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.
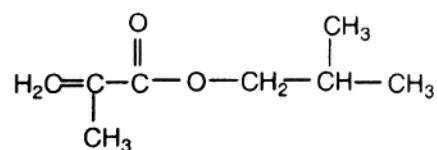
In the experiment, the Radical[TM] artificial nail monomer/polymer system was modified by adding 5% ethyl methacrylate
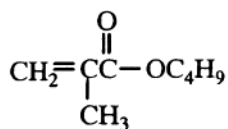
Butyl Methacrylate
Wenninger et al. 2002
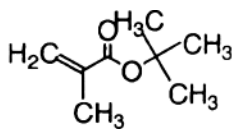
t-Butyl Methacrylate
ChemIDplus 2001

Isobutyl Methacrylate
Zeiger et al. 1987
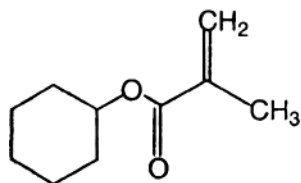
Cyclohexyl Methacrylate
ChemIDplus 2001
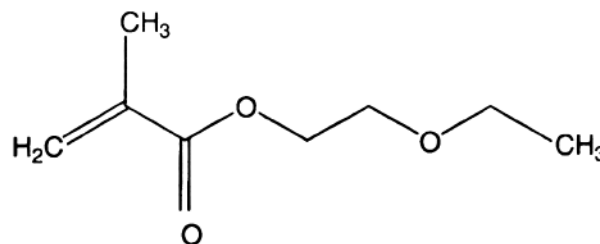
Ethoxyethyl Methacrylate
Jackson 2001
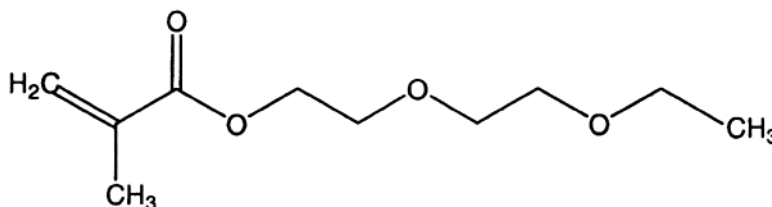
2-Ethoxy Ethoxy Ethyl Methacrylate
Jackson 2001
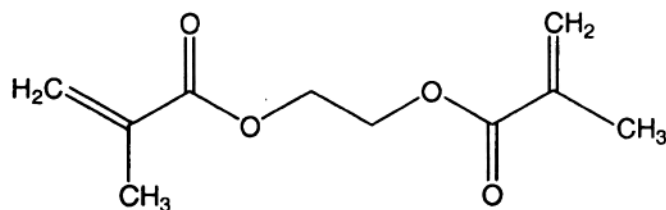
Ethylene Glycol Dimethacrylate
ChemIDplus 2001
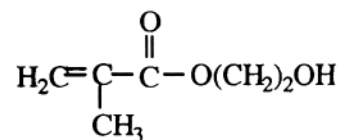
HEMA
Wenninger et al. 2002
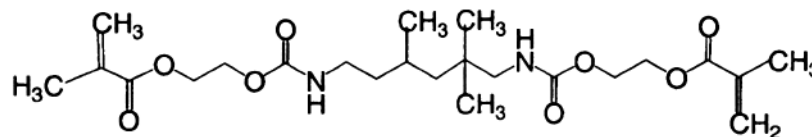
DI-HEMA Trimethylhexyl Dicarbamate- the 2,2,4 Isomer
Jackson 2001

FIGURE 1
Structure of Methacrylate Esters
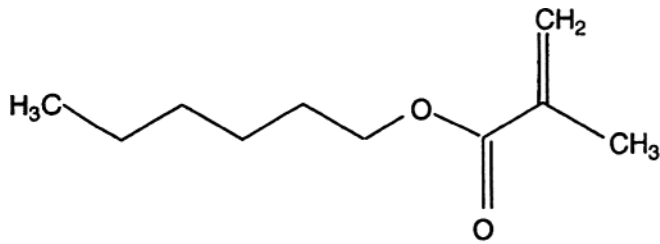
Hexyl Methacrylate
ChemIDplus 2001
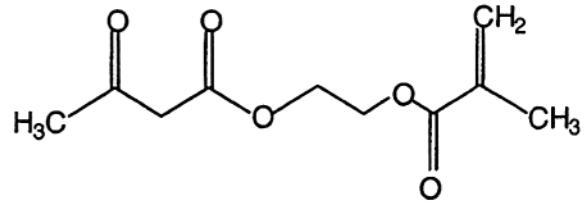
Hydroxyethylmethacrylate Acetoacetate
ChemIDplus 2001
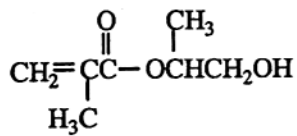
Hydroxypropyl Methacrylate
Wenninger et al. 2002
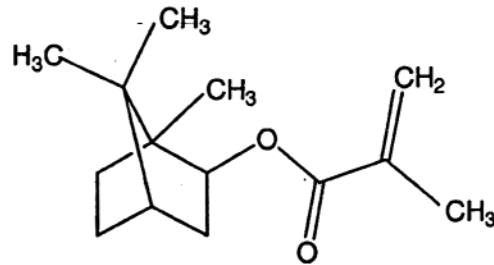
Isobornyl Methacrylate
ChemIDplus 2001
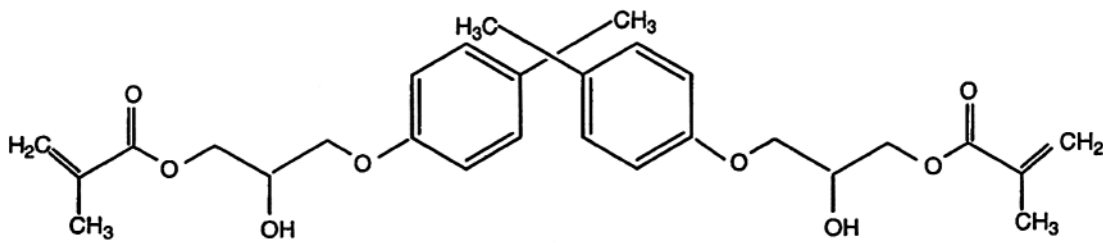
Isopropylidenediphenyl Bisglycidyl Methacrylate
ChemIDplus 2001
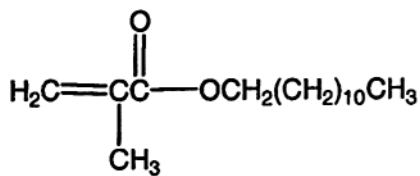
Lauryl Methacrylate
Wenninger et al. 2002
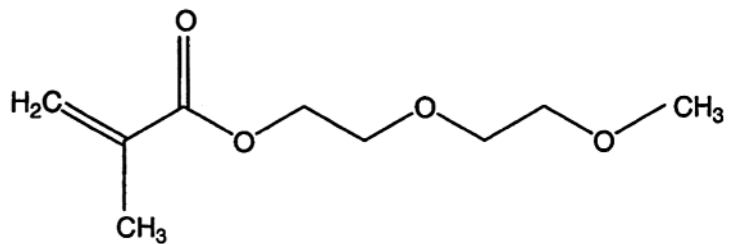
Methoxydiglycol Methacrylate
Jackson 2001

FIGURE 1
(Continued)
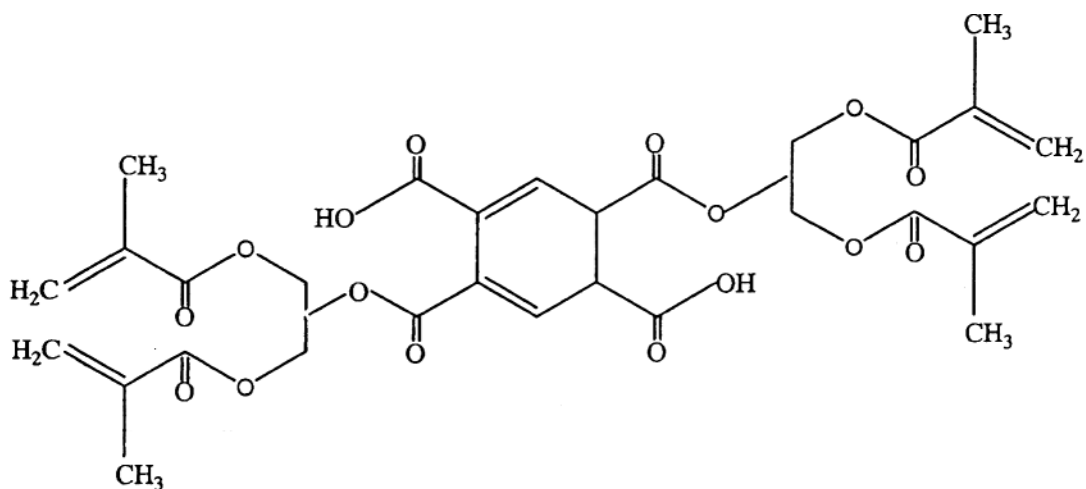
Pyromellitic Glycidyl Dimethacrylate
Jackson 2001

PEG-4 Dimethacrylate
Wenninger et al. 2002
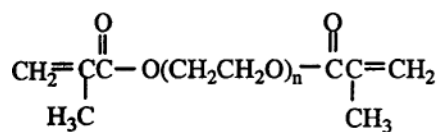
Tetrahydrofurfuryl Methacrylate
ChemIDplus 2001
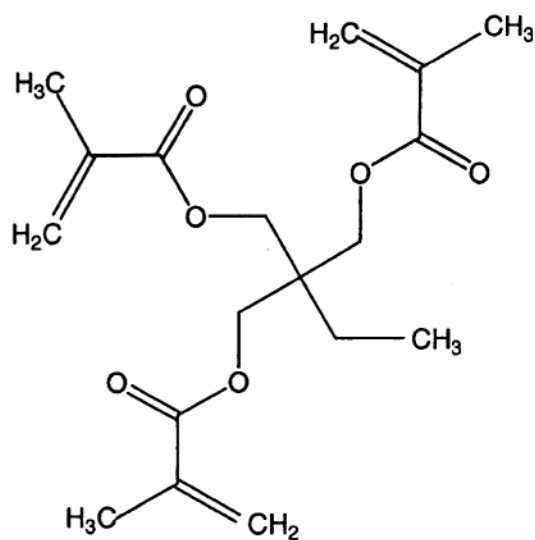
Trimethylolpropane Trimethacrylate
ChemIDplus 2001
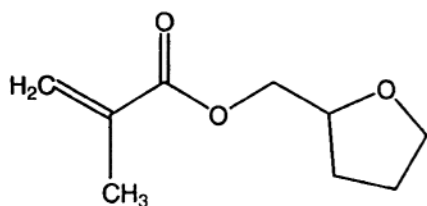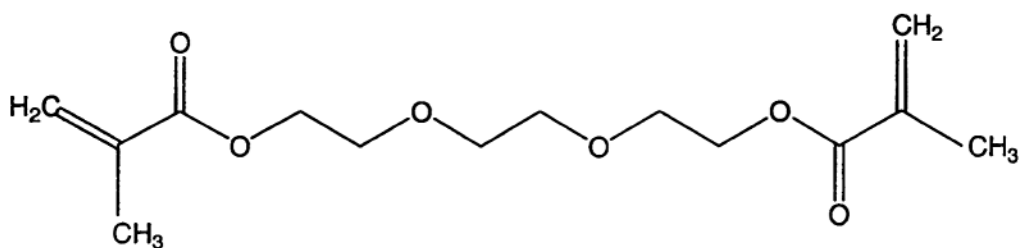
Triethylene Glycol Dimethacrylate
ChemIDplus 2001

FIGURE 1
(Continued)

Urethane Methacrylate (where R=$C_{10}H_{20}$)
Bjorkner 1984b
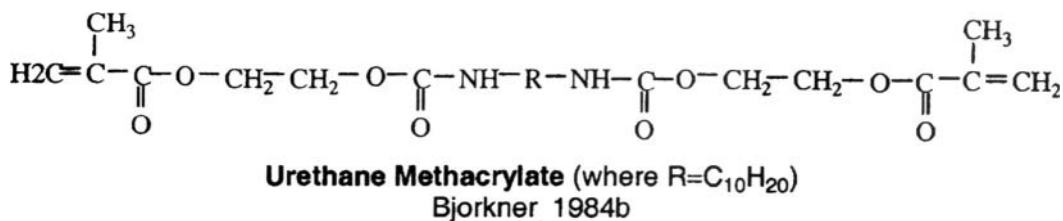
FIGURE 1
(Continued).

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[TM] 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 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; Wenninger et al. 2002; ChemIDplus 2001 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 2-((2-Methyl-1-oxoallyl)oxy)ethyl acetoacetate; Butanoic acid, 3-oxo, 2-((2-methyl-1-oxo-2-propenyl)oxy)ethyl ester	ABA and NMC 2001a 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 Propylene Glycol Monomethacrylate Methacrylic Acid, Monoester with 1,2-Propanediol; 1,2-Propanediol, 2-Methyl-, Monomethacrylate; 2-Propenoic Acid, 2-Methyl-, 2-Hydroxymethylethyl Ester	HSDB 2001; Wenninger et al. 2002; ChemIDplus 2001 Wenninger et al. 2002; ChemIDplus 2001 HSDB 2001

Name	CAS No.	Definition	Synonyms	References
Isobornyl Methacrylate	7534-94-3	the ester of isobornyl alcohol plus methacrylic acid	Methacrylic Acid, Isobornyl Ester; 2-Propenoic Acid, 2-Methyl-,1.7.7-Trimethylbicyclo(2.2.1)HEPT-2-YL Ester, Exo-	ABA and NMC 2001a	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	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	ChemIDplus 2001
			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	Bis-GMA;Bisphenol A-glycidyl methacrylate; 2-Propenoic acid, 2-methyl-, (1-methylethylidene)bis(4,1-phenyleneoxy(2-hydroxy-3,1-propanediyl))ester	ABA and NMC 2001a; ChemIDplus 2001	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	Dodecyl Methacrylate; Dodecyl 2-Methyl-2-Propenoate	Wenninger et al. 2002	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

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

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

Property	Descripton	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	Descripton	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	Descripton	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^{TM}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^{TM}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 tetrazorium 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 $66.6 \pm 2.4\%$ cell death. In comparison, 0.10% Ethoxyethyl Methacrylate caused $6.6 \pm 1.5\%$ 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.

Greim 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 postexposure 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. Greim 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 $LD_{0.02}$, $LD_{0.2}$, and the $LD_{2.0}$, 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.

Hematologic parameters were not very sensitive to HEMA at the doses tested. There were no significant differences in the means of corpuscule counts, in the means of hemoglobin and fibrinogen concentrations and in the mean coagulation times between HEMA and the controls. There were no significant changes in sodium and total calcium concentrations, however there were elevated concentrations of potassium at the end of the experiment. Chloride and creatine concentrations were decreased as well (Schneiderka et al. 1996).

Short-Term Lauryl Methacrylate Toxicity
Inhalation
Gage (1970) used unspecified concentrations of Lauryl Methacrylate to produce acute effects in Alderley Park rats after short exposures. Thereafter, the exposure period was extended and the concentration decreased until the animals survived 6 h exposures, 5 days/week for four weeks. Urine was collected overnight after the last day of exposure and on the following day the rats were killed. The experiments were performed until a concentration was reached that produced no toxic effects. At two month intervals, control rats were maintained in the chamber consistent with the exposure period. Rats (2/sex) were exposed to a saturated solution of Lauryl Methacrylate for twenty 6 h exposure periods (exact dose not available). No toxic signs were observed and necropsy was normal.

Short-Term Trimethylolpropane Trimethacrylate Toxicity
Oral
Hazelton Laboratories (1982) evaluated Trimethylolpropane Trimethacrylate for tolerance in pregnant rats to establish dose levels for a teratology study. Pregnant rats (6 per dose level) were given 500, 2500, or 5000 mg/kg/day of Trimethylolpropane Trimethacrylate by intubation from days 6 to 15 of gestation. Six rats received corn oil only and served as the control group. Rats were evaluated for mortality, clinical signs, body weights, food consumption, water consumption, gross pathology, and ovarian and uterine weights.

Trimethylolpropane Trimethacrylate-related effects were observed. Five of six rats died in the 5000 mg/kg/day group, but no rats in any other dose groups died. The following clinical observations were noted in the high-dose group: bloody crust (5 animals), wheezing (1 animal), labored respiration (1 animal), urine stains (6 animals), rough haircoat (2 animals), stains on fur (1 animal), soft feces (2 animals), hunched (2 animals), thin (6 animals), and depressed (1 animal). The mean weights and weight changes were decreased in high-dose rats from days 9 to 15. Mean food consumption was increased in high and low-dose rats from days 6 to 14, but these findings were not considered significant.

All six rats at 5000 mg/kg/day Trimethylolpropane Trimethacrylate had gross lesions in the lungs (dark red areas), liver (white or tan areas), kidneys (pelvis dilated), and stomach (smooth, thin areas). The mean ovarian and uterine weights were comparable between the control group and the Trimethylolpropane Trimethacrylate-treated groups data (Hazelton Laboratories 1982).

Dermal
In a workplace exposure guide, the American Industrial Hygiene Association (1981) stated that rabbits (number not given) had 300 mg/kg undiluted Trimethylolpropane Trimethacrylate applied to the skin 5 days per week for 2 weeks. Skin corrosion was noted but no organ effects were noted. No other details were available.

Subchronic Lauryl Methacrylate Toxicity
Oral
Rohm and Haas Co. (1966b) conducted a study in which adult purebred Beagles (3/sex/group) were dosed orally by capsule daily for 13 weeks with 0.2, 0.6, or 2.0 g/kg/day of a test material that contained C12 to C18 Methacrylate monomers. A control group was also included. Hematology, biochemistry and urine analyses were performed initially and at one and three months. Terminal sacrifice occurred at 13 weeks.

Only at the highest dose were compound effects observed in the form of emesis, diarrhea, mucoid feces or salivation. Some weight loss was also observed in this group. Observations and body weights were normal for all other dose groups and the control. Hematology, biochemistry and urine analyses were comparable between the control and treated groups. On gross examination there were no compound-related tissue alterations among test groups. No significant organ weight changes were observed, although mean liver/body weight ratios for male and female high dose dogs and mean kidney/body weight ratios for three female high dose dogs were slightly increased compared to controls.

Microscopic examination of tissue sections from control and treated dogs revealed compound-related cytologic alterations in the livers of two males and two females in the high dose group. Slight to moderate paleness and vacuolation of the cytoplasm and pigmentation of small yellowish granules were observed in some of the hepatic cells. Necrosis was not apparent and the changes appeared reversible (Rohm and Haas Co. 1966b).

Rohm and Haas Co. (1966c) fed albino rats a diet containing C12-C18 Methacrylate monomer (10/sex/group) at concentrations of 5000, 15,000 and 50,000 ppm for thirteen weeks. Control animals were fed a basal diet. Hematology, clinical chemistry and urine analyses were performed on five animals of each sex from each group at one and three months. The study was terminated at 13 weeks.

The appearance and behavior of test rats was comparable to controls. Growth and food consumption for the high dose females and males were significantly lower compared to the controls, while that of the low and mid-dose animals were comparable to the controls. No deaths occurred in any of the groups. Hematological, biochemical and urine analyses were comparable between test and control groups. No gross changes attributable to ingestion of the test material were observed.

Terminal body weights for the high dose group were significantly less than the controls. Liver weight was significantly less for the high dose males compared to the controls; however, the liver/body weight ratio for females was significantly increased compared to controls. The kidney/body weight ratio of the mid- and high-dose group females was significantly increased compared to controls. The higher organ/body weight ratios recorded for the high-dose group may have reflected the effect of reduced food consumption and decreased body weight gain. The differences were not supported by gross or microscopic examination of pertinent tissues. Microscopic examination of tissues from male and female rats did not reveal any compound-related lesions (Rohm and Haas Co. 1966c).

Chronic Methyl Methacrylate Toxicity

A study on the chronic inhalation toxicity and oncogenicity of methyl methacrylate in rats and hamsters by Lomax et al. (1997) was available. For 24 months male and female Fischer 344 rats (70 males and 70 females/group) were exposed to methyl methacrylate monomer vapors at 0, 25, 100, and 400 ppm (6 h/day, 5 days/week) and for 18 months. Female Lakeview golden hamsters (53–56 males and 56–59 females/group) were exposed to similar concentrations. 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 weeks 13 and 52, all surviving rats were killed during weeks 104 to 106. All surviving hamsters were killed at week 78.

Mortality, hematology, clinical chemistry, and urinalyses were not affected by methyl methacrylate exposure in rats. Male rat body weights were not affected by methyl methacrylate; however, female rats exposed to 400 ppm weighed less than controls after 52 weeks. The nasal cavity was the target organ for chronic toxicity in male and female rats exposed to 100 or 400 ppm where microscopic changes occurred primarily in olfactory epithelium lining the dorsal meatus and consisted of degeneration of neuroepithelium, basal cell hyperplasia and atrophy of Bowman's glands.

In hamsters, mortality, hematology, clinical chemistry, and urinalyses were not affected by methyl methacrylate exposure. Male and female hamsters exposed to 400 ppm methyl methacrylate weighed 9 to 12% less than controls after 48 weeks. No microscopic changes were observed in the nasal cavity of the hamsters. Chronic exposure to methyl methacrylate vapor did not cause tumors in hamsters or rats (Lomax et al. 1997).

Ocular Irritation

E I Dupont de Nemours & Co. Inc. (1976) placed a material composed of 71% Butyl Methacrylate/2-isocyanatoethyl methacrylate (48/52) and 29% ethyl acetate (0.1 ml undiluted) into the right conjunctival sac of each of two albino rabbits. The amount of residual monomer reported was ∼0.3% DWB to MRB. Observations were recorded at 1 and 4 hrs and on days 1, 2, 3, and 7 following treatment, with additional observations on days 14 and 21.

Moderate to severe corneal opacity, moderate to mild iritis and moderate to severe conjunctival irritation was produced in the unwashed treated eye. The washed treated eye had moderate corneal opacity, moderate to mild iritis and moderate conjunctival irritation. The washed treated eye was normal at 21 days, while the unwashed treated eye had a small area of mild opacity at 21 days.

A possible systemic effect of pupil constriction was also noted in both eyes. This material was classified as a moderate eye irritant capable of producing permanent mild corneal opacity (E I Dupont de Nemours & Co. Inc. 1976).

The Haskell Laboratories (1977b) reported the results of a study in which Butyl Methacrylate or Isobutyl Methacrylate (0.1 ml) was placed into the right conjunctival sac of each of two rabbits as an undiluted test material. Twenty seconds after contact, the treated eye of one rabbit was washed with tap water for one minute. The treated eye of the other rabbit was not washed. Observations were recorded at 1 and 4 hrs and on days 1, 2, 3, and 7 following treatment.

Effects on the cornea or iris were not observed for either treatment. The washed treated eye had mild redness and slight swelling for 1–4 h. The unwashed treated eye had mild redness and slight swelling for 1 h to 1 day. A mild discharge was observed at 4 h (Haskell Laboratories 1977b).

The British Petroleum Company (1981) assessed the eye irritancy of HEMA using three albino rabbits. Approximately 0.1 ml of neat HEMA was applied to one eye of each rabbit. Ocular irritation was scored at 3 hours, and 1, 2, 3, 7, and 15 days post-instillation.

HEMA caused immediate eye discomfort and resulted in large areas of corneal ulceration. Redness, discharge, and chemosis were also observed but most irritant effects were no longer present on day 15. The researchers concluded that HEMA was severely irritating to the rabbit eye and may cause permanent injury, especially if not washed quickly from the eye (British Petroleum Company 1981).

Rohm and Haas (1981) applied HEMA CD (88% HEMA, 1.5% Ethylene Glycol Dimethacrylate) to the conjunctival sac of three New Zealand white rabbits. Rabbit eyes were unwashed after 0.1 ml of HEMA CD was introduced. HEMA CD was classified as corrosive to rabbit eyes.

Andrews and Clary (1986) stated that PEG-4 Dimethacrylate and Trimethylolpropane Trimethacrylate were "virtually nonirritating" when instilled in rabbit eyes in the Draize test. No other information was available.

The Industrial Bio-Test Labs (1973) assessed the eye irritation caused by Trimethylolpropane Trimethacrylate using the Draize test. Undiluted Trimethylolpropane Trimethacrylate (1 ml) was instilled into the conjunctival sac of one eye in 6 rabbits. The irritation of the cornea, iris, and conjunctiva were scored (maximum = 110).

The average irritation scores at 1 minute, 1 hour, and 24 hours were 17.0, 8.1, and 0.0, respectively. Most irritation was noted in the conjunctiva. Trimethylolpropane Trimethacrylate

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.

Björkner et al. (1980a) assessed the sensitizing capacity of Trimethylolpropane Trimethacrylate using a GPMT. Twenty-four guinea pigs were used for each group. Trimethylolpropane Trimethacrylate (1%) was dissolved in an olive oil vehicle to improve dispersion for intradermal induction. For topical induction, Trimethylolpropane Trimethacrylate was tested at 25%. Challenge was performed using 0.1% and 0.5% Trimethylol propane Trimethacrylate in petrolatum.

Six of 24 and 16 of 24 guinea pigs became sensitized to 0.1% and 0.5% Trimethylolpropane Trimethacrylate, respectively. The controls were negative. One week later, at rechallenge, 7 of 24 guinea pigs and 10 of 24 control guinea pigs reacted to 0.5% Trimethylolpropane Trimethacrylate. The researchers concluded that Trimethylolpropane Trimethacrylate is a strong sensitizer (Björkner et al. 1980a).

In its workplace exposure guide, the American Industrial Hygiene Association (1981) stated that undiluted Trimethylolpropane Trimethacrylate did not cause sensitization in 10 guinea pigs. No other details were available.

Urethane Methacrylate

Björkner (1984b) assessed the sensitizing capacity of Urethane Methacrylate using the GPMT. Groups of fifteen guinea pigs were used. The animals were pretreated with 10% sodium lauryl sulfate in petrolatum. The purity of the Urethane Methacrylate used in this experiment was 98% according to the manufacturer; this correlated with HPLC analysis. Urethane Methacrylate (5%) was dissolved in an olive oil: acetone (10:1) vehicle to improve dispersion for intradermal induction. For topical induction, Urethane Methacrylate was tested at 100%. Challenge was performed using 0.015 g of Urethane Methacrylate at a concentration of 1% in petrolatum.

Only 2 of 15 guinea pigs became sensitized to Urethane Methacrylate. There was no cross-sensitization with an aromatic and aliphatic urethane acrylate. Urethane Methacrylate was considered a mild sensitizer (grade II) (Björkner 1984b).

Multiple Methacrylate Esters

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

Guinea pigs were induced with an intradermal injection (amount not stated) of 0.1 M or 1 M Butyl Methacrylate and challenged 21 days later with 0.1 ml aliquots of 1 M Butyl Methacrylate applied to the shaved area of the flank.

Guinea pigs were induced with an intradermal injection of 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} or 10^{-8} M Lauryl Methacrylate and were challenged 21 days later with 0.1 ml aliquots of 1 M Lauryl Methacrylate applied to the shaved area of the flank.

Guinea pigs were induced with an intradermal injection of 1, 10^{-1}, or 10^{-2} M Cyclohexyl Methacrylate and were challenged 21 days later with 0.1 ml aliquots of 1 M Cyclohexyl Methacrylate applied to the shaved area of the flank.

Guinea pigs were induced with an intradermal injection of 10^{-1}, 10^{-2}, or 10^{-3} M Hexyl Methacrylate and were challenged 21 days later with 0.1 ml aliquots of 1 M Hexyl Methacrylate applied to the shaved area of the flank.

The challenge phase was performed using the closed patch method for 24 h. Dermal response was evaluated 48 h after the challenge application. The vehicle used for the induction phase was olive oil and for the challenge phase was acetone.

Butyl Methacrylate, Cyclohexyl Methacrylate, and Hexyl Methacrylate were considered moderate sensitizers. Lauryl Methacrylate was considered a much stronger sensitizer, in fact it was the strongest sensitizer of the 13 methacrylates tested. Alkyl methacrylates with linear side chains having an even number of carbons were stronger sensitizers than those that had an odd number of carbons.

The sensitization rate for Butyl Methacrylate at induction concentrations of 0.1 and 1 M were 0 and 80%, respectively. The minimum induction concentration (MIC) was 0.1 M. The sensitization rate for Cyclohexyl Methacrylate at induction concentrations of 1, 10^{-1} and 10^{-2} M Cyclohexyl Methacrylate was 40.0, 20.0 and 0%, respectively. The MIC was determined as 10^{-1} M. The sensitization rate for Hexyl Methacrylate at induction concentrations of 10^{-1}, 10^{-2}, and 10^{-3} M Hexyl Methacrylate was 33.3, 0, and 0%, respectively. The MIC was determined as 10^{-1} M. The sensitization rate for Lauryl Methacrylate at induction concentrations of 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} M Lauryl Methacrylate was 100.0, 100.0, 30.0, 30.0 and 0%, respectively. The MIC was determined as 10^{-7} M (Kanazawa et al. 1999).

Cross-Reactions

The Haskell Laboratory (1969) tested for dermal irritation and sensitization effects of HEMA and Triethylene Glycol Dimethacrylate on guinea pigs. Each compound was tested on 15 male albino guinea pigs. Primary irritation was evaluated by applying 0.05 ml of HEMA (10, 25, or 98%) or Triethylene Glycol Dimethacrylate (2, 5, 10, and 98%) in a 1:1 acetone dioxane dilution to intact shaved skin. Sensitizing treatments were done by: nine topical applications of 0.05 ml of 25% HEMA or Triethylene Glycol Dimethacrylate (1st application was 5% and last 8 applications were 10%) to abraded skin of five animals, four 0.1 ml id injections of 1% test material in dimethylphtalate to a second group of five animals, and two 0.1 ml id injections of FCA followed 90 minutes later by a 0.1 ml of 1% test material in dimethylphtalate in the third group of five animals. After 14 days, the animals were challenged with 0.05 ml of 10% Triethylene Glycol Dimethacrylate or 25% HEMA on intact or abraded skin. One week later a second challenge was performed using 98% test material.

At first challenge, 25% HEMA caused no reaction in 14 guinea pigs and mild erythema in 1 guinea pig (intact skin); on abraded skin, 7 guinea pigs had mild erythema 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 4.76×10^{-4} to 1.58×10^{-3} without activation and 4.76×10^{-4} to 6.88×10^{-3} with activation (S9); Trimethylolpropane Trimethacrylate was tested at 6.57×10^{-5} to 1.63×10^{-4} without activation and 2.19×10^{-4} to 5.32×10^{-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 mutation 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.

REFERENCES

American Beauty Association/Nail Manufacturers Council (ABA/NMC). 2001a. Re: Butyl, Isobutyl, and Lauryl Methacrylate, 34 p.[2]

American Beauty Association (ABA). 2001b. Data submitted by ABA, Nail Manufacturers Council: Injury Report Submitted by Consumers (to FDA) for the Years 1987–1993, 5 p.[2]

[2]Available for review from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC, 20036, USA.

Andrews, L. S. and J. J. Clary. 1986. Review of the toxicity of multifunctional acrylates. *J Toxicol Environ Health* 19: 149–164.

American Industrial Hygiene Association. 1981. Workplace environmental exposure level guide: trimethylolpropane trimethacrylate. *Am. Ind. Hyg. Assoc. J.* 42: B-51–B-52.

Assessment Technologies, Inc. 1994. An environmental fate and ecotoxicology assessment of several methacrylic acid esters, with cover letter dated 06/16/94. NTIS Report No. OTS0557437.

Assessment Technologies, Inc. 1996. Methacrylates: an environmental assessment. NTIS Report No. OTS0558768.[2]

Autian, J. 1975. Structure-toxicity relationships of acrylic monomers. *Environ. Health. Perspect.* 11:141–52.

Benson, W. H., and R. A. Stackhouse. 1986. Evaluation of a new approach to the safety assessment of biomaterials. *Drug. Chem. Toxicol.* 9:275–84.

Biodynamics Inc. 1981. Initial submission: an acute intraperitoneal toxicity study of trimethylolpropane trimethacrylate in rats with cover letter dated 090492. NTIS Report No. OTS0571319.

Björkner, B. 1980a. Allergenicity of trimethylol propane trimethacrylate in ultraviolet curing inks in the guinea pig. *Acta. Derm. Venerol.* 60:528–531.

Björkner, B. 1980b. Contact allergy to 2-hydroxypropyl methacrylate (2-HPMA) in an ultraviolet curable ink. *Acta. Derm. Venerol.* 64:264–267.

Björkner, B., B. Niklasson, and K. Persson. 1984a. The sensitizing potential of di-(meth)acrylates based on bisphenol A or epoxy resin in the guinea pig. *Contact. Derm.* 10:286–304.

Björkner, B. 1984b. Sensitizing potential of urethane (meth)acrylates in the guinea pig. *Contact. Derm.* 11:115–119.

Björkner, B. 1984c. The sensitizing capacity of multifunctional acrylates in the guinea pig. *Contact. Derm.* 11:236–246.

Bong, J. L., and J. S. C. English. 2000. Allergic contact dermatitis from airborne exposure to acrylates. *Contact. Derm.* 43:242.

Bouillaguet, S., J. C. Wataha, M. Virgillito, L. Gonzalez, D. R. Rakich, and J.-M. Meyer. 2000. Effect of sub-lethal concentrations of HEMA (2-hydroxyethyl methacrylate) on THP-1 human monocyte-macrophages, in vitro.*Dent. Mater.* 16:213–217.

British Petroleum Company. 1981. Initial submission: irritation and mutagenicity tests of hydroxyethyl methacrylate and related studies with cover letter dated 082892. NTIS Report No. OTS0556083.

Brixham Environmental Lab. 1992. N-butyl methacrylate: determination of octanol water partition coefficient. NTIS Report No. OTS0537781.

Bushy Run Research Center. 1995. Initial submission: draft report, triethylene glycol dimethacrylate-carcinogenesis skin painting study in male mice, with cover letter dated 06/26/95. NTIS Report No. OTS0557901.

Cameron, T. P., A. M. Rogers-Back, T. E. Lawlor, J. W. Harbell, H. E. Seifried, and V. C. Dunkel. 1991. Genotoxicity of multifunctional acrylates in the Salmonella/mammalian-microsome assay and mouse lymphoma TK+/− assay. *Environ. Mol. Mutagen.* 17:264-271.

G. P. Cautilli, and W. J. Hozack. 1994. Analysis of fume emission from ultrasonic removal of methyl methacrylate cement in revision hip surgery. *Journal of Arthroplasty* 9:305–306.

ChemID. 2000. Butyl Methacrylate and Lauryl Methacrylate entries. *ChemID. database*. Bethesda, MD: National Library of Medicine.

ChemIDplus. 2001. Isobutyl Methacrylate entry. *ChemID. database*. Bethesda, MD: National Library of Medicine.

Chirila, T. V., L. N. Walker, I. J. Constable, D. E. Thompson, and G. D. Barrett. 1991. Cytotoxic effects of residual chemicals from polymeric biomaterials for artificial intraocular lenses. *J. Cataract. Refract. Surg.* 71:154–162.

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

Clemmensen, S. 1984. Cross-reaction patterns in guinea pigs sensitized to acrylic monomers. *Drug and Chemical. Toxicology.* 7:527–540.

Clemmensen, S. 1985. Sensitizing potential of 2-hydroxyethylmethacrylate. *Contact Derm.* 12:203–208.

Condé-Salazar, L., D. Guimaraens, L. V. Romero, M. A. Gonzalez, and A. Alomar. 1986. Occupational allergic contact dermatitis to artificial nails. *Contact. Derm.* 15:242.

Cosmetic Ingredient Review (CIR). 1999. Final Report of the Safety Assessment of Ethyl Methacrylate. Washington: CIR (23 pages).[2]

CIR. 2001. Final Report of the Safety Assessment of Methacrylic Acid. Washington: CIR (25 pages).[2]

Creative Nail Design. 2001. Differential scanning calorimetric analysis of twenty-two methacrylate monomers used in artificial monomer/polymer nail enhancement products. Unpublished data prepared by Schoon D dated 08/29/01 and submitted by Creative Nail Design (12 pages).[2]

Davy, K. W. M., and M. Braden. 1991. Residual monomer in acrylic polymers. *Biomaterials* 12:540–544.

Dearfield, K. L., C. S. Millis, K. Harrington-Brock, C. L. Doerr, and M. M. Moore. 1989. Analysis of the genotoxicity of nine acrylate/methacrylate compounds in L5178Y mouse lymphoma cells. *Mutagenesis* 4:381–393.

Deichmann, W. 1941. Toxicity of methyl, ethyl and n-butyl methacrylate. *Journal of Industrial Hygiene and Toxicology* 23:343–351.

Eastman Kodak Co. 1984. Basic toxicity of a butyl methacrylate solution. NTIS Report No. OTS0516721.

EI Dupont de Nemours & Co. 1976. Laboratory report on methacrylic acid, 2-isocyanatoethyl ester mixes. NTIS Report No. OTS0530198.

EI Dupont de Nemours & Co. 1993. Acute oral toxicity study with n-butyl methacrylate in male and female rats. NTIS Report No. OTS0538176.

Estlander, T., L. Kanerva, O. Kari, R. Jolanki, and K. Molsa. 1996. Occupational conjunctivitis associated with type IV allergy to methacrylates. *Allergy* 51:56–59.

European Commission. 2000. The rules governing cosmetic products in the European Union. Volume 1. Cosmetics legislation—Cosmetic products. http://dg3.eudra.org/F3/home.html.

Farmakovskaya, T. B., and Y. P. Tikhomirov. 1993. The influence of methyl methacrylate and butyl methacrylate on the reproductive function of animals during round-the-clock inhalation. *Reprod. Toxicol.* 7:520–521.

Fisher, A. A. 1980. Cross reactions between methyl methacrylate monomer and acrylic monomers presently used in acrylic nail preparations. *Contact. Dermatitis.* 6:345–347.

Fisher, A. A. 1990. Adverse nail reactions and paresthesia from "photobonded acrylate sculpted nails". *Cutis* 45:293.

Food and Drug Administration. 1976. Draize human sensitization test: Acrylates 1%. (Submitted by FDA in response to an FOI request-2000, 18 pages.)[2]

FDA. 1984. Concentration and frequency of use of cosmetic ingredients. *FDA database.* Washington, DC: FDA.

FDA. 2001. Frequency of use of cosmetic ingredients. *FDA database.* Washington, DC: FDA.

Foong, W. C., R. E. Howell, C. Karst, E. J. Sutow, D. W. Jones, and M. Mezei. 1990. In vitro cytotoxicity of methacrylate monomers. *J. Dent. Res.* 69:229.

Freeman, S., M.-S. Lee, and K. Gudmundsen. 1995. Adverse contact reactions to sculptured acrylic nails: 4 case reports and a literature review. *Contact. Derm.* 33:381–385.

Gage, J. C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. *Brit. J. Industr. Med.* 27:1–18.

General Electric Company. 1975. TSCA 8(e) Submittal Case #3: Acute inhalation toxicity in the albino rat AR 85124-Isobutyl Methacrylate. NTIS Report No. OTS0535667.

Geurtsen, W. 2000. Biocompatability of resin-modified filling materials. *Crit. Rev. Oral. Biol. Med.* 11:333–355.

Geurtsen, W., F. Lehmann, W. Spahl, and G. Leyhausen. 1998. Cytotoxicity of 35 dental resin composite monomers/additives in permanent 3T3 and three human primary fibroblast cultures. *J. Biomed. Mater. Res.* 41:474–480.

Gough, J. E., and S. Downes. 2001. Osteoblast cell death on methacrylate polymers involves apoptosis. *J. Biomed. Mater. Res.* 57:497–505.

Gould, D. H. 1987. Comparison of biological reactivity and toxicity of acrylate and methacrylate esters. *Toxic. Substances. Journal.* 7:1–15.

Greim, H., J. Ahlers, R. Bias, B. Broecker, H. Hollander, H. P. Gelbke, S. Jacob, et al. 1995. Assessment of structurally related chemicals: toxicity and ecotoxicity of acrylic acid and acrylic acid alkyl esters (acrylates), methacrylic acid and methacrylic acid alkyl esters (methacrylates). *Chemosphere* 31:2637–2659.

Hashimoto, Y., and M. Nakamura. 2000. Estrogenic activity of dental materials and bisphenol-A related chemicals. *Dent. Mater. J.* 19:245–262.

Haskell Laboratory. 1969. Initial submission: skin irritation and sensitization tests of triethylene glycol dimethacrylate, triethylene glycol diacrylate, triethylene glycol in guinea pigs with cover letter dated 10/15/92. NTIS Report No. OTS0555867.

Haskell Laboratories. 1977a. Two week subacute inhalation studies-n-butyl methacrylate. NTIS Report No. OTS0520964.

Haskell Laboratories. 1977b. Eye irritation test in rabbits. NTIS Report No. OTS0520965.

Haskell Laboratories. 1977c. Mutagenic activity of methacrylic acid, n-butyl ester in the salmonella/microsome assay. NTIS Report No. OTS0520966.

Haskell Laboratories. 1993a. Inhalation sensory irritation (RD50) study in mice with selected methacrylates and methacrylic acid. NTIS Report No. OTS0556655.

Haskell Laboratories. 1993b. Inhalation median lethal concentration (LC50) studies with methacrylates in rats: methacrylic acid, butyl methacrylate, ethyl methacrylate. NTIS Report No. OTS0556663.

Hazardous Substances Database (HSDB). 2000. Butyl Methacrylate and Lauryl Methacrylate entries. *HSDB database.* Bethesda, MD: National Library of Medicine.

HSDB. 2001. Isobutyl Methacrylate, Cyclohexyl Methacrylate, n-Hexyl Methacrylate, Ethylene Methacrylate, 2-Hydroxyethyl Methacrylate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate, Triethylene Glycol Dimethacrylate, Tetrahydrofurfuryl Methacrylate entries. *HSDB database.* Bethesda, MD: National Library of Medicine.

Hazelton Laboratories. 1961. Initial submission: acute oral toxicity study with 2-Hydroxypropyl Methacrylate in rats with cover letter dated 072192. NTIS Report No. OTS0544834.

Hazelton Laboratories. 1982. Initial submission: maternal tolerance study in rats with cover letter dated 102792. NTIS Report No. OTS0546549.

Hazelton Laboratories. 1983. Initial submission: letter from Rhone-Poulenc Inc to USEPA regarding teratology screen studies of various compounds in rats with attachments and cover letter dated 102792. NTIS Report No. OTS0571218.

Heil, J., G. Reifferscheid, P. Waldmann, G. Leyhausen, and W. Geurtsen. 1996. Genotoxicity of dental materials. *Mutat Res* 368:181–194.

Hemmer, W., Focke, M., Wantke, F., Gotz, M., and R. Jarisch. 1996. Allergic contact dermatitis to artificial fingernails prepared from UV light-cured acrylates. *J. Am. Acad. Dermatol.* 35:377–380.

Henriks-Eckerman, M. L., and L. Kanerva. 1997. Product analysis of acrylic resins compared to information given in material safety data sheets. *Contact. Dermatitis.* 36:164–165.

Hikage, S., A. Sato, S. Suzuki, C. F. Cox, and K. Sakaguchi. 1999. Cytotoxicity of dental resin monomers in the presence of S9 mix enzymes. *Dent. Mater.* 18:76–86.

Horna, A., J. Táborský, O. Dufka, P. Matoušek, and J. Churáček. 1985. Chromatography of monomers II. Glass capillary gas chromatography of C1-C18 alkyl esters of acrylic and methacrylic acids. *J. Chromatogr.* 325:367–378.

International Agency for Research on Cancer (IARC). 1994. Methyl Methacrylate. *IARC Monogr. Eval. Carcinog. Risks. Hum.* 60:445–474.

Industrial Bio-Test Labs. 1973. Report to Celanese Chemical Company: acute toxicity studies with Trimethylolpropane Trimethacrylate. NTIS Report No. OTS 0000544–0.

Industrial Bio-Test Labs. 1974. Report to Celanese Chemical Company: skin sensitization test with Trimethylolpropane Trimethacrylate in albino guinea pigs. NTIS Report No. OTS 0000544–0.

Jackson, E. M. 2001. A structure activity relationship (SAR) analysis of the genotoxic potential of butyl, isobutyl, and lauryl methacrylate. Unpublished data submitted by the Nail Manufacturers Council, May 15, 2001. (30 pages).[2]

Jacobs, M.-C., and R. J. G. Rycroft. 1995. Allergic contact dermatitis from cyanoacrylate? *Contact. Derm.* 33:71.

Jelovsek, F. R., D. R. Mattison, J. J. Chen. 1989. Prediction of risk for human developmental toxicity: how important are animal studies for hazard identification? *Obstet. Gynecol.* 74:624–636.

Kanazawa, Y., T. Yoshida, and K. Kojima. 1999. Structure-activity relationships in allergic contact dermatitis induced by methacrylates. Studies of the influence of side-chain length of methacrylates. *Contact. Dermatitis.* 40:19–23.

Kanerva, L., A. Lauerma, T. Estlander, K. Alanko, M. L. Henriks-Eckerman, and R. Jolanki. 1996. Occupational allergic contact dermatitis caused by photobonded sculptured nails and a review of (meth) acrylates in nail cosmetics. *Am. J. Contact. Dermat.* 7:109–115.

Kanerva, L., R. Jolanski, T. Leino, and T. Estlander. 1995. Occupational allergic contact dermatitis from 2-hydroxyethyl methacrylate and ethylene glycol dimethacrylate in a modified acrylic structural adhesive. *Contact. Derm.* 33:84–89.

Kanerva, L., T. Estlander, and R. Jolanki. 1989. Allergic contact dermatitis from dental composite resins due to aromatic epoxy and aliphatic acrylates. *Contact. Derm.* 20:201–211.

Kanerva, L., T. Estlander, and R. Jolanki. 1988. Sensitization to patch test acrylates. *Contact. Derm.* 18:10–15.

Kanerva, L., R. Jolanski, and T. Estlander. 1986. Occupational dermatitis due to an epoxy acrylate. *Contact. Derm.* 14:80–84.

Katono, H., A. Maruyama, K. Sanui, T. Okano, Y. Sakurai, et al. 1991. Thermo-responsive swelling and drug release switching of interpenetrating polymer networks composed of poly(acrylamide-co-butyl methacrylate) and poly(acrylic acid). *J. Controlled. Release.* 16:215–227.

Katsuno, K., A. Manabe, K. Itoh, Y. Nakamura, S. Wakumoto, H. Hisamitsu, and T. Yoshida. 1996. Contact dermatitis caused by 2-HEMA and GM dentin primer solutions applied to guinea pigs and humans. *Dent. Mater. J.* 15:22–30.

Katsuno, K., A. Manabe, K. Itoh, H. Hisamitsu, S. Wakumoto, Y, Nakamura, and T. Yoshida. 1995. A delayed hypersensitivity reaction to dentine primer in the guinea-pig. *J. Dent.* 23:295–299.

Katsuno, K., A. Manabe, T. Hasegawa, S. Nakayama, K. Itoh, S. Wakumotot, and H. Hisamitsu. 1992. Possibility of allergic reaction to dentin primer–application on the skin of guinea pigs. *Dent. Mater. J.* 11:77–82.

Kawaguchi, M, Y. Takahashi, T. Fukushima, and T. Habu. 1996. Effect of light-exposure duration on the amount of leachable monomers from light-activated reline material. *J. Prosthet. Dentistry.* 75:183–187.

Lawrence, W. H., G. E. Bass, W. P. Purcell, and J. Autian. 1972. Use of mathematical models in the study of structure-toxicity relationships of dental compounds: I. Esters of acrylic and methacrylic acids. *J. Dent. Res.* 51:526–535.

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

Lewis, R. J. Sr. 1993. *Hazardous Chemicals Desk Reference*, 3rd ed. New York: Van Nostrand Reinhold Co.

Lewis, R. J. Sr. 1997. *Hawley's Condensed Chemical Dictionary*, 13th ed. New York: Van Nostrand Reinhold Co.

Lewis, R. J. Sr. 2000. *Sax's Dangerous Properties of Industrial Materials*, 10th ed., Vols 1-3, New York: John Wiley & Sons, Inc.

Litton Bionetics Inc. 1979. Initial submission: mutagenicity evaluation of trimethylolpropane trimethacrylate in the mouse lymphoma forward mutation assay with cover letter dated 090492. NTIS Report No. OTS0571726.

Litton Bionetics Inc. 1985. Mutagenicity evaluation of ethylene glycol dimethacrylate and bis-glycidyl methacrylate in the mouse lymphoma forward mutation assay (final reports) with cover letter 031286. NTIS Report No. OTS0000367–2.

Lomax, L. G., N. D. Krivanek, and S. R. Frame. 1997. Chronic inhalation toxicity and oncogenicity of methyl methacrylate in rats and hamsters. *Food. Chem. Toxicol.* 35:393–407.

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

Mathias, C. G. T., T. M. Caldwell, and H. I. Maibach. 1979. Contact dermatitis and gastrointestinal symptoms from hydroxyethyl methacrylate. *British. J. of Dermatology* 100:447–449.

McCarthy, T. J., E. P. Hayes, C. S. Schwartz, and G. Witz. 1994. The reactivity of selected acrylate esters toward glutathione and deoxyribonucleosides in vitro: structure-activity relationships. *Fundamental and Applied Toxicology* 22:543–548.

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

Methacrylate Producers Association. 1998. Request for review of methacrylic acid and its basic esters. 3 pages.[2]

Ministry of Health and Welfare: Japan. 1998. Initial submission: Letter from Methacrylate Producers Association Inc to USEPA Re: summaries of methacrylate toxicity studies conducted in Japan, with attachments and cover letter dated 8/21/1999. NTIS Report No. OTS0559766.

Mir, G. M., W. H. Lawrence, and J. Autian. 1973a. Toxicological and pharmacological actions of methacrylate monomers. I. Effects on isolated, perfused rabbit heart. *J. Pharm. Sci.* 62:778–782.

Mir, G. M., W. H. Lawrence, and J. Autian. 1973b. Toxicological and pharmacological actions of methacrylate monomers. II. Effects on isolated guinea pig ileum. *J. Pharm. Sci.* 62:1258–1261.

Mir, G. M., W. H. Lawrence, and J. Autian. 1974. Toxicological and pharmacological actions of methacrylate monomers. III. Effects on respiratory and cardiovascular functions of anesthetized dogs. *J. Pharm. Sci.* 63:376–381.

Mobil Oil Corporation. 1990. An Ames Salmonella/mammalian microsome mutagenesis pre-incubation assay for the determination of potential mutagenicity of butyl methacrylate. NTIS Report No. OTS0522348.

Mobil Oil Corporation. 1991. An Ames Salmonella/mammalian microsome mutagenesis pre-incubation assay for the determination of potential mutagenicity of butyl methacrylate. NTIS Report No. OTS0530430.

Moore, M. M., A. Amtower, C. L. Doerr, K. H. Brock, and K. L. Dearfield. 1988. Genotoxicity of acrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate in L5178Y mouse lymphoma cells. *Environ. Mol. Mutagen.* 11:49–63.

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

Olea, N., R. Pulgar, P. Perez, F. Olea-Serrano, A. Rivas, A. Novillo-Fertrell, V. Pedraza, A. M. Soto, and C. Sonnenschein. 1996. Estrogenicity of resin-based composites and sealants used in dentistry. *Environ. Health Perspect* 104:298–305.

Parker, D., and J. L. Turk. 1983. Contact sensitivity to acrylate compounds in guinea pigs. *Contact. Dermatitis* 9:55–60.

Ratanasathien, S., J. C. Wataha, C. T. Hanks, and J. B. Dennison. 1995. Cytotoxic interactive effects of dentin bonding components on mouse fibroblasts. *J. Dent. Res.* 74:1602–1606.

Raymond, L. W. 1996. Pulmonary abnormalities and serum immunoglobulins in facsimile machine repair technicians exposed to butyl methacrylate fume. *Chest.* 109:1010–1018.

Registry of Toxic Effects of Chemical Substances (RTECS). 2000. Butyl and Lauryl Methacrylate entries. *RTECS database*. Bethesda, MD: National Library of Medicine.

Reichl, F. X., J. Durner, R. Hickel, K. H. Knuzelmann, A. Jewett, M. Y. Wang, W. Spahl, H. Kreppel, G. W. Moes, K. Kehe, U. Walther, W. Forth, and W. R. Hume. 2001a. Distribution and excretion of TEGDMA in guinea pigs and mice. *J. Dent. Res.* 80:1412–1415.

Reichl, F.-X., U. I. Walther, J. Durner, K. Kehe, R. Hickel, K.-H. Kunzelmann, W. Spahl, W. R. Hume, H. Benschop, and W. Forth. 2001b. Cytotoxicity of

dental composite components and mercury compounds in lung cells. *Dent. Mater.* 17:95–101.

Rhône-Poulenc Inc. 1992. Initial submission: DOT skin corrosion of sipomer HEM-HP-T in rabbits with cover letter dated 061992. NTIS Report No. OTS0541037.

Rohm and Haas Co. 1966a. Acute oral administration-rats-C12-C18 methacrylate monomers. (Submitted by EPA in response to an FOI request-2000, 3 pages).[2]

Rohm and Haas Co. 1966b. 13-week oral administration-dogs-C12-C18 methacrylate monomers. (Submitted by EPA in response to an FOI request-2000, 73 pages).[2]

Rohm and Haas Co. 1966c. Three month dietary administration-rats-C12-C18 methacrylate monomers. (Submitted by EPA in response to an FOI request-2000, 53 pages).[2]

Rohm and Haas Co. 1980. Initial submission: report on genetic toxicity study with 2-methyl-2-propenoic acid, 1,2-ethanediyl ester in *Salmonella typhimurium* with cover letter dated 081092. NTIS Report No. OTS0544418.

Rohm and Haas Co. 1981. Initial submission: acute range-finding rabbit eye/skin irritation studies (final report) with cover letter dated 072192. NTIS Report No. OTS0544769.

Rohm and Haas Co. 1994. Butyl methacrylate-skin irritation following 1 and 4 hour exposures in rabbits. NTIS Report No. OTS0557531.

Rustemeyer, T., J. de Groot, B. M. von Blomberg, P. J. Frosch, R. J. Scheper. 2001. Induction of tolerance and cross-tolerance to methacrylate contact sensitizers. *Toxicol. Appl. Pharmacol.* 176:195–202.

Rustemeyer, T., J. de Groot, B. M. von Blomberg, P. J. Frosch, and R. J. Scheper. 1998. Cross-reactivity patterns of contact-sensitizing methacrylates. *Toxicol. Appl. Pharmacol.* 148:83–90.

Saillenfait, A. M., P. Bonnet, F. Gallissot, A. Peltier, J. F. Fabriès. 1999. Developmental toxicities of methacrylic acid, ethyl methacrylate, n-butyl methacrylate and allyl methacrylates in rats following inhalation exposure. *Toxicological. Sciences* 50:136–145.

Sainio, E. L., K. Engstrom, M. L. Henriks-Eckerman, L. Kanerva. 1997. Allergenic ingredients in nail polishes. *Contact Dermatitis* 37:155–162.

Sandmeyer, E. E. and C. J. Kirwin. 1981. Esters of alkenylcarboxylic acids and monoalcohols. In: E. Clayton and FE Clayton, eds. *Patty's Industrial Hygiene and Toxicology*, 4th ed., Vol II Part A, John Wiley & Sons, NY, 2291–2303.

Sax, N. I. 1979. Dangerous Properties of Industrial Materials. 5th edn. New York: NY: Van Nostrand Reinhold Co.

Schneiderka, P., M. Roosová, K. Jojková, J. Prokeš, J. Labský, J. Vacík. 1996. Toxicity of monomers HEMA, DEGMA and AEMA, used in synthesis of hydrogels for medical applications. *Sborník lékařský* 97:351–367.

Schoon, D. 1994a. Differential scanning calorimeter determinations of residual monomer content in ethyl methacrylate fingernail formulations. Unpublished data submitted by the Nail Manufacturers Council. (15 pages).[2]

Schoon, D. 1994b. Addendum to: Differential scanning calorimeter determinations of residual monomer content in ethyl methacrylate fingernail formulations. Unpublished data submitted by the Nail Manufacturers Council. (6 pages).[2]

Schweikl, H. and G. Schmalz. 1999. Triethylene glycol dimethacrylate induces large deletions in the *hprt* gene of V79 cells. *Mutat. Res.* 438:71–78.

Schweikl, H., G. Schmalz, and K. Rackebrandt. 1998. The mutagenic activity of unpolymerized resin monomers in Salmonella typhimurium and V79 cells. *Mutat. Res.* 415:119–130.

Schweikl, H., G. Schmalz, and B. Bey. 1994. Mutagenicity of dentin bonding agents.*J Biomed Mater Res* 28:1061–1067. [eratum appears in *J. Biomed. Mater. Res.* 29:137].

Singh, A. R., W. H. Lawrence, and J. Autian. 1972. Embryo fetal toxicity and teratogenic effects of a group of methacrylate esters in rats. *J. Dent. Res.* 51:1632–1638.

Tosti, A., L. Guerra, C. Vincenzi, and A. M. Peluso. 1993. Occupational skin hazards from synthetic plastics. *Toxicol. Ind. Health.* 9:493–502.

Tosti, A., S. Rapacchiale, B. M. Piraccini, and A. M. Peluso. 1991. Occupational airborne contact dermatitis due to ethylene glycol dimethacrylate. *Contact. Derm.* 24:152–153.

Tucker, S. C., and M. H. Beck. 1999. A 15-year study of patch testing to (meth)acrylates. *Contact. Derm.* 40:278–279.

US EPA. 1985. The health and environmental effects of acrylate and methacrylate chemicals and the acrylate/methacrylate category. NTIS Report No. OTS0529004.

van der Walle, H. B., P. C. Delbressine, and E. Seutter. 1982. Concomitant sensitization to hydroquinone and P-methoxyphenol in the guinea pig; inhibitors in acrylic monomers. *Contact. Dermatitis.* 8:147–154.

van der Walle, H. B., and T. Bensink. 1982. Cross reaction pattern of 26 acrylic monomers on guinea pig skin. *Contact. Dermatitis.* 8:376–382.

Waegemaekers, T. H., and M. P. Bensink. 1984. Non-mutagenicity of 27 aliphatic acrylate esters in the salmonella-microsome test. *Mutat. Res.* 137:95–102.

Wenninger, J. A., R. C. Canterbery, G. N. McEwen, Jr. Eds. 2002. *International Cosmetic Ingredient Dictionary and Handbook*. 9th edn, vol.1-2. Washington, DC: CTFA.

Yoshii, E. 1997. Cytotoxicity effects of acrylates and methacrylates: relationships of monomer structures and cytotoxicity. *J. Biomed. Materials. Res.* 37:517–524.

Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, K. Mortelmans, and W. Speck. 1987. Salmonella Mutagenicity Tests: III. Results from the testing of 255 chemicals. *Environmental Mutagenesis* 9:1–110.

Zuccari, A. G., Y. Oshida, and B. K. Moore. 1997. Reinforcement of acrylic resins for provisional fixed restorations. Part I: Mechanical properties. *Biomed. Mater. Eng.* 7:327–343.