gas-chromatographic determination of impurities in butylmethacrylate]. *Izv. Akad. Nauk SSSR*, *Ser. Khim*., **5**, 1174-1176 [Russian; *Chem. Abstr*., **73**, 72849].

Wagner, D.E. (1990). Personal correspondence to EPA. Section 8(d) reporting. Mobil Oil Corporation, Princeton, NJ, 10 p.

Weiss, L.H. (1980). Hazardous Chemicals Data Book. Noyes Data Corp, NJ, 195.

Zueva, S.N., Kondakova, L.V., Batrakov, G.N. (1977). [Chromatographic method for determining the composition of waste gases from acrylate and methacrylate]. *Metody Anal. Kontrolya Proizvod. Khim. Prom-sti.*, **9**, 16-17 [Russian, *Chem. Abstr*., **88**, 125540].

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