Safety Assessment of Methacrylate Ester Monomers as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	November 10, 2021
Panel Meeting Date:	December 6-7, 2021

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D., Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa, A. Peterson, Ph.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Wilbur Johnson, Jr., Senior Scientific Analyst/Writer, CIR.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: November 10, 2021
Subject: Re-Review of the Safety Assessment of Methacrylate Ester Monomers

The Expert Panel for Cosmetic Ingredient Safety (Panel) previously issued a conclusion stating that 22 methacrylate ester monomers are safe as used in nail enhancement products when skin contact is avoided. The conclusion also states that products containing these ingredients should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates. A final report with this conclusion was published in 2005, and this report is included for your use (identified as *originalreport_MethacrylateEsterMonomers122021*). Minutes from the deliberations of the review that yielded this report are also included (*originalminutes_MethacrylateEsterMonomers_122021*).

Because it has been at least 15 years since the final report was published, in accordance with CIR Procedures, the Panel should consider whether the safety assessment should be reopened. Many of the ingredient names have changed, and one ingredient is no longer found in the *Dictionary*. An exhaustive search of the world's literature was performed for studies dated 2001 forward (*search_MethacrylateEsterMonomers_122021*). A synopsis of the relevant data is enclosed (*newdata_MethacrylateEsterMonomers_122021*).

Also included for your review are current and historical use data on methacrylate ester monomers (*usetable_MethacrylateEsterMonomers_122021*). Data submitted to the Food and Drug Administration (FDA) in 2001 did not include any uses for 21 of the methacrylate ester monomers that were reviewed; only Tetrahydrofurfuryl Methacrylate had reported use, in one nail extender product. However, concentration of use data received from the cosmetics industry in 2001 indicated that all ingredients had reported use, with maximum use concentrations of methacrylate ester monomers up to 85% (reported for Methoxydiglycol Methacrylate and Ethoxyethyl Methacrylate) in nail enhancement products.

The results of a concentration of use survey conducted by the Council in 2020, and 2021 FDA VCRP data, are included with this submission (*concentrations_MethacrylateEsterMonomers_122021*; *VCRP_MethacrylateEsterMonomers_122021*). Collectively, these data indicate use of 8 methacrylate ester monomers in products that are applied to the nail. The most frequently used methacrylate ester monomer is HEMA, which has 149 uses and a reported maximum use concentration of 79% (in other manicuring products). Di-HEMA Trimethylhexyl Dicarbamate has a reported maximum use concentration 91.8% (in nail extenders). Of the ingredients that are being reviewed, this is the highest reported maximum use concentration.

The included data profile identifies information from the published final report, as well as any new information that was identified since that original report was issued (*dataprofile_MethacrylateEsterMonomers_122021*).

If, upon review of the synopsis of new data and the updated use frequency and concentration of use data the Panel determines that a re-review is warranted, a full Draft Amended Report will be presented at an upcoming meeting.

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Methacrylate Ester Monomers Data Profile* – December 6-7, 2021 Panel – Wilbur Johnson, Jr.

	Use				Toxico-kinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	New Rpt	Old Rpt	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Bis(Glyceryl Dimethacrylate) Pyromellitate	**19**	**0**																											
Butylcarbamoethyl Methacrylate	**0**	**0**																					O					X	
Butyl Methacrylate	**0**	**0**	O	O	O	X	O X	O	O	O X		O X	O X		O X	O X	X				O			O X	O	X		O	X	O
t-Butyl Methacrylate	**0**	**0**						X	X	X		O X	X			O X	X				X			O				X		
Cyclohexylmethacrylate	**0**	**0**						X	X						X						X			O X				X		
Di-HEMA Trimethylhexyl Dicarbamate	**76**	**0**														O								X					O	O
2-Ethoxy Ethoxy Ethyl Methacrylate	**0**	**0**																													
Ethoxyethyl Methacrylate	**0**	**0**			O																								O		
Glycol Dimethacrylate	**17**	**0**		O	O	X		X	O X						X	O X	X				X		X	O X				O	O X	O X
HEMA	**149**	**0**			O	X	X	O X	O X			O X			O X	O X	X				O X		X	O X	O			O X	O X	O X
HEMA Acetoacetate	**0**	**0**						X	X			X			X	X					X							X		
Hexyl Methacrylate	**0**	**0**			O	X			X							O X					X			O X						
Hydroxypropyl Methacrylate	**40**	**0**							O						O	O					O			O	O				O X	O X
Isobornyl Methacrylate	**0**	**0**						X	X			X			X	X					X			X					X	
Isobutyl Methacrylate	**0**	**0**	O	O	O	X		O	O X	O						O X	X				X			X	O			O X		O
Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate	**1**	**0**														O								O					O	O
Lauryl Methacrylate	**1**	**0**		O	O	X			O X	O X			O		X		X							O						
Methoxydiglycol Methacrylate	**0**	**0**							X							X				X				X			X			
PEG-4 Dimethacrylate	**0**	**0**			O			O	O X							O X		O			O			O X				O		O
Tetrahydrofurfuryl Methacrylate	**0**	**1**				X			X			X			X						X			O				X	O X	O X
Triethylene Glycol Dimethacrylate	**0**	**0**			O	X	O X	X	O		X	X			X	O X		O X			O X			O X				X	O X	O X
Trimethylolpropane Trimethacrylate	**1**	**0**			O	X		O X	O X	O	O X	O X		O	O X	O X	X	O X			O X	O		O X				O X		

* "X" indicates that new data were available in this category for the ingredient; "O" indicates that data from the original assessment were available

Methacrylate Ester Monomers – 11/2-3/20;6/28/21;7/7-8/21;10/26/21

Ingredient	CAS #	InfoBase	SciFinder	PubMed		FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Butyl Methacrylate	44914-03-6 97-88-1	Yes		712 (3)			No	Yes	Yes	Yes	No	Yes (full report)	No	Yes	No	No	Yes (full report)	Yes
t-Butyl Methacrylate	585-07-9	Yes		19 (1)			No	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Cyclohexylmethacrylate (Was Cyclohexyl Methacrylate)	101-43-9	No		9 (1)			No	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Ethoxyethyl Methacrylate	51289-08-8	Yes		10 (0)			No	No	Yes	No	No	No	No	No	No	No	No	Yes
2-Ethoxy Ethoxy Ethyl Methacrylate (Removed from Dictionary? Name and CAS don't come up in search)	45127-97-7	No		2 (0)			No	No	No	No	No	No	No	No	No	No	No	Yes
Ethylene Glycol Dimethacrylate (Now, Glycol Dimethacrylate)	97-90-5	Yes		1584 (22)			No	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes
Hexyl Methacrylate (Removed from Dictionary? Name or CAS No. not there)	142-09-6	No		54 (1)			No	Yes	Yes	No	No	No	No	Yes	No	No	No	Yes
HEMA or 2-Hydroxyethyl Methacrylate	868-77-9	Yes		1622 (29)			Yes	Yes	Yes	Yes (full report)	No	Yes (full report)	No	No	No	No	No	Yes
Di-HEMA Trimethylhexyl Dicarbamate	41137-60-4 72869-86-4	Yes		0			No	No	No	No	No	No	No	No	No	No	No	Yes
Hydroxyethylmethacrylate Acetoacetate (Now HEMA Acetoacetate)	21282-97-3	No		0			Yes	No	No	No	No	No	No	No	No	No	No	Yes
Hydroxypropyl Methacrylate	923-26-2 27813-02-1	Yes		370 (7)			No	No	No	Yes	No	Yes (full report)	No	No	No	No	No	Yes
Isobornyl Methacrylate	7534-94-3	Yes		13 (0)			No	Yes	Yes	Yes (full report)	No	No	No	No	No	No	No	Yes
Isobutyl Methacrylate	97-86-9	Yes		34 (1)			No	Yes	Yes	Yes	No	Yes (full report)	No	Yes	No	No	Yes (full report)	Yes
Isopropylidenediphenyl Bisglycidyl Methacrylate (Now Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate)	1565-94-2	No		0			No	No	No	No	No	No	No	No	No	No	No	Yes
Lauryl Methacrylate	142-90-5 93804-49-0	Yes		138 (0)			No	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes
Methoxydiglycol Methacrylate	45103-58-0	Yes		0			No	Yes	Yes	No	No	No	No	No	No	No	No	Yes

Ingredient	CAS #	InfoBase	SciFinder	PubMed		FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
PEG-4 Dimethacrylate	109-17-1	Yes		5 (0)			No	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Pyromellitic Glycidyl Dimethacrylate (Now Bis(Glyceryl Dimethacrylate) Pyromellitate)	148019-46-9	No		5 (0)			No	No	No	No	No	No	No	No	No	No	No	Yes
Tetrahydrofurfuryl Methacrylate	2455-24-5	Yes		33 (3)			No	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Triethylene Glycol Dimethacrylate	109-16-0	Yes		967 (20)			No	Yes	Yes	Yes	No	Yes (full report)	No	No	No	No	No	Yes
Trimethylolpropane Trimethacrylate	3290-92-4	Yes		147 (1)			No	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes
Urethane Methacrylate (Now Butylcarbamoethyl Methacrylate)	65256-52-2	Yes		20 (0)			No	No	No	No	No	No	No	No	No	No	No	Yes

Search: 2001 forward

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus (Substances added to Food);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

DECEMBER 5, 2000 – Full Panel - INITIAL REVIEW/DRAFT REPORT

Butyl Methacrylate and Lauryl Methacrylate

A Scientific Literature Review (SLR) on Butyl and Lauryl Methacrylate was issued on August 21, 2000, and this report is being reviewed by the Panel for the first time. Data were not received during the 90-day comment period for the SLR.

Dr. Belsito noted that Butyl Methacrylate, as currently defined in the International Cosmetic Ingredient Dictionary and Handbook, is a fragrance material. No other functions of this ingredient in cosmetics are indicated. However, recognizing the potential for the use of this ingredient in products that are used to enhance nails, Dr. Belsito said that his Team determined that the review of Butyl Methacrylate is within the Panel's prerogative.

Dr Belsito also stated that the available data are insufficient for evaluating the safety of these two ingredients in cosmetics and that his Team determined that the following data are needed: (1) polymerization rate of Butyl and Lauryl Methacrylate (to be compared with that for Ethyl Methacrylate) and the amount of unreactive monomer that remains when these compounds are polymerized. [If these data are similar to those for Ethyl Methacrylate, then much of the data on Ethyl Methacrylate could be incorporated into the current report.], (2) impurities analysis, (3) genotoxicity studies, and (4) carcinogenicity studies. [items 3 and 4 relate to concerns about inhalation exposure.]

Concerning items 2, 3, and 4 above, Dr. Belsito noted that if the data from item 1 indicate that Butyl and Lauryl Methacrylate are similar to Ethyl Methacrylate, then data (items 2, 3, or 4) from the CIR report on Ethyl Methacrylate may be incorporated into the current report.

Dr. Schroeter said that if these ingredients are used in a special application system that results in no ingredient contact with the skin, then it could be concluded that Butyl and Lauryl Methacrylate are safe as used. However, he agreed with item 1 in the Belsito Team's list of data requests.

Dr. Klaassen asked if two-year carcinogenicity studies have been done on Butyl and Lauryl Methacrylate.

Dr. McLaughlin, with Methacrylate Producers Association, stated that Butyl and Lauryl Methacrylate have not undergone carcinogenicity testing. He also said that MMA has been tested in approximately seven lifetime studies and is not carcinogenic; therefore, the testing of Butyl Methacrylate for carcinogenicity was considered unnecessary. It was also noted that Butyl Methacrylate has been evaluated in a three-month inhalation study.

Given the confusion over the use of these ingredients that has been expressed, Dr. Andersen suggested that the Panel request information on the intended use of Lauryl and Butyl Methacrylate in cosmetics.

The Panel's informal data request is indicated below:

(1) Polymerization rate and extent of polymerization to determine the amount of unreacted monomer that could come in contact with the skin (inadvertant exposure)

(2) Impurities data

(3) Chronic inhalation toxicity data to address genotoxicity/carcinogenesis (and reproductive/developmental toxicity)

(4) Intended use of product

Note: The Panel acknowledged that Butyl Methacrylate is listed as a fragrance ingredient, but agreed that it may have uses in nail enhancing products. The Panel expressed interest in comparing the data on Butyl and Lauryl Methacrylates to Ethyl Methacrylate, and, if appropriate, incorporating the Ethyl Methacrylate data into this safety assessment.

FEBRUARY 13, 2001 – Full Panel - SECOND REVIEW/DRAFT REPORT

Butyl Methacrylate and Lauryl Methacrylate

Dr. Belsito recalled that at the December 4-5, 2000 Panel meeting, the Panel determined that the available data on these ingredients were insufficient for determining safety. The following informal data request was issued:

(1) Polymerization rate and extent of polymerization to determine the amount of unreacted monomer that could come in contact with the skin (inadvertant exposure)
(2) Impurities data
(3) Chronic inhalation toxicity data to address genotoxicity/carcinogenesis (and reproductive/developmental toxicity)
(4) Intended use of product

Note: The Panel acknowledged that Butyl Methacrylate is listed as a fragrance ingredient, but agreed that it may have uses in nail enhancing products. The Panel expressed interest in comparing the data on Butyl and Lauryl Methacrylates to Ethyl Methacrylate, and, if appropriate, incorporating the Ethyl Methacrylate data into this safety assessment.

Dr. Belsito noted that the Panel has issued a conclusion on the safety of Ethyl Methacrylate in cosmetics. The conclusion reads as follows: Based on the available data on the formulation of nail products containing Ethyl Methacrylate, the CIR Expert Panel concludes that this ingredient is safe as used when application is accompanied by directions to avoid skin contact because of the sensitizing potential of Ethyl Methacrylate.

Dr. Belsito also stated that the Panel needs to know whether other methacrylates are being used in artificial nail products. This concern is based on information, received from the National Starch and Chemical Company, indicating the possibility that isobutyl methacrylate is being used in cosmetics. Furthermore, Dr. Belsito noted that a nail product containing this ingredient was displayed at yesterday's Team meetings, and, thus, recommended that isobutyl methacrylate be added to the safety assessment.

Concerning the Panel's list of data requests (indicated above and on the preceding page), Dr. Belsito said that his Team requested the following changes/additions: (1) Item 1 should refer to Butyl, Lauryl, and Isobutyl Methacrylate. (2) Item 3 should be replaced with a request for mammalian genotoxicity data. (3) Any additional data relating to adverse reaction reports should be requested.

Dr. Bergfeld said that a request that the Panel receive a letter documenting any adverse effects was made during yesterday's Team meetings. She noted that this letter could be cited in the CIR report.

Dr. Bergfeld wanted to know which ingredient is being recommended for mammalian genotoxicity testing.
No ingredient preference for genotoxicity testing was stated by the Panel.

Dr. Belsito noted that the Panel had discussed the possibility of incorporating the seven carcinogenicity studies on methyl methacrylate into the report on Butyl and Lauryl Methacrylate. He also stated that any information that is missing from the current review that could be captured from the CIR report on Ethyl Methacrylate should be added as well.

Dr. Andersen noted that the Panel's review of Methyl Methacrylate is separate from its review of Lauryl and Butyl Methacrylate. He confirmed that the reviews will remain separate and that the Panel's intention is that of only incorporating carcinogenicity data on Methyl Methacrylate into the Draft Report.

Dr. Bergfeld confirmed that genotoxicity data on Methyl Methacrylate could be incorporated as well.

Dr. Belsito recalled that clarification of data from adverse reaction reports (FDA data included in American Beauty Association submission) was also requested from FDA on the preceding day. He said that the Panel needs to know the types of reactions that were observed, and also noted that the incidence of reactions observed is unclear.

Dr. Schroeter noted that a summary needs to be added to the Draft Report.

The Panel voted unanimously in favor of issuing the following informal data request:

(1) Polymerization rate and extent of polymerization (for Ethyl, Butyl, and Isobutyl Methacrylates and any other methacrylates that may be included in this safety assessment) to determine the amount of unreacted monomer that could come in contact with the skin (inadvertant exposure)
(2) Impurities data
(3) Mammalian genotoxicity data; if positive, carcinogenicity testing using NTP methodology may be needed
(4) Any additional adverse reaction reports that can be captured, with clarification as to how FDA's adverse reactions reporting system is set up
(5) Identification of any methacrylates that are being used in nail products

Concerning the Panel's request for adverse reaction reports, Dr. McEwen noted that data on reactions to products containing the methacrylates could be provided by CTFA.

Dr. Belsito reiterated that any information that is missing from the current review that could be captured from the CIR report

on Ethyl Methacrylate should be added as well.

Doug Schoon, with the American Beauty Association, wanted to know whether it is the intention of the Panel to use other methacrylates that are not included in the present review for comparative purposes or to add these ingredients to the present review.

Dr. Belsito said that the Panel's intention is that of reviewing all of the methacrylates that are being used in nail products as a group, so that the issues before the Panel will not need to be raised again during future safety assessments of methacrylates that could have been included in the current report.

JUNE 5, 2001 – Full Panel - THIRD REVIEW/DRAFT TENTATIVE REPORT

Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate

The CIR Draft Report on Butyl Methacrylate and Lauryl Methacrylate was reviewed at the February 12-13, 2001 Panel meeting. The Panel added Isobutyl Methacrylate to this safety assessment because evidence of its use in cosmetics was provided, and issued the following informal data request:

(1) Polymerization rate and extent of polymerization (for Ethyl, Butyl, and Isobutyl Methacrylates and any other methacrylates that may be included in this safety assessment) to determine the amount of unreacted monomer that could come in contact with the skin (inadvertant exposure)
(2) Impurities data
(3) Mammalian genotoxicity data; if positive, carcinogenicity testing using NTP methodology may be needed
(4) Any additional adverse reaction reports that can be captured, with clarification as to how FDA's adverse reactions reporting system is set up
(5) Identification of any methacrylates that are being used in nail products

To date, information relating to items 1 and 5 in the list has been received from the Nail Manufacturers Council of the American Beauty Association. Dr. Andersen noted that information on n-Butyl, Isobutyl, and Lauryl Methacrylate were provided, and that these data indicate that all have the same rapid polymerization properties as Ethyl Methacrylate.

Dr. Schroeter stated that, after reviewing the new data, his Team arrived at the following conclusion: Based on the available data and formulation of nail products containing Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate, the CIR Expert Panel concludes that these ingredients are safe as used when application is accompanied by directions to avoid skin contact because of the sensitizing potential of the Methacrylates.

Dr. Belsito said that he would not have any problems with this conclusion. However, he noted that the Panel was provided with information on other Methacrylate monomers that can be incorporated into nail products, and that his Team had discussed adding some of these monomers (specifically, the alkyl methacrylates) to the current report. Based on data on the structure-activity relationships of these monomers that were provided, he noted that it is likely that the Panel would reach the same conclusion for all of the methacrylates that will be reviewed in the CIR report.

Dr. Belsito added that similar compounds can be grouped; for example, one group could include n-butyl, isobutyl, tert-butyl, lauryl, n-hexyl, and 2-hydroxyethyl methacrylate. Additional groups would have to be created for, e.g., urethane methacrylate and dimethacrylate. Dr. Belsito noted that it is his understanding that the other methacrylate monomers will be added to the International Cosmetic Ingredient Dictionary and Handbook.

Dr. Andersen said that if the Panel reaches a tentative conclusion at today's meeting and also adds new ingredients to the review, the announcement of the report will be followed by a 90-day comment period. Comments as well as additional data could be submitted to CIR. Dr. Andersen also said that the Panel has the option of tabling the report, pending the addition of other ingredients.

Dr. Shank said that the Panel needs to be specific in terms of the alkyl methacrylates that will be added.

Dr. Andersen noted that n-Butyl, Isobutyl, and Lauryl Methacrylate all have the same rapid polymerization properties as Ethyl Methacrylate, and that this would lead to very little monomer being available for skin exposure. He said that this expectation,

together with safe practices of application, leads to a level of confidence that these three methacrylates could be considered safe.

Dr. Andersen expressed concern over extending the conclusion that was proposed by Dr. Schroeter to other methacrylates, without information indicating that these methacrylates would have the same properties as n-Butyl, Isobutyl, and Lauryl Methacrylate during cosmetic use.

Dr. Bergfeld said that if the Panel is willing to add other methacrylates to the present review, information on these methacrylates should be requested.

The Panel voted unanimously in favor of tabling the CIR report on Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate.

Dr. Bergfeld noted that the report is being tabled, pending the results of literature searches on other methacrylates. These methacrylates will be selected from a list of additional methacrylate monomers that was provided by the Nail Manufacturers Council of the American Beauty Association. Dr. Bergfeld said that it is anticipated that a decision as to which additional methacrylates can be incorporated into the CIR report will be made at the September 10-11, 2001 Panel meeting.

Mr. Doug Schoon, with the American Beauty Association, wanted to know if the information on polymerization rates of other methacrylate monomers that was submitted by the Nail Manufacturers Council is sufficient, and, if not, whether further information is needed. He noted that low levels of usage are associated with other methacrylates.

Dr. Andersen noted that the letter from the Nail Manufacturers Council indicates that butyl, isobutyl, and lauryl methacrylate represent less than 1% of the monomer that is used in the nail industry. Referring to this letter, he also said that he is under the impression that the polymerization rates of these three methacrylates are similar to that of ethyl methacrylate. Dr. Andersen stated that if these data are applicable to all 25 methacrylates, then a statement supporting this would have to be received from the Nail Manufacturers Council.

For clarity, the Panel's discussion and action on Butyl, Isobutyl, and Lauryl Methacrylate at today's meeting is summarized as follows:

The Panel considered new information indicating that Butyl, Isobutyl, and Lauryl Methacrylate represent only a small portion (on the order of 1%) of the methacrylates that are used in nail enhancement products and that they exhibit the same rapid polymerization as ethyl methacrylate on the nail, such that little monomer is available for exposure. On that basis, the Panel agreed that these ingredients would be considered safe as used in nail products. Because of the ongoing concern about the sensitization potential of methacrylates, the Panel agreed that it was necessary to add the caveat that application should be accompanied by directions to avoid skin contact. With this in mind, the Panel was uncertain as to how the 22 other methacrylates should be handled. Though these methacrylates are not listed in the International Cosmetic Ingredient Dictionary and Handbook, reportedly, they are used in a manner that is similar to that of Butyl, Isobutyl, and Lauryl Methacrylate. The Panel wanted additional supportive data to provide assurance that the 22 other methacrylates undergo similar rapid polymerization and are not available as monomers for any significant skin exposure. If so, the Panel would consider adding them to the current report. Pending receipt of that information, further discussion was tabled.

SEPTEMBER 11, 2001 – Full Panel - FOURTH REVIEW/DRAFT TENTATIVE REPORT

Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate

Dr. Belsito stated that Butyl, Isobutyl, and Lauryl Methacrylate were reviewed at the June 4-5, 2001 Panel meeting. He noted that it was determined that if the Panel were convinced that these monomers polymerize to the same extent, or greater, than Ethyl Methacrylate, then the Panel could arrive at the same conclusion that was issued on Ethyl Methacrylate. In 1999, the Panel issued an Amended Final Report with the following conclusion: Based on the available data on the formulation of nail products containing Ethyl Methacrylate, the CIR Expert Panel concludes that this ingredient is safe as used when application is accompanied by directions to avoid skin contact because of the sensitizing potential of Ethyl Methacrylate.

Dr. Belsito said that it was also brought to the Panel's attention that, in addition to the three monomers that are subject to this review, 19 other Methacrylates could potentially be used in nail products. Dr. Belsito noted that his Team decided that if it could be shown that these 19 Methacrylates polymerize to the same extent as Ethyl Methacrylate, then they could be added to the present report.

Upon further analysis of the additional Methacrylates, Dr. Belsito noted that two of them (2-[Diethylamino]Ethyl Methacrylate and 2-[Dimethylamino]Ethyl Methacrylate) are photocured Methacrylates. He also recalled Doug Schoon's comments at yesterday's meeting to the effect that the tri- and di-Methacrylates (except for the two just mentioned) included in the list of 19 do polymerize to the same extent (or greater) as Ethyl Methacrylate. Thus, Dr. Belsito noted that his Team concluded that the Panel's conclusion on Ethyl Methacrylate is also applicable to these Methacrylates.

Referring to Mr. Schoon's presentation on methacrylate monomers, Dr. Marks said that it should be made clear in the report discussion why a reduced number of methacrylates is included in Graph 3 (Set Time, 50% Spikes) and Graph 4 (Exotherm Data, 50% Spikes), compared to Graphs 1 and 2.

Dr. Bergfeld asked if Dr. Mark's Team had discussed the possibility that the 50% spike data (Graph 4) and 5% spike data (Graph 2) could be considered simultaneously, and deductive reasoning used to estimate values for the methacrylates that are not included in Graph 4.

Dr. Marks noted that this exercise had been discussed.

Dr. McEwen wanted to know if the Panel is proposing that a Tentative Final Report with the same conclusion that was determined for Ethyl Methacrylate should be issued at this meeting.

Dr. Belsito said that the proposed Tentative Final Report (with Ethyl Methacrylate conclusion) will also include the other Methacrylates (except for 2-[Diethylamino]Ethyl Methacrylate and 2-[Dimethylamino]Ethyl Methacrylate) that could potentially be used in nail products. He added that neither of the additional Methacrylates is listed in the International Cosmetic Ingredient Dictionary and Handbook, but that Mr. Schoon has applied for their inclusion.

Dr. McEwen said that the report discussion might contain a statement indicating that it is likely that different names for the 19 additional Methacrylates will be entered in the International Cosmetic Ingredient Dictionary and Handbook.

Dr. Belsito noted that, after curing, several of the Methacrylates that will be added to the review have a significantly high exothermic reaction, and that the temperature generated in that reaction should not result in damage to the nail plate. He said that Mr. Schoon agreed to provide these data.

Dr. Snyder asked that Mr. Schoon provide a corrected version of the handout that was distributed.

The Panel voted unanimously in favor of issuing a Tentative Final Report with a "safe with qualifications" conclusion on Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate, as well as additional Methacrylates (except for 2-[Diethylamino]Ethyl Methacrylate and 2-[Dimethylamino]Ethyl Methacrylate) that could potentially be used in nail products. The conclusion indicates that based on the available data on the formulation of nail products containing these ingredients, the CIR Expert Panel concludes that these ingredients are safe as used when application is accompanied by directions to avoid skin contact because of their sensitizing potential.

FEBRUARY 12, 2002– FULL PANEL - FIFTH REVIEW/DRAFT FINAL REPORT

Butyl Methacrylate, t-Butyl Methacrylate, Cyclohexyl Methacrylate, Ethoxyethyl Methacrylate, 2-Ethoxy Ethoxy Ethyl Methacrylate, Ethylene Glycol Dimethacrylate, Hexyl Methacrylate, HEMA, Hydroxyethylmethacrylate Acetoacetate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate, Isobutyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, Methoxydiglycol Methacrylate, Pyromellitic Glycidyl Dimethacrylate, Tetraethylene Glycol Dimethacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, Trimethylolpropane Trimethacrylate, Urethane Methacrylate, Urethane Dimethacrylate

Dr. Belsito stated that his Team revised (non-substantive changes) the Tentative conclusion that was approved at the September 10-11, 2001 Panel meeting to read as follows: Based on the available data, the CIR Panel concluded that the ingredients mentioned above (report conclusion will include all names) are safe as used in nail products when skin contact is avoided. Products containing these ingredients should be accompanied by directions to avoid skin contact because of the sensitizing potential of methacrylates. Additional changes in the report text that were recommended are included below.

Dr. Belsito said that the most substantive change in the report text, recommended in Teams, relates to the first paragraph in the section entitled Curing of Commercial Products (page 17). The last sentence in the paragraph should read as follows: The study established that there was sufficient reactivity of ethyl methacrylate in ethyl methacrylate nail enhancement systems, such that there are insignificant amounts of monomers after four hours of curing.

Dr. Marks recommended that the first paragraph of the Introduction contain the basis for reviewing all of the methacrylate compounds that are included in this safety assessment. He noted that this could be accomplished by moving the last paragraph of the Introduction to the beginning of this section. Furthermore, it was the consensus of Dr. Mark's Team that the report Introduction contain a statement indicating that CIR has published a safety assessment on Ethyl Methacrylate, and that this ingredient is the major Methacrylate that is used in nail enhancing products, representing over 90% of the monomer used in these products.

Dr. Belsito said that the reason why the Panel is reviewing the entire family of Methacrylates in this safety assessment should also be stated in the Cosmetic Use section. Furthermore, the additional Methacrylates that have been incorporated into this review should be included with the caveat that these ingredients have not been added to the International Cosmetic Ingredient Dictionary and Handbook, but that the Panel has been informed that they are being used in cosmetics and that the petitions will be made.

Dr. Belsito's Team recommended deletion of two secondary references (Jelovsek et al., 1989; Schardein et al., 1985) from the section on Reproductive and Developmental effects, in the absence of study details and primary references. Information from the secondary references, as summarized in text, is stated below:
Isobutyl Methacrylate tested positive as a developmental toxicant in rats. No other details were available (Jelovsek et al., 1989). Isobutyl Methacrylate was teratogenic in rats, but its teratogenicity in humans is not known. It is unknown if the data reflects a lack of sensitivity in humans or a lack of appropriate data (Schardein et al., 1985).

Dr. Marks recommended that the last sentence in the first paragraph of the Discussion be revised to read as follows: Moreover, the Panel received data showing that the rates of polymerization of these Methacrylates were similar to that of ethyl methacrylate, and that there would be little monomer available for exposure.

Based on the available data, the CIR Panel concluded that the Methacrylates included in this review are safe as used in nail products when skin contact is avoided. Products containing these ingredients should be accompanied by directions to avoid skin contact because of the sensitizing potential of methacrylates.

The Panel approved the preceding changes in the report text and voted unanimously in favor of issuing a Final Report with the following conclusion: Based on the available data, the CIR Panel concluded that Butyl Methacrylate, t-Butyl Methacrylate, Cyclohexyl Methacrylate, Ethoxyethyl Methacrylate, 2-Ethoxy Ethoxy Ethyl Methacrylate, Ethylene Glycol Dimethacrylate, Hexyl Methacrylate, HEMA, Hydroxyethylmethacrylate Acetoacetate, Hydroxypropyl Methacrylate, Isobornyl Methacrylate, Isobutyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, Methoxydiglycol Methacrylate, Pyromellitic Glycidyl Dimethacrylate, Tetraethylene Glycol Dimethacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, Trimethylolpropane Trimethacrylate, Urethane Methacrylate, and Urethane Dimethacrylate are safe as used in nail products when skin contact is avoided. Products containing these ingredients should be accompanied by directions to avoid skin contact because of the sensitizing potential of Methacrylate.

Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Bis(Glyceryl Dimethacrylate) Pyromellitate (previously, Pyromellitic Glycidyl Dimethacrylate)				**Butylcarbamoethyl Methacrylate (previously, Urethane Methacrylate)**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**19**	**NR**	**NR**	**5**	**NR**	**NR**	**NR**	**3**
Duration of Use								
Leave-On	*19*	*NR*	*NR*	*5*	*NR*	*NR*	*NR*	*3*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	19	NR	NR	5	NR	NR	NR	3
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	*NR*	NR	NR	NR	NR	NR
	Butyl Methacrylate				**t-Butyl Methacrylate**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**NR**	**NR**	**NR**	**7**	**NR**	**NR**	**NR**	**7**
Duration of Use								
Leave-On	*NR*	*NR*	*NR*	*7*	*NR*	*NR*	*NR*	*7*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	7	NR	NR	NR	7
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Cyclohexylmethacrylate (previously, Cyclohexyl Methacrylate)				**Di-HEMA Trimethylhexyl Dicarbamate**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**NR**	**NR**	NR	**2**	**76**	**NR**	**35.8-91.8**	**3**
Duration of Use								
Leave-On	*NR*	*NR*	*NR*	*2*	*76*	*NR*	*35.8-91.8*	*3*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*50.2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	2	76	NR	35.8-91.8	3
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2-Ethoxy Ethoxy Ethyl Methacrylate				**Ethoxyethyl Methacrylate**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**NA**	**NR**	**NA**	**75**	**NR**	**NR**	**NR**	**85**
Leave-On	*NA*	*NR*	*NA*	*85*	*NR*	*NR*	*NR*	*85*
Rinse-Off	*NA*	*NR*	*NA*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NA*	*NR*	*NA*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	NA	NR	NA	NR	NR	NR	NR	NR
Incidental Ingestion	NA	NR	NA	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NA	NR	NA	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NA	NR	NA	NR	NR	NR	NR	NR
Dermal Contact	NA	NR	NA	NR	NR	NR	NR	NR
Deodorant (underarm)	NA	NR	NA	NR	NR	NR	NR	NR
Hair - Non-Coloring	NA	NR	NA	NR	NR	NR	NR	NR
Hair-Coloring	NA	NR	NA	NR	NR	NR	NR	NR
Nail	NA	NR	NA	85	NR	NR	NR	85
Mucous Membrane	NA	NR	NA	NR	NR	NR	NR	NR
Baby Products	NA	NR	NA	NR	NR	NR	NR	NR
	Glycol Dimethacrylate (previously, Ethylene Glycol Dimethacrylate)				**HEMA**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**17**	**NR**	**1.2**	**5**	**149**	**NR**	**0.11-79**	**30**
Duration of Use								
Leave-On	*17*	*NR*	*1.2*	*5*	*149*	*NR*	*0.11-79*	*30*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	1	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	1	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	17	NR	1.2	5	148	NR	0.11-79	30
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	HEMA Acetoacetate (previously, Hydroxyethylmethacrylate Acetoacetate)				**Hexyl Methacrylate**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**NR**	**NR**	**NR**	**10**	**NR**	**NR**	**NR**	**5**
Duration of Use								
Leave-On	*NR*	*NR*	*NR*	*10*	*NR*	*NR*	*NR*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	10	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Hydroxypropyl Methacrylate				**Isobornyl Methacrylate**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**40**	**NR**	**0.8-23**	**25**	**NR**	**NR**	**8.3-20.2**	**5**
Duration of Use								
Leave-On	*40*	*NR*	*0.8-23*	*25*	*NR*	*NR*	*8.3-20.2*	*5*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	40	NR	0.8-23	25	30	NR	8.3-20.2	5
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Isobutyl Methacrylate				**Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate (previously, Isopropylidenediphenyl Bisglycidyl Methacrylate**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**NR**	**NR**	**0.0005**	**10**	**1**	**NR**	**4.3-9.5**	**5**
Duration of Use								
Leave-On	*NR*	*NR*	*0.0005*	*10*	*1*	*NR*	*4.3-9.5*	*5*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	19	NR	0.0005	10	1	NR	4.3-9.5	5
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	*NR*	NR	NR	NR	NR	NR

	Lauryl Methacrylate				**Methoxydiglycol Methacrylate**			
	2021[1]	**2001[2]**	**2020[3]**	**2001[2]**	**2021[1]**	**2001[2]**	**2020[3]**	**2001[2]**
Totals*	**1**	**NR**	**NR**	**5**	**NR**	**NR**	**24.8-65**	**85**
Duration of Use								
Leave-On	*1*	*NR*	*NR*	*5*	*NR*	*NR*	*24.8-65*	*85*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	5	NR	NR	24.8-65	85
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	PEG-4 Dimethacrylate				Tetrahydrofurfuryl Methacrylate			
	2021[1]	2001[2]	2020[3]	2001[2]	2021[1]	2001[2]	2020[3]	2001[2]
Totals*	**NR**	**NR**	**6.6-10**	**15**	**NR**	**1**	**20.6-38.2**	**7**
Duration of Use								
Leave-On	*NR*	*NR*	*6.6-10*	*15*	*NR*	*1*	*20.6-38.2*	*7*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	6.6-10	15	NR	1	20.6-38.2	7
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Triethylene Glycol Dimethacrylate				Trimethylolpropane Trimethacrylate			
	2021[1]	2001[2]	2020[3]	2001[2]	2021[1]	2001[2]	2020[3]	2001[2]
Totals*	**NR**	**NR**	**8.7-20**	**7**	**1**	**NR**	**25.3**	**5**
Duration of Use								
Leave-On	*NR*	*NR*	*8.7-20*	*7*	*1*	*NR*	*25.3*	*5*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	8.7-20	7	1	NR	25.3	5
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
**at the time of the 2003 safety assessment, concentration of use data were not reported by the FDA; however, industry provided a maximum concentration of use
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.
[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
NR – not reported
NA – this ingredient is no longer in use; therefore 2021 data are not applicable

1. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD. 2021. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2021; received January 21, 2021).

2. Escobar A, Yamarik TA. Final Report of the Safety Assessment of Methacrylate Ester Monomers Used in Nail Enhancement Products. *International Journal of Toxicology*. 2005;24:53-100.

3. Personal Care Products Council. 2021. Concentration of use by FDA product category. Methacrylate monomers. Unpublished data submitted by the Personal Care Products Council on 10-7-2020.

New Data – 22 Methacrylate Ester Monomers

Bis(Glyceryl Dimethacrylate) Pyromellitate) (formerly Pyromellitic Glycidyl Dimethacrylate)
Butylcarbamoethyl Methacrylate (formerly Urethane Methacrylate)
Butyl Methacrylate
t-Butyl Methacrylate
Cyclohexylmethacrylate (formerly Cyclohexyl Methacrylate)
Ethoxyethyl Methacrylate
2-Ethoxy Ethoxy Ethyl Methacrylate
Glycol Dimethacrylate (formerly Ethylene Glycol Dimethacrylate)
Hexyl Methacrylate
HEMA (2-Hydroxyethyl Methacrylate)
HEMA Acetoacetate (formerly Hydroxyethylmethacrylate Acetoacetate)
Di-HEMA Trimethylhexyl Dicarbamate
Hydroxypropyl Methacrylate
Isobornyl Methacrylate
Isobutyl Methacrylate
Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate (formerly Isopropylidenediphenyl Bisglycidyl Methacrylate)
Lauryl Methacrylate
Methoxydiglycol Methacrylate
PEG-4 Dimethacrylate
Tetrahydrofurfuryl Methacrylate
Triethylene Glycol Dimethacrylate
Trimethylolpropane Trimethacrylate

CHEMISTRY

Physical and Chemicals Properties

Butyl Methacrylate

In accordance with OECD TG 101, UV/Vis absorption spectra for Butyl Methacrylate were obtained.[1] The spectra indicate minor absorbance in the range of 290 - 700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 l $mol^{-1} \cdot cm^{-1}$.

Other Safety Assessments

The Research Institute for Fragrance Materials (RIFM) has published a fragrance ingredient safety assessment on Butyl Methacrylate.[2]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Butyl Methacrylate

The *in vitro* skin absorption potential of Butyl Methacrylate was evaluated in rat and human epidermis and through rat whole (viable) skin using glass diffusion cells.[3] One-hundred µl/cm^2 of neat Butyl Methacrylate was applied to the epidermal surface for 24 h. The rate of appearance of methacrylic acid and parent ester, Butyl Methacrylate, was measured in receptor fluid. The total amount of chemical that was absorbed during the time of exposure was 18% (over 24 h), 2% (over 24 h), and 0.4% (over 10 h) for rat and human epidermis and rat whole (viable) skin, respectively. It was concluded that Butyl Methacrylate was absorbed through rat and human epidermis; however, human epidermis was approximately 9 times less permeable to Butyl Methacrylate than rat epidermis. Only methacrylic acid appeared in the receptor chambers of skin that had Butyl Methacrylate applied to the surface. This suggested that all of the Butyl Methacrylate that is absorbed through the skin is hydrolyzed by carboxylesterases that are present in this tissue.

Hexyl Methacrylate

The absorption of Hexyl Methacrylate was evaluated through rat and human epidermis in an in vitro system.[4] The technique measured the rate of absorption of Hexyl Methacrylate across the epidermis. The test substance was applied (open application) for 48 h to epidermal membranes (from rat and human skin) at a dose of 100 µl/cm^2. Glass diffusion cells were used to measure the amount of Hexyl Methacrylate that is received into a receptor chamber with respect to time, following

application to the epidermal surface. The mean rate of absorption was 147 µg/cm^2/h respectively. Hexyl Methacrylate appeared to have been readily absorbed through rat and human epidermis.

Lauryl Methacrylate

The absorption of Lauryl Methacrylate was evaluated using whole rat skin and rat epidermis in an in vitro system (glass diffusion cells).[6] The amount of Lauryl Methacrylate received into the receptor chamber (with respect to time) after application of 100 µl/cm^2 to the epidermal surface was evaluated. The mean rate of absorption was 26.2 µg/cm^2/h for rat epidermis and 7.72 µg/cm^2/h for whole rat skin. The total amount of Lauryl Methacrylate that was absorbed during 24 h of exposure was 0.7 % (rat epidermis) and 0.26 % (rat whole skin). Dermal absorption was described as low. Because the presence of carboxyl esterases in the skin resulted in complete hydrolysis of the test substance, only the resulting metabolite, methacrylic acid, was demonstrated to pass through.

Computational

Glycol Dimethacrylate

The skin penetration potential of Glycol Dimethacrylate was evaluated based on a QSAR prediction.[7] The prediction model used in this investigation, for a set of methacrylate chemicals, is based on an established model. Prediction of the skin penetration characteristics was accomplished using the physicochemical properties used as a first level assessment of the ability of the chemical to cross the human epidermis. Based on the dermal penetration model for human skin, the predicted skin penetration for Glycol Dimethacrylate was determined to be low (6.109 µg/cm²/h).

HEMA

The dermal absorption (steady-state flux) of HEMA has been estimated by calculation using the principles defined in the Potts and Guy prediction model.[8] Based on a molecular weight of 130.1 g/mol and a log K_{ow} of 0.42, the predicted flux of HEMA is 151.3µg/cm²/h, indicating that the relative dermal absorption is high.

Tetrahydrofurfuryl Methacrylate

Based on a molecular weight of 170.21 g/mol and a log K_{ow} of 1.35, the predicted flux of Tetrahydrofurfuryl Methacrylate is 28.461 µg/cm²/h.[9] Based on this prediction, the relative dermal absorption of Tetrahydrofurfuryl Methacrylate is considered moderate.

Triethylene Glycol Dimethacrylate

The dermal absorption (steady-state flux) of Triethylene Glycol Dimethacrylate has been estimated by calculation using the principles defined in the Potts and Guy prediction model.[10] Based on a molecular weight of 286.32 g/mol and a log K_{ow} of 2.3, the predicted flux of Triethylene Glycol Dimethacrylate is 4.989 µg/cm²/h; the relative dermal absorption is low.

Trimethylolpropane Trimethacrylate

Dermin (estimation programs interface suite for Microsoft Windows v.4.11) was used to estimate the dermal permeability coefficient (K_p) for Trimethylolpropane Trimethacrylate.[11] A K_p value of 0.012 cm/h was calculated. Additionally, the log K_{ow} for Trimethylolpropane Trimethacrylate was estimated to be 4.50.

Absorption, Distribution, Metabolism, and Excretion

Butyl Methacrylate

A reliable experimental method, the in vivo (male Fischer 344 rats, i.v. dosing) and in vitro (not defined) investigations, as well as the physiologically based pharmacokinetic (PBPK) models developed from the data, showed that alkyl-methacrylate esters are rapidly absorbed and are hydrolyzed at exceptionally high rates to methacrylic acid by high capacity, ubiquitous carboxylesterases.[12] Furthermore, the removal of the hydrolysis product, methacrylic acid, also is very rapid (minutes). For Butyl Methacrylate, the half-life was 7.8 min and 99.7 % was removed by first-pass metabolism in the liver.

HEMA and Triethylene Glycol Dimethacrylate

The metabolism of HEMA and Triethylene Glycol Dimethacrylate was studied using A549 human lung cancer (epithelial-like) cells.[13] Two possible pathways for their metabolism to carbon dioxide are an epoxide pathway and a valine pathway. The formation of pyruvate is postulated in the epoxide pathway, and the formation of *L*-malate is associated with the valine pathway. The purpose of this study was to quantify formation of the intermediates pyruvate and *L*-malate, to demonstrate which pathway may be preferred in A549 cells. These cells were incubated with [^{14}C]HEMA or [^{14}C]Triethylene Glycol Dimethacrylate, and metabolites were identified and quantified by thin layer chromatography, at different time intervals, from the extracellular and intracellular fluid. Results indicated that in the metabolism of HEMA and Triethylene Glycol Dimethacrylate, more [^{14}C]pyruvate was formed when compared to [^{14}C]L-malate. Therefore, the epoxide pathway, with formation of the epoxy-intermediate 2,3-epoxymethacrylic acid, is the main route of metabolism of HEMA and Triethylene Glycol Dimethacrylate.

^{14}C-HEMA (20 mmol/kg body weight) was administered, via gastric tube, to 56 male ICR (CD-1) mice.[14] The test substance was taken up rapidly from the stomach and intestines and was widely distributed in the body. Most ^{14}C was excreted within 1 d as [^{14}C]CO_2.

The uptake and clearance of ^{14}C-Triethyleneglycol Dimethacrylate was examined using guinea pigs.[15] The test substance (0.02 mmol/kg by weight, labeled with a tracer dose of ^{14}C-Triethyleneglycol Dimethacrylate (0.7 Bq/g by weight)) was administered by gastric tube or by subcutaneous injection. Urine, feces, and exhaled carbon dioxide were collected for 24 h after dosing. The animals were killed at 24 h after initiation of the experiment. Various organs were removed and ^{14}C-radioactivity was measured. ^{14}C-Triethyleneglycol Dimethacrylate was taken up rapidly from the stomach and small intestine after gastric administration, and was widely distributed in the body following administration via both routes. Clearance from most tissues following gastric and intradermal administration was essentially complete within 1 d. Low fecal ^{14}C-levels (< 1% of administered dose) and urinary levels of approximately 15% after 24 h were noted after both routes of administration. Direct measurement of exhaled carbon dioxide showed that 60 to 65% of the administered dose of ^{14}C left the body via the lungs over a 24-h period. The authors noted that ^{14}C-pyruvate is formed in vivo, resulting possibly in the formation of toxic ^{14}C-Triethyleneglycol Dimethacrylate intermediates.

HEMA and Di-HEMA Trimethylhexyl Dicarbamate

According to the Scientific Committee on Consumer Safety (SCCS), the available evidence suggests that normal nail plate acts as a good barrier to the penetration of chemical substances in general, and that both methacrylate monomers (HEMA and Di-HEMA Trimethylhexyl Dicarbamate) polymerize rapidly under UV curing when applied as part of an artificial nail modelling system.[134] This leaves very little chance for the monomers to be absorbed in any appreciable amount through the nail plate. In view of this, the SCCS is of the opinion that HEMA and Di-HEMA Trimethylhexyl Dicarbamate, when applied appropriately to the nail plate at concentrations of up to 35% and 99%, respectively, as part of an artificial nail modelling system, are not likely to pose a risk of sensitization, provided that their use is restricted to the nail plate only and contact with the adjacent skin is avoided.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

t-Butyl Methacrylate

An acute dermal toxicity study on t-Butyl Methacrylate was performed using groups of 10 (5 males, 5 females/group) Sprague-Dawley rats.[16] The study was performed in accordance with OECD TG 402. Test substance application (under semi-occlusive gauze patch; dose = 2 g/kg) to the dorso-lumbar area was performed. The dose volume was 2.26 ml/kg. None of the animals died, and no signs or systemic toxicity were observed. No abnormalities were observed at gross necropsy. The LD_{50} was > 2 g/kg.

Cyclohexylmethacrylate

The acute dermal toxicity of Cyclohexylmethacrylate was evaluated in accordance with OECD TG 402.[17] Groups of 10 Wistar rats (5 males and 5 females) received a dose of 2 g/kg. The test substance was applied for 24 h, under a semi-occlusive wrap, to a 40 cm^2 area. Dosing was followed by a 14-d observation period. None of the animals died, and no systemic clinical signs were observed during clinical examination. Additionally, no local effects were observed. No macroscopic pathologic abnormalities were observed. The LD_{50} was > 2 g/kg.

Glycol Dimethacrylate

A study was performed to evaluate the acute dermal toxicity of Glycol Dimethacrylate. Groups of 10 (5 males, 5 females/group) Wistar rats were exposed (dorsal area of trunk; 10% of total body surface) for 24 h to the test substance (dose = 2 g/kg).[18] The application site was covered with a gauze dressing secured with non-irritating tape. The end of the application period was followed by a 14-d observation period. Necropsy of surviving animals was performed. None of the animals died. Signs of irritation (erythema grade of 2) were observed in 1of 5 female animals. Erythema (grade of 1) was observed in 2 of 5 female rats. Eschar was observed in 2 of 5 female rats. No signs of irritation were seen in male rats. Signs of irritation were reversible within the 14-d observation period. No treatment-related effects were observed at gross pathological examination. The LD_{50} was > 2 g/kg, and Glycol Dimethacrylate was classified as practically non-toxic.

HEMA

The acute dermal toxicity of HEMA (no vehicle) was evaluated using 6 male New Zealand White rabbits.[19] The test substance was applied (under occlusion (impervious cuff); dose: 5 g/kg) to the skin for 24 h. Dosing was followed by a 14-d observation period. Necropsy of surviving animals was performed. Transient skin irritation (well defined erythema, no edema) was observed. No effects were observed at gross pathological examination. The LD_{50} was determined to be > 5 g/kg, and HEMA was classified as practically nontoxic.

HEMA Acetoacetate

The acute dermal toxicity of HEMA Acetoacetate was evaluated using groups of 10 rats (5 males, 5 females per group) of the CD (Crl:CD SD) strain.[20] The test substance (dose = 2 g/kg bw) was applied for 24 h, under an occlusive patch, to the dorso-lumbar region (50 mm x 50 mm area). None of the animals died, and there was no systemic response to treatment. No dermal reactions were observed. Gross pathological examinations revealed no abnormalities. The LD_{50} was > 2 g/kg bw.

Isobornyl Methacrylate

In an acute dermal toxicity study, rabbits (number not stated) received a single dose of Isobornyl Methacrylate (3 g/kg bw).[21] Details relating to the test procedure are not included. An LD_{50} of > 3 g/kg was reported, and the test substance was classified as practically nontoxic in rabbits.

Trimethylolpropane Trimethacrylate

Trimethylolpropane Trimethacrylate was evaluated for acute dermal toxicity in accordance with OECD TG 402. Groups of 10 Wistar rats (5 males, 5 females per group) received a single, 24-h dermal application of the test substance (2 g/kg bw), under a semi-occlusive patch.[24] Dosing was followed by a 14-d observation period, after which all surviving animals were killed and necropsied. All rats gained weight over of the study period. None of the animals died, and the absence of clinical signs was noted. At necropsy, the following observations were made in 1 male rat: red foci on the thymus, red foci on the mandibular lymph nodes, and pale kidneys. Large mandibular lymph nodes and pelvic dilatation of the kidneys were observed in1 female rat. The absence of cutaneous reactions during the observation period was noted. Based on the results of this study, the acute dermal LD_{50} for male and female rats > 2 g/kg bw.

Oral

t-Butyl Methacrylate

The acute oral toxicity of t-Butyl Methacrylate was evaluated using groups of 6 Wistar/CHBB: THOM (SPF) rats (3 males, 3 females per group).[25] The test substance (10 g/100 ml (dose = 2 g/kg), in olive oil) was administered by gavage. Dosing was followed by a 14-d observation period. Necropsy of surviving animals was performed. None of the animals died. Reversible clinical signs (dyspnea and piloerection) were observed in females; no clinical signs were observed in males. Necropsy did not reveal any pathological findings. The LD_{50} was > 2 g/kg.

Cyclohexylmethacrylate

The acute oral toxicity of Cyclohexylmethacrylate was evaluated in accordance with OECD TG 401.[26] Groups of 10 Wistar rats (5 males and 5 females) received doses up to 19.28 g/kg by gavage. In the animals found dead, inflamed mucosa of the stomach and intestinal mucosa was observed. Gross internal lesions were not observed. The LD_{50} was 12.9 g/kg.

Glycol Dimethacrylate

A study evaluating the acute oral toxicity of Glycol Dimethacrylate (no vehicle) was performed using groups of 10 SPF Wistar rats (5 males, 5 females/group).[27] The following doses (1 per group) were administered via gavage: 7.94, 8.89, 10.00, 11.20, 12.60 ml/kg. Dosing was followed by a 14-d observation period. In all of the dose groups, mortalities occurred within 5 d. The mortalities (total) reported after 14 d are stated as follows: In the first group, 4 of 10 animals died, and 7 of 10 animals died in the second group. In the third dose group, 8 of 10 animals died, and all of the animals in the fourth and fifth groups died. Transient clinical signs (e.g., piloerection and tremor; 24-h duration) were reported. The LD_{50} was 8.7 g/kg, and Glycol Dimethacrylate was classified as non-toxic.

HEMA

HEMA (no vehicle) was evaluated in an acute oral toxicity study involving groups of 10 (5 males, 5 females/group) rats. Doses ranging from 3.4 g/kg to 6.74 g/kg were administered by gavage.[28] A 14-d observation period was observed after dosing. Necropsy of surviving animals was performed. Mortalities occurred within 24 h of dosing. Results at necropsy of animals that died included hemorrhages of the stomach and colon mucosa. At the end of the study, no pathological or anatomical changes were found in the cranium, chest, or abdominal cavity. Other findings (initially at 10 min and findings diminished at 24 h) were identified as: tremor, convulsion, ataxia, postural anomalies, reduced grip and limb tonus, increased body temperature, and piloerection. An LD_{50} of 5.56 g/kg was reported, and HEMA was classified as practically nontoxic.

HEMA Acetoacetate

An acute oral toxicity study on a HEMA Acetoacetate trade material was performed using 20 Wistar rats (Cr1:(WI)BR strain; 10 males, 10 females), in accordance with OECD TG 401.[29] The test substance was administered by oral gavage at single doses up to 5 g/kg bw. Dosing was followed by a 14-d observation period. None of the animals died and no clinical signs were observed. No abnormalities were observed at gross necropsy. There was no indication that tissues were maintained for microscopic examination. The LD_{50} was > 5 g/kg bw.

Hexyl Methacrylate

The acute oral toxicity of Hexyl Methacrylate was studied using 20 Wistar SPF rats (10 males and 10 females).[30] A single dose of 17.7 g/kg (dose volume: 20 ml/kg) was administered by gavage. Dosing was followed by a 14-d observation period. Eight of 20 animals died within the first 8 d after dosing. Gastrointestinal flush was observed in these animals. No macroscopic anomalies were observed in animals that died. Dosing with Hexyl Methacrylate caused reduced activity, disturbed coordination, hyperthermia, diarrhea, and piloerection at 20 min post-administration. These signs were not observed after 24 h, and normal behavior was observed in surviving animals. Hexyl Methacrylate was classified as having very low oral toxicity (LD_{50} > 17.7 g/kg).

Isobornyl Methacrylate

In an acute oral toxicity study, groups of 10 fasted Sprague-Dawley rats (5 males, 5 females/group) were given a single oral dose of Isobornyl Methacrylate at dose levels of 464 µl/kg (10% v/v) suspension in corn oil, 1000 µl/kg, 2150 µl/kg, 4640 µl/kg, and 10,000 µl/kg (undiluted).[31] An additional group of female rats received an additional dose of 21,500 µl/kg, and dosing was followed by a 14-d observation period. Necropsy findings (females at 464 and 4640 µl/kg) included yellow-appearing contents after animals were killed. Gastrointestinal inflammation and/or congestion of the lung lobes was observed in dead animals at the 2 highest dose levels. An oral LD_{50} of > 2 g/kg bw was reported, and Isobornyl Methacrylate was classified as practically nontoxic.

Groups of rats (number per group and strain not stated) were dosed orally (by gavage) with Isobornyl Methacrylate in an acute toxicity study.[32] The clinical signs included depression, hunched appearance, ataxia, excessive urination, and labored respiration. Animals that died during the study (number not stated) had gastrointestinal inflammation and/or congestion of the lung lobes at the 2 highest dose levels (i.e., ≈ 4.547 and 9.800 g/kg bw for males and 9.800 and 21.070 g/kg bw for females). The oral LD_{50} value was 3.100 g/kg bw (males) and 6.670 g/kg bw (females). Isobornyl Methacrylate was not considered to be an acutely toxic substance in this study.

Isobutyl Methacrylate

The acute oral toxicity of Isobutyl Methacrylate was evaluated in a study involving groups of 10 (5 males, 5 females/group) fasted Wistar rats, in accordance with OECD TG 401.[33] The test substance was administered (by gavage) at doses ranging from 8.88 to17.76 g/kg. A gross necropsy was performed on all animals found dead or at the end of the 14-d observation period. The clinical signs observed within the first 24 h included a generally reduced activity, staggering gait and ataxia, decreased tonus in muscles of extremities and abdomen, diarrhea, piloerection, discoloration of the mucosa and decreased body temperature. At the highest dose, 17.76 g/kg, dyspnea and salivation were also observed. Generally, all symptoms increased in a dose-dependent manner. No clinical symptoms were present in those animals that survived up to the observation points at 7 and 14 d post-exposure. Except for local effects at the site of first contact, hemorrhage in the intestinal tract, no target organ was identified. The LD_{50} was determined to be 9.59 g/kg.

Lauryl Methacrylate

In an acute oral toxicity study (OECD TG 401), groups of 10 fasted SPF Wistar rats (5 males, 5 females/ group) were given a single oral dose (by gavage) of Lauryl Methacrylate (in water) at a dose of 5 g/kg bw.[34] Dosing was followed by a 14-d observation period. At necropsy, test substance-related signs of toxicity were not clearly obvious when compared to controls. Similar incidences of red and white foci on the lung surface of the experimental and control rats. In 2 of 5 males and 1 of 5 females of the experimental group, slightly swollen liver margins were observed. An oral LD_{50} of > 5 g/kg bw was reported, and the test substance was classified as practically nontoxic.

Methoxydiglycol Methacrylate

The acute oral toxicity of Methoxydiglycol Methacrylate was evaluated using 5 female Sprague-Dawley rats, in accordance with OECD TG 425.[35] A single oral dose of 2 g/kg was administered by gavage. Dosing was followed by a 14-d observation period. All animals were examined for gross pathology. None of the animals died, and gross necropsy revealed no observable abnormalities. An oral LD_{50} of > 2 g/kg bw was reported.

PEG-4 Dimethacrylate

PEG-4 Dimethacrylate was evaluated in an acute oral toxicity study involving rats (number not stated).[36] The test substance was administered by gavage at a single oral dose of 5 g/kg bw. Details relating to the test protocol were not included. The LD_{50} was reported as > 5 g/kg body weight.

Tetrahydrofurfuryl Dimethacrylate

The acute oral toxicity of undiluted Tetrahydrofurfuryl Methacrylate was evaluated using groups of 10 fasted Sprague-Dawley rats (5 males, 5 females/group), in accordance with OECD TG 401.[37] The following single oral doses of the test substance were administered by oral gavage: 2.5, 3.75, 5.63, and 8.44 g/kg bw. Dosing was followed by a 14-d observation period. Mortalities were reported as follows: 1 female (at 2.5 g/kg bw), 3 females and 2 males (at 3.75 g/kg bw), 5 females and 4 males (at 5.63 g/kg bw), and 4 males and 5 females (at 8.44 g/kg bw). Decreased motor activity and respiratory rate were commonly observed up to 1 d after administration. Additionally, hematuria, griping, diarrhea, and lachrymose were

observed in 1 of 10 animals on day 1 (at 2.5 g/kg bw). In the 3.75 g/kg bw dose group, griping and lachrymose were observed in 2 of 10 animals on day 1, and hematuria was observed in 3 of 10 animals on day 1. In the 5.63 g/kg bw dose group, hematuria was observed in 5 of 10 animals and lachrymose was observed in 5 of 10 animals on day 1.

In all dose groups, the surviving animals appeared normal from day 2 forward. The common internal pathologies were: hepatic discoloration and/or necrosis; hematuria; urinary bladder hemorrhages; gastric intestinal tract injection, hemorrhages, and/or disintegration; and pancreatic hemorrhages. Renal hemorrhages and/or loss of color were observed commonly in the 2 highest dose groups. Other abnormalities that were observed with less frequency included hemorrhagic thymus and discoloration and/or necrosis of the spleen. An oral LD_{50} (combined) of 3.95 g/kg bw (95% confidence interval: 3.121 to 4.986 g/kg bw) was reported.

Trimethylolpropane Trimethacrylate

In an acute oral toxicity study (OECD TG 423), 6 Sprague Dawley female rats were given a single oral dose (2 g/kg bw, by gavage) of Trimethylolpropane Trimethacrylate.[38] The absence of the following was reported: mortalities, clinical signs, body weight changes, and abnormalities at macroscopic examination of main organs. However, red foci on the thymus, a large mandibular lymph node, and red foci on the mandibular lymph node were observed in 1 animal. Based on the results of this study, the oral LD_{50} was determined to be > 2 g/kg bw.

Inhalation

Butyl Methacrylate

In an OECD TG 403 study with acceptable restriction (no macroscopic observation at sacrifice), 6 groups of 5 male and 5 female Sprague-Dawley rats each were exposed for a single, 4-h period to atmospheres containing a mixture of Butyl Methacrylate aerosol and vapor in air.[39] Aerosol concentrations were determined by gravimetric analysis and vapor concentrations were determined by gas chromatography. During a 14-d recovery period, rats were weighed and observed for clinical signs of toxicity. Rats were exposed to 13.8, 18, 24, 27, 29, or 36 mg/l of Butyl Methacrylate, and the aerosol MMADs were 4.5, 6.0, 3.9, 6.7, 8.0 or 8.3 µm, respectively. Deaths occurred following exposure to Butyl Methacrylate at concentrations of 29 mg/l or greater. Some important effects of exposure included slight to severe weight loss and signs of respiratory tract irritation. Surviving rats had an overall weight gain by the end of the recovery period. Under the conditions of this study, it was not possible to calculate the LC_{50}. The approximate lethal concentration for Butyl Methacrylate was 29 mg/l.

t-Butyl Methacrylate

The acute inhalation toxicity of t-Butyl Methacrylate was evaluated using groups of 10 Sprague-Dawley rats (5 males, 5 females per group).[40] Exposure was described as nose/head only. Each rat was individually held in a tapered, polycarbonate restraining tube fitted onto a single tier of the exposure chamber. The duration of test substance exposure was 4 h at a concentration of 10.7 mg/l (pressure = 1 atm). None of the animals died. At necropsy, abnormalities were noted on the lungs of several animals, including areas that were pale, dark, raised, hardened or with a gray discoloration. Some animals also showed dark foci. No other abnormalities were detected in animals at necropsy.

Lauryl Methacrylate

Groups of 4 male Swiss Webster mice were exposed (whole-body, in exposure chamber) for a single, 30-min period to a concentration of Lauryl Methacrylate in air (460, 1500, 2100, 2900, or 3800 mg/m³) to assess sensory irritation potential.[42] Due to low vapor pressure, Lauryl Methacrylate was generated as an aerosol. Next, a post-exposure monitoring period of at least 10 min was observed. The mice were observed for clinical signs of toxicity and then killed. Respiratory function parameters were monitored during all pre-exposure, exposure, and post-exposure periods. The RD_{50} (concentration that will produce a 50 % depression in respiratory rate) was calculated. Exposure to 460, 1500, 2100, 2900, or 3800 mg/m^3 Lauryl Methacrylate caused both respiratory rate decreases and persistent breathing patterns of sensory irritation at the higher concentrations. The decrease in respiratory rate and the severity of irritation was dose-dependent. An RD_{50} of 3.9 mg/l was calculated, indicating a low potential for causing upper respiratory tract irritation.

Short-Term Toxicity Studies

Dermal

Triethylene Glycol Dimethacrylate

A 14-d cell proliferation study was performed.[43] Four groups of male Harlan Sprague-Dawley (C3H/HeNHsd strain) mice were treated with Triethylene Glycol Dimethacrylate at concentrations of 5, 25, 50, and 100% daily for 14 consecutive days. Triethylene Glycol Dimethacrylate was dissolved in acetone, except for when 100% Triethylene Glycol Dimethacrylate was applied. Single doses (50 µl) were applied topically to the clipped interscapular region of the back using a calibrated pipette. Other than the site of application, no effort was made to prevent oral ingestion (e.g., through the use of collars). Detailed clinical observations were made daily (starting on day 2), and skin lesions were scored (slight, moderate, and severe). On days 8 and 15, half of the animals in each group were killed. Necropsy included a visual examination of all body surfaces and orifices, and examination of all organs and tissues of the abdominal, thoracic, and cranial cavities. Mean

body weight was decreased (approximately 10% from the control groups) only in the 100% Triethylene Glycol Dimethacrylate group after 14 d. Skin sections were prepared for autoradiography, and the labeling index was calculated as the percentage of autoradiography-positive nuclei. Skin irritation and cell proliferation were the principle findings, and the incidence and severity were observed in a dose-related manner. Acanthosis (epidermal thickening) also tended to correlate with the increased rate of cell proliferation. Acanthosis, dermatitis, and hyperkeratosis were observed in all treatment groups. Other lesions (types not stated) occurred in fewer animals. Statistically significantly increased labeling index was observed for all doses, with the greatest increase (14-fold from acetone control) observed at the 100% dose.

Another 14-d study was performed.[43] Groups of male Harlan Sprague-Dawley (C3H/HeNHsd strain) mice (5/group) were treated for 14 consecutive days with Triethylene Glycol Dimethacrylate at concentrations of 0.5, 1, 2, 5, 10%, or 100%. Triethylene Glycol Dimethacrylate was dissolved in acetone, except for when 100% Triethylene Glycol Dimethacrylate was applied. Single doses (50 µl) were applied topically to the clipped interscapular region of the back using a calibrated pipette. Other than the application site, no effort was made to prevent oral ingestion (e.g., through the use of collars). A control group treated with acetone was included. Detailed clinical exams, including special attention to skin irritation and overt signs of neurotoxicity (although no specific neurotoxic evaluations were performed), were conducted daily. Animals were given a complete necropsy and treated skin was saved for standard histopathologic evaluations. Other than gross and microscopic lesions of the treated skin, no effects, including overt neurotoxic effects, from Triethylene Glycol Dimethacrylate concentrations up to 100% were observed after 14 d of treatment. Triethylene Glycol Dimethacrylate treatment resulted in desquamation/exfoliation at all concentrations, ulceration at 2% and higher, and eschar and discoloration at 5 and 10%. Triethylene Glycol Dimethacrylate treatment resulted in acanthosis in all animals. Dermatitis occurred in most animals, and intracorneal pustules and hyperkeratosis were diagnosed in all animals at concentrations of 50% and 100%, and in one animal at 25%. Dermal fibrosis was also seen in one animal in each of the 50 and 100% groups.

Triethylene Glycol Dimethacrylate (50 µl, in acetone) was applied (open application) to the shaved skin of 5 male C3H/HeNHsd mice/dose, at 50 µl of concentrations of 25 %, 50% and 100% (doses of 0.5, 1, and 2 g/kg bw/d) daily for 14 d.[23] No mortality, no significant clinical signs, and no necropsy findings in internal organs were observed in all dose groups. Desquamation and exfoliation were the only skin findings noted during the study and at necropsy in the 50% and 100% Triethylene Glycol Dimethacrylate treatment groups. Microscopic changes in the treated skin primarily consisted of dermatitis, intracorneal pustule formation, acanthosis, and hyperkeratosis. Epidermal necrosis or ulceration was not evident in any of the treated mice. The authors stated that the dermal LD_{50} for Triethylene Glycol Dimethacrylate in this study was greater than 2 g/kg bw, even if this dose was not only applied once in this study.

Trimethylolpropane Trimethacrylate

Trimethylolpropane Trimethacrylate (undiluted) was applied to the backs of groups of 10 albino rabbits (5 males, 5 females per group).[44] The animals were treated daily, 5 d/wk, for 2 wk (10 treatments total). Dosing (0.3 g/kg/d) was accomplished by dispensing the dose volume from a disposable syringe onto the animal's back and spreading it evenly over the area of exposure. Six animals were killed after 2 wk, and the remaining 4 were held for an additional 2-wk non-treatment period before the animals were killed. None of the animals died during the dosing period. Dosing at 0.3 g/kg/d caused signs of slight dermal irritation, with no eschar formation or necrotic skin. One female exhibited very slight weight loss. Microscopic examination of tissues obtained from rabbits treated for 2 wk indicated no evidence of a systemic effect. However, minimal to mild irritation was observed in skin samples. Examination of tissues from rabbits held for 2 wk after treatment indicated no evidence of a systemic effect. Only minimal epithelial hyperplasia and hyperkeratosis were observed.

Oral

Butyl Methacrylate

A combined repeated-dose toxicity study (with reproduction/developmental toxicity screening) (OECD TG 422) was performed.[2] The study involved groups of Crj: CD(SD) rats (10/sex/dose). The animals were gavaged with Butyl Methacrylate (purity: 99.6%) at doses of 0 (vehicle: sesame oil), 0.03, 0.1, 0.3, and 1 g/kg/d for 44 d (a total period of before, during, and after mating) in males and 14 d before mating and up to day 3 of lactation in females. Body weights among high-dose animals remained decreased throughout most of the treatment duration. Body weight gains decreased significantly among high-dose males throughout the treatment period and among high-dose females during the pre-mating period. Food consumption among high-dose animals decreased significantly throughout most of the treatment period. Urinalysis revealed a significant increase in ketone body and occult blood among high-dose animals. Hematological alterations included significant prolongation of prothrombin time. Blood chemistry analysis revealed a significant increase in urea nitrogen (high-dose males) and an increase in the albumin/globulin ratio (in all treated males, but statistically significant only among high-dose males). There were significant increases in chlorine levels among 0.1 g/kg/d and 1 g/kg/d dose group animals; these, however, remained within historical control ranges.

Necropsy revealed an atrophic kidney and atrophic testes among males. Females showed red spots/regions of the thymus and spots of the lung. These were all sporadic with no dose dependency and hence were not considered treatment-related. Organ weight analysis revealed significant decreases in absolute and relative weights of the spleen among 0.1, 0.3, and 1 g/kg/d dose group males. High-dose males also showed significant increases in relative kidney and absolute heart weights. High-dose females showed a significant decrease in absolute spleen and heart weights, along with an increase in

relative brain and thyroid gland weights. Histopathological alterations included atrophied red pulp of the spleen that increased dose-dependently in 3 of 9 males at the 0.1 g/kg/d dose, 4 of 8 males at the 0.3 g/kg/d dose, and 7 of 10 males at the 1 g/kg/d dose. Atrophy of the red pulp was attributed to the decreased extramedullary hematopoiesis. Only high-dose females (6 of 10) had atrophy of the red pulp in the spleen. The kidney showed no histopathological abnormalities attributable to test substance administration. The no-observed-effect level (NOEL) for repeat dose toxicity was considered to be 0.03 g/kg/d for males and 0.3 g/kg/d for females. Based on historical control data from the laboratory where the study was performed, effects seen at 0.1 and 0.3 g/kg/d were not statistically significant when compared with historical controls. Hence, the no-observable-adverse-effect-level (NOAEL) of this study was determined to be 0.3 g/kg/d.

HEMA

The short-term oral toxicity of HEMA was studied using groups of 24 Crj: CD(SD) rats (12 males and 12 females/group).[45,46] The test substance was administered by gavage at the following doses: 0 (vehicle: water), 0.03, 0.1, 0.3, and 1 g/kg/d. Male rats were dosed orally for 49 d. Female rats were dosed orally from 14 d before mating to d 3 of lactation. Prior to histopathological examination, males were killed on d 50 and females were killed on d 4 of lactation. One male and 6 females of the 1 g/kg group (12 animals of each sex) died during the treatment period. In males, blood urea nitrogen (BUN) was elevated or tended to be high at 0.03 g/kg or more, and the relative kidney weights were increased at 0.1 g/kg or more. At a dose of 1 g/kg, the following effects were reported in males: salivation, suppression of body weight gain, decrease in food consumption, increased potassium, chlorine, and inorganic phosphorous, decreased triglyceride, increased relative liver weights, and dilatation of renal tubules and collection tubules in the kidney. In females, the relative kidney weights were elevated or tended to be high at 0.1 g/kg or more. The following effects were observed in females dosed with 1 g/kg: salivation, decrease in locomotor activity, adoption of a prone position, lacrimation, soiled fur, hypothermia, bradypnea, suppression of body weight gain, decrease in food consumption, increases of absolute and relative kidney weights, neutrophil cellular infiltration in the papilla and medulla, and massive malacia in the medulla oblongata were seen at 1 g/kg. The NOAEL was determined to be 0.1 g/kg/d in this study.

Isobornyl Methacrylate

In a reproduction/developmental toxicity screening study (OECD TG 421), Sprague-Dawley rats (10 male and 10 females per dose group) received Isobornyl Methacrylate by daily oral (gavage) administration for 15 d before mating, through mating, gestation and the beginning of the lactation period (until day 5 post-partum).[47] The dose-levels were 0.025, 0.1, and 0.5 g/kg/d. Another group of 10 males and 10 females received the vehicle (corn oil) alone under the same experimental conditions and acted as a control group. The dose volume was 5 ml/kg. None of the animals died, and no clinical signs were noted. There was a statistically significant increase in liver weight (both sexes) and kidney (males only) at 0.5 g/kg bw/d. Microscopic findings in the liver included biliary proliferation/hypertrophy associated with fibrosis and macrophages infiltration (0.5 g/kg bw/d, males and females), disorganization of the hepatic cords (0.5 g/kg bw/d, males and females), and necrosis in the parenchyma (0.5 g/kg bw/d, males). The minimal hepatocellular degeneration in 1 of 10 males and the minimal biliary proliferation/hypertrophy in 3 of 10 animals observed in the 0.1 g/kg dose group were not considered clear signs of toxicity. The increase in acidophilic globules in the 0.1 and 0.5 g/kg dose groups (males) was considered to be related to micro-2μ-globulin, which is rat specific and, therefore, not relevant to human hazard assessment. Based on the experimental conditions of this study, the NOAEL for parental toxicity was 0.025 mg/kg bw/d (based on liver and kidney findings).

Tetrahydrofurfuryl Methacrylate

A combined repeated dose toxicity study and reproduction/developmental toxicity study on Tetrahydrofurfuryl Methacrylate (in corn oil) was performed in accordance with OECD TG 422.[48] The test substance was administered by gavage to groups of 20 Sprague Dawley rats (10 males, 10 females per group). The groups received an oral dose of 0.05, 0.12, or 0.3 g/kg bw/d (constant volume of 5 ml/kg bw) 7 d/wk. Male rats were dosed for 29 d (2 consecutive weeks prior to pairing and thereafter through the day before necropsy). Female rats were also dosed for 29 d (2 consecutive weeks prior to pairing and during pairing, post coitum and postpartum periods until d 3 postpartum, or the day before being killed). Vehicle control animals received corn oil. None of the animals died. Observation of animals at the time of removal from the cage and in an open arena (neurotoxicity assessment) did not reveal changes that were attributable to test substance administration. No significant clinical signs were observed. No relevant changes were recorded during the study, including the post mortem examinations of males at any dose level investigated. In particular, in male rats, the absence of findings was reported as follows: no effects were seen on body weight and body weight gain, clinical signs (including neurotoxicity assessment, motor activity and sensory reaction to stimuli), food consumption, clinical pathology investigations (hematology and clinical chemistry), macroscopic observations, organ weights, and histopathological examination. The following findings were reported for females: On day 20 post-coitum, a decrease in body weight and body weight gain (statistically significant) was evident in females dosed at 0.3 g/kg bw/d, when compared to controls. Decreases in food consumption were seen in high dose females (0.3 g/kg bw/d) when compared to controls during the post-coitum and postpartum periods, with statistical significance on days 7 and 14 post-coitum and day 4 postpartum. The authors noted that the study results indicate that the NOAEL for systemic toxicity was 0.3 g/kg bw/d for males and females.

Triethylene Glycol Methacrylate

A combined repeated dose toxicity study (with reproduction/developmental toxicity screening test) on Triethylene Glycol Dimethacrylate was performed in accordance with OECD TG 422.[49] The test substance was administered by gavage to groups of 20 Hsd: Sprague Dawley SD rats (10 males, 10 females per group). Doses of 0 (control), 0.1, 0.3, and 1 g/kg bw/d were administered. The treatment schedule included 2 wk before pairing, during pairing, post-coitum, and postpartum periods up to day 3 postpartum. The dosing period was approximately 5 and 8 wk for males and females, respectively. None of the animals died, and there were no clinical signs that were of toxicological significance. A statistically significant reduction in body weight (compared to controls) was observed in high dose males from d 15 of treatment until the animals were killed. Body weights of females were unaffected by treatment. Food consumption was comparable between the control and treatment groups.

No differences in motor activity, grip strength and sensory reactivity to stimuli were observed. The differences noted in land foot splay noted in low dose males and females were considered incidental because they were inconsistent between males (increase) and females (reduction), and were without any dose correlation. Results relating to hematology and urinalysis indicated no changes that were of toxicological significance. The statistically significant decrease in reticulocytes in females dosed with 1 g/kg bw/d was considered toxicologically irrelevant, because no associated alterations of the erythrocytes were observed. No changes in prothrombin time were noted. Bile acids showed a dose-related increase in almost all treated females. No other changes of toxicological significance were observed. Two males of the high dose group had an increase in urea (mean value 35% above controls). However, due to the low incidence, it was noted that this finding could not be conclusively attributed to treatment. Other statistically significant fluctuations of some biochemical parameters were recorded in treated animals, such as: chloride, calcium, sodium and potassium. Because these changes were of minimal magnitude and not consistent between sexes and/or not dose-related, they were considered incidental. No treatment-related changes were seen in selected organs/tissues evaluated in males or females. The NOAEL was 1 g/kg bw/d.

Trimethylolpropane Trimethacrylate

A combined repeated dose toxicity study with a reproduction/developmental toxicity screening test (OECD TG 422) on Trimethylolpropane Trimethacrylate (in corn oil) was performed using groups of Crl:CD(SD) rats.[50] The repeated dose toxicity test involved 3 groups of rats (5 males, 5 females per group). Trimethylolpropane Trimethacrylate was administered by gavage at the following doses: 0.1, 0.3 or 0.9 g/kg bw/d. The animals were treated daily for 5 consecutive weeks. A vehicle control group was also included. There were no treatment-related signs or mortalities in the study. Liver weights were slightly high in males and females dosed with 0.9 g/kg bw/d, and kidney weights were also high among females in this dose group. There were no associated hematological or biochemical changes, or macroscopic/microscopic abnormalities, to explain the difference in weight of the organs. There were no macroscopic abnormalities and no test substance-related lesions at microscopic examination. Based on the results of this study, it was concluded that the NOAEL for systemic toxicity was > 0.9 g/kg bw/d.

Inhalation

Butyl Methacrylate

In a 28-d repeated dose inhalation study (OECD TG 412), 10 male and 10 female rats were exposed (whole body) to 0, 310, 952 and 1891 ppm (0, 1.832, 5.626, 11.175 g/m^3, respectively) Butyl Methacrylate for 6 h/d and 5 d/wk for 4 wk.[57,58] Treatment-related effects included lacrimation, eye squinting, and labored breathing in the 952 and 1891 ppm (5.626 and 11.175 g/m^3) concentration groups throughout the study. There were no treatment-related effects on bw or feed consumption, and no deaths occurred. Hematological measurements and clinical chemistry values generally were unaffected by treatment. Despite increased relative kidney weights at the high concentration (1891 ppm (11.175 g/m^3)) in both sexes, and slight increases in serum BUN values (resulting in increased BUN:creatinine ratio), histopathology of the kidneys was normal. The only treatment-related histopathological finding was localized bilateral degeneration of olfactory epithelium lining the dorsal meatus of the nasal cavity, at 952 and 1891 ppm (5.626 and 11.175 g/m^3, respectively) in both sexes. Therefore, a no-observed-adverse-effect-concentration (NOAEC) for inhalation toxicity was considered to be 310 ppm, based on lesions observed in nasal cavities at higher doses. The NOAEC for systemic toxicity was considered to be 1891 ppm, the highest dose tested.

Glycol Dimethacrylate

Glycol Dimethacrylate was evaluated in an acute inhalation toxicity study involving 3 female rats (strain not stated).[41] The route of exposure was identified as vapor inhalation during air exposure (6 h per exposure) 5 d/wk over a 13-d period. The exposure concentration was 1 mg/l (120 ppm). Animals were killed at the end of the exposure period. None of the animals died during the study. The animals became lethargic during the exposures, but no definite symptoms developed. Results from post mortem examination indicated discoloration of the lungs. Histological examination of the lungs showed some thickening of the alveolar walls, with a lymphocytic reaction around the bronchioles. No signs of pathological changes were observed in other major organs (not specified). The LC_{Lo} was > 1 mg/l air.

Subchronic Toxicity Studies

Dermal

Triethylene Glycol Dimethacrylate

A 90-d toxicity study was performed.[43] Four groups of male Harlan Sprague-Dawley (C3H/HeNHsd strain) mice (10/group) were treated with Triethylene Glycol Dimethacrylate (5, 25, 50, or 100%) 5 d/wk (Monday through Friday) for 13 consecutive weeks. Triethylene Glycol Dimethacrylate was dissolved in acetone, except for when 100% Triethylene Glycol Dimethacrylate was applied. Single doses (50 µl) were applied topically to the clipped interscapular region of the back using a calibrated pipette. Other than the location of application, no effort was made to prevent oral ingestion (e.g., through the use of collars). Untreated and acetone-treated control groups were also used. Detailed examinations, including enhanced evaluation for skin lesions and behavioral function, were conducted weekly and starting 1 wk before dosing. Complete necropsy was performed. Cutaneous cell proliferation evaluations using the PCNA procedure were performed on 5 mice/group and 10 mice from the acetone-treated group at termination. Exfoliation/desquamation was observed in all animals of the 25%, 50%, and 100% dose groups at some time during the study. Ulceration and excoriation were also seen in a few animals from these groups, which had resolved by d 35. No findings were recorded in the 5% dose group.

The only treatment-related finding at necropsy, other than for treated skin, was an increase in liver weight of approximately 7% and 10% greater than control in the 50% and 100% treatment groups, respectively. There was no clinical or histopathological evidence of liver toxicity; thus, the etiology and biological significance of the increased weight was uncertain. Hyperkeratosis was observed in all animals from the 25%, 50%, and 100% dose groups; acanthosis was observed in 80% or 100% of the animals from these groups. A single animal was diagnosed with dermatitis from the 100% group. Grading of these lesions generally correlated with dose. No microscopic changes of the skin were noted at the 5% concentration.

Oral

Butyl Methacrylate

In a study conducted according to OECD TG 408, Butyl Methacrylate was administered daily to male and female Wistar rats by gavage at dose levels of 0, 0.06, 0.12, and 0.36 g/kg bw/d over a period of 3 consecutive months.[51,52] Control and high dose groups consisted of 15 animals per sex per group, whereas low and mid dose groups consisted of 10 animals per sex per group. After 3 mo of treatment, 10 animals per sex of all dose groups were killed. The remaining 5 animals per sex of control and high dose groups were maintained for another 28 d without administration of the test substance (recovery groups). At 0.36 g/kg bw/d, bw change significantly decreased in male animals from day 77 onward (-12.1% on days 84 and 91). Prothrombin time was significantly prolonged (+10%, males; +12%, females) and inorganic phosphate (+14%, males; +30%, females), total bilirubin levels (+17% in males), glucose levels (+13% in females) as well as urea levels (+36%, males; 21%, females) significantly increased. Calcium (-3% in males and females), globulin levels (-4% in females) and triglyceride levels (-24% in males and females) significantly decreased. Absolute kidney weight (+11% in females), relative kidney weight (+13% in males and females) and liver weight (+9%, males; +11%, females) significantly increased. Multifocal degeneration/regeneration of olfactory epithelium was observed in males (5 of 10) and females (7 of 10). After the recovery period, phosphate levels (+7% in males) and urea concentrations (+22% in females) were significantly increased.

At 0.120 g/kg bw/d, multifocal degeneration/regeneration of olfactory epithelium was observed in males (4 of 10) and females (2 of 10). At 0.06 g/kg bw/d, no test substance-related adverse findings were observed. Multifocal degenerative and regenerative olfactory epithelium of the nasal cavity was observed at the high dose (360 mg/kg bw/d) and mid dose (120 mg/kg bw/d) (4 of 10 males and 2 of 10 females). At 0.06 g/kg bw/d, no test substance-related adverse findings in the olfactory tissues were observed. Considering the short half-life of Butyl Methacrylate in blood (99.7 % removed in first pass by the liver) it was noted that it is unlikely that these effects were of systemic origin, but were local effects as a consequence of the dosing technique. This test substance-related effect was completely reversible, as no animal of the recovery group had any finding in the nose after 28 d after the cessation of exposure.

In conclusion, the oral administration of Butyl Methacrylate by gavage over a period of 3 mo (with a recovery period of 28 d) revealed toxicologically relevant signs of systemic toxicity at the high dose level of 0.36 g/kg bw/d, limited to effects on liver activity (increased liver weight, prolonged prothrombin time, lower serum globulin and triglyceride levels in males and/or females) and kidney weight (increased absolute weight in females). The NOAEL for these effects was 0.12 g/kg bw/d in both male and female Wistar rats.

t-Butyl Methacrylate

The subchronic oral toxicity of t-Butyl Methacrylate (in carboxymethylcellulose) was evaluated using groups of 30 (15 males, 15 females/group) Wistar rats, in accordance with OECD TG 408.[53] The 3 dose groups received doses of 0. 06, 0.12, and 0.36 g/kg/d by gavage for approximately 3 mo. Control rats were dosed orally with carboxymethylcellulose. Post-exposure recovery period (28 d) satellite groups consisted of control and high dose groups (5 rats per sex) only. All animals were killed for necropsy and histopathological examination. None of the animals died prematurely. During clinical

examinations, only microphthalmia was observed in 1 female of the 0.12 g/kg bw/d dose group. The body weight was significantly decreased in male animals of the 0.36 g/kg bw/d dose group toward the end of the study (-7% on days 84 and 91). This impairment of body weight data in high dose males was assessed as related to treatment with the test substance and indicative of general systemic toxicity. The body weight of the female animals in all test groups was not significantly influenced by the test substance during the dosing period. However, in female animals of the 360 mg/kg bw/d dose group, a significantly lower (-7.8%) weight was noted on day 98, at the beginning of the recovery period, only. In sensorimotor tests (males and females), there were no test substance-related findings. The same was true regarding motor activity measurements.

There were no test substance-related hematological findings. The increased kidney weights (+ 11%) in female animals of the 0.36 g/kg bw group are regarded as treatment-related, although there was no histopathologic correlate which could explain this weight increase. The increased relative brain, kidney, and liver weights in the 0.36 g/kg bw group of male animals are regarded as a consequence of the reduction in terminal body weight. In males and females of the 0.36 g/kg bw/d dose group, degeneration and regeneration of the olfactory epithelium was observed. The nasal cavities of animals of the recovery groups (control and 360 mg/kg body weight) were examined, and no abnormalities were detected. The following observations served as the basis for the NOAEL of 0.12 g/kg bw/d that was determined: effects on liver activity (increased liver weight, prolonged prothrombin time, lower serum globulin and triglyceride levels in males and/or females) and kidney weights (increased absolute weight in females) were also reported.

HEMA Acetoacetate

The subchronic oral toxicity of a HEMA Acetoacetate trade name mixture (composition not stated; corn oil vehicle) was evaluated using groups of 30 Sprague-Dawley rats (15 males, 15 females/group), in accordance with OECD TG 408.[54] The animals received the following doses by gavage for 13 wk (5 d/wk): 0 mg/kg bw, 0.05 g/kg bw, 0.15 g/kg bw, and 0.5 g/kg bw. The results of this oral study indicate that the test item had no potential to produce toxic effects when administered to rats at doses up to 0.5 g/kg bw/d. Based on the lack of treatment-related effects relating to clinical signs, ophthalmic examinations, feed consumption, weight gain, clinical pathology, organ weights, gross pathology, microscopic pathology, and functional observational battery results, the NOEL for subchronic exposure to the test substance was considered to be 0.5 g/kg bw/d for both male and female rats when administered 5 d/wk for 13 wk.

Isobornyl Methacrylate

The repeated-dose toxicity of Isobornyl Methacrylate was investigated in 2 subchronic dietary toxicity studies using rats and dogs.[32] In the subchronic dietary study (rats; protocol similar to OECD TG 408), Isobornyl Methacrylate was administered to groups of 30 rats (15 males, 15 females per group) at concentrations of 0, 1000, 3000, or 10,000 ppm (≈ 0, 0.05, 015, or 0.5 g/kg bw/d) for 3 mo. None of the animals died. Treatment-related effects included significantly decreased growth rate, food consumption, and mean terminal body weights in males and females at 10,000 ppm (compared to the controls). Increased liver weight relative to body weight (both sexes), and increased kidney and testis weight relative to body weight (males), was observed at 10,000 ppm. Histopathological findings in the liver at all concentrations ranged from biliary epithelial hyperplasia (at 1000 ppm) to severe bile duct hyperplasia (at 10,000 ppm) in both sexes. Histopathological changes in the kidneys of male and female rats were observed at all concentrations. At 10,000 ppm, hypertrophy of the deep proximal convoluted tubules was observed, while, at 3000 and 1000 ppm, varying degrees of protein inhibition (slightly more severe than controls), was considered to be treatment-related. In addition, hypercellularity of the bone marrow was observed in animals dosed with 10,000 ppm. A NOAEL could not be established because histopathologic changes were observed at all concentrations. The LOAEL for 3 mo of dietary exposure to Isobornyl Methacrylate was 1000 ppm (≈ 0.05 g/kg bw/d), based on histopathologic changes in the kidneys and liver at all doses.

In the subchronic dietary study involving dogs (protocol similar to OECD TG 409), Isobornyl Methacrylate was administered daily to groups of 8 dogs (4 males, 4 females per group) in the diet at concentrations of 0, 1000, 3000, or 10,000 ppm (≈ 0, 0.031, 0.095, or 0.352 g/kg bw/d) for 13 wk.[32] No deaths were reported at any concentration. Toxicologically-significant effects were limited to animals of the 10,000 ppm exposure group and included slightly increased BUN, increased liver-to-body weight ratio, and minimal to slight degenerative changes in epithelial cells of the proximal convoluted tubules. The NOAEL for 13 wk of dietary exposure to Isobornyl Methacrylate in dogs was 3000 ppm (≈ 0.095 g/kg bw/d). The LOAEL was based on clinical pathology (BUN), organ weights (liver), and histopathologic findings (kidney) at 10,000 ppm (≈ 0.352 g/kg bw/d).

Lauryl Methacrylate

A combined repeated-dose (oral gavage) toxicity study and reproduction/development toxicity screening test on Lauryl Methacrylate (in corn oil) was performed in accordance with OECD TG 422.[55] Three groups of 20 Sprague-Dawley rats (10 males, 10 females per group) were dosed for 15 d before mating, and through mating, gestation and the beginning of the lactation period (until day 5 post-partum). The test substance was administered at doses of 0.1, 0.3 and 1 g/kg/d. The control group (10 males and 10 females) received the vehicle only (corn/oil). The dose volume was 5 ml/kg. The males were killed at approximately 2 wk (week 6) after the end of the mating period. The females were killed on day 6 post-partum. Post-mortem examinations were performed. At 1 g/kg/d, hypersalivation was observed in males and females; lower body weight

gain was observed in females during the GD 0-7 interval, and increased plasma glucose concentrations were observed in males. At 0.3 g/kg/d, hypersalivation was also observed. At 0.1 g/kg/d, no treatment-related effects were observed. The authors noted that hypersalivation was not considered a sign of toxicity to Lauryl Methacrylate. There were no treatment-related findings at histopathological examination. Based on the experimental conditions of this study, the NOAEL for parental toxicity was considered to be 1 g/kg/d.

Trimethylolpropane Trimethacrylate

The subchronic oral (90 d) toxicity of Trimethylolpropane Trimethacrylate (in corn oil) was studied using groups of 20 Wistar rats (10 males, 10 females per group), in accordance with OECD TG 408.[56] The test item was administered daily (by oral gavage) at dose levels of 0, 0.1, 0.3 and 1 g/kg bw/d (dose volume = of 5 ml/kg bw). The control group was treated with corn oil only. Functional observational battery, locomotor activity, and grip strength were performed during week 13. All animals were killed, necropsied, and examined post mortem. Histological examinations were performed on organs and tissues from all control and high dose animals and all gross lesions from all animals. Dosing with Trimethylolpropane Trimethacrylate resulted in: no test substance-related deaths, and no relevant findings during daily observations, weekly observations (weeks 1 - 12) or functional observational battery (week 13), no differences of toxicological relevance in the fore- and hind limb grip strength values, no test substance-related differences in ophthalmoscopy, and no test substance-related effects on hematology, clinical biochemistry or urine parameters. The duration and pattern of the estrus cycles of test substance-treated females were similar to those of the control females.

At 1 g/kg bw/d, male rats had lower mean body weights and elevated food consumption values that were considered test substance-related. This high dose also caused low mean locomotor activity. Although the mean body weights of females were unaffected, there was a clear increase in absolute and relative food consumption. Differences in the liver and kidney weights of males and females dosed with 1 g/kg bw/d were considered test substance-related. No other differences of toxicological relevance were noted in rats dosed with 0.3 g/kg bw/d or 0.1 g/kg bw/d. The epithelial hyperplasia/ hyperkeratosis and erosion/ulcer(s) of the non-glandular gastric mucosa was indicative of direct contact irritancy on the non-glandular mucosa (forestomach). At 1 g/kg bw/d, males were more affected than females, while, at 0.3 g/kg bw/d, the finding was only present in 1 of 10 females. The occasional erosion/ulcer(s) of the glandular mucosa (also occasionally observed in controls) were not considered test substance-related. The centrilobular hepatocellular hypertrophy in females at 1 g/kg bw/d was the histological correlate of the increased liver weights recorded at necropsy. These findings were suggestive of an adaptive response to mixed function oxidase induction. The decreased prostate/coagulating gland weights recorded at necropsy at 1 g/kg bw/d were correlated histologically with decreased secretory content. In the absence of test substance-related effects in other male reproductive organs, the pathogenesis of this finding was said to have been unknown. In the spleen, the extramedullary hematopoiesis was slightly lower at 1 g/kg bw/d in males and females. The pathogenesis of this finding was classified as unknown. Based on the results of this study, 0.3 g/kg bw/d was established as the NOAEL and NOEL.

Inhalation

t-Butyl Methacrylate

The toxicity of t-Butyl Methacrylate (no vehicle) was evaluated in accordance with OECD TG 412.[59] The study involved groups of 10 (5 males, 5 females/group) rats of the Crl:CD BR strain. The 4 groups were exposed to 0, 310, 952 and 1891 ppm (0, 1.832, 5.626 and 11.175 g/m^3, respectively). Whole-body exposure occurred in an inhalation chamber. The duration of exposure was 4 wk, and the exposure frequency was 5 d/wk (6 h/d). No deaths were noted at any concentration tested. The only treatment-related signs of toxicity observed were inactivity, lacrimation, eye squinting, and labored breathing. These signs were noted only during the 6-h exposure. No treatment-related differences in hematology parameters were observed. The clinical chemistry data showed the following 2 parameters with statistically significant findings. A decrease in the alkaline phosphatase concentration (females: 310, 952, and 1891 ppm exposures). A statistically significant decrease in the triglyceride concentration (females: 952 ppm and 1891 ppm exposures). However, these findings were not of toxicological significance. The organ weight data showed a statistically significant increase in kidney weight to body weight ratio in males and females exposed at 1891 ppm. Gross pathology data were not available. Histopathologic evaluation revealed treatment-related observations in the nasal cavities. Microscopic examination of the nasal cavities of male and female rats exposed to 1891 ppm revealed slight and localized bilateral degeneration of olfactory epithelium lining the dorsal meatus. One male rat and one female rat exposed to 952 ppm had similar changes in the olfactory epithelium. Rats exposed to 310 ppm had no exposure-related nasal cavity microscopic changes.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

HEMA and Triethylene Glycol Dimethacrylate

Mouse embryonic stem cells stably transfected with a vector containing the gene for the green fluorescent protein (under control of the cardiac α-myosin heavy chain promoter) were differentiated in the presence of various concentrations of HEMA nor Triethylene Glycol Dimethacrylate (10^{-8} to 10^{-5} M) for 12 d.[61] Fluorescence was measured and values were

expressed as percent of control values. To distinguish between cytotoxic and embryotoxic effects, all compounds were tested in a standard 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide (MTT) assay. Neither HEMA nor Triethylene glycol Dimethacrylate influenced the differentiation process of embryonic stem cells toward cardiac myocytes. No cytotoxic effects were observed at any of the concentrations tested.

Animal

Oral

Butyl Methacrylate

In an OECD TG 414-compliant prenatal developmental toxicity study, Himalayan time-mated female rabbits (25 females/dose) were orally (via stomach tube) administered Butyl Methacrylate at doses of 0 (1% carboxymethylcellulose suspension in drinking water and a few drops Cremophor EL and 1 drop hydrochloric acid), 0.1, 0.3, and 1 g/kg/d on gestation days (GD) 6 through 28.[2] Does were euthanized at GD 29. A total of 7 high-dose treated does were euthanized due to abortion on GDs 24 – 28. There were significant reductions in food consumption and body weights of mid- and high-dose females. The mean gravid uterus weight was significantly reduced among high-dose females. At necropsy, stomach erosion, no feces in the small intestine, and watery feces in the intestine were observed among high-dose females. These findings were related to the significantly reduced food consumption and were considered to be treatment-related. A complete post-implantation loss in 2 individual does, secondary to distinct maternal toxicity, were observed at the highest dose. Significant reductions in fetal weights were observed at the highest dose. Slightly, but significantly higher, incidences of malformation (mainly severely fused sternebrae) and skeletal variations (delayed ossification and supernumerary ribs, commonly associated with decreased fetal weight and maternal stress) were observed at the highest dose. Therefore, mean fetal malformations and variations were also significantly higher in the high-dose group as compared to controls. No treatment-related developmental effects were observed among animals of the low- and mid-dose groups. Therefore, the NOAEL for maternal toxicity was considered to be 0.1 g/kg/d (based on reduced food consumption and body weight gain observed at ≥ 0.3 g/kg/d), and the NOAEL for developmental toxicity was considered to be 0.3 g/kg/d (based on abortions, decreased fetal growth, and skeletal alterations observed at 1 g/kg/d).

In a combined repeated dose toxicity and reproduction/developmental toxicity screening study (OECD TG 422), Crj: CD(SD) rats (10/sex/dose) were fed via gavage with Butyl Methacrylate at doses of 0 (vehicle: Sesame oil), 0.03, 0.1, 0.3, and 1 g/kg/d for 44 d (total period of before, during, and after mating) in males and 14 d before mating and up to d 3 of lactation in females.[2] No treatment-related effects were observed on reproductive performance, reproductive function (estrous cyclicity and sperm parameters), and reproductive organs of males and females treated with up to 1 g/kg/d. There were no treatment-related effects on gestation index, gestation length, or number of pups per litter. Furthermore, offspring viability and sex ratio of pups were unaffected due to treatment. Significant decreases in the number of corpora lutea and implantation sites were observed in dams treated at 1 g/kg/d. However, necropsy examination revealed no alterations in the implantation rate and anomalies of follicle formation in the ovary. Hence, the author considered that the decrease in the number of corpus lutea or implantation sites was due to abnormal ovulation. There were no effects on birth rate, gestation length, and nursing condition. Therefore, the NOAEL for reproductive toxicity was considered to be 1 g/kg/d for males (highest tested dose) and 0.3 g/kg/d for females (due to decrease in the number of corpus lutea or implantation); a NOAEL for developmental toxicity was considered to be 1 g/kg/d, the highest tested dose.

Cyclohexylmethacrylate

In this modified combined repeated-dose toxicity study and reproduction/developmental toxicity screening test (OECD TG 422), the test substance Cyclohexylmethacrylate was administered daily as an aqueous preparation to groups of 12 male and 12 female Wistar rats (F_0 animals) by gavage at doses of 0.1, 0.3, and 1 g/kg bw/d to screen for potential repeated dose, reproductive and developmental toxicity.[62] The duration of treatment covered a 10-wk premating period and 2-wk mating period in both sexes, approximately 3 wk post-mating in males, and the entire gestation period as well as 21 d of lactation and up to 15 d post-weaning, or 38 d post-mating for sperm negative females. In addition, groups of 10 males and 10 females, selected from F_1 pups to become F_1 rearing animals, were treated with the test substance at doses of 0, 0.1, 0.3, and 1 g/kg bw/d postweaning until puberty. The study was terminated with the terminal sacrifice of the rearing animals. Thus, the reliability regarding the possible reproductive and developmental properties was increased due to the longer premating treatment period (10 wk) and a postweaning follow-up of selected offspring until puberty.

Dysregulation of liver cell metabolism was detected in males and females treated with 1 g/kg bw/d, which was seen as an increase in serum total protein and globulin values (males and females), increase in cholesterol and potassium levels (males) and high albumin level and low creatinine values (females). Additionally, a marginal anemia was observed because of decreased red blood cell counts and hematocrit values. Furthermore, the liver showed a marked weight increase in animals of both sexes treated with 1 g/kg bw/d. A corresponding histopathological correlate in the form of hepatocellular centrilobular hypertrophy could only be detected in female rats. No further adverse or primary test substance-related effects were detected in animals at 1 g/kg bw/d. At 0.1 and 0.3 g/kg bw/d, no test substance-related adverse findings were determined. Under the conditions of this study, the test substance had no adverse effects on fertility and reproductive performance of the F_0 parental animals of both sexes up to 1 g/kg bw/d as mating behavior, conception, implantation, delivery and rearing of offspring were not influenced. The NOAEL for general, systemic toxicity of Cyclohexylmethacrylate

was 0.3 g/kg bw/d for male and female rats, based on functional impairment in rats at 1 g/kg bw/d. The NOAEL for fertility and reproductive performance was 1 g/kg bw/d for the F_0 parental rats, and the NOAEL for developmental toxicity in the F_1 progeny was 1 g/kg bw/d.

Glycol Dimethacrylate

In a developmental toxicity study (OECD TG 414), Glycol Dimethacrylate (purity: 97.5 %) was administered to female rats (Sprague-Dawley, Crl CD® (SD) IGS BR, Caesarian Obtained, barrier sustained-virus antibody free, (COBS-VAF®)) dosed by gavage at dose levels of 0, 0.025, 0.1 and 0.5 g/kg bw/d from days 6 through 20 of gestation.[63] The administration of 0.5 g/kg/d caused evident signs of maternal toxicity (1 female was killed on GD 15, clinical signs of poor health were observed in 3/22 surviving pregnant females, and there was transient bw loss and reduction of food consumption). At 0.1 g/kg/d, bw gain was transiently reduced, with no adverse outcome. There were no maternal effects at the dose level of 0.025 g/kg/d. None of the litter parameters recorded (implantations, live fetuses, % male/female fetuses, and fetal body weight) were affected. There were no treatment-related malformations and there were no treatment-related variations that were considered to be adverse. The maternal NOAEL was 0.1 g/kg bw/d, and the developmental NOAEL was 0.5 g/kg bw/d.

HEMA

HEMA (in water) was evaluated in a combined repeated dose and reproductive/developmental toxicity screening test (OECD TG 422) at doses of 0, 0.03, 0.1, 0.3 and 1 g/kg/d.[64,65] Groups of 24 Crj: CD(SD) rats (12 males, 12 females/group) were dosed by gavage. The exposure period for males was 49 d. The exposure period for females was from 14 d before mating to d 3 of lactation. The pre-mating exposure period for males and females was 14 d. Water served as the vehicle control. Males were killed on d 50 and females were killed on lactation d 4. Gross pathological and histopathological examinations were performed. There were no effects of the test substance on estrus frequency, copulation index, number of conceiving days, fertility index, length of gestation, number of corpora lutea or gestation index. There were no effects of the test substance on the number of live pups born, birth index, number of dead pups, number of pups born, delivery index, live birth index, sex ratio, viability index, external anomalies, body weight or necropsy findings. The NOAEL for reproductive/developmental toxicity was considered to be greater than 1 g/kg/d.

HEMA Acetoacetate

The teratogenic potential of HEMA Acetoacetate was evaluated using groups of mated female Hannover Wistar rats (25 to 26 rats/group), in accordance with OECD TG 414.[66] The following doses of the test substance were administered daily (by oral gavage) to pregnant rats on gestation days 6 - 19: 0.1, 0.3, and 1 g/kg bw/d. The dams were killed at gestation day 20, and the fetuses were examined for visceral and skeletal variations and malformations. Up to the highest dose of 1 g/kg bw/d, there was no evidence of maternal toxicity, embryotoxicity, fetotoxicity, or teratogenicity. Also, there were no malformations or developmental effects that were attributed to the 3 doses that were administered. Thus, an NOAEL of 1 g/kg bw/d was derived.

Isobornyl Methacrylate

In a reproduction/developmental toxicity screening study (OECD TG 421) Sprague-Dawley rats (10 male and 10 females per dose group) received Isobornyl Methacrylate by daily oral (gavage) administration for 15 d before mating, through mating, gestation and the beginning of the lactation period (until d 5 post-partum).[47] The dose-levels were 0.025, 0.1 and 0.5 g/kg/d. Another group of 10 males and 10 females received the vehicle, corn oil, alone, under the same experimental conditions and acted as a control group. The dose volume was 5 ml/kg. There was no effect of treatment on mating at any dose level. The male and female fertility indices were unaffected by treatment; all pregnant females had live births. The duration of gestation was similar in the test and control groups. There was no effect of treatment on the mean number of liveborn pups or on pup death after birth. There were no gross external pup abnormalities in the test or control group. No differences of toxicological importance were noted in male and female pup body weight gain. No relevant findings were observed in pups killed on day 6 post-partum. No treatment-related findings were found in the reproductive organs examined (testes, epididymides, and ovaries). The reproductive NOAEL was 0.5 g/kg bw/d.

Lauryl Methacrylate

A combined repeated dose (oral gavage) toxicity study and reproduction/development toxicity screening test on Lauryl Methacrylate (in corn oil) was performed in accordance with OECD TG 422.[55] Three groups of 20 Sprague-Dawley rats (10 males, 10 females per group) were dosed for 15 d before mating, and through mating, gestation and the beginning of the lactation period (until day 5 post-partum). The test substance was administered at doses of 0.1, 0.3, and 1 g/kg/d. The control group (10 males and 10 females) received the vehicle only (corn/oil). The dose volume was 5 ml/kg. The males were killed at approximately 2 wk (week 6) after the end of the mating period. The females were killed on day 6 post-partum. Post-mortem examinations were performed. Pups were examined for gross abnormalities on post-partum day 6. There were no substance-induced effects on male and female reproductive performance, nor on the progeny of the parental rats at any dose level. There were no treatment-related findings at histopathological examination. The NOEL for toxic effects on reproductive performance and on developmental toxicity was greater than or equal to 1 g/kg/d.

methyl methacrylate (used as read-across chemical for t-Butyl Methacrylate)

The reproductive toxicity of methyl methacrylate (in carboxymethylcellulose) was evaluated in a two-generation reproductive toxicity study involving groups of 50 Wistar rats (25 males, 25 females/group).[67] The study was performed in accordance with OECD TG 416. The animals were mated for a period of up to 2 wk. F_1 parental animals were not mated until 75 d after selection form the F_1 litters. The selection of parents from the F1 generation was after weaning (PND21). The test substance was administered by gavage to 3 groups at single doses of 0.05, 0.15, and 0.45 g/kg/d. Doses were administered until one day before the animals were killed. The control group received vehicle only. Other than effects on food consumption/body weight (in all groups except lowest dose group), no test substance-related adverse effects were observed in parental animals (P0 or F1). No reproductive effects were specified, and no test substance-related adverse effects were observed in F1 or F2 pups.

Tetrahydrofurfuryl Methacrylate

A combined repeated dose toxicity study and reproduction and developmental toxicity study on Tetrahydrofurfuryl Methacrylate (in corn oil) was performed in accordance with OECD TG 422.[48] The test substance was administered by gavage to groups of 20 Sprague Dawley rats (10 males, 10 females per group). The groups received an oral dose of 0.05, 0.12 or 0.3 g/kg bw/d (constant volume of 5 ml/kg bw) 7 d/wk. Male rats were dosed for 29 d (2 consecutive weeks prior to pairing and thereafter through the day before necropsy). Female rats were also dosed for 29 d (2 consecutive weeks prior to pairing and, thereafter, during pairing, post coitum and post-partum periods until d 3 post-partum or the day before being killed). Vehicle control animals received corn oil. Gestation length in all treatment groups was higher than in controls, and statistically significantly increased in the high dose group. The pre-birth loss was significantly increased at statistical analysis, in high dose females. This increase could be attributable to the prolonged gestation period, which probably caused pup suffering and death during or shortly after birth. An increased presence of missing or dead pups was noted in females receiving 0.3 g/kg bw/d. No other treatment-related findings were noted in pups. At necropsy, no treatment-related findings were noted in pups that died or in pups killed on d 4 postpartum. No difference in sex ratios was noted between the control and treated groups. No relevant differences in litter data were seen. Decreases in litter weights, seen in low- and mid-dose groups were due to the lower number of pups in treated groups with respect to the control. These findings were more evident in the mid-dose group, whereby the increased pup loss was attributed to single females. The NOAEL for reproductive and developmental toxicity was considered to be 0.3 g/kg bw/d for males and 0.12 g/kg bw/d for females and their litters.

Triethylene Glycol Dimethacrylate

The reproductive toxicity potential of Triethylene Glycol Dimethacrylate was investigated using male and female Crl:CD1(ICR) mice (4 dosage groups, 25 mice/sex/group).[68] Formulations of the test substance in reverse osmosis-processed deionized water (0, 0.01, 0.1, or 1.0 mg/kg/d) were administered (via intubation) once daily, beginning 28 d before cohabitation and continuing through mating (males) or through gestation day 17 (females). The following parameters were evaluated: viability, clinical signs, body weights, estrous cyclicity, necropsy observations, organ weights, sperm concentration/motility/morphology, cesarean-sectioning and litter observations, and histopathological evaluation of select tissues. No deaths or clinical signs related to test substance administration were observed. Furthermore, no significant changes in male and female body weights and body weight gains were recorded for any of the administered dosages. All mating and fertility parameters and all litter and fetal data were considered to be unaffected by test substance dosages as high as 1 mg/kg/d. Gross or histopathologic tissue changes attributable to the test substance were not observed. The reproductive and developmental no observed adverse effect level (NOAEL) for Triethylene Glycol Dimethacrylate was 1 mg/kg/d, the highest dose tested. The authors noted that comparison of conservatively estimated Triethylene Glycol Dimethacrylate exposures from dental treatments to the NOAEL of 1.0 mg/kg/d identified in this study indicates margins of exposure of at least 120- to 3000-fold, depending on the exposure scenario.

A combined repeated dose toxicity study and reproduction/developmental toxicity screening test on Triethylene Glycol Dimethacrylate was performed in accordance with OECD TG 422.[49] The test substance was administered by oral gavage to groups of 20 Hsd: Sprague Dawley SD rats (10 males, 10 females per group). Doses of 0 (control), 0.1, 0.3 and 1 g/kg bw/d were administered. The treatment schedule included 2 wk before pairing, during pairing, post coitum, and postpartum periods up to d 3 postpartum. The dosing period was approximately 5 and 8 wk for males and females, respectively. Measurements of copulatory index, fertility index, pre-coital interval and the number of copulation plugs did not show differences between treated and control groups. No significant differences were observed in the number of implantations, corpora lutea, total litter size, pre-implantation loss, pre-birth loss and gestation length between control and treated groups. Litter data and sex ratios were unaffected by treatment. Clinical signs of pups were comparable between groups. Decedent pups were found in all groups, without a dose relationship. Necropsy findings in decedent pups and in pups killed on d 4 postpartum did not reveal any treatment-related effects. A slight reduction in terminal body weight was noted in the mid- and high-dose males (statistically significant at high dose). Terminal body weights of females were unaffected by treatment. A slight increase in absolute and relative liver weight was observed in high dose females, when compared to controls. No relevant changes were detected at post mortem examination in treated animals, when compared to controls. No treatment-related changes were observed in selected organs/tissues evaluated in males or females, nor in abnormalities detected in all groups at post mortem, including the staging in the spermatogenic cycle. The NOAEL was considered to be 1 g/kg bw/d.

Trimethylolpropane Trimethacrylate

A combined repeated dose toxicity study and reproduction/developmental toxicity screening test (OECD TG 422) on Trimethylolpropane Trimethacrylate (in corn oil) was performed using groups of Crl:CD(SD) rats.[50] The reproductive toxicity test involved 3 groups of rats (5 males, 10 females per group). Males were treated daily for 5 consecutive weeks. Females were treated daily for 2 wk before pairing, throughout pairing, gestation and lactation, and until the day prior to termination on day 7 of lactation. Trimethylolpropane Trimethacrylate was administered by gavage at the following doses: 0.1, 0.3 or 0.9 g/kg bw/d. A vehicle control group was also included. Estrous cycle length, pre-coital interval and mating performance, and fertility of females was unaffected by treatment. There was a suggestion of a minor shift toward a slightly longer gestation length among females dosed with 0.9 g/kg bw/d. There were no clinical signs observed for F_1 offspring that were considered to be related to parental treatment. A statistically significant reduction in the mean number of implantation sites, associated with low litter size, were observed at the high dose of 0.9 g/kg bw/d. The number of corpora lutea present for each animal was not determined. Thus, the authors noted that it was not possible to assess whether this is a spontaneous finding related to a reduction in the number of eggs available for fertilization or indicative of a treatment-related pre-implantation loss. There was no effect on pre- or post-natal survival and on the sex ratio at any dose level. At 0.9 g/kg bw/d, mean male and female offspring body weights on d 1 of age were higher than in control rats; these differences were attributed to the slightly lower litter size and slight shift in gestation length observed in this group. There were no macroscopic abnormalities detected among the offspring that died during the early post-natal period, or at scheduled termination on d 7 of age that were attributable to parental treatment. Based on the results of this study, it was concluded that the NOAEL for reproductive/developmental toxicity was > 0.9 g/kg bw/d.

A prenatal developmental toxicity study on Trimethylolpropane Trimethacrylate (in corn oil) was performed in accordance with OECD TG 414.[69] Effects on the pregnant rat and development of the embryo and fetus after female exposure to the test substance from d 6 post coitum (implantation) to d 20 post coitum (the day prior to caesarean section) were evaluated. Four groups of 24 mated females per group were treated by gavage once daily at nominal dose levels of 0 (control group), 0.1, 0.3, and 1 g/kg bw/d. A standard dose volume of 4 ml/kg bw was administered. Control animals were dosed with vehicle (corn oil) only. All females were killed on day 21 post-coitum, and the fetuses were removed by caesarean section. All females survived until the scheduled necropsy. No clinical signs were recorded in any group, and the mean daily food consumption of all groups compared favorably. Although the mean absolute body weights were unaffected, a statistically significant lower mean body weight gain of the dams in the 1 g/kg bw/d dose group (40 vs. 46 % in the controls on day 21 post coitum) and a statistically significant decreased corrected body weight gain (corrected for the gravid uterus weight) in the 1 g/kg bw/d dose group (8.0 vs. 11.5 % in the controls on day 21) were considered test substance-related. The reproduction data (post-implantation loss and mean number of fetuses per dam) was unaffected by treatment, and no macroscopic findings were noted at any dose level. Mean placental weights of all groups were similar. The external examination of the fetuses showed no abnormalities that were of toxicological relevance, and sex ratios were unaffected. Fetuses of the 1 g/kg bw/d dose group had lower mean body weights (treatment-related). In conclusion based on the slightly lower mean body weight gain, the NOEL or maternal toxicity was considered to be 0.3 g/kg bw/d, whereas the NOAEL for maternal toxicity was considered to be 1 g/kg bw/d or higher. For prenatal development, the NOEL and the NOAEL were considered to be 0.3 g/kg bw/d, based on the lower mean fetal weights noted at the1g/kg bw/d dose.

Inhalation

Butyl Methacrylate

In a study comparable to an OECD TG 414 protocol study, groups of 22-25 pregnant female rats were given whole-body inhalation exposures to Butyl Methacrylate at target concentrations of 0, 100, 300, 600 or 1200 ppm for 6 h/d, during days 6 to 20 of gestation.[70] Maternal toxicity (decreased body weight gain) was observed at 300 to 1200 ppm. Feed consumption was decreased at 1200 ppm Butyl Methacrylate. No dam died during the test, and there were no adverse effects on the average number of implantations and live fetuses, incidence of non-live fetuses, or on resorptions. Fetal body weights of male pups were statistically significantly reduced at 1200 ppm, and fetal body weights of female pups were statistically significantly reduced at 600 ppm and 1200 ppm Butyl Methacrylate. There were no statistically significant differences between control and treated groups with respect to external, visceral, or skeletal malformations. A statistically significant increase in skeletal variations per litter occurred at 1200 ppm Butyl Methacrylate, when compared to controls. The authors concluded that the NOAEL for developmental toxicity was 300 ppm Butyl Methacrylate. There was no evidence of embryo-lethality or teratogenicity induced by Butyl Methacrylate.

GENOTOXICITY STUDIES

In Vitro

Butyl Methacrylate

The mutagenic activity of Butyl Methacrylate has been evaluated in a bacterial reverse mutation assay conducted in accordance with OECD TG 471, using the preincubation method.[72] *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with Butyl Methacrylate in dimethyl sulfoxide (DMSO) at

concentrations up to 1250 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of metabolic activation. Under the conditions of the study, Butyl Methacrylate was not mutagenic in the Ames test.

t-Butyl Methacrylate

The Ames test was used to evaluate the genotoxicity of t-Butyl Methacrylate (in DMSO) with metabolic activation (doses of 9.77, 19.5, 39.1, 78.1, 156, 313 and 625 µg/plate) and without metabolic activation (doses of 9.77, 19.5, 39.1, 78.1, 156, 313, 625 and 1250 µg/plate).[73] The following bacterial strains were used: *S. typhimurium* strains TA100, TA1535, TA98, and TA1537; *E. coli* strain WP2 uvrA. Results were negative for genotoxicity in all bacterial strains tested with and without metabolic activation.

Glycol Dimethacrylate

To assess DNA damage, human gingival fibroblasts were incubated with Glycol Dimethacrylate (0.01, 0.05, 0.1, 0.5 and 1 mM) for 24 h.[74] The level of DNA damage induced by the test substance was estimated using an alkaline version of the comet assay. This technique allows the amount of single- and double-strand DNA breaks to be assessed, as well as the number of alkali labile sites. Additionally, either human 8-oxoguanine DNA glycosylase (hOGG1) or Nth was used to detect oxidative DNA damage, particularly the oxidation of purines and pyrimidines, respectively. DNA damage was monitored after 15, 30, 60 and 120 min of repair incubation. The number of breaks and alkali-labile sites increased with increasing Glycol Dimethacrylate concentration, and this effect was statistically significant beginning at the 0.05 mM dose ($p = 0.008$).

The genotoxicity of Glycol Dimethacrylate (in DMSO) was evaluated in the chromosomal aberrations assay using cultured human lymphocytes.[75] The assay was performed, with and without metabolic activation, in accordance with OECD TG 473. Glycol Dimethacrylate was tested at concentrations up to 600 µg/ml without metabolic activation, and concentrations up to 1000 µg/ml with metabolic activation. Results were positive (clastogenic) without metabolic activation at a concentration of 600 µg/ml. No statistically or biologically significant increases in the percentage of aberrant cells, compared to the solvent control values, were observed at any of the Glycol Dimethacrylate concentrations with metabolic activation (at 72-h sampling time), or with or without metabolic activation (at the 96-h sampling time). Statistically significant increases in chromosomal aberrations were observed with Glycol Dimethacrylate (at 600 µg/ml) in the absence of metabolic activation and examined at a 72-h sampling time. Positive controls (mitomycin C and cyclophosphamide) induced the appropriate response, confirming the sensitivity of the test system. Therefore, Glycol Dimethacrylate caused chromosomal damage in human peripheral blood lymphocytes in vitro in the absence of metabolic activation in this study.

HEMA

DNA adducts as indicators of oxidative DNA damage have been indirectly demonstrated by modified comet assays.[76,77] HEMA, at 5 and 10 mM concentrations for 1 h, induced oxidative DNA lesions in both human peripheral blood lymphocytes and A549 human lung cells in vitro, as measured by increased DNA migration in endonuclease III (endo III) or formamidopyrimidine-DNA-glycosidase (Fpg) modified comet assays. As detected by these modified comet assays, the oxidative damage induced by 10 mM HEMA did not persist, apparently being repaired by 120 min. Hydrogen peroxide (20 mM for 10 min) as the positive control gave positive results with both enzymes.

The preceding study was followed by an evaluation of HEMA as an inducer of oxidative damage in human gingival fibroblasts in vitro.[76,78] As in the preceding study, HEMA (5 mM) induced DNA damage, as measured by modified comet assays using human gingival fibroblasts (6-h incubations). Hydrogen peroxide was again the positive control. Again, HEMA-induced oxidative damage adducts did not persist longer than 120 min.

Two screening tests were used to determine if HEMA damaged DNA in either bacterial and/or mammalian cells.[76,79] In the first, HEMA was applied to a *Salmonella* tester strain (TA 1535/pSK 1002) at concentrations ranging from 0.2 to 40 mM for 2 h with the SOS response (indicating DNA damage; SOS response is inducible DNA repair pathway) being measured calorimetrically. Results were negative at all concentrations tested. In the second screening test, the inhibition of DNA synthesis in human HeLa cells exposed to HEMA at the same concentrations for 90 min was determined by BrdU incorporation. Results were also negative at all concentrations.

DNA strand breaks, as measures of DNA damage, were determined for HEMA in several studies.[76,80] The alkaline comet assay was employed in a study of DNA single strand breaks (SSBs) (or alkali labile incomplete excision repair sites) of human peripheral blood lymphocytes (PBLs, non-stimulated) exposed in vitro to HEMA at concentrations ranging from 10^{-8} to 10^{-2} M for 60 min. Results were negative at concentrations of 10^{-8} and 10^{-7}M, but became positive at 10^{-6} M and higher, as assessed by increased DNA migration (greatest effect at 2.5×10^{-2} M). Cells maintained 84% viability, determined by trypan blue staining. A second study using the alkaline comet assay (by same investigators) was performed.[76,81] Both human PBLs (non-stimulated) and salivary gland tissue (from surgical removals) were exposed in vitro to HEMA at concentrations ranging from 10^{-7} to 2.5×10^{-2} M. Results for PBLs were essentially as in the original study, with the effect first observed at a concentration of 10^{-5} M (greatest at 2.5×10^{-2} M). Salivary gland tissue was somewhat more resistant, with a positive effect first observed at 10^{-3} M (greatest effect at 2.5×10^{-2} M). Cell viabilities were in the range of 70%, determined by trypan blue staining. Although the extent of DNA migration following exposure to HEMA was greater in

salivary gland tissue than in PBLs, suggesting a greater effect, the response in both tissues was only 8e10% of that seen in th*N*-methyl-*N*'-nitro-*N*-nitrosoguanidine' (MNNG) positive control, which is a strong DNA breaking agent.

DNA single-stranded DNA binding protein (SSB) (or alkali labile sites) and double strand breaks (DSBs) were both later studied in human PBLs in vitro (non-stimulated), employing different versions of the comet assay and in a DNA plasmid.[76,77] Exposures to HEMA at concentrations ranging from 1.0 to 10.0 mM for the cells (lower to study repair) and 0.3 to 10 mM for the plasmid were for 1 h. In addition, cell cycle changes were also determined in A549 human lung cells in this study. There was no effect on the DNA plasmid at any HEMA concentration (assessed by plasmid relaxation), even though this material was sensitive to DNA breakage induced by hydrogen peroxide. There was a concentration-dependent increase in SSBs, as assessed by increased DNA migration in the alkaline comet assay, but no increase in DSBs, as assessed in the neutral comet assay. Lack of DSB induction was confirmed by pulsed field electrophoresis. HEMA induced apoptosis in the PBLs following 6 h incubations, and caused a cell cycle arrest in A549 cells at the G0/G1 checkpoint. As was also observed for the strand breaks detected by modified comets (see above oxidative DNA damage), the SSBs (or alkali labile sites) in this study were repaired by 120 min.

The induction of γH2AX and other phosphorylated signaling proteins of the DNA damage response were again used as an indirect indicators of HEMA induced DSBs in a study in which BEAS-2B human lung cells were exposed at concentrations ranging from 0.5 to 4.0 mM for 24 h.[76,82] Also measured in this study were inductions of SSBs as reflected in the alkaline comet assay, cell proliferation and cell cycle changes, cell death and apoptosis (TUNEL assay), reactive oxygen species (ROS) production by fluorescent probe and GSH levels. Cell necrosis and apoptosis were determined by nuclear fluorescence microscopy. Increases in γH2AX, phospho-Chk2 and p53, as determined by both Western blotting and cytometry, were observed at 3.6 and 5.4 mM HEMA, with further increases with duration of exposure. Increased DNA migration in the alkaline comet assay was seen at 5.4 and 8.1mM HEMA, indicating induction of DNA SSBs. Cell death occurred at 2 and 4 mM exposures. Accumulation of cells in early S-phase was seen at 5.4 mM and apoptosis was observed at 5.0 mM, becoming significant at 7.5 mM. ROS production was significantly increased after exposure to 5.4 mM HEMA, then returned to normal. Significant GSH (reduced form of glutathione) reduction was seen only after 6 h of exposure at that concentration, after which it also returned to baseline.

In a modified comet assay, the genotoxicity (DNA damage) of HEMA in human gingival fibroblasts was evaluated at concentrations ranging from 1 to 10 mM.[18] The incubation period was 6 h. HEMA induced a mild, but statistically significant decrease in the viability of human gingival fibroblasts (10% decrease at 10 mM). HEMA also increased tail DNA in a dose-dependent manner, which was statistically significant ($p < 0.01$) at all concentrations tested. The neutral comet assay was used to detect the ability of HEMA (1 to 10 mM) to induce DNA double-strand breaks. A statistically significant ($p < 0.05$) increase in tail DNA at 1 mM and higher concentrations was observed. The kinetics of DNA repair in human gingival fibroblasts after treatment with HEMA was analyzed by measuring the extent of DNA damage in cells exposed to 5 mM HEMA immediately after exposure as well as 30, 60, 90, and 120 min thereafter. The exposed cells were able to remove approximately 90% of the damage to their DNA within 60 min.

The ability of HEMA to damage DNA (pUC19 plasmid DNA) was quantified by calculating the ratio of the open circular DNA to the total amount of DNA.[18] The plasmid used was sensitive to DNA-breaking agents. HEMA (1 to 10 mM) did not introduce DNA breaks in isolated DNA.

HEMA, at concentrations up to 5.0 mM did not induce mutations in the *Hprt* gene with or without metabolic activation.[76] Details relating to the test protocol and study results are not included.

Other data indicate that HEMA induced micronuclei (in V79 cells) in a dose-dependent manner at concentrations up to 4.0 mM in the absence of metabolic activation, where cell survival was greater than 50%, as determined by dye exclusion.[83] This response was abolished in the presence of metabolic activation. Similarly, HEMA was shown to increase micronuclei induction (in V79 cells) in a dose-dependent manner at concentrations up to 5.0 mM in the absence of metabolic activation.[84] Cell viability was approximately 80%, as determined by flowcytometry.

The mouse macrophage cell line (RAW 264.7 cells) was treated for 12 to 8 h with different concentrations of HEMA (0.082-0.00082 M), and the levels of apoptotic cell death were determined by propidium iodide staining.[85] Dose-dependent induction of DNA fragmentation was observed in the presence of HEMA treatment. Similarly, staining with propidium iodide and annexin V indicated that the death induced by HEMA was apoptotic.

The genotoxicity of HEMA (in water) was evaluated in the Ames test using the following bacterial strains, with and without metabolic activation: *S. typhimurium* strains TA98, TA100, TA1535, and *E. coli* strain WP2uvrA.[86] The test substance was evaluated at dose up to 5,000 µg/plate. Neither cytotoxicity nor mutagenic activity was noted in the bacterial strains tested, with or without metabolic activation. The positive and negative control results were in accordance with expected results.

HEMA Acetoacetate

An Ames test was performed to evaluate the genotoxicity of HEMA Acetoacetate (in DMSO), in accordance with to OECD TG 471.[87] The following *S. typhimurium* strains were tested, with and without metabolic activation, at doses up to 5000 ug/plate: TA1535; TA1537; TA1538; TA98 and TA100. The test substance induced no statistically significant dose-

related increases in the numbers of revertant colonies in each of the five tester strains. The positive control values were generally within the range expected for each bacterial strain and activation system. There was no toxicity to the bacterial strains tested. It was concluded that the test substance was not genotoxic to the *S. typhimurium* strains when tested at doses up to 5000 µg per plate.

HEMA and Triethylene Glycol Dimethacrylate

Peripheral blood mononuclear cells were treated with different concentrations of HEMA or Triethylene Glycol Dimethacrylate (0.000082, 0.00082, 0.0082, and 0.082 M) for 12 - 18 h.[85] The levels of DNA strand breaks, indicating apoptotic cell death, were determined by the transferase (Tdt) uridine triphosphate (UTP) nick-end labeling (TUNEL) assay. HEMA caused increases in strand breaks, while Triethylene Glycol Dimethacrylate induced lower levels of increase. At the higher concentrations of HEMA treatment, more cells were observed in the early apoptotic phase when assessed by staining with fluorescein isothiocyanate (FITC) annexin. Furthermore, a significant number of cells could also be seen in the later phases of apoptosis when treated with higher concentrations of HEMA.

In an assay involving human gingival fibroblasts, the cells were incubated with HEMA or Triethylene Glycol Dimethacrylate at concentrations up to 10 mM for up to 24 h.[88] At 1 h after incubation with either test substance, no statistically significant differences in DNA strand breaks were found at concentrations up to 10 mM, when compared to controls. At approximately 24 h after incubation, the same results for both chemicals were reported.

The cytotoxicity and induction of DNA double-strand breaks induced by HEMA or Triethylene Glycol Dimethacrylate in human gingival fibroblasts were evaluated.[22] The 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT)-based cell viability assay was used to determine the half-maximum effect concentration (EC_{50}) value for each chemical. The incubation period was 24 h for cells treated with HEMA (0.01 to 100 mM) or Triethylene Glycol Dimethacrylate (0.01 to 2.5 mM). An ED_{50} value of 11.20 ± 0.60 mmol/l was reported for HEMA, and an ED_{50} of 3.60 ± 0.20 mmol/l was reported for Triethylene Glycol Dimethacrylate. The induction of DNA double-strand breaks was evaluated using the sensitive γ-H2AX (sensitive molecular marker of DNA damage) DNA repair focus assay. This assay was used to monitor whether DNA double-strand breaks are formed in human gingival fibroblasts after 6 h of exposure to HEMA (1.12 mM, 3.7 mM, or 11.2 mM) or Triethylene Glycol Dimethacrylate (0.36 mM, 1.2 mM, or 3.6 mM). γ-H2AX foci were readily discernible in human gingival fibroblast nuclei by immunofluorescence. Microscopic enumeration of γ-H2AX foci revealed that HEMA or Triethylene Glycol Dimethacrylate treatment induced DSB-specific γ-H2AX foci rates statistically significantly above background values ($p < 0.001$). The Triethylene Glycol Dimethacrylate-induced foci rate at 1.2 mM was 2-fold higher than in cells treated with 1.12 mM HEMA. For each test substance, the yield of the average number of induced foci/cell was positively correlated with increasing compound concentration.

V79 fibroblasts were exposed for 24 h to increasing concentrations of Triethylene Glycol Dimethacrylate or HEMA.[89] The number of micronuclei in cell cultures exposed to 0.75 and 1.0 mmol/l Triethylene Glycol Dimethacrylate was approximately 5- to10-fold higher when compared to untreated controls. No micronuclei were counted in cell cultures treated with 1.5 and 3.0 mmol/l Triethylene Glycol Dimethacrylate because of severe cytotoxicity expressed by a very low number of surviving cells. A HEMA concentration of 6.0 mmol/l-induced numbers of micronuclei of approximately 8-fold higher than those detected in untreated controls. No micronuclei were identified in cell cultures treated with 8.0 mmol/l

Hexyl Methacrylate

The genotoxicity of Hexyl Methacrylate (in DMSO) was evaluated (with and without metabolic activation) in the Ames test using the following *S. typhimurium* strains, in accordance with OECD TG 471: [90] TA 98, TA 100, TA 1535, TA 1537, TA1538. At least 4 doses (up to 2500 µg/plate) were tested. The positive control chemicals (9-aminoacridine, sodium azide, benzo[a]pyrene, and 2-aminoantracene) induced a significant increase in the revertant frequency in all tester strains, either with or without metabolic activation. Results were negative for Hexyl Methacrylate, both with and without metabolic activation.

Isobornyl Methacrylate

The genotoxicity of Isobornyl Methacrylate (in DMSO) was evaluated in the Ames test (OECD TG 471) using the following bacterial strains: *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102, and *E. coli* WP2 uvrA.[91] The test substance was evaluated at doses up to 5000 µg/plate with and without metabolic activation. Results were negative with and without metabolic activation. Results for vehicle and positive controls were in accordance with the expected results.

Isobutyl Methacrylate

The Ames test (OECD TG 471) was performed to evaluate the genotoxicity of Isobutyl Methacrylate (in DMSO) using the following *S. typhimurium* strains: TA98, TA100, TA1535, and TA1537.[92] The test substance was evaluated at doses up to 10,000 µg/plate, with and without metabolic activation. Results were negative with and without metabolic activation in all of the strains tested. Results for vehicle and positive controls were in accordance with the expected results.

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Methoxydiglycol Methacrylate

The genotoxicity of Methoxydiglycol Methacrylate was evaluated in the Ames test (OECD TG 471), using the following bacterial strains: *S. typhimurium* strains TA97, TA98, TA100, and TA1535, and *E. coli* WP2 uvrA.[94] The test substance was evaluated at doses ranging from 0.001 to 5 µl/plate with and without metabolic activation. There was no evidence of mutagenic potential in this assay at doses up to 5 µl/plate, with and without metabolic activation.

PEG-4 Dimethacrylate

An Ames test (OECD TG 471) was performed to determine the potential for PEG-4 Dimethacrylate (in dimethyl sulfoxide) to induce mutations in the following bacterial strains: *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2uvrA with or without metabolic activation.[95] In the first experiment, PEG-4 Dimethacrylate was tested at concentrations up to 5000 µg/plate in strains TA1535, TA1537 and TA98. In the second experiment, PEG-4 Dimethacrylate was tested at concentrations up to 5000 µg/plate in strains TA1535, TA1537, TA98, TA100 and WP2uvrA. Test results indicated that PEG-4 Dimethacrylate was not mutagenic in any of the bacterial strains tested. The negative and strain-specific positive control values were within the laboratory historical control data ranges.

Triethylene Glycol Dimethacrylate

A study was designed to investigate oxidative DNA damage, the activation of ataxia-telangiectasia mutated (ATM), a reporter of DNA damage, and redox-sensitive signal transduction through mitogen-activated protein kinases (MAPKs), induced by Triethylene Glycol Dimethacrylate.[96] Test substance concentrations as high as 3 to 5 mM decreased THP-1 monocyte viability after a 24 h and 48 h exposure, and levels of 8-oxoguanine (8-oxoG) were increased by approximately 3- to 5-fold. The cells were partially protected from toxicity in the presence of *N*-acetylcysteine (NAC). Triethylene Glycol Dimethacrylate also induced a delay in the cell cycle. The number of THP-1 cells increased by approximately 2-fold in G1 phase, and 5-fold (in G2 phase) in cultures treated with 3 to 5 mM Triethylene Glycol Dimethacrylate. ATM was activated in THP-1 monocytes by Triethylene Glycol Dimethacrylate. Likewise, the test substance (3 mM) increased the amounts of phospho-p38 (mitogen-activated protein kinase) by approximately 3-fold, compared to untreated controls after a 24 h and 48 h exposure period. Phospho-ERK1/2 (extracellular signal-related kinase) was induced in a very similar way. The activation of both MAPKs was inhibited by NAC. The findings in this study suggest that the activation of various signal transduction pathways is related to oxidative stress caused by a resin monomer. Signaling through ATM indicates oxidative DNA damage and the activation of MAPK pathways indicates oxidative stress-induced regulation of cell survival and apoptosis.

To explore the presence of oxidized bases that could be produced by oxidative events during short-term treatment with Triethylene Glycol Dimethacrylate, the 8-hydroxyguanine DNA-glycosylase 1-modified comet assay was used.[97] Triethylene Glycol Dimethacrylate induced an early and rapid GSH-depletion in a concentration-dependent manner ($p < 0.05$). Triethylene Glycol Dimethacrylate (5 mM) reduced GSH to 57.8% ± 8.6% of control values after 30 min. There was no significant reduction in cell viability during 6 h of incubation, and only moderate ROS-formation was detected after 4 h of treatment with Triethylene Glycol Dimethacrylate. However, after 24 h, Triethylene Glycol Dimethacrylate concentrations of ≥ 2.5 mM induced a significant reduction of total cell numbers and cells' viability. Furthermore, Triethylene Glycol Dimethacrylate caused a concentration-dependent DNA damage in OKF6/TERT2 cultures, which was not associated with a detectable formation of 8-hydroxy-2'-deoxyguanosine in the cellular genome. According to the authors, the results of this study showed that Triethylene Glycol Dimethacrylate influences the intracellular redox metabolism and may exhibit pronounced cytotoxic and genotoxic effects in human immortalized oral keratinocytes. They also stated that it may be concluded that oxidative stress is not causative for Triethylene Glycol Dimethacrylate-dependent genotoxicity in these cells.

A study was performed to evaluate the cytotoxicity and genotoxicity of Triethylene Glycol Dimethacrylate.[98] Cell viability after exposure to Triethylene Glycol Dimethacrylate (5 mM) was evaluated using Chinese hamster ovary cells (CHO-K1). To examine cell viability, the cells were incubated with the test substance for 1 h. Each experiment included a positive control (hydrogen peroxide). Hydrogen peroxide caused pronounced DNA damage, which resulted in tail DNA of 30 to 40%. Triethylene Glycol Dimethacrylate (5 mM) decreased the viability to a level of 65% ($p < 0.001$). The plasmid relaxation assay involved pUC19 plasmids isolated from DH5a *E. coli* cells. The ability of Triethylene Glycol Dimethacrylate (5 mM) to damage DNA was quantified by calculating the ratio of the open circular DNA to the total amount of DNA. Triethylene Glycol Dimethacrylate did not introduce breaks in isolated DNA. The amount of open circular form of plasmid DNA to the total amount of DNA was calculated. Exposure to Triethylene Glycol Dimethacrylate (5 mM) did not cause statistically significant DNA damage when compared to the unexposed control.

The comet assay (with modifications; alkaline or neutral conditions) was performed using Chinese hamster ovary cells (CHO-K1 cells). Triethylene Glycol was tested at a concentration of 5 mM. The alkaline version enables detecting single and double DNA strand breaks as well as alkali labile sites. The percentage of DNA in the tail (% tail DNA) was analyzed. The neutral version of the comet assay detects DNA double strand breaks. The neutral version is not specific for double strand breaks, but when double strand breaks are present, they would increase the percentage of DNA in the tail. This quantity is positively correlated with the level of DNA breakage or/and alkali labile sites in the cell, and is negatively correlated with the level of DNA crosslinks. For the neutral version, this % tail DNA positively correlates with DNA double strand breaks. The mean value of the % tail DNA in a particular sample was taken as an index of the DNA damage in this

sample. Results for the alkaline version of the comet assay indicated that Triethylene Glycol Dimethacrylate (5 mM) caused significant DNA damage (tail DNA = 9.7%). Results for the neutral version of the comet assay indicated no change in the tail DNA. In an evaluation for apoptosis, Triethylene Glycol (5 mM) singly induced a pronounced increase in the apoptotic ratio of the CHO cells (ratio increased to > 12 times). The authors concluded that the results of these experiments indicate that Triethylene Glycol Dimethacrylate may exert significant cytotoxic and genotoxic effects.

In an in vitro mammalian cell gene mutation assay (OECD TG 476) using Chinese hamster V79 cells, the cell cultures were exposed to Triethylene Glycol Dimethacrylate (in DMSO) at concentrations of 22.7 to 2900 µg/ml, with and without metabolic activation.[99] The assay was performed in 2 independent experiments. The cells were exposed to the test substance for 4 h in the first experiment, with and without metabolic activation. The second experiment involved a treatment period of 24 h in the absence of metabolic activation, and 4 h in the presence of metabolic activation. The maximum dose of the test substance was 2900 µg/ml, corresponding to a molar concentration of ~10 mM. Relevant cytotoxic effects, indicated by a relative cloning efficiency or cell density below 50%, occurred in the first experiment at 1087.5 µg/ml and above (without metabolic activation) and at 2900 µg/ml (with metabolic activation). In the second experiment, cytotoxic effects were noted at 362.5 µg/ml and above (without metabolic activation). No substantial and reproducible dose-dependent increase in the mutation frequency was observed up to the maximum test concentration. Triethylene Glycol Dimethacrylate was classified as non-mutagenic in this assay. The positive controls induced the appropriate response.

Trimethylolpropane Trimethacrylate

Trimethylolpropane Trimethacrylate was evaluated for mutagenicity in the Ames test (OECD TG 471), using the following *S. typhimurium* strains, with and without metabolic activation: TA 1535, TA 1537, TA 98, TA 100 and TA 102.[100] Mutagenicity was evaluated at doses up to 5000 µg/plate in 2 experiments. In the second experiment (but not in the first), evidence of toxicity in the form of a marked reduction in revertant numbers was observed at a dose of 2500 µg/plate and greater in strains TA1535 and TA1537 (with metabolic activation) and at a dose of 5000 µg/plate in strain TA1537 (without metabolic activation). The positive controls induced the appropriate responses in the corresponding strains. Trimethylolpropane Trimethacrylate did not cause a substantial increase in revertant colony numbers over the control count in any of the bacterial strains, with or without metabolic activation. Thus, Trimethylolpropane Trimethacrylate was not considered to be mutagenic in this bacterial system.

In Vivo

Butyl Methacrylate

The clastogenic activity of Butyl Methacrylate was evaluated in an *in vivo* micronucleus test conducted in accordance with OECD TG 474.[101] The test material was administered (in corn oil) via intraperitoneal administration to groups of male and female Swiss CD-1 mice at doses of 0.5, 1, or 2 g/kg bw. Mice from each dose level were killed at 24 h or 48 h; the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow. Under the conditions of this study, Butyl Methacrylate was considered to be non-clastogenic in the in vivo micronucleus test.

t-Butyl Methacrylate

The mouse (Swiss mice) micronucleus assay was used to evaluate the genotoxicity of t-Butyl Methacrylate (in corn oil). Groups of 10 (5 males, 5 females/group) mice were injected i.p. with a single dose of the test substance (0.5, 1, and 2 g/kg).[102] The animals were killed at 24 h or 48 h post-exposure. At least 2000 polychromatic cells per animal were examined for the presence of micronuclei. The ratio of mature to polychromatic erythrocytes was also determined. Results were negative for genotoxicity at each administered dose. No statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PCE) over the control value was observed at any dose level. Slight increases in the ratio of mature to polychromatic erythrocytes, compared to the vehicle control, were observed at the 48-h sampling time for both male and female animals from the high-dose group.

Glycol Dimethacrylate

The genotoxicity of Glycol Dimethacrylate (in corn oil) was evaluated in the micronucleus test in accordance with OECD TG 474.[103] Groups of 10 mice of the CD-1 strain (5 males, 5 females/group) were used. The animals were dosed orally (single dose; method not stated) with the test substance (dose volume: 10 ml/10 g; dose: 1.2 g/kg). Control mice were dosed with corn oil. Cyclophosphamide served as the positive control. The animals were killed and bone marrow smears were prepared. At least 1000 pPCE were analyzed per animal for micronuclei. Glycol Dimethacrylate did not induce micronuclei, and was classified as non-mutagenic in this assay.

HEMA

A genotoxicity study involving *Drosophila melanogaster* was performed.[104] The somatic mutation and recombination test (SMART) was used to detect homologous recombination, point, and chromosome mutations. *Drosophila* larvae were incubated with HEMA at concentrations of 59 and 206 mM for 48 h, and mutational phenotypic changes were measured in adult fly wings. Results were negative.

HEMA was evaluated for micronuclei induction in bone marrow cells in vivo.[76] Male rats exposed to HEMA orally at doses of 0.5, 1 or 2 g/kg x 2 were killed 24 h post exposure and bone marrow micronuclei (MN- PCE) were measured in 2000 PCE per dose. PCE/normochromatic erythrocytes (NCE) ratios determined cytotoxicity. There were no increases in MN-PCE in any treatment group (compared to negative control), while the positive control (cyclophosphamide) yielded the expected significant increase.

Another micronucleus assay on HEMA involved groups of 5 male Sprague-Dawley rats.[105] The test substance in water, (dose volume = 10 ml/kg) was administered twice at 24-h interval by oral gavage at 3 doses of 0.5, 1 and 2 g/kg. At 24 h after the final dose, the animals were killed and bone marrow (from femur) samples were prepared and examined for the incidence of micronucleated polychromatic erythrocytes. The test substance did not induce statistically significant increases in micronucleated polychromatic erythrocytes in any treatment group, and results were considered negative. Results for vehicle and positive controls were in accordance with expected results.

Isobutyl Methacrylate

The genotoxicity of Isobutyl Methacrylate was evaluated in the micronucleus test (OECD TG 474) using groups of 12 NMRI mice (6 males, 6 females per group).[106] Test animals received a single oral dose of 5 g/kg (in 1% carboxymethylcellulose). The dose volume was 10 ml/kg. Bone marrow (femur) smears were prepared at 24h, 48 h, and 72 h post-dosing. Three animals died at the 48-h period, and 1 animal died at the 72-h period. The number of micronucleated polychromatic erythrocytes per 1000 cells was determined. The number of micronucleated PCE was not statistically significantly increased relative to the vehicle control in either sex, regardless of the collection time. A score of 1000 polychromatic erythrocytes was determined for each animal, indicating no genotoxic activity. Results for vehicle and positive controls were in accordance with expected results.

Lauryl Methacrylate

In a NMRI mouse bone marrow micronucleus assay (OECD TG 474), groups of NMRI mice (5 males, 5 females per group) were dosed orally with Lauryl Methacrylate at a dose of 0 mg/kg bw (control) or 5 g/kg bw.[107] The test article was suspended in 1% carboxymethylcellulose (negative control). The dose volume was 10 ml/kg bw. Bone marrow cells were collected for micronuclei analysis (1000 PCE per animal scored) at 24 h, 48 h, and 72 h. Lauryl Methacrylate did not induce micronuclei and was considered non-mutagenic. In comparison with the corresponding negative controls, there was no enhancement in the frequency of detected micronuclei at any preparation interval after test substance application. An appropriate reference mutagen was used as the positive control, and showed a distinct increase in induced micronucleus frequency.

Trimethylolpropane Trimethacrylate

A bone marrow micronucleus test (OECD TG 474) on Trimethylolpropane Trimethacrylate (in carboxymethylcellulose) was performed using groups of 10 NMRI mice (5 males, 5 females per group).[108] Three groups were given single oral (gavage) doses of 0.2, 0.6 and 2 g/kg bw. A fourth group served as the vehicle control. Bone marrow was extracted after 24 h (in all test groups) or after 48 h (in 2 g/kg bw group) of exposure, and the prepared slides were scanned to determine the frequency of micronuclei in 2000 PCEs for each animal. In addition, the PCE:NCE ratio was determined in the same sample and expressed as NCE/1000 PCE. No statistically significant increases in the frequency of micronucleated PCE were observed at any dose levels. The PCE:NCE ratio was slightly affected at a dose of 2 g/kg bw at 24 h and 48 h, indicating slight cytotoxicity. The positive control (cyclophosphamide, 30 mg/kg bw) induced the appropriate response. Based on the results of this study, Trimethylolpropane Trimethacrylate was considered non-mutagenic.

OTHER RELEVANT STUDIES

Cytotoxicity

Butyl Methacrylate, Glycol Dimethacrylate, HEMA, and Triethylene Glycol Dimethacrylate

The cytotoxicity of the following methacrylate monomers in the murine macrophage-like cell line RAW264.7 was evaluated: Butyl Methacrylate, Glycol Dimethacrylate, HEMA, and Triethylene Glycol Dimethacrylate. Cell cultures were incubated for 24 h at test substance concentrations of 0.0001 - 100 mM.[109] LC_{50} values were determined from dose-response curves. Cytotoxicity declined in the following order: Triethylene Glycol Dimethacrylate (LC_{50} = 5.151 ± 0.053 mM) > Glycol Dimethacrylate (LC_{50} = 6.768 ± 0.111 mM) > HEMA (LC_{50} = 7.700 ± 0.079 mM) > Lauryl Methacrylate (LC_{50} = 9.346 ± 0.05) > Butyl Methacrylate (LC_{50} = 12.921 ± 0.253).

Glycol Dimethacrylate

The cytotoxicity of Glycol Dimethacrylate was studied using human gingival fibroblasts (HGF).[74] The cells were treated for 24 h with an appropriate concentration of the test substance. To prepare the dilutions, Glycol Dimethacrylate was first mixed well in the medium by sonification and then diluted to the final concentrations of 0.01, 0.05, 0.1, 0.5 and 1 mM. All experiments were performed 3 times. The appearance of alterations in the nucleus after incubation with the test substance was monitored using fluorescence microscopy. Glycol Dimethacrylate increased the incidence of apoptosis after 24 h of incubation, beginning at 0.05 mM. Chromatin condensation, its marginalization, and cell shrinkage were apparent over the

range of test concentrations. The test substance also had an effect on the cell cycle, having increased (compared to control) the percentage of cells in the G0/G1 phase at concentrations of 0.1 and 1 mM.

Glycol Dimethacrylate was evaluated in a 4-h cytotoxicity assay involving human epidermal keratinocytes and dermal fibroblasts.[110] Results for Glycol Dimethacrylate were statistically significantly different from control keratinocytes at ≥ 100 µM Glycol Dimethacrylate and from fibroblasts at ≥ 500 µM Glycol Dimethacrylate.

HEMA

The viability of human lung epithelial cells, BEAS-2B, was investigated after exposure for 24 h to HEMA (2.5, 5, and 10 mM).[111] Exposure to HEMA (5 and 10 mM) reduced the viability of the BEAS-2B cells statistically significantly as a result of increased apoptosis, interruption of the cell cycle, and decreased cell proliferation.

Peripheral blood mononuclear cells from healthy non-sensitized individuals were incubated in the presence of HEMA at various concentrations (0.00164 M, 0.0082 M, and 0.0164 M) for 12 to 18 h.[85] A dose-dependent increase in the levels of HEMA-induced cell death was observed.

HEMA and Hydroxypropyl Methacrylate

The following 5 cell lines were exposed to HEMA or Hydroxypropyl Methacrylate (1 to 8 mM) for 24 h in the MTT assay: BEAS-2B cells (human bronchial epithelial cell line), A549 (human tumorigenic lung epithelial cell line), THP-1 cells (human cell-line derived from an acute monocytic leukemia patient), RAW264.7 (partially differentiated mouse macrophage cell line), and L929 (mouse fibroblast cell line).[112] In all cell lines, a dose-dependent decrease in cell viability was observed in the presence of HEMA or Hydroxypropyl Dimethacrylate. There was no statistically significant difference between the effect of HEMA and Hydroxypropyl Methacrylate, exposure, except for 8 mM HEMA and Hydroxypropyl Methacrylate to L929, where exposure to Hydroxypropyl Methacrylate resulted in lower cell viability than HEMA exposure.

Isobutyl Methacrylate

An in vitro MTT assay was performed to evaluate the cytotoxicity of Isobutyl Methacrylate in a carcinoma cell line derived from human salivary gland (HSG cells) and HGF cells.[113] Details relating to the test protocol were not included. The cytotoxic concentration for 50% cell death (CC_{50}) was 0.010 mM in HSG cells and 0.013 mM in HGF cells.

Lauryl Methacrylate

Using the MTT colorimetric assay, the cytotoxic effect of Lauryl Methacrylate on cell viability in HSG cells (salivary gland carcinoma cell line) and HGF cells was evaluated.[114] The following CC_{50} (cytotoxic concentration for 50% cell death) values were determined from dose-response curves: 0.001 mM (HSG cells) and 0.001 mM (HGF cells). The authors concluded that the mechanism of interaction with cell membranes remains unknown with respect to cytotoxicity.

Triethylene Glycol Dimethacrylate

A cytotoxicity assay on Triethylene Glycol Dimethacrylate was performed using 3D extracellular matrix cell cultures of human primary dental pulp stem cells (pulp tissues removed from third molars) was performed.[115] Triethylene Glycol Dimethacrylate (0.5, 1.5, and 2.5 mmol/l) was added after the microtissues were developed for 14 d. Increasing the concentration of Triethylene Glycol Dimethacrylate decreased cell viability and changed the morphology from spindle- to round-shaped cells. The percentages of dead cells increased statistically significantly ($p \leq 0.01$) in a concentration-dependent manner. Over the range of test concentrations (low to high), the increase was 2-fold, 3-fold, and 41-fold.

The effects of different concentrations (0.07 to 5 mM) and exposure times (0 - 72 h) of Triethylene Glycol Dimethacrylate on cell viability, proliferation, and morphology were determined using a real-time viability assay.[116] Solvents were not used because Triethylene Glycol Dimethacrylate is soluble in cell culture medium. Cells were metabolically labeled [using the stable isotope labeled amino acids in cell culture (SILAC) strategy]. The cells were then exposed to 0, 0.3, or 2.5 mM Triethylene Glycol Dimethacrylate for 6 or 16 h before liquid chromatography-tandem mass spectrometry (LC-MS/MS) analyses. Cells exposed to 0.3 mM Triethylene Glycol Dimethacrylate showed increased viability and time-dependent upregulation of proteins associated with stress/oxidative stress, autophagy, and cytoprotective functions. Cells exposed to 2.5 mM Triethylene Glycol Dimethacrylate showed diminished viability and a protein expression profile associated with oxidative stress, DNA damage, mitochondrial dysfunction, and cell cycle inhibition. Altered expression of immune genes was observed in both groups.

In a cytotoxicity assay, human THP-1 monocytes were incubated for 48 h with Triethylene Glycol Dimethacrylate at concentrations of 0, 0.5, 1, 2, 4, and 8 mM (0, 143.16, 286.32, 572.64, 1145.28, and 2290.56 mg/l).[117] The viability of cells incubated with 0.5 mM Triethylene Glycol Dimethacrylate was reduced to ~ 90%. Concentrations of 1 mM and higher were significantly cytotoxic.

Inflammatory Activity

HEMA

The inflammatory response in HGF treated with a relatively low HEMA concentration was investigated by studying reactive oxygen species (ROS) production, cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNF-α) gene expression, and prostaglandin E2 (PGE_2) release.[118] Cultured HGFs were exposed to HEMA (3 mmol/l) for 0, 24 or 96 h. ROS production was investigated by flow cytometry; TNF-α and COX-2 gene expression was determined by reverse transcription polymerase chain reaction (RT-PCR), and PGE_2 production was detected by an enzyme immunoassay. After 24- or 96-h of HEMA incubation, ROS levels were approximately 8-fold and 11-fold higher than controls, while COX-2 gene expression was approximately 2-fold or 4-fold higher than controls, respectively. Twenty-four-h exposure enhanced TNF-α mRNA levels by approximately 66%, while, after 96-h incubation, TNF-α gene expression was 5-fold higher than controls. Ninety-six-h HEMA treatment increased the PGE_2 concentration in the culture medium by approximately 17%, when compared to controls. It was concluded that HEMA treatment induced an inflammatory response in HGFs modulated by ROS production, as well as by the increase in TNF-α and COX-2 gene expression and by PGE_2 release.

CARCINOGENICITY STUDIES

Triethylene Glycol Dimethacrylate

A dermal carcinogenicity study on Triethylene Glycol Dimethacrylate was performed.[43,119] Four groups of male Harlan Sprague-Dawley (C3H/HeNHsd strain) mice (70/group) were treated with Triethylene Glycol Dimethacrylate (5, 25, or 50%; ~ 0.1, 0.5, or 1 g/kg bw/d) 5 d/wk (Monday through Friday) for 78 consecutive weeks. Triethylene Glycol Dimethacrylate was dissolved in acetone. Single doses (50 µl) were applied topically to the clipped interscapular region of the back using a calibrated pipette. Other than the location of application, no effort was made to prevent oral ingestion (e.g., through the use of collars). Untreated and acetone-treated control groups were also used. Animals were observed for mortality and overt signs of toxicity twice daily. Detailed examinations were conducted weekly. Cutaneous cell proliferation evaluations using the bromodeoxyuridine (BrdU) procedure were performed on 4 or 5 mice/group at 4, 13, 52, and 78 wk. All animals dying during the study and those killed at termination were necropsied, and histopathological examination was performed. An increase in mortality occurred in the 50% Triethylene Glycol Dimethacrylate group. There were no clinical or histological effects to which the increased mortality could be attributed. Therefore, it was uncertain whether Triethylene Glycol Dimethacrylate toxicity was directly responsible. There were no test substance-related effects on hematology, clinical chemistry, or body weight measurements. The authors noted that observations during the dosing phase suggested that oral consumption of the test material (resulting from contamination of the fur surrounding the treatment site) was likely, particularly at the high dose.

A concentration-related increase in kidney weight was observed in the 25% and 50% concentration groups at the terminal sacrifice. However, there were no correlating microscopic findings in the kidneys, and the biological significance of the increase in weight was uncertain. During treatment, signs of irritation, consisting primarily of exfoliation, were observed in all treatment groups. The time of onset, incidence, and severity of the exfoliation were dose related. Dermatitis, acanthosis, hyperkeratosis, and intracorneal pustules occurred in all groups, including controls. An increase in the incidence of acanthosis and hyperkeratosis occurred at concentrations of 25% and 50%, and an increase in dermatitis was observed at the high concentration only. There was no clear concentration relationship to the severity of the lesions in the mid and high concentration group, although the incidence tended to be slightly greater at the high concentration. There were no treatment-related skin lesions at the low concentration. The mean measured rate of epidermal basal cell proliferation of the mid and high concentration groups was consistently increased when compared to both control groups at each measurement. There were no clear differences between the mid and high concentration groups. The magnitude of the difference between treated and untreated animals was greater in the 2 early measurement periods (65 - 127% increase over control) compared to the increase at 12 and 18 mo (25 - 60% increase over control). The authors concluded that there is no concern for carcinogenesis from exposure to Triethylene Glycol Dimethacrylate. The NOAEL for local effects was 5% (~ 0.1 g/kg bw/d). When taking into consideration the increased mortality and effects on the kidneys in the 50% Triethylene Glycol Dimethacrylate group, the systemic NOAEL was determined to be 25% (~ 0.5 g/kg bw/d).

Trimethylolpropane Trimethacrylate

Fifty male C3H mice were exposed to 25 mg of undiluted Trimethylolpropane Trimethacrylate per day, corresponding to 0.833 g/kg bw/d (twice weekly) for 80 wk.[120] The test substance was applied to the interscapular region of the back (dose per cm^2 not stated). An untreated control group of 50 mice was also included. Five mice died during the study, and 4 mice were killed before the end of the study (reason not stated). Data on clinical signs were not included. A slight decrease in body weight was observed on the first 2 d after the initial application. Thereafter, body weight was increased, as noted at week 35. A decrease in body weight was observed at the end of the study (i.e., after week 75). The skin non-neoplastic lesions observed in treated animals were: ulcer (1of 46 mice), acanthosis (46 of 46 mice), fibrosis (24 of 46 mice), and hyperkeratosis (2 of 46 mice). The authors noted that acanthosis and fibrosis were chemically and/or mechanically induced. Both lesions were observed in non-treated animals (acanthosis: 43 of 48, fibrosis: 31of 48). Ulcer (7 of 48), abscess (1of 48), and dysplasia (1of 48) were also observed in non-treated mice. The following pathologic lesions were observed in the treated

animals: lung (pneumonia, 1 of 4 mice), liver (carcinoma, 1 of 4 mice; necrosis, 1 of 4 mice; same animal not associated with each) and lymphadentitis (2 of 4 mice). No skin tumors were present in mice treated with Trimethylolpropane Trimethacrylate. One mouse in the "no treatment" group had a squamous cell carcinoma. The authors concluded that no clinical signs or adverse histological changes were observed in male after 80-wk dermal exposure to Trimethylolpropane Trimethacrylate.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization studies are presented in Table 1.

Irritation

In Vitro

Methoxydiglycol Methacrylate

A study evaluating the skin irritation potential of Methoxydiglycol Methacrylate was performed using an in vitro skin corrosion test involving reconstructed human epidermis (OECD TG 431).[121] A test substance dose of 50 µl applied to the tissues for 3 min and 60 min. Methoxydiglycol Methacrylate was not corrosive under the conditions of this study.

Animal

t-Butyl Methacrylate

The skin irritation potential of t-Butyl Methacrylate was evaluated using 3 Vienna White rabbits, in accordance with OECD TG 404.[122] A semi-occlusive patch containing the test substance (0.5 ml) was applied for 4 h to a 2.5 x 2.5 cm area on the back. Reactions were scored, ranging from 1 h to day 15 after patch removal. Erythema (score of 1 to 3) was observed in all animals up to day 8 after patch removal. Edema (score of 1) was observed in 2 rabbits at 1 h after patch removal and in 1 rabbit at 24 h, 48 h, and 72 h after patch removal (same animal at each observation time). A mean erythema score (24 - 72 h) of 2.44 and a mean edema score (24 -72 h) of 0.33 were reported.

Cyclohexylmethacrylate

The skin irritation potential of Cyclohexylmethacrylate was evaluated using 6 New Zealand White rabbits.[123] The test substance (0.5 ml) was applied for 24 h, under an occlusive covering, to a 2.5 x 2.5 cm area of the flank. Reactions were scored at 24 h and 72 h after patch application. Erythema was observed in 2 animals at 24 h, and in 1 animal at 72 h. Edema was observed in 3 animals at 24 h. Reactions were scored at 24 h and 72 h after patch application according to the method of Draize. The mean erythema score (average value of the single scores (animals 1-6; erythema (intact skin), at 24h and 72 h) was determined to be 0.42 out of 4, and the mean edema score was 0 out of 4.

Glycol Dimethacrylate

A study was performed to evaluate the skin irritation potential of undiluted Glycol Dimethacrylate, using 6 New Zealand White rabbits.[124] The test substance (0.5 ml, under occlusive patch) was applied for 24 h to intact skin. Reactions were scored at 24 h and 72 h post application according to the Draize scale. The mean erythema score (average value of the single scores (animals 1-6; at 24h and 72h) was determined to be 0.42 out of 4, and the mean edema score was 0 out of 4. Glycol Dimethacrylate was classified as a non-irritant in this study.

HEMA

HEMA was tested in a primary skin irritation test involving 6 New Zealand White rabbits, according to the method of Draize.[125] The test substance (0.5 ml under occlusion) was applied for 24 h to a 2.5 cm x 2.5 cm test site (shaved and abraded). After 24 h, 2 animals had slight erythema. Within 72 h, the erythema observed was fully reversible. Edema was not observed. The test substance was classified as non-irritating to the skin.

HEMA Acetoacetate

Undiluted HEMA Acetoacetate was evaluated for skin irritation potential using 3 female New Zealand White rabbits, in accordance with OECD TG 404.[126] The test substance (0.5 ml) was applied for 4 h, under an occlusive patch secured with adhesive tape, to the back. The application site was evaluated at 1 h, 24 h, 48 h, and 72 h post-removal. No adverse reactions or corrosive effects were observed in any of the animals. The test substance was classified as non-irritating to the skin (primary irritation index = 0).

Hexyl Methacrylate

In a Draize irritation test involving 6 New Zealand White rabbits, Hexyl Methacrylate (undiluted, 0.5 ml under occlusive patch) was applied for 24 h to intact and scarified skin (2.5 x 2.5 cm area).[127] Reactions were scored at 24 h and 72 h post-application. The mean erythema score (average value of the single scores (animals 1-6; erythema (intact skin), at 24 h and 72 h)) was determined to be 1.667 out of 4, and the mean edema score was 1.9167 out of 4. Hexyl Methacrylate was classified as non-irritating to the skin.

Isobornyl Methacrylate

In a primary dermal irritation study, 3 New Zealand White rabbits were dermally exposed for 4 h (under semi-occlusive patch, secured with adhesive tape) to Isobornyl Methacrylate (0.5 ml).[128] The study was performed in accordance with OECD TG 404. Application to a 2.5 x 2.5 cm^2 site on the trunk was followed by a 7-d observation period. Reactions were scored according to the method of Draize. The mean erythema score (at 24 h and 72 h) was determined to be 2 (maximum score = 4) and the mean edema score was 2 (maximum score = 4). Isobornyl Methacrylate was classified as a mild irritant in this study.

Isobutyl Methacrylate

A skin irritation study on undiluted Isobutyl Methacrylate was performed using 6 New Zealand White rabbits.[129] The test substance (0.5 ml, under 6 cm^2 occlusive patch secured with adhesive tape) was applied for 2 h to abraded and intact skin sites. Reactions were evaluated at 24 h and 72 h. Mean irritation scores over 24 h and 72 h were 1.08 for erythema and 0.5 for edema. All scores were < 2.3. The highest mean erythema score was 2, in 1of 6 animals; the highest edema score was 1, in 2 of 6 animals. Isobutyl Methacrylate was considered slightly irritating to the skin. In another experiment (by same author), the test substance was applied to the skin for 24 h (details not included). Skin irritation potential was slightly higher, and was not fully reversible within the 72-h observation period.

Tetrahydrofurfuryl Methacrylate

In a primary dermal irritation study, Tetrahydrofurfuryl Methacrylate (0.5 ml, under occlusive patch) was applied for 24 h to the skin (~ 2.5 cm^2) of 6 rabbits.[131] Two application sites (intact and abraded skin) per animal were treated. Animals were observed for a period of 72 h, and reactions were evaluated using a scoring system that is similar to the one in OECD TG 404. Very slight dermal irritation was observed (in 1 of 6 animals) on intact and abraded skin after 24 h and 27 h, and in 1 of 6 animals (intact skin) after 24 h. Skin irritation was not observed in other animals in the study. At study termination, reversibility of irritation reactions was complete in half of the affected animals. Tetrahydrofurfuryl Methacrylate was not classified as a skin irritant in this study.

Triethylene Glycol Dimethacrylate

Four groups of male Harlan Sprague-Dawley (C3H/HeNHsd strain) mice were treated with Triethylene Glycol Dimethacrylate at concentrations of 5, 25, 50, and 100% daily for 14 consecutive days.[43] Triethylene Glycol Dimethacrylate was dissolved in acetone, except for when 100% Triethylene Glycol Dimethacrylate was applied. Single doses (50 µl) were applied topically to the clipped interscapular region of the back using a calibrated pipette. Other than the location of application, no effort was made to prevent oral ingestion (e.g., through use of collars). Detailed clinical observations were made daily starting on day 2, and skin lesions were scored (slight, moderate, and severe). The incidence and severity of skin irritation were observed in a dose-related manner in treated animals. Skin irritation was most consistently described histopathologically, with the most common microscopic alteration being acanthosis. Dose-related skin irritation consisting primarily of erythema and desquamation/exfoliation (scaling) was observed following 7 d of treatment. Erythema and desquamation/exfoliation occurred more frequently and/or were more severe at 14 d. Desquamation/exfoliation were observed at concentrations of 50% and 100%. Vitiligo (loss of pigmentation) was observed occasionally at 7 d, but was more prominent following 14 d of treatment. No other clinical signs were considered related to treatment. Other than skin lesions at the site of dosing, no treatment-related observations were made at necropsy.

In a primary dermal irritation study, 6 New Zealand White rabbits were dermally exposed (2.5 cm^2 skin area) for 24 h to 0.5 ml of Triethylene Glycol Dimethacrylate (under occlusive patch).[132] Two application sites per animal were treated; one site was left intact and the other was abraded. The animals were observed for 72 h. Irritation was scored using a scoring system that is similar to the one in OECD TG 404. No dermal irritation response was observed on intact skin. One of 6 animals had very slight edema (score = 1) after 24 h of contact on abraded skin; this effect was fully reversible within 72 h. Triethylene Glycol Dimethacrylate was classified as a non-irritant in this study.

Trimethylolpropane Trimethacrylate

The skin irritation potential of Trimethylolpropane Trimethacrylate was evaluated using 3 male New-Zealand White rabbits, in accordance with OECD TG 404.[133] The test substance was applied for 4 h, under a semi-occlusive patch (25 cm x 25 cm), to the dorsal flank. The animals were observed for 72 h, and skin irritation was scored according to the method of Draize. Very slight erythema was observed at the application site, and subsided within 24 h. Mean individual scores for erythema/edema at 24 h, 48 h, and 72 h post-removal were all 0. Trimethylolpropane Trimethacrylate was classified as a non-irritant in this study.

Sensitization

In Vitro

Glycol Dimethacrylate

The sensitization potential of Glycol Dimethacrylate was evaluated using the KeratinoSens™ assay (OECD TG 442D).[135] KeratinoSens™ cells (immortalized human keratinocytes transfected with a selectable plasmid) were exposed for

48 h to 12 concentrations (1 to 2000 µM) of the test substance. Cell viability was determined using the MTT assay. The quantitative dose response analysis of the luciferase activity exhibited a dose-dependent increase over the range of concentrations tested. Based on the dose-response relationship observed, Glycol Dimethacrylate was classified as a weak sensitizer.

HEMA

To evaluate the sensitizing potential of HEMA in cultured cells, THP-1 cells (human monocytic cell line) were treated with HEMA for 24 h at various concentrations, and the cell viability and expression levels of CD54 and CD86 (markers of antigen presenting cell activation) were determined by flow cytometry.[136] The viability of the cells gradually decreased with increasing concentration. HEMA induced significant expression of CD54 at concentrations greater than 400 µg/mL (3.2 mM). At concentrations greater than 723 µg/mL (5.5 mM), the expression level of CD54 decreased, and this decrease was accompanied by a reduction in cell viability. Additionally, HEMA induced the significant expression of CD86 at concentrations greater than 602 µg/mL (4.6 mM). The expression level of CD86 also decreased at concentrations greater than 1,250 µg/mL (9.6 mM). It is known that expression levels of either or both of CD54 and CD86 in THP-1 cells are increased by exposure to sensitizing substances. HEMA had sensitization potential in this study.

Animal

Butyl Methacrylate

A dermal sensitization study on Butyl Methacrylate (99.88%, in acetone:olive oil) was performed using female CBA/CaOlaHsd mice, in accordance with OECD TG 429 (local lymph node assay (LLNA)).[137] Three groups of 5 mice were treated daily with Butyl Methacrylate at concentrations of 25, 50, and 100% (w/w) in acetone:olive oil (4+1), by topical application to the dorsum of each ear lobe (left and right) for 3 consecutive days. A control group of 5 mice was treated with the vehicle only. Five d after the first topical application, the mice were injected intravenously (in tail vein) with radio-labelled thymidine (^{3}H-methyl thymidine). Approximately 5 h after intravenous injection, the mice were killed and the draining auricular lymph nodes were excised and pooled per animal. Single cell suspensions of lymph node cells were prepared from pooled lymph nodes, which were subsequently washed and incubated with trichloroacetic acid overnight. The proliferative capacity of pooled lymph node cells was determined by the incorporation of ^{3}H-methyl thymidine. The validation-/positive control experiment was performed with alpha-hexyl cinnamic aldehyde dissolved in acetone/olive oil (4 +1 v/v). During the study, no cases of mortality and no signs of systemic toxicity were observed.

On day 3, all treated animals had erythema on the ear skin (Score 1). On days 4 and 5, the animals treated with 25% and 50% of Butyl Methacrylate had erythema on ear skin (Score 1), and animals treated with a test concentration of 100% also had erythema on ear skin (Score 2). Furthermore, on day 6, the animals treated with concentrations of 50% and 100% had an ear erythema score of 1. It was noted that a test substance is classified as a sensitizer in the LLNA if the exposure to one or more test concentration results in a 3-fold or greater increase in the incorporation of ^{3}HTdR, when compared to concurrent controls. The estimated concentration of the test substance that is required to produce a stimulation index (SI) of 3 is referred to as the EC3 value. In this study, SI of 2.19, 3.28, and 5.41 were determined at test substance concentrations of 25, 50, and 100% in acetone:olive oil (4+1). A clear dose response was observed. The EC3 value was calculated, to be 43.6% (w/v) for Butyl Methacrylate. Therefore, Butyl Methacrylate was classified as a skin sensitizer when tested in this LLNA.

Cyclohexylmethacrylate

The skin sensitization potential of Cyclohexylmethacrylate was evaluated in the mouse LLNA, in accordance with OECD TG 429.[138] Groups of 6 CBA female mice were used, and Cyclohexylmethacrylate was tested at concentrations of 3%, 10%, and 30% (in acetone vehicle). The test substance was applied percutaneously to the dorsal part of each ear (25 µl per ear). Three consecutive applications were made to the same site on days 0 to 2. The animals were killed on day 5, and auricular lymph nodes were dissected. There were no signs of systemic toxicity. The test substance (all concentrations) induced statistically significant and biologically relevant response of the auricular lymph nodes. The concentration-dependent, statistically significant increase in ear weight at concentrations of 10% and 30% was associated with some irritation of ear skin. It was concluded that Cyclohexylmethacrylate had skin sensitizing effect. The threshold concentration for sensitization induction was < 3%.

Di-HEMA Trimethylhexyl Dicarbamate

The sensitization potential of Di-HEMA Trimethylhexyl Dicarbamate was evaluated at concentrations of 10, 25 and 50% (w/w) in DMF (dimethylformamide), using groups of 4 female CBA mice in the LLNA.[134] The 50% concentration was the highest non-irritant test concentration that did not show any signs of irritation or systemic toxicity up to day 8 after 3 d of exposure in 2 animals. Vehicle and positive control (hexyl cinnamic aldehyde) groups were included. The test substance (25 µl) was spread over the dorsal surface of the ear lobes once daily for 3 consecutive days. Five days after the first application, all mice were intravenously injected with 250 µl of [^{3}H] thymidine. SIs of 1.58, 1.70, and 4.44 were determined at concentrations of 10, 25, and 50% (w/w) in DMF, respectively. A clear dose response was observed. Based on the SI values, an EC3 value of 36.9% was calculated. A statistically significant increase in the disintegration per minute (DPM) values was

observed in all dose groups, when compared to the vehicle control group. Based on the calculated EC3 value, Di-HEMA Trimethylhexyl Dicarbamate was considered a weak sensitizer.

Glycol Dimethacrylate

A study was performed to evaluate the skin sensitization potential of Glycol Dimethacrylate (in acetone/olive oil (4:1 v/v)), using the mouse LLNA (OECD TG 429).[139] Groups of 4 to 5 female mice of the CBA strain were treated, by topical application on the dorsum of both ears, with 25 µl of several concentrations (not stated) of the test substance, or with an equal volume of the vehicle alone. The animals were treated daily for 3 consecutive days, followed by a 2-d non-treatment period before analysis. The assay involves measurement of lymphocyte proliferative responses that are induced in draining lymph nodes, following topical exposure of mice to the test substance. An EC3 value is derived, and this value is defined as the amount of a chemical sensitizer that is required to elicit a 3-fold increase in lymph node cell proliferative activity. An EC3 value of 35 was reported, classifying Glycol Dimethacrylate as an extremely weak sensitizer.

HEMA

The skin sensitization potential of HEMA was evaluated using male guinea pigs (Pirbright; sub-strain: Hoe: DHPK (SPF- LAC.) /Boe; 20 test and 10 controls) in accordance with a modified Buehler method.[140] The induction phase involved three 6-h exposures (1 per week; patch type not stated) to the test substance (0.5 ml, on left flank). The challenge phase involved three 6-h exposures (patch type not stated) to the test substance (0.5 ml, on right flank). Reactions were scored at 24 h and 48 h post-challenge. No animals showed signs of erythema or edema. The test substance did not cause delayed contact hypersensitivity.

HEMA and Triethylene Glycol Dimethacrylate

The skin sensitization potential of HEMA and Triethylene Glycol Dimethacrylate was evaluated in the Magnusson and Kligman maximization test, using groups of 5 guinea pigs.[141] For primary sensitization, the test substance (50 µl), emulsion of Freund's complete adjuvant with test substance (50 µl), and emulsion of Freund's complete adjuvant with distilled water (50 µl) were percutaneously injected on both the left and right sides of each animal in the group. At 7 d after primary sensitization, the back of each animal (including 6 injection sites) was shaven. Next, sodium lauryl sulfate solution was applied to the shaved area to increase skin permeability. For the secondary sensitization, a filter paper patch soaked with sodium lauryl sulfate and the test substance (200 µl) was applied for 48 h to the shaved area, using a cohesive stretch bandage. At 2 wk after the secondary sensitization, the back of each animal was shaved. During challenge, the test substance (100 µl) was applied for 24 h to shaved skin to induce delayed-type hypersensitivity. The site was covered with a cohesive stretch bandage during the application period. Skin reactions at 24 h and 48 h were evaluated according to International Contact Dermatitis Research Group criteria. An inflammatory reaction (mean score of 1.4; scales: 0 (no erythema) to 4 (severe erythema); 0 (no edema) to 3 (severe edema)) to HEMA was observed in 4 of 5 guinea pigs. Triethylene Glycol Dimethacrylate caused an inflammatory reaction in 3 of 5 guinea pigs (mean score = 0.6).

Hexyl Methacrylate

The skin sensitization potential of Hexyl Methacrylate was evaluated using the LLNA, in accordance with OECD TG 429.[142] Five groups of 5 female CBA/J mice were used. Three groups were treated with the test substance at concentrations of 25%, 50%, and 100 % (v/v; in acetone:olive oil 4:1 (v:v) mixture). The negative control group was treated with the vehicle, and the positive control group was treated with 25% α-Hexylcinnamaldehyde (v/v; in acetone:olive oil 4:1 (v:v) mixture). The test substance was applied on the dorsal surface of the ears (25 µl/ear) for 3 consecutive days (0, 1, and 2). There was no treatment on days 3 and 4. At day 5, cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl thymidine, and the values obtained were used to calculate SI. No mortality or signs of systemic toxicity were observed during the study. Irritation was not observed at the application site. The SI values were 1.44, 1.68, and 2.19 at concentrations of 25 %, 50%, and 100% (v/v), respectively. It was concluded that Hexyl Methacrylate had no sensitization potential at any of the 3 concentrations tested.

Isobornyl Methacrylate

Isobornyl Methacrylate was evaluated for skin sensitization potential using Dunkin-Hartley guinea pigs (10 males, and 10 females; control: 10 guinea pigs) in accordance with OECD TG 406 (guinea pig maximization test).[143] Test animals were treated via intradermal injection with 0.1 ml of Isobornyl Methacrylate (50 % in paraffin oil) in the presence of Freund's complete adjuvant. At day 8, 0.5 ml of the undiluted test substance was applied cutaneously to the injection sites for 48 h (under occlusive dressing). After a period of 12 d without treatment, a 24 h-challenge occlusive cutaneous application of 0.5 ml of the vehicle (left flank) and 0.5 ml of undiluted Isobornyl Methacrylate was performed. The cutaneous reactions were scored at 24 h and 48 h after removal of the dressing. No cutaneous reactions were recorded in all test animals. The sensitivity of the test animals was confirmed by use of 2,4-Dinitrobenzene (0.1 % and 0.5 %). The sensitization response was 100%. Based on the results of this study, Isobornyl Methacrylate was not considered to be a skin sensitizer.

Isobutyl Methacrylate

The skin sensitization potential of Isobutyl Methacrylate (in acetone:olive oil (4+1, v/v)) was evaluated in the mouse LLNA (OECD TG 429) using groups of 5 female CBA/CaOlaHsd mice.[144] SI were determined at concentrations of 25%,

50% and 100% w/v. No clinical signs and no systemic findings were observed after the first and second application (25% and 50%). Only the highest dose (100%) induced slight erythema on the ear skin of all 4 animals of the group. SI of 1.78, 3.64, and 5.13 were determined with the test substance at concentrations of 25%, 50% and 100% (w/v), respectively. The EC3 was calculated to be 41.4 %, and Isobutyl Methacrylate was classified as a dermal sensitizer. The positive control substance, α-hexylcinnamaldehyde, yielded an EC3 of 5.9 % (w/v).

Methoxydiglycol Methacrylate

The skin sensitization potential of Methoxydiglycol Methacrylate was evaluated in the maximization test (OECD TG 406) using groups of 20 Hartley albino guinea pigs (10 males, 10 females per group).[146] Five guinea pigs comprised the control group. There are two stages to the maximization test. The first stage is induction and consists of intradermal injections, followed in 7 d by topical application of the test substance. The second stage is the challenge, which consists of a topical application performed 14 d following completion of the induction phase. During challenge, the undiluted test substance was applied for 24 h (under occlusive patch) to the skin, at 2 wk after induction. Methoxydiglycol Methacrylate did not induce skin sensitization in this study.

PEG-4 Dimethacrylate

A study (mouse LLNA) was performed to determine whether PEG-4 Dimethacrylate induces skin sensitization in mice after 3 epidermal exposures.[147] At concentrations of 50% and 100%, no signs of systemic toxicity were observed, and only very slight irritation of the ears was observed. Therefore, 100% was selected as the highest test concentration. Three experimental groups of 5 female CBA/J mice were treated with test substance concentrations of 25, 50, or 100% w/w on 3 consecutive days, by open application on the ears. Five vehicle control animals were similarly treated, but with the vehicle alone (acetone:olive oil). Three d after the last exposure, all animals were injected with ^{3}H-methyl thymidine. After 5h, the draining (auricular) lymph nodes were excised and pooled for each animal. After precipitating the DNA of the lymph node cells, radioactivity measurements were performed. The activity was expressed as the number of DPM and a SI was subsequently calculated for each group. All auricular lymph nodes were of normal size, and there were no macroscopic abnormalities in the surrounding area. The SI values calculated for the 3 concentrations of 25, 50, and 100% were 1.0, 1.2, and 1.9, respectively. Because there was no indication that PEG-4 Dimethacrylate elicited an SI of 3 when tested up to a concentration of 100%, the test substance was considered a non-sensitizer.

Triethylene Glycol Dimethacrylate

The skin sensitization potential of Triethylene Glycol Dimethacrylate was evaluated in the mouse LLNA in accordance with OECD TG 429.[148] Groups of 5 female CBA/CaOlaHsd mice were used. The method of application of the 3 test concentrations (25, 50, and 100% (w/v) in acetone:olive oil (4+1, v/v)) was consistent with the protocol in the preceding study. A result is regarded as positive when the SI is ≥ 3. An EC3 value was calculated. No systemic findings were observed during the study period, and none of the animals died. Only the highest dose (100%) induced slight erythema on the ear skin on days 3 to 6 (Score 1). Animals treated with concentrations of 25 and 50% did not show any signs of local skin irritation. SIs of 1.40, 1.51, and 3.30 were determined with the test substance at concentrations of 25, 50, and 100%, respectively. The EC3 for Triethylene Glycol Dimethacrylate was calculated to be 91.6 %, classifying the test substance as a skin sensitizer. The positive control substance, α-hexylcinnamaldehyde, yielded an EC3 of 9.3% (w/v).

Trimethylolpropane Trimethacrylate

A Magnusson and Kligman maximzation test on Trimethylolpropane Trimethacrylate was performed using groups of 20 albino Dunkin Hartley guinea pigs (10 males, 10 females per group), in accordance with OECD TG 406.[149] The animals were intradermally induced with three injections (in shoulder region on each side of mid-line) of the following on d0: 0.1 ml of Freund's complete adjuvant, 25% w/v Trimethylolpropane Trimethacrylate in arachis oil, and 25% w/v Trimethylolpropane Trimethacrylate emulsion in Freund's complete adjuvant. After 1 wk, the same areas were topically induced (for 48 h) with 0.2 ml of undiluted Trimethylolpropane Trimethacrylate via an occlusive patch. After a 2-wk non-treatment period, a challenge patch with 75 % v/v or 100% v/v Trimethylolpropane Trimethacrylate (in arachis oil) was applied to the left or right flank, respectively. Control groups of 10 guinea pigs were treated with Freund's complete adjuvant, arachis oil, or 50% w/v arachis oil in Freund's complete adjuvant. Intradermal and topical induction indicated evidence of skin irritation. Skin reactions were observed at the challenge sites of the test or control animals at the 24-h or 48-h observation period. Trimethylolpropane Trimethacrylate produced a 0% (0/20) sensitization rate and was considered to be a nonsensitizer. Historical data on positive controls (ethyl 4-aminobenzoate 98%; 2,4-dinitrochlorobenzene; neomycin sulphate; and 2-mercaptobenzothiazole) exhibited evidence of sensitization.

Photosensitization/Phototoxicity

Butyl Methacrylate

There are no phototoxicity studies available for Butyl Methacrylate in experimental models.[1] UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity. Based on the lack of significant absorbance in the critical range, it was noted that Butyl Methacrylate does not present a concern for phototoxicity or photoallergenicity.

OCULAR IRRITATION STUDIES

In Vitro

Methoxydiglycol Methacrylate

The ocular irritation potential of Methoxydiglycol Methacrylate was evaluated using the bovine opacity and permeability test method (OECD TG 437).[150] Bovine corneas (isolated from eyes of 3 cattle) were exposed to the undiluted test substance (0.75 ml) for 10 min. The corneas were subsequently maintained in contact with fluorescein for 90 min. An in vitro irritation score (IVIS) of 11.33 was reported. The corrected mean opacity score was 10.67, and the corrected mean optical density (permeability) score was 0.044. Because the IVIS was less than 55, this result indicated that Methoxydiglycol Methacrylate did not cause serious eye damage.

Animal

t-Butyl Methacrylate

An ocular irritation study on t-Butyl Methacrylate was performed using 3 Vienna White rabbits, in accordance with OECD TG 405.[151] The test substance (0.1 ml) was instilled into the eye (unrinsed). Reactions were scored (1 h to day 8 post-instillation) according to the Draize scale. Ocular redness (scores ranging from 1 to 2) was observed in 2 of 3 animals (at 1 h to 72 h post-instillation). Chemosis was observed in 2 animals (1 animal at 1 h; another animal at 24 h). The mean score (24 to 72 h) for redness was 1.33. The mean score for chemosis (24 to 72 h) was 0.11.

Cyclohexylmethacrylate

The ocular irritation potential of Cyclohexylmethacrylate was evaluated in the Draize test using 6 New Zealand White rabbits.[152] The test substance (0.1 ml) was instilled into the left eye of each animal, and eyes were not rinsed. Reactions were scored for up to day 7 post-instillation. Slight to moderate erythema and chemosis, and slight to moderate discharge were observed in all animals at 1 h to 8 h post-instillation.

HEMA

HEMA (undiluted) was tested in an eye irritation test involving 6 New Zealand White rabbits, according to the method of Draize.[154] The test substance (0.5 ml) was instilled into one eye, and reactions were scored for up to 7 d post-instillation. Ocular rinsing was not included in the test protocol. The test substance was irritating to the eyes of rabbits.

HEMA Acetoacetate

The ocular irritation potential of undiluted HEMA Acetoacetate was evaluated in 3 New Zealand White rabbits, in accordance with OECD TG 405.[155] The test substance (0.1 ml) was instilled into one eye of each animal. Reactions were scored at 24 h, 48 h, and 72 h post-instillation. Injection of the conjunctival blood vessels or a crimson-red conjunctival appearance was evident in all animals throughout the first 24 h after instillation, having persisted in 2 animals for an additional 24 h. Slight discharge was observed in all animals at 1 h post-instillation. Chemosis was observed in 1 animal at 24 h post-instillation. The highest total mean irritation score of 4.7 was observed at 24 h. All reactions had cleared by 72 h post-instillation. HEMA Acetoacetate was classified as practically non-irritating to the eye.

Isobutyl Methacrylate

In an ocular irritation test involving 6 New Zealand White rabbits, Isobutyl Methacrylate (0.1 ml) was placed in the conjunctival sac of the right eye of each animal.[156] The lids were then gently held together for 1 second. Eyes were not rinsed after instillation. Untreated eyes served as controls. The eyes were evaluated for the following at 1 h, 24 h, 48 h, and 72 h: signs of corneal damage, iris reaction, and lesions of the conjunctivae (erythema, chemosis, discharge). Additionally, the cornea was examined with the aid of fluorescein after recording the observations at 24 h. No animal had corneal damage or iritis. The highest conjunctival score for erythema was 1.33, in 2 of 6 animals; the highest conjunctival score for chemosis was 1.33, in 1 of 6 animals. Isobutyl Methacrylate was considered slightly irritating to the eyes of rabbits.

Tetrahydrofurfuryl Methacrylate

Tetrahydrofurfuryl Methacrylate (0.1 ml) was instilled into the conjunctival sac of the left eye of 6 New Zealand White rabbits. Ocular rinsing was not performed.[158] During a 7-d observation period, ocular irritation was scored according to the method of Draize. Reactions in the cornea or iris were not observed. A transient conjunctival redness grade of 1 (some blood vessels hyperemic (injected)) to grade 2 (diffuse, crimson color; individual vessels not easily discernible) was observed, up to 72 h post-instillation, in 5 of 6 rabbits. A chemosis grade of 1 (some swelling above normal) was observed in 2 of 6 rabbits. Ocular irritation was not observed in other animals in the study. The ocular reactions observed were completely reversible within 4 d. Tetrahydrofurfuryl Methacrylate was classified as a non-irritant in the eyes of rabbits.

Triethylene Glycol Dimethacrylate

A primary ocular irritation study on Triethylene Glycol Dimethacrylate was performed in accordance with OECD TG 405.[159] The undiluted test substance (0.1 ml) was instilled into the conjunctival sac of 3 New Zealand White rabbits (1 male, 2 females). Eyes were not rinsed after instillation, which was followed by a 3-d observation period. Irritation reactions were

scored according to the method of Draize. Reactions were not observed in the iris or cornea. Only minimal redness (grade = 1) was observed in 1 of 3 rabbits at 1 h post-instillation. All eyes appeared normal at the 24 h, 48 h, and 72 h observations periods. Triethylene Glycol Dimethacrylate was classified as a non-irritant in this study.

Trimethylolpropane Trimethacrylate

The ocular irritation potential of Trimethylolpropane Trimethacrylate was studied using 3 male New Zealand White rabbits, in accordance with OECD TG 405.[160] The undiluted test substance (0.1 ml) was instilled into the right eye of each rabbit. Ocular rinsing was not performed. Untreated eyes served as controls. Ocular reactions were evaluated according to the method of Draize at 1 h, 24 h, 48 h, and 72 h post-instillation. Minimal conjunctival irritation was observed in all treated eyes at 1 h and 24 h post-instillation, and in 1 treated eye at 48 h. Irritation reactions had completely resolved within 72 h. Trimethylolpropane Trimethacrylate was classified as a non-irritant in this study.

CLINCAL STUDIES

Retrospective and Multicenter Studies

Retrospective and multicenter studies are presented in Table 2.

Methacrylate, Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate

A study involving 2353 female patients (with dermatitis) patch tested with methacrylates over a 3-yr period was performed.[161] The patch test protocol was not stated. Forty-three patients (1.82%) were diagnosed with allergic contact dermatitis caused by methacrylates in long-lasting nail polish. Among the positive allergens were: 2% Butylcarbamoethyl Methacrylate in petrolatum (6 patients), 2% Glycol Dimethacrylate in petrolatum (21 patients), 2% HEMA in petrolatum (39 patients), 2% Hydroxypropyl Methacrylate in petrolatum (41 patients), 2% Tetrahydrofurfuryl Methacrylate in petrolatum (31 patients), and 2% Triethylene Glycol Dimethacrylate in petrolatum (13 patients).

Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate

In a retrospective study, 11 European Environmental Contact Dermatitis Research Group (EECDRG) clinics collected information on cases of allergic contact dermatitis caused by nail acrylates, diagnosed by patch testing between 2013 and 2015.[162] Among 18,228 patients studied, 136 had allergic contact dermatitis caused by nail acrylates (0.75%; 95% CI: 0.60–0.90), representing 67.3% (95% CI: 60.4–73.7) of allergic contact dermatitis cases caused by acrylates. There were 135 females and 1 male in the study; 59 (43.4%) were exposed as consumers and 77 (56.6%) were occupationally exposed. Patch test chambers (Finn chambers, secured with adhesive tape) were applied for 48 h to the back. Reactions were scored according to European Society of Contact Dermatitis (ESCD) guidelines. Most patients had patch test reactions to 2 or more acrylates (often with ++ or +++ reactions), mainly to HEMA (92.5%), Hydroxypropyl Methacrylate (88.6%), and Glycol Dimethacrylate (69.2%).

In Malmo, Sweden, 1609 (632 male and 977 female) patients were patch tested with Glycol Dimethacrylate, HEMA, and other acrylate/methacrylate allergens from February of 2005 to June of 2007.[163] Finn chambers (8 mm, secured with adhesive tape) containing the test substance were applied for 2 d to the upper back. Reactions were scored on days 3, 4, and 7 according to ICDRG criteria. There were 26 (1.6%) of 1609 patients with positive patch tests to acrylate/methacrylate allergens. Of the 26, there were 14 positive reactions to HEMA (+ to +++) and 10 positive reactions (+ to +++) to Glycol Dimethacrylate. In Singapore, 1181 (547 male and 634 female) patients were patch tested with Glycol Dimethacrylate and HEMA from July of 2005 to June of 2007.[163] The same test protocol was used. There were 12 (1.0%) of 1181 patients with positive patch tests to acrylate/methacrylate allergens. Of the 12, there were 3 positive reactions to HEMA (+ reaction) and 6 positive reactions to Glycol Dimethacrylate.

A study was performed to evaluate the development and course of positive test reactions to Glycol Dimethacrylate and HEMA in allergic patients to elucidate the issue of patch-test sensitization.[164] Twelve patients with contact allergy to Glycol Dimethacrylate and HEMA were retested with a dilution series (2% to 0.002%, in ethanol). A patch test chamber (secured with adhesive tape) containing the test substance (20 ml on filter paper) was applied for 2 d to the upper back. Reactions were scored on d 3 through d 28. Eleven patients reacted to HEMA (2% to 0.02%), and 10 patients reacted to Glycol Dimethacrylate (2% to 0.02%). The clinical course was followed for 1 mo. During the study, 25 positive test reactions to HEMA and 19 positive reactions to Glycol Dimethacrylate were diagnosed. Within the 1st week, 21 positive reactions were noted for HEMA and 18 were noted for Glycol Dimethacrylate. After 10 d, another 2 reactions appeared for HEMA and 1 appeared for Glycol Dimethacrylate. All but 1 patient with the latter reactions also had positive reactions within the 1st week. After 1 mo, 12 reactions for HEMA and 10 reactions for Glycol Dimethacrylate remained.

Glycol Dimethacrylate, HEMA, Hydroxypropyl Dimethacrylate, and Triethylene Glycol Dimethacrylate

Test files at the Finnish Institute of Occupational Health were reviewed (from September (1994) to August (2006)) for allergic reactions to acrylic monomers in dental personnel, and clinical records of the sensitized patients were analyzed.[165] During this period, a total of 473 patients were tested with the methacrylate series. This included 55 dentists (12%), 192 dental nurses (41%), and 11 dental technicians (2%). Of the 473, 32 patients had allergic reactions (+, ++, or +++) to acrylic

monomers (i.e., to at least 1 acrylic monomer in the methacrylate series): 15 dental nurses, 9 dentists, and 8 dental technicians. Patch tests were performed using the Finn Chambers, according to recommendations of the International Contact Dermatitis Research Group. The tests were read twice or 3 times (on days 2 (or day 3) to days 5 and 6), depending on the day of their application. The most common positive allergens were HEMA and Glycol Dimethacrylate, both in 24 cases (75%) and Hydroxypropyl Dimethacrylate in 23 cases (72%). Tetrahydrofurfuryl Methacrylate was positive in 7 cases (22%). A less common allergen was Triethylene Glycol Dimethacrylate (4 reactions).

An observational, retrospective study involved patients (at a hospital in Valencia Spain) diagnosed with allergic contact dermatitis, due to acrylates used in sculpting artificial nails over a 26-yr period.[166] The following summary is taken from an English abstract of a publication in Spanish. Details relating to the patch test protocol are not included. In total, 15 patients were diagnosed: 14 beauticians and 1 client. Most cases were diagnosed in the past 2 yr. The most frequently affected areas were the fleshy parts of the fingers and hands. Three patients (3 beauticians and 1 client) presented with allergic asthma due to acrylates. All patients underwent patch testing with a standard battery of allergens and a battery of acrylates. The most frequent allergens were Glycol Dimethacrylate (13/15, 86.7 %), HEMA (13/15, 86.7 %), Triethylene Glycol Dimethacrylate (7/15, 46.7 %), and Hydroxypropyl Methacrylate (5/15, 33.3%).

Contact allergy to 1 or more methacrylates was found in 116 (74.4%) of 156 nail technicians or nail product users, all women.[167] One hundred thirty-eight (88.5%) were occupationally exposed, and 18 (11.5%) were consumers. In addition, there was a statistically significant increase in methacrylate allergic contact dermatitis during 2014 – 2018 (100/127 cases [79%]) when compared with 2009 – 2013 (16/29 cases [55%]). The patch test procedure was described as follows: A 5- to 7-mm ribbon of the patch test preparation (equivalent to 20 mg) was placed in 8-mm Finn chambers on adhesive tape and immediately applied for 48 h, under occlusion, to the patient's upper back. The most common sensitizer among the 156 allergic individuals was Glycol Dimethacrylate, which was positive in 113 cases (72.4%); among patients with a positive acrylate patch test, the rate was 97.4%.

A study (from 2004 to 2013) was performed to analyze the frequency of allergic contact dermatitis caused by methacrylates used in artificial nails.[168] Among the 114, 440 patients (72,244 were female) patch tested, 87 patients both worked as nail artists/cosmetologists and suspected nail cosmetics as the cause of dermatitis. Among these, 47.1% reacted to at least one methacrylate, most often to HEMA (1% concentration; n = 27 (of 74 patients)) and Hydroxypropyl Methacrylate (2% concentration; n = 26 (of 75 patients).

Glycol Dimethacrylate, HEMA, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate

A study was performed to evaluate the incidence and the risk of cross-sensitization to formaldehyde and the following methacrylate monomers: Triethylene Glycol Dimethacrylate, Glycol Dimethacrylate, HEMA, and Tetrahydrofurfuryl Methacrylate.[169] A total of 139 participants were included in the study, i.e., occupationally exposed dental professionals, students of the 3rd, 4th and 6th year of dental medicine, and occupationally unexposed dental patients. Patch-tests (using patch test chambers) were performed according to the Jadassohn & Bloch classical methods for diagnosis of contact allergy. Patches were applied to the back, and reactions were scored on day 2 according to ICDRG recommendations. For the allergic-to-formaldehyde students of the 3rd and 4th year of dental medicine, the incidence of cross-sensitization to formaldehyde and the following methacrylate monomers were: Triethylene Glycol Dimethacrylate (20.6%), Glycol Dimethacrylate (20.7%), HEMA (20.7%), and Tetrahydrofurfuryl Methacrylate (20.6%). Contact allergy to Triethylene Glycol Dimethacrylate was diagnosed among 27.1% of the students of the 3rd and 4th year of dental medicine. In the group of occupationally unexposed dental patients, the prevalence of contact allergy to methacrylate monomers was: Glycol Dimethacrylate (20.7%), HEMA (44.9%), and Tetrahydrofurfuryl Methacrylate (38%). The authors noted that students of the 3rd and 4th year of dental medicine could be outlined as a group at risk of sensitization to Triethylene Glycol Dimethacrylate. They also agreed that, due to the ubiquitous occurrence of formaldehyde and the wide use of composite resins and bonding agents containing Triethylene Glycol Dimethacrylate, Glycol Dimethacrylate, HEMA, and Tetrahydrofurfuryl Methacrylate in dentistry, the group of dental patients could be at risk of cross-sensitization to formaldehyde and some methacrylic monomers.

A study was performed to evaluate the frequency and the risk of concomitant sensitization to methacrylate monomers in students of dentistry.[170] A total of 262 participants were included in the study: students of dentistry (110 participants), students from the dental technician school (38 participants), dental professionals (65 participants), and dental patients (control group; 49 participants). Patches (in test chamber) were applied to the back, and reactions were scored on the second day (48 h after patch application, several hours after patch removal, with the control revision on the third day (72 h after patch test application). Reactions were scored according to ICDRG recommendations. Among the group of dental students, the highest frequency of concomitant sensitization was to Triethylene Glycol Dimethacrylate (15.5%). In the group of patients, the highest frequency of concomitant sensitization was to Glycol Dimethacrylate (16.4%). The frequency of concomitant sensitization among dental professionals was much lower, with the highest rate to Triethylene Glycol Dimethacrylate (7.7%).

Glycol Methacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate

The patch testing of methacrylates was performed using 8-mm Finn Chambers. The test substance (15 µl in petrolatum), under occlusion, was applied to the back for 48 h.[142] Contact allergy to one or more methacrylates was found in 16 of 28 patients (57%) evaluated; all allergies were classified as occupational and clinically relevant. Positive reactions to some of the methacrylates tested were: 2% Glycol Methacrylate in petrolatum (10 patients), 2% HEMA in petrolatum (10 patients), 2% Hydroxypropyl Methacrylate in petrolatum (9 patients), 2% Tetrahydrofurfuryl Methacrylate in petrolatum (4 patients), and 2% Triethylene Glycol Dimethacrylate in petrolatum (5 patients).

Nail technicians were evaluated for contact dermatitis reactions to methacrylates.[171] Patch testing was performed using 8-mm Finn chambers attached to adhesive tape. A Finn chamber containing the test substance (20 mg in petrolatum), under occlusion, was applied to the back of each dermatology patient for 48 h. The following positive reactions were observed: Glycol Dimethacrylate (2% in petrolatum: 10 of 63 patients), HEMA (2% in petrolatum: 10 of 63 patients), Hydroxypropyl Methacrylate (2% in petrolatum: 9 of 56 patients), Tetrahydrofurfuryl Methacrylate (2% in petrolatum: 4 of 25 patients), and Triethylene Glycol Dimethacrylate (2% in petrolatum: 5 of 31 patients).

In a 7-yr study involving 2263 patients, 122 (112 females and 10 males) were patch tested with methacrylates. Of the 122, 37 had a positive reaction to a methacrylate.[172] Twenty-five cases (67.6%) were occupational. Hand eczema with pulpitis was observed in 32 patients. Twenty-eight cases were related to artificial nails, 3 were related to dental materials, and 2 were industrial workers. Positive reactions were as follows: Butyl Methacrylate (2% in petrolatum: 5 reactions), Glycol Dimethacrylate (2% in petrolatum: 12 reactions), HEMA (2% in petrolatum: 30 reactions), Hydroxypropyl Methacrylate (2% in petrolatum: 29 reactions), Tetrahydrofurfuryl Methacrylate (2% in petrolatum: 7 reactions), and Triethylene Glycol Dimethacrylate (2% in petrolatum: 76 reactions).

HEMA

A retrospective study involving 577 patients with allergic contact dermatitis was performed.[173] Patients with positive patch test reactions to a liquid skin adhesive containing 2-octyl cyanoacrylate were identified, and test results concerning methacrylates and ethyl cyanoacrylate adhesive were evaluated. Patch tests were applied to the upper back with Finn chambers on occlusive tape for 48 h. Reactions were scored on days 2, 3, and 7. A reaction that was stronger than a + reaction was considered positive. HEMA was tested at a concentration of 2% in petrolatum. A positive patch test reaction to HEMA was observed in 1 of 8 patients tested.

A retrospective chart review of patients attending the contact dermatitis clinic in Ottawa, Ontario, Canada, between January 1998 and February 2008 was conducted.[174] The charts of 44 patients (37 female, 7 male) who had a positive reaction to at least one acrylate compound were reviewed. Patch testing was performed using Finn chambers. Patches were applied to the back and remained in place for 48 h. Final patch test readings were conducted at 96 h. The top allergens in the screening group were ethyl acrylate (28 positive reactions), methyl methacrylate (25 positive reactions), and HEMA (30 positive reactions).

A total of 1293 consecutive female patients were patch tested (protocol not stated) with HEMA from January of 2017 to July of 2019.[175] Of these, 31 (2.4%) had a positive patch test reaction. The maximum patch test reactions for the HEMA-positive patients were + in 19 (61.3%), ++ in 9 (29%), and +++ in 3 (9.7%). Among the 31 HEMA-sensitized individuals, 22 reactions were judged by the dermatologist to be of current clinical relevance, while 5 were of past relevance.

Patch testing of nail care products and common allergens was conducted in accordance with North American Contact Dermatitis Group (NACDG) standards.[176] Of the 38,775 patients tested, 769 (2.0%) had: more than 1 allergic patch test reaction associated with a nail care product (n = 746); irritant contact dermatitis associated with a nail care product (n = 14); or both (n = 9). Primary body sites included the face (43.0%) and hands (27.6%). The top 5 allergens were (HEMA (273/482, 56.6%), methyl methacrylate (210/755, 27.8%), ethyl acrylate (190/755, 25.2%), ethyl-2-cyanoacrylate (12/175, 6.9%) and tosylamide (273/755, 36.2%). The frequency of allergic reactions to HEMA ($p = 0.0069$) and ethyl acrylate ($p = 0.0024$) increased statistically significantly over the study period, whereas allergy secondary to tosylamide was statistically significantly decreased ($p < 0.0001$).

HEMA and Hydroxypropyl Methacrylate

In total, 5920 patients were consecutively patch tested with methacrylate monomers.[177] The amount of test substance applied was enough to fill the well of the disc, but not extrude when the patch was applied to the patient's back. Patches were applied for 48 h under occlusion. Reactions were scored according to ESCD guidelines on days 2 and 4. Overall, 102 of 5920 (1.7%) tested positive to HEMA. Among the top methacrylates that elicited a positive reaction were HEMA (n = 102, 1.7%) and Hydroxypropyl Methacrylate (n = 61, 1%).

Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate

A 4-yr retrospective study of patients with suspected allergic contact dermatitis from artificial nails was performed using 55 female patients with hand eczema.[178] The methodology of the patch test procedure was in accordance with ICDRG guidelines. A chamber containing the test substance was applied for 2 d, and reactions were scored on the second and third

day after application. The most frequent allergens triggering allergic contact dermatitis were HEMA (17 positive reactions) and Hydroxypropyl Methacrylate (17 positive reactions), followed by Glycol Dimethacrylate (13 positive reactions).

Isobornyl Methacrylate

Sixteen patients (13 males, 3 females) with skin and nail reactions to acrylics (from 1978 to 1987) were evaluated. The patch test protocol is not included.[179] Five patients were atopic and 11 were occupational. The 5 cases included 4 of the 5 nail cases and one case with a denture reaction. Thirteen had contact dermatitis, two had nail dystrophy, and one had both contact dermatitis and nail dystrophy. Of the 14 cases with contact dermatitis, 11 were allergic, 1 was irritant, and 2 were not determined. Most were patch-tested according to standard methodology with Finn chambers on adhesive tape. Patch testing was usually performed with the standard screening series of the NACDG and one or more acrylic chemicals. Acrylics were tested in petrolatum. Results of patch testing with Isobornyl Methacrylate (1 %) showed 2 of 2 patients with negative reactions.

Case Reports

Glycol Dimethacrylate and HEMA

An atopic male patient (occupation: flamenco guitarist) who had used acrylic nails to strengthen his nails developed dystrophy, onycholysis and paronychia of the first four nails of the right hand.[180] The lesions were confined to the fingers, where acrylic materials were used in order to strengthen the nails for playing the guitar. When use of the acrylic nails was discontinued, improvement of the lesions was observed. Intense itching and worsening of the lesions were reported after use of the acrylic nails resumed. The patient was diagnosed with occupational allergic contact dermatitis, likely caused by acrylic nails, which contain many kinds of acrylic monomers. Patch test (protocol not stated) results for Glycol Dimethacrylate and HEMA were positive (++ reactions to both chemicals) on days 2 and 4.

Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate

A dentist with occupational asthma and rhinoconjunctivitis was patch tested with methacrylates.[181] Patch tests were performed using the Finn chamber technique, according to ICDRG recommendations. Results were as follows: Glycol Dimethacrylate (2% in petrolatum, 2+ reaction), HEMA (1% in petrolatum, 2+ reaction), and Hydroxypropyl Methacrylate (2% in petrolatum, 2+ reaction).

Facial edema, cheilitis, and stomatitis were observed in a female patient after 3 overnight applications of a tooth-whitening gel containing HEMA.[182] These signs resolved slowly without treatment 3 d after use of the product was stopped. Patch testing (Finn chamber on adhesive tape) was performed. Reactions were scored at days 2 and 4 according to ICDRG guidelines. Positive (+) patch test reactions to Glycol Dimethacrylate and HEMA were reported. A second case report involved a female patient who complained of 4 episodes of discomfort of the buccal mucosa after repeated exposures to a temporary filling (used during complicated root canal treatment) containing HEMA. Positive (++) patch test reactions to HEMA and Hydroxypropyl Methacrylate were reported.

A female patient presented with dermatitis of both hands (mainly on fingers), which began after approximately 6 mo of use of an acrylic-based nail kit.[183] Patch testing (TRUE test) was performed, and reactions were scored on days 2 and 4. Positive patch test reactions (++) to the following methacrylate monomers were reported: Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate. After approximately 2 mo, the patient reported that several of the reactions had developed into depigmented lesions, described as 2 large patches corresponding to HEMA and Glycol Dimethacrylate, and 2 small patches corresponding to Hydroxypropyl Methacrylate. The patient had no family history of vitiligo. Treatment with a strong topical corticosteroid had no effect on the depigmented lesions. Lesion biopsies were not performed.

The following signs were observed in a nonatopic female patient: painful erythematous, edematous, and focally erosive stomatitis of the palate and gums, corresponding to the sites of contact with her denture (made on an acrylic base).[184] The stomatitis started 6 mo after use of the dental prosthesis, and had resolved in 2 wk after removal of the prosthesis and treatment with a steroid. The composition of the acrylic base was identified as hot polymerized resins (Glycol Dimethacrylate, methyl methacrylate, and polymethylmethacrylate). Patch test results indicated positive reactions to Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate. It was stated that the patient's positive reactions to Hydroxypropyl Methacrylate and HEMA (both absent from acrylic base) could be judged as cross reactions.

Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, and Tetrahydrofurfuryl Methacrylate

A nonatopic female patient (no previous skin disease or allergies) presented with bilateral chronic palmar hand eczema (of 2-yr duration).[185] Clinical examination showed dermatitis with scales and underlying vesicles on the thenar region of the left hand, and mild dermatitis on the palmar region of the right hand. She was not exposed to acrylates on her job as a florist, but had applied acrylic nails, such as gel nails, as well as long-lasting nail polish on herself and others in her leisure time. Patch testing revealed the following positive reactions: Glycol Dimethacrylate (++), HEMA (+), Hydroxypropyl Methacrylate (++), Tetrahydrofurfuryl Methacrylate (++), ethyl acrylate (++), butyl acrylate (+), and tetraethylene glycol diacrylate (++). Signs and symptoms of hand eczema disappeared when exposure to acrylates was removed.

Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate

Four patients with allergic contact dermatitis were evaluated.[186] Three of the patients had non-specific dry fingertip dermatitis involving the hyponychium of all fingers and paresthesia. One patient had hand dermatitis without involvement of the fingertips. The mean duration of symptoms was 6.7 mo (range: 1 – 12 mo). None of the patients had ever used acrylic or gel nails. Patch tests (test chambers, secured with adhesive tape) were applied to the skin for 2 d. Testing involved a 2% concentration of each test substance in petrolatum. Reactions were scored on days 2 and 4 according to ESCD guidelines. Results were as follows [3 patients reacted to Hydroxypropyl Methacrylate, HEMA, and Glycol Dimethacrylate.]: Glycol Dimethacrylate (++ reaction in 1 patient; + reaction in 2 patients); HEMA (++ reaction in 2 patients; + reaction in 1 patient); Hydroxypropyl Methacrylate (+++ reaction in 1 patient; ++ reaction in 1 patient; + reaction in 1 patient); Tetrahydrofurfuryl Methacrylate (+ reaction in 2 patients); and Triethylene Glycol Dimethacrylate (negative reactions).

A female patient with no history of atopic dermatitis noticed erythema on her earlobes after having worn clip-on earrings several times over a period of approximately 5 mo.[187] The earlobes were in contact with resin of the earrings. An analysis of the resin resulted in detection of tetrahydrofurfuryl acrylate. Patch testing was performed according to ICDRG recommendations. A Finn chamber containing the test substance was applied to the upper back. Reactions were evaluated on days 2, 3, and 7. Patch testing revealed positive reactions to tetrahydrofurfuryl acrylate (2% in petrolatum; + and ++ reactions) and Tetrahydrofurfuryl Methacrylate (2% in petrolatum; + reactions). Results for other methacrylates are: Glycol Dimethacrylate (2% in petrolatum; negative), HEMA (2% in petrolatum; negative), Hydroxypropyl Methacrylate (2% in petrolatum; negative), and Triethylene Glycol Dimethacrylate (2% in petrolatum; negative).

Other Clinical Reports

Butyl Methacrylate, Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate

Twenty-seven patients (26 women and 1 man), all in contact with artificial nails, were tested for contact allergy to acrylic compounds known to be present in nail cosmetics.[188] Of these, 16 were professional beauticians and 11 were customers. Most of the patients had fingertip and/or nailfold dermatitis. Each test substance (in petrolatum) was applied to the back using a test chamber secured with adhesive tape. The chambers were removed at day 2, and reactions were scored according to ICDRG guidelines on days 2 and 4. Results (positive reactions/number tested) are reported as follows: Butyl Methacrylate (0/12), Glycol Dimethacrylate (20/26), HEMA (25/27), Hydroxypropyl Methacrylate (6/11), Tetrahydrofurfuryl Methacrylate (1/4), and Glycol Dimethacrylate (3/12).

Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate

Nail salon technicians seen in an occupational medicine clinic in 2015 and 2016 were identified, and their patch test results and clinical features were summarized. Six female patients were identified.[189] Common presentations included erythematous dermatitis of the dorsa of the hands, palms, and forearms and fissures on the fingertips. Less common sites of eruptions included the periorbital region, cheeks, posterior ears, neck, sacral area, lateral thighs, and dorsa of the feet. Patch rests (protocol not stated) were performed. All 6 patients had a positive reaction (allergic contact dermatitis) to Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate. Four patients had a positive reaction to Tetrahydrofurfuryl Methacrylate. Three patients had a positive reaction to Triethylene Glycol Dimethacrylate.

Ten patients who had contact allergy to methacrylates or acrylates and had used acrylic glues at work were patch tested.[190] Patch tests (Finn chambers) were performed in accordance with ICDRG recommendations, using a test concentration of 2% (w/w) Triethylene Glycol Dimethacrylate in petrolatum. "The tests were read 2 or 3 times on d 2-(d 3)-d 4/5/6, depending on the day of their application." Of the 10 patients, 7 had a positive reaction to 2% Triethylene Glycol Dimethacrylate in petrolatum.

HEMA

A study was conducted among women dental workers and a comparison group of workers occupationally unexposed to HEMA and other dental restorative materials.[71] The source population of the study was composed of women belonging to the national trade unions of dentists, dental nurses and hygienists, dental technicians and dental laboratory workers, as well as pharmacists, secretaries and receptionists in health care. The final study population included 222 cases of miscarriage and 498 controls (births). Exposure to HEMA was assessed by the frequency of restoration cementation, and replacement of composite resin restorations or glass ionomer restorations (if a product including HEMA was used). Information on pregnancies was obtained from national registers and outpatient units of hospitals. An occupational hygienist assessed exposure to acrylate compounds, disinfectants and solvents. Odds ratios (ORs) and confidence intervals (CIs) were estimated using conditional logistic regression. The ORs adjusted for confounding factors were increased for moderate-exposure and high-exposure categories of mercury amalgam (OR of 2 and 95% CI of 1.0 to 4.1 and OR of 1.3 and 95% CI of 0.6 to 2.5, respectively). The risk was slightly increased for the highest-exposure category of HEMA (OR 1.4 and 95% CI of 0.7 to 2.6). Thus, no strong association or consistent dose-response relationship was observed between exposure to chemical agents in dental work and the risk of miscarriage. A slightly increased risk was found for exposure to mercury amalgam, some

acrylate compounds, solvents and disinfectants. It was noted that these findings indicate that the possibility of a weak association between exposure to these agents and an increased risk of miscarriage cannot be excluded.

Table 1. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO IRRITATION STUDY		
Methoxydiglycol Methacrylate	50 µl	Reconstructed human epidermis	In vitro skin corrosion test (OECD TG 431). Applied to tissues for 3 min and 60 min	Not corrosive	[121]
t-Butyl Methacrylate	0.5 ml	3 Vienna White rabbits	Skin irritation test (OECD TG 404). Semi-occlusive patch containing test substance applied for 4 h to 2.5 x 2.5 cm area on back. Reactions scored, ranging from 1 h to day 15 after patch removal	Erythema (score of 1 to 3) observed in all animals up to day 8 after patch removal. Edema (score of 1) observed in 2 rabbits at 1 h after patch removal and in 1 rabbit at 24 h, 48 h, and 72 h after patch removal (same animal at each observation time). Mean erythema score (24 - 72 h) of 2.44 and amean edema score (24 -72h) of 0.33 reported	[122]
Cyclohexylmethacrylate	0.5 ml	6 New Zealand White rabbits	Test substance applied for 24 h, under occlusive covering, to 2.5 x 2.5 cm area of flank. Reactions scored at 24 h and 72 h after patch application according to method of Draize	Erythema observed in 2 animals at 24 h, and in 1 animal at 72 h. Edema observed in 3 animals at 24 h. Mean erythema score (average value of single scores (animals 1-6; erythema (intact skin), at 24h and 72h) determined to be 0.42 out of 4, and mean edema score was 0 out of 4.	[123]
Glycol Dimethacrylate	0.5 ml	6 New Zealand White rabbits	Test substance (under occlusive patch) applied for 24 h to intact skin. Reactions scored at 24 h and 72 h post application according to Draize scale	Mean erythema score (average value of single scores (animals 1-6; at 24h and 72h) determined to be 0.42 out of 4, and mean edema score was 0 out of 4. Glycol Dimethacrylate classified as non-irritant	[124]
HEMA	0.5 ml	6 New Zealand White rabbits	The test substance (under occlusion) applied for 24 h to 2.5 x 2.5 cm test site (shaved and abraded)	After 24 h, 2 animals had slight erythema. Within 72 h, erythema observed was fully reversible. Edema not observed. Test substance classified as non-irritating	[125]
HEMA Acetoacetate	0.5 ml	3 female New Zealand White rabbits	Skin irritation test (OECD TG 404). Test substance applied for 4 h, under occlusive patch secured with adhesive tape, to back. Application site evaluated at 1 h, 24 h, 48 h, and 72 h post-removal	No adverse reactions or corrosive effects observed in any of the animals. Test substance classified as non-irritating (primary irritation index = 0).	[126]
Hexyl Methacrylate	0.5 ml	6 New Zealand White rabbits	Draize irritation test. Hexyl Methacrylate (under occlusive patch) applied for 24 h to intact and scarified skin (2.5 x 2.5 cm area). Reactions scored at 24 h and 72 h post-application	Mean erythema score (average value of the single scores (animals 1-6; erythema (intact skin), at 24 h and 72 h)) determined to be 1.667 out of 4, and mean edema score was 1.9167 out of 4. Hexyl Methacrylate classified as non-irritating	[127]
Isobornyl Methacrylate	0.5 ml	3 New Zealand White rabbits	Skin irritation test (OECD TG 404). Application to 2.5 x 2.5 cm^2 site on trunk, followed by 7-d observation period. Animals dermally exposed for 4 h (under semi-occlusive patch, secured with adhesive tape) to test substance. Reactions scored according to method of Draize.	Mean erythema score (at 24 h and 72 h) determined to be 2 (maximum score = 4) and mean edema score was 2 (maximum score = 4). Isobornyl Methacrylate classified as mild irritant	[128]
Isobutyl Methacrylate	0.5 ml	6 New Zealand White rabbits	Test substance (under 6 cm^2 occlusive patch secured with adhesive tape) applied for 2 h to abraded and intact skin sites. Reactions evaluated at 24 h and 72 h.	Mean irritation scores over 24 h and 72 h were 1.08 for erythema and 0.5 for edema. All scores were < 2.3. Highest mean erythema score was 2, in 1of 6 animals; highest edema score was 1, in 2 of 6 animals. Isobutyl Methacrylate considered slightly irritating	[129]
Isobutyl Methacrylate	Not stated	Not stated	Test substance applied to skin for 24 h (details not included). 72-h observation period.	Skin irritation potential slightly higher, and not fully reversible within 72-h observation period (conclusion relates to test immediately above).	[129]

Table 1. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Tetrahydrofurfuryl Methacrylate	0.5 ml	6 rabbits	Test substance (0.5 ml, under occlusive patch) applied for 24 h to skin (~ 2.5 cm²). Two application sites (intact and abraded skin) per animal treated. Animals observed for 72 h, and reactions evaluated using scoring system similar to that in OECD TG 404.	Very slight dermal irritation observed (in 1 of 6 animals) on intact and abraded skin after 24 h and 27 h, and in 1 of 6 animals (intact skin) after 24 h. Skin irritation not observed in other animals in study. At study termination, reversibility of irritation reactions complete in half of affected animals. Tetrahydrofurfuryl Methacrylate classified as non-irritant	[131]
Triethylene Glycol Dimethacrylate	5, 25, 50, and 100% (single 50 µl dose per concentration)	4 groups of male Harlan Sprague-Dawley (C3H/HeNHsd strain) mice	Treated with test substance (at 5%, 25%, and 50% (in acetone) and 100%) daily for 14 consecutive days. Single doses applied topically to the clipped interscapular region of the back using a calibrated pipette. Other than the location of application, no effort was made to prevent oral ingestion (e.g., through use of collars). Detailed clinical observations made daily starting on day 2, and skin lesions were scored (slight, moderate, and severe).	Dose-related skin irritation consisting primarily of erythema and desquamation/exfoliation (scaling) observed following 7 d of treatment. Erythema and desquamation/exfoliation occurred more frequently and/or were more severe at 14 d. Desquamation/exfoliation observed at concentrations of 50% and 100%. Vitiligo (loss of pigmentation) observed occasionally at 7 d, but was more prominent following 14 d of treatment. No other clinical signs considered related to treatment. Other than skin lesions at site of dosing, no treatment-related observations made at necropsy.	[43]
Triethylene Glycol Dimethacrylate	0.5 ml	6 New Zealand White rabbits	Animals dermally exposed (2.5 cm² skin area) for 24 h to test substance (under occlusive patch). Two application sites per animal treated; one site left intact and the other was abraded. Animals observed for 72 h. Irritation scored using scoring system similar to that in OECD TG 404	No dermal irritation response observed on intact skin. One of 6 animals had very slight edema (score = 1) after 24 h of contact on abraded skin; Effect fully reversible within 72 h. Triethylene Glycol Dimethacrylate classified as non-irritant	[132]
Trimethylolpropane Trimethacrylate		3 male New-Zealand White rabbits	Skin irritation test (OECD TG 404). Test substance applied for 4 h, under semi-occlusive patch (25 cm x 25 cm), to dorsal flank. Animals observed for 72 h, and skin irritation scored according to the method of Draize	Very slight erythema was observed at application site, and subsided within 24 h. Mean individual scores for erythema/edema at 24 h, 48 h, and 72 h post-removal were all 0. Trimethylolpropane Trimethacrylate classified as a non-irritant	[133]

Table 1. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Glycol Dimethacrylate	(1 to 2000 µM)	KeratinoSensTM cells (immortalized human keratinocytes transfected with a selectable plasmid)	KeratinoSens™ assay. Cells exposed for 48 h, and cell viability determined using MTT assay	Quantitative dose response analysis of luciferase activity exhibited dose-dependent increase over range of concentrations tested. Based on the dose-response relationship observed, Glycol Dimethacrylate classified as a weak sensitizer.	[135]
HEMA	400 µg/ml (3.2 mM), 602 µg/ml (4.6 mM), 723 µg/ml (5.5 mM), 1,250 µg/ml (9.6 mM)	THP-1 cells (human monocytic cell line)	Sensitizing potential of HEMA in cultured cells evaluated. Cells treated for 24 h, and cell viability and expression levels of CD54 and CD86 (markers of antigen presenting cell activation) determined by flow cytometry.	Viability of the cells gradually decreased with increasing concentration. HEMA induced significant expression of CD54 at concentrations greater than 400 µg/mL (3.2 mM). At concentrations greater than 723 µg/mL (5.5 mM), expression level of CD54 decreased; this decrease accompanied by reduction in cell viability. HEMA induced significant expression of CD86 at concentrations greater than 602 µg/mL (4.6 mM). Expression level of CD86 also decreased at concentrations greater than 1,250 µg/mL (9.6 mM). Expression levels of either or both CD54 and CD86 in THP-1 cells known to be increased by exposure to sensitizing substances. HEMA determined to have sensitization potential	[136]
Butyl Methacrylate	25, 50, and 100% (w/w) in acetone:olive oil (4+1)	3 groups of 5 female CBA/CaOlaHsd mice	LLNA (OECD TG 429). Animals treated daily, by topical application, to dorsum of each ear lobe (left and right) for 3 consecutive days. Control group of 5 mice treated with vehicle only. Five d after first topical application, mice injected i.v. (in tail vein) with radio-labelled thymidine (^{3}H-methyl thymidine). Approximately 5 h after injection, mice killed and draining auricular lymph nodes excised and pooled per animal. Single cell suspensions of lymph node cells prepared from pooled lymph nodes, which were subsequently washed and incubated with trichloroacetic acid overnight. Proliferative capacity of pooled lymph node cells determined by incorporation of ^{3}H-methyl thymidine. Validation-/positive control experiment performed with alpha-hexyl cinnamic aldehyde dissolved in acetone/olive oil (4 +1 v/v).	No cases of mortality; no signs of systemic toxicity. On day 3, all treated animals had erythema on ear skin (Score 1). On days 4 and 5, animals treated with 25% and 50% of Butyl Methacrylate had erythema on ear skin (Score 1), and animals treated with 100% also had erythema on ear skin (Score 2). On day 6, animals treated with 50% and 100% had ear erythema score of 1. Stimulation indices (SI) of 2.19, 3.28, and 5.41 determined at concentrations of 25, 50, and 100% in acetone:olive oil (4+1). Clear dose response observed. EC3 value calculated, to be 43.6% (w/v) for Butyl Methacrylate, classifying test substance as sensitizer	[137]
Cyclohexylmethacrylate	3%, 10%, and 30% (in acetone vehicle)	Groups of 6 CBA female mice	LLNA (OECD TG 429). Test substance applied percutaneously to dorsal part of each ear (25 µl per ear). Three consecutive applications made to same site on days 0 to 2. Animals killed on day 5, and auricular lymph nodes dissected.	No signs of systemic toxicity. Test substance (all concentrations) induced statistically significant and biologically relevant response of auricular lymph nodes. Concentration-dependent, statistically significant increase in ear weight at concentrations of 10% and 30% associated with some irritation of ear skin. Cyclohexyl-methacrylate had skin sensitizing effect. Threshold concentration for sensitization induction was < 3%.	[138]

Table 1. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Di-HEMA Trimethylhexyl Dicarbamate	25 µl of 10, 25 and 50% (w/w) in DMF [50% concentration was highest non-irritant concentration that did not cause irritation or systemic toxicity up to day 8 after 3 d of exposure in 2 animals.]	Groups of 4 female CBA mice. Vehicle and positive control (hexyl cinnamic aldehyde) groups included	LLNA. The test substance spread over dorsal surface of ear lobes once daily for 3 consecutive d. Five d after first application, all mice intravenously injected with 250 µl of [^{3}H]-thymidine	SIs of 1.58, 1.70 and 4.44 determined at concentrations of 10, 25, and 50% (w/w) in DMF, respectively. Clear dose response observed. Based on SI values, an EC3 value of 36.9% calculated. Statistically significant increase in disintegrations per minute (DPM) values observed in all dose groups, when compared to vehicle control group. Based on calculated EC3 value, Di-HEMA Trimethylhexyl Dicarbamate considered to be weak sensitizer	134
Glycol Dimethacrylate (in acetone/olive oil (4:1 v/v)),	25 µl of several concentrations (not stated)	Groups of 4 to 5 female mice of the CBA strain	LLNA (OECD TG 429). Topical application (on the dorsum of both ears) of test substance or with equal volume of vehicle alone. Animals treated daily for 3 consecutive days, followed by 2-d non-treatment period	An EC3 value of 35 reported, classifying Glycol Dimethacrylate as extremely weak sensitizer	139
HEMA	0.5 ml	Male guinea pigs (Pirbright; sub-strain: Hoe: DHPK (SPF- LAC.) /Boe; 20 test and 10 controls)	Modified Buehler method. Induction phase involved three 6-h exposures (1 per week; patch type not stated) to test substance (0.5 ml, on left flank). Challenge phase involved three 6-h exposures (patch type not stated) to the test substance (0.5 ml, on right flank). Reactions scored at 24 h and 48 h post-challenge.	No animals showed signs of erythema or edema. No evidence of delayed contact hypersensitivity	140
HEMA and Triethylene Glycol Dimethacrylate (separate tests)	50 µl, 100 µl, and 200 µl	Groups of 5 guinea pigs	Magnusson and Kligman maximization test. For primary sensitization, test substance (50 µl), emulsion of Freund's complete adjuvant with test substance (50 µl), and emulsion of Freund's complete adjuvant with distilled water (50 µl) percutaneously injected on left and right sides of each animal At 7 d after primary sensitization, back of each animal (including 6 injection sites) shaven. Next, sodium lauryl sulfate solution applied to shaved area to increase skin permeability. For the secondary sensitization, filter paper patch soaked with sodium lauryl sulfate and test substance (200 µl) applied for 48 h to shaved area, using cohesive stretch bandage. At 2 wk after secondary sensitization, back of each animal shaved. During challenge, test substance (100 µl) applied for 24 h to shaved skin to induce delayed-type hypersensitivity. Site covered with cohesive stretch bandage during application period. Skin reactions at 24 h and 48 h evaluated according to International Contact Dermatitis Research Group criteria	Inflammatory reaction (mean score of 1.4; scales: 0 (no erythema) to 4 (severe erythema); 0 (no edema) to 3 (severe edema)) to HEMA observed in 4 of 5 guinea pigs. Triethylene Glycol Dimethacrylate caused inflammatory reaction in 3 of 5 guinea pigs (mean score = 0.6)	141
Hexyl Methacrylate	25 µl of 5%, 50%, and 100 % (v/v; in acetone:olive oil 4:1 (v:v) mixture)	Groups of 5 female CBA/J mice	Three groups treated with test substance. Negative control group treated with vehicle, and positive control group treated with 25% α-Hexylcinnamaldehyde (v/v; in acetone:olive oil 4:1 (v:v) mixture). Test substance applied on dorsal surface of ears (25 µl/ear) for 3 consecutive days (0, 1, and 2). No treatment on days 3 and 4. At day 5, cell proliferation in local lymph nodes measured by incorporation of tritiated methyl thymidine. SI calculated	No mortality or signs of systemic toxicity observed. Irritation not observed at application site. SI values were 1.44, 1.68, and 2.19 at concentrations of 25 %, 50%, and 100% (v/v), respectively. No sensitization potential at concentrations tested	142

Table 1. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Isobornyl Methacrylate	50 % in paraffin oil (0.1 ml and 0.5 ml)	Dunkin-Hartley guinea pigs (10 males, and 10 females; control: 10 guinea pigs)	Guinea pig maximization test (OECD TG 406). Test animals treated via intradermal injection with 0.1 ml of Isobornyl Methacrylate (50 % in paraffin oil) in presence of Freund's complete adjuvant. At day 8, 0.5 ml of undiluted test substance applied cutaneously to injection sites for 48 h (under occlusive dressing). After 12 d without treatment, 24 h-challenge occlusive cutaneous application of 0.5 ml of vehicle (left flank) and 0.5 ml of undiluted Isobornyl Methacrylate performed. Cutaneous reactions scored at 24 h and 48 h after removal of dressing. Sensitivity of test animals confirmed by use of 2,4-Dinitrobenzene (0.1 % and 0.5 %) [sensitization response was 100%].	No cutaneous reactions recorded in test animals. Isobornyl Methacrylate classified as non-sensitizer	[143]
Isobutyl Methacrylate (in acetone:olive oil (4+1, v/v))	25%, 50% and 100% w/v	Groups of 5 female CBA/CaOlaHsd mice	LLNA (OECD TG 429). Stiumulaton indices determined	No clinical signs and no systemic findings observed after first and second application (25% and 50%). Highest dose (100%) induced slight erythema on ear skin of all 4 animals. SI of 1.78, 3.64, and 5.13 determined at concentrations of 25%, 50% and 100% (w/v), respectively. EC3 was 41.4 %, and Isobutyl Methacrylate classified as dermal sensitizer. Positive control, α-hexylcinnamaldehyde, yielded EC3 of 5.9 % (w/v)	[144]
methacrylic acid ester (read-across for Lauryl Methacrylate)	5%, 10%, and 25%	Groups of 4 female CBA/CaOlaHsd mice	LLNA (OECD TG 429). Mice treated daily with test substance; topical application to dorsum of each ear lobe (right and left) for 3 consecutive days. Control group treated with vehicle only.	None of the animals died, and no evidence of systemic toxicity. Local effects (ear reddening) only observed at highest concentration (25%) at 24 h after second and 1 h after third application, but not on day 6. SI of 0.99, 2.11, and 2.66 determined at concentrations of 5%, 10%, and 25%, respectively. No dose-response relationship observed. EC3 value could not be determined, because no concentration induced a SI value > 3. Test substance classified as non-sensitizer	[145]
Methoxydiglycol Methacrylate	Undiluted	Groups of 20 Hartley Albino guinea pigs (10 males, 10 females per group). 5 guinea pigs in control group.	Maximization test (OECD TG 406). Induction consisted of intradermal injections, followed in 7 d by topical application of test substance. Challenge phase consisted of topical application performed 14 d following completion of induction. During challenge, undiluted test substance applied for 24 h (under occlusive patch) to skin, at 2 wk after induction.	Methoxydiglycol Methacrylate classified as non-sensitizer	[146]
PEG-4 Dimethacrylate	50% and 100% w/w (in acetone/olive oil)	Groups of 5 female CBA/J mice	LLNA. Mice treated with test substance for 3 consecutive days, by open application on the ears. Control group treated with vehicle using same procedure. Three d after last exposure, all animals injected with ^{3}H-methyl thymidine. After 5h, draining (auricular) lymph nodes excised and pooled for each animal. After precipitating the DNA of lymph node cells, radioactivity measurements performed. Activity expressed as number of DPM, and SI calculated for each group	At concentrations of 50% and 100%, no signs of systemic toxicity; very slight irritation of ears observed. All auricular lymph nodes of normal size; no macroscopic abnormalities in surrounding area. SI values calculated for the 3 concentrations of 25%, 50% and 100% were 1.0, 1.2 and 1.9, respectively. PEG-4 Dimethacrylate did not elicit SI of 3 when tested up to 100%, aand was considered a non-sensitizer	[147]

Table 1. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Triethylene Glycol Dimethacrylate	(25%, 50%, and 100% (w/v) in acetone:olive oil (4+1, v/v))	Groups of 5 female CBA/CaOlaHsd mice	LLNA (OECD TG 429). Protocol same as in study immediately above. EC3 value calculated.	No systemic findings or deaths. Only the highest concentration (100%) induced slight erythema on the ear skin on days 3 to 6 (score= 1). SIs of 1.40, 1.51 and 3.30 were determined at concentrations of 25%, 50% and 100%, respectively. EC3 for Triethylene Glycol Dimethacrylate was 91.6 %, classifying test substance as a skin sensitizer. Positive control substance, α-hexylcinnamaldehyde, yielded EC3 of 9.3% (w/v).	[148]
Trimethylolpropane Trimethacrylate	25%, 75%, and 100% (in arachis oil or Freund's complete adjuvant)	Groups of 20 albino Dunkin Hartley guinea pigs (10 males, 10 females per group)	Magnusson and Kligman maximzation test. Animals intradermally induced with 3 injections (in shoulder region on each side of mid-line) of the following on d 0 : 0.1 ml of Freund's complete adjuvant, 25% w/v Trimethylolpropane Trimethacrylate in arachis oil, and 25% w/v Trimethylolpropane Trimethacrylate emulsion in Freund's complete adjuvant. After 1 wk, same areas topically induced (for 48 h) with 0.2 ml of undiluted Trimethylolpropane Trimethacrylate via occlusive patch. After 2-wk non-treatment period, challenge patch with 75 % v/v or 100% v/v Trimethylolpropane Trimethacrylate (in arachis oil) applied to left or right flank, respectively. Control groups of 10 guinea pigs treated with Freund's complete adjuvant, arachis oil, or 50% w/v arachis oil in Freund's complete adjuvant	Intradermal and topical induction indicated evidence of skin irritation. Skin reactions observed at challenge sites of test or control animals at the 24-h or 48-h observation period. Trimethylolpropane Trimethacrylate produced 0% (0/20) sensitization rate and was considered a nonsensitizer. Historical data on positive controls (ethyl 4-aminobenzoate 98%; 2,4-dinitrochlorobenzene; neomycin sulphate; and 2-mercaptobenzothiazole) produced evidence of sensitization.	[149]

Table 2. Retrospective and multicenter studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Butylcarbamoethyl Methacrylate, Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate	2%	2353 female patients (with dermatitis)	Patch tested with methacrylates over a 3-yr period (protocol not stated)	Test resuts indicated that all methacrylates were positive allergens. 2% Butylcarbamoethyl Methacrylate in petrolatum (6 patients), 2% Glycol Dimethacrylate in petrolatum (21 patients), 2% HEMA in petrolatum (39 patients), 2% Hydroxypropyl Methacrylate in petrolatum (41 patients), 2% Tetrahydrofurfuryl Methacrylate in petrolatum (31 patients), and 2% Triethylene Glycol Dimethacrylate in petrolatum (13 patients).	[161]
Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate	Not stated	136 allergic contact dermatitis patients (135 females, 1 male)	Patch test chambers (Finn chambers, secured with adhesive tape) applied for 48 h to the back. Reactions scored according to European Society of Contact Dermatitis (ESCD) guidelines	Most patients had patch test reactions to 2 or more acrylates (often with ++ or +++ reactions), mainly to HEMA (92.5%), Hydroxypropyl Methacrylate (88.6%), and Glycol Dimethacrylate (69.2%).	[162]

Table 2. Retrospective and multicenter studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Glycol Dimethacrylate and HEMA	Not stated	1609 (632 male and 977 female) patients in In Malmo, Sweden	Patch testing from February of 2005 to June of 2007. Finn chambers (8 mm, secured with adhesive tape) containing the test substance applied for 2 d to upper back. Reactions scored on days 3, 4, and 7 according to ICDRG criteria	26 (1.6%) of 1609 patients with positive patch tests to acrylate/methacrylate allergens. Of the 26, were 14 positive reactions to HEMA (+ to +++) and 10 positive reactions (+ to +++) to Glycol Dimethacrylate.	[163]
Glycol Dimethacrylate and HEMA	Not stated	1181 (547 male and 634 female) patients in Singapore	Patch testing (protocol immediately above) from July of 2005 to June of 2007	12 (1.0%) of 1181 patients with positive patch tests to acrylate/methacrylate allergens. Of the 12, were 3 positive reactions to HEMA (+ reaction) and 6 positive reactions to Glycol Dimethacrylate	[163]
Glycol Dimethacrylate and HEMA	dilution series (2% to 0.002%, in ethanol)	12 patients with contact allergy to Glycol Dimethacrylate and HEMA	Patch test chamber (secured with adhesive tape) containing the test substance (20 ml on filter paper) was applied for 2 d to the upper back. Reactions were scored on d 3 through d 28	Eleven patients reacted to HEMA (2% to 0.02%), and 10 patients reacted to Glycol Dimethacrylate (2% to 0.02%). Clinical course followed for 1 mo. 25 positive test reactions to HEMA and 19 positive reactions to Glycol Dimethacrylate diagnosed. Within 1st week, 21 positive reactions noted for HEMA and 18 noted for Glycol Dimethacrylate. After 10 d, another 2 reactions to HEMA and 1 to Glycol Dimethacrylate. All but 1 patient with the latter reactions also had positive reactions within the 1st week. After 1 mo, 12 reactions for HEMA and 10 reactions for Glycol Dimethacrylate remained	[164]
Glycol Dimethacrylate, HEMA, Hydroxypropyl Dimethacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate	Not stated	473 patients tested with methacrylate series. Among these were: 55 dentists (12%), 192 dental nurses (41%), and 11 dental technicians (2%).	Test files at Finnish Institute of Occupational Health reviewed (from September (1994) to August (2006)) for allergic reactions to acrylic monomers in dental personnel, and clinical records of sensitized patients analyzed. Patch tests performed using Finn Chambers, according to recommendations of International Contact Dermatitis Research Group. Tests read twice or 3 times (on day 2 (or day 3) to days 5 and 6)), depending on day of application	Of the 473, 32 patients had allergic reactions (+, ++, or +++) to acrylic monomers (i.e., to at least 1 acrylic monomer in the methacrylate series): 15 dental nurses, 9 dentists, and 8 dental technicians. Most common positive allergens were HEMA and Glycol Dimethacrylate, both in 24 cases (75%) and Hydroxypropyl Dimethacrylate in 23 cases (72%). Tetrahydrofurfuryl Methacrylate positive in 7 cases (22%); less common allergen was Triethylene Glycol Dimethacrylate (4 reactions)	[165]
Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, and Triethylene Glycol Dimethacrylate	Not stated	15 patients (14 beauticians and 1 client) (at a hospital in Valencia Spain) diagnosed with allergic contact dermatitis, due to acrylates used in sculpting artificial nails over a 26-yr period. Three patients (3 beauticians and 1 client) presented with allergic asthma due to acrylates.	Observational, retrospective study. Patch test protocol not stated	most frequent allergens were Glycol Dimethacrylate (13/15, 86.7 %), HEMA (13/15, 86.7 %), Triethylene Glycol Dimethacrylate (7/15, 46.7 %), and Hydroxypropyl Methacrylate (5/15, 33.3%).	[166]

Table 2. Retrospective and multicenter studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Glycol Dimethacrylate	Not stated	156 female nail technicians or nail product users. Contact allergy to 1 or more methacrylates found in 116 (74.4%). 138 (88.5%) occupationally exposed, and 18 (11.5%) w consumers	A 5- to 7-mm ribbon of the patch test preparation (equivalent to 20 mg) was placed in 8-mm Finn chambers on adhesive tape and immediately applied for 48 h, under occlusion, to the patient's upper back	Most common sensitizer among 156 allergic individuals was Glycol Dimethacrylate, which was positive in 113 cases (72.4%); among patients with positive acrylate patch test, the rate was 97.4%	[167]
HEMA and Hydroxypropyl Methacrylate	1% HEMA and 2% Hydroxypropyl Methacrylate	114, 440 patients (72,244 female) total. Of these, 87 patients both worked as nail artists/cosmetologists and suspected nail cosmetics as cause of dermatitis	Study (from 2004 to 2013) performed to analyze frequency of allergic contact dermatitis caused by methacrylates used in artificial nails. Patch test procedure not stated	Among the 87, 47.1% reacted to at least one methacrylate, most often to HEMA (1% concentration; n = 27 (of 74 patients)) and Hydroxypropyl Methacrylate (2% concentration; n = 26 (of 75 patients).	[168]
Glycol Dimethacrylate, HEMA, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate	Not stated	139 participants (occupationally exposed dental professionals, students of the 3rd, 4th and 6th yr of dental medicine, and occupationally unexposed dental patients)	Study performed to evaluate incidence and risk of cross-sensitization to formaldehyde and methacrylate monomers. Patch-tests (using patch test chambers) were performed according to the Jadassohn & Bloch classical methods for diagnosis of contact allergy. Patches were applied to the back, and reactions were scored on day 2 according to ICDRG recommendations	Sensitization to formaldehyde and the following methacrylate monomers were: Triethylene Glycol Dimethacrylate (20.6%), Glycol Dimethacrylate (20.7%), HEMA (20.7%), and Tetrahydrofurfuryl Methacrylate (20.6%). Contact allergy to Triethylene Glycol Dimethacrylate diagnosed among 27.1% of the students of the 3rd and 4th yr of dental medicine. In the group of occupationally unexposed dental patients, prevalence of contact allergy to methacrylate monomers was: Glycol Dimethacrylate (20.7%), HEMA (44.9%), and Tetrahydrofurfuryl Methacrylate (38%). Authors noted that students of the 3rd and 4th yr of dental medicine could be outlined as a group at risk of sensitization to Triethylene Glycol Dimethacrylate. Also agreed that, due to ubiquitous occurrence of formaldehyde and wide use of composite resins and bonding agents containing Triethylene Glycol Dimethacrylate, Glycol Dimethacrylate, HEMA, and Tetrahydrofurfuryl Methacrylate in dentistry, group of dental patients could be at risk of cross-sensitization to formaldehyde and some methacrylic monomers	[169]

Table 2. Retrospective and multicenter studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Glycol Dimethacrylate and Triethylene Glycol Dimethacrylate	Not stated	262 participants: students of dentistry (110 participants), students from the dental technician school (38 participants), dental professionals (65 participants), and dental patients (control group; 49 participants).	Patches (in test chamber) were applied to the back, and reactions were scored on the second day (48 h after patch application, several hours after patch removal, with the control revision on the third day (72 h after patch test application). Reactions were scored according to ICDRG recommendations	Among the dental students, highest frequency of concomitant sensitization was to Triethylene Glycol Dimethacrylate (15.5%). In patients, highest frequency of concomitant sensitization was to Glycol Dimethacrylate (16.4%). Frequency of concomitant sensitization among dental professionals was much lower, with highest rate associated with Triethylene Glycol Dimethacrylate (7.7%)	[170]
Glycol Methacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate	2%	28 patients	The patch testing of methacrylates was performed using 8-mm Finn Chambers. The test substance (15 µL in petrolatum), under occlusion, was applied to the back for 48 h	Contact allergy to one or more methacrylates was found in 16 of 28 patients (57%) evaluated; all allergies were classified as occupational and clinically relevant. Positive reactions to some of the methacrylates tested were: 2% Glycol Methacrylate in petrolatum (10 patients), 2% HEMA in petrolatum (10 patients), 2% Hydroxypropyl Methacrylate in petrolatum (9 patients), 2% Tetrahydrofurfuryl Methacrylate in petrolatum (4 patients), and 2% Triethylene Glycol Dimethacrylate in petrolatum (5 patients)	[142]
Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate	2% in petrolatum (20 mg)	Different patient groups (groups of 25 to 63)	Patch testing performed using 8-mm Finn chambers attached to adhesive tape. Finn chamber containing test substance (20 mg in petrolatum, under occlusion) applied to back for 48 h	The following positive reactions observed: Glycol Dimethacrylate (2% in petrolatum): 10 of 63 patients), HEMA (2% in petrolatum: 10 of 63 patients), Hydroxypropyl Methacrylate (2% in petrolatum: 9 of 56 patients), Tetrahydrofurfuryl Methacrylate (2% in petrolatum: 4 of 25 patients), and Triethylene Glycol Dimethacrylate (2% in petrolatum: 5 of 31 patients)	[171]
Butyl Methacrylate, Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Tetrahydrofurfuryl Methacrylate, and Triethylene Glycol Dimethacrylate	2% in petrolatum	2,263 patients total; 122 (112 females and 10 males) tested with methacrylates	Patch testing (procedure not stated)	Of the 122 patients, 37 had a positive reaction to a methacrylate; 25 cases (67.6%) were occupational. Hand eczema with pulpitis observed in 32 patient; 28 cases related to artificial nails, 3 related to dental materials, and 2 were industrial workers. Positive reactions: Butyl Methacrylate (5 reactions), Glycol Dimethacrylate (12 reactions), HEMA (30 reactions), Hydroxypropyl Methacrylate (29 reactions), Tetrahydrofurfuryl Methacrylate (7 reactions), and Triethylene Glycol Dimethacrylate (76 reactions)	[172]
HEMA	2% in petrolatum	577 patients with allergic contact dermatitis; 8 tested with HEMA	Retrospective study. Patch tests applied to upper back with Finn chambers on occlusive tape for 48 h. Reactions scored on days 2, 3, and 7. Reaction stronger than a + reaction considered positive	Positive patch test reaction to HEMA observed in 1 of 8 patients tested	[173]

Table 2. Retrospective and multicenter studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Methyl Methacrylate and HEMA	Not stated	44 patients (37 female, 7 male) who had a positive reaction to at least one acrylate compound	Patch testing performed using Finn chambers. Patches applied to back for 48 h. Final patch test readings at 96 h.	Top allergens in screening group were ethyl acrylate (28 positive reactions), methyl methacrylate (25 positive reactions), and HEMA (30 positive reactions)	[174]
HEMA	Not stated	1293 consecutive female patients	Patch tested (protocol not stated) with HEMA from January of 2017 to July of 2019	Of the patients tested, 31 (2.4%) had positive patch test reaction. Maximum patch test reactions for the HEMA-positive patients were + in 19 (61.3%), ++ in 9 (29%), and +++ in 3 (9.7%). Among the 31 HEMA-sensitized individuals, 22 reactions judged by the dermatologist to be of current clinical relevance, while 5 were of past relevance	[175]
HEMA and Methyl Methacrylate	Not stated	38,775 patients	Patch testing of nail care products and common allergens conducted in accordance with NACDG standards	Of the patients tested, 769 (2.0%) had: more than 1 allergic patch test reaction associated with a nail care product (n = 746); irritant contact dermatitis associated with a nail care product (n = 14); or both (n = 9). Primary body sites included face (43.0%) and hands (27.6%). Top 5 allergens were (HEMA (273/482, 56.6%), methyl methacrylate (210/755, 27.8%), ethyl acrylate (190/755, 25.2%), ethyl-2-cyanoacrylate (12/175, 6.9%) and tosylamide (273/755, 36.2%). Frequency of allergic reactions to HEMA ($p = 0.0069$) and ethyl acrylate ($p = 0.0024$) increased statistically significantly over study period, whereas allergy secondary to tosylamide statistically significantly decreased ($p < 0.0001$)	[176]
HEMA and Hydroxypropyl Methacrylate	Amount of test substance applied was enough to fill the well of the disc, but not extrude when the patch was applied to patient's back	5920 patients consecutively patch tested with methacrylate monomers	Patches applied for 48 h under occlusion. Reactions scored according to European Society of Contact Dermatitis (ESCD) guidelines on days 2 and 4	Overall, 102 of 5920 (1.7%) tested positive to HEMA. Among top methacrylates that elicited a positive reaction were HEMA (n = 102, 1.7%) and Hydroxypropyl Methacrylate (n = 61, 1%)	[177]
Glycol Dimethacrylate, HEMA, and Hydroxypropyl Methacrylate	Not stated	55 female patients with hand eczema	4-yr retrospective study of patients with suspected allergic contact dermatitis from artificial nails. Methodology of patch test procedure in accordance with ICDRG guidelines. Chamber containing test substance was applied for 2 d; reactions scored on second and third day after application	Most frequent allergens triggering allergic contact dermatitis were HEMA (17 positive reactions) and Hydroxypropyl Methacrylate (17 positive reactions), followed by Glycol Dimethacrylate (13 positive reactions).	[178]
Isobornyl Methacrylate	1%	Sixteen patients (13 males, 3 females) with skin and nail reactions to acrylics (from 1978 to 1987). 2 patients tested with Isobornyl Methacrylate	Most were patch-tested according to standard methodology with Finn chambers on adhesive tape. Patch testing usually performed with standard screening series of the NACDG and one or more acrylic chemicals.	2 of 2 patients with negative reactions	[179]

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

Methacrylate ester monomers are used in as artificial nail builders in nail enhancement products. They undergo rapid polymerization to form a hard material on the nail that is then shaped. While Ethyl Methacrylate is the primary monomer used in nail enhancement products, other methacrylate esters are also used. This safety assessment addresses 22 other methacrylate esters reported by industry to be present in small percentages as artificial nail builders in cosmetic products. They function to speed up polymerization and/or form cross-links. Only Tetrahydrofurfuryl Methacrylate was reported to the FDA to be in current use. The polymerization rates of these methacrylate esters are within the same range as Ethyl Methacrylate. While data are not available on all of these methacrylate esters, the available data demonstrated little acute oral, dermal, or i.p. toxicity. In a 28-day inhalation study on rats, Butyl Methacrylate caused upper airway irritation; the NOAEL was 1801 mg/m^3. In a 28-day oral toxicity study on rats, t-Butyl Methacrylate had a NOAEL of 20 mg/kg/day. Beagle dogs dosed with 0.2 to 2.0 g/kg/day of C12 to C18 methacrylate monomers for 13 weeks exhibited effects only in the highest dose group: weight loss, emesis, diarrhea, mucoid feces, or salivation were observed. Butyl Methacrylate (0.1 M) and Isobutyl Methacrylate (0.1 M) are mildly irritating to the rabbit eye. HEMA is corrosive when instilled in the rabbit eye, while PEG-4 Dimethacrylate and Trimethylolpropane Trimethacrylate are minimally irritating to the eye. Dermal irritation caused by methacrylates is documented in guinea pigs and rabbits. In guinea pigs, HEMA , Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, and Trimethylolpropane Trimethacrylate are strong sensitizers; Butyl Methacrylate, Cyclohexyl Methacrylate, Hexyl Methacrylate, and Urethane Methacrylate are moderate sensitizers; Hydroxypropyl Methacrylate is a weak sensitizer; and PEG-4 Dimethacrylate and Triethylene Glycol Dimethacrylate are not sensitizers. Ethylene Glycol Dimethacrylate was not a sensitizer in one guinea pig study, but was a strong sensitizer in another. There is cross-reactivity between various methacrylate esters in some sensitization tests. Inhaled Butyl Methacrylate, HEMA, Hydroxypropyl Methacrylate, and Trimethylolpropane Trimethacrylate can be developmental toxicants at high exposure levels (1000 mg/kg/day). None of the methacrylate ester monomers that were tested were shown to have any endocrine disrupting activity. These methacrylate esters are mostly non-mutagenic in bacterial test systems, but weak mutagenic responses were seen in mammalian cell test systems. Chronic dermal exposure of mice to PEG-4 Dimethacrylate (25 mg, 2× weekly for 80 weeks) or Trimethylolpropane Trimethacrylate (25 mg, 2× weekly for 80 weeks) did not result in increased incidence of skin or visceral tumors. The carcinogenicity of Triethylene Glycol Dimethacrylate (5, 25, or 50%) was assessed in a mouse skin painting study (50 μl for 5 days/week for 78 weeks), but was not carcinogenic at any dose level tested. The Expert Panel was concerned about the strong sensitization and cross- or co-reactivity potential of the methacrylate esters reviewed in this report. However, data demonstrated the rates of polymerization of these Methacrylates were similar to that of Ethyl Methacrylate and there would be little monomer available exposure to the skin. In consideration of the animal toxicity data, the CIR Expert Panel decided that these methacrylate esters should be restricted to the nail and must not be in contact with the skin. Accordingly, these methacrylate esters are safe as used in nail enhancement products when skin contact is avoided.

INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

CHEMISTRY

Definition and Structure

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

PHYSICAL AND CHEMICAL PROPERTIES

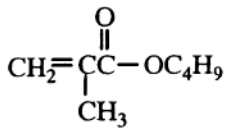
The physical and chemical properties of Butyl, Isobutyl, and Lauryl Methacrylate are shown in Table 2. Although both Butyl Methacrylate and Lauryl Methacrylate were reported as insoluble in water (see Table 1), Assessment Technologies, Inc., (1996) cited their solubility in water as 134–141 mg/L and <0.10–19.0 mg/L, respectively.

Curing of Commercial Products

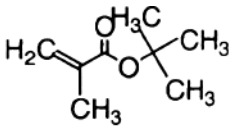
In the CIR Final Report on the Safety Assessment of Ethyl Methacrylate, there were data submitted by Schoon (1994a; 1994b), on the extent of curing and the amount of unreacted monomer in two fingernail formulations containing ethyl methacrylate. The study established there was sufficient polymerization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

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

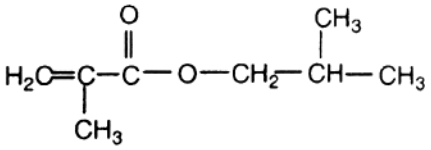
In the experiment, the Radical^{TM} artificial nail monomer/polymer system was modified by adding 5% ethyl methacrylate



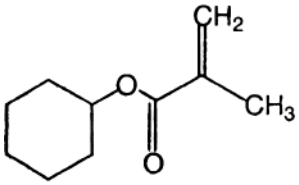
Butyl Methacrylate
Wenninger et al. 2002



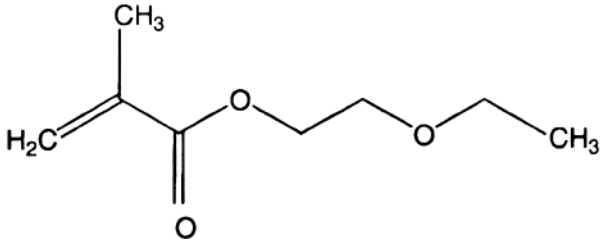
t-Butyl Methacrylate
ChemIDplus 2001



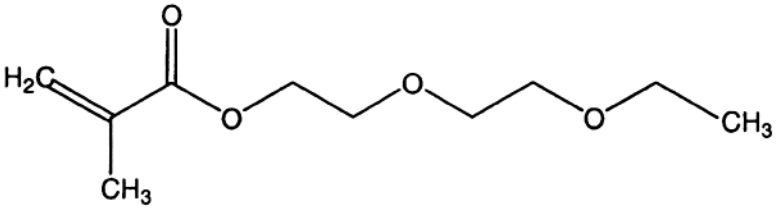
Isobutyl Methacrylate
Zeiger et al. 1987



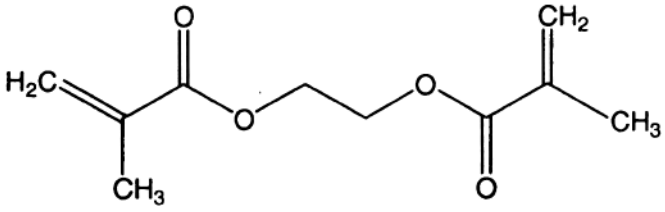
Cyclohexyl Methacrylate
ChemIDplus 2001



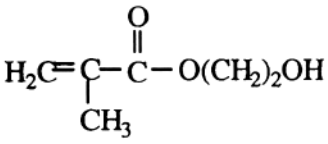
Ethoxyethyl Methacrylate
Jackson 2001



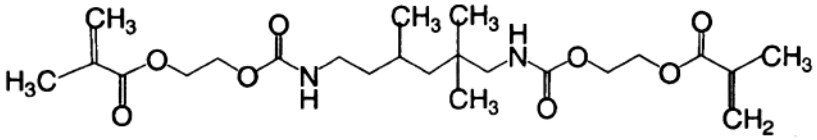
2-Ethoxy Ethoxy Ethyl Methacrylate
Jackson 2001



Ethylene Glycol Dimethacrylate
ChemIDplus 2001

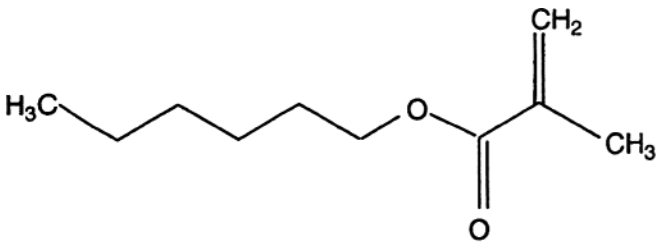


HEMA
Wenninger et al. 2002

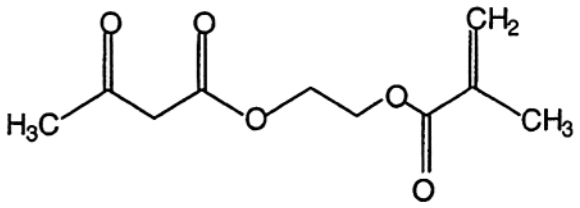


DI-HEMA Trimethylhexyl Dicarbamate- the 2,2,4 Isomer
Jackson 2001

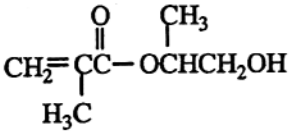
FIGURE 1
Structure of Methacrylate Esters



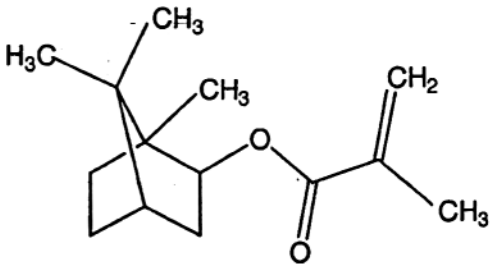
Hexyl Methacrylate
ChemIDplus 2001



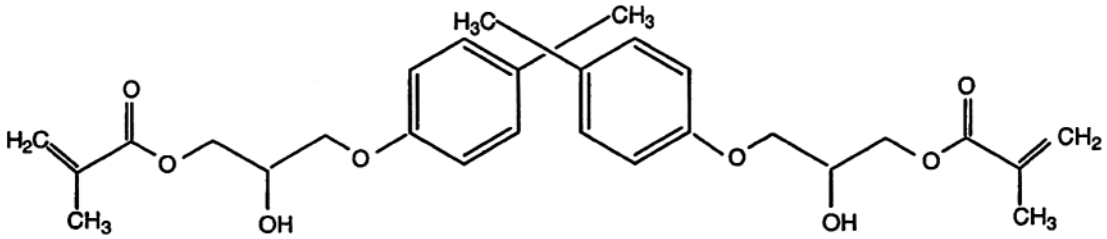
Hydroxyethylmethacrylate Acetoacetate
ChemIDplus 2001



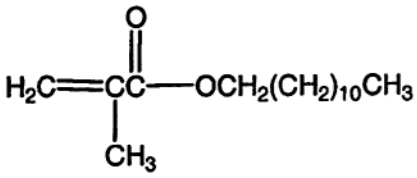
Hydroxypropyl Methacrylate
Wenninger et al. 2002



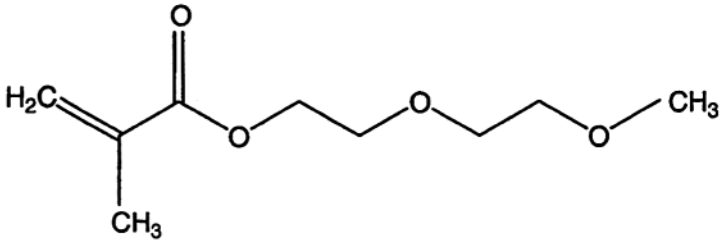
Isobornyl Methacrylate
ChemIDplus 2001



Isopropylidenediphenyl Bisglycidyl Methacrylate
ChemIDplus 2001

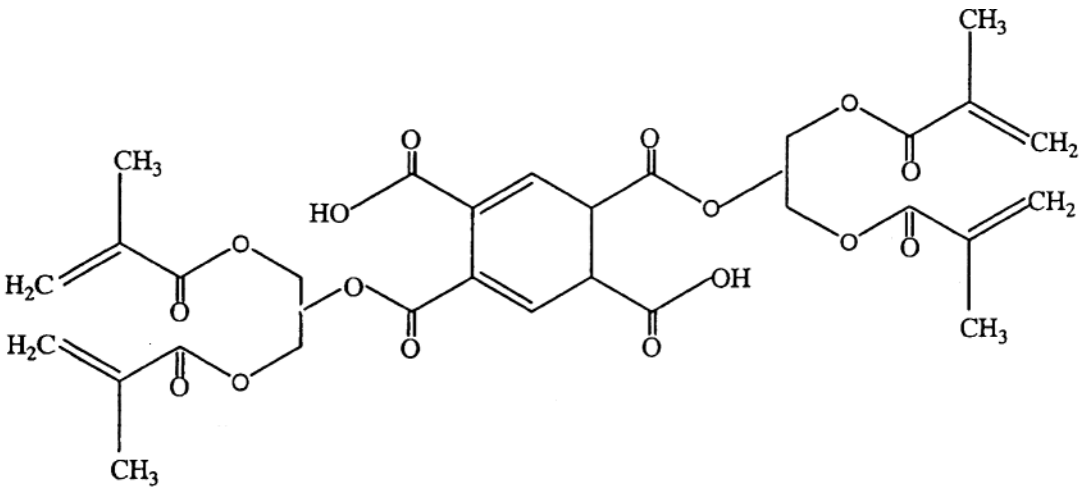


Lauryl Methacrylate
Wenninger et al. 2002

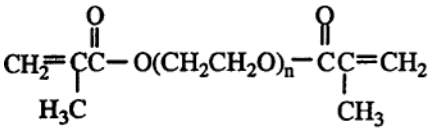


Methoxydiglycol Methacrylate
Jackson 2001

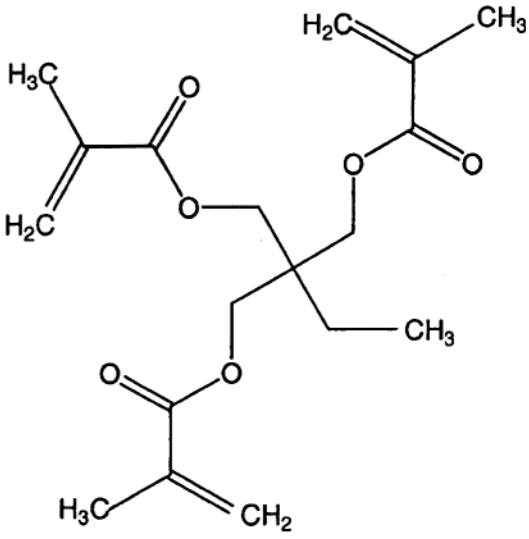
FIGURE 1
(Continued)



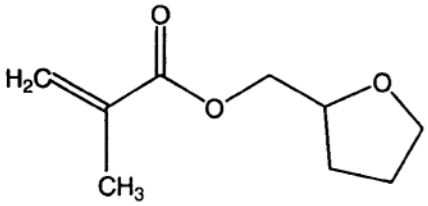
Pyromellitic Glycidyl Dimethacrylate
Jackson 2001



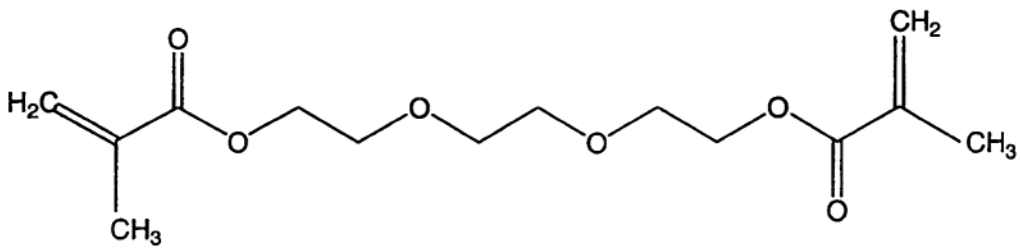
PEG-4 Dimethacrylate
Wenninger et al. 2002



Trimethylolpropane Trimethacrylate
ChemIDplus 2001

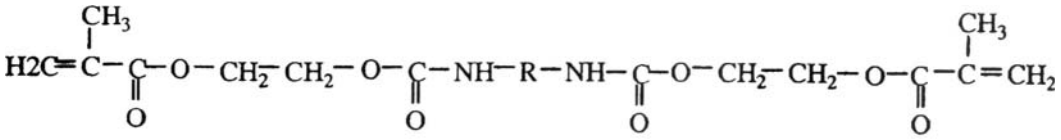


Tetrahydrofurfuryl Methacrylate
ChemIDplus 2001



Triethylene Glycol Dimethacrylate
ChemIDplus 2001

FIGURE 1
(Continued)



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

FIGURE 1
(Continued).

to establish a normalized baseline to compare reactivity of various test monomers. Each of the 22 test monomers were added at a concentration of 5% (by weight) to the Radical™ artificial nail monomer/polymer system (see Table 3). The results reported most test monomers at 5% concentrations had faster set times than the 5% ethyl methacrylate standard. At 3.84 minutes, 5% Hexyl Methacrylate was the slowest to set, 0.74 minutes slower than the set time for 5% ethyl methacrylate. At 285.83 mJ/m^2, t-Butyl Methacrylate had the lowest total exotherm, which was 50.75 mJ/m^2 lower than the total exotherm for 5% ethyl methacrylate.

Fifty percent ethyl methacrylate had a set time of 5.93 minutes and total exotherm of 76.26 mJ/m^2 (see Table 4). The results reported all six test monomers at 50% concentrations had faster set times than the 50% ethyl methacrylate standard. The 50% HEMA test monomer took 1.82 minutes to set, which was 4.13 minutes faster than the set time for 50% ethyl methacrylate. HEMA had the highest total exotherm which was 1130.30 mJ/m^2, which was 1054.04 mJ/m^2 higher than the total exotherm for 5% ethyl methacrylate. Fifty percent 2-Ethoxy Ethoxy Ethyl Methacrylate had a set time of 5.39 minutes and a total exotherm of 267.87 which was most similar to 50% ethyl methacrylate. Faster set times and increased exotherms are strong indicators of increased reactivity. The data on the 22 Methacrylates included in this report have similar levels of reactivity as compared to ethyl methacrylate. Therefore, the polymerization rate and the amount of unreacted monomer in ethyl methacrylate are similar to the polymerization rate and the amount of unreacted monomer in the Methacrylates included in this report (Creative Nail Design 2001).

Method of Manufacture

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

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

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

Analytical Methods

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

Henriks-Eckerman and Kanerva (1997) identified the presence of Butyl Methacrylate (0.05%) in an acrylic adhesive using gas chromatography-mass spectrometry (GC-MS).

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

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

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

Impurities

Certificates of Analysis for other methacrylates used in the artificial nail industry including Butyl Methacrylate, Isobutyl Methacrylate, and Lauryl Methacrylate stated that impurities generally are in the range of less than 0.05%. The only known impurities are methacrylic acid and other methacrylates and acrylates (ABA/NMC 2001a).

USE

Cosmetic

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

TABLE 1
Definitions and synonyms for methacrylate esters

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

(Continued on next page)

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

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

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

(Continued on next page)

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

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

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

TABLE 2
Physical and chemical properties of methacrylate esters

Property	Descripton	Reference
	Butyl Methacrylate	
Molecular weight	142.19	Sax 1979; HSDB 2000; Assessment Technologies, Inc. 1996; Sandmeyer and Kirwin 1981
Appearance/odor	Colorless liquid; readily polymerizes; ester odor	Lewis 1993; Sax 1979; HSDB 2000
Boiling point	163.0–170.5°C	Lewis 1993; Sax 1979; Assessment Technologies, Inc. 1996
	160°C	HSDB 2000; Sandmeyer and Kirwin 1981
melting point	−75°C	HSDB 2000
density	0.895	Lewis 1993; Sax 1979; HSDB 2000; Assessment Technologies, Inc. 1996
Flash point	130°F (54.4°C); 126°F	Lewis 1993; Sax 1979
	106°F; 41.1°C	Sandmeyer and Kirwin 1981
Solubility	Insoluble in water	Lewis 1993; HSDB 2000; Sandmeyer and Kirwin 1981
	Very soluble in alcohol and ether	Sandmeyer and Kirwin 1981
Octanol/water partition coefficient	2.88	HSDB 2000
	3.01	Brixham Environmental Lab 1992; Assessment Technologies, Inc. 1996
	1.97	Yoshii 1997
Maximum absorption	214 nm	HSDB 2000
	t-butyl Methacrylate	
Color/form	Colorless liquid	Lewis 1997
Boiling point	66°C	Lewis 1997
Density	0.877	Lewis 1997
Flash point	92°F	Lewis 1997
	Isobutyl Methacrylate	
Molecular weight	142.20; 142.22	Lewis 2000; HSDB 2001
Color/form	Liquid	Lewis 1997; HSDB 2001
Boiling point	155°C	Lewis 1997; HSDB 2001
Melting point	−34°C	Assessment Technologies 1994
Density	0.8858; 0.882 g/ml	Lewis 1997; HSDB 2001
Flash point	49°C	Lewis 1997; HSDB 2001
Solubility	>10% in alcohol or ether	HSDB 2001
Octanol/water partition coefficient	2.66	HSDB 2001
	1.88	Yoshii 1997
	Cyclohexyl Methacrylate	
Molecular weight	168.23	HSDB 2001
Color/form	Colorless liquid	HSDB 2001
Boiling point	210°C	HSDB 2001; Lewis 1997
Density	0.9626	HSDB 2001; Lewis 1997
Solubility	Insoluble in water	HSDB 2001

(Continued on next page)

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

Property	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™monomer liquid (neat)	2.78	5.0	650.9	8.0
Standard	Ethyl methacrylate (spike)	3.10	4.8	336.58	14.0
1	HEMA	2.85	5.0	672.07	4.4
2	Hydroxypropyl Methacrylate	2.72	6.4	607.16	5.1
3	Methoxydiglycol Methacrylate	2.88	3.3	327.96	3.9
4	Ethoxyethyl Methacrylate	3.63	6.8	367.84	7.6
5	Pyromellitic Glycidyl Dimethacrylate	2.52	4.6	794.23	3.5
6	Isobornyl Methacrylate	3.27	11.7	342.34	9.3
7	Ethylene Glycol Dimethacrylate	2.97	4.8	405.13	10.3
8	Hydroxyethylmethacrylate Acetoacetate	2.86	6	461.5	1.8
9	Urethane Methacrylate	2.78	2.1	396.11	7.5
10	Isopropylidenediphenyl Bisglycidyl Methacrylate	3.03	5.8	302.13	10.9
11	Butyl Methacrylate	3.54	9.7	380.57	6.5
12	Isobutyl Methacrylate	3.53	11.4	362.13	11.1
13	t-butyl Methacrylate	3.82	3.6	285.83	6.9
14	Lauryl Methacrylate	3.6	4.4	308.7	5.8
15	Cyclohexyl Methacrylate	3.2	9.3	313.26	9.3
16	Di-HEMA Trimethylhexyl Dicarbamate	2.76	3.9	416.9	10.5
17	Hexyl Methacrylate	3.84	5.8	298.77	14.6
18	Triethylene Glycol Dimethacrylate	2.74	4.4	413.64	9.8
19	Tetrahydrofurfuryl Methacrylate	3.15	7.1	578.7	2.6
20	PEG-4 Dimethacrylate	3.2	8.0	378.66	9.8
21	Trimethylolpropane Trimethacrylate	2.66	5.3	536.19	3.2
22	2-Ethoxy Ethoxy Ethyl Methacrylate	2.83	4.4	555.10	10.3

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

Sample number	Test monomers (50% concentration)	Set time (min)	Std. Dev. (%)	Total exotherm (mJ/m^2)	Std. Dev. (%)
Standard	Radical™monomer liquid (standard)	2.78	5.0	650.9	8.0
Standard	Ethyl methacrylate (standard)	5.93	27.8	76.26	52.9
1	HEMA	1.82	1.0	1130.30	6.3
2	Hydroxypropyl Methacrylate	2.25	3.9	785.00	5.0
3	Methoxydiglycol Methacrylate	5.11	1.3	111.78	1.7
4	Ethoxyethyl Methacrylate	4.35	3.2	136.16	7.2
19	Tetrahydrofurfuryl Methacrylate	3.82	7.6	546.1	10.3
22	2-Ethoxy Ethoxy Ethyl Methacrylate	5.39	4.0	267.87	9.1

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

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

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

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

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

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

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

GENERAL BIOLOGY

Absorption, Distribution, Metabolism and Excretion

The absorption, distribution, and excretion of ^{14}C labeled Triethylene Glycol Dimethacrylate was measured 24 hours after administration to guinea pigs and mice. Guinea pigs received 0.02 mmol/kg ^{14}C labeled Triethylene Glycol Dimethacrylate by subcutaneous injection or gastric tube. Mice received a 0.1 ml volume of 10 nanomoles ^{14}C labeled Triethylene Glycol Dimethacrylate by gastric tube, subcutaneous injection, and iv injection (Reichl et al. 2001a).

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

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

In order to measure enzymatic hydrolysis, Butyl Methacrylate was incubated with purified porcine liver carboxylesterase stock solution. The volume of carboxylesterase stock solution (10.7 μg/ml) added to the solution was adjusted for each experiment to standardize the enzymatic activity of the samples. Butyl Methacrylate, at a concentration of 5 to 250 μM (n = 5) had a K_m of 72 $\pm$ 28 μM, a V_{max} of 1.84 $\pm$ 0.64 nmol/min and a V_{max}/K_m ratio of 26 l/min. The investigators concluded that α-methyl substitution does not have a significant effect on hydrolysis in comparison with the acrylate analog (McCarthy and Witz 1997).

Cytotoxicity

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

that Butyl Methacrylate and Lauryl Methacrylate were less toxic than the positive control (dibutyl tin diacetate). A dose dependent concentration effect was observed for each compound. A significant difference between Butyl Methacrylate and Lauryl Methacrylate was observed at 0.01 M. Lauryl Methacrylate was more toxic than Butyl Methacrylate and was ranked just beneath the positive control, which may be related to its high molecular weight.

Benson and Stackhouse (1986) performed a bacterial luminescence inhibition assay (an alternative assay to assess the toxicity of compounds) using *Photobacterium phosphoreum* and six consecutive concentrations of Butyl Methacrylate which increased by a factor of 1.5 on a mg/kg basis. After 5, 15 and 30 min of incubation, light measurements were performed. A control was also used to correct for time-dependent drift in light output. The concentration that inhibited luminescence by 50% was 37, 49 and 55 mg/L (at 5, 15 and 30 min, respectively).

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

A significant increase in LDH release was found in the L2 cells after an 8-hour incubation with HEMA (4 mmol/l) and Triethylene Glycol Dimethacrylate (2 mmol/l) and in A549 cells with HEMA (14 mmol/l) and Triethylene Glycol Dimethacrylate (15 mmol/l). In L2 cells, the EC_{50} for HEMA at 6, 12, 24, 36, and 48 hours was 5.46, 4.66, 3.68, 3.22, and 0.59 mmol/l, respectively. In L2 cells, the EC_{50} for Triethylene Glycol Dimethacrylate at 6, 12, 24, 36, and 48 hours was 3.37, 1.30, 1.47, 1.58, and 0.42 mmol/l, respectively (Reichl et al. 2001b).

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

The CSR for 50 μg/ml of Isopropylidenediphenyl Bisglycidyl Methacrylate with S9 mix was 92.6%, and without S9 mix was 6.6%. The CSR for Ethylene Glycol Dimethacrylate, HEMA, and Triethylene Glycol Dimethacrylate exhibited a statistically significant reduction in cytotoxicity in the presence of S9 mixture. The IC_{50} values for Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Triethylene Glycol Dimethacrylate without S9 in JTC-12 cells were 135 (0.068 M), 220 (1.692 M), 39 (0.681 M), and 400 μg/ml (1.398 M), respectively. The IC_{50} values for Ethylene Glycol Dimethacrylate, HEMA, Isopropylidenediphenyl Bisglycidyl Methacrylate, and Triethylene Glycol Dimethacrylate with S9 in JTC-12 cells were $<$200 ($<$0.425 M), 500 (3.842 M), 820 (4.141 M), and $<$1000 μg/ml ($<$3.496 M), respectively (Hikage et al. 1999).

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

The methacrylate monomers tested had ED_{50} values that ranged from 0.06 to 2.52 mM. The most toxic methacrylates tested were Isopropylidenediphenyl Bisglycidyl Methacrylate (0.08–0.14 mM), Di-HEMA Trimethylhexyl Dicarbamate (0.06–0.47 mM), and Triethylene Glycol Dimethacrylate (0.12–0.26 mM). Ethylene Glycol Dimethacrylate (0.46–2.31 mM) and HEMA (1.77-2.52 mM) were moderately toxic (Geurtsen et al. 1998).

Yoshii (1997) evaluated the cytotoxicity of Butyl Methacrylate, Isobutyl Methacrylate, Ethoxyethyl Methacrylate, Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Lauryl Methacrylate, PEG-4 Dimethacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate in the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H 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 $\pm$ 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 mutantion frequency in V79 cell cultures without metabolic activation. However, the mutagenicity of Triethylene Glycol Dimethacrylate was destroyed in the presence of metabolic activation. The researchers concluded that Triethylene Glycol Dimethacrylate acted through a clastogenic mechanism which is not detected by Ames tester strains (Schweikl et al. 1998).

Ethyl Methacrylate

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

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

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

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

CARCINOGENICITY

PEG-4 Dimethacrylate

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

Triethylene Glycol Dimethacrylate

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

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

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

Trimethylolpropane Trimethacrylate

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

Methyl Methacrylate

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

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

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

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

In a workplace exposure guide, the American Industrial Hygiene Association (1981) stated that Trimethylolpropane Trimethacrylate was a mild to moderate skin irritant in a single application patch test (number of volunteers not given) at concentrations of 1% and 10%. At 0.1% there was no irritation.

Dermal Sensitization

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

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

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

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

Reproductive and Developmental Toxicity

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

Case Reports

A 50-year-old woman used artificial nails for 1.5 years and for several months prior to seeking treatment, a paronychial and eyelid dermatitis occurred two days after each new application of artificial nails. Patch test results using 5% Butyl Methacrylate in petrolatum and 1% Butyl Methacrylate in ethyl alcohol demonstrated +2 reactions (erythema, papules, and vesicles) at 48 and 96 hours. Methyl methacrylate and ethyl methacrylate at 5% in petrolatum or 1% in ethyl alcohol caused +2 reactions at 48 and 96 hours. The eyelid and paronychial dermatitis resolved with discontinuation of artificial nail usage (Marks et al. 1979).

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

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

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

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

A case of occupational allergic contact dermatitis was reported in a 20-year-old dental assistant. After 3 months of working with dental resins, she developed a hand eczema on the fingers of the right hand which spread to the left hand and eyelids. She had been handling materials without gloves. She was given the dental screening series patch test. She had a +2 reaction to Isopropylidenediphenyl Bisglycidyl Methacrylate (2%) and had a positive reaction to concentrations as low as 0.0002%. Twenty control people were tested and none had a positive reaction (Kanerva et al. 1986).

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

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

A 24-year-old hairdresser and manicurist had nearly constant hand eczema for 6 years. She had been using various acrylated nail glues over this time period. Her current nail glue was 99.95% ethyl cyanoacrylate and 0.005% undefined acrylic contaminants. She was patch tested with the acrylates series and her nail glue (10% in petrolatum). She reacted to Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, and her nail glue (as well as nickel, para-phenylenediamine, glyceryl thioglycolate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate). Fifteen controls were also tested with the nail glue and all were negative except an elderly woman who had a weak irritant reaction. The researchers could not rule out the possibility that the hairdresser's reactions may be due to the contaminants in the ethyl cyanoacrylate nail glue (Jacobs and Rycroft 1995).

A 38-year-old non-atopic woman had developed allergic contact dermatitis from textile dyes but had been without symptoms. She had been working installing car rear-view mirrors on a production line for the past 6 years. For 2 years she had been experiencing a dry and fissured dermatitis on both hands. The dermatitis spread to her arms, chest, neck, and face and she developed rhinitis and tenderness of the mucous membranes of the nose. She also had paresthesia of the fingertips but her dermatitis cleared while she was away from work. She was patch tested with the expoxy and methacrylate series. Penloc glue was used to adhere the rear-view mirror to the windshield, it was found to contain by GC-MS, Ethylene Glycol Dimethacrylate (0.4%), HEMA (24.6%), and Tetrahydrofurfuryl Methacrylate (% not stated). The major component was isobornyl acrylate (61.9%). The patient had +3 reactions to the Penloc glue at concentrations of 0.2, 0.6, and 2%. The patient was patch tested using Ethylene Glycol Dimethacrylate, HEMA, Hydroxypropyl Methacrylate, Isopropylidenediphenyl Bisglycidyl Methacrylate, Tetrahydrofurfuryl Methacrylate, Triethylene Glycol Dimethacrylate, and Di-HEMA Trimethylhexyl Dicarbamate at a concentration of 2%. The patient had no reaction to Isopropylidenediphenyl Bisglycidyl Methacrylate and Di-HEMA Trimethylhexyl Dicarbamate. However, all other Methacrylates mentioned above resulted in +2 to +3 reactions (Kanerva et al. 1995).

A 47-year-old female cosmetician who had severe atopic dermatitis in her youth, but had been without symptoms for 20 years, developed dermatitis on her right thumb that subsequently spread to both hands and face after she started to work with photobonded nails and chemically cured nail cosmetics. Two patch testing sessions were performed on the back (48-hour occlusion) using 2% Butyl Methacrylate, 2% Ethylene Glycol Dimethacrylate, 2% HEMA, 2% Hydroxypropyl Methacrylate, 2% Tetrahydrofurfuryl Methacrylate, 2% Triethylene Glycol Dimethacrylate, and 2% Di-HEMA Trimethylhexyl Dicarbamate. Readings were performed on days two, three and four. HEMA, Hydroxypropyl Methacrylate, Ethylene Glycol Dimethacrylate, and Triethylene Glycol Dimethacrylate all resulted in a +2 reading in this series of patch testing. There was a +1 reaction to Butyl Methacrylate and no reactions to Tetrahydrofurfuryl Methacrylate and Di-HEMA Trimethylhexyl Dicarbamate. Additionally, the patient had an allergic patch test result to her own nail strengthener preparation that contained 2.2% Butyl Methacrylate and her own monomer liquid for sculptured nails with 5% Triethylene Glycol Dimethacrylate (Kanerva et al. 1996).

Case reports of female repair technicians of facsimile machines, in which Butyl Methacrylate fumes were either not confirmed or confirmed up to 0.60 mg/m^3, reported symptoms of eye and upper respiratory tract irritation, chest tightness, congestion, dry cough, dyspnea, lung crackles and elevated

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

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

Patch Testing Results

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

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

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

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

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

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

Five women with photobonded acrylic nails had pruritic and paronychial and subonychial dermatitis for several months and 2 patients had dermatitis of the lower lids and cheeks. The symptoms developed 6 months to 3 years after the first applications of artificial nails. Monthly renewal of the nails caused a strong exacerbation of the dermatitis within 24 hours. Patients were patch tested with Ethylene Glycol Dimethacrylate (2.0%), HEMA (0.02%, 0.2, and 0.6%), Hydroxypropyl Methacrylate (0.02, 0.2, and 0.6%), Isopropylidenediphenyl Bisglycidyl Methacrylate (2.0%), Triethylene Glycol Dimethacrylate (2.0%), and Di-HEMA Trimethylhexyl Dicarbamate (0.2 and 0.6%). Five of five patients reacted positively to Ethylene Glycol Dimethacrylate (+2 and +3 reactions). Two patients (+1 reactions), 4 patients (+2 reactions), and 5 patients (+3 reactions) reacted to 0.02%, 0.2%, and 0.6% HEMA, respectively. One patient (+2 reaction), 5 patients (+1 and +2 reactions), and 5 patients (+1, +2, and +3 reactions) reacted positively to 0.02%, 0.2%, and 0.6% Hydroxypropyl Methacrylate, respectively. All patients had no reaction to Isopropylidene-diphenyl Bisglycidyl Methacrylate. Five of 5 patients reacted positively (1 patient was questionably positive) to Triethylene Glycol Dimethacrylate. One patient and two patients reacted positively to 0.2% (+1 reaction) and 0.6% (+1 and +2 reactions) Di-HEMA Trimethylhexyl Dicarbamate (Hemmer et al. 1996).

Consumer Adverse Reaction Reports

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

Occupational Exposure

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

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

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

SUMMARY

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

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

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

The reported oral LD_{50} values of Methacrylates were $>$6.3 g/kg in rabbits, $>$2000 mg/kg to 25,530 mg/kg in rats, and 16.00 ml/kg to $>$3200 mg/kg in mice. The reported ip LD_{50} values of Methacrylates were 1.110 ml/kg to 3900 mg/kg in rats and 0.497 ml/kg to 2889 mg/kg in mice. The reported dermal LD_{50} values of Methacrylates were $>$10 ml/kg to $>$3000 mg/kg in rabbits and $>$20 ml/kg in guinea pigs. The reported inhalation LC_{50} values of Methacrylates were 29 mg/l to 28,469 mg/m^3 in rats and $>$17.01 mg/l to 29.74 mg/l in mice. An intravenous dose of 1.24 ml of 3344×10^{-6} M Lauryl Methacrylate was rapidly fatal to dogs.

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

In a subchronic oral toxicity study, Beagle dogs were dosed with 0.2 to 2.0 g/kg/day of C12 to C18 Methacrylate monomers for 13 weeks. Hematology, biochemistry, and urine analyses were comparable between controls and test groups. Only the highest dose group had effects such as weight loss, emesis, diarrhea, mucoid feces, or salivation observed. In another study, rats were fed the C12 to C18 Methacrylate monomers at concentrations between 5000 to 50,000 ppm for 13 weeks. Body weights, growth, and food consumption were significantly decreased in the highest dose group. Hematological, biochemical, and urine analyses were comparable between test groups and controls. Kidney and liver weights were increased in the high dose group as compared to controls. Microscopic examination of tissues did not reveal any compound-related lesions.

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

Butyl Methacrylate (0.1 M) and Isobutyl Methacrylate (0.1 M) are mildly irritating to the rabbit eye. HEMA is corrosive

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

The dermal irritation caused by Methacrylates has been documented in guinea pigs and rabbits. Undiluted or high concentration Methacrylates are typically moderate irritants that can result in erythema and/or edema. Lower concentration Methacrylates are typically mild or slightly irritating. The Methacrylates PII ranged from 0.08 to 5.6, depending on which Methacrylate was tested and whether the site was abraded or intact skin.

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

The effects of Butyl Methacrylate, HEMA, Hydroxypropyl Methacrylate, and Trimethylolpropane Trimethacrylate on the reproductive parameters and/or the developmental parameters of the offspring of rats were evaluated. Rats were dosed for 9 to 49 days. The Butyl Methacrylate NOEL was 1000 mg/kg/day in parental males and 300 mg/kg/day in parental females; there were no effects on any reproductive parameters in males or developmental parameters in offspring. The HEMA NOEL was 1000 mg/kg/day (maximum dose tested) in both sexes and in the developing pups. The Hydroxypropyl Methacrylate NOEL was 1000 mg/kg/day (maximum dose tested) in both sexes and in the developing pups. Trimethylolpropane Trimethacrylate caused fetotoxic effects such as increased resorptions (mean incidence 25.4%), decreased fetal viability (mean survival 74.6%), decreased fetal weights, and decreased fetal lengths at a dose of 2500 mg/kg/day.

The threshold concentration for embryotoxic and teratogenic effects in rats exposed to Butyl Methacrylate via inhalation was 0.1 mg/m^3.

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

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

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

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

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

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

Patients previously exposed to Methacrylate elicited positive reactions to patch tests with concentrations as low as 1% Butyl Methacrylate, 2% Ethylene Glycol Dimethacrylate, 0.02% HEMA, 0.02% Hydroxypropyl Methacrylate, 1%

Isobutyl Methacrylate, 0.0002% Isopropylidenediphenyl Bisglycidyl Methacrylate, 2% Tetrahydrofurfuryl Methacrylate, 2% Triethylene Glycol Dimethacrylate, 0.02% Di-HEMA Trimethylhexyl Dicarbamate. Most of these patients were employed in dentistry or were artificial nail technicians.

DISCUSSION

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

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

CONCLUSION

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

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2021 VCRP Data

Bis(Glyceryl Dimethacrylate) Pyromellitate

Nail Polish and Enamel	08E	19
Total		**19**

Butylcarbamoethyl Methacrylate - No FDA data

Butyl Methacrylate - No FDA data

t-Butyl Methacrylate - No FDA data

Di-HEMA Trimethylhexyl Dicarbamate

Basecoats and Undercoats	08A	8
Nail Extenders	08D	2
Nail Polish and Enamel	08E	61
Other Manicuring Preparations	08G	5
Total		**76**

Cyclohexylmethacrylate - No FDA data

2-Ethoxy Ethoxy Ethyl Methacrylate - No FDA data

Glycol Dimethacrylate

Nail Extenders	08D	1
Nail Polish and Enamel	08E	13
Other Manicuring Preparations	08G	3
Total		**17**

HEMA

Eyebrow Pencil	03A	1
Basecoats and Undercoats	08A	15
Nail Extenders	08D	1
Nail Polish and Enamel	08E	121
Other Manicuring Preparations	08G	11
Total		**149**

HEMA Acetoacetate - No FDA data

Hexyl Methacrylate - No FDA data

Hydroxypropyl Methacrylate

Basecoats and Undercoats	08A	3
Nail Polish and Enamel	08E	35
Other Manicuring Preparations	08G	2
Total		**40**

Isobornyl Methacrylate

Basecoats and Undercoats	08A	8
Nail Extenders	08D	4
Nail Polish and Enamel	08E	14
Other Manicuring Preparations	08G	4
Total		**30**

Isobutyl Methacrylate - No FDA data

Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate

Basecoats and Undercoats	08A	1
Total		**1**

Lauryl Methacrylate

Other Manicuring Preparations	08G	1
Total		**1**

Methoxydiglycol Methacrylate - No FDA data

PEG-4 Dimethacrylate - No FDA data

Tetrahydrofurfuryl Methacrylate - No FDA data

Triethylene Glycol Dimethacrylate - No FDA data

Trimethylolpropane Trimethacrylate

Nail Polish and Enamel	08E	1
Total		**1**

Personal Care Products Council
Committed to Safety, Quality & Innovation

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: October 13, 2020

SUBJECT: Concentration of Use by FDA Product Category: Methacrylate Monomers

Concentration of Use by FDA Product Category – Methacrylate Monomers*

(names in parentheses are the names used in the original CIR report)

Butyl Methacrylate
t-Butyl Methacrylate
Cyclohexylmethacrylate
Ethoxyethyl Methacrylate
2-ethoxy ethoxy ethyl methacrylate
Glycol Dimethacrylate (ethylene glycol dimethacrylate)
hexyl methacrylate
HEMA
Di-HEMA Trimethylhexyl Dicarbamate
HEMA Acetoacetate (hydroxyethylmethacrylate acetoacetate)
Hydroxypropyl Methacrylate
Isobornyl Methacrylate
Isobutyl Methacrylate
Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate (isopropylidenediphenyl bisglycidyl methacrylate)
Lauryl Methacrylate
Methoxydiglycol Methacrylate
PEG-4 Dimethacrylate
Bis(Glyceryl Dimethacrylate) Pyromellitate (pyromellitic glycidyl dimethacrylate)
Tetrahydrofurfuryl Methacrylate
Triethylene Glycol Dimethacrylate
Trimethylolpropane Trimethacrylate
urethane methacrylate

Ingredient	Product Category	Maximum Concentration of Use
Glycol Dimethacrylate	Basecoats and undercoats (8A)	1.2%
HEMA	Basecoats and undercoats (8A)	11.2-28.4%
HEMA	Nail extenders (8D)	0.44-10%
HEMA	Nail polish and enamel (8E)	18.8-27%
HEMA	Other manicuring preparations (8G)	0.11-79%
Di-HEMA Trimethylhexyl Dicarbamate	Basecoats and undercoats (8A)	35.8-61.5%
Di-HEMA Trimethylhexyl Dicarbamate	Nail extenders (8D)	91.8%
Di-HEMA Trimethylhexyl Dicarbamate	Nail polish and enamel (8E)	62.8-80.2%
Di-HEMA Trimethylhexyl Dicarbamate	Nail polish and enamel removers (8F)	50.2%
Hydroxypropyl Methacrylate	Basecoats and undercoats (8A)	0.8-11.1%
Hydroxypropyl Methacrylate	Nail extenders (8D)	10-18%
Hydroxypropyl Methacrylate	Nail polish and enamel (8E)	18.8-23%
Hydroxypropyl Methacrylate	Other manicuring preparations (8G)	15.4%
Isobornyl Methacrylate	Basecoats and undercoats (8A)	12.7-20.2%
Isobornyl Methacrylate	Nail polish and enamel (8E)	8.3-19.8%
Isobornyl Methacrylate	Other manicuring preparations (8G)	19.9%
Isobutyl Methacrylate	Basecoats and undercoats (8A)	0.0005%

Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate	Basecoats and undercoats (8A)	9.5%
Isopropylidenediphenyl Bisoxyhydroxypropyl Methacrylate	Nail polish and enamel (8E)	4.3-4.4%
Methoxydiglycol Methacrylate	Nail extenders (8D)	24.8%
Methoxydiglycol Methacrylate	Other manicuring preparation (8G)	65%
PEG-4 Dimethacrylate	Nail extenders (8D)	6.6-10%
Tetrahydrofurfuryl Methacrylate	Basecoats and undercoats (8A)	20.6%
Tetrahydrofurfuryl Methacrylate	Nail polish and enamel (8E)	38.2%
Triethylene Glycol Dimethacrylate	Nail polish and enamel (8E)	8.7%
Triethylene Glycol Dimethacrylate	Other manicuring preparations (8G)	19.6-20%
Trimethylolpropane Trimethacrylate	Nail extenders (8D)	1-25.3%
Trimethylolpropane Trimethacrylate	Nail polish and enamel (8E)	1.1%

*Ingredients included in the title of the table but not found in the table were included in the concentration of us survey, but no uses were reported. An ingredient in all lower-case letters has not been assigned an INCI name.

Information collected in 2020
Table prepared October 7, 2020