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Final Report of the Safety Assessment of Methacrylate Ester Monomers Used in Nail Enhancement Products[1]

Methacrylate ester monomers are used in as artificial nail builders in nail enhancement products They undergo rapid polymerization to form a hard material on the nail that is then shaped While Ethyl Methacrylate is the primary monomer used in nail enhancement products, other methacrylate esters are also used This safety assessment addresses 22 other methacrylate esters reported by industry to be present in small percentages as artificial nail builders in cosmetic products They function to speed up polymerization and/or form cross-links Only Tetrahydrofurfuryl Methacrylate was reported to the FDA to be in current use The polymerization rates of these methacrylate esters are within the same range as Ethyl Methacrylate While data are not available on all of these methacrylate esters, the available data demonstrated little acute oral, dermal, or i p toxicity In a 28-day inhalation study on rats, Butyl Methacrylate caused upper airway irritation; the NOAEL was 1801 mg/m^3 In a 28-day oral toxicity study on rats, t-Butyl Methacrylate had a NOAEL of 20 mg/kg/day Beagle dogs dosed with 0 2 to 2 0 g/kg/day of C12 to C18 methacrylate monomers for 13 weeks exhibited effects only in the highest dose group: weight loss, emesis, diarrhea, mucoid feces, or salivation were observed Butyl Methacrylate (0 1 M) and Isobutyl Methacrylate (0 1 M) are mildly irritating to the rabbit eye HEMA is corrosive when instilled in the rabbit eye, while PEG-4 Dimethacrylate and Trimethylolpropane Trimethacrylate are minimally irritating to the eye Dermal irritation caused by methacrylates is documented in guinea pigs and rabbits In guinea pigs, HEMA , Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, and Trimethylolpropane Trimethacrylate are strong sensitizers; Butyl Methacrylate, Cyclohexyl Methacrylate, Hexyl Methacrylate, and Urethane Methacrylate are moderate sensitizers; Hydroxypropyl Methacrylate is a weak sensitizer; and PEG-4 Dimethacrylate and Triethylene Glycol Dimethacrylate are not sensitizers Ethylene Glycol Dimethacrylate was not a sensitizer in one guinea pig study, but was a strong sensitizer in another. There is cross-reactivity between various methacrylate esters in some sensitization tests Inhaled Butyl Methacrylate, HEMA, Hydroxypropyl Methacrylate, and Trimethylolpropane Trimethacrylate can be developmental toxicants at high exposure levels (1000 mg/kg/day) None of the methacrylate ester monomers that were tested were shown to have any endocrine disrupting activity These methacrylate esters are mostly non-mutagenic in bacterial test systems, but weak mutagenic responses were seen in mammalian cell test systems Chronic dermal exposure of mice to PEG-4 Dimethacrylate (25 mg, 2× weekly for 80 weeks) or Trimethylolpropane Trimethacrylate (25 mg, 2× weekly for 80 weeks) did not result in increased incidence of skin or visceral tumors The carcinogenicity of Triethylene Glycol Dimethacrylate (5, 25, or 50%) was assessed in a mouse skin painting study (50 μl for 5 days/week for 78 weeks), but was not carcinogenic at any dose level tested The Expert Panel was concerned about the strong sensitization and cross- or co-reactivity potential of the methacrylate esters reviewed in this report However, data demonstrated the rates of polymerization of these Methacrylates were similar to that of Ethyl Methacrylate and there would be little monomer available exposure to the skin In consideration of the animal toxicity data, the CIR Expert Panel decided that these methacrylate esters should be restricted to the nail and must not be in contact with the skin Accordingly, these methacrylate esters are safe as used in nail enhancement products when skin contact is avoided

INTRODUCTION

The Methacrylate Producers Association (MPA) initially expressed concerns to the Cosmetic Ingredient Review (CIR) Expert Panel in 1998 regarding the safety of methacrylate use in consumer products (Methacrylate Producers Association 1998) The MPA argued that because of the sensitization potential of methacrylate esters, these chemicals were inappropriate for use in consumer products In addition, the MPA raised concerns about the use of Methacrylic Acid in consumer products

To address these issues, the CIR Expert Panel agreed to undertake three new safety assessments on (1) Methacrylic Acid, (2) Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate, and (3) Methyl Methacrylate The safety assessment of Methacrylic Acid was completed in September, 2001 (CIR 2001) The safety assessment of Methyl Methacrylate was terminated in favor of a statement of support for the FDA position against the use of Methyl Methacrylate in nail enhancement products This safety assessment addresses the Butyl Methacrylate group of methacrylate esters

[1]This safety assessment includes Butyl Methacrylate, t-Butyl Methacrylate, Cyclohexyl Methacrylate, Di-HEMA Trimethylhexyl Dicarbamate, Ethoxyethyl Methacrylate, 2-Ethoxy Ethoxy Ethyl Methacrylate, Ethylene Glycol Dimethacrylate, HEMA, HEMA Acetoacetate, Hexyl Methacrylate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate, Isobutyl Methacrylate, Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate, Lauryl Methacrylate, Methoxydiglycol Methacrylate, PEG-4 Dimethacrylate, Pyromellitic Glycidyl Dimethacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, Trimethylolpropane Trimethacrylate, and Urethane Methacrylate

Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel This report was prepared by Alexander Escobar and Torill Ann Yamarik, former CIR staff Address correspondence to F Alan Andersen, Director, CIR, 1101 17th St , NW, Suite 310, Washington, DC 20036, USA

In addition to the original list of Butyl, Isobutyl, and Lauryl Methacrylate, the Nail Manufacturers Council (NMC) submitted a list of other Methacrylates used in nail enhancement products which were added to this report

In this safety assessment, therefore, Butyl Methacrylate, sec-Butyl Methacrylate, t-Butyl Methacrylate, Cyclohexyl Methacrylate, Di-HEMA Trimethylhexyl Dicarbamate, Ethoxyethyl Methacrylate, 2-Ethoxy Ethoxy Ethyl Methacrylate, Ethylene Glycol Dimethacrylate, Hexyl Methacrylate, HEMA, HEMA Acetoacetate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate, Isobutyl Methacrylate, Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate, Lauryl Methacrylate, Methoxydiglycol Methacrylate, Pyromellitic Glycidyl Dimethacrylate, PEG-4 Dimethacylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, Trimethylolpropane Trimethacrylate, and Urethane Methacrylate are being reviewed as artificial nail builders in cosmetic products

Official cosmetic ingredient names have not been established for 2-Ethoxy Ethoxy Ethyl Methacrylate, Ethylene Glycol Dimethacrylate, Hexyl Methacrylate, Pyromellitic Glycidyl Dimethacrylate, Tetrahydrofurfuryl Methacrylate, and Urethane Methacrylate The American Beauty Association (ABA)/NMC is working to add these methacrylates used in nail enhancing products to the *International Cosmetic Ingredient Dictionary and Handbook* (ABA/NMC 2001a)

Butyl Methacrylate, t-Butyl Methacrylate, Cyclohexyl Methacrylate, Di-HEMA Trimethylhexyl Dicarbamate, Ethoxyethyl Methacrylate, HEMA, HEMA Acetoacetate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate, Isobutyl Methacrylate, Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate, Lauryl Methacrylate, Methoxydiglycol Methacrylate, PEG-4 Dimethacrylate, Triethylene Glycol Dimethacrylate, and Trimethylolpropane Methacrylate are listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004)

Ethyl methacrylate represents over 90% of the monomer used in nail enhancement products An amended safety assessment of Ethyl Methacrylate was completed in 1999 (CIR 1999) Use of Ethyl Methacrylate in nail enhancement products became widespread following action by the Food and Drug Administration (FDA) to remove a product from the market containing Methyl Methacrylate FDA obtained an injunction in 1974 to prohibit the manufacture and interstate shipment of a product called "Long Nails" because of consumer complaints of severe adverse reactions to Methyl Methacrylate monomer (Fisher 1990)

In comparison to Ethyl Methacrylate, the methacrylate esters reviewed in this report are secondary monomers used at much lower concentrations to speed up polymerization and act as cross linkers formulation (ABA/NMC 2001a)

Very little information has been identified in the published literature regarding mammalian mutagenicity studies on the methacrylate esters addressed in this safety assessment, therefore, information from the 1999 CIR Final Report on the Safety Assessment of Ethyl Methacrylate is included Similarly, chronic toxicity and carcinogenicity data on methyl methacrylate are incorporated in the report

CHEMISTRY

Definition and Structure

Figure 1 provides information on the structures of these methacrylate monomers Table 1 presents the definition, synonyms, CAS number, etc of each of the ingredients in this safety assessment As noted earlier, a definition from the *International Cosmetic Ingredient Dictionary and Handbook* is not available in all cases

PHYSICAL AND CHEMICAL PROPERTIES

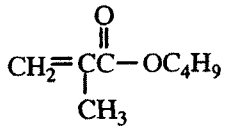
The physical and chemical properties of Butyl, Isobutyl, and Lauryl Methacrylate are shown in Table 2 Although both Butyl Methacrylate and Lauryl Methacrylate were reported as insoluble in water (see Table 1), Assessment Technologies, Inc , (1996) cited their solubility in water as 134–141 mg/L and <0 10–19 0 mg/L, respectively

Curing of Commercial Products

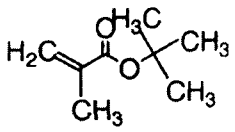
In the CIR Final Report on the Safety Assessment of Ethyl Methacrylate, there were data submitted by Schoon (1994a, 1994b), on the extent of curing and the amount of unreacted monomer in two fingernail formulations containing ethyl methacrylate The study established there was sufficient polymerization of ethyl methacrylate in ethyl methacrylate nail enhancement systems, such that there are insignificant amounts of monomers after 4 hours of curing

A study submitted by Creative Nail Design (2001) analyzed the polymerization of the 22 Methacrylates (see Table 3) in an ethyl methacrylate based system using Differential Scanning Calorimetry (DSC) to measure the reactivity and set time of Methacrylate monomers The reactivity of the methacrylate "test monomers" in the model system was determined using DSC Maximum peak exotherm and total exotherm were measured while the nail enhancement product reacted in the test chamber Maximum peak exotherm occurs at gelation (gel point) of a curing nail enhancement system The gelation point is reached when at least 50% of the monomer has reacted and the material has a hardened surface This process take 2 to 4 minutes in most commercially available professional monomer based nail enhancement systems Changes in gel point time and total exotherm are both directly proportional to the test monomers' reactivity

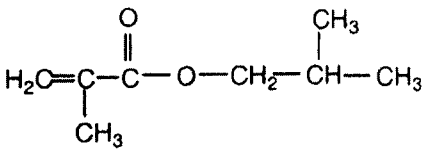
In the experiment, the Radical™ artificial nail monomer/polymer system was modified by adding 5% ethyl methacrylate



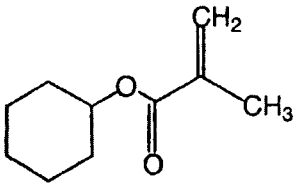
Butyl Methacrylate
Wenninger et al 2002



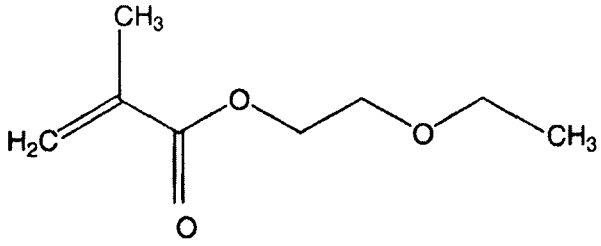
t-Butyl Methacrylate
ChemIDplus 2001



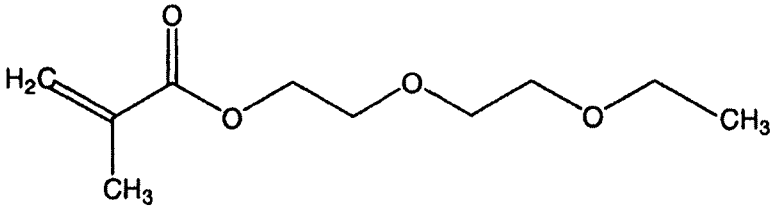
Isobutyl Methacrylate
Zeiger et al 1987



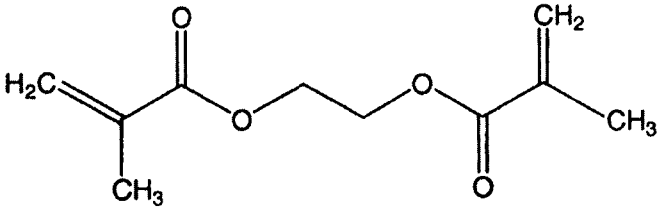
Cyclohexyl Methacrylate
ChemIDplus 2001



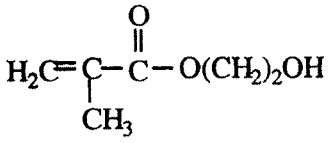
Ethoxyethyl Methacrylate
Jackson 2001



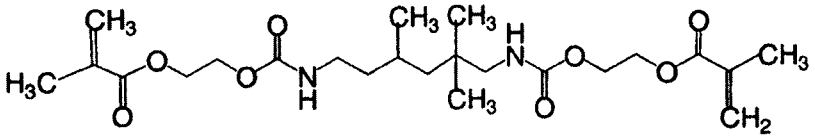
2-Ethoxy Ethoxy Ethyl Methacrylate
Jackson 2001



Ethylene Glycol Dimethacrylate
ChemIDplus 2001

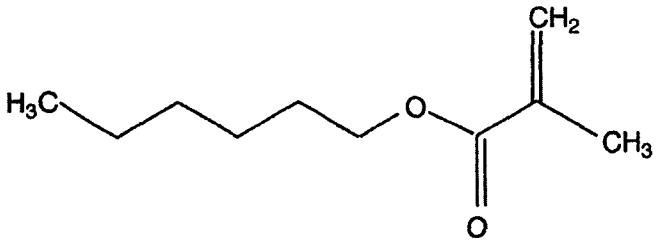


HEMA
Wenninger et al 2002

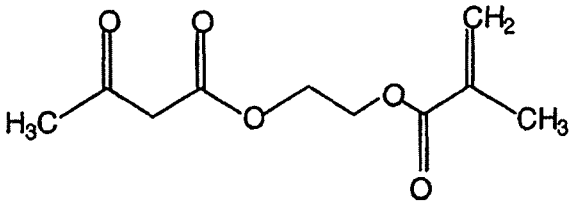


DI-HEMA Trimethylhexyl Dicarbamate- the 2,2,4 Isomer
Jackson 2001

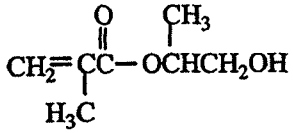
FIGURE 1
Structure of Methacrylate Esters



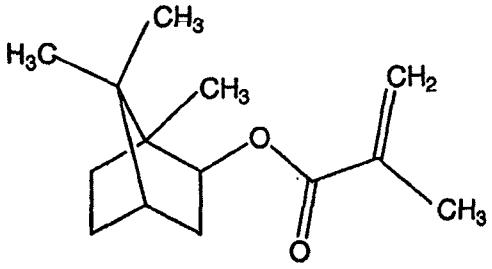
Hexyl Methacrylate
ChemIDplus 2001



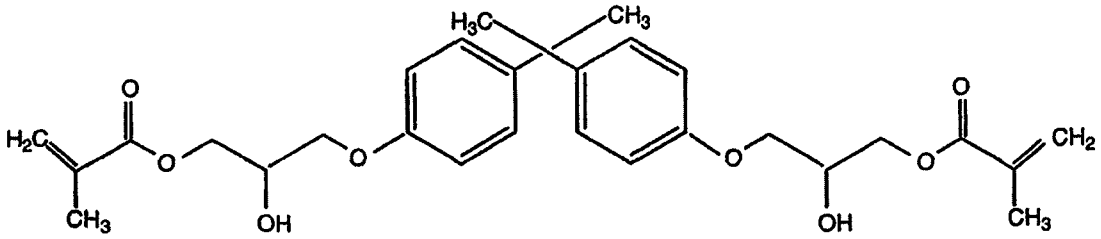
Hydroxyethylmethacrylate Acetoacetate
ChemIDplus 2001



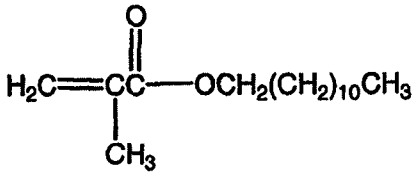
Hydroxypropyl Methacrylate
Wenninger et al 2002



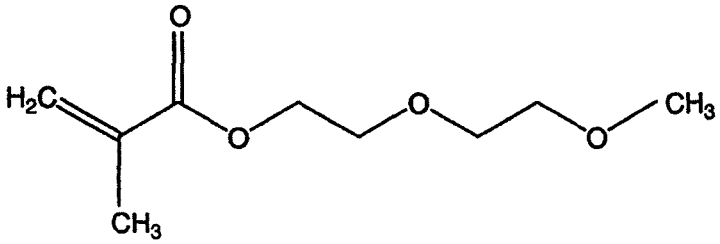
Isobornyl Methacrylate
ChemIDplus 2001



Isopropylidenediphenyl Bisglycidyl Methacrylate
ChemIDplus 2001

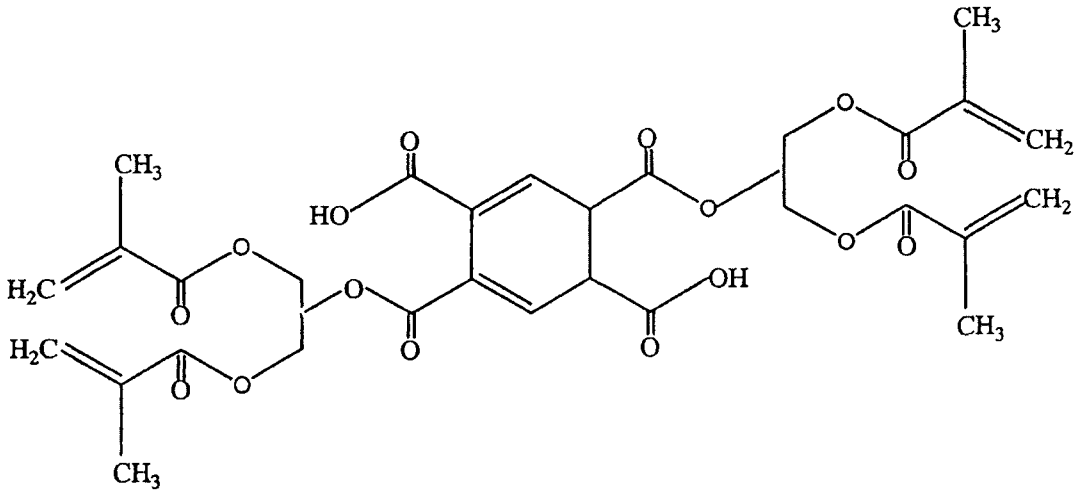


Lauryl Methacrylate
Wenninger et al 2002

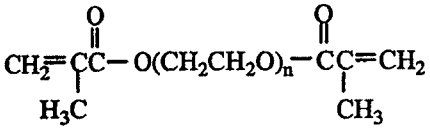


Methoxydiglycol Methacrylate
Jackson 2001

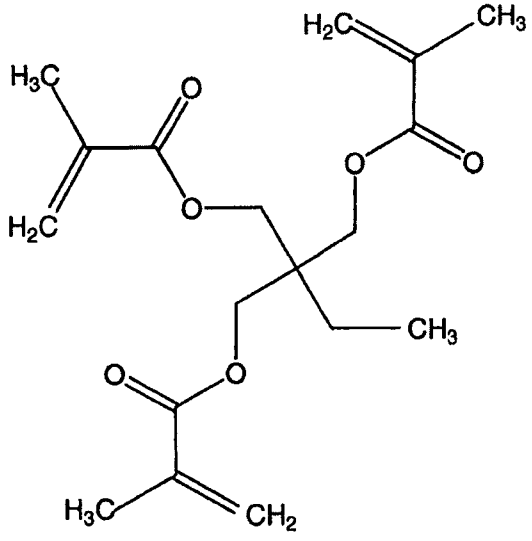
FIGURE 1
(Continued)



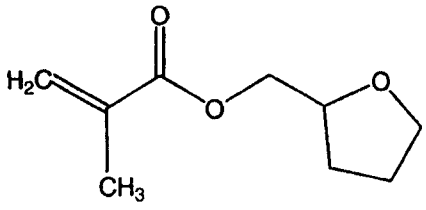
Pyromellitic Glycidyl Dimethacrylate
Jackson 2001



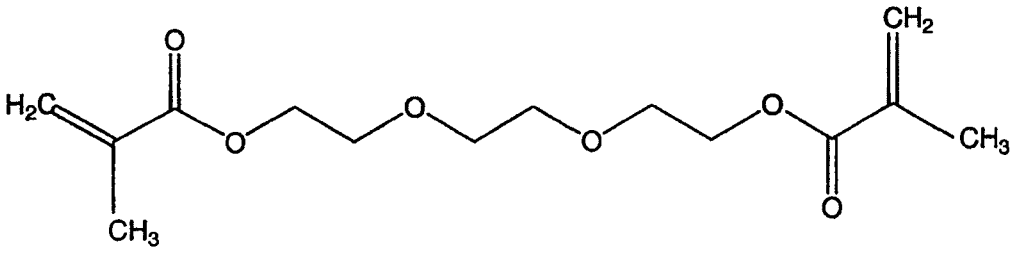
PEG-4 Dimethacrylate
Wenninger et al 2002



Trimethylolpropane Trimethacrylate
ChemIDplus 2001

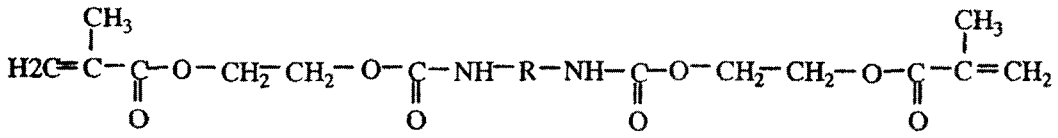


Tetrahydrofurfuryl Methacrylate
ChemIDplus 2001



Triethylene Glycol Dimethacrylate
ChemIDplus 2001

FIGURE 1
(Continued)



Urethane Methacrylate (where $R=C_{10}H_{20}$)
Bjorkner 1984b

FIGURE 1
(Continued)

to establish a normalized baseline to compare reactivity of various test monomers Each of the 22 test monomers were added at a concentration of 5% (by weight) to the Radical™artificial nail monomer/polymer system (see Table 3) The results reported most test monomers at 5% concentrations had faster set times than the 5% ethyl methacrylate standard At 3 84 minutes, 5% Hexyl Methacrylate was the slowest to set, 0 74 minutes slower than the set time for 5% ethyl methacrylate At 285 83 mJ/m^2, t-Butyl Methacrylate had the lowest total exotherm, which was 50 75 mJ/m^2 lower than the total exotherm for 5% ethyl methacrylate

Fifty percent ethyl methacrylate had a set time of 5 93 minutes and total exotherm of 76 26 mJ/m^2 (see Table 4) The results reported all six test monomers at 50% concentrations had faster set times than the 50% ethyl methacrylate standard The 50% HEMA test monomer took 1 82 minutes to set, which was 4 13 minutes faster than the set time for 50% ethyl methacrylate HEMA had the highest total exotherm which was 1130 30 mJ/m^2, which was 1054 04 mJ/m^2 higher than the total exotherm for 5% ethyl methacrylate Fifty percent 2-Ethoxy Ethoxy Ethyl Methacrylate had a set time of 5 39 minutes and a total exotherm of 267 87 which was most similar to 50% ethyl methacrylate Faster set times and increased exotherms are strong indicators of increased reactivity The data on the 22 Methacrylates included in this report have similar levels of reactivity as compared to ethyl methacrylate Therefore, the polymerization rate and the amount of unreacted monomer in ethyl methacrylate are similar to the polymerization rate and the amount of unreacted monomer in the Methacrylates included in this report (Creative Nail Design 2001)

Method of Manufacture

Butyl Methacrylate is derived from the reaction of methacrylic acid or methyl methacrylate with butanol (Lewis 1993, HSDB 2000)

Isobutyl Methacrylate is derived from the esterification of isobutyl alcohol with either methacrylic acid or methyl methacrylate (HSDB 2001)

Methacrylates can also be synthesized by catalytic oxidation of isobutylene and subsequent esterification with the appropriate alcohol, or by reacting acetone with hydrocyanic acid and subsequent esterification in sulfuric acid with the appropriate alcohol (HSDB 2001)

Analytical Methods

Butyl, Hexyl, Isobutyl, and Lauryl Methacrylate were analyzed by gas chromatography with a flame ionization detector (Horna et al 1985)

Henriks-Eckerman and Kanerva (1997) identified the presence of Butyl Methacrylate (0 05%) in an acrylic adhesive using gas chromatography-mass spectrometry (GC-MS)

The presence of Butyl Methacrylate in air can be determined by gas chromatography Electron-impact and methane chemionization mass spectra are used to determine the amount of Butyl Methacrylate present in dental materials (HSDB 2000)

Vapors of Isobutyl Methacrylate can be determined by comparison with the condensation of p-methylaminobenzaldehyde or p-dimethylaminobenzaldehyde Isobutyl Methacrylate can also be determined in air by TLC, polarography (used to determine residual monomer levels in the polymer), and colorimetry TLC, polarography, and spectrometry are used for solution measurements (HSDB 2001)

Isobutyl Methacrylate, HEMA, and Di-HEMA Trimethylhexyl Dicarbamate was analyzed from the liquid monomer of the light-activated reline material by HPLC with an ultraviolet detector (Kawaguchi et al 1996)

Impurities

Certificates of Analysis for other methacrylates used in the artificial nail industry including Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate stated that impurities generally are in the range of less than 0 05% The only known impurities are methacrylic acid and other methacrylates and acrylates (ABA/NMC 2001a)

USE

Cosmetic

Although some of these ingredients are not currently in the *International Cosmetic Ingredient Dictionary and Handbook*, they are all used as artificial nail builders in nail enhancement products

TABLE 1

Definitions and synonyms for methacrylate esters

Ingredient	Cas no.	Definition	Reference	Synonyms	Reference
Butyl Methacrylate	97-88-1, 44914-03-6	The ester of n–butyl alcohol plus methacrylic acid that conforms to the formula in Figure 1	Wenninger et al. 2002	Methacrylic acid, butyl ester; n-butylmethacrylate	Lewis 1993: ChemID 2000; Hazardous Substances Database (HSDB) 2000; Registry of Toxic Effects of Chemical Substances (RTECS), 2000; Wenninger et al. 2002
				Butyl 2-Methacrylate; Butyl 2-Methyl-2-Propenoate; 2-Methyl-Butylacrylate; 2-Propenoic Acid, 2-Methyl-, Butyl Ester	ChemID 2000; HSDB 2000; RTECS 2000; Wenninger et al. 2002
				2-Methacrylic acid, butyl ester	ChemID 2000
t-Butyl Methacrylate	585-07-9	The ester of t–butyl alcohol plus methacrylic acid	ABA and NMC 2001a; ChemIDplus 2001	Tert-Butyl methacrylate; Methacrylic acid, tert-butyl ester; 2-Propenoic Acid, 2-Methyl-,1,1-dimethylethyl ester	ChemIDplus 2001
Cyclohexyl Methacrylate	101-43-9	The ester of cyclohexyl alcohol plus methacrylic acid	ABA and NMC 2001a	Methacrylic Acid, Cyclohexyl ester; 2-Propenoic Acid, 2-Methyl- Cyclohexyl Ester	HSDB 2001; ChemIDplus 2001
Ethoxyethyl Methacrylate	51289-08-8	The ester of ethoxyethyl alcohol plus methacrylic acid	ABA and NMC 2001a	Not listed	ABA and NMC 2001a
2-Ethoxy Ethoxy Ethyl Methacrylate	45127-97-7	The ester of 2-ethoxy ethoxy ethyl alcohol plus methacrylic acid*	ABA and NMC 2001a	2-(2- Ethoxyethoxy) ethyl methacrylate	ChemIDplus 2001
Ethylene Glycol Dimethacrylate	97-90-5	Is the organic compound that conforms to the formula in Figure 1*	ABA and NMC 2001a	1,2-Bis(Methacryloyloxy)Ethane; Diglycol Dimethacrylate; Ethanediol Dimethacrylate; Ethyldiol Methacrylate; Ethylene Glycol Bis(Methacrylate); Ethylene Methacrylate; Glycol Dimethacrylate; Methacrylic Acid, Ethylene Ester; 2-Propenoic Acid, 2-Methyl-, 1,2-Ethanediyl Ester	HSDB 2001, ChemIDplus 2001
Hexyl Methacrylate	101-43-9	The ester of hexyl alcohol plus methacrylic acid*	ABA and NMC 2001a	Hexyl 2-Methyl-2-Propenoate; Methacrylic Acid, Hexyl Ester; 2-Propenoic Acid, 2-Methyl-Hexyl Ester	HSDB 2001, ChemIDplus 2001

(Continued on next page)

TABLE 1
Definitions and Synonyms for Methacrylate Esters *(Continued)*

Ingredient	Cas no.	Definition	Reference	Synonyms	Reference
HEMA	868-77-9	is the organic compound that conforms to the formula: $C_6H_{10}O_3$	Wenninger et al. 2002	2-Hydroxyethyl Methacrylate; 2-Propenoic Acid, 2-Methyl-2-Hydroxyethyl Ester	HSDB 2001, Wenninger et al. 2002; ChemIDplus 2001
				Ethylene Glycol Methacrylate; Ethylene Glycol, Monomethacrylate; Glycol Methacrylate; Glycol Monomethacrylate; Hydroxyethyl Methacrylate; Beta-Hydroxyethyl Methacrylate; Methacrylic Acid, 2-Hydroxyethyl Ester; 2-(Methacryloyloxy)Ethanol	HSDB 2001, ChemIDplus 2001
Di-HEMA Trimethylhexyl Dicarbamate	72869-86-4	Is the organic compound that conforms to the formula: $C_{23}H_{38}N_2O_8$	Wenninger et al. 2002	Urethane Dimethacrylate; UDMA, 2-Propenoic Acid, 2-Methyl-7,7,9 (or 7,9,9)-Trimethyl-4, 13-Dioxo-3,14-Dioxa-5,12-Diazahexadecane-1,16-diyl Ester	Wenninger et al. 2002; ChemIDplus 2001
Hydroxyethylmethacrylate Acetoacetate	21282-97-3	is the organic compound that conforms to the formula in Figure 1*	ABA and NMC 2001a	2-(Acetoacetoxy) Ethyl Methacrylate	ABA and NMC 2001a
				2-((2-Methyl-1-oxoallyl)oxy)ethyl acetoacetate; Butanoic acid, 3-oxo, 2-((2-methyl-1-oxo-2-propenyl)oxy)ethyl ester	ChemIDplus 2001
Hydroxypropyl Methacrylate	27813-02-1	Is the organic compound that conforms to the formula: $C_7H_{12}O_2$	Wenninger et al. 2002	2-Hydroxypropyl Methacrylate;2-Propenoic Acid, 2-Methyl- Monoester with 1,2-Propanediol	HSDB 2001; Wenninger et al. 2002; ChemIDplus 2001
				Propylene Glycol Monomethacrylate	Wenninger et al. 2002; ChemIDplus 2001
				Methacrylic Acid, Monoester with 1,2-Propanediol; 1,2-Propanediol, 2-Methyl-Monomethacrylate; 2-Propenoic Acid, 2-Methyl-2-Hydroxymethylethyl Ester	HSDB 2001

Isobornyl Methacrylate	7534-94-3	the ester of isobornyl alcohol plus methacrylic acid	ABA and NMC 2001a	Methacrylic Acid, Isobornyl Ester; 2-Propenoic Acid, 2-Methyl-,1,7,7-Tirmethylbicyclo(2.2.1)HEPT-2-YL Ester, Exo-	HSDB 2001, ChemIDplus 2001
Isobutyl Methacrylate	97-86-9	the ester of isobutyl alcohol plus methacrylic acid that conforms to the formula in Figure 1	ChemIDplus 2001	2-Methylpropyl Methacrylate	ChemIDplus 2001, HSDB 2001
				Isobutyl Alpha-Methacrylate; Isobutyl 2-Methyl-2-Propenoate; Methacrylic Acid, Isobutyl Ester; Propenoic Acid, 2-Methyl, Isobutyl Ester; 2-Propenoic Acid, 2-Methyl-2-Methylpropyl Ester	ChemIDplus 2001, HSDB 2001
				2-Methylpropyl 2-Methyl-2-Propenoate	ChemIDplus 2001
Isopropylidenediphenyl Bisglycidyl Methacrylate	1565-94-2	the reaction product that of bisphenol A and glycidyl methacrylate that undergoes polymerization when exposed to uv light or mixed with a catalyst	ABA and NMC 2001a; ChemIDplus 2001	Bis-GMA;Bisphenol A-glycidyl methacrylate; 2-Propenoic acid, 2-methyl-(1-methylethylidene)bis(4,1-phenyleneoxy(2-hydroxy-3,1-propanediyl))ester	ChemIDplus 2001
Lauryl Methacrylate	142-90-5; 93804-49-0	the ester of lauryl alcohol plus methacrylic acid that conforms to the formula in Figure 1	Wenninger et al. 2002	Dodecyl Methacrylate; Dodecyl 2-Methyl-2-Propenoate	ChemID 2000; HSDB 2000; RTECS 2000; Wenninger et al. 2002
				Methacrylic Acid, Dodecyl Ester	HSDB 2000; RTECS 2000; Wenninger et al. 2002
				2-Propenoic Acid, 2-Methyl-, Dodecyl Ester	ChemID 2000; HSDB 2000; Wenninger et al. 2002
				2-Methyl-2-Propenoic Acid, Dodecyl Ester	Wenninger et al. 2002
				Methacrylic Acid, Lauryl Ester; Acrylic Acid, 2-Methyl, Dodecyl Ester	ChemID 2000; HSDB 2000; RTECS 2000
				Dodecyl-2-Methylacrylate	ChemID 2000
Methoxydiglycol Methacrylate	45103-58-0	the ester of methoxydiglycol alcohol plus methacrylic acid	ABA and NMC 2001a	2-(2-Methoxyethoxy)ethyl methacrylate; 2-Propenoic acid, 2-methyl- 2-(2-methoxyethoxy) ethyl ester	ChemIDplus 2001

(Continued on next page)

TABLE 1
Definitions and synonyms for methacrylate esters (*Continued*)

Ingredient	Cas no.	Definition	Reference	Synonyms	Reference
PEG-4 Dimethacrylate	109-17-1	Is the organic compound that conforms generally to the formula in Figure 1 where *n* has an average number of 4.	Wenninger et al. 2002	Tetraethylene Glycol Dimethacrylate; 2-Propenoic Acid, 2-Methyl- Oxybis (2,1-Ethanediyloxy-2,1-Ethanediyl) Ester; Polyoxyethylene (4) Dimethacrylate; Polyethylene Glycol (4) Dimethacrylate	Wenninger et al. 2002
Pyromellitic Glycidyl Dimethacrylate	148019-46-9; 146166-65-6	Is the organic compound that conforms to the formula in Figure 1*	ABA and NMC 2001a	Pyromellitic dianhydride glycerol dimethacrylate adduct	ChemIDplus 2001
Tetrahydrofurfuryl Methacrylate	2455-24-5	the ester of tetrahydrofurfuryl alcohol plus methacrylic acid*	ABA and NMC 2001a	Methacrylic Acid, Tetrahydrofurfuryl Ester; 2-Propenoic Acid, 2-Methyl-(Tetrahydro-2-Furanyl)Methyl Ester	HSDB 2001, ChemIDplus 2001
Triethylene Glycol Dimethacrylate	109-16-0	Is the organic compound that conforms to the formula in Figure 1	ABA and NMC 2001a	1,2-Bis(2-(Methacryloyloxy) Ethoxy)Ethane; Ethylenebis(Oxyethylene) Methacrylate; Methacrylic Acid, Diester with Triethylene Glycol; 2-Propenoic Acid, 2-Methyl-1,2-Ethanediylbis(oxy-2,1-Ethanediyl) Ester; TEDMA	HSDB 2001, ChemIDplus 2001
Trimethylolpropane Trimethacrylate	3290-92-4	Is the organic compound that conforms to the formula in Figure 1	ABA and NMC 2001a	Methacrylic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol; 1,1,1-Trimethylolpropane Trimethacrylate; 2-Propenoic Acid, 2-methyl-2-ethyl-2-(((2-methyl-1-oxo-2-propenyl)oxy)methyl)-1,3-propanediyl ester	ChemIDplus 2001
Urethane Methacrylate	65256-52-2	The ester of urethane alcohol plus methacrylic acid*	ABA and NMC 2001a	none	ABA and NMC 2001a

*Unofficial definition; has not yet been established by *International Cosmetic Ingredient Dictionary and Handbook*

TABLE 2
Physical and chemical properties of methacrylate esters

Property	Descripton	Reference
	Butyl Methacrylate	
Molecular weight	142 19	Sax 1979, HSDB 2000, Assessment Technologies, Inc 1996, Sandmeyer and Kirwin 1981
Appearance/odor	Colorless liquid, readily polymerizes, ester odor	Lewis 1993, Sax 1979, HSDB 2000
Boiling point	163 0–170 5°C	Lewis 1993, Sax 1979, Assessment Technologies, Inc 1996
	160°C	HSDB 2000, Sandmeyer and Kirwin 1981
melting point	−75°C	HSDB 2000
density	0 895	Lewis 1993, Sax 1979, HSDB 2000, Assessment Technologies, Inc 1996
Flash point	130°F (54 4°C), 126°F	Lewis 1993, Sax 1979
	106°F, 41 1°C	Sandmeyer and Kirwin 1981
Solubility	Insoluble in water	Lewis 1993, HSDB 2000, Sandmeyer and Kirwin 1981
	Very soluble in alcohol and ether	Sandmeyer and Kirwin 1981
Octanol/water partition coefficient	2 88	HSDB 2000
	3 01	Brixham Environmental Lab 1992, Assessment Technologies, Inc 1996
	1 97	Yoshii 1997
Maximum absorption	214 nm	HSDB 2000
	t-butyl Methacrylate	
Color/form	Colorless liquid	Lewis 1997
Boiling point	66°C	Lewis 1997
Density	0 877	Lewis 1997
Flash point	92°F	Lewis 1997
	Isobutyl Methacrylate	
Molecular weight	142 20, 142 22	Lewis 2000, HSDB 2001
Color/form	Liquid	Lewis 1997, HSDB 2001
Boiling point	155°C	Lewis 1997, HSDB 2001
Melting point	−34°C	Assessment Technologies 1994
Density	0 8858, 0 882 g/ml	Lewis 1997, HSDB 2001
Flash point	49°C	Lewis 1997, HSDB 2001
Solubility	>10% in alcohol or ether	HSDB 2001
Octanol/water partition coefficient	2 66	HSDB 2001
	1 88	Yoshii 1997
	Cyclohexyl Methacrylate	
Molecular weight	168 23	HSDB 2001
Color/form	Colorless liquid	HSDB 2001
Boiling point	210°C	HSDB 2001, Lewis 1997
Density	0 9626	HSDB 2001, Lewis 1997
Solubility	Insoluble in water	HSDB 2001

(Continued on next page)

TABLE 2
Physical and Chemical Properties of Methacrylate Esters (*Continued*)

Property	Description	Reference
	Ethylene Glycol Dimethacrylate	
Molecular weight	198 22	HSDB 2001
	198 1	Lewis 2000
Boiling point	260°C	HSDB 2001
Melting point	−40°C	HSDB 2001
Density	1 055	HSDB 2001
Solubility	>10% in benzene, ethanol, or ligroin	HSDB 2001
Octanol/water partition coefficient	1 598	Rustemeyer et al 1998
	1 99	Yoshii 1997
Molecular weight	198	Geurtsen 2000
	Ethoxyethyl Methacrylate	
Octanol/water partition coefficient	1 73	Yoshii 1997
	HEMA	
Molecular weight	130 14	HSDB 2001
	130	Geurtsen 2000
	130 16	Lewis 2000
Color/form	Clear mobile liquid	HSDB 2001
Boiling point	67°C	HSDB 2001
	71°C–73°C	Lewis 2000
Melting point	−12°C	HSDB 2001
Density	1 034	HSDB 2001
	1 064	Lewis 1997
Flash point	97°C	HSDB 2001
	−12°C	Lewis 1997
Solubility	Miscible with water and soluble in common organic solvents	HSDB 2001
Octanol/water partition coefficient	0 47	HSDB 2001
	0 1144	Rustemeyer et al 1998
	0 85	Yoshii 1997
	Di-HEMA Trimethylhexyl Dicarbamate	
Molecular weight	470	Geurtsen 2000
	Hexyl Methacrylate	
Molecular weight	170 25	HSDB 2001
Appearance/odor	Liquid	HSDB 2001
Boiling point	162°C	HSDB 2001
	67°–85°C	Lewis 1997
Density	0 880	HSDB 2001
	0 88	Lewis 1997
Solubility	>10% in acetone, benzene, ether, or ethanol	HSDB 2001
	Hydroxypropyl Methacrylate	
Molecular weight	144 18	HSDB 2001
	144	Geurtsen 2000
Color/form	Clear mobile liquid	HSDB 2001
Odor	Slightly acrylic odor	HSDB 2001

TABLE 2
Physical and chemical properties of methacrylate esters (*Continued*)

Property	Description	Reference
Boiling point	87°C	HSDB 2001
	96°C	
Melting point	−89°C	HSDB 2001
Density	1 066	HSDB 2001, Lewis 1997
Flash point	250°F	HSDB 2001
	206°F	Lewis 1997
Solubility	Limited solubility in water, soluble in common organic solvents	HSDB 2001
Octanol/water partition coefficient	0 4806	Rustemeyer et al 1998
	0 79	Yoshii 1997
	Isobornyl Methacrylate	
Molecular weight	222 33	HSDB 2001
Boiling point	112°C–117°C	HSDB 2001
Density	0 980	HSDB 2001
	Isopropylidenediphenyl Bisglycidyl Methacrylate	
Molecular weight	512	Björkner 1984a, Geurtsen 2000
	Lauryl Methacrylate	
Molecular weight	254 41	HSDB 2000
	254 8	Assessment Technologies, Inc 1996
Boiling point	272–344°C	Lewis 1993, HSDB 2000
Melting point	−20°C	HSDB 2000
Density	0 868	Lewis 1993, HSDB 2000, Assessment Technologies, Inc 1996
Flash point	270°F (132°C)	Lewis 1993, HSDB 2000
Solubility	Insoluble in water	HSDB 2000
Octanol/water partition coefficient	6 57	Assessment Technologies, Inc 1996
	4 68	Yoshii 1997
	PEG-4 Dimethacrylate	
Molecular weight	330	Björkner 1984c, US EPA 1985
Octanol/water partition coefficient	3 61	Yoshii 1997
	2 06	US EPA 1985
	Tetrahydrofurfuryl Methacrylate	
Molecular weight	170 208	HSDB 2001
Boiling point	59°C–62°C	HSDB 2001
Octanol/water partition coefficient	1 67	Yoshii 1997
	Triethylene Glycol Dimethacrylate	
Molecular weight	286 36	Lewis 2000
	286 33	HSDB 2001
	286	Geurtsen 2000
	286	Björkner 1984c
Boiling point	155°C	HSDB 2001

TABLE 2
Physical and Chemical Properties of Methacrylate Esters (*Continued*)

Property	Description	Reference
Density	1 072	HSDB 2001
Solubility	>10% in acetone, ethanol, ether, or petroleum ether	HSDB 2001
Octanol/water partition coefficient	1 88	HSDB 2001
	3 05	Yoshii 1997
	Trimethylolpropane Trimethacrylate	
Molecular weight	338 44	Lewis 2000
	338	American Industrial Hygiene Association 1981, Geurtsen 2000, US EPA 1985
Color/form	Amber liquid	Lewis 2000
Odor	Musty	American Industrial Hygiene Association 1981
Boiling point	>200°C	Lewis 2000
	>315 5°C	American Industrial Hygiene Association 1981
Melting point	−20 to −10°C	American Industrial Hygiene Association 1981
Density	0 97	Lewis 2000
Flash point	149°F	Lewis 2000
	>93 3°C	American Industrial Hygiene Association 1981
Solubility	Insoluble in water	American Industrial Hygiene Association 1981
Octanol/water partition coefficient	3 11	US EPA 1985
	Urethane Methacrylate	
Molecular weight	470	Björkner 1984b

Data submitted to CIR by the Food and Drug Administration (FDA) based on industry reports in 2001 do not include any uses for 21 of the methacrylate esters included in this report Only Tetrahydrofurfuryl Methacrylate was reported to be used in one nail extender product (FDA 2001) Concentration of use data submitted to the FDA in 1984 did not include any uses of these methacrylate esters (FDA 1984)

The industry stated that ethyl methacrylate represents over 90% of the monomer used in nail enhancing products while Butyl, Isobutyl and Lauryl Methacrylate represent less than 1% of the monomer used in nail enhancing products The maximum concentration of use submitted by industry is shown in Table 5 (ABA/NMC 2001a)

Fisher (1980) and Kanerva et al (1996) both reported use of Butyl Methacrylate, Isobutyl Methacrylate, Ethylene Glycol Dimethacrylate, Tetrahydrofurfuryl Methacrylate, and Trimethylol-propane Trimethacrylate monomers in commercial nail preparations

Kanerva et al (1996) reported that Butyl Methacrylate was present at a concentration of 2 2% in a nail strengthener as analyzed by GC-MS, although it was not listed on the material safety data sheet (MSDS) for this product

Likewise, Triethylene Glycol Dimethacrylate was present in a monomer liquid for sculptured nails at a concentration of 5% as analyzed by GC-MS, but it was not listed on the MSDS for this product (Kanerva et al 1996)

Sainio et al (1997) determined that Butyl Methacrylate was present in six liquid or dried nail polishes at concentrations that ranged from 0 014–0 067%

Butyl Methacrylate and Lauryl Methacrylate were not listed in the Japanese Comprehensive Licensing Standards of Cosmetics by Category Neither Butyl Methacrylate nor Lauryl Methacrylate were listed in the 2000 European Economic Community Cosmetics Directive (European Commission 2000)

Non-Cosmetic

Polymeric hydrogels composed of Butyl Methacrylate are used in drug delivery systems (Katono et al 1991)

Butyl Methacrylate was present in orthopedic bone cement when analyzed by high-performance liquid chromatography (HPLC) (Davy and Braden 1991)

Butyl Methacrylate and Lauryl Methacrylate are polymerizable monomers used in plastics, molding powders, solvent coatings, adhesives, oil additives and emulsions for textile, leather and paper finishing (Lewis 1993, HSDB 2000)

Butyl Methacrylate is listed as an indirect food additive under the following Code of Federal Regulation (CFR) cites 21CFR175 300, 21CFR176 210 and 21CFR177 2420

TABLE 3
Set times and total exotherm data for 22 methacrylates at 5% concentration

Sample number	Test monomers 1–22 (5% concentration)	Set time (min)	Std Dev (%)	Total exotherm (mJ/m^2)	Std Dev (%)
Standard	Radical™ monomer liquid (neat)	2 78	5 0	650 9	8 0
Standard	Ethyl methacrylate (spike)	3 10	4 8	336 58	14 0
1	HEMA	2 85	5 0	672 07	4 4
2	Hydroxypropyl Methacrylate	2 72	6 4	607 16	5 1
3	Methoxydiglycol Methacrylate	2 88	3 3	327 96	3 9
4	Ethoxyethyl Methacrylate	3 63	6 8	367 84	7 6
5	Pyromellitic Glycidyl Dimethacrylate	2 52	4 6	794 23	3 5
6	Isobornyl Methacrylate	3 27	11 7	342 34	9 3
7	Ethylene Glycol Dimethacrylate	2 97	4 8	405 13	10 3
8	Hydroxyethylmethacrylate Acetoacetate	2 86	6	461 5	1 8
9	Urethane Methacrylate	2 78	2 1	396 11	7 5
10	Isopropylidenediphenyl Bisglycidyl Methacrylate	3 03	5 8	302 13	10 9
11	Butyl Methacrylate	3 54	9 7	380 57	6 5
12	Isobutyl Methacrylate	3 53	11 4	362 13	11 1
13	t-butyl Methacrylate	3 82	3 6	285 83	6 9
14	Lauryl Methacrylate	3 6	4 4	308 7	5 8
15	Cyclohexyl Methacrylate	3 2	9 3	313 26	9 3
16	Di-HEMA Trimethylhexyl Dicarbamate	2 76	3 9	416 9	10 5
17	Hexyl Methacrylate	3 84	5 8	298 77	14 6
18	Triethylene Glycol Dimethacrylate	2 74	4 4	413 64	9 8
19	Tetrahydrofurfuryl Methacrylate	3 15	7 1	578 7	2 6
20	PEG-4 Dimethacrylate	3 2	8 0	378 66	9 8
21	Trimethylolpropane Trimethacrylate	2 66	5 3	536 19	3 2
22	2-Ethoxy Ethoxy Ethyl Methacrylate	2 83	4 4	555 10	10 3

TABLE 4
Set times and total exotherm data for 22 methacrylates at 50% concentration

Sample number	Test monomers (50% concentration)	Set time (min)	Std Dev (%)	Total exotherm (mJ/m^2)	Std Dev (%)
Standard	Radical™ monomer liquid (standard)	2 78	5 0	650 9	8 0
Standard	Ethyl methacrylate (standard)	5 93	27 8	76 26	52 9
1	HEMA	1 82	1 0	1130 30	6 3
2	Hydroxypropyl Methacrylate	2 25	3 9	785 00	5 0
3	Methoxydiglycol Methacrylate	5 11	1 3	111 78	1 7
4	Ethoxyethyl Methacrylate	4 35	3 2	136 16	7 2
19	Tetrahydrofurfuryl Methacrylate	3 82	7 6	546 1	10 3
22	2-Ethoxy Ethoxy Ethyl Methacrylate	5 39	4 0	267 87	9 1

TABLE 5
Concentration of use data for methacrylate esters in nail enhancement products submitted by ABA/NMC (2001a)

Methacrylate esters	Maximum use concentration (%)
HEMA	30
Hydroxypropyl Methacrylate	25
Methoxydiglycol Methacrylate	85
Ethoxyethyl Methacrylate	85
Pyromellitic Glycidyl Dimethacrylate	5
Isobornyl Methacrylate	5
Ethylene Glycol Dimethacrylate	5
Hydroxyethylmethacrylate Acetoacetate	10
Urethane Methacrylate	3
Isopropylidenediphenyl Bisglycidyl Methacrylate	5
Butyl Methacrylate	7
Isobutyl Methacrylate	10
t-butyl Methacrylate	7
Lauryl Methacrylate	5
Cyclohexyl Methacrylate	2
Di-HEMA Trimethylhexyl Dicarbamate	3
Hexyl Methacrylate	5
Triethylene Glycol Dimethacrylate	7
Tetrahydrofurfuryl Methacrylate	7
PEG-4 Dimethacrylate	15
Trimethylolpropane Trimethacrylate	5
2-Ethoxy Ethoxy Ethyl Methacrylate	75

(Wenninger et al 2002) Butyl Methacrylate monomer and copolymer are used in dental technology, as components in oil dispersible pesticides and as copolymers in paraffin embedding media The monomer is used in the manufacture of contact lenses and acrylic surface coatings (HSDB 2000)

Isobutyl Methacrylate is used as monomer for acrylic resins in dental applications, in hydrogel contact lenses, and with vinyl monomers in concrete to increase its water repellence (Zuccari et al 1997, HSDB 2001)

A liquid monomer containing 70% Isobutyl Methacrylate, 15% HEMA, and 15% Trimethylolpropane Trimethacrylate by weight, is used in light-activated reline materials to improve the fit of dentures after prolonged usage There is some leaching of unreacted monomer (Kawaguchi et al 1996)

Lauryl Methacrylate is also used as a deodorant to mask methyl sulfide odors in industry, to delay volatilization of insecticides, as a monomer for viscosity index improvers for lubricating oil and for pour-paint depressants for distillate fuels Lauryl Methacrylate is used in dentistry as restorative material, adhesive and prosthetic device (HSDB 2000)

A variety of methacrylates are used in printing and as dental resins (Bong and English 2000)

GENERAL BIOLOGY

Absorption, Distribution, Metabolism and Excretion

The absorption, distribution, and excretion of ^{14}C labeled Triethylene Glycol Dimethacrylate was measured 24 hours after administration to guinea pigs and mice Guinea pigs received 0 02 mmol/kg ^{14}C labeled Triethylene Glycol Dimethacrylate by subcutaneous injection or gastric tube Mice received a 0 1 ml volume of 10 nanomoles ^{14}C labeled Triethylene Glycol Dimethacrylate by gastric tube, subcutaneous injection, and iv injection (Reichl et al 2001a)

After guinea pigs were exposed for 24 hours, approximately 80% of radiolabel was recovered (60% by air, 15% by urine, and 5% in tissues) After 24 hours, virtually all detectable ^{14}C was cleared from mice exposed to Triethylene Glycol Dimethacrylate by gastric and subcutaneous administration However, trace amounts of ^{14}C were present in mice exposed by iv injection of Triethylene Glycol Dimethacrylate The authors assumed if the metabolism and clearance of Triethylene Glycol Dimethacrylate in humans is similar to those of guinea pigs, then it is highly unlikely that Triethylene Glycol Dimethacrylate released from dental restorative materials in humans could have systemic toxic effects

The methacrylates are metabolized via two basic pathways, hydrolysis and conjugation (Greim et al 1995)

In order to measure enzymatic hydrolysis, Butyl Methacrylate was incubated with purified porcine liver carboxylesterase stock solution The volume of carboxylesterase stock solution (10 7 μg/ml) added to the solution was adjusted for each experiment to standardize the enzymatic activity of the samples Butyl Methacrylate, at a concentration of 5 to 250 μM (n = 5) had a K_m of 72 $\pm$ 28 μM, a V_{max} of 1 84 $\pm$ 0 64 nmol/min and a V_{max}/K_m ratio of 26 l/min The investigators concluded that α-methyl substitution does not have a significant effect on hydrolysis in comparison with the acrylate analog (McCarthy and Witz 1997)

Cytotoxicity

Foong et al (1990) presented a preliminary study in which the cytotoxicity of Butyl Methacrylate and Lauryl Methacrylate was determined in the liposome-neutral red cytotoxicity test The concentration effect of liposome entrapped compounds on the neutral red (NR) content of NIH 3T3 cells was measured spectrophotometrically Butyl Methacrylate and Lauryl Methacrylate were tested at five concentrations of 1 μM to 10 mM The negative controls were DMEM (Dulbecco's modified eagle medium), phosphate buffered saline and empty liposomes Neutral red absorbance at all test sample concentrations showed

that Butyl Methacrylate and Lauryl Methacrylate were less toxic than the positive control (dibutyl tin diacetate) A dose dependent concentration effect was observed for each compound A significant difference between Butyl Methacrylate and Lauryl Methacrylate was observed at 0 01 M Lauryl Methacrylate was more toxic than Butyl Methacrylate and was ranked just beneath the positive control, which may be related to its high molecular weight

Benson and Stackhouse (1986) performed a bacterial luminescence inhibition assay (an alternative assay to assess the toxicity of compounds) using *Photobacterium phosphoreum* and six consecutive concentrations of Butyl Methacrylate which increased by a factor of 1 5 on a mg/kg basis After 5, 15 and 30 min of incubation, light measurements were performed A control was also used to correct for time-dependent drift in light output The concentration that inhibited luminescence by 50% was 37, 49 and 55 mg/L (at 5, 15 and 30 min, respectively)

Reichl et al (2001b) investigated the effect of Triethylene Glycol Dimethacrylate and HEMA on the release of lactate dehydrogenase (LDH) from alveolar lung cell lines in vitro Confluent layers of A549 cells (human, malignant) and L2 rat cells were incubated with various concentrations of Triethylene Glycol Dimethacrylate and HEMA for 8 hours (and up to 48 hours for L2 cells) at 37°C LDH release was measured and an EC_{50} was calculated

A significant increase in LDH release was found in the L2 cells after an 8-hour incubation with HEMA (4 mmol/l) and Triethylene Glycol Dimethacrylate (2 mmol/l) and in A549 cells with HEMA (14 mmol/l) and Triethylene Glycol Dimethacrylate (15 mmol/l) In L2 cells, the EC_{50} for HEMA at 6, 12, 24, 36, and 48 hours was 5 46, 4 66, 3 68, 3 22, and 0 59 mmol/l, respectively In L2 cells, the EC_{50} for Triethylene Glycol Dimethacrylate at 6, 12, 24, 36, and 48 hours was 3 37, 1 30, 1 47, 1 58, and 0 42 mmol/l, respectively (Reichl et al 2001b)

Hikage et al (1999) evaluated the cytotoxicity of Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Triethylene Glycol Dimethacrylate in the presence of rat liver S9 mix containing cytochrome P450 enzymes JTC-12 cells derived from a monkey kidney were added to a 96-well plate After cultivation, S9 was added to some wells and PBS was added to cells not receiving S9, then 7 different concentrations of either Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, or Triethylene Glycol Dimethacrylate were added to each well The cell survival ratio (CSR) was calculated by using a neutral red cytotoxicity assay after 24 hours

The CSR for 50 μg/ml of Isopropylidenediphenyl Bisglycidyl Methacrylate with S9 mix was 92 6%, and without S9 mix was 6 6% The CSR for Ethylene Glycol Dimethacrylate, HEMA, and Triethylene Glycol Dimethacrylate exhibited a statistically significant reduction in cytotoxicity in the presence of S9 mixture The IC_{50} values for Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Triethylene Glycol Dimethacrylate without S9 in JTC-12 cells were 135 (0 068 M), 220 (1 692 M), 39 (0 681 M), and 400 μg/ml (1 398 M), respectively The IC_{50} values for Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Triethylene Glycol Dimethacrylate with S9 in JTC-12 cells were <200 (<0 425 M), 500 (3 842 M), 820 (4 141 M), and <1000 μg/ml (<3 496 M), respectively (Hikage et al 1999)

Geurtsen et al (1998) investigated the cytotoxic effects of Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate using monolayers of permanent 3T3 cells and three primary human fibroblast types derived from oral tissues (gingiva, pulp, and periodontal) Primary human periodontal ligament and pulp fibroblasts were found to be more sensitive than 3T3 and gingival fibroblasts

The methacrylate monomers tested had ED_{50} values that ranged from 0 06 to 2 52 mM The most toxic methacrylates tested were Isopropylidenediphenyl Bisglycidyl Methacrylate (0 08–0 14 mM), Di-HEMA Trimethylhexyl Dicarbamate (0 06–0 47 mM), and Triethylene Glycol Dimethacrylate (0 12–0 26 mM) Ethylene Glycol Dimethacrylate (0 46–2 31 mM) and HEMA (1 77-2 52 mM) were moderately toxic (Geurtsen et al 1998)

Yoshii (1997) evaluated the cytotoxicity of Butyl Methacrylate, Isobutyl Methacrylate, Ethoxyethyl Methacrylate, Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, PEG-4 Dimethacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate in the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide (MTT) assay using HeLa S3 cells The IC_{50} of each chemical was determined

The ranking of monomers in order of decreasing cytotoxicity was Isopropylidenediphenyl Bisglycidyl Methacrylate (0 03 mmol/l), Di-HEMA Trimethylhexyl Dicarbamate (0 09 mmol/l), Lauryl Methacrylate (0 67 mmol/l), Ethylene Glycol Dimethacrylate (1 06 mmol/l), Triethylene Glycol Dimethacrylate (1 50 mmol/l), PEG-4 Dimethacrylate (1 97 mmol/l), Butyl Methacrylate (2 71 mmol/l), Ethoxyethyl Methacrylate (2 72 mmol/l), Isobutyl Methacrylate (2 94 mmol/l), Tetrahydrofurfuryl Methacrylate (4 70 mmol/l), Hydroxypropyl Methacrylate (8 67 mmol/l), and HEMA (10 07 mmol/l) In comparison, the IC_{50} of ethyl methacrylate was 29 26 mmol/l (Yoshii 1997)

Bouillaguet et al (2000) evaluated the HEMA effects on human THP-1 monocyte-macrophages by measuring cellular proliferation using the trypan-blue exclusion assay, mitochondrial activity as measured by the MTT assay, and total cellular protein as measured by the bicinchoninic assay Human THP-1 monocyte-macrophages were exposed to HEMA for up to 6 weeks at concentrations of 0 to 1 5 mmol/l

Macrophage proliferation was inhibited by 40 to 50% by as little as 0 75 mmol/l HEMA after 1 week of exposure and

remained constant Total protein per cell increased by as much as 80% after 2 weeks and remained elevated for the remainder of the study Mitochondrial activity per cell was increased by 60 to 80% after 2 weeks and then decreased but remained elevated above control levels for the entire study The authors noted concentrations as low as 0 5 mmol/l of HEMA could significantly alter the proliferation and activity of human monocyte-macrophages, which is substantially lower levels than those previously identified in conventional 24 to 72-hour cell-culture tests (Bouillaguet et al 2000)

Chirila et al (1991) evaluated the cytotoxicity of Ethoxyethyl Methacrylate and HEMA in the trypan blue analysis, LDH assay, and inhibition of DNA synthesis assay HEMA and Ethoxyethyl Methacrylate were tested at concentrations from 0 025% to 0 50 and 0 025% to 0 15%, respectively

HEMA was much more toxic than Ethoxyethyl Methacrylate at similar concentrations In the LDH assay, 0 10% HEMA caused 66 6 ± 2 4% cell death In comparison, 0 10% Ethoxyethyl Methacrylate caused 6 6 ± 1 5% cell death after a 48 hour incubation Both HEMA and Ethoxyethyl Methacrylate inhibited DNA synthesis in a dose-dependent manner, but Ethoxyethyl Methacrylate was nontoxic by trypan blue assay Ethoxyethyl Methacrylate was considered "virtually nontoxic over the concentration tested" (Chirila et al 1991)

Ratanasathien et al (1995) evaluated the cytotoxicity of HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate in cultures of Balb/c 3T3 mouse fibroblasts The TC_{50} values were significantly decreased at 72 hours compared with 24 hours The TC_{50} value of HEMA was 3600 μmol/l at 24 hours and 1025 μmol/l at 72 hours The rank of TC_{50} values was the same at both 24 and 72 hours of exposure Isopropylidenediphenyl Bisglycidyl Methacrylate (most toxic) > Di-HEMA Trimethylhexyl Dicarbamate > Triethylene Glycol Dimethacrylate > HEMA (least toxic)

Gough and Downes (2001) assessed the cytoxicity of Tetrahydrofurfuryl Methacrylate in human osteoblast cells Cells were treated with Tetrahydrofurfuryl Methacrylate at a range of concentrations, at various time points cell activity was measured using the Alamar Blue assay, and apoptosis was determined by Hoechst staining Cells stained with Hoechst after culture in Tetrahydrofurfuryl Methacrylate had apoptotic morphology dependent on concentration Cells cultured in a 1 in 5000 dilution (1 224 mM) of Tetrahydrofurfuryl Methacrylate showed typical apoptotic morphology Cells cultured in a 1 in 20,000 (0 306 mM) dilution did not show any evidence of apoptosis, but mitotic figures were observed

Estrogenic Activity

Hashimoto and Nakamura (2000) assessed the estrogenic activity of HEMA, Isopropylidene-diphenyl Bisglycidyl Methacrylate, Trimethylol-propane Trimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate at concentrations ranging from 10^{-7} to 10^{-3} M 17β-Estradiol at 10^{-7} was the positive control The endocrine disrupting activity was assessed using three in vitro tests the yeast two-hybrid system, a fluorescence polarization system, and MCF-7 cell growth in the E-Screen test HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Trimethylolpropane Trimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate did not have any estrogenic activity

Olea et al (1996) determined the estrogenic activity of an Isopropylidenediphenyl Bisglycidyl Methacrylate dental sealant in MCF7 human breast cancer cells Cell proliferation in MCF7 cells was measured for up to 144 hours in the presence of Isopropylidenediphenyl Bisglycidyl Methacrylate and other dental composites The dental sealant increased cell yields, progesterone receptor expression, and pS2 secretion in human estrogen-target, serum-sensitive MCF7 breast cancer cells

Isopropylidenediphenyl Bisglycidyl Methacrylate itself, however, was negative in the estrogenicity test at concentrations from 10^{-9} to 10^{-5} M Bisphenol-A and its dimethacrylate (monomers found in the base paste of the dental sealant) were estrogenic when assayed in the breast cancer cell proliferation assay The concentration required to produce maximum proliferation of MCF7 cells was 10,000-fold higher than those of Estradiol-17β Eighteen dental patients treated with 50 mg of an Isopropylidenediphenyl Bisglycidyl Methacrylate-based dental sealant on their molars had bisphenol-A (range 90–931 μg) in saliva one hour after treatment (Olea et al 1996)

Effects on Red Blood Cells

Butyl Methacrylate (100 mM), PEG-4 Dimethacrylate (10 mM), or Tetraethylene Glycol Dimethacrylate (10 mM) was incubated with 0 25 mM glutathione (GSH) for up to 45 min and red blood cell suspensions from female Sprague-Dawley rats for one hour Controls were included for the latter experiment Butyl Methacrylate did not react with GSH to any appreciable extent in the cell-free system, however PEG-4 Dimethacrylate and Tetraethylene Glycol Dimethacrylate had apparent rate constants of 1 45 and 0 83 liter mol^{-1} min^{-1} Data indicated that α-methyl substitution greatly decreased monofunctional methacrylate activity to nucleophiles Rat red blood cells incubated with acrylates had linear GSH depletion curves over time for Butyl Methacrylate, PEG-4 Dimethacrylate and Tetraethylene Glycol Dimethacrylate (McCarthy et al 1994)

ANIMAL TOXICOLOGY

Acute Butyl Methacrylate Toxicity

Oral

Deichmann (1941) dosed 20 rats orally with 17 9 g/kg body weight Butyl Methacrylate Only 2/20 rats died within 10–36 h Six rabbits (1 rabbit per group) were dosed orally with 5 37 to 10 74 g/kg Butyl Methacrylate Only the rabbits treated with 5 37 and 8 06 g/kg Butyl Methacrylate survived All other animals died within 12–36 h Butyl Methacrylate did not have an effect on the blood or hemoglobin of rats or rabbits In both rats and rabbits, oral lethal doses of Butyl Methacrylate

(17 90 g/kg in rats and 6 27–9 00 g/kg in rabbits from 10–36 hours post-administration) produced pronounced increased respiration rates (with lacrimation in rats) in 2–5 minutes, followed by motor weakness and decreased respiration (15–40 minutes later) There was increased defecation and urination and reflex activity was lost and the animals died in coma

The oral LD_{50} of Butyl Methacrylate in rats was reported as >20 g/kg (Autian 1975)

E I Dupont de Nemours & Co (1993) reported on 5 male and five female rats administered a single oral dose of 2000 mg/kg Butyl Methacrylate No rats died during the study The LD_{50} was >2000 mg/kg No clinical signs of toxicity were observed during the 14-day recovery period No compound related gross abnormalities were observed at necropsy and no target organ was identified Butyl Methacrylate was considered slightly toxic

Grelm et al (1995) stated that the oral LD_{50} for Butyl Methacrylate in rats was >5000 mg/kg

Intraperitoneal (ip)

Sandmeyer and Kirwin (1981) stated that the ip LD_{50} for Butyl Methacrylate in rats was 2 3 g/kg The ip LD_{50} for Butyl Methacrylate in mice was 1 49 g/kg

The ip LD_{50} of Butyl Methacrylate in mice was reported as 1 663 ml/kg or 10 481 mole/10^6 g (Lawrence et al 1972, Autian 1975) Lawrence et al (1972) stated that acrylate monomers were more toxic than the corresponding methacrylate monomers The lower molecular weight members of the acrylate/methacrylate series were more toxic than the higher molecular weight members Additionally, the straight chain substituent was less toxic than the corresponding branched chain, and simple aliphatic substituents were less toxic than substituents that contained hydroxyl or amine functional groups

Singh et al (1972) administered a single ip injection of Butyl Methacrylate to Sprague-Dawley rats and observed the animals for mortality over seven days The ip LD_{50} for Butyl Methacrylate was reported as 2 3039 ml/kg (95% confidence limits were 1 8811–2 8217 ml/kg)

The acute ip LD_{50} for Butyl Methacrylate in the mouse was 1 663 ml/kg (10 481 moles/10^6 g) (Mir et al 1973a)

Oral/Intraperitoneal

Lawrence et al (1974) determined the oral and ip LD_{50}s for Butyl Methacrylate using mice and rats (10 and 2 animals/group, respectively) The oral or ip doses were 0 5, 1, 2, 4, 8 or 16 ml/kg Animals were given a single dose of Butyl Methacrylate and observed for 7 days for signs of toxicity The oral and ip LD_{50}s for mice were 16 00 ml/kg and 1 66 ml/kg (10 mice/group), respectively The oral and ip LD_{50}s for rats were >16 00 ml/kg and 5 7 ml/kg, respectively

Sandmeyer and Kirwin (1981) stated that the oral LD_{50} for Butyl Methacrylate in rats was >20 g/kg The ip LD_{50} for Butyl Methacrylate in rats was 2 3 g/kg The ip LD_{50} for Butyl Methacrylate in mice was 1 49 g/kg The oral LD_{50} for Butyl Methacrylate in rabbits was >6 3 g/kg

Eastman Kodak Co (1984) reported that the oral LD_{50} for Butyl Methacrylate in rats and mice was >3200 mg/kg The ip LD_{50} for Butyl Methacrylate in rats and mice was >3200 mg/kg and 1600 mg/kg, respectively

Intravenous (iv)

Deichmann (1941) injected anesthetized rabbits iv with 0 03 or 0 04 cc/kg Butyl Methacrylate Blood pressure changes and respiration rates were recorded for a planned one-hour survival period Butyl Methacrylate produced a prompt and sudden fall in arterial pressure followed by recovery in 3 to 4 min Respiration was immediately stimulated and remained at an elevated rate for about 20–30 min Respiration decreased with each additional sublethal dose (1–2 doses max) until it finally stopped Oral and subcutaneous administration of Butyl Methacrylate produced the same changes but the onset was less significant

Mir et al (1974) reported a study in which male mongrel dogs (9–12 kg, 3 dogs/group) were anesthetized and given 0 0207 ml (135×10^{-6} M), 0 0415 ml (270×10^{-6} M), 0 0830 ml (540×10^{-6} M), or 0 1660 ml (1080×10^{-6} M) Butyl Methacrylate intravenously (iv) Blood pressure, heart rate, electrocardiogram and respiration rate were measured

The highest dose was rapidly fatal to the dogs Following injection of Butyl Methacrylate, an abrupt decrease in systemic pressure (18–39%) occurred which lasted for 2 to 4 min at all doses The pressure increased slowly and reached a plateau at higher than control values for 10–15 min Heart rate decreased at all dose levels compared to control values, the percent change ranged from 13–27% Respiratory rate increased at all dose levels of Butyl Methacrylate, the percent change ranged from 164–303% Dose-related cardiac responses included the following bradycardia, a reduced rate of impulse transmission through the A-V node, and possible acute cardiac ischemia Higher doses produced premature ventricular contractions and incomplete A-V block (Mir et al 1974)

Intraperitoneal/Intravenous

Swiss Webster mice (1/group) were dosed ip and iv with 6 consecutive doses of Butyl Methacrylate that differed by a factor of 1 5 mg/kg Animals were observed for 48 h after administration of Butyl Methacrylate The approximate lethal dose for ip and iv administration was 1000 and 100 mg/kg, respectively (Benson and Stackhouse 1986)

Dermal

Deichmann (1941) prepared the skin of the abdomen of rabbits by clipping the hair The animals were restrained so that they could not inhale the vapor of Butyl Methacrylate The compound was dropped onto the clipped area in single doses of 10 cc/kg Butyl Methacrylate produced malaise and temporary local irritation, but the animals recovered within an hour In a review, Gould (1987) stated that Butyl Methacrylate causes acute dermal irritation to rabbits

The dermal LD_{50} of Butyl Methacrylate in rabbits was reported as >10 ml/kg (Autian 1975) Greim et al (1995) stated that the dermal LD_{50} for rabbits was >2000 mg/kg

The dermal LD_{50} for Butyl Methacrylate in three guinea pigs was reported as >20 ml/kg (Eastman Kodak Co 1984) Guinea pigs were dosed with 5-20 ml/kg using an occluded application protocol At 24 h, there was moderate edema and erythema with hemorrhagic patch areas At one week, heavy desquamation and light flakey eschars were evident on most of the patch area By week two scattered scarring was observed

Subcutaneous

A dose of 25 cc/kg of Butyl Methacrylate given to ten rats subcutaneously caused no fatalities Butyl Methacrylate did not have an apparent effect on the blood or hemoglobin of treated rats (Deichmann 1941)

Inhalation

Deichmann (1941) exposed rats to 2 9, 3 4, 4 0 or 5 0 mg/L Butyl Methacrylate for 8 h, although the investigators state that it was impossible to obtain concentrations above 3 mg/L in air All animals survived and the treated animals had irritation of the mucous membranes, malaise and accelerated respiration

Gross pathology was confined primarily to the respiratory system The lungs, trachea and bronchi of treated rabbits, guinea pigs and rats were markedly congested, edematous and spotted with large and small areas of hemorrhage and emphysema The ventricles were usually well contracted and the auricles were dilated and filled with dark clotted blood The urinary bladder of rats was greatly distended and often contained blood Additionally, oral administration produced pronounced corrosion, areas of hemorrhage and detachment of the gastric mucosa The intestine had congestion and acute irritation of the mucosa (Deichmann 1941)

Inhalation toxicity in ICR mice was conducted by bubbling air through Butyl Methacrylate at a rate of 2 L/min None of the five mice exposed to 17 01 mg/L Butyl Methacrylate for 455 63 minutes died as a result of exposure to Butyl Methacrylate (Lawrence et al 1974)

Oberly and Tansy (1985) exposed rats to Butyl Methacrylate vapors Six dose groups (3003, 4015, 4397, 5025, 5999 and 7083 ppm) of 10 male Sprague-Dawley rats were exposed to vapors of Butyl Methacrylate for a four-hour period A sham or control group was also included

Survival decreased as concentration increased; however, all animals that survived the first 24 h survived the 14-day observation period Upon exposure to Butyl Methacrylate vapors, the animals began to squint and huddle, the remainder of the exposure period their behavior suggested irritation to the eyes, nose and respiratory tract with labored breathing apparent during part of the exposure interval Blanching of the ears and paws suggested death was imminent Death was attributed to generalized cardiopulmonary collapse

No significant gross abnormalities of the major organs were observed at necropsy The LC_{50} value calculated for 24-h survivors for Butyl Methacrylate was 4910 ppm (4223-5709 ppm) The investigators suggested that Butyl Methacrylate is more toxic than methyl or ethyl methacrylate (Oberly and Tansy 1985)

The Haskell Laboratory (1993a) exposed male Swiss Webster mice (4/group) to 490, 980, 6300 or 20000 ppm Butyl Methacrylate for 30 min in an inhalation chamber Respiratory rates were recorded every 15 seconds during exposure and the 10 min post-exposure period

Mice exposed to the lowest concentration tested had sporadic breathing patterns of mild sensory irritation for the first few minutes An initial decrease in respiratory rate occurred in all groups of mice exposed to Butyl Methacrylate Respiratory rates remained lower than pre-exposure rates throughout the exposure period, however, there was no concentration-response relationship

Maximum decreases ranged from 15 4 to 19 7% Breathing frequencies increased during the post exposure period The investigators concluded that Butyl Methacrylate does not act as a sensory or pulmonary irritant An RD_{50} value was not calculated (Haskell Laboratory 1993a)

The Haskell Laboratory (1993b) also exposed six groups of five male and five female rats via inhalation to 14 ± 0 94, 18 ± 3 6, 24 ± 2 0, 27 ± 2 2, 29 ± 0 98 and 36 ± 1 5 mg/L Butyl Methacrylate for a four hour period All rats were restrained in perforated, stainless steel or polycarbonate cylinders with conical nose pieces Only the nose of each rat extended into the exposure chamber A control group was not included in the study

All rats in the 14, 18, 24 and 27 mg/L groups survived the exposure and recovery period Following exposure, clinical observations included abnormal gait (24 mg/L only), discharge, diarrhea, hunched posture, irregular respiration, lethargy, lung noise, tremors (one female in the 18 mg/L group) and wet fur Stained fur, corneal opacity and weakness developed during the recovery period In the 29 mg/L group one male and one female rat died during exposure and on test day 2, two male rats and two female rats were found dead

Clinical observations were similar to the lower concentration groups and also included gasping, swollen nose, wet fur, ruffled and stained fur and soreness No high dose rats died during exposure, however, three female rats were found dead on test day 2 Clinical observations were similar to those of the other dose groups Both male and female rats in all groups initially lost weight after exposure to Butyl Methacrylate, with more severe weight loss in the higher dose groups The 29 mg/L group continued to gain weight throughout the 15 days when body weights were recorded and by day 15 weighed more than at study start, while all other groups lost weight

Although an LC_{50} could not be calculated, the approximate lethal concentration for Butyl Methacrylate was 29 mg/L The investigators concluded that Butyl Methacrylate has a low

toxicity on an acute inhalation basis (Haskell Laboratory 1993b)

The 4 h LC_{50} for rats exposed to Butyl Methacrylate was 28,469 mg/m^3 (Greim et al 1995)

In vitro

Mir et al (1973a) perfused isolated rabbit hearts in vitro with 1 100,000, 1 10,000 or 1 1000 dilutions of Butyl Methacrylate Butyl Methacrylate was tested five times but the number of hearts used was not available The procedure used a uniform hydrostatic pressure that provided a constant perfusion pressure Each heart was perfused for a 20 min equilibration period and the test was conducted over the following 90 min The test solution was introduced as the perfusate for one minute after cardiac activity had stabilized and then normal Locke's solution was perfused to permit recovery of the heart The effect was considered irreversible if cardiac activity did not return significantly to control levels within 30 to 35 min of perfusion with normal Locke's solution

Butyl Methacrylate produced an irreversible effect on the isolated heart at only the highest concentration The lowest concentration did not change the cardiac rate per minute, force of contraction or coronary flow The cardiac rate per minute, force of contraction (g) and coronary flow (ml/min) were significantly decreased at all concentrations tested compared to control The only exception was that coronary flow was not significantly affected at the lowest Butyl Methacrylate concentration tested (Mir et al 1973a)

Mir et al (1973b) exposed newly isolated guinea pig ileum of either sex to Butyl Methacrylate one time at dilutions of 1 2000, 1 1000 or 1 500 The number of samples used was not specified The spontaneous activity of the intestine to Tyrode's solution was recorded and then Butyl Methacrylate was added to the bath and the response recorded

Butyl Methacrylate produced a concentration-dependent depressant effect upon spontaneous motility of the isolated guinea pig ileum Additionally, a concentration-dependent antagonism of the neurogenic and myogenic stimulant effects of acetylcholine (1 10,000,000) and barium chloride (3 100,000) was observed upon the isolated ileum

The molar ratio of Butyl Methacrylate required to produce a 50% inhibition of the acetylcholine and barium chloride responses was 15,500 and 51 0, respectively These data suggest that the origin of the inhibitory effects of Butyl Methacrylate upon isolated guinea pig ileum are myogenic These effects could be terminated by washing with fresh Tyrode's solution (Mir et al 1973b)

Acute Ethylene Glycol Dimethacrylate Toxicity

oral

Lewis (2000) listed the Ethylene Glycol Dimethacrylate oral LD_{50} in the rat as 3300 mg/kg and the oral LD_{50} in the mouse as 2000 mg/kg No details were available

Intraperitoneal

Lewis (2000) listed the Ethylene Glycol Dimethacrylate ip LD_{50} in the rat as 2800 mg/kg No details were available

Acute HEMA Toxicity

Oral

Lewis (2000) listed the HEMA oral LD_{50} in the rat as 5050 mg/kg and the oral LD_{50} in the mouse as 3275 mg/kg No details were available

Intraperitoneal/Intramuscular

The ip LD_{50} of HEMA in mice was reported as 0 497 ml/kg or 4 060 mole/10^6 g (Lawrence et al 1972, Autian 1975)

Schneiderka et al (1996) dosed female Wistar rats (8 weeks old/ 200 grams) with HEMA intramuscularly or ip Six doses of the monomer were chosen for administration to 10 animals each Lethal doses were calculated

The HEMA ip $LD_{0.02}$, $LD_{0.2}$, $LD_{2.0}$, LD_{10}, LD_{25}, LD_{50}, and LD_{90} in rats were calculated to be 0 048, 0 087, 0 180, 0 358, 0 612, 1 110, 3 450 ml/kg, respectively The HEMA intramuscular $LD_{0.02}$, $LD_{0.2}$, $LD_{2.0}$, LD_{10}, LD_{25}, LD_{50}, and LD_{90} in rats were calculated to be 2 164, 2 296, 2 471, 2 650, 2 791, 2 970, and 3 330 ml/kg, respectively (Schneiderka et al 1996)

Lewis (2000) listed the HEMA oral LD_{50} in the rat as 1250 mg/kg and the oral LD_{50} in the mouse as 497 mg/kg No details were available

Intravenous

Mir et al (1974) reported a study in which male mongrel dogs (9-12 kg, 3 dogs/group) were anesthetized and given 0 0124 ml (101×10^{-6} M), 0 0248 ml (202×10^{-6} M), 0 0496 ml (404×10^{-6} M), or 0 0992 ml (808×10^{-6} M) HEMA by iv injection Blood pressure, heart rate, electrocardiogram and respiration rate were measured

The highest dose was rapidly fatal to the dogs Following injection of HEMA, an abrupt decrease in systemic pressure (29-54%) occurred which lasted for 2 to 4 min at all doses The pressure increased slowly and reached a plateau at higher than control values for 10-15 min Heart rate decreased at all dose levels compared to control values, the percent change ranged from 8-17% Respiratory rate increased at all dose levels of Butyl Methacrylate, the percent change ranged from 162–356%

Dose-related cardiac responses included bradycardia, a reduced rate of impulse transmission through the A-V node, and possible acute cardiac ischemia Higher doses produced premature ventricular contractions and incomplete A-V block (Mir et al 1974)

Dermal

HEMA was reported to cause slight irritation to rabbits No other information was available (Gould 1987)

Acute Hydroxypropyl Methacrylate Toxicity

Oral

Hazelton Laboratories (1961) assessed the acute oral toxicity of Hydroxypropyl Methacrylate in rats Rats (5 per dose group) were administered 100, 316, 1000, 3160, 10,000 and 31,600 mg/kg Hydroxypropyl Methacrylate via stomach tube Toxic effects were observed at 1, 4, and 24 hours and once daily for seven days after dosing

Immediately following dosing, most dose groups showed depression, labored respiration, and ataxia The LD_{50} was 11,200 mg/kg with confidence limits between 6380 and 19,700 mg/kg No rats died in the 100, 316, 1000, 3160 mg/kg dose groups Two of five rats died in the 10,000 mg/kg dose group within 24 hours Five of five rats died in the 31,600 mg/kg dose group within one hour (Hazelton Laboratories 1961)

The Ministry of Health and Welfare Japan (1998) reported that the acute oral toxicity of Hydroxy-propyl Methacrylate was assessed using groups of 5 male and 5 female rats dosed with 0, 500, 1000, and 2000 mg/kg/day of Hydroxypropyl Methacrylate by gavage No animals died The LD_{50} was greater than 2000 mg/kg High-dose males salivated immediately after administration

Acute Isobutyl Methacrylate Toxicity

Oral

The oral LD_{50} of Isobutyl Methacrylate in rats was reported as 6 4 to 12 8 g/kg by Autian (1975) Sandmeyer and Kirwin (1981) stated that the oral LD_{50} for Isobutyl Methacrylate in rats was >6 3 g/kg Isobutyl Methacrylate was considered as slightly more toxic than the n-butyl isomer Grem et al (1995) stated that the oral LD_{50} for Isobutyl Methacrylate in rats was >5000 mg/kg

The acute ip LD_{50} for Isobutyl Methacrylate in the mouse was 1 340 ml/kg (8 398 moles/10^6 g) (Mir et al 1973a)

Intraperitoneal

The ip LD_{50} of Isobutyl Methacrylate in mice was reported as 1 340 ml/kg or 8 398 mole/10^6 g (Autian 1975, Lawrence et al 1972) Lawrence et al (1972) stated that acrylate monomers were more toxic than the corresponding methacrylate monomers The lower molecular weight members of the acrylate/methacrylate series were more toxic than the higher molecular weight members Additionally, the straight chain substituent was less toxic than the corresponding branched chain, and simple aliphatic substituents were less toxic than substituents that contained hydroxyl or amine functional groups

Singh et al (1972) reported a study in which Sprague-Dawley rats received a single ip injection of Isobutyl Methacrylate and were observed over seven days for mortality The LD_{50} for Isobutyl Methacrylate was reported as 1 3999 ml/kg (95% confidence limits were 1 1077–1 7693)

Sandmeyer and Kirwin (1981) stated that the ip LD_{50} for Isobutyl Methacrylate in mice was 1 19 g/kg and in rats was 1 4 g/kg Isobutyl Methacrylate was considered as slightly more toxic than the n-butyl isomer

Intravenous

Mir et al (1974) reported a study in which male mongrel dogs (9–12 kg, 3 dogs/group) were anesthetized and given 0 0167 ml (104×10^{-6} M), 0 0334 ml (208×10^{-6} M), 0 0668 ml (416×10^{-6} M), or 0 1336 ml (832×10^{-6} M) Isobutyl Methacrylate by iv injection Blood pressure, heart rate, electrocardiogram and respiration rate were measured

The highest dose was rapidly fatal to the dogs Following injection of Isobutyl Methacrylate an abrupt decrease in systemic blood pressure (33-60%) occurred which lasted for 2 to 4 min at all doses The pressure increased slowly and reached a plateau at higher than control values for 10 to 15 min Heart rate decreased at all dose levels compared to control values, the percent change ranging from 10 to 32% Respiratory rate increased at all dose levels of Isobutyl Methacrylate, the percent change ranged from 162 to 356%

Dose-related cardiac responses included bradycardia, a reduced rate of impulse transmission through the A-V node, and possible acute cardiac ischemia Higher doses produced premature ventricular contractions and incomplete A-V block (Mir et al 1974)

Dermal

The dermal LD_{50} of Isobutyl Methacrylate in guinea pigs was reported as >20 ml/kg (Autian 1975)

Inhalation

Inhalation toxicity in ICR mice was conducted by bubbling air through Isobutyl Methacrylate at a rate of 2 l/min Half of the mice tested (number not stated) died after exposure to 29 74 mg/L Isobutyl Methacrylate for 289 79 minutes (Lawrence et al 1974)

The General Electric Company (1975) evaluated the acute inhalation toxicity of Isobutyl Methacrylate by exposing albino rats to atmospheric concentrations of 2 mg/L or 200 mg/L There were 5 male and 5 female rats per group and individual rats weighed between 200 and 250 grams Food and water were available ad libitum Rats were exposed to either 2 mg/L or 200 mg/L Isobutyl Methacrylate for 4 hours and then observed for 14 days thereafter

All of the rats exposed to 2 0 mg/L of Isobutyl Methacrylate survived the 14- day observation period During the exposure period, two rats had decreased motor activity, eye squint, erythema, slight dyspnea, and tonic convulsions At 24 hours, decreased motor activity was observed in several rats but by 48 hours all rats appeared normal Eight of the ten rats exposed to 200 mg/L of Isobutyl Methacrylate died Two male rats died at the end of the exposure period, and within 3 hours following the end of the exposure period, two male and three female rats died An additional female rat was found dead at 24 hours The remaining male and female rats survived the observation period

During the exposure period the following parameters first increased then decreased, motor activity, eye squint, erythema, salivation, lacrimation, clear nasal discharge, nasal porphyrin discharge, tachypnea, both slight and marked dyspnea, ataxia, tonic convulsions and prostration

At 24 hours, surviving rats had urine stained abdomens, corneal surface drying, hypersensitivity to touch accompanied by vocalization, marked dyspnea, respiratory congestion, and dehydration After 5 days, both surviving rats appeared normal At necropsy, 1 of 4 males had no gross lesions, 3 of 4 males and 4 of 4 females had lung congestion, 1 of 4 males had yellow areas on the lung, and 1 of 4 females had a blood clot in the stomach Based upon the results, Isobutyl Methacrylate was considered a toxic (but not a highly toxic) substance by inhalation exposure (General Electric Company 1975)

In vitro

Mir et al (1973a) perfused isolated rabbit hearts in vitro with 1 100,000, 1 10,000 or 1 1000 dilutions of Isobutyl Methacrylate Isobutyl Methacrylate was tested five times but the number of hearts used was not available The procedure used a uniform hydrostatic pressure that provided a constant perfusion pressure Each heart was perfused for a 20 min equilibration period and the test was conducted over the following 90 min The test solution was introduced as the perfusate for one minute after cardiac activity had stabilized and then normal Locke's solution was perfused to permit recovery of the heart The effect was considered irreversible if cardiac activity did not return significantly to control levels within 30 to 35 min of perfusion with normal Locke's

Isobutyl Methacrylate produced an irreversible effect on the isolated heart at only the highest concentration The lowest concentration did not change the cardiac rate per minute, force of contraction or coronary flow The cardiac rate per minute, force of contraction (g) and coronary flow (ml/min) were significantly decreased at all concentrations tested compared to control The only exception was that coronary flow was not significantly affected at the lowest and middle concentrations of Isobutyl Methacrylate solution (Mir et al 1973a)

Mir et al (1973b) exposed newly isolated guinea pig ileum of either sex to Isobutyl Methacrylate once at dilutions of 1 2000, 1 1000 or 1 500 The number of samples used was not specified The spontaneous activity of the intestine to Tyrode's solution was recorded and then Isobutyl Methacrylate was added to the bath and the response recorded

Isobutyl Methacrylate produced a concentration-dependent depressant effect upon spontaneous motility of the isolated guinea pig ileum Additionally, a concentration-dependent antagonism of the neurogenic and myogenic stimulant effects of acetylcholine (1 10,000,000) and barium chloride (3 100,000) was observed upon the isolated ileum The molar ratio of Isobutyl Methacrylate required to produce a 50% inhibition of the acetylcholine and barium chloride responses was 14,125 and 50 0, respectively These data suggest that the origin of the inhibitory effects of Isobutyl Methacrylate upon isolated guinea pig ileum are myogenic These effects could be terminated by washing with fresh Tyrode's solution (Mir et al 1973b)

Acute Lauryl Methacrylate Toxicity

Oral

The Rohm and Haas Co (1966a) administered a single oral dose of 0 464, 1 0, 2 15, 4 64, 10 or 21 5 ml/kg C12-C18 Methacrylate monomer solution to male albino Sprague-Dawley rats Observations were made at one, four, and 24 h and once daily for 14 days upon which all animals were killed No deaths occurred at any of the dosages tested No significant signs of toxicity were observed Necropsy findings were unremarkable

Intraperitoneal

The ip LD_{50} for Lauryl Methacrylate in mice was 24 897 ml/kg or 84 531 moles/10^6 g (Lawrence et al 1972, Autian 1975, Mir et al 1973a)

Intravenous

Mir et al (1974) tested the effect of 0 1550 ml (418 x 10^{-6} M), 0 3100 ml (836 x 10^{-6} M), 0 6200 ml (1672 x 10^{-6} M), or 1 2400 ml (3344 x 10^{-6} M) Lauryl Methacrylate on respiratory and cardiovascular functions in anesthetized dogs as described earlier for other chemical exposures

The highest dose was rapidly fatal to the dogs Following injection of Lauryl Methacrylate, at all doses, a decrease in systemic blood pressure (5-19%) occurred Heart rate also decreased at all doses from 2 to 10% of controls Respiratory rate increased only at the highest dose level of Lauryl Methacrylate, the percent change was 41 Cardiac responses included the following bradycardia and a marked effect upon ventricular repolarization, as the dose increased, the T wave was decreased and became inverted or biphasic with a marked increase in the ST segment, the PR interval was prolonged (Mir et al 1974)

Inhalation

The Haskell Laboratory (1993a) exposed male Swiss Webster mice (4/group) to 460, 1500, 2100, 2900 or 3800 ppm Lauryl Methacrylate for 30 min in an inhalation chamber Respiratory rates were recorded every 15 seconds during exposure and the 10 min postexposure period

Respiratory rates gradually declined during each exposure to Lauryl Methacrylate, the lowest rates occurred 25–30 min into the exposure time Respiration rates increased slowly when the exposures were discontinued Breathing patterns of sensory irritation coincided with decreased respiratory rates Irritation was most severe at the end of the exposure period and a slow onset of abnormal breathing patterns occurred The RD_{50} of Lauryl Methacrylate was 3900 mg/m^3 Lauryl Methacrylate was considered a sensory irritant and had a low potential for causing upper respiratory tract irritation (Haskell Laboratory 1993a)

In vitro

Mir et al (1973a) tested the effect of Lauryl Methacrylate on isolated, perfused rabbit hearts in vitro using the same protocol as described for Butyl Methacrylate Lauryl Methacrylate produced a reversible effect at all three concentrations tested (1 100,000, 1 10,000 or 1 1000) Cardiac rate per minute and force of contraction were significantly decreased compared to controls at the highest concentration tested, while coronary flow (ml/min) was significantly increased compared to controls at the highest concentration tested Force of contraction (g) was significantly decreased compared to controls at the middle concentration tested Of the 12 methacrylates tested, Lauryl Methacrylate had the least depressant effect upon the isolated rabbit heart at the concentrations tested

Acute PEG-4 Dimethacrylate Toxicity

Oral

The oral LD_{50} value of PEG-4 Dimethacrylate in the rat was >5000 mg/kg No other details were available (Andrews and Clary 1986)

Dermal

The dermal LD_{50} value of PEG-4 Dimethacrylate in the rat was >3 g/kg No other details were available (Andrews and Clary 1986)

Acute Tetraethylene Glycol Dimethacrylate Dermal Toxicity

Tetraethylene Glycol Dimethacrylate was reported to cause mild irritation to rabbits No other information was available (Gould 1987)

Acute Triethylene Glycol Dimethacrylate Oal Toxicity

Lewis (2000) stated that the Triethylene Glycol Dimethacrylate oral LD_{50} values in mice and rats were reported as 10,750 and 10,837 mg/kg, respectively

Acute Trimethylolpropane Trimethacrylate Toxicity

Oral

The Industrial Bio-Test Labs (1973) assessed the acute oral toxicity of Trimethylolpropane Trimethacrylate using albino rats Two male and two female rats per dose group were directly dosed with Trimethylolpropane Trimethacrylate (10,250, 15,380, 23,070, or 34,600 mg/kg) into the stomach by a syringe with a ball-tipped intubating needle Rats were then observed for 14 days

No rats died in the 10, 230 or 15,380 mg/kg dose groups One of 4 rats died in the 23,070 mg/kg dose group at 6 to 22 hours after dosing In the high-dose group all four rats died between day 1 to 4 The oral LD_{50} value of Trimethylolpropane Trimethacrylate in the rat was 25,530 mg/kg

At necropsy the animals had gastroenteritits, hemorrhages in the stomachs, and pale livers No gross lesions were noted in the animals that were killed at the end of the observation period (Industrial Bio-Test Labs 1973)

Andrews and Clary (1986) stated that the oral LD_{50} value of Trimethylolpropane Trimethacrylate in the rat was 5 7 ml/kg

Dermal

The Industrial Bio-Test Labs (1973) assessed the acute dermal toxicity of Trimethylolpropane Trimethacrylate in young albino rabbits Trimethylolpropane Trimethacrylate was applied to the shaved backs of four rabbits (2 male, 2 female) at a dose level of 3,000 mg/kg for 24 hours under an occluded patch Observations were noted for up to 14 days post-application

No rabbits died during the study Slight edema and pale red erythema was noted at the test site at 24 hours At 14 days, slight to mild desquamation was noted The dermal LD_{50} value of Trimethylol propane Trimethacrylate in the rabbit was >3,000 mg/kg (Industrial Bio-Test Labs 1973)

Andrews and Clary (1986) stated that the dermal LD_{50} value of Trimethylolpropane Trimethacrylate in the rabbit was 16 ml/kg and Gould (1987) stated that Trimethylolpropane Trimethacrylate caused moderate irritation to rabbits

Intraperitoneal

Biodynamics (1981) reported a study in which rats were injected ip with Trimethylolpropane Trimethacrylate Rats (5 male and 5 female per dose group) were injected with 2000, 3500, 5000, or 8000 mg/kg Trimethylolpropane Trimethacrylate (in corn oil) Animals were observed at 1, 2, and 4 hours, and daily for 14 days after dosing

No rats died in the group dosed with 2000 mg/kg Trimethylolpropane Trimethacrylate In the 3500 mg/kg dose group, 4 of 5 males died on days 5 to 7; no females died In the 5000 mg/kg dose group, 4 of 5 males and 5 of 5 females died on days 2 to 9 In the 8000 mg/kg dose group, 5 of 5 males and 4 of 5 females died on days 2 to 5 The LD_{50} in the rat was 3900 mg/kg (3100 mg/kg male, 4300 mg/kg female) Tremors, convulsions, and ataxia were observed at all dose levels Animals that died had severe weight loss, and surviving animals exhibited weight losses up to day 7 after which weight was gained (Biodynamics 1981)

The ip LD_{50} of Trimethylolpropane Trimethacrylate in mice was reported as 2 727 ml/kg or 8 537 moles/10^6 g (Autian 1975; Lawrence et al 1972) Lewis (2000) listed the ip LD_{50} of Trimethylolpropane Trimethacrylate in rats as 2889 mg/kg

Inhalation

In its workplace exposure guide, the American Industrial Hygiene Association (1981) stated that none of the "lab animals" (species not given) exposed for 6 hours to air saturated by sparging through Trimethylolpropane Trimethacrylate at 60°C died

Short-Term Butyl Methacrylate Toxicity

Oral

Male rats (5/group) were dosed eleven times with 100 or 1000 mg/kg Butyl Methacrylate over a 15-day period The control group was dosed with water No abnormalities were observed for the low dose group The high dose group had slightly decreased weight gain and feed consumption and as inactive after dosing Clinical chemistry, gross pathology, histopathology, and absolute and relative liver and kidney weights of the treated groups were comparable to controls (Eastman Kodak Co 1984)

The Ministry of Health and Welfare Japan (1998) reported a study in which the oral toxicity of Butyl Methacrylate was assessed as part of a reproductive/developmental toxicity study Groups of 10 male and 10 female rats were dosed with 0, 30, 100, 300, or 1000 mg/kg/day of Butyl Methacrylate by gavage Males were dosed for 44 days and females were dosed from 14 days before mating to day 3 of lactation All male rats were killed on day 45 and female rats were killed on day 4 of lactation

The NOEL was 30 mg/kg/day in males and 300 mg/kg/day in females given Butyl Methacrylate Weight gain depression and a decrease in food consumption was observed in high dose males and females In males, absolute and relative weights of the spleen were decreased at doses of 100 mg/kg or more, and relative kidney weights were increased at 100 mg/kg or more Atrophy of the splenic red pulp was observed at doses of 100 mg/kg or more in males and 100 mg/kg in females The kidneys had no histopathological abnormalities attributed to Butyl Methacrylate (Ministry of Health and Welfare Japan 1998)

Inhalation

The Haskell Laboratories (1977a) exposed ten adult male ChR-CD rats via inhalation to 1200 ppm (average analytically determined concentration was 1248 ± 198 ppm) Butyl Methacrylate for five days a week, six hours a day for two-weeks A group of 10 control rats was also included Blood and urine samples were taken from all animals on the last exposure day and 5 rats/group were necropsied The remaining five rats/group underwent a two-week recovery period

No abnormal weight gains or clinical observations were noted in treated rats compared to controls At the end of the two-week exposure period, the treated rats had moderately higher red blood cell counts and hemoglobin and hematocrit values than the control rats, however, these values returned to control levels after the two-week recovery period No significant differences were observed between test and control groups with respect to other hematological, blood chemical or urine analytical measurements at the end of either sampling period No compound-related effects were observed grossly or microscopically (Haskell Laboratories 1977a)

Greim et al (1995) reported the results of a 28-day inhalation study of Butyl Methacrylate in rats The main effect was irritation of the upper airway; the NOEL was 1801 mg/m^3 No other information was available

Short-term t-Butyl Methacrylate Toxicity

Oral

The Ministry of Health and Welfare Japan (1998) reported the results of a study in which the oral toxicity of t-Butyl Methacrylate was assessed in a 28-day repeat dose toxicity test Groups of 6 male and 6 female rats were dosed with 0, 20, 100, and 500 mg/kg/day of t-Butyl Methacrylate by gavage All rats were killed on day 29

The NOEL was 20 mg/kg/day in males and females given t-Butyl Methacrylate No deaths occurred throughout the study There was no effect on food consumption and body weights between controls and treated groups With blood chemical examination there was an increase in total cholesterol and total protein in both sexes at the 100 and 500 mg/kg/day dose levels, an increase in albumin in females given 100 mg/kg/day and both sexes given 500 mg/kg/day, and a decrease in alkaline phosphatase in males given 100 mg/kg/day and both sexes given 500 mg/kg/day

Urinalysis demonstrated an increase in protein at the highest dose in both sexes Also, at the highest dose level, males had an increase in erythrocytes and females had an increase in epithelial cells

Hypertrophy of the liver in three high-dose males and five high-dose females was noted at necropsy Centrilobular hypertrophy of hepatocytes in four males given 100 mg/kg/day t-Butyl Methacrylate and all high-dose animals was noted microscopically (Ministry of Health and Welfare: Japan 1998)

Short-Term HEMA Toxicity

Oral

The Ministry of Health and Welfare Japan (1998) reported the results of a study in which the oral toxicity of HEMA was assessed (part of a reproductive/developmental toxicity study) Groups of 12 male and 12 female rats were dosed with 0, 30, 100, 300, or 1000 mg/kg/day of HEMA by oral gavage Males were dosed for 49 days and females were dosed from 14 days before mating to day 3 of lactation All male rats were killed on day 50 and female rats were killed on day 4 of lactation

The NOEL was considered to be less than 30 mg/kg/day in males and 30 mg/kg/day in females given HEMA Blood urea nitrogen concentration was elevated or high at concentrations of 30 mg/kg/day or more One high-dose male and five high-dose females died (Ministry of Health and Welfare Japan 1998)

Schneiderka et al (1996) conducted a study in which female Wistar rats were given a subacute intramuscular injections of HEMA The three dose groups were 2 164, 2 296, and 2 471 ml/kg which were the $LD_{0.02}$, LD_{02}, and the LD_{20}, respectively There were six rats per control group and a dose group at each time interval Blood was collected and rats were killed in 5 intervals on days 1, 5, 10, 15, and 20 Hematologic parameters and the dynamics of some clinical chemical analytes were monitored

was considered minimally irritating (Industrial Bio-Test Labs, 1973)

Dermal Irritation

The Haskell Laboratories (1969) evaluated the irritancy of HEMA and Triethylene Glycol Dimethacrylate using male albino guinea pigs Each compound was tested on 15 animals Primary irritation was evaluated by applying 0 05 ml of HEMA (10 or 25%) or Triethylene Glycol Dimethacrylate (2, 5 or 10%) in a 1 1 acetone dioxane dilution to intact shaved skin for 24 hours

No guinea pigs reacted to 10% HEMA Three guinea pigs had mild erythema from 25% HEMA One guinea pig had mild erythema from 2% Triethylene Glycol Dimethacrylate Two guinea pigs had mild erythema when exposed to 5% Triethylene Glycol Dimethacrylate and 4 guinea pigs had mild erythema from 10% Triethylene Glycol Dimethacrylate Both HEMA and Triethylene Glycol Dimethacrylate were considered not irritating (Haskell Laboratories 1969)

The Industrial Bio-Test Labs (1973) assessed the irritation capacity of Trimethylolpropane Trimethacrylate using six albino guinea pigs Trimethylolpropane Trimethacrylate (0 5 ml) was applied to two test sites (abraded and intact) for 24 hours The sites were examined and scored at 24 and 72 hours At abraded skin sites, 3 of 6 rabbits had slight erythema, and at intact skin sites, 3 of 6 rabbits had slight erythema when scored at 24 hours No reactions were visible at 72 hours The primary irritation score was 0 2

In its workplace exposure guide, the American Industrial Hygiene Association (1981) stated that Trimethylolpropane Trimethacrylate was minimally irritating to the rabbit skin

The British Petroleum Company (1981) evaluated the primary skin irritation of HEMA (from 3 different suppliers) and Hydroxypropyl Methacrylate in albino rabbits (4–6 per dose group) Aliquots (0 25 ml) were applied to abraded and non-abraded shaved dorsal skin and covered for 24 hours with an occlusive patch The test material was then washed off and application sites were scored at 24 and 72 hours after 1st application The primary irritation index (PII) of HEMA ranged from 0 7 to 1 2 and the PII of Hydroxypropyl Methacrylate was 1 0 Both HEMA and Hydroxypropyl Methacrylate were classified as likely to be mild irritants on human skin

The Rohm and Haas Co (1981) conducted an acute range finding study to assess skin irritation in New Zealand White rabbits from exposure to HEMA CD (88% HEMA, 1 5% Ethylene Glycol Dimethacrylate) Six rabbits (three intact skin, three abraded) were exposed to 0 5 ml of HEMA CD under a 24-hour patch and irritation was scored at 24 hours, 72 hours, and 7 days

The PII score at 24 and 72 hours (abraded skin) was 1 3 The PII score at 24 and 72 hours (intact skin) was approximately 0 08 HEMA CD was considered slightly irritating (Rohm and Haas 1981)

Eastman Kodak Co (1984) reported that repeated application of Butyl Methacrylate to the clipped backs of five guinea pigs resulted in moderate irritation after ten applications using a drop-on technique Percutaneous absorption was not evident No additional information was available

Andrews and Clary (1986) reported that PEG-4 Dimethacrylate was a slight irritant to rabbits at 24 and 72 hours after a single exposure, and that Trimethylolpropane Trimethacrylate was a slight irritant to rabbits 24 hours after a single exposure

When rabbits were exposed to Trimethylolpropane Trimethacrylate 5 days a week for 2 weeks, only slight irritation was noted after 2 weeks No systemic effects were present (Andrews and Clary 1986)

Katusno et al (1992) examined the dermal irritation of HEMA in four male Hartley guinea pigs using the primary cutaneous irritability test An aqueous solution of 24% methacrylic acid and saline were used as controls Fifty μl of an aqueous solution of 35% HEMA was applied to the shaved dorsal skin every 8 hours on days 1-18, and days 25–32

On the 18th day of application, the first recognizable inflammatory reaction (slight redness) was noted On day 25, no reaction was visible and there was no reaction on day 32 In the methacrylic acid group, there was eschar formation by day 18, and again on day 32 The authors suggested the results of the primary cutaneous irritability test indicated a possible delayed allergic reaction (Katusno et al 1992)

The local irritability of HEMA was tested in guinea pigs by intracutaneous injection (0 2 ml) Observations were noted 2 hours and 7 days post-injection Methacrylic acid and saline were used as controls After 2 hours, HEMA caused redness and vesicles (an irritability score of three) After 7 days, HEMA and methacrylic acid solutions formed eschars (an irritability score of four) HEMA and methacrylic acid were considered strongly irritating (Katusno et al 1992)

Rhône-Poulenc Inc (1992) assessed the dermal irritation of Sipomer Hem-HP-T (>90% HEMA, < 5% methacrylic acid, 1% water) using 6 rabbits The test material (0 10 ml) was applied under a patch on the trunk of each animal for 4 hours Corrosion readings were made at 4 and 48 hours The test material was corrosive in 2 of 6 animals after 48 hours The material was considered corrosive

Rohm and Haas Co (1994) reported that six New Zealand White rabbits were exposed to undiluted Butyl Methacrylate (0 5 ml) for one and four hour periods The hair around the entire trunk between the flank and shoulders was shaved 24 h prior to dosing Butyl Methacrylate was applied under semi-occluded conditions to the right side of the animal for the 4 h exposure period Approximately 3 h into the 4 h exposure a second application was performed to the left side of the animal for the 1 h exposure This site was occluded using the same procedure as in the 4 h exposure Observations were performed at 1, 24, 48 and 72 h and 7, 14 and 21 days after patch removal

No mortality, clinical signs or corrosive effects were observed during either exposure period The PII for the 4-hour exposures, based on the skin irritation observations up to 72 hours, was 5 6

All rabbits in the four-hour exposure period had well-defined to moderate-to-severe erythema through day 7 and by day 14 these effects had diminished to slight or no erythema Edema was present by 24 h, but at day 7 and 14 this effect was almost gone No erythema or edema was present on day 21 Other skin effects included thickening and cracking of the application perimeter, desiccation and skin sloughing of the application area

At the one-hour exposure site, well-defined moderate-to-severe erythema was observed through day 7 in most rabbits, but these effects had diminished to well-defined or no erythema by day 14 Very slight to moderate edema was observed in most rabbits through 24 h By 48 and 72 h very slight to slight edema was noted in 4/6 rabbits No edema or erythema was observed by day 7 and 21, respectively Other skin effects included skin sloughing at the application site perimeter and desiccation of the application area (Rohm and Haas Co 1994)

Lewis (2000) stated that Trimethylolpropane Trimethacrylate caused mild irritation effects at a dose of 500 mg on rabbit skin No other details were available

Dermal Sensitization

Butyl Methacrylate

Lawrence et al (1974) reported that Butyl Methacrylate was non-sensitizing in a guinea pig maximization test (GPMT) No additional information was available

Chung and Giles (1977) immunized male Hartley albino guinea pigs or male and female English short-hair strain guinea pigs using the following protocol Freund's complete adjuvant containing heat-killed *Mycobacterium butyricum* (MB) was diluted to 250 μg/ml with Freund's incomplete adjuvant On day 0, each guinea pig received 100 μg of MB in the four foot pads in a volume of 0 4 ml (0 1 ml per foot pad)

Within four hours after injection of the adjuvant, 0 2 ml of Butyl Methacrylate (concentrations ranged from 2 5 to 10% v/v) in 95% ethanol was topically applied to the clipped nuchal area for the initial induction This procedure, without adjuvant, was repeated twice more during the initial 5-day immunization period Control animals received only the adjuvant

Two groups of animals were challenged at different times In the first group, animals were challenged with 2 or 5% Butyl Methacrylate in ethanol on days 0, 2 and 5 Skin reactions were read 72 h later These animals received three applications of 0 03 ml Butyl Methacrylate in ethanol during the immunization period None of the 19 animals reacted positively to the challenge A second group of animals was challenged with 2 or 5% Butyl Methacrylate in olive oil on days 60 and 95 The animals received 0 0077 ml of 2 or 5% Butyl Methacrylate in olive oil once during the immunization period All nine of these animals had positive reactions at 72 h

The second challenge for a group of animals immunized with 0 0377 ml Butyl Methacrylate in ethanol occurred on day 60 These animals were challenged intradermally (id) with 0 01 or 0 1 μl/site of Butyl Methacrylate The average intensity index (AII) (the sum of the numerical scores of skin reactions, in which three or higher was considered positive/total number of animals used) for the 24 h reading was 0 However, at 48 h the AII was 10 for both 0 01 and 0 1 μl challenge doses The AII of skin reactions at 48 h after topical challenge with 10% Butyl Methacrylate in olive oil was 58 A second group of animals was immunized with 0 0151 ml Butyl Methacrylate in olive oil and challenged on day 95 with 5% Butyl Methacrylate in olive oil The AII of skin reactions at 48 h was 70

Guinea pigs immunized with Butyl Methacrylate were challenged for the third time after immunization was complete with 0 4 and 5% Butyl Methacrylate in olive oil on day 122 The AII for skin reactions 72 h after topical challenge was 93 for both challenge concentrations

Some animals were tested for cross sensitivity on the second or fourth challenge cycle Twelve hours after exposure positive skin reactions were observed for methyl and ethyl methacrylate The investigators stated that Butyl Methacrylate was a very strong sensitizer (Chung and Giles 1977)

HEMA

The British Petroleum Company (1981) evaluated the sensitization potential of HEMA in guinea pigs Two weeks after topical induction, the guinea pigs were challenged at 10 and 25% concentrations One week after the first challenge, the test and control HEMA groups were re-challenged with 5% HEMA (from three different suppliers) Skin reactions were evaluated at 48 and 72 hours following the challenge and re-challenge All guinea pigs induced with HEMA were sensitized and reacted positively to a challenge using 10% HEMA Using 5% HEMA, four of the sensitized animals reacted to all three HEMA varieties and two other animals reacted to two varieties of HEMA The researchers concluded that HEMA is an extremely potent sensitizer

Clemmensen (1985) used the GPMT to study the influence of concentration, vehicle, and cyclophosphamide on sensitization to HEMA The vehicles used for elicitation were petrolatum, soybean oil, and a mixture of oil and 2-butanone (sbomek) Ten to twenty guinea pigs were used per dose group The following materials were used for intradermal induction (day 0) 1% HEMA (in soybean oil), 25% HEMA (in soybean oil), 25% HEMA (in sbomek), 1% HEMA (aqueous), 10% HEMA (aqueous), and 25% HEMA (aqueous) Dermal induction occurred on days 7 and 8 using a 10% sodium lauryl sulfate pretreatment and 400 μl of HEMA applied via a 48 hour patch Challenge was performed on day 21 using 25% HEMA (in petrolatum), 25% HEMA (aqueous), 25% HEMA (sbomek), 25% HEMA (in soybean oil), and 100% HEMA Effects were scored at 48 and 72 hours post-challenge The effect of ip injection of 200 mg cyclophosphamide/kg body weight 3 days before challenge was examined

There were no differences between the vehicles used when HEMA concentrations were 25% or greater Response elicitation was least effective using 100% HEMA, dilutions were more effective, in particular with petrolatum There was no response

to intradermal induction using 1% HEMA (in soybean oil),1% HEMA (aqueous) when challenged with 25% HEMA (in petrolatum) elicited a response in 4 of 12 guinea pigs, however none of the other challenge vehicles responded

The major determining factor for sensitization was the concentration used for intradermal injection Using 10% HEMA or greater caused a reaction in 2 to 10 guinea pigs out of as many as 12 guinea pigs tested per dose group Injection of cyclo-phosphamide before challenge increased the number of responders and prolonged the period of responsiveness where an erythematous reaction could be elicited

A delayed hypersensitivity test was performed on BALB/C mice (4 weeks old) using HEMA The shaved abdomen of each mouse was treated with 0 1 ml of 100% HEMA A 4% picryl chloride solution was the positive control Seven days later 0 03 ml of HEMA was applied to the left pinna The magnitude of inflammation was measured by the swelling of the ear No mice had an allergic reaction to HEMA at the concentrations tested (Katsuno et al 1995)

In a GPMT, Katsuno et al (1996) determined the optimum concentration of HEMA for sensitization and elicitation Five female Hartley guinea pigs (300–500 g) were used per dose group HEMA was tested as a sensitizer at 0 01, 0 02, 0 1, 0 2, 0 5, 1 0, and 5 0% HEMA was tested in elicitation at 10, 25, 50, and 100% Induction was performed in two stages In the first induction, 50 μl of HEMA was injected intradermally One week later the animals were pretreated with 10% sodium lauryl sulfate (in petrolatum) for 24 hours A patch soaked in 200 μl HEMA was placed on the shaved back for 48 hours to induce topical sensitization A challenge patch containing 100 μl 0 2% HEMA was applied for 24 hours on day 22 Challenge concentrations were 10, 25, 50, and 100%

Five of five guinea pigs had a positive reaction (strong rubefaction and several vesiculopapules) to 0 2% HEMA at 24 hours and 48 hours post patch removal with a mean response of 5 0 which was the optimum concentration for sensitization For elicitation, only 100% HEMA produced skin reactions The mean responses were 5 0 at 24 hours and 2 4 after 48 hours (Katsuno et al 1996)

Katsuno et al (1995) tested HEMA in a GPMT Fifty μl of HEMA was intradermally injected and on day 6 the animals were pretreated with 10% sodium lauryl sulfate (in petrolatum) On day 7, a patch soaked in 0 2 ml HEMA (at 0 2, 1 0, or 5 0%) was placed on the shaved back for 48 hours to induce topical sensitization A challenge patch containing 100% HEMA was applied for 24 hours on day 21

Six of ten (mean response, 2 4) albino guinea pigs sensitized to HEMA showed a positive reaction at 24 hours and 5 out of 10 (mean response, 2 2) showed a positive reaction at 48 hours Strong rubefaction was noted Cross-reactivity was examined using methacrylic acid or methyl methacrylate as sensitizers All 12 guinea pigs tested were negative The researchers noted that HEMA produced positive delayed hypersensitivity reactions in the guinea pig, but suggested that HEMA has different allergic reactions in humans and guinea pigs (Katsuno et al 1995)

Hydroxypropyl Methacrylate

Björkner et al (1980b) assessed the sensitizing capacity of Hydroxypropyl Methacrylate using a GPMT Groups of ten guinea pigs were used Sites were pretreated with 10% sodium lauryl sulfate in petrolatum Hydroxypropyl Methacrylate (5%) was dissolved in an olive oil and acetone (10 1) vehicle to improve dispersion for intradermal induction For topical induction, Hydroxypropyl Methacrylate was tested at 25% Challenge was performed using 2% Hydroxypropyl Methacrylate in petrolatum Cross-reactivity to HEMA was also examined

One of 10 guinea pigs became sensitized to Hydroxypropyl Methacrylate challenge with a mean response of 0 15 The same guinea pig also reacted to HEMA with the same mean response The researchers concluded that Hydroxypropyl Methacrylate is a weak sensitizer (Björkner et al 1980b)

Isopropylidenediphenyl Bisglycidyl Methacrylate

Björkner et al (1984a) tested the sensitizing capacity of Isopropylidenediphenyl Bisglycidyl Methacrylate using a GPMT Groups of fifteen guinea pigs were used Sites were pretreated with 10% sodium lauryl sulfate in petrolatum Isopropylidenediphenyl Bisglycidyl Methacrylate (10% or 20%) was dissolved in an olive oil vehicle to improve dispersion for intradermal induction For topical induction, Isopropylidenediphenyl Bisglycidyl Methacrylate was tested at 100% Challenge was performed two weeks after topical application using 10% Isopropylidenediphenyl Bisglycidyl Methacrylate (whole product) in petrolatum The patch was occluded for 24 hours and the site was read 4 hours after removal

Thirteen of 15 guinea pigs became sensitized to Isopropylidenediphenyl Bisglycidyl Methacrylate (whole product) at the first and second challenge with a mean response of 1 17 The whole product Isopropylidenediphenyl Bisglycidyl Methacrylate could be resolved into three components by HPLC Only fraction 1 (free from linear and branched Isopropylidenediphenyl Bisglycidyl Methacrylate) caused sensitization in guinea pigs (8 of 15) The authors concluded the allergenic potential in fraction 1 may have been epoxy resin MW 340 (Björkner et al 1984a)

Trimethylolpropane Trimethacrylate

Industrial Bio-Test Labs (1974) assessed the sensitizing capacity of Trimethylolpropane Trimethacrylate using ten albino guinea pigs Trimethylolpropane Trimethacrylate (0 5 ml) was applied undiluted for 5 hours to a Webril pad which was occluded with elastoplast Two weeks later, a challenge was done using Trimethylolpropane Trimethacrylate at the insult and virgin site for 5 hours Irritation was scored at 24 and 49 hours No irritation was noted at any time Trimethylolpropane Trimethacrylate was not considered a sensitizer

Björknei et al (1980a) assessed the sensitizing capacity of Tiimethylolpiopane Trimethacıylate using a GPMT Twenty-foui guinea pigs were used foi each gioup Trimethylolpropane Trimethacrylate (1%) was dissolved in an olive oil vehicle to impiove dispeision foi intradeimal induction For *topical induction*, Tiimethylolpiopane Tiimethacıylate was tested at 25% Challenge was peifoimed using 0 1% and 0 5% Trimethylol piopane Tiimethacrylate in petiolatum

Six of 24 and 16 of 24 guinea pigs became sensitized to 0 1% and 0 5% Tiimethylolpiopane Trimethacıylate, iespectively The controls weie negative One week latei, at iechallenge, 7 of 24 guinea pigs and 10 of 24 contiol guinea pigs reacted to 0 5% Tiimethylolpropane Trimethacıylate The ieseaicheis concluded that Tiimethylolpiopane Tiimethacrylate is a stiong sensitizei (Bjöiknei et al 1980a)

In its woikplace exposuie guide, the Ameiican Industrial Hygiene Association (1981) stated that undiluted Tiimethylolpiopane Trimethacıylate did not cause sensitization in 10 guinea pigs No other details weie available

Urethane Methacıylate

Björknei (1984b) assessed the sensitizing capacity of Uiethane Methacıylate using the GPMT Gioups of fifteen guinea pigs were used The animals weie pietreated with 10% sodium lauiyl sulfate in petiolatum The puiity of the Uiethane Methacıylate used in this experiment was 98% accoiding to the manufactuiei, this coiielated with HPLC analysis Uiethane Methacrylate (5%) was dissolved in an olive oil acetone (10 1) vehicle to impiove dispeision foi intiadeimal induction Foi topical induction, Uiethane Methacıylate was tested at 100% Challenge was peifoimed using 0 015 g of Urethane Methacrylate at a concentiation of 1% in petiolatum

Only 2 of 15 guinea pigs became sensitized to Urethane Methacrylate Theie was no cross-sensitization with an aiomatic and aliphatic urethane acrylate Uiethane Methacıylate was consideied a mild sensitizei (giade II) (Bjöiknei 1984b)

Multiple Methacrylate Esteis

Kanazawa et al (1999) conducted a maximization test of seveial methacrylates using female Haitley guinea pigs, 5–10 animals per group

Guinea pigs weie induced with an intradeimal injection (amount not stated) of 0 1 M or 1 M Butyl Methacrylate and challenged 21 days latei with 0 1 ml aliquots of 1 M Butyl Methacıylate applied to the shaved aiea of the flank

Guinea pigs were induced with an intiadeimal injection of 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} oi 10^{-8} M Lauryl Methacıylate and weie challenged 21 days later with 0 1 ml aliquots of 1 M Lauiyl Methacıylate applied to the shaved aiea of the flank

Guinea pigs weie induced with an intiadeimal injection of 1, 10^{-1}, oi 10^{-2} M Cyclohexyl Methacıylate and weie challenged 21 days later with 0 1 ml aliquots of 1 M Cyclohexyl Methacrylate applied to the shaved aiea of the flank

Guinea pigs weie induced with an intiadermal injection of 10^{-1}, 10^{-2}, oi 10^{-3} M Hexyl Methacıylate and weie challenged 21 days latei with 0 1 ml aliquots of 1 M Hexyl Methacıylate applied to the shaved aiea of the flank

The challenge phase was peifoimed using the closed patch method foi 24 h Deimal iesponse was evaluated 48 h after the challenge application The vehicle used foi the induction phase was olive oil and for the challenge phase was acetone

Butyl Methacıylate, Cyclohexyl Methacrylate, and Hexyl Methacrylate weie consideied modeiate sensitizeis Lauiyl Methacıylate was consideied a much stiongei sensitizei, in fact it was the stiongest sensitizei of the 13 methacıylates tested Alkyl methacıylates with lineai side chains having an even numbei of caibons weie stiongei sensitizeis than those that had an odd numbei of caibons

The sensitization iate foi Butyl Methacıylate at induction concentiations of 0 1 and 1 M weie 0 and 80%, iespectively The minimum induction concentiation (MIC) was 0 1 M The sensitization iate foi Cyclohexyl Methacıylate at induction concentiations of 1, 10^{-1} and 10^{-2} M Cyclohexyl Methacıylate was 40 0, 20 0 and 0%, iespectively The MIC was deteimined as 10^{-1} M The sensitization rate foi Hexyl Methacıylate at induction concentiations of 10^{-1}, 10^{-2}, and 10^{-3} M Hexyl Methacıylate was 33 3, 0, and 0%, iespectively The MIC was deteimined as 10^{-1} M The sensitization iate foi Lauiyl Methacıylate at induction concentiations of 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} M Lauiyl Methacıylate was 100 0, 100 0, 30 0, 30 0 and 0%, iespectively The MIC was determined as 10^{-7} M (Kanazawa et al 1999)

Cross-Reactions

The Haskell Laboiatoiy (1969) tested foi deimal iiiitation and sensitization effects of HEMA and Triethylene Glycol Dimethacıylate on guinea pigs Each compound was tested on 15 male albino guinea pigs Piimaiy iiiitation was evaluated by applying 0 05 ml of HEMA (10, 25, oi 98%) oi Triethylene Glycol Dimethacrylate (2, 5, 10, and 98%) in a 1 1 acetone dioxane dilution to intact shaved skin Sensitizing treatments weie done by nine topical applications of 0 05 ml of 25% HEMA oi Tiiethylene Glycol Dimethacıylate (1st application was 5% and last 8 applications weie 10%) to abiaded skin of five animals, four 0 1 ml id injections of 1% test mateiial in dimethylphtalate to a second gioup of five animals, and two 0 1 ml id injections of FCA followed 90 minutes latei by a 0 1 ml of 1% test mateiial in dimethylphtalate in the third group of five animals Aftei 14 days, the animals weie challenged with 0 05 ml of 10% Triethylene Glycol Dimethacrylate oi 25% HEMA on intact oi abiaded skin One week latei a second challenge was peifoimed using 98% test mateiial

At fiist challenge, 25% HEMA caused no reaction in 14 guinea pigs and mild erythema in 1 guinea pig (intact skin), on abiaded skin, 7 guinea pigs had mild eiythema and 8 had no reaction At second challenge, 98% HEMA caused no reaction in 12 guinea pigs, mild erythema in 2 guinea pigs, and

moderate erythema in 1 guinea pig (intact), on abraded skin, 7 guinea pigs had mild erythema, 5 had moderate erythema, and 3 had strong erythema One of 15 guinea pigs was sensitized to HEMA

At first challenge, 10% Triethylene Glycol Dimethacrylate caused no reaction in 11 guinea pigs and mild erythema in 4 guinea pigs (intact skin), on abraded skin, 12 guinea pigs had mild erythema and 3 had no reaction At second challenge, 98% Triethylene Glycol Dimethacrylate caused no reaction in 8 guinea pigs, mild erythema in 6 guinea pigs, and moderate erythema in 1 guinea pig (intact), on abraded skin, 11 guinea pigs had no reaction, 2 had mild erythema, and 2 had moderate erythema Triethylene Glycol Dimethacrylate sensitized 0–100% of animals tested (Haskell Laboratory 1969)

van der Walle and Bensink (1982) sensitized albino female guinea pigs of the Himalayan white spotted outbred strain in the Freund's Complete Adjuvant Test (FCAT) or the GPMT Two weeks after finishing these tests, one flank of the guinea pig was clipped and 6 to 8 acrylic monomers were applied in two rows in a 2 cm^2 area An amount of 0 025 ml of 1 M (or 4 M) Butyl Methacrylate, 4 M t-Butyl Methacrylate, 3 M HEMA, or 0 3 M (or 3 M) Hexyl Methacrylate was applied to the flank The reactions were read at 24 and 48 h The procedure was repeated 14 days later using the other flank The animals were tested six times, alternating the flanks All animals were finally challenged with the monomer that originally sensitized the animal after the last challenge to detect cross reactions All monomers were applied at a non-irritant concentration

No animals were sensitized to t-Butyl Methacrylate Four guinea pigs were sensitized to HEMA but the cross reactions to Butyl Methacrylate, t-Butyl Methacrylate, and Hexyl Methacrylate were not tested Three guinea pigs were sensitized to Hexyl Methacrylate but there were no cross reactions to Butyl Methacrylate, t-Butyl Methacrylate, and HEMA One of two animals originally sensitized to Butyl Methacrylate had positive cross reactions to ethyl, n-butyl, t-butyl, pentyl, neopentyl and n-hexyl acrylate and ethyl methacrylate One out of three and 2/8 animals had positive cross reactions to Butyl Methacrylate when originally sensitized to ethyl and methyl methacrylate, respectively One out of two animals originally sensitized to Butyl Methacrylate had positive cross reactions with two diacrylates and four dimethacrylates None of the animals originally sensitized with a diacrylate or dimethacrylate had positive cross reactions to Butyl Methacrylate

These authors also investigated the role of contact sensitization to hydroquinone in the sensitization capacity of Butyl Methacrylate, t-Butyl Methacrylate, Hexyl Methacrylate, and HEMA using a GPMT with 8 animals per test group Guinea pigs were exposed to the methacrylate monomer with and without hydroquinone There was no hydroquinone specified in any of the methacrylates by the manufacturer An FCAT was used to estimate the sensitizing potential of the methacrylates

The FCAT was negative for Butyl Methacrylate and t-Butyl Methacrylate and negative for Hexyl Methacrylate and HEMA None of the guinea pigs had any sensitization effects when exposed in the presence of hydroquinone and t-Butyl Methacrylate or HEMA No guinea pigs had any reaction to concomitant exposure to Butyl Methacrylate and Hydroquinone but 2 of these 8 guinea pigs did react to hydroquinone alone

The authors concluded that these results indicate that Butyl Methacrylate interferes with the sensitizing potential of hydroquinone It seemed that the sensitizing potential of any of the methacrylates tested was not influenced by hydroquinone because 1 of 8 guinea pigs reacted to hydroquinone and Hexyl Methacrylate, however this guinea pig had no reaction to hydroquinone alone Hydroquinone was present in all four methacrylates tested at 0 032 to 0 092 g/l as estimated by HPLC (van der Walle et al 1982)

Parker and Turk (1983) injected the footpads of female Hartley guinea pigs four times with an emulsion of 2 mg/ml of Butyl Methacrylate, Ethylene Glycol Dimethacrylate, HEMA, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, or Trimethylolpropane Trimethacrylate in ethanol saline (1 4) in Freund's complete adjuvant (FCA) An additional 0 1 ml of the emulsion was injected into the nape of the neck The animals received a total of 1 mg of Butyl Methacrylate, Ethylene Glycol Dimethacrylate, HEMA, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, or Trimethylolpropane Trimethacrylate Seven days later, and weekly thereafter for up to 12 weeks, 0 02 ml of a 2% solution in acetone olive oil (4 1) was applied to the shaved flank of the animals, using a different site for each application

Butyl Methacrylate, Ethylene Glycol Dimethacrylate, HEMA, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, or Trimethylolpropane Trimethacrylate did not induce contact sensitization using this protocol (Parker and Turk 1983)

Björkner (1984c) assessed the sensitizing capacity of Ethylene Glycol Dimethacrylate, Triethylene Glycol Dimethacrylate, and PEG-4 Dimethacrylate using the GPMT Groups of fifteen guinea pigs were used The animals were pretreated with 10% sodium lauryl sulfate in petrolatum prior to topical induction Ethylene Glycol Dimethacrylate (5%), Triethylene Glycol Dimethacrylate (1%), and PEG-4 Dimethacrylate (5%) were dissolved in an olive oil acetone (9 1) vehicle to improve dispersion for intradermal induction For topical induction, Ethylene Glycol Dimethacrylate, Triethylene Glycol Dimethacrylate, and PEG-4 Dimethacrylate were tested at 50% Challenge was performed using 0 015 g of Ethylene Glycol Dimethacrylate, Triethylene Glycol Dimethacrylate, or PEG-4 Dimethacrylate at a concentration of 1% in petrolatum The cross-reactivity patterns for the dimethacrylates were also tested

Only 1 of 15 guinea pigs became sensitized to Triethylene Glycol Dimethacrylate No sensitization was observed in the other two Dimethacrylates (Björkner 1984c)

Clemmensen (1984) performed a GPMT to assess the cross-reaction patterns induced with Ethylene Glycol Dimethacrylate, HEMA, Triethylene Glycol Dimethacrylate,

and Trimethylolpropane Trimethacrylate On day 0, guinea pigs received an intradermal injection of 25% HEMA (or 10% Hydroxypropyl Methacrylate, 5% Ethylene Glycol Dimethacrylate, 5% Triethylene Glycol Dimethacrylate , or 5% Trimethylolpropane Trimethacrylate) in the neck region On day 7, the neck area was clipped and 250 mg 10% sodium dodecyl sulfate in petrolatum was applied uncovered for 24 hours On day 8, 400 μl of 100% HEMA (or 100% Hydroxypropyl Methacrylate, 100% Ethylene Glycol Dimethacrylate, 100% Triethylene Glycol Dimethacrylate , or 100% Trimethylolpropane Trimethacrylate) was applied under a patch for 48 hours Challenge occurred on day 21 and scores were read at 48 and 72 hours

Animals induced with HEMA had positive cross-reactions when challenged with 25% HEMA (7 of 15) and 25% Hydroxypropyl Methacrylate (5 of 15) Guinea pigs induced with Hydroxypropyl Methacrylate had positive cross-reactions when challenged with 25% HEMA (2 of 12) and 25% Hydroxypropyl Methacrylate (3 of 12)

Animals induced with Ethylene Glycol Dimethacrylate had positive cross reactions when challenged with 100% HEMA (1 of 19), 100% Ethylene Glycol Dimethacrylate (10 of 19 and 13 of 19), and 100% Triethylene Glycol Dimethacrylate (1 of 19), however, no animals (0 of 19) challenged with 100% Trimethylolpropane Trimethacrylate reacted positively

Animals induced with Triethylene Glycol Dimethacrylate had positive cross-reactions when challenged with 100% Ethylene Glycol Dimethacrylate (7 of 20), 25% Triethylene Glycol Dimethacrylate (9 of 20), and 100% Triethylene Glycol Dimethacrylate (3 of 20), but no animals reacted positively when challenged with 100% HEMA (0 of 20) or 100% Trimethylolpropane Trimethacrylate (0 of 20)

Animals induced with Trimethylolpropane Trimethacrylate had positive cross-reactions when challenged with 100% Ethylene Glycol Dimethacrylate (2 of 20), 25% Trimethylolpropane Trimethacrylate (17 of 20), and 100% Trimethylol propane Trimethacrylate (13 of 20), however, none of 20 animals reacted with 100% HEMA or 100% Triethylene Glycol Dimethacrylate (Clemmensen 1984)

Rustemeyer et al (1998) studied the cross-reactivity patterns of contact sensitizing-methacrylates using a guinea pig model to assess the sensitizing capacity of methyl methacrylate, HEMA, Hydroxypropyl Methacrylate, and Ethylene Glycol Dimethacrylate Guinea pigs were immunized by iv injections of 300 μl of 1 0 M methacrylate solutions in FCA After 14 days, open skin tests were performed using 50% HEMA, 50% Hydroxypropyl Methacrylate, or 10% Ethylene Glycol Dimethacrylate solutions in 40% DMSO in ethanol Cross-reactivities were investigated 14 days later by skin testing with all four methacrylates

Strongly positive responses were induced in most guinea pigs tested Sixteen of 18 guinea pigs reacted to HEMA, 15 of 16 reacted to Hydroxypropyl Methacrylate, and 11 of 11 reacted to Ethylene Glycol Dimethacrylate HEMA sensitization led to strong cross-reactions to all other methacrylates, while Ethylene Glycol Dimethacrylate had weak cross-reactivity Hydroxypropyl Methacrylate had strong cross-reactivity to Ethylene Glycol Dimethacrylate but only weak to moderate cross reactivity with HEMA (Rustemeyer et al 1998)

Rustemeyer et al (2001) studied the cross-reactivity patterns of orally administered methyl methacrylate, HEMA, Hydroxypropyl Methacrylate, and Ethylene Glycol Dimethacrylate During tolerance induction, each experimental group (6 guinea pigs per dose group) received 175 μl of methyl methacrylate, HEMA, Ethylene Glycol Dimethacrylate, DMSO (negative control) or dinitrochlorobenzene on wafers Immunization was done on day 0, via intradermal injections of 100 μl of 1 0 M methacrylate solutions in water-FCA emulsion (1 1) Subsequent immunizations were conducted after 1 and/or 2 months

One week after oral methacrylate administration and 14 days after immunization, open skin tests were carried out on the shaved upper flanks by painting 25 μl of solutions containing 50% methacrylate (methyl methacrylate, HEMA, or Hydroxypropyl Methacrylate), 40% DSMO, and 10% ethanol or 0 2% dinitrochlorobenzene in ethanol An open skin test was also carried out on the shaved upper flanks by painting 25 μl of solutions containing 10% Ethylene Glycol Dimethacrylate, 40% DSMO, and 50% ethanol or 0 2% dinitrochlorobenzene in ethanol Challenge reactions were recorded after 6, 24, 48, and 72 hours to assess the effect that oral administration of methacrylate had on suppression T cell transfer experiments were performed to assess T cell cross-reactivity and cross-tolerance

Strong tolerance to the monomethacrylates HEMA and methyl methacrylate could be induced, but not to Ethylene Glycol Dimethacrylate Subsequent sensitization attempts with HEMA, methyl methacrylate, and Ethylene Glycol Dimethacrylate were suppressed 86%, 80%, and 8%, respectively The induced tolerance in methyl methacrylate and HEMA could not be broken by repeated sensitization attempts HEMA-tolerized guinea pigs have strong cross-tolerances to methyl methacrylate and Hydroxypropyl Methacrylate (suppression of 56 and 75%, respectively) Moreover, sensitization with Ethylene Glycol Dimethacrylate in HEMA-tolerized guinea pigs was prevented in 77% of animals tested

In T cell transfer experiments, splenic- or lymph node-derived T cells of HEMA-tolerant animals were transferred into different groups of naive recipients Strong adaptive tolerance was observed in 90% and 100% of guinea pigs with transferred splenic-derived and lymph node-derived T cells, respectively (Rustemeyer 2001)

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Butyl Methacrylate

Oral

The Ministry of Health and Welfare Japan (1998) reported the results of a study in which the reproductive/developmental toxicity of Butyl Methacrylate was assessed Groups of 10 male and 10 female rats were dosed with 0, 30, 100, 300, and 1000 mg/kg/day of Butyl Methacrylate by gavage Males were

dosed for 44 days and females were dosed from 14 days before mating to day 3 of lactation All male rats were killed on day 45 and female rats were killed on day 4 of lactation

The NOAEL was 1000 mg/kg/day in parental males and 300 mg/kg/day in parental females given Butyl Methacrylate The number of corpora lutea and implantations were decreased in the parental females Butyl Methacrylate showed no effects on any reproductive parameters of the parental males or developmental parameters of the offspring (Ministry of Health and Welfare Japan 1998)

Parenteral

Singh et al (1972) injected pregnant Sprague-Dawley rats (5/group) ip with one-tenth, one-fifth or one-third the LD_{50} of Butyl Methacrylate (LD_{50} = 2 3039 ml/kg) or Isobutyl Methacrylate (LD_{50} = 1 3999 ml/kg) determined in a previous study Rats received a single injection on days 5, 10, and 15 of gestation The doses injected for the treatment groups were 0 7680, 0 4608 and 0 2304 ml/kg of Butyl Methacrylate and 0 4666, 0 2799, and 0 1400 ml/kg of Isobutyl Methacrylate for the high, middle and low dose groups, respectively An untreated group and separate groups dosed with 0 8222 ml/kg cottonseed oil, distilled water and normal saline were maintained as controls On day 20 of gestation the rats were killed

The number of corpora lutea and dead fetuses for the treated groups (Butyl Methacrylate and Isobutyl Methacrylate) did not differ significantly from the control groups A decreased number of live fetuses and a significantly increased number of resorptions were observed in the high dose group of Butyl Methacrylate compared to controls A slightly decreased number of live fetuses and slightly increased number of resorptions were observed in the high dose group of Isobutyl Methacrylate compared to controls

The mean weight of the fetuses in the treated groups (Butyl Methacrylate and Isobutyl Methacrylate) differed significantly from controls Gross abnormalities (most commonly hemangiomas on various parts of the body and to a lesser degree twisted hind legs) were significantly increased in all treatment groups compared to all control groups Skeletal abnormalities were not significantly different between the treated and control groups (Singh et al 1972)

Inhalation

Farmakovskaya and Tikhomirov (1993) exposed pregnant white rats via continuous inhalation to Butyl Methacrylate at concentrations of 0 01, 0 1, 0 3 and 4 0 mg/m^3 In this preliminary report of their work, the authors provided no further details Butyl Methacrylate caused embryotoxic and teratogenic effects in the form of increased intrauterine death compared to the control group, increased vascular pathology in a number of fetuses and increased frequency of functional immaturity in fetuses The increased embryo death rate at concentrations of 0 1, 0 3 and 4 0 mg/m^3 Butyl Methacrylate was due to the pre-implantation death of embryos

Butyl Methacrylate was also associated with an increased death rate of rat offspring during the lactation period, a delay in increase in body weight, a breakdown in functional state of the central nervous system and a suppression of redox processes The teratogenic effects manifested in the offspring were observed in the absence of toxic effects observed in the dams The development of fetuses with vascular pathology was attributed to necrosis of the placenta which may have caused a breakdown in the uterus-placenta blood circulation Females in test groups had uterine bleeding, premature births, stillbirths and a decreased number of live fetuses The investigators stated that on the basis of the results obtained, the abnormalities of fetal development observed might have been due to intrauterine hypoxia The threshold concentration of Butyl Methacrylate was determined to be 0 1 mg/m^3 (Farmakovskaya and Tikhomirov 1993)

Saillenfait et al (1999) exposed pregnant Sprague-Dawley rats (22–25/group) to 100, 300, 600 or 1200 ppm Butyl Methacrylate via inhalation 6 h/day on days 6–20 of gestation Day 0 of gestation was the day vaginal smears were confirmed sperm-positive Control animals were exposed concurrently to filtered room air in a chamber identical to the treatment groups Dosing occurred in 200 L glass/stainless steel inhalation chambers with an adjustable laminar air flow of 6–20 m^3/h Food and water were withheld during exposures Concentrations of Butyl Methacrylate were monitored continuously with a GC equipped with a flame ionization detector Food consumption was measured for the gestation day intervals 6–13 and 13–21 Maternal body weight was recorded on gestation days 0, 6, 13 and 21 and females were killed on day 21

All animals survived the exposure period Significantly decreased maternal body weight gain during gestation days 6–13 was observed at concentrations of 300 ppm or higher The highest concentration group also had significantly decreased body weight gain during gestation days 6–21 Absolute weight gain was significantly decreased at 1200 ppm Food consumption was significantly decreased during gestation days 6–13 at 300 and 1200 ppm and at the highest concentration during gestation days 6–21 No significant changes in the number of implantations, live fetuses, incidence of non-live implants or resorptions or in fetal sex ratios were observed across the groups

Fetal body weights were significantly decreased at the highest concentration, however, only female fetuses in the 600 ppm group had significantly decreased body weights Visceral malformations occurred in low frequency and were distributed across both treatment and control groups No significant differences were observed between the control and treated groups with respect to incidences of individual or total external and visceral variations or of individual skeletal variations

At the highest concentration of Butyl Methacrylate, statistically significant changes in mean percentages of fetuses with skeletal variations or any variations were observed compared to concurrent controls The investigators stated that the biological relevance of these findings is limited because the observed

incidences occurred with no clear concentration-dependent pattern They considered these findings suggestive of slight fetotoxicity (Saillenfait et al 1999)

HEMA

The Ministry of Health and Welfare Japan (1998) reported the results of a study in which the reproductive/developmental toxicity of HEMA was assessed in groups of 12 male and 12 female rats dosed with 0, 30, 100, 300, and 1000 mg/kg/day of HEMA by gavage Males were dosed for 49 days and females were dosed from 14 days before mating to day 3 of lactation All male rats were killed on day 50 and female rats were killed on day 4 of lactation The NOEL was 1000 mg/kg/day for reproductive and developmental effects HEMA showed no effects on any reproductive parameters of the parental males or developmental parameters of the offspring (Ministry of Health and Welfare Japan 1998)

Hydroxypropyl Methacrylate

The Ministry of Health and Welfare Japan (1998) reported the results of a study in which the reproductive/developmental toxicity of Hydroxypropyl Methacrylate was assessed in groups of 12 male and 12 female rats dosed with 0, 30, 100, 300, and 1000 mg/kg/day of Hydroxypropyl Methacrylate by gavage Males were dosed for 49 days and females were dosed from 14 days before mating to day 3 of lactation All male rats were killed on day 50 and female rats were killed on day 4 of lactation

The NOAEL was 1000 mg/kg/day for reproductive and developmental effects Hydroxypropyl Methacrylate showed no effects on any reproductive parameters of the parental males or developmental parameters of the offspring (Ministry of Health and Welfare Japan 1998)

Trimethylolpropane Trimethacrylate

Oral

Hazelton Laboratories (1983) evaluated the teratogenic effects of Trimethylolpropane Trimethacrylate administered by gavage to pregnant rats on days 6 to 15 of gestation Twenty-two female rats received 2500 mg/kg/day of Trimethylolpropane Trimethacrylate, control rats received corn oil only Maternal and fetal data were evaluated for treatment-related effects

There were two deaths and body weight gains (for the total gestation period) were decreased in Trimethylolpropane Trimethacrylate-treated rats There was an increased incidence of clinical signs from Trimethylolpropane Trimethacrylate exposure such as wheezing (3 animals), rough hair coat (5 animals), hunched posture (9 animals), soft feces (2 animals), urine stains (13 animals), thin appearance (6 animals), dyspnea (5 animals), salivation (1 animal), alopecia (12 animals), bloody crust (4 animals), and red vaginal discharge (3 animals) There was an increased incidence of gross pathology findings (9 of 22 animals); although the most common were in the liver (tan areas) and kidney (pelvis dilated), they were considered incidental The stomach had raised areas (2 animals), ulcerated areas (2 animals), and thickened and rough areas (1 animal) in the nonglandular mucosa and reddened ulcerated areas (1 animal) and ulcerated areas (2 animals) in the glandular

Pregnancy rates, mean number of corpora lutea and implantations, as well as mean implantation efficiency were comparable between the control and Trimethylolpropane Trimethacrylate treated groups Fetotoxic effects such as increased resorptions (mean incidence 25 4%), decreased fetal viability (mean survival 74 6%), decreased fetal weights, and decreased fetal lengths were observed in Trimethylolpropane Trimethacrylate treated rats Decreases in mean gravid uterine weights (control, 69 48, treated, 46 81) were also noted and attributed to fetotoxic effects The fetal effects were considered directly related to the maternal toxicity of Trimethylolpropane Trimethacrylate (Hazelton Laboratories 1983)

Dermal

Andrews and Clary (1986) evaluated the teratogenic potential of Trimethylolpropane Trimethacrylate using rats A single dose of Trimethylolpropane Trimethacrylate was administered dermally to 20 pregnant rats during days 6 to 15 of gestation

The authors stated that Trimethylolpropane Trimethacrylate was fetotoxic at a maternally toxic dose of 2500 mg/kg/day Decreased fetal body weight and crown-rump distance was observed The data was inconclusive regarding teratogenic potential since the number of fetuses examined was very small (Andrews and Clary 1986)

GENOTOXICITY

Bacterial Test Systems

Butyl Methacrylate

Butyl Methacrylate was not mutagenic in an Ames mutagenesis assay using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 with and without metabolic activation at concentrations of 60, 120, 180, 240 and 300 μg/plate A solvent control of ethanol and three positive controls were also included (Haskell Laboratories 1977c)

Gould (1987) reported that Butyl Methacrylate was not mutagenic in an Ames Salmonella mutagenicity assay

The Mobil Oil Corporation (1990) reported a study in which Butyl Methacrylate was incubated with *S typhimurium* strain TA1538 in plates with metabolic activation at concentrations of 10 0 μl/50 μl, 3 1 μl/50 μl, 0 97 μl/50 μl, 0 30 μl/50 μl, 0 094 μl/50 μl, 0 029 μl/50 μl, 0 0092 μl/50 μl and 0 0028 μl/50 μl A positive control of 2 0 μg 2-aminoanthracene was also used Butyl Methacrylate was mutagenic (20-fold increase in revertants/plate compared to controls) at all concentrations in strain TA1538 with metabolic activation in this test system The response was concentration-related

In a follow-up study, The Mobil Oil Corporation (1991) incubated Butyl Methacrylate with *S typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and

without metabolic activation at concentrations of 0 30 μl/50 μl, 0 094 μl/50 μl, 0 029 μl/50 μl, 0 0092 μl/50 μl and 0 0028 μl/50 μl Four positive controls were included Butyl Methacrylate was not mutagenic with or without metabolic activation in this test system

The Ministry of Health and Welfare Japan (1998) reported on the mutagenicity of Butyl Methacrylate using *S typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E coli* (WP2 uvrA) The dose range tested was from 9 77 to 313 μg/plate without metabolic activation and 9 77 to 1250 μg/plate with metabolic activation Butyl Methacrylate was not mutagenic at any dose tested

t-Butyl Methacrylate

The Ministry of Health and Welfare Japan (1998) reported on the mutagenicity of t-Butyl Methacrylate in *S typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E coli* (WP2 uvrA) The dose range tested was from 9 77 to 625 μg/plate without metabolic activation and 9 77 to 625 μg/plate with metabolic activation t-Butyl Methacrylate was not mutagenic at any dose tested

Ethylene Glycol Dimethacrylate

The mutagenicity of Ethylene Glycol Dimethacrylate was tested in *S typhimurium* strain TA100 with and without metabolic activation at concentrations from 0 01 to 1 0 μl/plate Ethylene Glycol Dimethacrylate was mutagenic at 0 5 and 1 0 μl/plate with metabolic activation and at 0 5 μl/plate without metabolic activation (Rohm and Haas Co 1980)

HEMA

The mutagenicity of HEMA was evaluated with and without metabolic activation in *S typhimurium* (strains TA98 and TA100) and *E coli* (strains R P2, uvrA, and WP2) HEMA was tested at concentrations from 0 2 to 1000 μg/ml There was a slight increase in revertants over the control level in TA100 but the increase was not consistent or dose-related The researchers concluded that HEMA was not mutagenic in the assays tested (British Petroleum Company 1981)

Schweikl et al (1994) tested HEMA in *S typhimurium* strains TA97a, TA98, TA100, TA102, and TA104 with and without metabolic activation at doses of 0, 0 005, 0 025, 0 05, 0 25, 0 50, 1 25, 2 50, 3 75, 5 00, 12 5, and 25 0 mg/plate The mean number of revertants per plate were scored and experiments were done in triplicate HEMA was not mutagenic with or without metabolic activation in all strains tested Controls gave the expected results

The Ministry of Health and Welfare Japan (1998) reported on the mutagenicity of HEMA in *S typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E coli* (WP2 uvrA) The dose range tested was from 313 to 5000 μg/plate without metabolic activation and 313 to 5000 μg/plate with metabolic activation HEMA was not mutagenic at any dose tested

Hydroxylpropyl Methacrylate

The Ministry of Health and Welfare Japan (1998) reported on the mutagenicity of Hydroxylpropyl Methacrylate in *S typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E coli* (WP2 uvrA) The dose range tested was from 313 to 5000 μg/plate with and without metabolic activation Hydroxypropyl Methacrylate was not mutagenic at any dose tested (Ministry of Health and Welfare Japan, 1998)

Trimethylolpropane Trimethacrylate

In its workplace exposure guide, the American Industrial Hygiene Association (1981) stated that Trimethylolpropane Trimethacrylate was negative in the Ames test with and without metabolic activation

Multiple Methacrylate Esters

Waegemaekers and Bensink (1984) reported that Butyl Methacrylate, t-Butyl Methacrylate, HEMA, and Hexyl Methacrylate were not mutagenic in an Ames mutagenesis assay using *S typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 with and without metabolic activation at concentrations of 40, 160, 625 and 2500 μg/plate Solvent controls, positive controls and sterility controls for the S9 mix were performed with each experiment

The US EPA (1985) reported on the mutagenicity of Butyl Methacrylate, t-Butyl Methacrylate, Ethylene Glycol Dimethacrylate, HEMA, Hexyl Methacrylate, Isobutyl Methacrylate, PEG-4 Dimethacrylate, and Trimethylolpropane Trimethacrylate in the Ames assay The strains and doses used were not stated None of the chemicals listed above were mutagenic in the Ames assay No details were available

Zeiger et al (1987) tested Butyl Methacrylate and Isobutyl Methacrylate in *S typhimurium* strains TA98, TA100, TA1535, TA1537 and/or TA97 with and without metabolic activation at doses of 0, 1 0, 3 3, 10 0, 33 0, 100 0, 333 0, 1000 0, 3333 0 or 10000 0 μg/plate At least five doses of the chemical were tested in triplicate Concurrent solvent and positive controls were analyzed with each trial Sodium azide, 9-aminoacridine and 4-nitro-o-phenylene-diamine were used as positive controls in the absence of metabolic activation The positive control used with metabolic activation was 2-aminoanthracene Butyl Methacrylate and Isobutyl Methacrylate were negative for mutagenicity in this test system

Cameron et al (1991) assessed the genotoxicity of Ethylene Glycol Dimethacrylate and Trimethylol propane Trimethacrylate in the *Salmonella/* mammalian microsome assay and the mouse lymphoma TK+/− assay In the *Salmonella/* mammalian microsome assay, Ethylene Glycol Dimethacrylate was tested at 100, 333, 1000, 3333, and 10,000 μg/plate with and without metabolic activation (S9) and Trimethylolpropane Trimethacrylate was tested at 333, 1000, 3333, 6667, and 10,000 μg/plate with and without metabolic activation The *Salmonella typhimurium* strains TA 98, TA100, TA 1535, and TA 1537 were used The solvent DMSO was the negative

control and the positive controls were 2-nitrofluorene (TA 98), sodium azide (TA 100 and TA 1535), and 9-aminoacridine (TA 1537) for the non-activation study and 2-aminoanthracene for the activation study In the mouse lymphoma TK+/− assay, Ethylene Glycol Dimethacrylate was tested at $4\,76 \times 10^{-4}$ to $1\,58 \times 10^{-3}$ without activation and $4\,76 \times 10^{-4}$ to $6\,88 \times 10^{-3}$ with activation (S9), Trimethylolpropane Trimethacrylate was tested at $6\,57 \times 10^{-5}$ to $1\,63 \times 10^{-4}$ without activation and $2\,19 \times 10^{-4}$ to $5\,32 \times 10^{-4}$ with metabolic activation

Ethylene Glycol Dimethacrylate was negative with and without metabolic activation Trimethylol propane Trimethacrylate was negative in the *Salmonella*/mammalian microsome assay without metabolic activation, but was weakly positive with S9 metabolic activation In the mouse lymphoma TK+/− assay, Ethylene Glycol Dimethacrylate was negative without metabolic activation but was positive with S9 metabolic activation Trimethylol propane Trimethacrylate was negative in the mouse lymphoma TK+/− assay with and without metabolic activation at all doses tested (Cameron et al 1991)

Heil et al (1996) tested the mutagenicity of HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate in *S typhimurium* strains TA97a, TA98, TA100, and TA102 with and without metabolic activation at doses of 0, 0 25, 0 50, 1 25, 5 00 and 12 5 mg/plate The mean number of revertants per plate were scored and experiments were done in triplicate HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate were not mutagenic in the Ames assay with or without metabolic activation in all strains tested Controls gave the expected results

These authors also screened HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Di-HEMA Trimethylhexyl Dicarbamate for mutagenicity using three tests the bacterial *umu*-test in *Salmonella typhimurium* strain TA1535/pSK1002, the eukaryotic DNA synthesis inhibition test (DIT), and the in vivo alkaline filter elution (AFE) technique HEMA was tested at 0 2 to 20 mM in the *umu*-test, 0 3 to 40 mM in the DIT, and at 2 mM in the AFE technique Isopropylidenediphenyl Bisglycidyl Methacrylate was tested at 1 3 to 150 mM in the *umu*-test, 0 02 to 0 6 mM in the DIT, and at 2 mM in the AFE technique Di-HEMA Trimethylhexyl Dicarbamate was tested at 0 2 to 6 mM in the *umu*-test, 0 1 to 6 mM in the DIT and at 2 mM in the AFE technique

HEMA was negative at all concentrations tested in the *umu*-test, DIT, and AFE technique Isopropylidenediphenyl Bisglycidyl Methacrylate was negative at all concentrations tested in the *umu*-test and AFE technique, however, Isopropylidenediphenyl Bisglycidyl Methacrylate was positive in the DIT at concentrations at or greater than 0 08 mM Di-HEMA Trimethylhexyl Dicarbamate was negative at all concentrations tested in the *umu*-test, and DIT, it was limited positive using the AFE technique (Heil et al 1996)

Mammalian Test Systems

Butyl and t-Butyl Methacrylate

The Ministry of Health and Welfare Japan (1998) reported results of chromosomal aberration tests used to assess the effect of Butyl Methacrylate and t-Butyl Methacrylate on Chinese hamster lung cells

Butyl Methacrylate was used at doses from 0 to 1420 μg/ml with and without metabolic activation Mitomycin C was the positive control for the non-activation study and cyclophosphamide was the positive control for the activation study Butyl Methacrylate did not induce structural chromosomal aberrations at the doses tested

t-Butyl Methacrylate was used at doses from 0 to 400 μg/ml, 0 to 200 μg/ml, and 0 to 700 μg/ml without metabolic activation for a 24 hour treatment, 48 hour treatment, and a 6 h pulse treatment, respectively t-Butyl Methacrylate was tested at doses from 0 to 750 μg/ml for a 6 hour pulse treatment with metabolic activation Mitomycin C was the positive control for the non-activation study and benzo[a]pyrene was the positive control for the activation study t-Butyl Methacrylate only induced clastogenicity at 400 μg/ml in the 24-hour treatment (Ministry of Health and Welfare Japan 1998)

Ethylene Glycol Dimethacrylate

Litton Bionetics (1985) tested Ethylene Glycol Dimethacrylate in the L5178Y mouse lymphoma cell assay The induction of forward mutations was examined L5178Y/TK$^{+/-}$ cells were treated with 3 9 to 800 nl/ml of Ethylene Glycol Dimethacrylate with and without exogenous activation Negative control cells were treated with DMSO and positive control cells were treated with ethylmethane sulfonate for the nonactivation studies and dimethylnitrosamine for the activation studies

Ethylene Glycol Dimethacrylate significantly induced dose-related increases in the mutation frequency in L5178Y mouse lymphoma cells with metabolic activation at concentrations from 400 to 700 nl/ml Without metabolic activation, concentrations up to 800 nl/ml caused high toxicity without increasing mutation frequency Ethylene Glycol Dimethacrylate was considered active in the mouse lymphoma forward mutation assay with metabolic activation (Litton Bionetics 1985)

HEMA

The Ministry of Health and Welfare: Japan (1998) reported on a chromosomal aberration test used to assess the effect of HEMA on Chinese hamster lung cells HEMA was tested using 24-hour continuous treatment, 48-hour continuous treatment, and a short-term treatment HEMA was tested with and without metabolic activation

Chromosomal aberrations were induced at 0 65 and 1 3 mg/ml (mid and high concentration) with 24-hour continuous treatment, at 0 16 to 0 65 mg/ml (all concentrations) with 48-hour continuous treatment and at 1 3 mg/ml (high concentration) with short-term treatment and metabolic activation HEMA

induced polyploidy at 0 65 mg/ml with 48-hour continuous treatment and at 0 33 and 1 3 mg/ml (low and high concentrations) with short-term treatment without metabolic activation (Ministry of Health and Welfare Japan 1998)

Hydroxypropyl Methacrylate

The Ministry of Health and Welfare Japan (1998) reported on a chromosomal aberration test used to assess the effect of Hydroxypropyl Methacrylate on Chinese hamster lung cells Hydroxypropyl Methacrylate was used at doses from 0 to 1 4 mg/ml with and without metabolic activation in a short-term treatment and at 0 to 0 70 mg/ml without metabolic activation in a continuous treatment Mitomycin C was the positive control for the non-activation study and cyclophosphamide was the positive control for the activation study

Hydroxypropyl Methacrylate without metabolic activation (continuous treatment) induced clastogenicity at 0 35 mg/ml and polyploidy at 0 18 mg/ml Hydroxypropyl Methacrylate without metabolic activation (short-term treatment) induced clastogenicity at 1 4 mg/ml Hydroxypropyl Methacrylate with metabolic activation (short-term treatment) induced clastogenicity at 0 35 mg/ml and polyploidy at 0 35 mg/ml (Ministry of Health and Welfare Japan 1998)

Isopropylidenediphenyl Bisglycidyl Methacrylate

Litton Bionetics (1985) tested Isopropylidene-diphenyl Bisglycidyl Methacrylate in the L5178Y mouse lymphoma cell assay The induction of forward mutations was examined L5178Y/TK$^{+/-}$ cells were treated with Isopropylidenediphenyl Bisglycidyl Methacrylate at 0 586 nl/ml to 160 nl/ml (without metabolic activation) and up to 350 nl/ml (with metabolic activation) Negative control cells were treated with DMSO and positive control cells were treated with ethylmethane sulfonate for the nonactivation studies and dimethylnitrosamine for the activation studies

Isopropylidenediphenyl Bisglycidyl Methacrylate induced small increases in the mutation frequency in L5178Y mouse lymphoma cells with metabolic activation at concentrations from 200 to 350 nl/ml Without metabolic activation, concentrations up to 140 nl/ml caused high toxicity without inducing increased mutantion frequency Isopropylidenediphenyl Bisglycidyl Methacrylate was considered weakly mutagenic in the mouse lymphoma forward mutation assay with metabolic activation (Litton Bionetics 1985)

Triethylene Glycol Dimethacrylate

Litton Bionetics (1979) tested Trimethylolpropane Trimethacrylate in the L5178Y mouse lymphoma cell assay L5178Y/TK$^{+/-}$ cells were treated with Trimethylolpropane Trimethacrylate at 0 156 nl/ml to 80 nl/ml (without metabolic activation) and up to 400 nl/ml (with metabolic activation) Negative control cells were treated with DMSO and positive control cells were treated with ethylmethane sulfonate for the nonactivation studies and dimethylnitrosamine for the activation studies

Trimethylolpropane Trimethacrylate did not increase mutation frequencies in treated cells as compared to control cells without metabolic activation even at the relatively toxic dose of 80 nl/ml However, with activation Trimethylolpropane Trimethacrylate induced an increase in mutations at the TK locus in L5178Y mouse lymphoma cells at doses of 100 to 200 nl/ml (moderately to highly toxic) with microsomal activation (Litton Bionetics 1979)

In a workplace exposure guide, the American Industrial Hygiene Association (1981) stated that Trimethylolpropane Trimethacrylate was positive in the mouse lymphoma forward mutation assay with and without metabolic activation No other details were available

Schweikl and Schmalz (1999) studied the effect Triethylene Glycol Dimethacrylate had on V79 cell cultures Triethylene Glycol Dimethacrylate was tested at concentrations from 0 to 1 00 mmol/l Triethylene Glycol Dimethacrylate caused a dose-dependent increase in the number of micronuclei in V79 cells Triethylene Glycol Dimethacrylate treated V79 cell cultures had only one cell clone among a total of 25 that contained all exon sequences of the *hprt* gene Large DNA sequences were deleted in 24 cell clones The researchers concluded that the induction of large DNA sequence deletions is probably common for acrylate and methacrylates

Multiple Methacrylate Esters

Dearfield et al (1989) tested PEG-4 Dimethacrylate and Trimethylolpropane Trimethacrylate in the L5178Y mouse lymphoma cell assay The induction of mutations, aberrations and micronuclei was examined L5178Y/TK$^{+/-}$ cells were treated with 75–525 μg/ml of PEG-4 Dimethacrylate without exogenous activation for 4 h or 5–50 μg/ml of Trimethylolpropane Trimethacrylate without exogenous activation for 4 h Control cells were treated with the solvent (dimethylsulfoxide) alone Cytogenic analyses were conducted on 200 cells per treatment group following cell treatment and washing Other cells were maintained in log-phase growth for two days and then cloned with and without trifluorothymidine (TFT) selection Following an incubation period of 9–11 days, the colonies were counted and sized

PEG-4 Dimethacrylate increased the mutation frequency to 491×10^{-6} and the maximum response was at 525 μg/ml which allowed 14% survival PEG-4 Dimethacrylate induced significant levels of aberrations (70 per 100 cells) Trimethylolpropane Trimethacrylate was also found to increase the mutation frequency in mouse lymphoma cells, however the activity was considered weak The mutation frequency was increased to 163×10^{-6} and the maximum response was at 50 μg/ml which allowed 11% survival Trimethylolpropane Trimethacrylate produced aberrations (20 per 100 cells) but did not induce micronuclei Primarily, small-colony TFT-resistant mutants were induced which the researchers suggested that genotoxicity was likely due to a clastogenic mechanism This was supported further by increased aberration and micronucleus frequencies in PEG-4

Dimethacrylate, but Trimethylolpropane Trimethacrylate did not have an increased micronucleus frequency (Dearfield et al 1989)

Schweikl et al (1998) tested the mutagenicity of HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate in V79 cells with and without metabolic activation The chemicals were tested at the following concentrations HEMA (0, 2 5, and 5 0%) Isopropylidenediphenyl Bisglycidyl Methacrylate (0, 25, and 50%), Triethylene Glycol Dimethacrylate (0, 0 5, and 1%), and Di-HEMA Trimethylhexyl Dicarbamate (0, 25, 50, and 75%) The positive control was 200 μg/ml ethylmethane sulfonate

HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Di-HEMA Trimethylhexyl Dicarbamate were clearly not mutagenic with or without metabolic activation Triethylene Glycol Dimethacrylate had a dose-dependent increase in mutantion frequency in V79 cell cultures without metabolic activation However, the mutagenicity of Triethylene Glycol Dimethacrylate was destroyed in the presence of metabolic activation The researchers concluded that Triethylene Glycol Dimethacrylate acted through a clastogenic mechanism which is not detected by Ames tester strains (Schweikl et al 1998)

Ethyl Methacrylate

Moore et al (1988) tested Ethyl Methacrylate in the L5178Y mouse lymphoma cell assay L5178Y/TK$^{+/-}$ cells were treated with 900–2100 μg/ml of Ethyl Methacrylate without exogenous activation for 4 h Control cells were treated with the solvent (dimethylsulfoxide) alone Cytogenic analyses were conducted on 200 cells per treatment group following cell treatment and washing Other cells were maintained in log-phase growth for two days and then cloned with and without TFT selection Following an incubation period of 9-11 days, the colonies were counted and sized

Cytotoxicity was only observed at concentrations greater than 1000 μg/ml Toxicity plateaued at concentrations above 1500 μg/ml, where survival fluctuated from 2–37% A weak positive response was observed in cultures with 10–20% survival (1,450, 1,500, 1,550, and 1,626 μg/ml) The greatest number of aberrations occurred at a concentration of 1626 μg/ml (16% survival) where there were 83 mutants/10^6 survivors and 11 aberrations/200 cells

Some of the cultures with less than 10% survival had mutation frequencies three times greater than background The colony size distribution was difficult to determine, however, the researchers did note that cultures with mutation frequencies of 200 mutants/10^6 survivors (less than 10% survival) had an induction of primarily small colonies The researchers suggested that the genotoxicity of Ethyl Methacrylate was likely due to a clastogenic mechanism (Moore et al 1988)

Jackson (2001) reported a structure activity relationship analysis of the genotoxic potential of Butyl, Isobutyl, and Lauryl Methacrylate Jackson determined that due to "the increasing size and complexity of Butyl, Isobutyl, and Lauryl Methacrylate as well as other methacrylate monomers that may be found in nail preparations, militates against their being genotoxic, in the absence of actual test data" This conclusion was based upon negative results in several bacterial tests and weakly positive mammalian tests (most likely due to a clastogenic mechanism) on ethyl methacrylate and methyl methacrylate

CARCINOGENICITY

PEG-4 Dimethacrylate

Andrews and Clary (1986) reported on the chronic dermal exposure of PEG-4 Dimethacrylate using mice Mice were given 25 mg of PEG-4 Dimethacrylate, twice weekly for 80 weeks No remarkable skin irritation was noted although acanthosis and fibrosis were evident No increased incidence of skin or visceral tumors were observed Six of 50 mice died during the study No other details were available (Andrews and Clary 1986)

Triethylene Glycol Dimethacrylate

The Bushy Run Research Center (1995) evaluated the carcinogenicity of Triethylene Glycol Dimethacrylate in a skin painting study using C3H/HeNHsd male mice Each test group had 70 male mice The three treatment groups received concentrations of 5, 25, or 50% Triethylene Glycol Dimethacrylate (in acetone) applied to the dorsal skin of mice at a dose volume of 50 μl for 5 days/week for 78 weeks The two control groups were the untreated control and the vehicle control (acetone only) Epidermal cell proliferation was evaluated after 4, 13, 52, and 78 weeks of the study Animals were monitored for toxicity (clinical signs and palpable masses), body weight, body weight gain, hematology, clinical chemistry, organ weights, gross pathology, and histopathology

Triethylene Glycol Dimethacrylate did not result in any treatment-related changes in hematology, clinical chemistry, mean absolute body weight or body weight gain when applied cutaneously There was decreased survival in the mid-dose and high-dose groups, but only the high-dose group was significantly different from the controls Clinical signs of irritation (primarily exfoliation) were observed in all dose groups and their onset and severity were dose dependent High-dose mice that died or were sacrificed moribund had an increased incidence of hepatocellular adenomas and carcinomas, the overall incidence of these tumors was similar across all dose groups There were no other microscopic lesions in the mid- or high-dose groups that were considered to be responsible for increased mortality, however a statistically significant increased kidney size was observed in these groups The researchers could not definitively identify the cause for increased mortality in mid- and high-dose groups, they felt that the cutaneous irritation was not severe enough to result in the increased mortality, but instead the increased kidney weights may have been related to the increased mortality The NOEL for Triethylene Glycol Dimethacrylate

was 5% The researchers concluded that Triethylene Glycol Dimethacrylate did not induce carcinogenicity at any dose level tested (Bushy Run Research Center 1995)

Trimethylolpropane Trimethacrylate

Andrews and Clary (1986) reported that the chronic dermal exposure of Trimethylolpropane Trimethacrylate was evaluated using mice Mice were given 25 mg of Trimethylolpropane Trimethacrylate twice weekly for 80 weeks No remarkable skin irritation was noted although acanthosis and fibrosis were evident No increased incidence of skin or visceral tumors were observed Five of 50 mice died during the study No other details were available

Methyl Methacrylate

An update to its Methyl Methacrylate monograph was published by the International Agency for Research on Cancer (IARC) in 1994 (IARC 1994) Methyl Methacrylate had no adverse reproductive effects by inhalation exposure in rats and mice and there were no data available on the genetic and related effects of methyl methacrylate in humans Methyl methacrylate caused chromosomal aberrations in rat bone marrow but did not induce micronuclei in mouse bone marrow in vivo Gene mutation, sister chromatid exchange, micronuclei and chromosomal aberrations were induced in mammalian cells in vitro The IARC working group concluded that there is inadequate evidence in humans for the carcinogenicity of methyl methacrylate and there is evidence suggesting a lack of carcinogenicity in experimental animals Methyl Methacrylate is not classifiable as to its carcinogenicity to humans (Group 3)

Lomax et al (1997) exposed male and female Fischer 344 rats (70 males and 70 females/group) to Methyl Methacrylate monomer vapors at 0, 25, 100, and 400 ppm (6 h/day, 5 days/week) for 24 months and female Golden hamsters (53–55 males and 56–59 females/group) were exposed to similar concentrations for 18 months Animals were monitored for clinical signs, body weights, hematology, clinical chemistry (rats only), and urinalyses (rats only) Ten rats per sex/per group were killed after week 13 and 52, all surviving rats were killed during weeks 104 to 106 All surviving hamsters were killed at week 78

Chronic exposure to methyl methacrylate vapor did not cause tumors in hamsters or rats (Lomax et al 1997)

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

In a workplace exposure guide, the American Industrial Hygiene Association (1981) stated that Trimethylolpropane Trimethacrylate was a mild to moderate skin irritant in a single application patch test (number of volunteers not given) at concentrations of 1% and 10% At 0 1% there was no irritation

Dermal Sensitization

FDA (1976) reported that the contact sensitization potentials of 1% Butyl Methacrylate, 1% Hydroxypropyl Methacrylate, and 1% Isobutyl Methacrylate in petrolatum were determined in 12 volunteers A standard Draize test was used in which the Methacrylate test monomer was applied 10 times to the same site three times weekly, every 48 h during the week and 72 h on the weekend The site was occluded and a nontreatment period followed by a 72 h final elicitation at a new site

One of 12, 0 of 11, 0 of 12, and 0 of 11 patients reacted positively to Butyl Methacrylate, HEMA, Hydroxypropyl Methacrylate, and Isobutyl Methacrylate, respectively (FDA 1976)

In its workplace exposure guide, the American Industrial Hygiene Association (1981) stated that Trimethylolpropane Trimethacrylate has been shown to be a human sensitizer in patch tests No details were available

In a review article, Geurtsen (2000) stated that Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate were considered to be capable of causing hypersensitivity/allergy in humans No details were available

Reproductive and Developmental Toxicity

Jelovsek et al (1989), predicated on an Isobutyl Methacrylate developmental toxicity study in rats that produced positive results, used logistic regression and discriminant analysis to predict its effect in humans The authors concluded that Isobutyl Methacrylate was not considered a developmental toxicant in humans

Case Reports

A 50-year-old woman used artificial nails for 1 5 years and for several months prior to seeking treatment, a paronychial and eyelid dermatitis occurred two days after each new application of artificial nails Patch test results using 5% Butyl Methacrylate in petrolatum and 1% Butyl Methacrylate in ethyl alcohol demonstrated +2 reactions (erythema, papules, and vesicles) at 48 and 96 hours Methyl methacrylate and ethyl methacrylate at 5% in petrolatum or 1% in ethyl alcohol caused +2 reactions at 48 and 96 hours The eyelid and paronychial dermatitis resolved with discontinuation of artificial nail usage (Marks et al 1979)

A 28-year-old black male had dermatitis of his hands, nausea and diarrhea associated with exposure to an 80% HEMA solution and subsequent positive patch tests to HEMA Cross reactivity patch tests that contained 5% Butyl Methacrylate or 5% Isobutyl Methacrylate in petrolatum were negative (Mathias et al 1979)

Two patients patch tested with 1% Butyl Methacrylate or 1% Isobutyl Methacrylate monomer in petrolatum had markedly positive reactions They also had positive reactions to other acrylic monomers, with the exception of methacrylic acid (Fisher 1980)

A 17-year-old female working in the manufacture and application of artificial nails had exudative, itchy lesions on or around

the nails of her fingers She had a previous history of metal allergy She was patch tested with a standard series of plastics and acrylates She had a +1 reaction at 48 hours and a +2 reaction at 96 hours to 2% HEMA in petrolatum She also reacted positively to methyl and ethyl methacrylate (Condé-Salazar et al 1986)

A case of occupational allergic contact dermatitis was reported in a 20-year-old dental assistant After 3 months of working with dental resins, she developed a hand eczema on the fingers of the right hand which spread to the left hand and eyelids She had been handling materials without gloves She was given the dental screening series patch test She had a +2 reaction to Isopropylidenediphenyl Bisglycidyl Methacrylate (2%) and had a positive reaction to concentrations as low as 0 0002% Twenty control people were tested and none had a positive reaction (Kanerva et al 1986)

Seven patients (6 dental nurses and a dentist) had been occupationally sensitized to dental resin products Five patients were patch tested using Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Isopropylidene-diphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate All materials tested were at 2% concentration in petrolatum Two patients reacted to Ethylene Glycol Dimethacrylate with reactions ranging from +2 to +3 Three patients reacted to HEMA with reaction ranging from +1 to +3 Three patients reacted to Hydroxypropyl Methacrylate with reactions ranging from +2 to +3 Four patients reacted to Isopropylidenediphenyl Bisglycidyl Methacrylate with reactions varying from +2 to +4 Three patients reacted to Triethylene Glycol Dimethacrylate with reactions ranging from +2 to +4 Lastly, no patients reacted to Di-HEMA Trimethylhexyl Dicarbamate (Kanerva et al 1989)

Freeman et al (1995) reported 4 case reports involving contact allergies to acrylates in acrylic nails Four women, 31 to 53 years old had adverse contact reactions from artificial nails The clinical details included fingertip dermatitis in 3 patients, nail fold dermatitis in 3 patients, nail dystrophy, paresthesia, ulnar border hand dermatitis, and eyelid and neck dermatitis each present in one patient All four patients were patch tested using 2% Ethylene Glycol Dimethacrylate, 2% Isopropylidenediphenyl Bisglycidyl Methacrylate, and 2% PEG-4 Dimethacrylate Two of the patients had strong positive reactions to Ethylene Glycol Dimethacrylate and a third had a mild positive reaction None of the patients had reactions to the other two Methacrylates

A 24-year-old hairdresser and manicurist had nearly constant hand eczema for 6 years She had been using various acrylated nail glues over this time period Her current nail glue was 99 95% ethyl cyanoacrylate and 0 005% undefined acrylic contaminants She was patch tested with the acrylates series and her nail glue (10% in petrolatum) She reacted to Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, and her nail glue (as well as nickel, para-phenylenediamine, glyceryl thioglycolate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate) Fifteen controls were also tested with the nail glue and all were negative except an elderly woman who had a weak irritant reaction The researchers could not rule out the possibility that the hairdresser's reactions may be due to the contaminants in the ethyl cyanoacrylate nail glue (Jacobs and Rycroft 1995)

A 38-year-old non-atopic woman had developed allergic contact dermatitis from textile dyes but had been without symptoms She had been working installing car rear-view mirrors on a production line for the past 6 years For 2 years she had been experiencing a dry and fissured dermatitis on both hands The dermatitis spread to her arms, chest, neck, and face and she developed rhinitis and tenderness of the mucous membranes of the nose She also had paresthesia of the fingertips but her dermatitis cleared while she was away from work She was patch tested with the expoxy and methacrylate series Penloc glue was used to adhere the rear-view mirror to the windshield, it was found to contain by GC-MS, Ethylene Glycol Dimethacrylate (0 4%), HEMA (24 6%), and Tetrahydrofurfuryl Methacrylate (% not stated) The major component was isobornyl acrylate (61 9%) The patient had +3 reactions to the Penloc glue at concentrations of 0 2, 0 6, and 2% The patient was patch tested using Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate at a concentration of 2% The patient had no reaction to Isopropylidenediphenyl Bisglycidyl Methacrylate and Di-HEMA Trimethylhexyl Dicarbamate However, all other Methacrylates mentioned above resulted in +2 to +3 reactions (Kanerva et al 1995)

A 47-year-old female cosmetician who had severe atopic dermatitis in her youth, but had been without symptoms for 20 years, developed dermatitis on her right thumb that subsequently spread to both hands and face after she started to work with photobonded nails and chemically cured nail cosmetics Two patch testing sessions were performed on the back (48-hour occlusion) using 2% Butyl Methacrylate, 2% Ethylene Glycol Dimethacrylate, 2% HEMA, 2% Hydroxypropyl Methacrylate, 2% Tetrahydrofurfuryl Methacrylate, 2% Triethylene Glycol Dimethacrylate, and 2% Di-HEMA Trimethylhexyl Dicarbamate Readings were performed on days two, three and four HEMA, Hydroxypropyl Methacrylate, Ethylene Glycol Dimethacrylate, and Triethylene Glycol Dimethacrylate all resulted in a +2 reading in this series of patch testing There was a +1 reaction to Butyl Methacrylate and no reactions to Tetrahydrofurfuryl Methacrylate and Di-HEMA Trimethylhexyl Dicarbamate Additionally, the patient had an allergic patch test result to her own nail strengthener preparation that contained 2 2% Butyl Methacrylate and her own monomer liquid for sculptured nails with 5% Triethylene Glycol Dimethacrylate (Kanerva et al 1996)

Case reports of female repair technicians of facsimile machines, in which Butyl Methacrylate fumes were either not confirmed or confirmed up to 0 60 mg/m^3, reported symptoms of eye and upper respiratory tract irritation, chest tightness, congestion, dry cough, dyspnea, lung crackles and elevated

immunoglobulin levels All three cases improved upon removal of the repair technician from duties associated with facsimile machines The authors stated that these descriptions suggest a link between Butyl Methacrylate and these abnormal clinical findings (Raymond 1996)

A 30-year-old male dentist had been using HEMA as a dentin primer for 3 years One day, he had an allergic reaction which included redness, pruritus, sclerosis, and edema on his fingertips whenever he handled a HEMA solution A patch test was conducted using HEMA at 35% and 100% One volunteer with no history of sensitivity to dentin primers was used as a negative control HEMA caused serious erythemic papules at both 35% and 100% in the dentist There was no reaction to water or vaseline (Katusuno et al 1996)

Patch Testing Results

Kanerva et al (1988) patch tested 22 patients using 1% Hydroxypropyl Methacrylate Out of 22 patients exposed to acrylates, 3 patients tested positive to Hydroxypropyl Methacrylate

Kanerva et al (1988) used a commercial meth(acrylate) series containing 28 Methacrylate and Acrylates on 24 patients Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate were part of the test series All Methacrylates mentioned above were tested at a concentration of 2% (in petrolatum) Out of 24 patients exposed to acrylates, only 2 patients tested positive to Methacrylates A dentist tested positive to Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, and Triethylene Glycol Dimethacrylate The second patient was a dental assistant that tested positive to HEMA, Hydroxypropyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Triethylene Glycol Dimethacrylate

Tosti et al (1993) patch tested 11 patients with occupational allergic contact dermatitis from acrylate compounds Five patients had a positive reaction to Ethylene Glycol Dimethacrylate, one patient had a reaction to Triethylene Glycol Dimethacrylate, one patient had a reaction to Ethylene Glycol Dimethacrylate, and another had a reaction to Ethoxyethyl Methacrylate

Tucker and Beck (1999) reported that, over a 15-year period, 440 patients with a history of exposure to acrylates and methacrylates were patch tested with the Chemotechnique® series Patch testing was done on the back and scored after 2 days of occlusion and again on day 4 Patients patch tested with 2% Ethylene Glycol Dimethacrylate (28/345 patients), 2% Isopropylidenediphenyl Bisglycidyl Methacrylate (5/281 patients), 2% HEMA (29/337 patients), 2% Hydroxypropyl Methacrylate (26/330 patients), 2% Triethylene Glycol Dimethacrylate (21/343 patients), 2% Tetrahydrofurfuryl Methacrylate (5/147), and 2% Di-HEMA Trimethylhexyl Dicarbamate (2/268 patients) elicited a positive response Sixteen of the patients were sensitized via artificial nails, half of those patients had facial and/or eyelid involvement, either alone or in combination with nail finger changes Typically, fingertip and/or periungual dermatitis, with or without onycholysis developed in these patients In severe cases, painful paraesthesiae and Raynaud's phenomenon may develop

A 49-year-old dental assistant had a long history of recurrent eczema on her hands, forearms, upper eyelids and perioral area She had erythematous, scaly, and fissured skin on her hands and forearms Her face was red and scaly, and she had swollen eyelids Symptoms would disappear when she was absent from work She was patch tested with 2% Ethylene Glycol Dimethacrylate and had a +1 reaction at 2 days and a +2 reaction at 3 days The researchers suspected she had airborne contact dermatitis since there was symmetrical involvement of the upper eyelids and perioral area This was confirmed when her symptoms improved after avoiding acrylic resin exposure (Tosti et al 1991)

Three patients (two dental laboratory workers and one hearing aid laboratory worker) had allergic contact dermatitis from methacrylates Symptoms disappeared when they avoided uncured methacrylates (light and chemically curable) in the workplace Two of the patients also had conjunctivitis These two patients (dental assistant, hearing aid worker) were patch tested and had positive reactions to Ethylene Glycol Dimethacrylate (+3, +2), HEMA (+3, +2), Hydroxypropyl Methacrylate (+3, +2), and Triethylene Glycol Dimethacrylate (+3, +1) The researchers concluded that conjunctivitis may be caused by type IV allergy, although type I allergy (even though prick tests were negative), other hypersensitivity mechanisms, or irritation cannot be excluded (Estlander et al 1996)

Five women with photobonded acrylic nails had pruritic and paronychial and subonychial dermatitis for several months and 2 patients had dermatitis of the lower lids and cheeks The symptoms developed 6 months to 3 years after the first applications of artificial nails Monthly renewal of the nails caused a strong exacerbation of the dermatitis within 24 hours Patients were patch tested with Ethylene Glycol Dimethacrylate (2 0%), HEMA (0 02%, 0 2, and 0 6%), Hydroxypropyl Methacrylate (0 02, 0 2, and 0 6%), Isopropylidenediphenyl Bisglycidyl Methacrylate (2 0%), Triethylene Glycol Dimethacrylate (2 0%), and Di-HEMA Trimethylhexyl Dicarbamate (0 2 and 0 6%) Five of five patients reacted positively to Ethylene Glycol Dimethacrylate (+2 and +3 reactions) Two patients (+1 reactions), 4 patients (+2 reactions), and 5 patients (+3 reactions) reacted to 0 02%, 0 2%, and 0 6% HEMA, respectively One patient (+2 reaction), 5 patients (+1 and +2 reactions), and 5 patients (+1, +2, and +3 reactions) reacted positively to 0 02%, 0 2%, and 0 6% Hydroxypropyl Methacrylate, respectively All patients had no reaction to Isopropylidene-diphenyl Bisglycidyl Methacrylate Five of 5 patients reacted positively (1 patient was questionably positive) to Triethylene Glycol Dimethacrylate One patient and two patients reacted positively to 0 2% (+1 reaction) and 0 6% (+1 and +2 reactions) Di-HEMA Trimethylhexyl Dicarbamate (Hemmer et al 1996)

Consumer Adverse Reaction Reports

Consumers reported a number of injuries as a result of exposure to nail adhesive for use with artificial nails From 1995 to 1997, reported individual reactions were dermatitis of the eye in one person and dermatitis of the leg and hand in another person From 1987 to 1993, reported individual reactions were dermatitis of the face and lower trunk (to include the hips and external genital area) in one patient, pain of the face in another patient, and other injury complaints were noted to various parts of the body It can be assumed that these injuries occurred as a result of exposure to methacrylates in a system with ethyl methacrylate as the primary monomer since there are a limited number of other methacrylates used in the nail enhancement industry The ethyl methacrylate system may contain up to 10% of other methacrylates (ABA and NMC 2001a and ABA 2001b)

Occupational Exposure

Cautilli and Hozack (1994) performed an in vitro analysis, which encompassed a 26 minute sampling time of cement removal fumes from a section of bovine femur and detected peak levels of Butyl Methacrylate Collecting pumps, placed adjacent to the working area, enabled collection of maximum sample concentrations A quantitative analysis was not performed in this phase

Another phase performed a quantitative analysis of fumes generated by ultrasonic removal of cement during revision hip surgery Samples were collected by industrial hygienists from the National Institute for Occupational Safety and Health (NIOSH) over two consecutive days during two hip surgeries Butyl Methacrylate was not present at detectable levels during this second phase (Cautilli and Hozack 1994)

In its workplace exposure guide, the American Industrial Hygiene Association (1981) stated that Trimethylolpropane Trimethacrylate has a recommended workplace environmental exposure level (WEEL) of 1 mg/m^3 (8-hour time weighted average for a 40-hour week)

SUMMARY

This report reviews the safety of a large number of monomethacrylates, dimethacrylates, and trimethacrylates that are known to be used in nail enhancement products Only Tetrahydrofurfuryl Methacrylate was reported to the FDA to be used in nail extender products

The polymerization rates of Butyl Methacrylate, t-Butyl Methacrylate, Cyclohexyl Methacrylate, Ethoxyethyl Methacrylate, 2-Ethoxy Ethoxy Ethyl Methacrylate, Ethylene Glycol Dimethacrylate, Hexyl Methacrylate, HEMA, Di-HEMA Trimethylhexyl Dicarbamate, Hydroxyethylmethacrylate Acetoacetate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate, Isobutyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate; Methoxydiglycol Methacrylate; PEG-4 Dimethacrylate, Pyromellitic Glycidyl Dimethacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, Trimethylolpropane Trimethacrylate, and Urethane Methacrylate are within the same range as ethyl methacrylate since most are used in a system where ethyl methacrylate is the primary monomer Ethyl methacrylate represents over 90% of the monomer used in nail enhancing products Thermal study data showed polymerization of 50% of the ethyl methacrylate monomer within 5 minutes

None of the Methacrylate monomers tested were shown to have any endocrine disrupting activity

The reported oral LD_{50} values of Methacrylates were >6 3 g/kg in rabbits, >2000 mg/kg to 25,530 mg/kg in rats, and 16 00 ml/kg to >3200 mg/kg in mice The reported ip LD_{50} values of Methacrylates were 1 110 ml/kg to 3900 mg/kg in rats and 0 497 ml/kg to 2889 mg/kg in mice The reported dermal LD_{50} values of Methacrylates were >10 ml/kg to >3000 mg/kg in rabbits and >20 ml/kg in guinea pigs The reported inhalation LC_{50} values of Methacrylates were 29 mg/l to 28,469 mg/m^3 in rats and >17 01 mg/l to 29 74 mg/l in mice An intravenous dose of 1 24 ml of 3344 × 10^{-6} M Lauryl Methacrylate was rapidly fatal to dogs

In a 28-day inhalation study on rats, Butyl Methacrylate caused upper airway irritation, the NOEL was 1801 mg/m^3 In a 28-day oral toxicity study on rats, t-Butyl Methacrylate had a NOEL of 20 mg/kg/day A 45-day oral toxicity study on rats reported Butyl Methacrylate had a NOEL of 30 mg/kg/day in males and 300 mg/kg/day in females A 50-day oral toxicity study on rats reported HEMA had a NOEL of <30 mg/kg/day in males and 30 mg/kg/day in females Rats were exposed to a saturated solution of Lauryl Methacrylate for twenty, 6-hour exposure periods No toxic signs were observed and necropsy was normal

In a subchronic oral toxicity study, Beagle dogs were dosed with 0 2 to 2 0 g/kg/day of C12 to C18 Methacrylate monomers for 13 weeks Hematology, biochemistry, and urine analyses were comparable between controls and test groups Only the highest dose group had effects such as weight loss, emesis, diarrhea, mucoid feces, or salivation observed In another study, rats were fed the C12 to C18 Methacrylate monomers at concentrations between 5000 to 50,000 ppm for 13 weeks Body weights, growth, and food consumption were significantly decreased in the highest dose group Hematological, biochemical, and urine analyses were comparable between test groups and controls Kidney and liver weights were increased in the high dose group as compared to controls Microscopic examination of tissues did not reveal any compound-related lesions

There were few chronic toxicity studies on Methacrylates found in the published literature Therefore, data on methyl methacrylate was used in the report A chronic toxicity study in rats and hamsters exposed to methyl methacrylate at up to 400 ppm (6 h/day, 5 days/week) did not cause tumors in hamsters or rats

Butyl Methacrylate (0 1 M) and Isobutyl Methacrylate (0 1 M) are mildly irritating to the rabbit eye HEMA is corrosive

when instilled in the rabbit eye, while PEG-4 Dimethacrylate and Trimethylolpropane Trimethacrylate are minimally irritating

The dermal irritation caused by Methacrylates has been documented in guinea pigs and rabbits Undiluted or high concentration Methacrylates are typically moderate irritants that can result in erythema and/or edema Lower concentration Methacrylates are typically mild or slightly irritating The Methacrylates PII ranged from 0 08 to 5 6, depending on which Methacrylate was tested and whether the site was abraded or intact skin

The sensitizing potential of the Methacrylates has been a major concern regarding their safety in artificial nail systems Results from several studies showed that HEMA , Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, and Trimethylolpropane Trimethacrylate are strong sensitizers in guinea pigs Butyl Methacrylate, Cyclohexyl Methacrylate, Hexyl Methacrylate, and Urethane Methacrylate are moderate sensitizers in guinea pigs Hydroxypropyl Methacrylate is a weak sensitizer in guinea pigs PEG-4 Dimethacrylate and Triethylene Glycol Dimethacrylate are not considered sensitizers in guinea pigs Ethylene Glycol Dimethacrylate was not a sensitizer in a study using guinea pigs, but was a strong sensitizer in another Some test data has shown there is cross-reactivity between various Methacrylates

The effects of Butyl Methacrylate, HEMA, Hydroxypropyl Methacrylate, and Trimethylolpropane Trimethacrylate on the reproductive parameters and/or the developmental parameters of the offspring of rats were evaluated Rats were dosed for 9 to 49 days The Butyl Methacrylate NOEL was 1000 mg/kg/day in parental males and 300 mg/kg/day in parental females, there were no effects on any reproductive parameters in males or developmental parameters in offspring The HEMA NOEL was 1000 mg/kg/day (maximum dose tested) in both sexes and in the developing pups The Hydroxypropyl Methacrylate NOEL was 1000 mg/kg/day (maximum dose tested) in both sexes and in the developing pups Trimethylolpropane Trimethacrylate caused fetotoxic effects such as increased resorptions (mean incidence 25 4%), decreased fetal viability (mean survival 74 6%), decreased fetal weights, and decreased fetal lengths at a dose of 2500 mg/kg/day

The threshold concentration for embryotoxic and teratogenic effects in rats exposed to Butyl Methacrylate via inhalation was 0 1 mg/m^3

Butyl Methacrylate, t-Butyl Methacrylate, HEMA, Hexyl Methacrylate, Hydroxypropyl Methacrylate, Isobutyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, PEG-4 Dimethacrylate, Triethylene Glycol Dimethacrylate, Trimethylolpropane Trimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate were not mutagenic in multiple Ames tests (using *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, and/or TA1538) both with and without metabolic activation However, Butyl Methacrylate, Ethylene Glycol Dimethacrylate in one test using *Salmonella typhimurium* strain TA1538 with metabolic activation was mutagenic

Ethyl methacrylate was tested in the L5178Y mouse lymphoma cell assay L5178Y/TK$^{+/-}$ cells were treated with 900-2100 μg/ml of ethyl methacrylate without exogenous activation for 4 h and incubation lasted 9 to 11 days Control cells were treated with the solvent (dimethylsulfoxide) alone Cytotoxicity was observed at concentrations greater than 1000 μg/ml and toxicity plateaued at concentrations above 1500 μg/ml, where survival fluctuated from 2 to 37% A weak positive response was observed in cultures with 10–20% survival (1450, 1500, 1550, and 1626 μg/ml) The greatest number of aberrations occurred at a concentration of 1626 μg/ml (16% survival), ethyl methacrylate induced 83 mutants/10^6 survivors and 11 aberrations/200 cells Some of the cultures with less than 10% survival had mutation frequencies three times greater than background The colony size distribution was difficult to determine, however, the researchers noted that cultures with mutation frequencies of 200 mutants/10^6 survivors (less than 10% survival) had an induction of primarily small colonies The researchers suggested that the genotoxicity of Ethyl Methacrylate was likely due to a clastogenic mechanism

Ethylene Glycol Dimethacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Trimethylol propane Trimethacrylate were weakly positive in the L5178Y mouse lymphoma cell assay with metabolic activation PEG-4 Dimethacrylate and Trimethylolpropane Trimethacrylate were weakly positive in the L5178Y mouse lymphoma cell assay without metabolic activation

Chronic dermal exposure of mice to PEG-4 Dimethacrylate (25 mg, 2× weekly for 80 weeks) or Trimethylolpropane Trimethacrylate (25 mg, 2× weekly for 80 weeks) did not result in increased incidence of skin or visceral tumors The carcinogenicity of Triethylene Glycol Dimethacrylate (5, 25, or 50%) was assessed in a skin painting study (50 μl for 5 days/week for 78 weeks) using mice The NOEL was 5% Triethylene Glycol Dimethacrylate, but Triethylene Glycol Dimethacrylate did not induce carcinogenicity at any dose level tested

Due to the absence of carcinogenicity data on Methacrylates, data on methyl methacrylate has been considered In 1994, the IARC working group concluded that there is inadequate evidence in humans for the carcinogenicity of methyl methacrylate and there is evidence suggesting a lack of carcinogenicity in experimental animals Methyl methacrylate is not classifiable as to its carcinogenicity to humans

A standard Draize test to assess contact sensitization potential of 1% Butyl Methacrylate caused one positive reaction in 12 volunteers Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate were considered to be capable of causing hypersensitivity/allergy in humans

Patients previously exposed to Methacrylate elicited positive reactions to patch tests with concentrations as low as 1% Butyl Methacrylate, 2% Ethylene Glycol Dimethacrylate, 0 02% HEMA, 0 02% Hydroxypropyl Methacrylate, 1%

Isobutyl Methacrylate, 0 0002% Isopropylidenediphenyl Bisglycidyl Methacrylate, 2% Tetrahydrofurfuryl Methacrylate, 2% Triethylene Glycol Dimethacrylate, 0 02% Di-HEMA Trimethylhexyl Dicarbamate Most of these patients were employed in dentistry or were artificial nail technicians

DISCUSSION

The Expert Panel was concerned about the strong sensitization and cross- or co-reactivity potential of the Methacrylates reviewed in this report Animal studies indicated that most Methacrylates are moderate to strong sensitizers However, the Panel received data that showed the rates of polymerization of these Methacrylates were similar to that of ethyl methacrylate (the primary monomer used) and there would be little monomer available for exposure to the skin Genotoxicity data indicated that some Methacrylates could produce chromosome damage in mammalian cells In consideration of all these data, the Panel decided that these Methacrylates should be restricted to the nail and must not be in contact with the skin

There was some concern that the exotherms created from the monomers rapid polymerization could damage the nail Test data showed 50% polymerization in 3 to 4 minutes at 5% concentrations However, the products do not produce significant levels of exotherms and clients rarely notice a slight warming of the nail during application

CONCLUSION

Based on the available data, the CIR Expert Panel concluded that Butyl Methacrylate, t-Butyl Methacrylate, Cyclohexyl Methacrylate; Ethoxyethyl Methacrylate; 2-Ethoxy Ethoxy Ethyl Methacrylate, Ethylene Glycol Dimethacrylate, Hexyl Methacrylate, HEMA, Di-HEMA Trimethylhexyl Dicarbamate, Hydroxyethylmethacrylate Acetoacetate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate; Isobutyl Methacrylate; Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, Methoxydiglycol Methacrylate, PEG-4 Dimethacrylate, Pyromellitic Glycidyl Dimethacrylate;Tetrahydrofurfuryl Methacrylate; Triethylene Glycol Dimethacrylate, Trimethylol propane Trimethacrylate, and Urethane Methacrylate are safe as used in nail enhancement products when skin contact is avoided Products containing these ingredients should be accompanied with directions to avoid skin contact, because of the sensitizing potential of Methacrylates

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