Joint Assessment of Commodity Chemicals No. 36

n-Butyl Methacrylate
Isobutyl Methacrylate

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

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THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced and are continuing to write reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a producer, government official or consumer can be informed on the up-to-date position with regard to safety information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed. To assist ourselves and others working in this field we have published a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to our Technical Report No. 71 entitled "Inventory of Critical Reviews on Chemicals".

This document presents a critical evaluation of the toxicology and ecotoxicology of the 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). The abbreviation *n*-BMA/*i*-BMA is used in this report whenever the text is applicable to both isomers.

The *n*-BMA and *i*-BMA isomers are reviewed in the same document because of the close similarity of their chemical structure, physical and chemical properties, environmental profiles and toxicity data. Furthermore the two esters are frequently produced in the same production plant and their use pattern is very similar. The decision to review both *n*-BMA and *i*-BMA together was based on the contention that there are no fundamental differences between the toxicity and environmental profiles of the alcoholic moieties of *n*-butanol and isobutanol (IPCS, 1987).

To compensate for the scarcity of data on some endpoints, available information on structurally analogous compounds and hydrolysis products is offered in Chapter 9. These data were employed in the hazard assessment of *n*-BMA/*i*-BMA.

n-Butyl Methacrylate (CAS No. 97-88-1) and Isobutyl Methacrylate (CAS No. 97-86-9)

CONTENTS

1. SUMMARY AND CONCLUSIONS

Because of the close similarity of their chemical structure, production methods and use pattern, the two isomers of butyl methacrylate, *n*-butyl methacrylate (*n*-BMA) and isobutyl methacrylate (*i*-BMA) are considered together in this report. The abbreviation *n*-BMA/*i*-BMA is used whenever the text is applicable to both isomers.

At room temperature, *n*-BMA/*i*-BMA is a clear, colourless, flammable liquid with a faint, characteristic ester odour. Both compounds have a low solubility in water and are soluble in most organic solvents.

In the EU, about 30 kt of *n*-BMA and 8 kt of *i*-BMA were produced in 1994. Environmental releases during production and major industrial uses are very low.

When released into the environment, the majority (95 %) of *n*-BMA/*i*-BMA will partition into the atmosphere. The atmospheric half-life of *n*-BMA/*i*-BMA has been estimated to be between 5.6 and 7.5 hours depending on the parameters of the calculation. In water *n*-BMA/*i*-BMA is readily biodegradable. A moderate bioaccumulation potential is expected. A half-life of 13 hours for *n*-BMA and 5.6 hours for *i*-BMA has been calculated for volatilisation from a model river. In soil, *n*-BMA is characterised by moderate adsorption, while *i*-BMA was found to be strongly adsorbed.

n-BMA/*i*-BMA is of moderate toxicity (EC_{50}: 10-100 mg/l) to bacteria, fish and *Daphnia*. *i*-BMA had a high toxicity (< 0.1 mg/l) towards green algae when tested in a closed system based on a 96-h NOEC of 0.047 mg/l. However, this effect was reversible and represented an algistatic rather than an algicidal action of *i*-BMA. When tested in a standard open test system the toxicity of *n*-BMA to green algae could not be measured conclusively because of the rapid loss of the material during the exposure time. The test results of the algae studies indicate that the hazard identified by the growth inhibition observed with *i*-BMA in a closed system should be viewed in the light of the reversibility of the effect and the probable volatilisation under open exposure conditions which represent more closely the normal environmental situation. This accounts for the lower toxicity of *n*-BMA observed in an open test system.

From the physico-chemical data it is anticipated that *n*-BMA/*i*-BMA is rapidly absorbed after oral or inhalation exposure. *In vitro* studies using isolated rat liver microsomes or porcine liver esterase showed rapid hydrolysis of *n*-BMA yielding methacrylic acid and *n*-butanol. No *in vivo* metabolism data are available on *n*-BMA/*i*-BMA, but from the *in vitro* data rapid hydrolysis to methacrylic acid and the corresponding alcohol can be anticipated. *n*-BMA did not bind to glutathione (GSH) *in vitro*. It is expected that after hydrolysis the respective cleavage products methacrylic acid and *n*-butanol or

isobutanol are further metabolised by normal physiological pathways ultimately to CO_2. The interpretation of the toxicological data is based on these assumptions.

In mammals *n*-BMA/*i*-BMA is of low acute toxicity by the oral, dermal or inhalation route of exposure. They have local irritating properties to rabbit skin and eyes. Respiratory tract irritation was observed after inhalation exposure of rats to *n*-BMA. Although no data on respiratory irritation are available for *i*-BMA it is expected to have similar effects as *n*-BMA. Whilst *n*-BMA is a weak skin sensitiser in guinea pigs, there is no such evidence for *i*-BMA. From the available human clinical data it can be concluded that the sensitisation potential to humans of *n*-BMA is low.

A repeat dose oral study in mice is available which, although of limited reliability, indicates that *n*-BMA is of low oral toxicity. A reliable 28-day exposure inhalation study in rats is available for *n*-BMA. The lead effect in this study was the formation of nasal lesions indicative of a local irritant effect in the olfactory region of the nose with no indications of systemic toxicity.

Neither *n*-BMA nor *i*-BMA was mutagenic in a number of gene mutation assays with *Salmonella typhimurium*. *i*-BMA was not clastogenic in a mouse micronucleus assay. Despite the rather limited database, taking into account the close structural similarity of the two isomers and data on other methacrylic acid esters, there is no immediate concern for genotoxicity.

For the endpoints carcinogenicity, chronic toxicity and toxicity to reproduction, no reliable data are available for either ester. However, information concerning potential hazards of *n*-BMA/*i*-BMA may in part be inferred from studies with methyl methacrylate which like *n*-BMA/*i*-BMA is metabolised to methacrylic acid in animals and in humans.

Given the lack of carcinogenicity observed with methyl methacrylate and the lack of genotoxic potential of *n*-BMA/*i*-BMA, there is no immediate concern with regard to a possible carcinogenic potential of *n*-BMA/*i*-BMA. The Task Force is not aware of any reliable data on the carcinogenicity of *n*-butanol and isobutanol.

With regard to chronic toxicity the lead effect for methyl methacrylate long term inhalation exposure was local nasal irritation. The lead effect in a 28-day *n*-BMA study is consistent with this pattern of toxicity and therefore suggests that this study is an appropriate and relevant indicator of chronic toxicity.

Due to the paucity of data, no firm conclusions can be made on the potential toxicity to reproduction. However, the data available for methyl methacrylate and *n*-butanol and isobutanol suggest that there

is no need for immediate concern for possible developmental effects arising from inhalation exposure to non-maternally toxic concentrations of *n*-BMA/*i*-BMA.

Limited data available from repeated dose studies with *n*-BMA, methyl methacrylate, methacrylic acid and a fertility study with *n*-butanol did not reveal any indications for possible toxic effects on the reproductive organs.

The sensitisation potential of *n*-BMA to humans is low.

Despite the use of *n*-BMA/*i*-BMA for many years, no adverse systemic health effects have been observed. The lead effect of *n*-BMA/*i*-BMA identified in acute and subchronic animal studies is the local irritation at the site of contact following exposure by the inhalation route, the major route of occupational exposure. From the available studies it can be concluded that upper respiratory tract irritation is the most common effect of inhalation exposure to *n*-BMA/*i*-BMA.

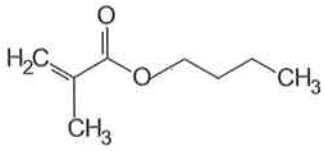
2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 IDENTITY

2.1.1 *n*-Butyl Methacrylate

Name:	*n*-Butyl methacrylate (*n*-BMA)
IUPAC name:	Butyl 2-methyl-2-propenoate
Synonyms:	Butyl 2-methacrylate 2-Methyl-2-propenoate, butyl- Methacrylic acid, butyl ester
Danish:	Butylmethacrylat
Dutch:	*n*-Butylmethacrylaat 2-Methylbutylacrylaat
Finnish:	Butyyli metakrylaatti
French:	Méthacrylate de butyle Méthacrylate de *n*-butyle
German:	*n*-Butylmethacrylat Methacrylsäure butyl ester
Greek:	Μεθακρυλικός *n*-βουτυλεστέρας
Italian:	*n*-Butilmetacrilato
Norwegian:	Butylmetakrylat
Portuguese:	Metacrilato de *n*-butilo
Spanish:	Metacrilato de butilo
Swedish:	Butylmetakrylat
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
EINECS No:	202-615-1
Formula:	$C_8H_{14}O_2$
Molecular mass:	142.20

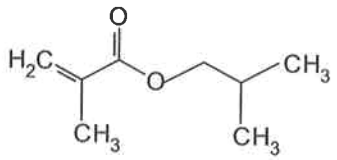
Structural formula:



2.1.2 Isobutyl Methacrylate

Name:	Isobutyl methacrylate (*i*-BMA)
IUPAC name:	Isobutyl 2-methylpropenoate
Synonyms:	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
Danish:	Isobutylmethacrylat
Dutch:	Isobutylmethacrylaat
Finnish:	Isobutyyli metakrylaatti
French:	Méthacrylate de d'isobutyle
German:	Isobutylmethacrylat
Greek:	Μεθακρυλικός ισοβουτυλεστέρας
Italian:	Isobutilmetacrilato
Norwegian:	Isobutylmetakrylat
Portuguese:	Metacrilato de isobutilo
Spanish:	Metacrilato de isobutilo
Swedish:	Isobutylmetakrylat
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
EINECS No:	202-613-0
Formula:	$C_8H_{14}O_2$
Molecular mass:	142.20

Structural formula:



2.2 PHYSICAL AND CHEMICAL PROPERTIES

At room temperature, *n*-BMA/*i*-BMA is a clear, colourless, flammable liquid 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 1 and 2.

n-BMA

A typical commercial sample of *n*-BMA has a specified purity of ≥ 99.0 % (w/w) and contains water (0.05 % w/w) and other impurities. The identity of these impurities will vary depending on the production process (Section 3.1) and may include traces of methacrylic acid and methyl methacrylate.

i-BMA

A typical commercial sample of *i*-BMA has a specified purity of ≥ 98.5 % (w/w) and contains water (≤ 0.01-0.02 %, maximum 0.1 % w/w) and other impurities. The identity of these impurities will vary depending on the production process (Section 3.1) and may include traces of methacrylic acid and methyl methacrylate.

n-BMA/i-BMA

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 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 monomethylether of hydroquinone (MeHQ, synonym *p*-methoxyphenol) (10-100 ppm, maximum < 0.1 % w/w).

Table 1: Physical and Chemical Properties of *n*-BMA

Parameter, units	Value	Reference
Melting temperature, °C, approximately	–25	Company data sheets[a]
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 Krich, 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
	0.9836	Weast *et al*, 1989
Viscosity, mPa×s at 20 °C	1.1-1.2	Company data sheets[a]
at 21 °C	3.116	HSDB, 1994
Refractive index, n_D at 20 °C	1.422	Kirk-Othmer, 1981
	1.424	Degussa, 1989
Vapour pressure, hPa at 20 °C	2.40	Company data sheets[a]
	6.1	HSDB, 1994
Vapour density at 20 °C (air=1)	4.8	HSDB, 1994
Threshold odour concentration, ppm	0.015-0.06	Company data sheets[a]
	0.025	Shepel'skaya, 1978
Surface tension, mN/m at 20 °C	35	HSDB, 1994
Solubility in water, g/kg at 20 °C	< 0.45	Company data sheets[a]
	0.882[b]	Lissi *et al*, 1983
Solubility of water in *n*-BMA, g/kg at 20 °C	0.04	Company data sheets[a]
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[b]	Fujisawa and Masuhara, 1981; Dillingham *et al*, 1983
	2.88[b]	Tanii and Hashimoto, 1982
	3.01[b]	Morris *et al*, 1992a
	2.26[c]	Fujisawa and Masuhara, 1981
Partition coefficient, K_{oc} (organic carbon/water), calculated at 20 °C	8.9-61.5[d]	Kenaga and Goring, 1978
	74.8-421	According to CEC, 1994a
at 25 °C	878[e]	Swann *et al*, 1983
	63.6	According to SRC, 1994
Henry's Law constant, Pa×m^3/mol, at 25 °C	11[f]	Hine and Mokerjee, 1975
Flash point, °C, closed cup	46	Röhm, 1995a
	49	Degussa, 1968
Explosion limits, % at 65-96 °C and 1,000 hPa	2-8	Company datasheets[a]; HSDB, 1994
Auto-flammability, ignition temperature, °C	315	Degussa, 1990
	400-496	Degussa, 1968

a Rohm and Haas, 1993; ICI Acrylics, 1994; Degussa, 1995a; Röhm, 1996a
b Shake flask method
c High performance liquid chromatography (HPLC) method
d Based on log P_{ow} = 2.26-3.01
e Based on log P_{ow} of 2.88 and regression equation of Lyman *et al* (1982)
f Calculated; reported as 1.09×10^{-4} atm×m^3/mol

Table 2: Physical and Chemical Properties of *i*-BMA

Parameter, units	Value	Reference
Melting temperature, °C	–37 - –34	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]
Viscosity, mPa×s at 20 °C	0.9	Company data sheets[a]
Refractive index, n_D at 20 °C	1.4197-1.420	Nemec and Kirch, 1981; Degussa, 1989
Vapour pressure, hPa at 20 °C	2.4-4	Deichman, 1981; Company data sheets[a]
Vapour density at 20 °C (air=1)	4.9	Deichman, 1981
Threshold odour concentration, ppm	0.016-0.069	ICI Acrylics, 1994
Surface tension, mN/m at 24 °C	23.5[b]	DIPPR, 1995
Solubility in water, g/kg at 20 °C	0.133	Mao, 1995
Solubility of water in *i*-BMA, g/kg at 20 °C	0.005	Röhm, 1995b
Miscible with most organic solvents	Yes	Weast *et al*, 1989; ICI Acrylics, 1994
Fat solubility, mg/100 g at 37 °C	No data	
Partition coefficient, log P_{ow} (octanol/water), measured at 20 °C	2.66[c]	Tanii and Hashimoto, 1982
	2.01[d]	Fujisawa and Masuhara, 1981
Partition coefficient (soil) , K_{oc} (organic carbon/water) at 20 °C	1480-3920	Christensen, 1995a
	42.05-171.3	Calculated according to CEC, 1994a
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	DIPPR, 1995
	ca. 2-8	Degussa, 1995a,b
Auto-flammability, ignition temperature, °C	367-400	Company data sheets[a]; Degussa, 1994

a Elf Atochem, 1993; ICI Acrylics, 1994; Degussa, 1995b,c; Röhm, 1996b
b Calculated according to Sugden, 1924
c Shake flask method
d High performance liquid chromatography (HPLC) method

2.3 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

2.4 ANALYTICAL METHODS

n-BMA/*i*-BMA may be analysed and detected by common chromatographic techniques as reviewed by Nemec and Kirch (1981) e.g. gas chromatography (GC) or high performance liquid chromatography (HPLC). These techniques are used for assaying the purity of methacrylate monomers, monomer content in mixtures with other monomers, in solutions and (residual levels) in polymers.

2.4.1 Purity of *n*-BMA/*i*-BMA

n-BMA/*i*-BMA can be assayed for purity by capillary gas chromatography (GC) using a flame ionisation detector (FID) (Röhm, 1993a). Impurities present in concentrations of 10 ppm or higher may be identified and quantified by coupled mass spectrometry (GC/MS) and calibration of the peak area.

2.4.2 *n*-BMA/*i*-BMA in Products

Residual Monomer

Residual *n*-BMA/*i*-BMA in polymeric products can be determined by GC headspace analysis. The material under investigation is dissolved in or extracted with a solvent of low volatility like dimethylformamide. Subsequently the sample is equilibrated at elevated temperature and analysed by GC/FID (Röhm, 1993b). With a *n*-BMA/*i*-BMA copolymer the quantitation limit was determined to be 2 ppm. This method may also be used for the determination of residual monomer concentrations in dispersions/emulsions.

Residual *n*-BMA/*i*-BMA in aqueous polymer emulsions was determined by GC (Miller and Harper, 1983). The samples were analysed by direct injection or following extractive distillation with cyclohexane. The extraction method showed better reproducibility and precision.

Mixtures and Polymers

Mass spectrometry (MS) has been used to identify *n*-BMA, and other acrylic monomers in resin-based dental materials (Gjoes *et al*, 1983). The materials were either injected directly or dissolved in dichloromethane to separate solid filler materials. Mass spectra were determined for most components of dental resins.

Alkyl(meth)acrylate monomers such as *n*-BMA/*i*-BMA can be detected in their mixtures or in polymers by reaction with *n*-butylthiol in the presence of NaOH catalyst, followed by separation and determination of the obtained thioethers by GC (Horna *et al*, 1991; Churacek *et al*, 1991).

The composition of polymers can be investigated by pyrolysis and subsequent chromatographic analysis of the pyrolysate. Bates *et al* (1989) used capillary pyrolysis GC/FID for the analysis of pyrolysate from several alkyd paint resins and polymers. GC/MS was used to identify the constituents of the pyrolysate. In one of the investigated lacquers BMA (isomer not specified) was identified as one of the constituents.

Dispersion and Emulsion Polymers

n-BMA/*i*-BMA can be determined directly in *n*-BMA/*i*-BMA containing copolymer dispersions when the polymer has been removed by a dissolution/precipitation sequence (dissolved in tetrahydrofuran and then precipitated by methanol/water) prior to analysis. Depending on the composition of the dispersion a detection limit of 10 ppm may be achieved (Röhm, 1996c).

2.4.3 *n*-BMA/*i*-BMA in Air

The most common methods to determine *n*-BMA/*i*-BMA in air use a combination of three techniques: (i) sorption onto materials such as activated carbon, Tenax and XAD; (ii) heat or solvent desorption, and (iii) analysis by GC or GC/MS.

A method applicable to all airborne organic gases and vapours (e.g. *n*-BMA/*i*-BMA) except to very-low-mass compounds has been described. The compounds were adsorbed onto Tenax, desorbed by heating, concentrated into a narrow band in a U-tube trap cooled in liquid nitrogen and then injected directly into a GC/MS combination. Compounds such as methyl methacrylate, BMA (isomer not specified) and terpenes were detected at mg/m^3 levels in the flue gases of pottery kilns where they were present as a result of thermal depolymerisation of a methyl methacrylate/BMA containing polymer in printing films for pottery and china (Morgan and Bradley, 1989). A similar method for the determination of airborne *n*-BMA/*i*-BMA has been described by Krost *et al*, 1982. These authors used again Tenax adsorption followed by thermal desorption and concentration of the sample in a nickel capillary trap cooled in liquid nitrogen. Subsequently the vapours were analysed by capillary GC/MS with different capillary column materials depending on the polarity of the investigated material. Breakthrough volumes and detection limits were described for a number of chemicals of different classes (but not for *n*-BMA/*i*-BMA).

Henriks-Eckerman (1990, 1992) studied the sampling efficiency of an air collection device. An XAD-2 column was used together with a glass-fibre prefilter and a back-up by activated charcoal. The recovery of organic air pollutants (5-100 mg of each in 150-200 l of air) was > 80 % for most compounds with the exception of very polar ones. For BMA (isomer not specified) a recovery ≥ 90 % was found under different experimental conditions.

Alkyl(meth)acrylate monomers such as *n*-BMA/*i*-BMA can be detected in their mixtures or in polymers by reaction with *n*-butylthiol in the presence of NaOH catalyst, followed by separation and determination of the obtained thioethers by GC. Combined with an adsorption/desorption step the method is also suitable for the detection of methacrylates in air. By this method a minimum of 1.5 µg of the respective thioether may be detected (Horna *et al*, 1991; Churacek *et al*, 1991).

n-BMA/*i*-BMA can be determined in workplace air by means of NIOSH method 1450, involving adsorption on activated carbon by active sampling (4 l/h) followed by desorption with carbon disulphide and analysis by GC/FID. The 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, 1996d). Using a similar method Degussa (1992) achieved a detection limit of 1 µg/sample (17 µg/m^3). Froines and Gabarant (1986a,b) used gas liquid chromatography (GLC) with FID to determine *i*-BMA in the air of an artificial nail sculpting shop. The compound was sampled by adsorption onto passive dosimeter badges or by pumping air through tubes filled with 150 mg activated charcoal (flow rate 20 ml/min), both followed by desorption with carbon disulphide, and analysis by GLC-FID.

2.4.4 *n*-BMA/*i*-BMA in Aqueous Solutions and Dispersions

n-BMA/*i*-BMA in aqueous solutions may be determined by direct GC or HPLC analysis or extracted with solvent followed by GC analysis of the extract. In the presence of polymer, e.g. polymer emulsions/dispersions, either solvent extraction or headspace analysis is recommended (Section 2.4.2).

n-BMA/*i*-BMA in aqueous solutions may be determined by HPLC with UV detection. In ecotoxicological tests *n*-BMA/*i*-BMA concentrations have been analysed using GC with C18 reversed-phase columns; the detection limit was 0.05 mg/l (Smyth *et al,* 1992; Christensen 1995b; Mao, 1995; Putt, 1995a,b). In an algal toxicity study GC-FID was used to determine the test concentration of *i*-BMA. The test substance was extracted from the culture medium with hexane. The detection limit was 1.3 µg/l (Hoberg, 1995).

2.4.5 Biological Media

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 an extraction or headspace technique are expected to be more useful.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 PRODUCTION

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).

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

3.2 STORAGE

To prevent polymer formation, the *n*-BMA/*i*-BMA monomer is stabilised by the addition of an inhibitor such as MeHQ (Section 2.2). The effectiveness of phenolic inhibitors depends on the presence of oxygen. To prevent polymer formation, the monomers must therefore be stored under air (not under inert gases), in the dark 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 a pressure relief valve.

3.3 TRANSPORT

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.

3.4 USE

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

monomer and copolymer) 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

Concrete can be made water repellent by the polymerisation of vinyl monomers on the surface. A treatment that may be practical for highway bridge decks is the application of methyl methacrylate, isodecyl methacrylate, or *i*-BMA.

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 3.

Table 3: 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	-

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 EMISSIONS

4.1.1 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).

4.1.2 Emissions During Production and Use

n-BMA/*i*-BMA may be released into the environment in fugitive and stack emissions or in wastewater during its production and use in the manufacture of large volume resins and polymers. Estimated releases into the environment from monomer and polymer production in the EU are summarised in Table 4.

Table 4: Releases from Production into the Environment in the EU in 1994 (CEFIC, 1996)

Emissions	*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).

Other Sources

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

Residual Levels in Polymers and Polymer Dispersions

Residual levels of *n*-BMA/*i*-BMA monomers in solid polymers and polymer dispersions are always < 1 %, for solid polymers typically in the range 0.1-0.5 % and for polymer dispersions ≤ 0.01-0.1 % (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 in 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).

4.2 ENVIRONMENTAL DISTRIBUTION

The theoretical distribution of *n*-BMA/*i*-BMA has been estimated using the generic fugacity model of Mackay *et al* (1992). The calculations indicate that the majority will partition into the atmosphere (97 % of *n*-BMA and 95 % of *i*-BMA), while 2.6 % of the emitted *n*-BMA and 5 % of *i*-BMA will remain in the water phase. Negligible amounts will be found in soils and sediments (Table 5).

Table 5: Estimated Distribution Between Environmental Compartments at 25 °C (ICI Acrylics, 1994; Röhm, 1994)

Compartment	*n*-BMA (%)	*i*-BMA (%)
Air	97.24	94.87
Water	2.57	5.05
Soil	0.10	0.04
Sediment	0.09	0.04
Suspended matter aquatic	0.00	0.00
Biota	0.00	0.00

4.3 ENVIRONMENTAL FATE AND BIOTRANSFORMATION

4.3.1 Atmospheric Fate

n-BMA

In the atmosphere, *n*-BMA will react with photochemically produced hydroxyl radicals (•OH). The atmospheric half-life of *n*-BMA has been calculated to be 7.5 hours, according to the model of Atkinson (1987) (SRC as quoted in HSDB, 1994).

Elf Atochem (1996) calculated a half-life of 4.6 hours for *n*-BMA using a hydroxyl radical concentration of 1.5×10^6 •OH/cm^3 and an ozone concentration of 7×10^{11} mol/cm^3, according to the model of SRC (1995).

i-BMA

An atmospheric half-life of 5.74 hours was calculated for photooxidation of *i*-BMA in the presence of 5×10^5 •OH/cm^3 and 7×10^{11} molecules ozone per cm^3 according to the model of Atkinson (1987) (calculated by SRC as quoted in HSDB, 1994).

Elf Atochem (1996) calculated a half-life of 4.6 hours for *i*-BMA using a hydroxyl radical concentration of 1.5×10^6 •OH/cm^3 and an ozone concentration of 7×10^{11} mol/cm^3, according to the model of SRC (1995).

4.3.2 Aquatic Fate

n-BMA

A half-life of 13 hours has been estimated for volatilisation of *n*-BMA from a model river of 1 m depth, flowing 1 m/s with a wind speed of 3 m/s (calculated by SRC according to the method of Lyman *et al*, 1982 as quoted in HSDB, 1994).

i-BMA

A half-life of 5.62 hours was estimated for *i*-BMA for volatilisation from a model river (calculated according to the method of Lyman *et al*, 1982 as quoted in HSDB, 1994) and of 4.2 days from a model

pond including absorption (calculated with EXAMS II of US-EPA, 1987) (SRC as quoted in HSDB, 1994).

4.3.3 Terrestrial Fate

n-BMA

K_{oc} values from 8.9 to 878 have been calculated for *n*-BMA (Table 1). These indicate a low to moderate soil mobility of *n*-BMA.

i-BMA

K_{oc} values of 42.05 to 171.3 have been calculated for *i*-BMA (Table 2).

The adsorption and desorption properties of *i*-BMA were investigated according to OECD Guideline 106 in 3 different types of soil: loam, sillty loam and sandy loam. The study included an adsorption phase followed by 2 subsequent desorption phases (16 h/phase). The *i*-BMA:soil ratio's for the 3 soils were 50:1, 65:1 and 52:1 and the respective K_{oc} values averaged 1,480, 3,650 and 3,920. Based on these results, *i*-BMA was considered to be tightly bound to the 3 soils tested (Christensen, 1995a).

4.3.4 Biodegradation

Aerobic

n-BMA/i-BMA

In a closed bottle test based on the consumption of oxygen (OECD Guideline 301 D), a biodegradation of 76 % was achieved within 28 days for *n*-BMA and 74.3 % for *i*-BMA. The "pass" level of 60 % being reached within 10 days of exceeding the 10 % level, *n*-BMA/ *i-BMA* can be considered as readily biodegradable (Elf Atochem, 1995a,b).

In a modified MITI test (OECD Guideline 302 C), a biodegradation of 38 % was achieved within 28 days both for *n*-BMA/*i*-BMA. However, volatilisation of the test compounds from the aqueous phase could not be excluded (Röhm, 1988a,b).

n-BMA

n-BMA was found to have degraded by 32.8 % (dissolved oxygen depletion) after 28 days in a closed bottle test (OECD Guideline 301 D) (Ouelette, 1995). On the basis of the rate of biodegradation of the reference substance (sodium benzoate), the inoculum used in this study seems less active than the one used by Elf Atochem above. Another explanation could be the possible volatilisation of the test substance, although it is difficult to draw this conclusion from the report.

The Modified Zahn-Wellens test was found to be an inappropriate system for assessing the biodegradation of *n*-BMA, because the test substance was rapidly volatilised from the aerated test solution. After 3 hours, the initial test concentration (nominal 74.6 mg/l measured 50 mg/l) had already declined by 82.8 % and by day 2 98.2 % had been released from the aerated test solution (Christensen, 1995b).

4.3.5 Bioaccumulation

n-BMA/i-BMA

For *n*-BMA/*i*-BMA *n*-octanol/water partition coefficients (log P_{ow}) have been measured in the range from 2.26 to 3.01 (Fujisawa and Masuhara, 1981; Tanii and Hashimoto, 1982; Morris *et al*, 1992a). The bioconcentration factors for both esters, estimated according to the method of Lyman *et al* (1990), are in the range of 31 to 114 using the log P_{ow}-values mentioned above. From the *n*-octanol/water partition coefficient and the theoretical bioconcentration factor a moderate bioaccumulation potential was estimated for *n*-BMA/*i*-BMA.

4.3.6 Evaluation

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

When released into the environment, the majority (95 %) of *n*-BMA/*i*-BMA will partition into the atmosphere. The atmospheric half-lives of *n*-BMA/*i*-BMA have been estimated to be between 5.6 and 7.5 hours depending on the parameters of the calculation.

In water, *n*-BMA/*i*-BMA is readily biodegradable. A moderate bioaccumulation potential is expected.

A respective half-life of 13 hours for *n*-BMA and 5.6 hours for *i*-BMA has been calculated for volatilisation from a model river.

In soil, *n*-BMA is characterised by moderate adsorption, while *i*-BMA was found to be strongly adsorbed.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 ENVIRONMENTAL LEVELS

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

5.2 HUMAN EXPOSURE LEVELS AND HYGIENE STANDARDS

5.2.1 Non-occupational Exposure

No data are available.

5.2.2 Occupational Exposure

n-BMA

The available data on occupational exposure levels of *n*-BMA during monomer production and polymerisation are summarised in Table 6.

Table 6: Occupational Exposure Levels of *n*-BMA during Monomer Production and Polymerisation (CEFIC, 1996)

Work place	Year of measurement	Sample type[a]	Concentration[b] (mg/m^3)	
			TWA	Short-term level
Production				
All operations	1992-94	NS	0.09-0.16	-
Filling	1992-93	NS	-	ND-0.37
Laboratory	1992-93	Area	0.2	< 0.5-3.77
NS	1992	Area	0.9	-
Pumphouse	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 Personal = monitoring in the worker's breathing zone
Area = background monitoring at the work place
NS = not stated

b TWA = time-weighted average exposure concentration (4 to 8-h working period)
Short-term level = exposure concentration during short period (5 min - 1 h)
ND = not detectable (detection limit not stated)

Workplace concentrations of *n*-BMA and other vapours during the extrusion of acrylic sheets were reported to range between < 0.1 and 8 ppm under normal conditions and between < 0.1 and 16.5 ppm 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 7.

Table 7: Occupational Exposure Levels of *i*-BMA during Monomer Production and Polymerisation (CEFIC, 1996)

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

a Personal = monitoring in the worker's breathing zone
Area = background monitoring at the work place
NS = not stated

b TWA = time-weighted average exposure concentration (4 to 8-h working period)
Short-term level = exposure concentration during short period (5 min - 1 h)
ND = not detectable (detection limit not stated)

Froines and Grabant (1986a,b) have reported on workplace concentrations of *i*-BMA during the preparation of synthetic nails (Table 8).

Table 8: Exposure of Manicurists to *i*-BMA during Preparation of Synthetic Nails (Froines and Garabant, 1986a,b)

Nail shop	Measurements	Exposure concentration (mg/m^3)			
		Intermittent[a]		Continuous[b]	
	(No.)	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**

Work place concentrations between < 0.03 and 0.29 ppm of butyl methacrylate (isomer not specified) were reported by a polymer company (no further data available) (Hi-Tek Polymers, 1989).

Median concentrations of butyl methacrylate (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).

5.2.3 Hygiene Standards

Only Norway and Sweden have adopted an official occupational exposure limit (OEL) value for *n*-BMA/*i*-BMA: 50 ppm or 300 mg/m^3 (TWA, time-weighted average concentration during an 8-h working period) and a short-term exposure limit (STEL, 15 min) of 75 ppm or 450 mg/m^3 with a notation "A" (allergenic) or "S" (sensitising) respectively (Arbeidstilsynet, 1995; AFS, 1996).

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.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 MICROORGANISMS

n-BMA

The influence of *n*-BMA on the growth of *Pseudomonas putida* was investigated. The concentration, which caused no growth inhibition after 18 hours of exposure was found to be 31.7 mg/l (EC_0). The EC_{50} value was reported to be greater than 253.6 mg/l (Röhm, 1988c). Another study reported an EC_{50} value of 37 mg *n*-BMA/l for luminescent bacteria (species not known) after an exposure of 5 minutes (Benson and Stackhouse, 1986).

i-BMA

The influence of *i*-BMA on the growth of *Pseudomonas fluorescens* was investigated. The concentration, which caused no growth inhibition after 16 hours of exposure was found to be above 281 mg/l (EC_0) (Röhm, 1988d).

6.2 AQUATIC ORGANISMS

n-BMA

In a 96-h flow-through study the LC_{50} value of *n*-BMA was determined for the freshwater fish species *Pimephales promelas* (fathead minnow). The LC_{50} was reported to be 11 mg/l. A concentration of 7 mg/l did not show any toxic effects, while 100 % mortality (LC_{100}) was observed at a concentration of 20 mg *n*-BMA/l. In this study the mean measured values ranged from 54 % to 75 % of nominal concentrations of *n*-BMA in the test vessels (Morris *et al*, 1992b).

The 48-h EC_{50} (mobility) for the freshwater crustacean *Daphnia magna* was reported to be 32 mg/l (static conditions, sealed vessels) (Kent *et al*, 1993) and 29 mg/l (static conditions, test concentrations remained constant throughout the assay) (Elf Atochem, 1994a). No toxic effects could be determined in *D. magna* at a measured concentration of 23 mg *n*-BMA/l. The EC_{100} -value was found to be 75 mg/l (Kent *et al*, 1993).

The 21-day EC_{50} for *D. magna* (reproduction) (flow-through conditions) was empirically estimated to be > 8.4 mg *n*-BMA/l, the highest concentration maintained during the test. The LOEC was 4.9 mg/l, the

NOEC was 2.6 mg/l. Based on these data the MATC (Maximum Acceptable Toxicant Concentration) was between 2.6 and 4.9 mg/l (Putt, 1995a).

A growth inhibition of 50 % (based on biomass) was observed after an exposure of 96 hours in the freshwater algae *Selenastrum capricornutum* at a measured concentration of 57 mg *n*-BMA/l at the beginning of the test. After 96 hours, however, only very low amounts of *n*-BMA (< 0.05 mg/l) were present in the solution due to volatilisation of the test compound. No effect was noted at a concentration of 26 mg/l (Smyth *et al*, 1992).

i-BMA

The 48-h LC_{50} value of *i*-BMA for the freshwater fish species *Leuciscus idus melanotus* (golden orfe) was reported to be 92 mg/l. No mortality could be determined in this static study at a nominal concentration of 80 mg/l. The LC_{100}-value was found to be 100 mg/l (Röhm, 1988d).

The 96-h LC_{50} value to rainbow trout (*Oncorhynchus mykiss*) was calculated to be 20 mg *i*-BMA/l, with a NOEC of 4.6 mg/l based on mean measured concentrations (flow-through conditions). Sublethal effects were seen at lower concentrations (6.9 to 17 mg/l), with 15 % mortality at 28 mg/l (Sousa, 1995)

The 48-h EC_{50} for *D. magna* was found to be 23 mg/l (static conditions, test concentrations remained constant throughout the assay). No toxic effect was observed at a measured concentration of 4.5 mg/l (Elf Atochem, 1994b).

The 48-h EC_{50} for *D. magna* was estimated as > 29 mg/l, the highest achievable mean measured exposure concentration under flow-through conditions. The NOEC was determined to be 22 mg/l. At 29 mg/l, all mobile daphnids exhibited lethargic behaviour and were pale in colour. No such effects were observed among daphnids exposed to lower treatment levels (0-22 mg/l) (Putt, 1995b).

The effect of *i*-BMA on the freshwater green algae *S. capricornutum* was studied in a closed test system to minimise volatilisation of the test compound. Based on measured concentrations the 96-h EC_{50} value for cell density was calculated to be 0.29 mg *i*-BMA/l, with a NOEC of 0.047/l (Hoberg, 1995). The 96-h EC_{50} value for growth rate was estimated to be > 0.74 mg *i*-BMA/l, with a NOEC of 0.047 mg/l. Supplemental exposure at test termination showed that *i*-BMA at a concentration of 0.74 mg/l has an algistatic (reversible) rather than an algicidal (non-reversible) effect on the growth of *S. capricoruntum* once diluted to a non-inhibitory concentration (0.031 mg/l) (Hoberg, 1995).

6.3 SUMMARY AND EVALUATION

n-BMA/*i*-BMA is of moderate toxicity (EC_{50}: 10-100 mg/l) to bacteria, fish and *Daphnia*. *i*-BMA had a high toxicity (< 0.1 mg/l) towards green algae when tested in a closed system based on a 96-h NOEC of 0.047 mg/l. However, this effect was reversible and represented an algistatic rather than an algicidal action of *i*-BMA. When tested in a standard open test system the toxicity of *n*-BMA to green algae could not be measured conclusively because of the rapid loss of the material during the exposure time.

The test results of the algae studies indicate that the hazard identified by the growth inhibition observed with *i*-BMA in a closed system should be viewed in the light of the reversibility of the effect and the probable volatilisation under open exposure conditions which represent more closely the normal environmental situation. This is in accordance with the lower toxicity of *n*-BMA observed in an open test system.

7. KINETICS AND METABOLISM

7.1 BODY DISTRIBUTION

Male rats received 6.7 mmol/kgbw of [1-^{14}C-butyl]methacrylate (equivalent to 10 mBK/kgbw) by intraperitoneal (i.p.) injection 2, 12, 24 or 48 hours before they were killed. 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 [Section 7.2.2 below] it is uncertain whether the distributed radioactivity was attributable to intact *n*-BMA, *n*-butanol or its metabolites. The data presented does not substantiate the authors' claim that *n*-BMA/*i*-BMA covalently binds to plasma protein.

7.2 *IN VITRO* METABOLISM

7.2.1 Reaction with Glutathione

Rate constants for the reaction of different acrylates and methacrylates with free 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).

7.2.2 Hydrolysis Catalysed by Liver Enzymes

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*-Butanol 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; McCarthy, 1995). However, half-lives calculated from these kinetic constants are of the same order of magnitude for both, EMA (1.2 seconds) and BMA (1.8 seconds).

7.2.3 Other Studies

In isolated liver microsomes from rats pretreated with phenobarbital, incubation with *n*-BMA in the presence of NADPH decreased the content of cytochrome P_{450}. I.p. injection of *n*-BMA did not affect the level of cytochrome P_{450} in liver microsomes (Kotlovskii *et al*, 1987).

Cytochrome P_{450} binding spectra on *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 monooxygenases (Kotlovskii *et al*, 1985) (abstract only available).

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).

7.2.4 Summary

After i.p. administration of ^{14}C-*n*-BMA to rats, radioactivity was rapidly distributed to all major organs. The highest levels of radioactivity were found in liver and kidney 2-12 hours after administration.

n-BMA is rapidly hydrolysed by liver esterases yielding methacrylic acid and *n*-butanol *in vitro*. There are no reliable data to indicate *in vivo* rates.

n-BMA does not react with GSH *in vitro*.

7.3 EVALUATION

From the physico-chemical data it is anticipated that *n*-BMA/*i*-BMA is rapidly absorbed after oral and inhalation exposure. Rapid hydrolysis is predicted from the *in vitro* data.

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 (Section 9.1 and Appendix A). The CEFIC Methacrylates Sector Group has commissioned studies to obtain quantitative data on kinetics and metabolism *in vivo*.

Conjugation with GSH does not appear to play an important role for *n*-BMA/*i*-BMA biotransformation as evidenced in *in vitro* experiments.

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

8.1 ACUTE TOXICITY

8.1.1 Oral

LD_{50} values following oral administration of *n*-BMA/*i*-BMA to mice, rats and rabbits are detailed in Table 9 and 10.

Table 9: Acute Oral Toxicity *n*-BMA

Species	LD_{50} (mg/kgbw)	References
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 10: 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, incoordination, hypotonia, diarrhoea and cyanosis.

8.1.2 Dermal

LD_{50} values following dermal administration of *n*-BMA to rabbits are detailed in Table 11.

Table 11: Acute Dermal toxicity of *n*-BMA

Species	LD_{50} (mg/kgbw)	References
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.

8.1.3 Inhalation

LC_{50} values following administration of *n*-BMA/*i*-BMA vapour by inhalation are detailed in Table 12-14.

Table 12: Acute Inhalation Toxicity of *n*-BMA/*i*-BMA[a]

Species	Duration (h)	LC_{50} (ppm)	References
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 13: Acute Inhalation Toxicity of *n*-BMA

Species	Duration (h)	LC_{50} (ppm)	References
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 14: Acute Inhalation Toxicity of *i*-BMA

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

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

Inhalation of 17,9 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).

8.1.4 Intraperitoneal

LD_{50} values following administration of *n*-BMA/*i*-BMA via the i.p. route are detailed in Table 15 and 16.

Table 15: Intraperitoneal Toxicity of *n*-BMA

Species	LD_{50} (mg/kgbw)	References
Rat	2,400	Paulet and Vidal, 1975
Rat	2,073[a]	Lawrence *et al*, 1972
Rat	5,136[b]	Lawrence *et al*, 1972
Mouse	1,000	Benson and Stackhouse, 1986
Mouse	1,490[c]	Lawrence *et al*, 1972

a Reported as 2.3 ml/kg
b Reported as 5.7 ml/kg
c Reported as 1.66 ml/kg

Table 16: Intraperitoneal Toxicity of *i*-BMA

Species	LD_{50} (mg/kgbw)	References
Rat	981-1,568	Singh *et al*, 1972a,b
Mouse	1,194[a]	Lawrence *et al*, 1972

a Reported as 1.34 ml/kg

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

8.1.5 Other routes

Subcutaneous

Following subcutaneous (s.c.) injection of mice with *n*-BMA, the LD_{50} was 2,600 mg/kgbw (Kustova *et al*, 1979). No toxic effects are reported in the abstract.

Intravenous

An approximate lethal dose (lowest dose at which mortality was observed) in Swiss Webster mice was reported to be 100 mg butyl methacrylate/kgbw (isomer not indicated). No data on the toxic effects were given in the publication (Benson and Stackhouse, 1986).

8.1.6 Summary

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

8.2 SKIN, RESPIRATORY TRACT AND EYE IRRITATION, SENSITISATION

8.2.1 Skin Irritation

n-BMA

In two earlier studies with rabbits, local irritative reactions were reported following uncovered application of the undiluted liquid (Deichmann, 1941; Smyth *et al*, 1969). Strong irritation with extremely strong erythema, blistering oedema and some degree of burn was observed in a study on rabbits (Powell *et al*, 1970). According to the FDA Draize test 0.5 ml *n*-BMA was applied undiluted, under an occlusive patch for 24 hours, to the intact and abraded skin of 6 New-Zealand albino rabbits. The cutaneous reactions were observed 24 hours and 72 hours after the application. Slight irritation, score 1.92/8, was observed in one study (Röhm, 1977b), while in a second study well-defined to moderate erythema, and barely-perceptible to moderate oedema of the skin were exhibited 24 hours following application. Induration of the skin was also noted in 2 cases. Reactions persisted to 72 hours. The primary irritation score was 3.79/8 (Elf Atochem, 1980a).

When 0.5 ml *n*-BMA was applied to the skin of rabbits under semi-occlusive and occlusive patch for one and 4 hours slight erythema was produced and for 4 hours slight oedema (4/6 animals) 1 hour

after removal of the patch. Oedema regressed between day 1 and 3. Four out of 6 animals had fully recovered by day 7. The flank of 2/6 animals where *n*-BMA was applied under occlusive patch for 4 hours still showed a very slight erythema on day 7. *n*-BMA was considered slightly irritant (primary irritation score 1-1.9/8) (Degussa, 1982).

Adult New Zealand rabbits (3 of either sex) received 0.5 ml *n*-BMA under semi-occlusive or occlusive patch on the shaved skin. After 1 and 4 hours of exposure the patch was removed and the results assessed after 1, 24, 48 and 72 hours and 7 days later. In all cases the primary irritancy did not persist, and *n*-BMA was classified as non-irritant (Potokar *et al*, 1985).

Four adult New Zealand white rabbits received 0.5 ml *n*-BMA under semi-occlusive patch on shaved skin areas for 4 hours. The results were assessed 0.5, 1, 24, 48 and 72 hours and up to 14 days after application. *n*-BMA produced mild to moderate erythema in all rabbits throughout the study. Slight to mild oedema was observed in 3 rabbits. Two rabbits exhibited epidermal scaling and sloughing of the skin from day 6 after application throughout the remainder of the study. These 2 rabbits exhibited superficial necrosis during this interval and 1 exhibited areas of necrosis (Sarver, 1993b).

No effects were observed following 31 daily applications of undiluted *n*-BMA to shaved areas on the neck of rats (ICI, 1949).

Application of *n*-BMA under occluded patch to the depilated abdominal skin of 3 guinea pigs for 24 hours resulted in strong irritation. Repeated application of *n*-BMA to the clipped backs of guinea pigs by a drop-on technique resulted in moderate exacerbation of the irritative response after 10 applications (Eastman Kodak, 1984).

i-BMA

A dose of 0.5 ml of *i*-BMA was applied undiluted, under an occlusive patch for 24 hours, to the intact and abraded skin of 6 New-Zealand albino rabbits. The cutaneous reactions were observed 24 hours and 72 hours after the application. Well-defined erythema and barely perceptible to moderate oedema of the skin were exhibited 24 hours following application. Reactions persisted until 72 hours. The primary irritation score was 4.16/8. *i*-BMA was considered irritant (Elf Atochem, 1980b).

In another study, under the same exposure conditions, the primary irritation score was 1.83/8 and *i*-BMA was considered slightly irritant (Röhm, 1977c).

Six applications of 0.1 ml *i*-BMA were made on alternate days to each of 3 rats. Slight desquamation developed after the second application, erythema after the fourth application, and bleeding and

wrinkling after the fifth. Evidence of new skin formation was seen after the sixth application. *i*-BMA was considered moderately irritating (ICI, 1977a).

8.2.2 Eye Irritation

n-BMA

One drop (approximately 0.016 mg) of undiluted *n*-BMA instilled into the conjunctival sac of rabbits caused immediate signs of mild irritation. After 12 hours there was slight irritation of the conjunctiva, but the appearance of the eye was normal within 24 hours (ICI, 1959).

Instillation of the neat liquid (0.5 ml) into the eyes of rabbits produced a slight irritant reaction (Smyth *et al*, 1969).

Iritis and palpebral irritation with oedema were observed when 0.1 ml of neat *n*-BMA was applied directly into the superior temporal quadrant of the right eye of albino rabbits. The irritation was reported by the authors as being grade 2 on a scale of 0-3 (Powell *et al*, 1970).

When 0.1 ml undiluted *n*-BMA was applied into the conjunctival sac of one eye of six New-Zealand white rabbits, the ocular reactions were observed at 24, 48 and 72 hours after the instillation. Slight to well defined redness of the conjunctivae was observed in four out of six animals (Elf Atochem, 1980a).

In a study with rabbits, a very slight irritation was observed on the conjunctiva of 2 out of 3 animals at 24 hours after instillation. The reaction disappeared on day 2 (Röhm, 1988e).

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 (Deichmann, 1941).

In a 4-week vapour inhalation study in rats, clinical symptoms 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

When 0.1 ml of undiluted *i*-BMA was placed into the conjunctival sac of one eye of six New-Zealand white rabbits, the ocular reactions were observed at 24, 48 and 72 hours after the instillation. Slight enanthema and chemosis were observed in some animals (Elf Atochem, 1980b).

In other studies, under the conditions of exposure detailed above, *i*-BMA was considered as not irritating in one study (Röhm, 1988f) and slightly irritating in another (ICI, 1977a).

One drop (0.016 mg) of undiluted *i*-BMA was instilled into the conjunctival sac of the eye of 3 rabbits. There was slight initial pain. A transient redness of the conjunctiva was seen within the first few hours. No eye effects were seen on days 1, 2, 3, 4 and 7 after instillation. *i*-BMA was considered slightly irritating (ICI, 1977a).

8.2.3 Respiratory Tract Irritation

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.

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, 3,079, 4,044, 4,500, 48,839 and 6,091 ppm) *n*-BMA for 4 hours (Kelly, 1993) produced clinical symptoms 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 1891 ppm *n*-BMA, clinical symptoms consistent with irritancy to the respiratory tract such as laboured breathing were seen during the first day of exposure to 1,891 ppm *n*-BMA (Hagan *et al*, 1993; Section 8.3). The NOEL was 310 ppm.

Although the above studies were conducted with *n*-BMA, it is expected that *i*-BMA will 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 with a concomitant reflex change in respiratory rate, and which can be used to extrapolate 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 this test is inappropriate for prediction of the respiratory tract irritancy of *n*-BMA/*i*-BMA in man.

8.2.4 Sensitisation

n-BMA

Guinea Pig Maximisation Test

n-BMa was not sensitising in a number of Guinea Pig Maximisation (GPM) tests (Table 17).

Freund's Complete Adjuvant Test

No 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 17).

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).

The above studies by Chung and Giles (1977) are complex and difficult to evaluate.

Table 17: Guinea Pig Sensitisation Tests

Test method	Induction	Challenge	Result[d]	Reference
n-BMA				
Maximisation	d 1: 2 % in liquid paraffin and FCA 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

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)

i-BMA

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

8.2.5 Evaluation

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

n-BMA/*i*-BMA is not sensitising according to the results of standard Guinea Pig Maximisation tests, while *n*-BMA produced weak sensitisation after an additional challenge at day 35 (2 of 10 animals showed a positive reaction).

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. 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.

8.3 REPEATED DOSE TOXICITY

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.

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, lacrimation, 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.

8.3.1 Summary

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

The lead 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 nose, the NOEL being 310 ppm with no evidence for systemic toxicity. In 2 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.

8.4 GENETIC TOXICOLOGY

8.4.1 *In Vitro* Bacterial Gene Mutation Assays

n-BMA/*i*-BMA has been tested in a number of gene mutation assays in *Salmonella typhimurium* 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 *S. 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 ^{3} 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, BMA was found to be negative both with and without metabolic activation (Aroclor-induced rat liver S9). The investigators concluded that 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.

8.4.2 *In Vivo* Chromosome Damage Assays

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).

8.4.3 Summary and Evaluation

Neither *n*-BMA nor *i*-BMA were mutagenic in a number of gene mutation assays with *S. typhimurium*. *i*-BMA was not clastogenic in a mouse micronucleus assay. Despite the limited database, taking into account the close structural similarity of the 2 isomers, there is no immediate concern for genotoxicity.

8.5 CHRONIC TOXICITY AND CARCINOGENICITY

No data are available for carcinogenicity and no reliable data are available for chronic toxicity.

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.

8.5.1 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 nose. This endpoint has also been observed in inhalation studies conducted with methyl methacrylate and other volatile esters and confirmed in chronic inhalation studies as the lead effect by this route of exposure. It is anticipated that *i*-BMA will have a similar toxicity.

Further information for use in risk assessment may be gained by direct analogy to methyl methacrylate, for which there is sufficient relevant data, see Chapter 9.

8.6 REPRODUCTIVE TOXICITY

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).

8.6.1 Evaluation

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. In addition, the control group treated with normal saline and cotton-seed oils also showed gross and skeletal abnormalities. 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 (OECD, 1987a,b,c).

An initial hazard assessment for reproductive toxicity can be performed using the data obtained for methyl methacrylate and *n*-butanol and isobutanol, see Chapter 9.

9. OTHER CONSIDERATIONS AND SUPPORTIVE DATA FOR TOXICOLOGICAL HAZARD ASSESSMENT OF BUTYL METHACRYLATE

It is acknowledged that there is a paucity of data on the chronic and reproductive toxicity of *n*-BMA/ *i*-BMA and their *in vivo* metabolism. However, from our knowledge on the group of structurally-related methacrylic acid esters it is possible to base an initial hazard assessment on the following hypothesis. It can be expected from the data on methyl methacrylate and the complementary information from *in vitro* metabolism studies with *n*-BMA that a major route of metabolism will be hydrolysis of the esters followed by metabolism of the cleavage products, methacrylic acid and *n*-butanol or isobutanol respectively. This assumption is also supported by data on acrylic acid esters (methyl acrylate, ethyl acrylate, butyl acrylate), indicating that hydrolysis constitutes a major route of their metabolism in experimental animals. (Silver and Murphy, 1981, Sanders *et. al.*, 1988, Delbressine *et. al.*, 1981). Due to the high levels of non-specific esterases in blood, liver and other tissues it can be expected that effects after chronic administration or on reproduction may in part be mediated by the cleavage products. Furthermore, data on methyl methacrylate may be relevant for the assessment of potential hazards from *n*-BMA/*i*-BMA as it is expected to be subject to a comparable metabolic pathway. This is supported by the fact that both MMA and n-BMA produce irritation at the site of contact after repreated inhalation exposure which is thought to be due to hydrolysis of the ester by local tissue esterases and formation of MAA. Therefore we include a brief summary of the available data on methyl methacrylate and the products of hydrolysis of *n*-BMA/*i*-BMA with regard to the endpoints of concern.

9.1 METABOLISM

9.1.1 Hydrolysis

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 recently demonstrated in the upper airways when methyl methacrylate was administered to rats by the inhalation route (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 V_{max} could be lower than that for methyl methacrylate due to the increased chain length of the alcohol (McCarthy and Witz, 1991, see also Chapter 7.2.2). However, the kinetic constants of enzymatic hydrolysis by liver esterases of

different acrylic and methacrylic acid esters indicate that their half lives are in the same order of magnitude (between 0.5 and 3 seconds) (Miller *et al*, 1981; Frederick and Chang-Mateu, 1990; McCarthy and Witz, 1995).

9.1.2 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 CO_2.

Studies conducted with *n*-butanol indicated that it was a substrate of the alcohol-dehydrogenase (Rietbrock and Abshagen, 1971; Saito, 1975). The main metabolic pathway following oral administration of radiolabeled *n*-butanol to rats is rapid oxidation ultimately yielding carbon dioxide. A minor part is excreted in urine as glucuronide or sulfate (Di Vincenco and Hamilton, 1979). After repeated ingestion of *n*-butanol saturated drinking water in rabbits small amounts of the following urinary metabolites were identified; acetaldehyde, acetic acid, *n*-butyraldehyde and unchanged *n*-butanol (Saito, 1975).

In rabbits receiving oral doses of 2 ml isobutanol/kgbw blood levels of isobutanol reached about 0.8 mg/ml after 30 minutes. Almost complete elimination from blood was observed 5 hours after administration (Saito, 1975).

Evaluation

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 (Appendix A). This is in close analogy to the data available on methyl methacrylate. The CEFIC Methacrylates Sector Group has commissioned studies to obtain quantitative data on kinetics and metabolism *in vivo.*

9.2 CHRONIC TOXICITY STUDIES

The longest duration repeat exposure inhalation study on *n*-BMA is the 28-day inhalation study in the rat (Hagan *et al*, 1993).

Methyl Methacrylate

Extensive data on methyl methacrylate suggests that its toxicology profile provides little cause for concern. Perhaps the key studies worthy of consideration are a chronic drinking water study and two chronic inhalation studies.

Two-year administration of methyl methacrylate to male and female wistar rats via 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 of relative kidney weights in the females (Borzelleca *et al*, 1964), which is considered to be a functional adaptation to the significantly reduced water intake (ECETOC, 1995).

In a chronic inhalation study, F344/N rats and $B6C3F_1$ mice (male and female in both cases) were exposed to methyl methacrylate concentrations between 250 and 1,000 ppm during 102 weeks. The toxicity effects focused on 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 chronic 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 (Rohm and Haas, 1979; Lomax *et al*, 1994). For a further discussion of the chronic toxicity of methyl methacrylate, see ECETOC (1995).

Hydrolysis Products

While repeated-exposure studies exist for methacrylic acid and isobutanol, and could be used for extrapolation to the toxicity of *i*-BMA, caution must be taken in such extrapolation due 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 to be not 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.

Evaluation

The lead health effect seen in the chronic inhalation studies with methyl methacrylate was nasal passage lesions. Since these were also the lead health effect in the 28-day inhalation study on *n*-BMA, this indicates strongly that this study is a valid indicator for chronic toxicity. This is expected, since evidence is accruing to demonstrate that nasal passage lesions resulting from exposure to acrylate and methacrylate esters arise rapidly as a result of enzymatic hydrolysis in the target tissue. Beyond 28 days exposure further adaptation of the tissue occurs, a phenomenon observed following exposure to many other chemicals as well as these esters where nasal lesions are induced. A possible carcinogenic effect of isobutanol can at present not be completely excluded. Therefore once reliable data on metabolism of the esters and the carcinogenicity of the alcohols are available the hazard assessment will have to be reconsidered.

9.3 REPRODUCTIVE TOXICITY

9.3.1 Developmental Toxicity

While the studies by Singh *et al* (1972a,b) indicate that *n*-BMA/*i*-BMA may have adverse effects on the developing embryo or foetus after i.p. administration of high dose levels of the undiluted substances to the rat, the route of administration is questionable for this study type and adequate detail is lacking in the publication (Section 8.6.1).

Data are available on the developmental toxicity of methyl methacrylate and butanol.

Methyl Methacrylate

A series of studies conducted with the closely-related structural analogue methyl methacrylate have shown no teratogenic effects following inhalation exposure of rats and mice (ECETOC, 1995). 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, embryo- or foetotoxicity was observed in 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 8.6 for *n*-BMA/*i*-BMA and again reported positive findings. The study findings of Solomon *et al* provided data more appropriate for hazard assessment.

Hydrolysis Products

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).

Evaluation

Taken together, the data available for methyl methacrylate and butanol do not suggest a concern for possible developmental effects on *n*-BMA/*i*-BMA arising from inhalation exposure to non-maternally toxic concentrations.

9.3.2 Fertility and Effects on Reproductive Organs

In the 28-day inhalation study there was no evidence for an effect of *n*-BMA on male or female reproductive organs. Some limited information on relative hazard is available on methyl methacrylate, methacrylic acid and *n*-butanol.

No effects on reproductive organs were observed in 2 year inhalation studies in rats and mice with methyl methacrylate (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 male fertility was not affected (Nelson *et al*, 1989a,b).

Evaluation

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.

9.3.3 Conclusion

Based on the available data on methyl methacrylate and *n*-BMA/*i*-BMA hydrolysis products, and the assumption that ester hydrolysis is the key to toxicity of *n*-BMA/*i*-BMA, there is no need for immediate concern with regard to possible chronic toxicity, carcinogenicity or reproductive effects of *n*-BMA/*i*-BMA. Therefore an initial hazard assessment for these endpoints can be performed using this data base (Section 10.3).

10. EFFECTS ON HUMANS

10.1 ACUTE AND SUBCHRONIC TOXICITY

No data are available.

10.2 IRRITATION AND SENSITISATION

10.2.1 Skin Irritation and Sensitisation

One case of a positive patch test reaction to *n*-BMA (1 %, solvent not stated) 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 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 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 reported that the sensitising agent in these preparation was ethyl methacrylate and the patients 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.

One of 347 patients tested in German dermatological clinics between 1992 and 1995 for possible contact allergy to *n*-BMA (2% in petrolatum) showed a positive reaction. The authors concluded that *n*-BMA does not play a role in human contact allergy. *i*-BMA was not evaluated (Schnuch, 1996).

10.2.2 Evaluation

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

10.3 HAZARD ASSESSMENT

For the endpoints mutagenicity, carcinogenicity and toxicity to reproduction only limited data are available on *n*-BMA/*i*-BMA itself. 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. Studies with methyl methacrylate considering these endpoints suggest that *n*-BMA/*i*-BMA is unlikely to have a mutagenic or carcinogenic potential *in vivo* and is not expected to cause significant adverse effects to the reproductive organs or to the developing embryo or foetus by relevant exposure routes. The main population likely to be exposed to butyl methacrylate are workers involved in production and in industrial manufacture of polymers used in products such as coatings, oil additives and adhesives. Consumer exposure and indirect exposure to the monomer via the environment are considered negligible.

The lead effect of *n*-BMA/*i*-BMA identified in acute and subchronic animal studies is the local irritation at the site of contact by the inhalation route, the major route of occupational exposure. From the available studies it can be concluded that upper respiratory tract irritation is the most common effect from inhalation exposure to *n*-BMA/*i*-BMA. It is generally accepted that the rat is more sensitive to nasal irritants than man due to physiological and anatomical differences. 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). Therefore, as a model for inhalation hazard of irritant chemicals, this more sensitive species provides an additional safety factor when evaluating the risk to man. It is concluded that the NOEL of 310 ppm observed in a 4-week rat inhalation study can be used as the basis for a risk evaluation in man.

11. FIRST AID AND SAFE HANDLING ADVICE

11.1 FIRST AID AND MEDICAL TREATMENT

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

11.1.1 Skin and Eye Injuries

Clothing contaminated with *n*-BMA/*i*-BMA should be removed and either discarded or laundered before re-use. Affected areas of skin should be washed with copious quantities of water. The skin should be rinsed for at least 10 minutes. If the eyes are splashed, they should be irrigated immediately with eye-wash solution or clean water, holding the eyelids apart for at least 10 minutes. A physician should be consulted.

11.1.2 Inhalation

The patient should be taken into fresh air, kept warm and at rest if difficulty in breathing is experienced. If the patient stops breathing, artificial respiration should be administered until qualified medical personnel is able to take over. Medical aid should be summoned immediately.

11.1.3 Ingestion

If *n*-BMA/*i*-BMA has been swallowed, do not induce vomiting. Never give anything by mouth to an unconscious person. A physician should be consulted immediately.

11.2 SAFE HANDLING

11.2.1 Safety at Work

The main risk of injury stems from *n*-BMA/*i*-BMA's irritating action on the skin and mucous membranes. Contact with the skin and eyes should therefore be avoided as should inhalation of high concentrations of *n*-BMA/*i*-BMA vapour. *n*-BMA/*i*-BMA should be used only in well ventilated areas. *n*-BMA/*i*-BMA vapour is denser than air; and will accumulate in pits and confined spaces.

Suitable respiratory equipment must be worn on occasions when exposure to *n*-BMA/*i*-BMA vapour above the recommended exposure limit is likely.

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.

11.2.2 Storage Safety

n-BMA/*i*-BMA is stable in the presence of a polymerisation inhibitor. *n*-BMA/*i*-BMA is susceptible to polymerisation initiated by prolonged heating or a catalyst. Therefore, the following precautions must always be observed when storing *n*-BMA/*i*-BMA.

- *n*-BMA/*i*-BMA must be stored under air as the stabiliser (hydroquinone monomethylether) is only effective in the presence of oxygen
- *n*-BMA/*i*-BMA should not be stored under an inert gas.
- Storage should be below 30 °C and out of direct sunlight. During long-term storage, stabiliser levels should be checked routinely.
- *n*-BMA/*i*-BMA should be stored and shipped in bulk containers with a pressure relief valve to prevent the container from rupturing in the event of polymerisation.
- Care should be taken to prevent contamination, as contaminants can render the stabiliser ineffective or promote polymerisation.

11.2.3 Fire Safety and Extinguishants

n-BMA/*i*-BMA is classified as a flammable liquid. It can form an explosive mixture in air; adequate ventilation should be provided and smoking prohibited. Precautions should be maintained to eliminate all sources of ignition. *n*-BMA/*i*-BMA may polymerise on heating. Sealed containers may rupture if hot. Heat, UV-light, peroxide, azo-compounds, alkalis and oxidising agents may cause rapid polymerisation resulting in explosion.

Fires can be extinguished with water, alcohol-resistant foam, dry powder or CO_2. If fire does break out, neighbouring tanks and pipelines must be kept cool with plenty of water, otherwise the heat generated by the fire will cause their contents to polymerise.

11.2.4 Protection against Fire and Explosion

To avoid ignition, the following precautions are recommended.

- All plant and equipment should be explosion-proof as laid down in national standards
- All containers must be earthed
- All sources of ignition must be excluded

- No smoking is allowed
- No welding should be done until all tanks and pipelines have been drained and thoroughly flushed with water or hot caustic soda.

11.3 MANAGEMENT OF SPILLAGE AND WASTE

In all cases of spillage all sources of ignition must be excluded. Smoking and sparks must be avoided. Small spills of a few litres can be soaked up with suitable absorbent materials such as sand or earth. *n*-BMA/*i*-BMA should not be absorbed onto sawdust or other combustible materials. Larger spills must be prevented from spreading by the use of earth or sand and the material should be pumped into containers for recycle or disposal.

Surfaces contaminated with *n*-BMA/*i*-BMA should be washed well, first with alcohol and then with soap and water. All wastes should be sealed in vapour-tight plastic bags for eventual disposal.

Waste quantities of *n*-BMA/*i*-BMA can be incinerated in accordance with local, state or national regulations. Empty storage drums must be decontaminated before recycling.

When aqueous waste containing *n*-BMA/*i*-BMA is discharged to adapted biological waste-water treatment plants it is expected to be mineralised. No disturbance of the bacterial activity of sewage treatment plants is expected if *n*-BMA/*i*-BMA is properly diluted.

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

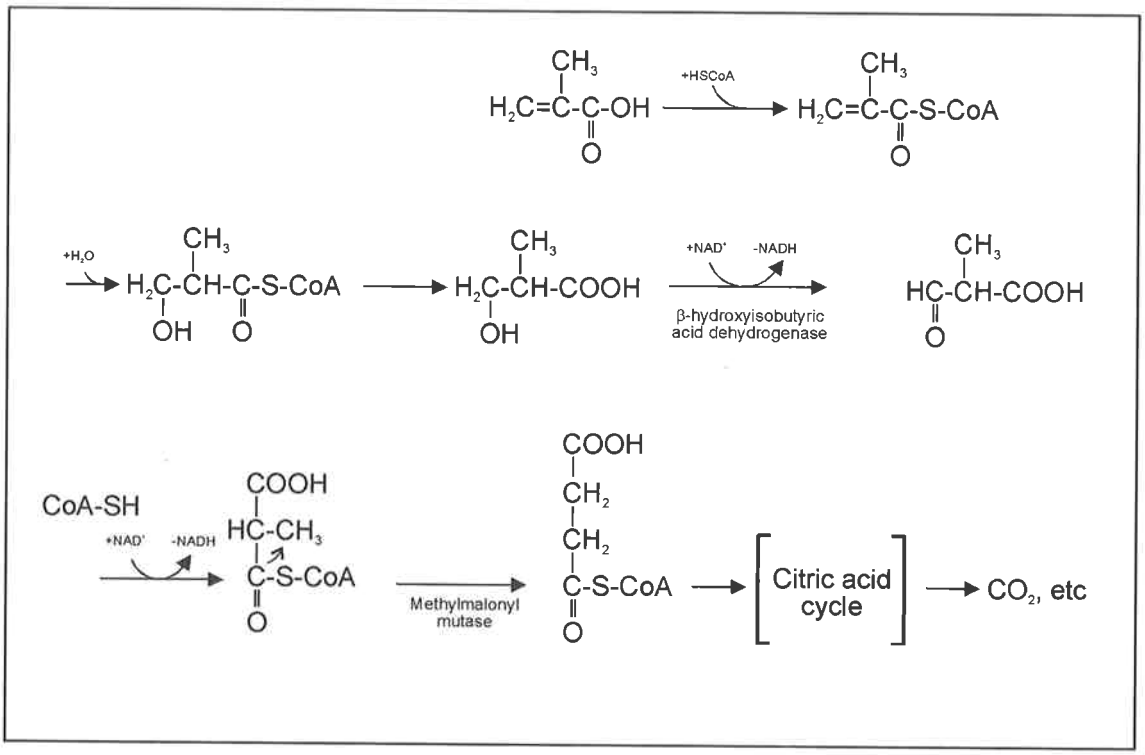
APPENDIX A. METABOLISM OF METHACRYLIC ACID, *n*-BUTANOL AND ISOBUTANOL

A.1 METHACRYLIC ACID

It has been demonstrated from studies with methyl methacrylate that endogenously generated methacrylic acid will be metabolised utilising the pathway present in mammalian cells for the metabolism of valine, the ultimate metabolites being CO_2 and water (Figure A.1); for details, see ECETOC (1996).

Figure A.1: Main Metabolic Pathway of Methacrylic Acid

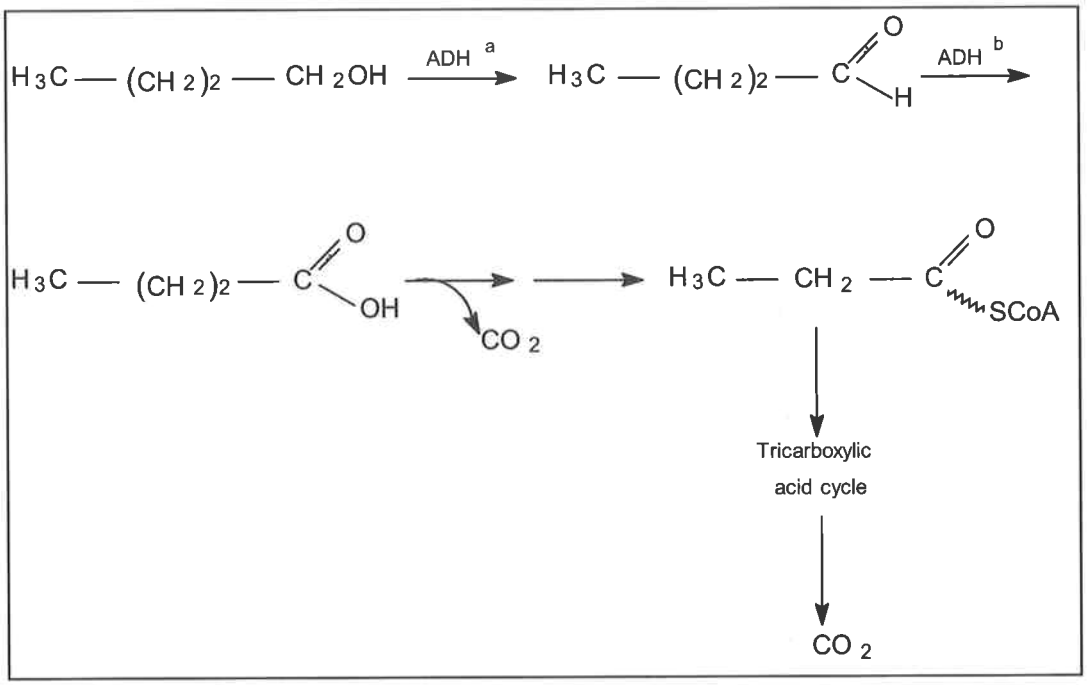
(ECETOC, 1996 after ICI, 1977; Bratt and Hathway, 1977)



A.2 *n*-BUTANOL

In animals, *n*-butanol is absorbed though the lungs and gastrointestinal tract. No information is available regarding dermal absorption. The majority of the dose of *n*-butanol in animals (rats, rabbits and dogs) is converted by alcohol dehydrogenase to the corresponding aldehyde, which is further metabolised via the tricarboxylic acid cycle (Figure A.2). Minor amounts of *n*-butanol are either exhaled unchanged or conjugated with activated glucuronic acid or sulphate and excreted in the urine (IPCS, 1987).

Figure A.2: Metabolism of *n*-Butanol (based on IPCS, 1987)

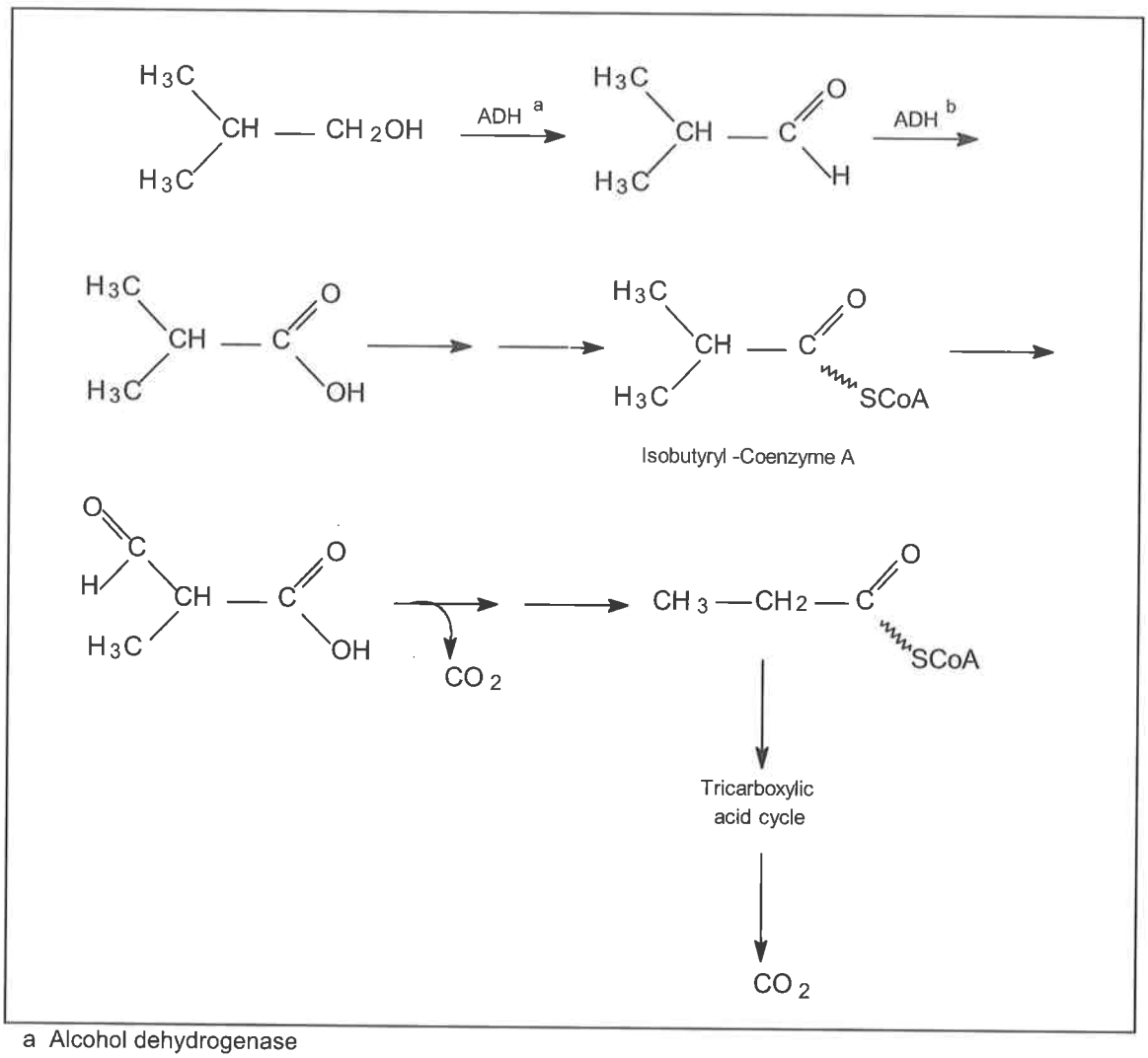


a Alcohol dehydrogenase
b Aldehyde dehydrogenase

A.3 ISOBUTANOL

In rabbits, isobutanol is absorbed through the skin, lungs and gastrointestinal tract. It is metabolised by alcohol dehydrogenase to isobutyric acid via the aldehyde and may enter the tricarboxylic acid cycle, possibly via succinate (Figure A.3) (Saito, 1975; IPCS, 1987).

Figure A.3: Metabolism of Isobutanol (after IPCS, 1987)



a Alcohol dehydrogenase
b Aldehyde dehydrogenase

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