Amended Safety Assessment of Acrylates Copolymers as Used in Cosmetics

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The 2018 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, D.P.A. This safety assessment was prepared by Monice M. Fiume, Senior Director

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Director, CIR
Date: February 23, 2018
Subject: Strategy for Acrylates Copolymer and Related Ingredients Re-Review

In 2002, CIR published the Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients. Based on the available data, the Panel concluded that the acrylates copolymers named in that report are safe for use in cosmetics when formulated to avoid irritation. Because it has been 15+ years since this document was published, it is time for a re-review.

In addition to the ingredients that were included in the 2002 review, there are 65 possible "add-ons" that have not yet been looked at by CIR. Ethyl Methacrylate (issued as an amended report) was published in 2002; this conclusion superseded that published in 1995. This would be another ingredient for consideration for inclusion; it is also due for re-review.

Enclosed please find a table of definitions, functions, and frequency of use of all the ingredients that were included in the initial safety assessment of Acrylates Copolymers and Related Ingredients [found in *acryco032018w2_list 1*], and for the proposed add-on ingredients [*acryco032018w2_list 2*].

Accordingly, CIR is requesting the Panel's guidance on inclusion of these 65 ingredients in this re-review.

Additionally, the following reports on similar ingredients have been issued; as supporting material, definitions, functions, and frequency of use of the ingredients included in these reports is also included:

- Crosslinked Alkyl Acrylates – published in 2017 [*acryco032018w2_list 3*]
  - conclusion: safe in the present practices of use and concentration, except when polymerized in benzene; Acrylates C10-30 Alkyl Acrylate Crosspolymer may be polymerized in benzene, and the available data were insufficient to make a determination of safety for this ingredient when polymerized in benzene
- Polymethyl Methacrylate, Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer – published in 2011 [*acryco032018w2_list 4*]
  - conclusion: safe in the practices of use and concentration
- Carbomers-934, -910, -934P, 940, -941, and -962 – published in 1982; reaffirmed in 2003 [*acryco032018w2_list 5*]
  - conclusion: safe in the present practices of use and concentration
  - now simply known as Carbomer (defined as defined a homopolymer of acrylic acid crosslinked with an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene)

Please determine whether any of the ingredients from these reports should be included as a part of this re-review.

The previous reports are attached for your use:

- Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients (2002) [*acryco032018w2_prev 1*]
- Amended Final Report on the Safety Assessment of Ethyl Methacrylate (2002) [*acryco032018w2_prev 2*]
- Final Report on Ethyl Methacrylate (1995) [*acryco032018w2_prev 3*]
- Safety Assessment of Cross-Linked Alkyl Acrylates as Used in Cosmetics (2017) [*acryco032018w2_prev 4*]

- Final report of the Cosmetic Ingredient Review Expert Panel Safety Assessment of Polymethyl Methacrylate (PMMA), Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer (2011) [*acryco032018w2_prev 5*]
- Carbomers-934, -910, -934P, -940, -941, and -962 (1982) [*acryco032018w2_prev 6*]

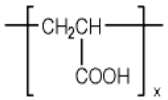
Minutes from the original deliberations of the Acrylates Copolymer and 33 Related Ingredients report, and from the other reports named above, have been included:

- Acrylates Copolymers and related ingredients [*acryco032018w2_min 1*]
- Ethyl Methacrylate; amended and original report deliberations [*acryco032018w2_min 2*]
- Crosslinked Alkyl Acrylates [*acryco032018w2_min 3*]
- Polymethyl Methacrylate, Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer [*acryco032018w2_min 4*]
- Carbomers – minutes are not available

List of Acrylates Copolymers and 33 Related Ingredients reviewed in 2002

Acrylates/Ammonium Methacrylate Copolymer
Acrylates Copolymer
Acrylates/Hydroxyesters Acrylates Copolymer
Acrylates/Steareth-50 Acrylate Copolymer
Acrylates/Steareth-20 Methacrylate Copolymer
Acrylates/VA Copolymer
Acrylates/VP (VA) Copolymer (delete? - included in Vinylpyrrolidone Polymers 2018 report)
Ammonium Acrylates Copolymer
Ammonium Polyacrylate
Ammonium Styrene/Acrylates Copolymer
Ammonium VA/Acrylates Copolymer
AMP-Acrylates Copolymer
Ethylene/Acrylic Acid Copolymer
Ethylene/Acrylic Acid/VA Copolymer
Ethylene/Calcium Acrylate Copolymer
Ethylene/Magnesium Acrylate Copolymer
Ethylene/Methacrylate Copolymer
Ethylene/Sodium Acrylate Copolymer
Ethylene/Zinc Acrylate Copolymer
Lauryl Acrylate/VA Copolymer
Methacryloyl Ethyl Betaine/Acrylates Copolymer
Polyacrylic Acid
Potassium Aluminum Polyacrylate
Potassium Polyacrylate
Sodium Acrylate/Acrolein Copolymer
Sodium Acrylates Copolymer
Sodium Polyacrylate
Sodium Styrene/Acrylates Copolymer
Steareth-10 Allyl Ether/Acrylates Copolymer
Styrene/Acrylates Copolymer
Styrene/Acrylates/Ammonium Methacrylate Copolymer
VA/Butyl Maleate/Isobornyl Acrylate Copolymer
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer
VP/Dimethylaminoethylmethacrylate Copolymer

Definitions, Functions, and 2018/1998 Frequency of Use (FOU) of Acrylates Copolymers and 33 Related Ingredients reviewed in 2002

Ingredient Name	Definition	Function(s)	2018/1998 FOU
Acrylates/Ammonium Methacrylate Copolymer	a copolymer of ammonium methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; hair fixatives	26/1
Acrylates Copolymer	a copolymer of two or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	adhesives; artificial nail builders; binders; dispersing agents - nonsurfactant; film formers; hair fixatives; skin-conditioning agents - emollient; skin-conditioning agents - miscellaneous	**3174/227**
Acrylates/Hydroxyesters Acrylates Copolymer	a copolymer of one or more monomers consisting of acrylic acid, methacrylic acid, or their simple esters, and one or more monomers of hydroxyacrylate esters	film formers	35
Acrylates/Steareth-50 Acrylate Copolymer	a copolymer of the ester of acrylic acid and Steareth-50 (q.v.) and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous	NR
Acrylates/Steareth-20 Methacrylate Copolymer	a copolymer of the ester of methacrylic acid and Steareth-20 (q.v.) and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous	32/35
Acrylates/VA Copolymer	a copolymer of Vinyl Acetate (q.v.) and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; hair fixatives	1
~~Acrylates/VP (VA) Copolymer~~ - Part of Vinylpyrrolidone Polymers 2018 report	a copolymer of N-Vinyl Pyrrolidone and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	binders; dispersing agents - nonsurfactant; film formers; hair fixatives	
Ammonium Acrylates Copolymer	the **ammonium salt** of a polymer of two or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; viscosity increasing agents - aqueous	60/21
Ammonium Polyacrylate	the **ammonium salt** of Polyacrylic Acid	emulsion stabilizers; film formers	15
Ammonium Styrene/Acrylates Copolymer	the **ammonium salt** of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters	dispersing agents - nonsurfactant; film formers	2
Ammonium VA/Acrylates Copolymer	the **ammonium salt** of a polymer of vinyl acetate and two or more monomers consisting of acrylic acid, methacrylic acid or their simple ester	binders; dispersing agents - nonsurfactant; film formers; hair fixatives	NR
AMP-Acrylates Copolymer	the **aminomethyl propanol salt** of Acrylates Copolymer	film formers	36
Ethylene/Acrylic Acid Copolymer	a copolymer of ethylene and acrylic acid monomers	binders; film formers; viscosity increasing agents - nonaqueous	320/6
Ethylene/Acrylic Acid/VA Copolymer	a copolymer of ethylene, acrylic acid and vinyl acetate monomers	binders; film formers; viscosity increasing agents - nonaqueous	NR
Ethylene/Calcium Acrylate Copolymer	a copolymer of ethylene and calcium acrylate monomers	binders; film formers	NR
Ethylene/Magnesium Acrylate Copolymer	a copolymer of ethylene and magnesium acrylate monomers	binders; film formers	NR
Ethylene/Methacrylate Copolymer	a copolymer of ethylene and methyl methacrylate monomers	film formers	60/5
Ethylene/Sodium Acrylate Copolymer	a copolymer of ethylene and sodium acrylate monomers	binders; film formers; viscosity increasing agents - aqueous	1/1
Ethylene/Zinc Acrylate Copolymer	a copolymer of ethylene and zinc acrylate monomers	film formers	NR
Lauryl Acrylate/VA Copolymer	a copolymer of lauryl acrylate and vinyl acetate monomers	film formers	NR
Methacryloyl Ethyl Betaine/Acrylates Copolymer	a polymer of methacryloyl ethyl betaine and two or more monomers of methacrylic acid or its simple esters	dispersing agents - nonsurfactant; film formers; hair fixatives	12
Polyacrylic Acid	the polymer of acrylic acid that conforms generally to the formula: 	binders; emulsion stabilizers; film formers; viscosity increasing agents - aqueous	111/19
Potassium Aluminum Polyacrylate	a mixture of the **potassium and aluminum salts** of Polyacrylic Acid	absorbents; binders; viscosity increasing agents - aqueous	NR
Potassium Polyacrylate	the **potassium salt** of Polyacrylic Acid	emulsion stabilizers; viscosity increasing agents - aqueous	NR
Sodium Acrylate/Acrolein Copolymer	a polymer consisting of sodium acrylate and acrolein monomers	binders; film formers; viscosity increasing agents - aqueous	NR
Sodium Acrylates Copolymer	the **sodium salt** of a polymer consisting of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers; viscosity increasing agents - aqueous	179/5

Definitions, Functions, and 2018/1998 Frequency of Use (FOU) of Acrylates Copolymers and 33 Related Ingredients reviewed in 2002

Ingredient Name	Definition	Function(s)	2018/1998 FOU
Sodium Polyacrylate			**952/8**
Sodium Styrene/Acrylates Copolymer	the **sodium salt** of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers; viscosity increasing agents - aqueous	17/2
Steareth-10 Allyl Ether/Acrylates Copolymer	a copolymer of the allyl ether of Steareth-10 and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers; viscosity increasing agents - nonaqueous	12/6
Styrene/Acrylates Copolymer	a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers; opacifying agents	479/102
Styrene/Acrylates/Ammonium Methacrylate Copolymer	a polymer of styrene, ammonium methacrylate and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters	dispersing agents - nonsurfactant; film formers	106/1
VA/Butyl Maleate/Isobornyl Acrylate Copolymer	a copolymer of vinyl acetate, butyl maleate and isobornyl acrylate monomers	film formers	2/5
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer	a copolymer of vinylcaprolactam, vinylpyrrolidone and Dimethylaminoethyl Methacrylate monomers	film formers; hair fixatives	70/6
VP/Dimethylaminoethylmethacrylate Copolymer	a polymer prepared from vinylpyrrolidone and dimethylaminoethylmethacrylate monomers	binders; dispersing agents - nonsurfactant; film formers; hair fixatives	72/43

POTENTIAL ADD-ONS

65 Previously Unreviewed Ingredients

Acrylates/Beheneth-25 Methacrylate Copolymer
Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer
Acrylates/C5-8 Alkyl Acrylate Copolymer
Acrylates/C10-30 Alkyl Methacrylate Copolymer
Acrylates/C12-22 Alkyl Methacrylate Copolymer
Acrylates/Ceteareth-20 Methacrylate Crosspolymer
Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2
Acrylates/Ceteth-20 Methacrylate Copolymer
Acrylates/C26-28 Olefin Copolymer
Acrylates Crosspolymer-3
Acrylates Crosspolymer-4
Acrylates Crosspolymer-5
Acrylates/Ethylhexyl Acrylate Copolymer
Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer
Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Acrylates/Laureth-25 Methacrylate Copolymer
Acrylates/Lauryl Methacrylate Copolymer
Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer
Acrylates/Methoxy PEG-4 Methacrylate Copolymer
Acrylates/Methoxy PEG-15 Methacrylate Copolymer
Acrylates/Methoxy PEG-23 Methacrylate Copolymer
Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer
Acrylates/Palmeth-25 Acrylate Copolymer
Acrylates/Steareth-30 Methacrylate Copolymer
Acrylates/Stearyl Methacrylate Copolymer
Acrylates/VA Crosspolymer
Acrylic Acid/C12-22 Alkyl Acrylate Copolymer
Acrylic Acid/Stearyl Acrylate Copolymer
Ammonium Acrylates/Ethylhexyl Acrylate Copolymer
Ammonium Acrylates/Methyl Styrene/Styrene Copolymer
Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer
Behenyl Methacrylate/t-Butyl Methacrylate Copolymer
Butyl Acrylate/Cyclohexyl Methacrylate Copolymer
Butyl Acrylate/Ethylhexyl Methacrylate Copolymer
Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer
Butyl Methacrylate/Acryoyloxy PG Methacrylate Copolymer
C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer
Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer
Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer
Glyceryl Acrylate/Acrylic Acid Copolymer
Glyceryl Polymethacrylate
Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Lauryl Acrylate Crosspolymer
Lauryl Acrylate/VA Crosspolymer
Methoxy PEG-23 Methacrylate/Glyceryl Diisostearate Methacrylate Copolymer
Methyl Methacrylate/PEG/PPG-4/3 Methacrylate Crosspolymer
Polyacrylate-1 Crosspolymer
Poly C10-30 Alkyl Acrylate
Poly(Methoxy PEG-9 Methacrylate)
Polybutyl Acrylate
Polybutyl Methacrylate
Polyethylacrylate
Polyhydroxyethylmethacrylate
Polyisobutyl Methacrylate
Polymethyl Acrylate
Polypropyl Methacrylate
Polystearyl Methacrylate
Potassium Acrylate Crosspolymer
Potassium Acrylates Copolymer
Potassium Acrylates/Ethylhexyl Acrylate Copolymer
Sodium Acrylates/Beheneth-25 Methacrylate Crosspolymer
Sodium Acrylates/Ethylhexyl Acrylate Copolymer
Sodium Acrylate/Vinyl Alcohol Copolymer
Sodium Polymethacrylate

Previously Reviewed, But Similar

Ethyl Methacrylate – reviewed in 2002

Crosslink Substance

diallyl maleate
divinylbenzene
ethylene glycol dimethacrylate
glycol dimethacrylate
methylene bis-acrylamide
N,N'-methylenebisacrylamide
pentaerythritol, allyl ether
triallylisocyanurate
trimethylolpropane diallyl ether
trimethylolpropane triacrylate
vinyloxazoline

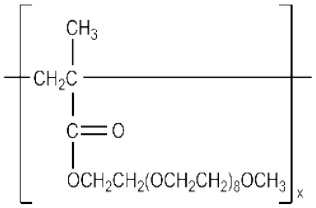
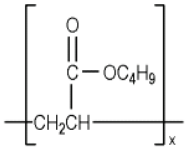
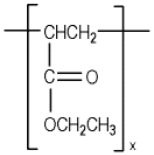
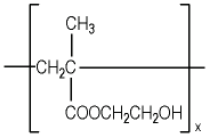
Definitions, Functions, and 2018 FOUof 65 previously unreviewed similar ingredients

Ingredient Name	Definition	Function(s)	FOU
Copolymers			
Acrylates/Beheneth-25 Methacrylate Copolymer	a copolymer of the ester of methacrylic acid and Beheneth-25 (q.v.) and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous	91
Acrylates/Beheneth-25 Methacrylate/Steareth-30 Methacrylate Copolymer	a copolymer of beheneth-25 methacrylate, steareth-30 methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers	NR
Acrylates/C5-8 Alkyl Acrylate Copolymer	copolymer of C5-8 alkyl acrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	emulsion stabilizers; film formers; viscosity increasing agents - aqueous	NR
Acrylates/C10-30 Alkyl Methacrylate Copolymer	the copolymer of C10-30 alkyl methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous	NR
Acrylates/C12-22 Alkyl Methacrylate Copolymer	the copolymer of C12-22 alkyl methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	film formers	9
Acrylates/Ceteth-20 Methacrylate Copolymer	a copolymer formed from the ester of methacrylic acid and Ceteth-20 , and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous	NR
Acrylates/C26-28 Olefin Copolymer	a polymer of C26-28 olefins and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - nonaqueous	NR
Acrylates/Ethylhexyl Acrylate Copolymer	a copolymer of ethylhexyl acrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	film formers	60
Acrylates/Hydroxyethyl Acrylate/Lauryl Acrylate Copolymer	a copolymer of hydroxyethyl acrylate, lauryl acrylate, and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	film formers	NR
Acrylates/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	a copolymer of hydroxyethyl acrylate, butyl acrylate and methoxyethyl acrylate	film formers	NR
Acrylates/Laureth-25 Methacrylate Copolymer	the copolymer of laureth-25 methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous	NR
Acrylates/Lauryl Methacrylate Copolymer	a copolymer of Lauryl Methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers	NR
Acrylates/Methoxy PEG-4 Methacrylate Copolymer	a copolymer of methoxy PEG-4 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	hair conditioning agents	NR
Acrylates/Methoxy PEG-15 Methacrylate Copolymer	a copolymer of methoxy PEG-15 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	dispersing agents - nonsurfactant	NR
Acrylates/Methoxy PEG-23 Methacrylate Copolymer	a copolymer of methoxy peg-23 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	film formers	NR
Acrylates/Palmeth-25 Acrylate Copolymer	a copolymer of the ester of acrylic acid and ethoxylated Palm Alcohol with an average of 25 moles of ethylene oxide and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	viscosity increasing agents - aqueous	9
Acrylates/Steareth-30 Methacrylate Copolymer	a copolymer of the ester of methacrylic acid and Steareth-30 and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters	viscosity increasing agents - aqueous	NR
Acrylates/Stearyl Methacrylate Copolymer	a copolymer of stearyl methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters	emulsion stabilizers; viscosity increasing agents - aqueous	NR
Acrylic Acid/C12-22 Alkyl Acrylate Copolymer	a copolymer of acrylic acid and C12-22 alkyl acrylate	binders; emulsion stabilizers; viscosity increasing agents - nonaqueous	NR
Acrylic Acid/Stearyl Acrylate Copolymer	a polymer of acrylic acid and stearyl acrylate monomers	emulsion stabilizers; film formers; surfactants - emulsifying agents	NR
Ammonium Acrylates/Ethylhexyl Acrylate Copolymer	a copolymer of ethylhexyl acrylate and the ammonium salt of one or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters	film formers	60
Ammonium Acrylates/Methyl Styrene/Styrene Copolymer	a copolymer consisting of ammonium acrylate, methyl styrene and styrene monomers	film formers	5
Ammonium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	**ammonium salt** of Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	film formers	NR
Behenyl Methacrylate/t-Butyl Methacrylate Copolymer	a copolymer of behenyl methacrylate and t-butyl methacrylate monomers	film formers	5

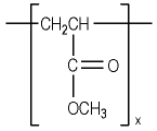
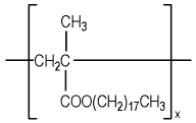
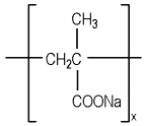
Definitions, Functions, and 2018 FOUof 65 previously unreviewed similar ingredients

Ingredient Name	Definition	Function(s)	FOU
Butyl Acrylate/Cyclohexyl Methacrylate Copolymer	a copolymer of butyl acrylate and cyclohexyl methacrylate	film formers	NR
Butyl Acrylate/Ethylhexyl Methacrylate Copolymer	a copolymer of butyl acrylate and 2-ethylhexyl methacrylate monomers	film formers; hair fixatives	NR
Butyl Acrylate/Hydroxyethyl Methacrylate Copolymer	a copolymer consisting of n-butyl acrylate and 2-hydroxyethyl methacrylate monomers	film formers	NR
Butyl Methacrylate/Acryoyloxy PG Methacrylate Copolymer	a polymer of Butyl Methacrylate and acryloyloxy propylene glycol methacrylate monomers	film formers	NR
C12-22 Alkyl Acrylate/Hydroxyethylacrylate Copolymer	a copolymer of C12-22 alkyl acrylate and hydroxyethylacrylate	binders; emulsion stabilizers; viscosity increasing agents - nonaqueous	NR
Cyclohexyl Methacrylate/Ethylhexyl Methacrylate Copolymer	a copolymer of cyclohexyl methacrylate and ethylhexyl methacrylate	film formers	NR
Ethylhexyl Acrylate/Methoxy PEG-23 Methacrylate/Vinyl Acetate Copolymer	a copolymer of methoxy PEG-23 methacrylate, Vinyl Acetate, and Ethylhexyl Acrylate	hair fixatives	NR
Ethylhexyl Acrylate/Methyl Methacrylate Copolymer	a copolymer of ethylhexyl acrylate and methyl methacrylate	film formers	5
Glyceryl Acrylate/Acrylic Acid Copolymer	a copolymer of glyceryl acrylate and acrylic acid	skin-conditioning agents - humectant; viscosity increasing agents - aqueous	383
Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	the copolymer of hydroxyethyl acrylate and methoxyethyl acrylate	film formers	NR
Methoxy PEG-23 Methacrylate/Glyceryl Diisostearate Methacrylate Copolymer	a copolymer of methoxy PEG-23 methacrylate and glyceryl diisostearate methacrylate monomers	skin protectants	NR
Poly C10-30 Alkyl Acrylate	a polymer of the ester of acrylic acid and C10-30 alcohol	binders; emulsion stabilizers; viscosity increasing agents - nonaqueous	19
Potassium Acrylates Copolymer	the **potassium salt** of a polymer consisting of acrylic acid, methacrylic acid or one of their simple esters	binders; film formers	16
Potassium Acrylates/Ethylhexyl Acrylate Copolymer	the **potassium salt** of Acrylates/Ethylhexyl Acrylate Copolymer	film formers	NR
Sodium Acrylates/Ethylhexyl Acrylate Copolymer	a copolymer of ethylhexyl acrylate and the sodium salt of one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters	film formers	NR
Sodium Acrylate/Vinyl Alcohol Copolymer	a polymer of sodium acrylate and vinyl alcohol monomers	binders; emulsion stabilizers; film formers; viscosity increasing agents - aqueous	NR
Crosspolymers			
Acrylates/Ceteareth-20 Methacrylate Crosspolymer	copolymer of the ester of methacrylic acid and Ceteareth-20 (q.v.) and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters, crosslinked with ethylene glycol dimethacrylate	viscosity increasing agents - aqueous	NR
Acrylates/Ceteareth-20 Methacrylate Crosspolymer-2	a copolymer of the ester of methacrylic acid and Ceteareth-20 (q.v.) and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters, crosslinked with diallyl maleate	bulking agents; chelating agents; emulsion stabilizers; opacifying agents; viscosity increasing agents - aqueous	NR
Acrylates Crosspolymer-3	a copolymer of acrylic acid, methacrylic acid or one of its simple esters, crosslinked with trimethylolpropane triacrylate and trimethylolpropane diallyl ether	film formers; hair fixatives; viscosity increasing agents - aqueous	4
Acrylates Crosspolymer-4	a copolymer of acrylic acid, methacrylic acid or one of its simple esters, crosslinked with trimethylolpropane triacrylate	emulsion stabilizers; film formers; surfactants - dispersing agents; viscosity increasing agents - aqueous	16
Acrylates Crosspolymer-5	a copolymer of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with an allyl ether of pentaerythritol	viscosity increasing agents - aqueous	NR
Acrylates/Lauryl Methacrylate/Tridecyl Methacrylate Crosspolymer	a copolymer of lauryl methacrylate, tridecyl methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with vinyloxazoline	film formers	NR
Acrylates/Methoxy PEG-90 Methacrylate Crosspolymer	a copolymer of methoxy PEG-90 methacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked by glycol dimethacrylate	skin protectants	NR

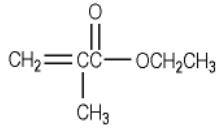
Definitions, Functions, and 2018 FOUof 65 previously unreviewed similar ingredients

Ingredient Name	Definition	Function(s)	FOU
Acrylates/VA Crosspolymer	a copolymer of vinyl acetate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with triallylisocyanurate	film formers	1
Lauryl Acrylate Crosspolymer	a polymer of lauryl acrylate crosslinked with divinylbenzene	hair fixatives	NR
Lauryl Acrylate/VA Crosspolymer	a copolymer of lauryl acrylate and vinyl acetate crosslinked with divinylbenzene	abrasives	NR
Methyl Methacrylate/PEG/PPG-4/3 Methacrylate Crosspolymer	a random copolymer of methyl methacrylate and PEG/PPG-4/3 methacrylate crosslinked with ethylene glycol dimethacrylate	film formers	1
Polyacrylate-1 Crosspolymer	a copolymer of one or more simple esters of acrylic or methacrylic acid, C1-4 dialkyl-amino C1-6 alkyl methacrylate, PEG/PPG-30/5 allyl ether, PEG 20-25 C10-30 alkyl ether methacrylate, hydroxy C2-6 alkyl methacrylate crosslinked with ethylene glycol dimethacrylate	film formers; hair conditioning agents; hair fixatives; viscosity increasing agents - aqueous	14
Potassium Acrylate Crosspolymer	the **potassium salt** of a polymer of Acrylic Acid (q.v.) crosslinked with N,N'-methylenebisacrylamide	absorbents; slip modifiers	NR
Sodium Acrylates/Beheneth-25 Methacrylate Crosspolymer	the **sodium salt** of a copolymer of acrylic acid, methacrylic acid or one or more of its simple esters and beheneth-25 methacrylate, crosslinked with methylene bis-acrylamide	dispersing agents - nonsurfactant; skin-conditioning agents - miscellaneous; viscosity increasing agents - aqueous	NR
Homopolymers			
Poly(Methoxy PEG-9 Methacrylate)	the polymer that conforms generally to the formula: 	film formers; skin-conditioning agents - humectant; skin-conditioning agents - occlusive	NR
Polybutyl Acrylate	a polymer of n-butyl acrylate that conforms generally to the formula: 	binders; film formers	NR
Polybutyl Methacrylate	the homopolymer of butyl methacrylate	film formers	NR
Polyethylacrylate	the polymer of ethyl acrylate that conforms generally to the formula: 	binders; dispersing agents - nonsurfactant; film formers; hair fixatives	NR
Polyhydroxyethylmethacrylate	the organic compound that conforms to the formula: 	binders	NR
Polyisobutyl Methacrylate	the homopolymer of isobutyl methacrylate	film formers	NR

Definitions, Functions, and 2018 FOUof 65 previously unreviewed similar ingredients

Ingredient Name	Definition	Function(s)	FOU
Polymethyl Acrylate	the polymer that conforms to the formula: 	film formers	1
Polypropyl Methacrylate	the homopolymer of propyl acrylate	film formers	NR
Polystearyl Methacrylate	the polymer of stearyl methacrylate that conforms to the formula: 	film formers	NR
Sodium Polymethacrylate	the polymer that conforms generally to the formula: 	binders; emulsion stabilizers; film formers; viscosity increasing agents - aqueous	62
Esters			
Glyceryl Polymethacrylate	the ester of glycerin and polymethacrylic acid	film formers	337

Amended Report Published in 2002

Ingredient Name	Definition	Function(s)	FOU
Ethyl Methacrylate	the ester of ethyl alcohol and methacrylic acid. It conforms to the formula: 	artificial nail builders	12 (2018)/NR (1994)

Crosslinked Alkyl Acrylates (2017)

Acrylates/C10-30Alkyl Acrylate Crosspolymer
Acrylates/C12-13 Alkyl Methacrylates/Methoxyethyl Acrylate Crosspolymer
Acrylates Crosspolymer
Acrylates/Ethylhexyl Acrylate Crosspolymer
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer
Acrylates/PEG-4 Dimethacrylate Crosspolymer
Acrylates/Steareth-20 Methacrylate Crosspolymer
Acrylates/Vinyl Isodecanoate Crosspolymer
Acrylates/Vinyl Neodecanoate Crosspolymer
Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer
Allyl Methacrylates Crosspolymer
Butyl Acrylate/Glycol Dimethacrylate Crosspolymer
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer
Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer
Methacrylic Acid/PEG-6 Methacrylate/PEG-6 Dimethacrylate Crosspolymer
PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer
Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates Crosspolymer-2
Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer
Sodium Acrylates/Vinyl Isodecanoate Crosspolymer
Stearyl/Lauryl Methacrylate Crosspolymer

Crosslink Substance
allyl methacrylate
ethylene glycol diglycidyl ether
ethylene glycol dimethacrylate
glycol dimethacrylate
hexanediol diacrylate
PEG-4 dimethacrylate
PEG-6 dimethacrylate
polyalkenyl polyether
pentaerythritol, allyl ether
sucrose, allyl ether
triethylene glycol dimethacrylate
trimethylolpropane, allyl ether
vinyloxazoline

Definitions, Functions, and 2018/2011 Frequency of Use (FOU) of 23 crosslinked alkyl acrylates

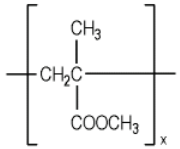
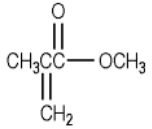
Ingredient Name	Definition	Function(s)	2018/2011 FOU
Acrylates/C10-30 Alkyl Acrylate Crosspolymer	a copolymer of C10-30 alkyl acrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with an allyl ether of sucrose or an allyl ether of pentaerythritol	emulsion stabilizers; viscosity increasing agents - aqueous; viscosity increasing agents - nonaqueous	**3161/1696**
Acrylates/C12-13 Alkyl Methacrylates/ Methoxyethyl Acrylate Crosspolymer	a copolymer of C12-13 alkyl methacrylates, methoxyethyl acrylate, and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with vinyloxazoline	hair fixatives	NR
Acrylates Crosspolymer	a copolymer of acrylic acid, methacrylic acid or one of its simple esters, crosslinked with glycol dimethacrylate	absorbents	5/2
Acrylates/Ethylhexyl Acrylate Crosspolymer	a copolymer of 2-ethylhexylacrylate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with ethylene glycol dimethacrylate	binders	3/NR
Acrylates/Ethylhexyl Acrylate/Glycidyl Methacrylate Crosspolymer	a copolymer of 2-ethylhexyl acrylate, glycidyl methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with triethylene glycol dimethacrylate	film formers	NR
Acrylates/PEG-4 Dimethacrylate Crosspolymer	a copolymer of one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked by PEG-4 dimethacrylate	film formers	NR
Acrylates/Steareth-20 Methacrylate Crosspolymer	a copolymer of steareth-20 methacrylate and one or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters, crosslinked with an allyl ether of pentaerythritol or an allyl ether of trimethylolpropane	dispersing agents - nonsurfactant; film formers	4/NR
Acrylates/Vinyl Isodecanoate Crosspolymer	a copolymer of the ester of vinyl isodecanoate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with polyalkenyl polyether	dispersing agents - nonsurfactant; emulsion stabilizers; viscosity increasing agents - aqueous	30/33
Acrylates/Vinyl Neodecanoate Crosspolymer	a copolymer of vinyl neodecanoate and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters crosslinked with an allyl ether of trimethylolpropane or pentaerythritol	emulsion stabilizers; film formers; viscosity increasing agents - aqueous	14/10
Allyl Methacrylate/Glycol Dimethacrylate Crosspolymer	a highly crosslinked polymer of allyl methacrylate and ethylene glycol dimethacrylate	oral care agents; skin protectants; skin-conditioning agents - emollient; skin-conditioning agents - miscellaneous	NR
Allyl Methacrylates Crosspolymer	a copolymer of allyl methacrylates crosslinked with glycol dimethacrylate	emulsion stabilizers; opacifying agents; viscosity increasing agents - nonaqueous	31/48
Butyl Acrylate/Glycol Dimethacrylate Crosspolymer	a homopolymer of butyl acrylate crosslinked with glycol dimethacrylate	absorbents; film formers	1
C8-22 Alkyl Acrylates/Methacrylic Acid Crosspolymer	a copolymer of C8-22 alkyl acrylate and methacrylic acid crosslinked with hexanediol diacrylate	film formers; hair fixatives; hair-waving/straightening agents	2
Glycol Dimethacrylate/Vinyl Alcohol Crosspolymer	a crosslinked copolymer of vinyl alcohol and glycol dimethacrylate	film formers	NR
Lauryl Methacrylate/Glycol Dimethacrylate Crosspolymer	a crosslinked copolymer of lauryl methacrylate and ethylene glycol dimethacrylate monomers	film formers; hair fixatives	99/63
Lauryl Methacrylate/Sodium Methacrylate Crosspolymer	a copolymer of lauryl methacrylate and sodium methacrylate crosslinked with ethylene glycol dimethacrylate	slip modifiers; surface modifiers	4/1
Methacrylic Acid/PEG-6 Methacrylate/PEG-6 Dimethacrylate Crosspolymer	a copolymer of methacrylic acid and PEG-6 methacrylate crosslinked with PEG-6 dimethacrylate	film formers	NR
PEG/PPG-5/2 Methacrylate/Methacrylic Acid Crosspolymer	copolymer of methacrylic acid and polyethylene glycol, polypropylene glycol methacrylate containing an average of 5 moles of ethylene oxide and 2 moles of propylene oxide, crosslinked with glycol dimethacrylate	film formers	NR
Potassium Acrylates/C10-30 Alkyl Acrylate Crosspolymer	the potassium salt of Acrylates/C10-30 Alkyl Acrylate Crosspolymer	film formers	2
Sodium Acrylates Crosspolymer-2	the sodium salt of a copolymer of acrylic acid, methacrylic acid or one or more of its simple esters crosslinked with ethylene glycol diglycidyl ether	absorbents	NR
Sodium Acrylates/C10-30 Alkyl Acrylate Crosspolymer	the sodium salt of Acrylates/C10-30 Alkyl Acrylate Crosspolymer	film formers	96/6

Definitions, Functions, and 2018/2011 Frequency of Use (FOU) of 23 crosslinked alkyl acrylates

Ingredient Name	Definition	Function(s)	2018/2011 FOU
Sodium Acrylates/Vinyl Isodecanoate Crosspolymer	the sodium salt of Acrylates/Vinyl Isodecanoate Crosspolymer	dispersing agents - nonsurfactant; emulsion stabilizers; viscosity increasing agents - aqueous	NR
Stearyl/Lauryl Methacrylate Crosspolymer	a copolymer of stearyl methacrylate and lauryl methacrylate crosslinked with ethylene glycol dimethacrylate	skin-conditioning agents - miscellaneous	NR

Polymethyl Methacrylate
Methyl Methacrylate Crosspolymer
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer

Definitions, Functions, and 2018/2008 Frequency of Use (FOU)

Ingredient Name	Definition	Function(s)	2018/2008 FOU
Polymethyl Methacrylate	the polymer of methyl methacrylate that conforms to the formula: 	Bulking Agents; Film Formers	922/892
Methyl Methacrylate Crosspolymer	the organic compound that conforms to the formula:  Methyl Methacrylate is included in the INCI database as a reference for the definition of other INCI Names, and might not be a marketed cosmetic ingredient.	Anticaking Agents; Artificial Nail Builders; Dispersing Agents - Nonsurfactant; Opacifying Agents	422/144
Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer	a crosslinked copolymer of methyl methacrylate and ethylene glycol dimethacrylate monomers	Film Formers	38/7

Carbomers (1982)

Names used in 1982, all now technical names for "Carbomer"

Carbomer-934
Carbomer-910
Carbomer-934P
Carbomer-940
Carbomer-941
Carbomer-962

Possible Crosslinking Agents

allyl ether of pentaerythritol
allyl ether of sucrose
allyl ether of propylene

Definition, Function, and 2018 FOU

Ingredient Name	Definition	Function(s)	FOU
Carbomer	a homopolymer of acrylic acid crosslinked with an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene	emulsion stabilizers; viscosity increasing agents - aqueous	6441

Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients[1,2]

Ingredients in the Acrylates Copolymer group all contain the monomers acrylic acid or methacrylic acid or one of their salts or esters. These ingredients are considered similar in that they are uniformly produced in chemical reactions that leave very little residual monomer. Although residual acrylic acid may be as high as 1500 ppm, typical levels are 10 to 1000 ppm. There is sufficient odor if residual monomers are present to cause producers to keep levels as low as possible. These ingredients function in cosmetics as binders, film formers, hair fixatives, suspending agents, viscosity-increasing agents, and emulsion stabilizers. Concentrations may be as high as 25% if used as a binder, film former, or fixative; or as low as 0.5% if used as a viscosity-increasing agent, suspending agent, or emulsion stabilizer. These very large polymers exhibit little toxicity. In rabbits and guinea pigs, Acrylates Copolymer did produce irritation, but no evidence of sensitization was found. The principle concern regarding the use of these polymer ingredients is the presence of toxic residual monomers. In particular, although 2-ethylhexyl acrylate was not genotoxic, it was carcinogenic when applied at a concentration of 21% to the skin of C3H mice. Lower concentrations (2.5%) and stop-dose studies at high concentrations (43%) were not carcinogenic. 2-Ethylhexyl acrylate was not carcinogenic in studies using NMRI mice. Whether an increase in carcinogenesis was seen or not, there was evidence of severe dermal irritation in these 2-ethylhexyl acrylate studies. Another concern regarding residual monomers was inhalation toxicity. Although the acrylic acid monomer is a nasal irritant, exposure to the monomer from use of these polymers in cosmetic formulations would always be less than the established occupational exposure limits for nasal irritation. Although there appears to be a huge variation in the mix of monomers used in the synthesis of these polymers, they are similar in that the polymers, except for dermal irritation, are not significantly toxic, and residual monomer levels are kept as low as possible. Although the monomers may be toxic, the levels that would be found in cosmetic formulations are not considered to present a safety risk. Accordingly, these Acrylate Copolymers are considered safe for use in cosmetic formulations when formulated to avoid irritation.

Received 27 March 2002; accepted 25 June 2002.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Monice Zondlo Fiume, former Scientific Analyst. Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

[2]Related Cosmetic Ingredients: Ammonium Acrylates Copolymer, Ammonium VA/Acrylates Copolymer, Sodium Acrylates Copolymer, Ethylene/Acrylic Acid Copolymer, Ethylene/Calcium Acrylate Copolymer, Ethylene/Magnesium Acrylate Copolymer, Ethylene/Sodium Acrylate Copolymer, Ethylene/Zinc Acrylate Copolymer, Ethylene/Acrylic Acid/VA Copolymer, Acrylates/PVP Copolymer, Acrylates/VA Copolymer, Steareth-10 Allyl Ether/Acrylates Copolymer, Acrylates/Steareth-50 Acrylate Copolymer, Acrylates/Steareth-20 Methacrylate Copolymer, Acrylates/Ammonium Methacrylate Copolymer, Styrene/Acrylates Copolymer, Styrene/Acrylates/Ammonium Methacrylate Copolymer, Ammonium Styrene/Acrylates Copolymer, Sodium Styrene/Acrylates Copolymer, Acrylates/Hydroxyesters Acrylates Copolymer, Methacryloyl Ethyl Betaine/Acrylates Copolymer, Lauryl Acrylate/VA Copolymer, VA/Butyl Maleate/Isobornyl Acrylate Copolymer, Ethylene/Methacrylate Copolymer, Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer, Sodium Acrylates/Acrolein Copolymer, PVP/Dimethylaminoethylmethacrylate Copolymer, AMP-Acrylates Copolymer, Polyacrylic Acid, Ammonium Polyacrylate, Potassium Aluminum Polyacrylate, Potassium Polyacrylate, Sodium Polyacrylate.

INTRODUCTION

This report covers a large number of polymers that contain the monomers acrylic acid or methacrylic acid or one of their salts or esters. Table 1 lists each of the ingredients along with the monomers that are polymerized to create the copolymer.

Some of these monomers have previously been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel, namely, PVP (polyvinyl pyrrolidone), steareth-10, steareth-20, and polymers containing VA (vinyl acetate), which are components of some of the copolymers included in this safety assessment. Significant toxicity issues regarding these ingredients were not found, and it was concluded that PVP (Andersen 1998), steareth-10 and steareth-20 (Elder 1988), PVP/VA copolymer (Elder 1983a), and VA/CA (vinyl acetate/crotonic acid) copolymer (Elder 1983b) were safe as used as cosmetic ingredients.

Ethyl methacrylate also has been reviewed by the CIR Expert Panel (Andersen 1995; CIR 1999). In an amended final safety assessment based on the available data on the formulation of nail products containing Ethyl Methacrylate, this ingredient was found safe as used when application is accompanied by directions to avoid skin contact because of the sensitizing potential of Ethyl Methacrylate.

Because acrylic acid is a major component of most, if not all, of the copolymers included in this review, relevant data on acrylic acid and some of its esters are summarized where applicable.

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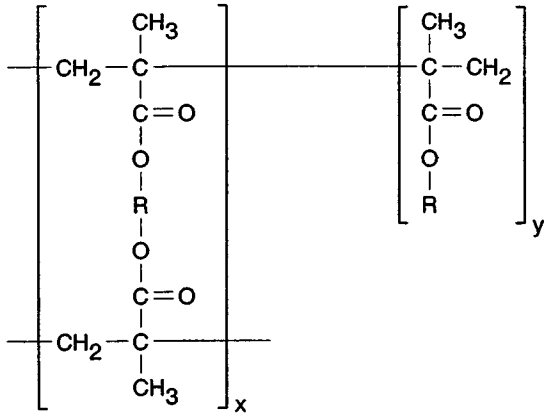
TABLE 1
Ingredients descriptions (Wenninger, Canterbery, and McEwen 2000)

Ingredient	Components
Acrylates Copolymer	Two or more of acrylic acid, methacrylic acid, or one of their simple esters
Ammonium Acrylates Copolymer	Two or more of acrylic acid, methacrylic acid, or one of their simple esters
Ammonium VA/Acrylates Copolymer	Vinyl acetate and two or more of acrylic acid, methacrylic acid, or one of their simple esters
Sodium Acrylates Copolymer	One or more of acrylic acid, methacrylic acid, or one of their simple esters
Ethylene/Acrylic Acid Copolymer	Ethylene and acrylic acid
Ethylene/Calcium Acrylate Copolymer	Ethylene and calcium acrylate
Ethylene/Magnesium Acrylate Copolymer	Ethylene and magnesium acrylate
Ethylene/Sodium Acrylate Copolymer	Ethylene and sodium acrylate
Ethylene/Zinc Acrylate Copolymer	Ethylene and zinc acrylate
Ethylene/Acrylic Acid/VA Copolymer	Ethylene, acrylic acid and vinyl acetate
Acrylates/PVP Copolymer	PVP and one or more of acrylic acid, methacrylic acid, or one of their simple esters
Acrylates/VA Copolymer	Vinyl acetate and one or more of acrylic acid, methacrylic acid, and one of their simple esters (contains 2-ethylhexyl acrylate)
Steareth-10 Allyl Ether/Acrylates Copolymer	Allyl ether of steareth-10 and one or more of acrylic acid, methacrylic acid, or one of their simple esters
Acrylates/Steareth-50 Acrylate Copolymer	Ester of acrylic acid and one or more of steareth-50 and acrylic acid, methacrylic acid, or one of their simple esters
Acrylates/Steareth-20 Methacrylate Copolymer	Ester of methacrylic acid and steareth-20 and one or more of acrylic acid, methacrylic acid, or one of their simple esters
Acrylates/Ammonium Methacrylate Copolymer	Ammonium methacrylate and one or more of acrylic acid, methacrylic acid, or one of their simple esters
Styrene/Acrylates Copolymer	Styrene, acrylic acid, methacrylic acid, or one or their simple esters
Styrene/Acrylates/Ammonium Methacrylate Copolymer	Styrene, ammonium methacrylate, and acrylic acid, methacrylic acid, or one of their simple esters
Ammonium Styrene/Acrylates Copolymer	Styrene and acrylic acid, methacrylic acid, or one of their simple esters
Sodium Styrene/Acrylates Copolymer	Styrene and acrylic acid, methacrylic acid, or one of their simple esters
Acrylates/Hydroxyesters Acrylates Copolymer	One or more of acrylic acid, methacrylic acid, or one of their simple esters and one or more of hydroxyacrylate esters
Methacryloyl Ethyl Betaine/Acrylates Copolymer	Methacryloyl ethyl betaine and two or more of methacrylic acid or its simple esters
Lauryl Acrylate/VA Copolymer	Lauryl acrylate and vinyl acetate
VA/Butyl Maleate/Isobornyl Acrylate Copolymer	Vinyl acetate, butyl maleate, and isobornyl acrylate
Ethylene/Methacrylate Copolymer	Ethylene and methyl methacrylate
Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer	Vinylcaprolactam, vinylpyrrolidone, and dimethylaminoethyl methacrylate
Sodium Acrylates/Acrolein Copolymer	Sodium acrylate and acrolein
PVP/Dimethylaminoethylmethacrylate Copolymer	Vinylpyrrolidone and dimethylaminoethylmethacrylate
AMP-Acrylates Copolymer	Aminomethyl propanol salt of Acrylates Copolymer
Polyacrylic Acid	Acrylic acid
Ammonium Polyacrylate	Acrylic acid
Potassium Aluminum Polyacrylate	Acrylic acid
Potassium Polyacrylate	Acrylic acid
Sodium Polyacrylate	Acrylic acid

CHEMISTRY

Definition and Structure

Acrylates Copolymer. Acrylates Copolymer is a copolymer of two or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000) and has the basic chemical structure (Klein and DeSapio 1989) shown below.



Acrylates Copolymer

The smallest, or primary, units of Acrylates Copolymer are individual particles <1 μ in diameter which partially fuse to form agglomerates ranging in size from approximately 20–80 μ; agglomerates are held together by electrostatic forces and mechanical entanglement to form larger aggregates of 200–1200 μ (Klein and DiSapio 1989).

Acrylates Copolymer is also known as Acrylic/Acrylate Copolymer and Acrylic/Acrylates Copolymer (Wenninger, Canterbery, and McEwen 2000).

Ammonium Acrylates Copolymer. Ammonium Acrylates Copolymer is the ammonium salt of a polymer of two or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000).

Ammonium VA/Acrylates Copolymer. Ammonium VA/Acrylates Copolymer is the ammonium salt of a polymer of vinyl acetate and two or more monomers consisting of acrylic acid, methacrylic acid, or their simple esters (Wenninger, Canterbery, and McEwen 2000). It is also known as Ammonium Vinyl Acetate/Acrylates Copolymer.

Sodium Acrylates Copolymer. Sodium Acrylates Copolymer is the sodium salt of a polymer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000).

Ethylene/Acrylic Acid Copolymer. Ethylene/Acrylic Acid Copolymer (CAS No. 9010-77-9) is a copolymer of ethylene and acrylic acid monomers (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid with Ethene (Wenninger, Canterbery, and McEwen 2000); 2-Propenoic Acid, Polymer with Ethene; Acrylic Acid, Polymer with Ethene; Ethylene Acrylic Acid (Chemline 1996); Acrylic Acid, Polymer with Ethylene; Acrylic Acid Copolymer with Ethylene; Acrylic Acid-Ethene Copolymer; Acrylic Acid-Ethylene Copolymer; Acrylic Acid-Ethylene Polymer; and Acrylic Acid-Polyethylene Polymer (Chemical Abstracts 1996).

Ethylene/Calcium Acrylate Copolymer. Ethylene/Calcium Acrylate Copolymer (CAS No. 26445-96-5) is a copolymer of ethylene and calcium acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot x$Ca (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Calcium Salt (Wenninger, Canterbery, and McEwen 2000); Acrylic Acid, Polymer with Ethylene, Calcium Salt (Chemline 1996); Ethene, Polymer with 2-Propenoic Acid, Calcium Salt; Ethylene, Polymer with Acrylic Acid, Calcium Salt; Acrylic Acid-Ethylene Copolymer Calcium Salt (Chemical Abstracts 1996).

Ethylene/Magnesium Acrylate Copolymer. Ethylene/Magnesium Acrylate Copolymer is a copolymer of ethylene and magnesium acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot x$Mg (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Magnesium Salt.

Ethylene/Sodium Acrylate Copolymer. Ethylene/Sodium Acrylate Copolymer (CAS No. 25750-82-7) is a copolymer of ethylene and sodium acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot x$Na (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Sodium Salt (Wenninger, Canterbery, and McEwen 2000); Acrylic Acid, Polymer with Ethylene, Sodium Salt (Chemline 1996); Ethene, Polymer with 2-Propenoic Acid, Sodium Salt; Ethylene, Polymer with Acrylic Acid, Sodium Salt; Acrylic Acid-Ethylene Copolymer Sodium Salt; Acrylic Acid-Ethylene Polymer Sodium Salt; and Ethylene-Acrylic Acid Polymer Sodium Salt (Chemical Abstracts 1996).

Ethylene/Zinc Acrylate Copolymer. Ethylene/Zinc Acrylate Copolymer (CAS No. 59650-68-9; Chemical Abstracts 1996) is a copolymer of ethylene and zinc acrylate monomers and has the empirical formula $(C_3H_4O_2 \cdot C_2H_4)_x \cdot x$Zn (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Zinc Salt (Wenninger, Canterbery, and McEwen 2000); 2-Propenoic Acid, Zinc Salt, Polymer with Ethene; and Ethene, Polymer with Zinc Di-2-Propenoate (Chemical Abstracts 1996).

Ethylene/Acrylic Acid/VA Copolymer. Ethylene/Acrylic Acid/VA Copolymer (CAS No. 26713-18-8) is a copolymer of ethylene, acrylic acid, and vinyl acetate monomers (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene and Ethenyl Acetate (Wenninger, Canterbery, and McEwen 2000); Acrylic Acid, Polymer with Ethylene and Vinyl Acetate (Chemline 1996); Ethylene, Polymer with Acrylic Acid and Vinyl Acetate; Ethylene-Acrylic Acid-Vinyl Acetate Copolymer; Ethylene-Acrylic Acid-Vinyl

Acetate Polymer; Ethylene-Vinyl Acetate-Acrylic Acid Copolymer; Ethylene-Vinyl Acetate-Acrylic Acid Polymer; Acrylic Acid-Ethylene-Vinyl Acetate Copolymer; Acrylic Acid-Ethylene-Vinyl Acetate Polymer; Acrylic Acid-Ethylene-Vinyl Acetate Terpolymer; Ethene, Polymer with Ethenyl Acetate and 2-Propenoic Acid; Acetic Acid Ethenyl Ester, Polymer with Ethene and Ethenyl Acetate; and Acetic Acid Vinyl Ester, Polymer with Acrylic Acid and Ethylene (Chemical Abstracts 1996).

Acrylates/PVP Copolymer. Acrylates/PVP Copolymer (CAS No. 26589-26-4) is a copolymer of PVP and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000). It is also known as Methacrylic Acid, Polymer with Ethyl Methacrylate and 1-Vinyl-2-Pyrrolidinone; PVP/Ethyl Methacrylate/Methacrylic Acid Copolymer (Wenninger, Canterbery, and McEwen 2000); 2-Propenoic Acid, 2-Methyl, Polymer with 1-Ethenyl-2-Pyrrolidinone and Ethyl 2-Methyl-2-Propenoate; *N*-Vinyl-2-Pyrrolidone, Methacrylic Acid, Ethyl Methacrylate Polymer; 1-Ethylene-2-Pyrrolidinone, Methacrylic Acid, Ethyl Methacrylate Polymer (Chemline 1996); 2-Propenoic Acid, 2-Methyl-, Ethyl Ester, Polymer with 1-Ethenyl-2-Pyrrolidinone and 2-Methyl-2-Propenoic Acid; 2-Pyrrolidinone, 1-Ethenyl-, Polymer with Ethyl 2-Methyl-2-Propenoate and 2-Methyl-2-Propenoic Acid; 2-Pyrrolidinone, 1-Vinyl-, Polymer with Ethyl Methacrylate and Methacrylic Acid; and Methacrylic Acid, Ethyl Ester, Polymer with Methacrylic Acid and 1-Vinyl-2-Pyrrolidinone (Chemical Abstracts 1996).

Acrylates/VA Copolymer. Acrylates/VA Copolymer (CAS No. 25067-02-1) is a copolymer of vinyl acetate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger et al. 2000). It is also known as 2-Propenoic Acid, 2-Ethylhexyl Ester, Polymer with Ethenyl Acetate; Vinyl Acetate/Acrylate Copolymer; Vinyl Acetate, 2-Ethylhexyl Acrylate Copolymer (Wenninger, Canterbery, and McEwen 2000); Acrylic Acid, 2-Ethylhexyl Ester, Polymer with Vinyl Acetate; Poly(Vinyl Acetate-2-Ethylhexyl Acrylate) (Chemline 1996); 2-Ethylhexyl Acrylate-Vinyl Acetate Copolymer; 2-Ethylhexyl Acrylate-Vinyl Acetate Polymer; Vinyl Acetate-2-Ethylhexyl Acrylate Copolymer; Acetic Acid Vinyl Ester, Polymer with 2-Ethylhexyl Acrylate; and Acetic Acid Ethenyl Ester, Polymer with 2-Ethylhexyl 2-Propenoate (Chemical Abstracts 1996).

Steareth-10 Allyl Ether/Acrylates Copolymer. Steareth-10 Allyl Ether/Acrylates Copolymer (CAS No. 109292-17-3) is a copolymer of the allyl ether of Steareth-10 (q.v.) and one or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000). *Quantum vis* (q.v.) translates to "as much as you please."

Acrylates/Steareth-50 Acrylate Copolymer. Acrylates/Steareth-50 Acrylate Copolymer is a copolymer of the ester of acrylic acid and Steareth-50 (q.v.) and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000).

Acrylates/Steareth-20 Methacrylate Copolymer. Acrylates/Steareth-20 Methacrylate Copolymer is a copolymer of the ester of methacrylic acid and Steareth-20 (q.v.) and one or more monomers of acrylic acid, methacrylic acid, or one their simple esters (Wenninger, Canterbery, and McEwen 2000).

Acrylates/Ammonium Methacrylate Copolymer. Acrylates/Ammonium Methacrylate Copolymer is a copolymer of ammonium methacrylate and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000). It is also known as Acrylate/Ammonium Methacrylate Copolymer.

Styrene/Acrylates Copolymer. Styrene/Acrylates Copolymer (CAS No. 9010-92-8) is a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid, Butyl Ester, Polymer with Ethylbenzene and Styrene/Acrylate Copolymer.

Styrene/Acrylates/Ammonium Methacrylate Copolymer. Styrene/Acrylates/Ammonium Methacrylate Copolymer is a polymer of styrene, ammonium methacrylate, and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000). It is also known as Styrene/Acrylate/Ammonium Methacrylate Copolymer.

Ammonium Styrene/Acrylates Copolymer. Ammonium Styrene/Acrylates Copolymer is the ammonium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000).

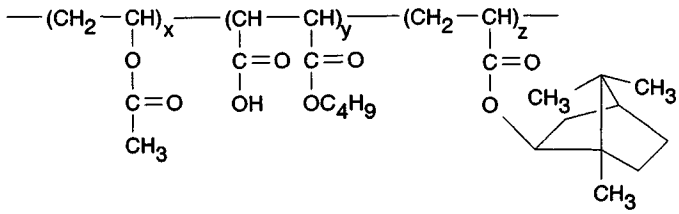
Sodium Styrene/Acrylates Copolymer. Sodium Styrene/Acrylates Copolymer (CAS No. 9010-92-8) is the sodium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000).

Acrylates/Hydroxyesters Acrylates Copolymer. Acrylates/Hydroxyesters Acrylates Copolymer is a copolymer of one or more monomers consisting of acrylic acid, methacrylic acid, or their simple esters, and one or more monomers of hydroxyacrylate esters (Wenninger, Canterbery, and McEwen 2000).

Methacryloyl Ethyl Betaine/Acrylates Copolymer. Methacryloyl Ethyl Betaine/Acrylates Copolymer is a polymer of methacryloyl ethyl betaine and two or more monomers of methacrylic acid or its simple esters (Wenninger, Canterbery, and McEwen 2000). It is also known as Methacryloyl Ethyl Betaine/Methacrylates Copolymer.

Lauryl Acrylate/VA Copolymer. Lauryl Acrylate/VA Copolymer is a copolymer of lauryl acrylate and vinyl acetate monomers (Wenninger, Canterbery, and McEwen 2000).

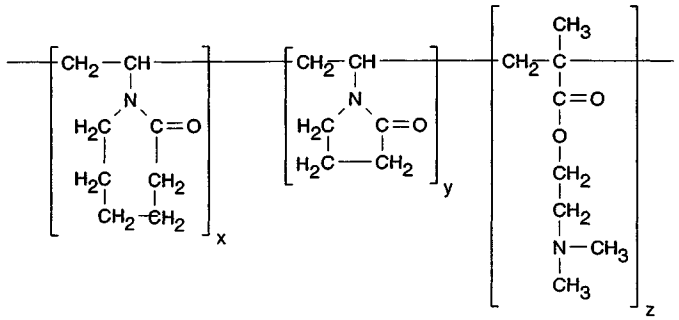
VA/Butyl Maleate/Isobornyl Acrylate Copolymer. VA/Butyl Maleate/Isobornyl Acrylate Copolymer is a copolymer of vinyl acetate, butyl maleate, and isobornyl acrylate monomers (Wenninger, Canterbery, and McEwen 2000) and has the following structure (Patel and Petter 1992):



VA/Butyl Maleate/Isobornyl Acrylate Copolymer

Ethylene/Methacrylate Copolymer. Ethylene/Methacrylate Copolymer is a copolymer of ethylene and methyl methacrylate monomers (Wenninger, Canterbery, and McEwen 2000).

Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer. Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer is a copolymer of vinylcaprolactam, vinylpyrrolidone, and dimethylaminoethyl methacrylate (q.v.) monomers (Wenninger, Canterbery, and McEwen 2000) and has the following chemical structure (Patel and Petter 1992):



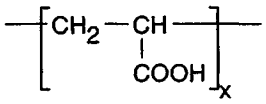
Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer

Sodium Acrylates/Acrolein Copolymer. Sodium Acrylates/Acrolein Copolymer is a polymer consisting of sodium acrylate and acrolein monomers (Wenninger, Canterbery, and McEwen 2000).

PVP/Dimethylaminoethylmethacrylate Copolymer. PVP/Dimethylaminoethylmethacrylate Copolymer (CAS No. 30581-59-0) is a polymer prepared from vinylpyrrolidone and dimethylaminoethylmethacrylate monomers (Wenninger, Canterbery, and McEwen 2000). It is also known as 2-Propenoic Acid, 2-Methyl-, 2-(Dimethylamino)Ethyl Ester, Polymer with 1-Ethenyl-2-Pyrrolidinone (Wenninger, Canterbery, and McEwen 2000); Methacrylic Acid, 2-(Dimethylamino)Ethyl Ester, Polymer with 1-Vinyl-2-Pyrrolidinone (Chemline 1996); 2-Pyrrolidinone, 1-Ethenyl-, Polymer with 2-(Dimethylamino)-Ethyl 2-Methyl-2-Propenoate; 2-Pyrrolidinone, 1-Vinyl-, Polymer with 2-(Dimethylamino)Ethylmethacrylate; Dimethylaminoethyl Methacrylate-*N*-Vinylpyrrolidinone Copolymer; Dimethylaminoethyl Methacrylate-*N*-Vinylpyrrolidone Copolymer; Dimethylaminoethyl Methacrylate-Vinylpyrrolidone Copolymer; *N,N*-Dimethylaminoethyl Methacrylate-*N*-Vinylpyrrolidone Copolymer; *N,N*-Dimethylaminoethyl Methacrylate-Vinylpyrrolidone Copolymer; 2-(Dimethylamino)-Ethyl Methacrylate-*N*-Vinyl-2-Pyrrolidinone Copolymer; 2-(Dimethylamino)Ethyl Methacrylate-*N*-Vinyl-2-Pyrrolidone Copolymer; 2-(Dimethylamino)Ethyl Methacrylate-*N*-Vinylpyrrolidinone Copolymer; *N*-Vinylpyrrolidinone-Dimethylaminoethyl Methacrylate Polymer; and *N*-Vinylpyrrolidone-Dimethylaminoethyl Methacrylate Copolymer (Chemical Abstracts 1996).

AMP-Acrylates Copolymer. AMP-Acrylates Copolymer is the aminomethyl propanol salt of Acrylates Copolymer (q.v.) (Wenninger, Canterbery, and McEwen 2000).

Polyacrylic Acid. Polyacrylic Acid (CAS No. 9003-01-4) is the polymer of acrylic acid that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Polyacrylic Acid

Polyacrylic Acid is also known as 2-Propenoic Acid, Homopolymer (International Agency for Research on Cancer [IARC] 1979; Wenninger, Canterbery, and McEwen 2000; Registry of the Toxic Effects of Chemical Substances [RTECS] 1996); Acrylic Acid Homopolymer; Acrylic Acid Polymer; Acrylic Acid Resin; Acrylic Polymer; Acrylic Resin; Atactic Poly(Acrylic) Acid; Polyacrylate; Poly(Acrylic Acid) (IARC 1979; RTECS 1996); Acrylic Acid, Polymers (RTECS 1996); Propenoic Acid Polymer (Chemline 1996); and Carboxypolymethylene (Chemical Abstracts 1996).

Ammonium Polyacrylate. Ammonium Polyacrylate (CAS No. 9003-03-6) is the ammonium salt of Polyacrylic Acid (q.v.) and has the empirical formula $(C_3H_4O_2)_x \cdot xH_3N$ (Wenninger, Canterbery, and McEwen 2000). It is also known as Poly(Acrylic Acid), Ammonium Salt; 2-Propenoic Acid, Homopolymer, Ammonium Salt (Wenninger, Canterbery, and McEwen 2000) Acrylic Acid, Polymers, Ammonium Salt; and Ammonium Homopolymer, 2-Propenoate (Chemline 1996).

Potassium Aluminum Polyacrylate. Potassium Aluminum Polyacrylate is a mixture of the potassium and aluminum salts of Polyacrylic Acid (q.v.) (Wenninger, Canterbery, and McEwen 2000).

Potassium Polyacrylate. Potassium Polyacrylate (CAS No. 25608-12-2) is the potassium salt of Polyacrylic Acid (q.v.) and has the empirical formula $(C_3H_4O_2)_x \cdot xK$ (Wenninger, Canterbery, and McEwen 2000). It is also known as Polyacrylic Acid, Potassium Salt (Wenninger, Canterbery, and McEwen 2000); 2-Propenoic Acid, Homopolymer, Potassium Salt; Acrylic Acid, Polymers, Potassium Salt; and Potassium Homopolymer, 2-Propenoate;(Chemline 1996).

Sodium Polyacrylate. Sodium Polyacrylate (CAS No. 9003-04-7) is the sodium salt of Polyacrylic Acid and has the empirical formula $(C_3H_4O_2)_x \cdot xNa$ (Wenninger, Canterbery, and McEwen 2000). It is also known as Polyacrylic Acid, Sodium Salt; 2-Propenoic Acid, Homopolymer, Sodium Salt (Wenninger,

Canterbery, and McEwen 2000); Acrylic Acid, Polymers, Sodium Salt; Sodium Homopolymer, and 2-Propenoate; Propenoic Acid (Chemline 1996).

Physical and Chemical Properties

Acrylates Copolymer. As manufactured by one company, Acrylates Copolymer is a white, mobile liquid with a slightly acrylic odor that is 30% solids and has a pH 3.0 (Allied Colloids 1997). It has a specific gravity of 1.05 g/cm^3 (25°C), viscosity as supplied of 50 cPs (25°C), and a viscosity, 3.33% aqueous solution, of 10,000 cPs. Another company reported that different Acrylates Copolymers may appear as a hazy solution, clear solution, milky white dispersion, clear viscous liquid, or white granules (BFGoodrich Specialty Chemicals 1997). These Acrylates Copolymers, which exist as 29% to 100% solids, have molecular weights of 5000 to 210,000 Da, pH of 6.7 to 8.0, specific gravity of 1.04 to 1.2, acid number of 60 or 65, and viscosity of 10 to 2,000,000 cP. A third company reported it manufactures Acrylates Copolymer as a copolymer of ethyl acrylate, methyl methacrylate, methacrylic acid, and acrylic acid that is a solution consisting of 25% solids (Amerchol 1997). A sample of Acrylates Copolymer (approximately 24% solids) was miscible in water, had a freezing point of 0°C, a melting point of 99.9°C, and a vapor pressure of 18.4 mm Hg at 20°C (Bushy Run Research Center 1993a).

Ammonium Acrylates Copolymer. Ammonium Acrylates Copolymer, as manufactured by one company, is produced as a 30% solution in propylene glycol (5%) and water (65%) at a pH of 7.5 (Allied Colloids 1997). This product is a colorless, clear to slightly translucent liquid with a slight acrylic odor. It has an acid value of 19.0 and a density of 1.0 g/cm^3 (20°C).

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate, a component of Acrylates/VA Copolymer, has a reported octanol/water partition coefficient of 3.67 or 4.32 (IARC 1994).

VA/Butyl Maleate/Isobornyl Acrylate Copolymer. VA/Butyl Maleate/Isobornyl Acrylate Copolymer, supplied as a 50% solution in ethanol, is a clear, pale yellow solution at 25°C that consists of 48% to 52% solids (Patel and Petter 1992). It has a pH of 4.5 to 5.5, an acid number (mg KOH/g solid) of 170 to 190, a K-value (1% solids *w/v* in ethanol) of 33 to 39, and a Brookfield viscosity (25°C) of 2.500 to 3.000 cps.

Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer. Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer is a fine, white powder that has a moisture content of 2% maximum and a relative viscosity of 1.45 to 1.75 (25°C) (Patel and Petter 1992). It is soluble in water and alcohol and is compatible with hydrocarbon propellants.

Polyacrylic Acid. Polyacrylic Acid is a clear, brittle, hygroscopic solid that has a molecular weight of 10,000 to 800,000 and a melting point of 106°C (glass-transition temperature) (Miller 1964). Polyacrylic Acid is soluble in water (deliquescent), dioxane, dimethylformamide, ethanol, methanol, and isopropanol and it is insoluble in ether, benzene, and cyclohexane.

Manufacture and Production

Linear polymers of acrylic acid are produced by combining the monomer with a free-radical initiator, usually an azo compound or peroxide, which is largely consumed by the reaction (Thompson, Aardema, and LeBoeuf 1989); azo compounds as an initiator are no longer used in the personal care industry (Cottrell, personal communication). The size of the polymer is determined by controlling the environment in which the polymerization occurs. Polymers of acrylic acid are characterized by their average molecular weight, but many species of greater and lesser molecular weight are present and unreacted monomer and catalysts can also be present.

Hydroquinone and monomethyl ether of hydroquinone are incorporated into acrylic acid and its esters and used as inhibitors to prevent spontaneous polymerization during shipping or storage (Union Carbide Chemical Co. 1998a). The acrylate esters normally have the inhibitors removed prior to polymerization. Acrylic esters and acrylic acid can be polymerized and copolymerized in four ways, by emulsion, suspension, solvent, or bulk polymerization (Union Carbide Chemical Co. 1998a). Emulsion polymerization of acrylates, the most widely used method, produces high-molecular-weight products and solvent polymerization produces lower molecular weight polymers. Bulk polymerization is used mainly for the manufacture of casting and molding resins.

Acrylates Copolymer. One company manufactures Acrylates Copolymer by emulsion polymerization in an aqueous medium (Allied Colloids 1997). It is produced as 30% solids at a pH of 3.0.

Ammonium Acrylates Copolymer. One company manufactures Ammonium Acrylates Copolymer by solution polymerization (Allied Colloids 1997). It is produced as a 30% solution in propylene glycol (5%) and water (65%), at a pH of 7.5.

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is used almost exclusively as a chemical intermediate in the manufacture of polymeric chemicals (Tyler 1993). Commercially, the most important reaction of 2-ethylhexyl acrylate is polymerization through a free-radical mechanism, with resulting formation of a variety of polymer types. Biologically important is the Michael addition reaction, i.e., the nucleophilic addition of a compound with an active hydrogen across the double bond. Thus, 2-ethylhexyl acrylate has the potential to react under physiological conditions with biologically important chemicals, such as glutathione (GSH) and possibly nucleic acids.

Polyacrylic Acid. Polyacrylic Acid is produced commercially by polymerizing an aqueous solution of $\leq$25% acrylic acid at 90°C to 100°C in the presence of a peroxydisulfate initiator or at 60°C using redox initiators, that is, a combination of potassium peroxydisulfate and potassium metabisulfite (Miller 1964). Production of polyacrylates is $>$1 million tons per year (Thompson, Aardema, and LeBoeuf 1989).

Sodium Polyacrylate. Sodium Polyacrylate is produced by the polymerization of acrylic acid and subsequent hydrolysis of

the Polyacrylic Acid with an aqueous sodium hydroxide solution (Rothschild 1991).

Analytical Methods

Acrylates Copolymer. Acrylates Copolymer was analyzed using gas chromatography (GC) (Chemir/Polytech Laboratories, Inc. 1996).

Polyacrylic Acid. Polyacrylic Acid can be determined by pyrolysis-GC (Szocik, Szelejewska, and Linkiewicz 1970), differential thermal analysis (Concilio and Jahnke 1972), conductometric titration of aqueous solutions (Crisp, Lewis, and Wilson 1975), and by a turbidimetric method for concentrations in the range of 5 to 40 mg/kg (ppm) (Wimberley and Jordan 1971).

Ultraviolet Absorbance

Ethylene/Acrylic Acid Copolymer. The ultraviolet (UV) absorption spectra of a low-molecular-weight formula of an Ethylene/Acrylic Acid Copolymer in *n*-hexane was determined (Food and Drug Administration [FDA] 1998a). The spectrum had a "broad background absorption, increasing in intensity toward shorter wavelengths with weak superimposed maxima near 256 and 280 microns. The absorption near 280 [microns] could be attributable to Ionol [not defined], since the copolymer contains 150 ppm Ionol."

Published data on the UV absorbance of the other ingredients included in this review were not found.

Impurities

Linear polymers of acrylic acid may contain unreacted starting material and catalysts (Thompson, Aardema, and LeBoeuf 1989). The Emulsion Polymers Council, Inc. (EPC) submitted the response of 10 companies to a survey regarding the amount of residual acrylic acid in polymers sold for cosmetic use; residual concentrations are "typically between 10 to 1000 ppm with an upper limit of 1500 ppm" (EPC 1999). The EPC felt that the responding companies represented the majority of the production of acrylate polymers sold for cosmetic use.

Acrylates Copolymer. Using GC with two runs per sample, three samples of Acrylates Copolymer had the following amounts of residual monomer: <0.2 ppm (below the limit of detection) to 0.8 ppm acrylic acid; 0.8 to 2.6 ppm methyl methacrylate; 1.3 to 3.9 ppm ethylene glycol dimethacrylate (Chemir/Polytech Laboratories, Inc. 1996).

A company reported that in its production of Acrylates Copolymer it controls impurities in the form of residual, unreacted monomer, i.e., ethyl acrylate, methyl methacrylate, methacrylic acid, and acrylic acid, to ≤20 ppm (Amerchol 1997).

Additional information submitted to CIR gave residual monomer information for two polymers, both defined as Acrylates Copolymer. In the first, the residual monomer concentrations were 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively (CTFA 1999a). In the second polymer, the residual monomer concentrations were 1500 ppm stearyl acrylate and 200 ppm methacrylic acid (CTFA 1999b).

Acrylates/VA Copolymer. Two polymer producers reported that Acrylates/VA Copolymer contains <100 to 1000 ppm residual 2-ethylhexyl acrylate (Basic Acrylic Monomer Manufacturers [BAMM] 1999). The residual concentrations are dependent on the end-use application of the product. However, the 10 respondents of the survey by the EPC reported that they did not produce acrylate polymers with 2-ethylhexyl acrylate for use in the cosmetic industry (EPC 1999).

"Very low residual quantities of free monomer [2-ethylhexyl acrylate]" remain in pressure-sensitive adhesives that are high-molecular-weight polymers (Tyler 1993). In latex coatings, residual 2-ethylhexyl acrylate concentrations are generally 800 ppm or less. In a resin system composed of 45 parts 2-ethylhexyl acrylate, 50 parts styrene, and 5 parts acrylic acid, the amounts of residual 2-ethylhexyl acrylate and residual styrene were 0.15% and 0.27%, respectively (Union Carbide Chemical Co. 1998a).

As a commercial product, 2-ethylhexyl acrylate can contain 40 to 160 ppm hydroquinone and 10 to 220 ppm monomethyl ether of hydroquinone, both of which are inhibitors (IARC 1994).

Polyacrylic Acid. Detailed information on the possible presence of unreacted monomer in the polymer Polyacrylic Acid was not available to the IARC Working Group (IARC 1979). However, acrylic acid was detected in Polyacrylic Acid by UV spectroscopy, at 195 nm, with a limit of detection of 300 mg/kg (ppm).

Sodium Polyacrylate. A 90,000-Da sodium hydroxide-neutralized Polyacrylic Acid contained 77.5% Sodium Polyacrylate, 3.3% free acrylic acid, and 18.1% water (Nolen et al. 1989). A 4500-Da sodium hydroxide–neutralized Polyacrylic Acid contained 43.3% solids and 0.09% residual monomer.

USE

Cosmetic

The ingredients reviewed in this report have the functions shown in Table 2 (Wenninger, Canterbery, and McEwen 2000).

Product formulation data submitted to the Food and Drug Administration (FDA) in 1998 reported that Acrylates Copolymer was used in 227 cosmetic formulations, Ammonium Acrylates Copolymer was used in 21 formulations, Sodium Acrylates Copolymer was used in 5 formulations, Ethylene/Acrylic Acid Copolymer was used in 6 formulations, Ethylene/Sodium Acrylate Copolymer was used in 1 formulation, Acrylates/PVP Copolymer was used in 4 formulations, Steareth-10 Allyl Ether/Acrylates Copolymer was used in 6 formulations, Acrylates/Steareth-20 Methacrylate Copolymer was used in 35 formulations, Acrylates/Ammonium Methacrylate Copolymer was used in 1 formulation, Styrene/Acrylates Copolymer was used in 102 formulations, Styrene/Acrylates/Ammonium Methacrylate Copolymer was used in 1 formulation, Sodium Styrene/Acrylates Copolymer was used in 2 formulations, VA/Butyl

TABLE 2
Ingredient functions (Wenninger, Canterbery, and McEwen 2000)

Ingredient	Function
Acrylates Copolymer	Binder, film former, hair fixative, suspending agent—nonsurfactant
Ammonium Acrylates Copolymer	Binder, film former, viscosity increasing agent—aqueous
Ammonium/VA Acrylates Copolymer	Binder, film former, hair fixative, suspending agent—nonsurfactant
Sodium Acrylates Copolymer	Binder, film former, viscosity-increasing agent—aqueous
Ethylene/Acrylic Acid Copolymer	Binder, film former, viscosity-increasing agent—nonaqueous
Ethylene/Calcium Acrylate Copolymer	Binder, film former
Ethylene/Magnesium Acrylate Copolymer	Binder, film former
Ethylene/Sodium Acrylate Copolymer	Binder, film former, viscosity increasing agent—aqueous
Ethylene/Zinc Acrylate Copolymer	Film former
Ethylene/Acrylic Acid/VA Copolymer	Film former, viscosity increasing agent—nonaqueous
Acrylates/PVP Copolymer	Binder, film former, hair fixative, suspending agent—nonsurfactant
Acrylates/VA Copolymer	Binder, film former, hair fixative
Steareth-10 Allyl Ether/Acrylates Copolymer	Film former, viscosity-increasing agent—nonaqueous
Acrylates/Steareth-50 Acrylate Copolymer	Viscosity-increasing agent—aqueous
Acrylates/Steareth-20 Methacrylate Copolymer	Viscosity-increasing agent—aqueous
Acrylates/Ammonium Methacrylate Copolymer	Binder, film former, hair fixative
Styrene/Acrylates Copolymer	Film former
Styrene/Acrylates/Ammonium Methacrylate Copolymer	Film former, suspending agent—nonsurfactant
Ammonium Styrene/Acrylates Copolymer	Film former, suspending agent—nonsurfactant
Sodium Styrene/Acrylates Copolymer	Film former, viscosity-increasing agent—aqueous
Acrylates/Hydroxyesters Acrylates Copolymer	Film former
Methacryloyl Ethyl Betaine/Acrylates Copolymer	Film former, hair fixative, suspending agent—nonsurfactant
Lauryl Acrylate/VA Copolymer	Film former
VA/Butyl Maleate/Isobornyl Acrylate Copolymer	Film former
Ethylene/Methacrylate Copolymer	Film former
Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer	Film former, hair fixative
Sodium Acrylates/Acrolein Copolymer	Binder, film former, viscosity-increasing agent—aqueous
PVP/Dimethylaminoethylmethacrylate Copolymer	Binder, film former, hair fixative, suspending agent—nonsurfactant
AMP-Acrylates Copolymer	Film former
Polyacrylic Acid	Binder, emulsion stabilizer, film former, viscosity-increasing agent—aqueous
Ammonium Polyacrylate	Emulsion stabilizer, film former
Potassium Aluminum Polyacrylate	Absorbent, binder, viscosity-increasing agent—aqueous
Potassium Polyacrylate	Absorbent, binder, viscosity-increasing agent—aqueous
Sodium Polyacrylate	Film former, hair fixative, viscosity-increasing agent—aqueous

Maleate/Isobornyl Acrylate Copolymer was used in 5 formulations, Ethylene/Methacrylate Copolymer was used in 5 formulations, Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer was used in 6 formulations, PVP/Dimethylaminoethylmethacrylate Copolymer was used in 43 formulations, Polyacrylic Acid was used in 19 formulations, and Sodium Polyacrylate was used in 8 formulations (FDA 1998b) (Table 3). The other ingredients considered in this safety assessment were not reported as being used in 1998.

Acrylates Copolymer can be used for polymeric adsorbent entrapment, with entrapment defined as "the process of adsorption using a porous, convoluted matrix throughout which actives such as emollients, sunscreens, skin protectants or similar ingredients are dispersed" (Klein and DiSapio 1989). Acrylates Copolymer adsorbs other ingredients without shrinking or swelling.

Acrylates Copolymer in a urethane/Acrylate Copolymer system can be used as a micromatrix entrapment system "in which the entrapped material is dissolved, dispersed, adsorbed, or absorbed throughout the particle" (Scholz et al. 1993). The micromatrix entrapment system is insoluble and pressure insensitive, can be used with hydrophobic and hydrophilic systems, and is only limited by the amount of free water.

Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992). However, one company

TABLE 3
Product types in which ingredients are used (FDA 1998b)

Product category	Total no. of formulations in category	Total no. containing ingredient
	Acrylates Copolymer	
Eyebrow pencil	91	1
Eyeliner	514	6
Eye shadow	506	8
Mascara	167	17
Other eye makeup preparation	120	1
Powders (fragrance preparations)	247	8
Hair sprays (aerosol fixatives)	261	3
Hair dyes and colors	1572	10
Hair bleaches	113	3
Other hair-coloring preparations	59	1
Blushers (all types)	238	18
Face powders	250	27
Foundations	287	4
Lipstick	790	36
Makeup bases	132	2
Other makeup preparations	135	7
Basecoats and undercoats	48	16
Nail creams and lotions	17	1
Nail polish and enamel	80	21
Other manicuring preparations	61	15
Deodorants (underarm)	250	3
Cleansing preparations	653	3
Face and neck preparations (excluding shaving)	263	1
Body and hand preparations (excluding shaving)	796	2
Moisturizing preparations	769	5
Paste masks (mud packs)	255	3
Other skin care preparations	692	5
1998 total Acrylates Copolymer		**227**
	Ammonium Acrylates Copolymer	
Eyeliner	514	3
Mascara	167	18
1998 total Ammonium Acrylates Copolymer		**21**
	Sodium Acrylates Copolymer	
Hair dyes and color	1572	5
1998 total Sodium Acrylates Copolymer		**5**
	Ethylene/Acrylic Acid Copolymer	
Blushers (all types)	238	1
Foundations	287	2
Makeup fixatives	11	1
Other skin care preparations	692	2
1998 total Ethylene/Acrylic Acid Copolymer		**6**
	Ethylene/Sodium Acrylate Copolymer	
Eye shadow	506	1
1998 total Ethylene/Sodium Acrylate Copolymer		**1**

(Continued on next page)

TABLE 3
Product types in which ingredients are used (FDA 1998b) *(Continued)*

Product category	Total no. of formulations in category	Total no. containing ingredient
Acrylates/PVP Copolymer		
Tonics, dressings, and other hair-grooming aids	549	2
Wave sets	5555	2
1998 total Acrylates/PVP Copolymer		**4**
Steareth-10 Allyl Ether/Acrylates Copolymer		
Hair dyes and color	1572	6
1998 total Steareth-10 Allyl Ether/Acrylates Copolymer		**6**
Acrylates/Steareth-20 Methacrylate Copolymer		
Baby shampoos	21	1
Other baby products	29	1
Other bath preparations	159	1
Other fragrance preparations	148	1
Hair conditioners	636	1
Hair sprays (aerosol fixatives)	261	1
Shampoos (noncoloring)	860	6
Tonics, dressings, and other hair-grooming aids	549	6
Hair bleaches	113	5
Nail polish and enamel removers	34	1
Bath soaps and detergents	385	1
Shaving cream	139	2
Cleansing preparations	653	7
Moisturizing preparations	769	1
1998 total Acrylates/Steareth-20 Methacrylate Copolymer		**35**
Acrylates/Ammonium Methacrylate Copolymer		
Mascara	167	1
1998 total Acrylates/Ammonium Methacrylate Copolymer		**1**
Styrene/Acrylates Copolymer		
Eyeliner	514	3
Permanent waves	192	8
Tonics, dressings, and other hair-grooming aids	549	1
Hair dyes and colors	1572	66
Hair bleaches	113	1
Basecoats and undercoats	48	1
Nail polish and enamel	80	7
Bath soaps and detergents	385	1
Deodorants (underarm)	250	1
Other personal cleanliness products	291	6
Cleansing preparations	653	2
Face and neck preparations (excluding shaving)	263	4
Body and hand preparations (excluding shaving)	796	1
1998 total Styrene/Acrylates Copolymer		**102**
Styrene/Acrylates/Ammonium Methacrylate Copolymer		
Eyeliner	514	1
1998 total Styrene/Acrylates/Ammonium Methacrylate Copolymer		**1**
Sodium Styrene/Acrylates Copolymer		
Shampoos (noncoloring)	860	2
1998 total Sodium Styrene/Acrylates Copolymer		**2**

(Continued)

TABLE 3
Product types in which ingredients are used (FDA 1998b) *(Continued)*

Product category	Total no. of formulations in category	Total no. containing ingredient
VA/Butyl Maleate/Isobornyl Acrylate Copolymer		
Other hair preparations	276	5
1998 total VA/Butyl Maleate/Isobornyl Acrylate Copolymer		**5**
Ethylene/Methacrylate Copolymer		
Blushers (all types)	238	1
Foundations	287	1
Makeup bases	132	1
Other makeup preparations	135	2
1998 total Ethylene/Methacrylate Copolymer		**5**
Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer		
Hair sprays (aerosol fixatives)	261	2
Tonics, dressings, and other hair-grooming aids	549	3
Other hair preparations	275	1
1998 total Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer		**6**
PVP/Dimethylaminoethylmethacrylate Copolymer		
Mascara	167	3
Hair conditioners	636	4
Tonics, dressings, and other hair-grooming aids	549	21
Wave sets	55	2
Other hair preparations	276	13
1998 total PVP/Dimethylaminoethylmethacrylate Copolymer		**43**
Polyacrylic Acid		
Tonics, dressings, and other hair-grooming aids	549	1
Foundations	287	1
Leg and body paints	4	1
Nail polish and enamel	80	2
Bath soaps and detergents	385	2
Aftershave lotion	216	1
Cleansing preparations	653	3
Face and neck preparations (excluding shaving)	263	1
Body and hand preparations (excluding shaving)	796	2
Night preparations	188	1
Paste masks (mud packs)	255	2
Other skin care preparations	692	2
1998 total Polyacrylic Acid		**19**
Sodium Polyacrylate		
Hair spray (aerosol fixative)	261	1
Shampoos (noncoloring)	860	1
Other hair preparations	276	1
Bath soaps and detergents	385	2
Other skin care preparations	692	3
1998 total Sodium Polyacrylate		**8**

reported that Acrylates Copolymer and a mixture containing 30% Ammonium Acrylates Copolymer have "typical use" concentrations of 3% to 10% and 2% to 10%, respectively, as supplied, in cosmetic formulations; however, one "prototype formulation" proposed a mixture containing 30% Ammonium Acrylates Copolymer be used at 15% (Allied Colloids 1997). Another company reported using Acrylates Copolymer at concentrations of 7.5% and 21.87% (BFGoodrich Specialty Chemicals 1997).

A third company reported that Acrylates Copolymer is "typically used" at concentrations of 5% to 10% on a solids basis (20% to 40%) (Amerchol 1997). A survey by the EPC (to which 10 companies responded) reported that the estimated concentrations of acrylate polymers used in final cosmetic products are typically 2.5% to 6.0%, with a maximum of 7.5% to 25%, in binders, film formers, and fixatives and typically 0.5%, with a maximum of 2.0%, in viscosity-increasing agents, suspending agents, and emulsion stabilizers (EPC 1999). Nolen et al. (1989) reported that Sodium Polyacrylate is used as a dispersing agent in detergent formulations at concentrations of 1% to 5%.

In 1984, it was reported to the FDA that Acrylates Copolymer was used in 317 cosmetic formulations, some of which contained concentrations of >50%, Ammonium Acrylates Copolymer was used in 22 formulations at concentrations ≤5%, Ammonium/VA Acrylates Copolymer was used in 5 formulations at concentrations ≤25%, Ethylene/Acrylic Acid Copolymer was used in 2 formulations at ≤25%, Styrene/Acrylates Copolymer was used in 46 formulations at concentrations ≤25%, Styrene/Acrylates/Ammonium Methacrylate Copolymer was used in 21 formulations at unknown concentrations and at concentrations of 5% to 10%, Ammonium Styrene/Acrylates Copolymer was used in 2 formulations at unknown concentrations and at concentration of ≤0.1%, PVP/Dimethylaminoethylmethacrylate Copolymer was used in 1 formulation at 5% to 10%, Polyacrylic Acid was used in 3 formulations at concentrations of 0.1% to 5%, Ammonium Polyacrylate was used in one formulation at 25% to 50%, and Potassium Aluminum Polyacrylate was used in one formulation at 1% to 5%. The other ingredients named in this review were not reported to be used in 1984 (FDA 1984).

International

The ingredients in this review are not listed in Annex II (list of substances that must not form part of the composition of cosmetic products) or Annex III (list of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Economic Community 1995). With the exception of Acrylates Copolymer and Sodium Polyacrylate, the ingredients in this review are also not listed in the *Comprehensive Licensing Standards of Cosmetics by Category* (CLS) (Yakuji Nippo, Ltd. 1994).

Acrylates Copolymer. Acrylates Copolymer, as Hydroxyethyl Acrylate · Butyl Acrylate · Methoxyethyl Acrylate Copolymer Solution or Hydroxyethyl Acrylate · Methoxyethyl Acrylate Copolymer Solution, is listed in the CLS and must conform to the specifications of the *Japanese Cosmetic Ingredient Codex* (Yakuji Nippo, Ltd. 1994). It can be used without restriction in all CLS categories except lipsticks and lip creams and dentifrices.

Sodium Polyacrylate. Sodium Polyacrylate is listed in the CLS and must conform to the specifications of the *Japanese Standards of Cosmetic Ingredients* (Yakuji Nippo, Ltd. 1994). It can be used in all CLS categories without restriction.

Noncosmetic

Acrylates Copolymer. 'Acrylate Ester Copolymer Coating,' copolymers of acrylic acid, and copolymers of acrylic acid and its methyl, ethyl, butyl, propyl, or octyl esters are reportedly cleared for indirect food additive use according to certain specifications (Rothschild 1991).

Ethylene/Acrylic Acid Copolymer. Ethylene/Acrylic Acid Copolymers are reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Ethylene/Sodium Acrylate Copolymer. Ethylene/Sodium Acrylate Copolymer is reportedly cleared for food additive use (Rothschild 1991).

Acrylates/VA Copolymer. Vinyl Acetate Copolymers, produced by copolymerizing vinyl acetate with one or more monomers, including acrylic acid, are cleared for use under §176.170 (components of paper and paperboard in contact with aqueous and fatty foods) and §176.180 (components of paper and paperboard in contact with dry food) under certain conditions (Rothschild 1991). The finished copolymers must contain at least 50 weight percent of polymer units derived from vinyl acetate and contain no more than 5 weight percent of total polymer units derived from the other monomers.

2-Ethylhexyl acrylate is cleared in the production of acrylic copolymers and vinyl acetate copolymers under §176.170 (components of paper and paperboard in contact with aqueous and fatty foods) (Rothschild 1991). 2-Ethylhexyl acrylate is cleared in homo- and copolymer formation under §175.105 (adhesives), and polymers, homopolymers, and copolymers of 2-ethylhexyl acrylate are cleared as the basic polymer under §176.180 (components of paper and paperboard in contact with dry food. It is also cleared in polymer formation under §177.1010 (semirigid and rigid acrylic and modified acrylic plastics). 2-Ethylhexyl acrylate–ethyl acrylate copolymers, prepared by copolymerization of 2-ethylhexyl acrylate and ethyl acrylate in a 7:3 weight ratio and having a number of average molecular weight range of 5800 to 6500 Da and a refractive index of N_D^{250} of 1.4130 to 1.4190, are cleared under §177.1210 (closures with sealing gaskets for food containers). 2-Ethylhexyl acrylate–methyl methacrylate–acrylic acid copolymers are cleared as modifiers for epoxy resins in §175.300 (resinous and polymer coatings) under §177.1210. "There is a minute possibility of potential ingestion from migration of very small quantities of residual monomer [2-ethylhexyl acrylate] during incidental contact of food which comes in contact with polymeric materials used in packaging" (Tyler 1993).

Styrene/Acrylates Copolymer. Styrene Acrylate–based copolymers and styrene with ethyl acrylate and/or methacrylic acid are reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Ethylene/Methacrylate Copolymer. Ethylene/Methacrylic Acid Copolymer is reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Polyacrylic Acid. Acrylic acid polymer, and its methyl and ethyl esters, homopolymers of acrylic acid, and homopolymers

and polymers of acrylic acid and its methyl, ethyl, butyl, propyl, or octyl esters are reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Polyacrylic Acid and its salts are used as textile warp sizes for man-made fiber monofilaments (especially nylon) and as thickeners for use in latex paints, natural and synthetic rubber, textile printing pastes, and wallcovering binders (IARC 1979). Other applications include use as flocculants, fluid loss–control additives in oil-well drilling muds, scale-inhibitor additives in formulations for treating cooling-water systems, sequestrants, and as temporary binders for ceramics before firing.

Ammonium Polyacrylate. Ammonium Polyacrylate is reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991).

Sodium Polyacrylate. Sodium Polyacrylate is reportedly cleared for indirect food additive use under certain conditions (Rothschild 1991). Sodium Polyacrylate has use as a dispersing and thickening agent and as a flocculating agent for water purification (Hicks et al. 1989).

Acrylic Acid. Acrylic acid is mostly used "captively" in the production of other acrylates (IARC 1979).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Published absorption, distribution, metabolism, and excretion data on the ingredients included in this report were not found. Information on the absorption, distribution, metabolism, and excretion of acrylic acid and its esters is summarized. The monomers should have greater potential for absorption and penetration than the copolymers.

Dermal

Acrylic Acid and Methyl Acrylate. Groups of three fasted male Sprague-Dawley rats were dosed dermally with acrylic acid to determine the absorption and distribution (Winter and Sipes 1993). One hundred microliters of a 4% (*v/v*) solution of 1-^{14}C-acrylic acid in acetone (approximately 30 μCi/kg, 501 μg/cm^2) was applied through a skin-mounted aluminum trap that covered an 8.4-cm^2 area of skin on the mid-thoracic region of the back. A total of 96% of the radioactivity was recovered, with the majority of it (73%) recovered in the skin trap. Sixteen percent of the radioactivity was recovered in expired carbon dioxide and 6% was recovered from the dosing site; 0.9%, 0.4%, and 0.2% were recovered in the urine, tissues, and feces, respectively.

Groups of 15 male Fischer 344 rats and C3H/HeNCrlBR mice were given a single dermal dose of acrylic acid to determine absorption and metabolism (Black et al. 1995). The rats were dosed with 10 or 40 mg/kg (5 or 10 μCi/animal, respectively) and the mice were dosed with 10 or 40 mg/kg (5 or 20 μCi/animal, respectively). The doses were prepared by diluting acrylic acid in acetone to a final concentration of 1 ml/100 ml and administering a volume of 0.95 or 3.8 ml/kg; the dose was applied to a 1.0 × 2.5-cm (low-dose rats), 2.5 × 4.0-cm (high-dose rats), or 1.0 × 1.0-cm (both groups mice) clipped shoulder region on the back of each animal, and "nonocclusive dose-containment devices" were used. Immediately following dosing, five animals per group were placed in metabolism cages and urine, feces, and expired $^{14}CO_2$ were collected at various intervals. The animals were killed after 1, 8, or 72 hours.

TABLE 4
Metabolic fate of radioactive label in rats and mice with dermal application of [^{14}C]-Acrylic Acid (Black et al. 1995)

	Rats		Mice	
Location	10 mg/kg	40 mg/kg	10 mg/kg	40 mg/kg
$^{14}CO_2$	13.5 ± 1.0	19.7 ± 2.2	9.3 ± 1.2	9.6 ± 2.2
Volatilized dose	41.3 ± 5.8	26.5 ± 6.9	70.9 ± 9.6	49.9 ± 12.6
Urine	0.8 ± 0.1	2.0 ± 0.7	0.3 ± 0.1	0.4 ± 0.1
Feces	0.5 ± 0.2	0.8 ± 0.1	0.4 ± 0.1	0.2 ± 0.1
Tissues	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.1	0.0 ± 0.0
Carcass	2.8 ± 0.9	1.7 ± 0.5	0.5 ± 0.1	0.8 ± 0.8
Dose site	1.4 ± 0.6	1.0 ± 0.3	1.5 ± 2.3	0.2 ± 0.1
Total recovery	61.1 ± 5.3	52.2 ± 7.6	84.0 ± 10.5	61.5 ± 14.0

Absorption and elimination of acrylic acid were rapid and nearly complete after 8 hours for both dose groups of rats and mice. Seventy-two hours after administration, the distribution shown in Table 4, given as percent of administered dose, was reported based on 5 animals/group.

For both rats and mice, the amount of radioactivity found in the fat was greater after 72 hours than it was after 1 and 8 hours.

In guinea pigs that were exposed dermally to methyl [2,3-^{14}C]acrylate, radioactivity was seen in the subcutaneous (SC) tissues and throughout the body (IARC 1999).

Oral

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer.

A group of six male Wistar albino rats was given a single oral dose of 100 mg/kg 2-ethylhexyl [2,3-^{14}C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 24 hours, 50.6% of the radioactivity was excreted in expired air; most of it was exhaled within 3 hours. A total of 40.2% of the dose was excreted in the urine in 48 hours (38.0% of it was excreted in 24 hours), whereas only 1.2% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 93%.

Acrylic Acid and Methyl, Ethyl, and Butyl Acrylates. Twenty-six Sprague-Dawley rats were dosed orally with [^{11}C]-acrylic acid (Kutzman, Meyer, and Wolf 1982). Six were killed after 1.5 minutes and groups of five were killed after 10, 20, 40, or 65 minutes. The [^{11}C]-acrylic acid was rapidly absorbed from the stomach and the uptake appeared biphasic. Radioactivity

in most tissues increased gradually with time, and the relative retention values of the liver, adipose tissue, and small intestine increased markedly between 40 and 60 minutes. $^{11}CO_2$ was expired rapidly, and elimination appeared biphasic. After 65 minutes, the animals retained 37% of the dose. The relative radioactivity of the urine "increased rapidly" with time, and urine collected after 65 minutes contained 1.8% of the dose per gram.

Groups of three male Sprague-Dawley rats were given a single oral dose of 4, 40, or 400 mg/kg of [2,3-^{14}C]-acrylic acid or 2, 20, or 200 mg/kg [2,3-^{14}C]-ethyl acrylate in 0.5% aqueous methylcellulose (25 μCi/kg) at a volume of 10 ml/kg (DeBethizy et al. 1987). Urine, feces, and expired carbon dioxide were collected at various intervals up to 72 hours after dosing, and the animals were then killed. Acrylic acid and ethyl acrylate were eliminated rapidly, primarily in expired carbon dioxide (44% to 65%). Thirty-five percent to 60% of the acrylic acid and approximately 60% of the ethyl acrylate was eliminated within 8 hours. Urinary excretion of radioactive metabolites was greater with ethyl acrylate. Within 72 hours, 90% to 76% of the radioactivity was recovered from the animals dosed with 4 and 400 mg/kg acrylic acid; 19% to 25% was recovered in the tissues, with most being found in adipose tissue, (9% to 15%). With ethyl acrylate, 108% to 73% of the dose was recovered with 2 to 200 mg/kg; 13% to 10% was found in the tissues, with the most generally being found in muscle tissue (5.6% to 5%), and 28% to 8% was excreted in the urine.

DeBethizy et al. (1987) also dosed male Sprague-Dawley rats orally in quadruplicate with 4, 40, 400, and 1000 mg/kg acrylic acid or 2, 20, 100, or 200 mg/kg ethyl acrylate in 0.5% methylcellulose at a volume of 5 ml/kg with and without pretreatment with the carboxylesterase inhibitor tri-*o*-cresyl phosphate [TOCP]. Control animals were given 2 ml/kg corn oil with and without pretreatment. The animals were killed 1 hour after dosing. A "pronounced increase" in glandular and nonglandular stomach weights, edema, and hemorrhage were observed with >40 mg/kg acrylic acid. Acrylic acid, >4 mg/kg, significantly depleted nonprotein sulfhydryl [NPSH] content in the glandular stomach, but no significant effect on NPSH in the blood or liver was observed. Pretreatment with TOCP did not have a significant effect on stomach weight or NPSH content. With ethyl acrylate, a significant increase in forestomach weight was observed with the 200-mg/kg dose; no significant change in glandular stomach weight was observed. Treatment with TOCP enhanced the increase in forestomach weight. A linear depletion of NPSH content of the forestomach and glandular stomach was observed 1 hour after dosing with 2 and 20 mg/kg; NPSH content did not change with doses of 100 or 200 mg/kg. No significant dose-dependent effect of ethyl acrylate on NPSH concentration in the blood and liver was seen. Pretreatment with TOCP did not affect the depletion of NPSH content in the glandular stomach or forestomach; however, 100 and 200 mg/kg ethyl acrylate did induce a significant depletion of hepatic NPSH concentration.

Three fasted male Sprague-Dawley rats were given 400 mg/kg [1,2,3-$^{13}C_3$]-acrylic acid coadministered with [2,3-^{14}C]-acrylic acid (40 to 46 μCi/kg) in distilled water by gavage (Winter et al. 1992). Urine, feces, and expired air were collected for 72 hours, and the animals were then killed. Total recovery was 98%. The majority of the radioactivity, 78%, was recovered in expired carbon dioxide. Approximately 13% of the radioactivity was recovered in the tissues, with almost 5% of the dose found in the muscle, 3% found in the liver, 2% found in the skin, and 1% found in adipose tissue. The tissue-to-blood radioactivity concentration ratios were 11.1, 3.2, 2.6, 2.4, 2.1, and 2.0 for the liver, kidneys, adipose tissue, stomach, spleen, and large intestine, respectively. Approximately 6% of the dose was eliminated in the urine and 1% was eliminated in the feces. Nuclear magnetic resonance spectroscopy did not detect unchanged acrylic acid in the urine.

Groups of three fasted male Sprague-Dawley rats were dosed orally with acrylic acid to determine the absorption and distribution (Winter and Sipes 1993). The animals were given 400 mg/kg purified [1-^{14}C]-acrylic acid (44 μCi/kg) in distilled water. Urine, feces, and expired air were collected for 72 hours, and the animals were then killed. A total of 98% of the radioactivity was recovered after administration, with the majority of it (83%) recovered in expired carbon dioxide. Nine percent, 5%, and 1.3% of the radioactivity was recovered in the feces, urine, and tissues, respectively.

Groups of 15 male Fischer 344 rats and C3H/HeNCrlBR mice were given a single oral dose of acrylic acid to determine absorption and metabolism (Black et al. 1995). The rats were dosed with 40 or 150 mg/kg (20 μCi/animal) and the mice were with 40 or 150 mg/kg (20 or 10 μCi/animal, respectively). The doses were prepared by diluting acrylic acid to a concentration of 4 or 15 mg/ml in filtered water, and the dose was administered by gavage at a volume of 10 ml/kg. Immediately following dosing, five animals per group were placed in metabolism cages and urine, feces, and expired $^{14}CO_2$ were collected at various intervals. The animals were killed after 1, 8, or 72 hours.

Following administration, absorption and elimination of acrylic acid were rapid and nearly complete after 8 hours for rats of the low-dose group and after 24 hours for rats of the high-dose groups and for mice of both groups. Seventy-two hours after administration, the distribution shown in Table 5, given as percent of administered dose, was reported based on 5 animals/group.

For both rats and mice, elimination of radioactivity from fat was slower than it was from other tissues.

A group of six male Wistar albino rats was given a single oral dose of 100 mg/kg methyl [2,3-^{14}C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 24 hours, 38.6% of the radioactivity was excreted in expired air; most of it was exhaled within 2 hours. A total of 51.2% of the dose was excreted in the urine in 48 hours (38.0% of it was excreted in 24 hours), whereas only 1.5% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 91.3%.

Two hours after oral administration of methyl [2,3-^{14}C]-acrylate to guinea pigs, the radioactivity was distributed in internal organs, especially the liver and bladder, and in the brain.

TABLE 5
Metabolic fate of radioactive label in rats and mice given a single oral dose of [^{14}C]-Acrylic Acid (Black et al. 1995)

	Rats		Mice	
Location	40 mg/kg	150 mg/kg	40 mg/kg	150 mg/kg
Exhaled $^{14}CO_2$	90.3 ± 1.0	81.6 ± 1.8	76.8 ± 2.8	80.0 ± 4.1
Exhaled volatiles	0.1 ± 0.2	0.2 ± 0.4	0.1 ± 0.0	0.1 ± 0.0
Urine	2.9 ± 0.2	4.2 ± 1.0	3.0 ± 1.4	3.4 ± 1.3
Feces	0.7 ± 0.0	0.6 ± 0.1	1.2 ± 0.4	1.2 ± 1.2
Tissues	0.3 ± 0.2	0.3 ± 0.1	0.3 ± 0.0	0.1 ± 0.1
Carcass	0.8 ± 0.1	1.0 ± 0.2	0.8 ± 0.1	0.3 ± 0.1
Total recovery	95.2 ± 0.9	88.1 ± 2.0	82.5 ± 2.1	86.9 ± 6.1

After 16 hours, it was seen only in mucous linings of the stomach, intestines, and mouth epithelium.

Groups of three male Fisher 344 rats were dosed orally with 100, 200, or 400 mg/kg [2,3-^{14}C]-ethyl acrylate (50 to 60 μCi/kg; approximately 90% to 92% of the radioactivity was [2,3-^{14}C]-ethyl acrylate and the remainder was [^{14}C]-acrylic acid) in corn oil at a volume of 5 ml/kg (Ghanayem, Burka, and Matthews 1987). (Ethyl acrylate was inhibited with 15 to 20 ppm hydroquinone monomethyl ether.) Expired air was the major route of excretion; approximately 70% of the 200 mg/kg dose was expired as $^{14}CO_2$ within 24 hours of dosing. Approximately 10% and 4% of this dose was recovered in the urine and feces, respectively, in 24 hours. At all doses, >90% of the dose was absorbed from the stomach within 4 hours of administration. Radioactivity was distributed in all major tissues; total recovery was 74% to 82% (excluding that found in the carcass). Four hours after dosing, the greatest concentration of radioactivity was found in the glandular stomach, forestomach, small intestine, adrenal glands, and liver of animals dosed with 100 mg/kg, in the forestomach, glandular stomach, small intestine, liver, and thymus gland of the animals dosed with 200 mg/kg, and in the glandular stomach, small intestine, liver, forestomach, and kidneys of the animals dosed with 400 mg/kg.

Male Fischer 344 rats were given an oral dose of 4, 40, or 400 mg/kg butyl [2,3-^{14}C]-acrylate (specific activity 7, 20, or 20 μCi/kg, respectively) in corn oil (Sanders, Burka, and Matthews 1988). Subgroups of three animals per dose were killed at various intervals between 15 minutes and 3 days after dosing. The majority of the dose was excreted in CO_2; 74.2%, 65.5%, and 78.0% of the 4-, 40-, and 400-mg/kg doses, respectively, were excreted in expired air 24 hours after administration. In these dose groups, 12.6%, 7.7%, and 7.6%, respectively, of the dose was excreted in the urine at 24 hours. In animals of the 4-mg/kg group, the greatest concentrations in the tissues were found in the muscle, skin, blood, and liver (5.9%, 3.4%, 1.9%, and 1.9% of the dose, respectively). In animals of the 40- and 400-mg/kg groups, the greatest concentrations at 24 hours were in the adipose tissue, muscle, and skin (8.6%, 5.4%, and 2.9%, respectively, for the 40-mg/kg animals and 5.7%, 5.7%, and 3.2%, respectively, for the 400-mg/kg animals).

Inhalation

Acrylic Acid. Groups of female Sprague-Dawley rats were exposed to a maximum of 29 μg/kg [^{11}C]-acrylic acid by inhalation using a dynamic nose-exposure apparatus with a 1-minute exposure time or orally (Kutzman, Meyer, and Wolf 1982). Thirteen rats were nose-exposed; 10 were killed 1.5 minutes after exposure and the remaining three were killed 65 minutes after exposure.

The animals accumulated 18.3% of the radioactivity delivered to the nose cone. For the animals killed after 1.5 minutes, 28.4% of the activity was associated with the snout and 42.9% of the activity was in the head minus the snout. The upper respiratory tract also had "relatively large amounts" of [^{11}C]-acrylic acid. For the animals killed after 65 minutes, approximately 25% of the administered ^{11}C was retained and 8.1% of the activity was associated with the snout. Approximately 65% of the radioactivity had been expired as $^{11}CO_2$, and elimination appeared biphasic. The relative radioactivity of the liver and adipose tissue increased "markedly" between 1.5 and 65 minutes.

Parenteral

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer.

A group of six male Wistar albino rats was given a single intraperitoneal (IP) dose of 100 mg/kg 2-ethylhexyl [2,3-^{14}C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 72 hours, a total of 77.9% of the radioactivity was excreted in expired air (75.1% of it was excreted in 24 hours); most of it was exhaled within 3 hours. A total of 9.6% of the dose was excreted in the urine in 72 hours (4.3% and 4.6% were excreted in 0 to 24 and 24 to 48 hours, respectively), while only 2.9% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 90.4%. The total amount of the dose found in the tissues was 6.51%, 3.95%, 3.10%, 2.37%, and 1.07% after 3, 10, 24, 48, and 72 hours, respectively. At 3 hours, the greatest specific activity was in the liver, kidneys, and plasma (3.76, 1.91, and 1.56 kBq/g, respectively); at 10 hours, it was in the spleen, liver, and kidneys (1.75, 1.73, and 1.38 kBq/g, respectively); and at 24 hours, it was in the liver, spleen, and kidneys (1.40, 1.26, and 1.24 kBq/g, respectively). In erythrocytes, the loss of ^{14}C was biphasic, whereas in plasma, it was monophasic with a half-life of 22 hours.

Methyl and Butyl Acrylate. A group of six male Wistar albino rats was given a single IP dose of 100 mg/kg methyl [2,3-^{14}C]-acrylate (specific activity 3.7 MBq/kg) in soybean oil (Sapota 1988). Within 48 hours, a total of 54.4% of the radioactivity was excreted in expired air (51.8% of it was expired in 24 hours); most of it was exhaled within 2 hours. A total of

40.0% of the dose was excreted in the urine in 24 hours (38.7% of it was excreted in 24 hours), whereas only 1.5% of the dose was excreted in the feces in 72 hours. Total excretion in 72 hours was 95.9%. The total amount of the dose found in the tissues was 6.72%, 2.43%, 1.89%, and 1.21% after 1, 8, 24, and 48 hours, respectively. At 1 and 8 hours, the greatest specific activity was in the liver, kidneys, and lungs (3.62, 3.55, and 2.70 kBq/g, respectively, at 1 hours and 1.75, 1.73, and 1.38 kBq/g, respectively, at 8 hours), and at 24 hours, it was in the liver, lungs, and spleen (0.85, 0.61, and 0.60 kBq/g, respectively). In erythrocytes, the loss of ^{14}C was biphasic. In plasma, elimination was also biphasic, with fast and slow compartment half-lives of 5 and 34 hours, respectively.

Following IP injection of methyl [2,3-^{14}C]-acrylate to guinea pigs, radioactivity was concentrated in the peritoneum and the liver and seen in most other organs after 1 hours; radioactivity was generally not detected after 24 or 48 hours, except for some retention in mucous linings (IARC 1999). Following IP dosing of methyl [2,3-^{14}C]-acrylate to male guinea pigs, 35% and 40% of the radioactivity was excreted in expired air as $^{14}CO_2$ after 8 and 72 hours, respectively.

Male Fischer 344 rats were given an IP dose of 40 mg/kg butyl [2,3-^{14}C]-acrylate (specific activity 20 μCi/kg) in a 1:1:8 *v/v* solution of ethanol, Emulphor EL-620, and water at 1 ml/kg (Sanders, Burka, and Matthews 1988). Subgroups of three animals per dose were killed at various intervals between 15 minutes and 3 days after dosing. Butyl acrylate was rapidly delivered to all major tissues; peak concentrations were seen at or before 15 minutes in all tissues except adipose tissue. There was a rapid initial decrease in radioactivity in all major tissues, except adipose tissue, during the first 2 hours after dosing; the elimination slowed to a negligible rate and remained relatively constant between 2 hours and 3 days after dosing. Fifteen minutes after dosing, 154.3, 98.6, and 51.4 μg/g radioactivity was found in the kidneys, liver, and blood, respectively; the amounts found in the liver, kidneys, and blood were 86.0, 78.7, and 27.0 μg/g, respectively, after 45 minutes; 53.5, 33.7, and 18.5 μg/g, respectively, after 2 hours; and 45.0, 23.0, and 19.8 μg/g, respectively, after 6 hours. (The radioactivity concentration in adipose tissue at 15 minutes, 45 minutes, 2 hours, and 6 hours was 10.8, 10.6, 8.5, and 14.0 μg/g, respectively.) The majority of the dose was excreted in CO_2. After 24 hours, 45.3% of the dose was excreted in expired air and 15.6% was excreted in the urine. The greatest amount of radioactivity was found in the adipose tissue, muscle, and skin at this time (12.2%, 5.2%, and 2.7% of the dose, respectively).

In Vitro

Acrylic Acid. The disposition of [^{14}C]-acrylic acid was determined in vitro using clipped dorsal skin from male rats according to the method of Frantz et al. (1990) (Black et al. 1995). One percent (*v/v*) [^{14}C]-Acrylic Acid, 95 μl, was applied to the exposed epidermal surface (1.77 cm^2), and an evaporation trap was fitted over the skin. Over a 6-hour period, 23.9% ± 5.4% of the dose was absorbed in the effluent or was found in the skin and at least 60% of the dose was evaporated. Total recovery of the applied dose was approximately 85%.

Immunologic Effects

Acrylates/PVP Copolymer. Copolymers were obtained by radical copolymerization of acrylic acid and *N*-vinyl pyrrolidone; these copolymers contained 25 to 91 mole percent acrylic acid links and had a molecular weight of 300,000 to 400,000 Da (Nadzhitmitdinov et al. 1979). The immunostimulating action of these copolymers was studied using mice. The copolymers increased the migration of stem cells, the migration of B and T lymphocytes, and intensified the cooperative interaction between T and B lymphocytes.

Polyacrylic Acid. Groups of six female NMRI/HAN mice were injected intraperitoneally with 2×10^8 sheep erythrocytes (SRBCs) to determine whether administration of Polyacrylic Acid (molecular weight 20,000 to 30,000 Da), a B-cell mitogen, at a "nonoptimal time" would have a suppressive effect on primary immune response (Diamantstein et al. 1976). The mice were injected intraperitoneally with 1 mg Polyacrylic Acid in 0.5 ml phosphate-buffered saline (PBS) 30 minutes or 2, 3, or 4 days prior to immunization with SRBCs. The kinetics of the response to SRBCs were then examined by injecting a group of mice with 1 mg Polyacrylic Acid on the day that gave the optimal conditions for immunosuppression; the number of plaque-forming cells (PFCs) and of hemolysin titres were determined 2, 3, 4, and 5 days after immunization. The adjuvant effect of 1 mg Polyacrylic Acid was tested under known optimal conditions, i.e., IP injection 30 minutes before immunization with 2×10^6 SRBCs/0.5 ml, and the direct (19S) PFC response was determined in individual spleens after days 2, 3, 4, and 5.

Polyacrylic Acid had an immunosuppressive effect on the response to SRBCs. The maximum decrease in the PFC response was in the groups dosed with Polyacrylic Acid 3 and 4 days before immunization and the maximum reduction in hemolysin titres was observed in the group dosed with Polyacrylic Acid 3 days before immunization. Hence, to examine the kinetics of the response, Polyacrylic Acid was injected on day 3 prior to immunization; a reduction in the numbers of PFCs and hemolysin titres was observed 2, 3, 4, and 5 days after immunization. A second injection of Polyacrylic Acid 30 minutes prior to immunization with SRBCs abolished the immunosuppressive effect. Under optimal conditions (assessing the adjuvant effect), Polyacrylic Acid significantly increased the number of PFCs on all days.

A Polyacrylic Acid-IgG (PAIGP) complex was prepared and its influence on a number of immunological reactions were examined (Klauser et al. 1990). The complex had a Polyacrylic Acid:IgG weight ratio of 0.143 and a mean molecular weight 1.77×10^6. Complement consumption was determined using a modified version of the hemolytic complement consumption of Kabat and Mayer (1971). Increasing concentrations of PAIGP consumed complement in a dose-dependent manner. The 50%

effective concentration was 2.3 μg/ml PAIGP; the hemolytic activity of the complement was almost completely lost at concentrations of 50 μg/ml PAIGP.

The activation of phagocytic cells by PAIGP was examined using luminol enhanced chemiluminescence. PAIGP stimulated chemiluminescence of isolated human polymorphonuclear (PMN) leukocytes in the presence and absence of autologous serum and in the presence of human citrated blood. The chemiluminescence of leukocytes increased in a dose-dependent manner. In the presence and absence of serum, monoclonal antibodies against leukocyte antigens (anti-Leu 11B) dose-dependently inhibited the chemiluminescence induction by PAIGP. Also, the formation of superoxide anion by PMN leukocytes activated by PAIGP was measured using ferricytochrome *c*; superoxide was released. Additionally, the release of elastase from stimulated human PMN leukocytes in whole blood was examined. PAIGP was a weak inducer of elastase release.

Mitochondrial Effects

Acrylic Acid. Hepatic mitochondria from adult male Sprague-Dawley rats were used to determine the effects of acrylic acid (Custodio et al. 1998). Addition of acrylic acid to succinate-energized mitochondria that were preloaded with 40 nmol calcium/mg protein caused a dose-dependent stimulation of mitochondrial swelling. Incubation of isolated mitochondria with 20 μM calcium and 1 mM acrylic acid caused a "rapid and profound decrease in light scattering." In examining the effect on membrane potential, acrylic acid caused a "slight (10–15 mV) but direct depolarization of membrane potential." The effect of acrylic acid on mitochondrial GSH concentrations were also determined. The distribution of mitochondrial GSH between the matrix and the extramitochondrial medium was not altered by 1 mM acrylic acid. Acrylic acid increased the sensitivity of isolated mitochondria in vitro to the calcium-dependent induction of the mitochondrial permeability transition.

ANIMAL TOXICOLOGY

Acute Toxicity

Dermal

Acrylates Copolymer. The acute dermal toxicity of Acrylates Copolymer (approximately 24% solids) was determined using five male and five female New Zealand white rabbits (Bushy Run Research Center 1993a). A dose of 16 g/kg was applied for 24 hours under an occlusive patch to a shaved area on the dorsal surface of each animal. The amount of test article/dose area ranged from approximately 96 (for females) to 97 mg/cm^2 (for males). The animals were killed 14 days after dosing. All animals survived until study termination. Erythema, edema, desquamation (one animal), and alopecia (one animal) were observed.

The acute dermal toxicity of Acrylates Copolymer (containing 1500 ppm stearyl acrylate, 200 ppm methacrylic acid; Cosmetic, Toiletry, and Fragrance Association [CTFA] 1999b) was determined using five male and five female New Zealand white rabbits (MB Research Laboratories 1999a). A dose of 2 g/kg moistened with mineral oil was applied under an occlusive patch for 24 hours to clipped intact skin on the dorsal area of the trunk. The test site was scored 24, 48, and 72 hours and 7 and 14 days after dosing using the Draize scale. None of the animals died during the study. No reactions were observed; the modified primary irritation index (PII) was 0, and the dermal LD_{50} was >2 g/kg.

Ethylene/Acrylic Acid Copolymer. An Ethylene/Acrylic Acid polymer had a "low order of acute toxicity" when applied dermally (Union Carbide Chemical Co. 1998b). A dose of 16.0 ml/kg of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was applied to the skin of four rabbits; none of the animals died (Union Carbide Chemical Co. 1998c). Study details were not provided.

Acrylates/VA Copolymer. The dermal LD_{50} of Vinyl Acetate/Maleate/Acrylate Copolymer solution was determined using 10 New Zealand White rabbits, five per sex (Bio/dynamics Inc. 1984a). The test material, 5 g/kg, was applied undiluted at a dose volume of 5.05 ml/kg under an occlusive patch to a clipped area of the back. The patches were removed after 24 hours and excess material was removed. The animals were observed for 14 days after dosing and then were killed. Severe dermal effects that generally persisted until study termination, i.e., necrosis followed by eschar formation, fissuring, and/or exfoliation of the eschar tissue, were observed at the test site for most animals. Generally, signs of toxicity were not observed, with the exception of nasal discharge. All animals survived until study termination except one male; it could not be determined whether the death was treatment-related because no lesions were observed at necropsy. The dermal LD_{50} of Vinyl Acetate/Maleate/Acrylate Copolymer solution using rabbits was >5 g/kg.

Acrylic Acid. The range of the dermal LD_{50} of acrylic acid reported for rabbits was 295 to 950 mg/kg (IARC 1979).

Oral

Acrylates Copolymer. The acute oral toxicity of Acrylates Copolymer (approximately 24% solids) was determined using Sprague-Dawley rats (Bushy Run Research Center 1993a). In preliminary testing, two female rats were dosed with 4 or 16 ml/kg Acrylates Copolymer; neither animal died. In the definitive test, a group of five male and five female rats were dosed with 16 ml/kg Acrylates Copolymer. The animals were killed 14 days after dosing. All animals survived until study termination. Signs of toxicity were not reported.

The oral LD_{50} of Acrylates Copolymer was determined using 10 Wistar rats, 5 males and 5 females (BASF 1994a). The animals were dosed with an aqueous solution of 2 g/kg Acrylates Copolymer (supplied as a white powder) and observed for 14 days. One male had an impaired general state and dyspnea, but appeared normal after 1 day. All animals survived until study

termination, and the oral LD_{50} of Acrylates Copolymer using rats was >2 g/kg.

The oral LD_{50} of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) was determined using five male and five female Wistar albino rats (MB Research Laboratories 1996a). The animals were given a single oral dose of 5 g/kg and observed 1, 2, and 4 hours and daily for 14 days after dosing. The oral LD_{50} was >5 g/kg.

The oral LD_{50} of Acrylates Copolymer, 30% total solids and pH 7 to 7.4, was determined using fasted white rats (number of animals not specified) (BFGoodrich Specialty Chemicals 1997). The animals were dosed with ≤9 g/kg Acrylates Copolymer and observed for 7 days. All animals survived until study termination, and the LD_{50} of Acrylates Copolymer using rats was >9 g/kg.

The oral LD_{50} of a 15% solution of Acrylates Copolymer, 100% solids, in ammonia water was determined using fasted white rats (number of animals not specified) (BFGoodrich Specialty Chemicals 1997). The animals were dosed with ≤7.5 g/kg Acrylates Copolymer and observed for 7 days. All animals survived until study termination, and the LD_{50} of Acrylates Copolymer using rats was >7.5 g/kg.

The oral LD_{50} of Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively; CTFA 1999b) was determined using five male and five female Wistar albino rats (MB Research Laboratories 1999b). The animals were given a single oral dose of 2 g/kg and observed 1, 2, and 4 hours and daily for 14 days after dosing. The oral LD_{50} was >2 g/kg.

Ethylene/Acrylic Acid Copolymer. The acute oral toxicity of a heptane extract of an Ethylene/Acrylic Acid Copolymer mixed with mineral oil (containing 59.0% low-molecular-weight Ethylene/Acrylic Acid Copolymer and 41% mineral oil; residual acrylic acid was not detected in the copolymer using a method sensitive to 10 ppm) was determined using groups of six male and six female Sprague-Dawley rats (FDA 1998c). Doses of 0.5, 1, 2, and 4 g/kg were administered as a 25% suspension in corn oil. No test article–related lesions were observed, and all animals survived the 2-week observation period following dosing. The oral LD_{50} for rats was >4 g/kg.

In a similar study, the oral LD_{50} of a heptane extract of Ethylene/Acrylic Acid Copolymer (containing 56.5% low-molecular-weight Ethylene/Acrylic Acid Copolymer and <43.5% mineral oil) was determined using groups of six male and six female Sprague-Dawley rats (FDA 1998d). Doses of 0.625, 1.23, 2.5, and 5.0 g/kg were used were administered as a 34.9% suspension in corn oil. The rat oral LD_{50} was >5.0 g/kg.

An Ethylene/Acrylic Acid polymer had a "low order of acute toxicity" via the peroral route (Union Carbide Chemical Co. 1998b). The oral LD_{50} in rats of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was 41.50 ml/kg (Union Carbide Chemical Co. 1998c).

The oral LD_{50} of a low-molecular-weight formula of Ethylene/Acrylic Acid Copolymer (35% acrylic acid) was >5.0 g/kg (Dow Chemical Co. 1998.)

Acrylates/VA Copolymer. The oral LD_{50} of Vinyl Acetate/Maleate/Acrylate Copolymer solution was determined using 10 fasted Sprague-Dawley (CDR) albino rats, 5 males and 5 females (Bio/dynamics Inc. 1984b). The animals were given 5 g/kg of undiluted test material by gavage in a dose volume of 5.05 ml/kg. The animals were observed for 14 days after dosing and then killed. Nasal and oral discharge, wet rales, soft stools, and hypoactivity were observed within 24 hours after dosing; other signs of toxicity occurred sporadically in single animals. All animals appeared normal on days 11 to 14. All animals survived until study termination. The oral LD_{50} of Vinyl Acetate/Maleate/Acrylate Copolymer solution using rats was >5 g/kg.

Polyacrylic Acid. The oral LD_{50} of Polyacrylic Acid using rats was reported to be 2.5 g/kg (Berth et al. 1975).

Sodium Polyacrylate. Groups of one male and one female CSE rat were given a single oral dose of 0.005, 0.01, 0.025, 0.050, or 0.1 g/kg of 10% (*w/v*) Sodium Polyacrylate, molecular weight 3500 Da, and of 5% (*w/v*) Sodium Polyacrylate, molecular weight 13.1×10^6 Da, and groups of four male and four female rats were dosed with 0.15 or 1 g/kg of both Sodium Polyacrylates (Hicks et al. 1989). The animals were observed continuously and all surviving animals were killed 10 h after dosing. Significant effects were not observed.

The oral LD_{50} for 15% aqueous Sodium Polyacrylate using groups of 10 rats was >40 g/kg (Finnegan and Dienna 1953).

Acrylic Acid and Methyl, Ethyl, and Butyl Acrylate. The oral LD_{50} of acrylic acid for rats was 2100 to 3200 mg/kg (IARC 1979). The oral LD_{50} of glacial acrylic acid for rats was 193 to 350 mg/kg. Dow Chemical Co. (1998) reported the oral LD_{50} of glacial acrylic acid for rats was 0.34 ml/kg.

The oral LD_{50} of undiluted acrylic acid was 0.34 ml/kg for male rats (DePass et al. 1983). The oral LD_{50} of a 10% aqueous dilution of acrylic acid was 2.59 ml/kg for male Carworth-Wistar rats.

The National Toxicology Program (NTP) conducted a series of studies on ethyl acrylate–induced gastric toxicity. Comparing single and repetitive dosing, Ghanayem, Maronpot, and Matthews (1985a) treated groups of eight male Fischer 344 rats by gavage with ethyl acetate in corn oil at 100, 200, and 400 mg/kg doses one time; and with ethyl acetate in corn oil at a 200-mg/kg dose once, twice, or four times. Control groups were given corn oil only. In the glandular stomach, the end points were mucosal congestion, submucosal edema, submucosal inflammation, and superficial mucosal necrosis. In the forestomach, the end points were mucosal edema (with or without vescicles), erosions or ulcers, mucosal hyperplasia, submucosal edema, submucosal inflammation, and vacuolization of tunica muscularis. The acute effect of ethyl acetate was dose-dependent. Repeated exposure caused similar damage to the glandular stomach and the forestomach, but the damage increased in severity. The time

course of stomach lesions increased in incidence and severity with time up to 8 hours after treatment. The authors also noted that a single 200-mg/kg dose of ethyl acrylate given subcutaneously produced no gastric toxicity and that the same dose via IP administration produced only mild gastric changes.

Ghanayem, Maronpot, and Matthews (1985b) extended this work by examining the effect of different acrylates. Male Fischer 344 rats were given a single oral dose of (a) 2 mmol acrylic acid, (b) methyl acrylate inhibited with 200 ppm hydroquinone monomethyl ether (HQMME), (c) ethyl acrylate inhibited with 15 to 20 ppm HQMME, or (d) butyl acrylate inhibited with 10 to 55 ppm HQMME, all in 5 ml/kg corn oil. Control animals were given corn oil only. The animals were killed 4 hours after dosing. Methyl acrylate and ethyl acrylate produced stomach lesions. Acrylic acid and butyl acrylate did not. If the volume of corn oil in which the ethyl acrylate was decreased (increasing the concentration of ethyl acrylate, but not the dose), gastric edema increased, up to a halving of the corn oil volume, and decreased when the corn oil volume was reduced to 1.25 ml. To further investigate the role of the vehicle, butyl acrylate (no stomach lesions in corn oil) was administered in a water-Emulphor vehicle (Emulphor is a polyethoxylated vegetable oil). Significant edema was observed in both the forestomach and the glandular stomach. Speculating that the water vehicle potentiated the partitioning of butyl acrylate in the stomach tissue compared to stomach contents, the authors concluded that the rate of delivery of acrylates influences gastric toxicity and that certain acrylate ester structures are needed to produce gastric toxicity.

In the third study in this series, Ghanayem, Maronpot, and Matthews (1986) gave 14 daily gavage doses of 100 or 200 mg/kg of ethyl acrylate to male Fischer 344 rats. Rats were killed at various times following the end of dosing. No glandular stomach lesions were observed after 14 daily doses, suggesting to the authors that the glandular stomach adapted to resist the effect of ethyl acrylate. Fewer gastric lesions were seen in the forestomach of animals receiving the repeated doses than had been seen previously with a single or double exposure. As a function of time after dosing, forestomach lesions decreased.

Inhalation

Acrylates Copolymer. The acute inhalation toxicity of Acrylates Copolymer (approximately 24% solids) was determined using a group of five male and five female Sprague-Dawley rats (Bushy Run Research Center 1993a). "A substantially saturated vapor was produced by enclosing 140 g [Acrylates Copolymer] in a sealed 120 liter animal chamber for approximately 17 hours under static conditions." The animals were placed in the chamber for 6 hours. The animals were killed 14 days after dosing. All animals survived until study termination. Signs of toxicity were not reported.

The LC_{50} of Acrylates Copolymer as a liquid aerosol was determined using 10 Wistar rats, 5 males and 5 females (BASF 1994b). The animals were exposed to 5.2 mg/l Acrylates Copolymer in a single 4-hour dose, and the animals were observed for 14 days. The mass median aerodynamic diameter was 1.4 μm. The animals appeared normal throughout the study, and lesions were not found during gross examination. The LC_{50} of Acrylates Copolymer for rats was >5.2 mg/l.

Ethylene/Acrylic Acid Copolymer. In an inhalation study in which six rats were exposed for 8 hours to a "substantially saturated vapor" of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, for 8 hours, none of the animals died (Union Carbide Chemical Co. 1998c).

Acrylic Acids. The LC_{50} for rats exposed to acrylic acid vapors for 4 hours was 3600 mg/m^3 (1200 ppm) (IARC 1979). In single inhalation studies using rats, 12 mg/l (4000 ppm) acrylic acid did not kill any of six rats exposed for 4 hours, whereas vapor concentrations approaching saturation in air killed half of a test group of rats (number of rats not stated) in 3.5 hours.

Parenteral

Ethylene/Acrylic Acid Copolymer. The IP LD_{50} for rats of an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was 8.57 ml/kg (Union Carbide Chemical Co. 1998b).

Acrylates/PVP Copolymer. The intravenous toxicity of a copolymer of acrylic acid and *N*-vinyl pyrrolidone was determined using white mice (Nadzhitmitdinov et al. 1979). Six copolymers, molecular weight 300,000 to 400,000 Da, were made containing 25 to 91 mole percent acrylic acid links. The copolymers containing 85% and 91% acrylic acid were toxic, with LD_{50} values of 120 and 100 mg/kg, respectively. The copolymers containing 69% and 70% acrylic acid were slightly toxic, with LD_{50} values of 350 and 225 mg/kg, respectively. The copolymers containing 25% and 45% acrylic acid were nontoxic, with LD_{50} values of 800 and 625 mg/kg, respectively.

Sodium Polyacrylate. Groups of one male and one female CSE rat were given a single intravenous, (IV), IP, or SC dose of 5, 10, 25, 50, or 100 mg/kg of 10% (*w/v*) Sodium Polyacrylate, molecular weight 3500 Da, and of 5% (*w/v*) Sodium Polyacrylate, molecular weight 13.1×10^6 Da (Hicks et al. 1989). Additionally, groups of five male and five female rats were dosed intravenously or intraperitoneally with 25 or 50 mg/kg and groups of seven male and seven female rats were dosed intravenously or intraperitoneally with 100 mg/kg of the high-molecular-weight Sodium Polyacrylate. Five male and five female rats were pretreated with a single IP dose of 110 mg/kg calcium chloride in aqueous solution, followed 15 minutes later by IP dosing with a single IP dose of 100 mg/kg the high-molecular-weight Sodium Polyacrylate. Groups of three male and three female rats were given a SC dose of 100 mg/kg of the low- or high-molecular weight Sodium Polyacrylate. The animals were observed continuously and all surviving animals were killed 10 hours after dosing.

Adverse effects were reported, including dyspnea, an immobile, crouched posture, and cyanosis, after IV and IP administration of 25 to 100 mg/kg of the high-molecular weight Sodium

Polyacrylate. IV dosing generally led to rapid death, usually within 30 minutes; however, some animals survived 9 hours after dosing and some of the animals dosed with 25 mg/kg survived 10 hours after dosing (study termination). Following IP dosing, adverse effects were observed after ≥3 hours and death occurred, preceded by tremors and convulsions, approximately 30 minutes after the onset of the adverse effects. Necropsy findings of animals that died due to test-article administration included arterial and venous vascular engorgement, ecchymoses in most organs, on muscle surfaces, and, in SC tissue, petechial hemorrhages on individual blood vessel, blood accumulation in the intestinal lumen, occasional gastric hemorrhages, coronary vessel hemorrhages, bloodstained pericardial fluid, and red discoloration of the lungs. Toxic effects were not observed upon dosing with the low-molecular-weight Sodium Polyacrylate. Likewise, toxic effects were not observed upon SC dosing with either the low- or high-molecular-weight Sodium Polyacrylate (Hicks et al. 1989).

In a continuation of this work, Hicks et al. (1989) dosed nine rats (sex not specified) intraperitoneally with 100 mg/kg of the high-molecular weight Sodium Polyacrylate. Three animals were killed after 1, 2, and 3 hours to determine the onset and progression of internal lesions. In animals killed after 1 hour, cardiovascular function was normal and hemorrhagic lesions and discoloration were not observed. Hemorrhage was not seen after 2 hours, and changes were minor. Three hours after dosing, hemorrhages were observed in the pericardium, lungs, intestines, stomach, and cranium.

Groups of four male rats were anesthetized, prepared for recording of respiration, systemic arterial blood pressure, heart rate, and electrocardiogram, and dosed intravenously with ≤40 mg/kg of both Sodium Polyacrylates (Hicks et al. 1989). Doses of 5 to 20 mg/kg of the high-molecular-weight Sodium Polyacrylate caused transient depressor effects on blood pressure, whereas doses of 24 to 40 mg/kg caused marked bradycardia and cardiac arrhythmias, decreased the frequency of respiration, and caused more prolonged depressor effects.

Six male rats were dosed intraperitoneally with 110 mg/kg of the high-molecular-weight Sodium Polyacrylate and were prepared for blood pressure, heart rate, and electrocardiogram after 2 to 2.5 hours (Hicks et al. 1989). These animals generally died after 4 to 5 hours, and changes, including the development of steep depressor effects, were mostly observed 30 minutes prior to death.

Acrylic Acid. The IP LD_{50} of acrylic acid for rats was 24 mg/kg (IARC 1979).

Short-Term Toxicity

Oral

Acrylic Acid, Ethyl Acrylate, and Methyl Methacrylate. Groups of five male and five female Fischer 344 rats were used in a dose range–finding study (DePass et al. 1983). The animals were dosed daily with approximate concentrations of 0.15%, 0.30%, or 0.60% acrylic acid in water. The animals were weighed three times during the study, observed daily for signs of toxicity, and killed on day 7.

None of the animals died during the study. The dosages attained were 210, 420, and 680 mg/kg/day for the males and 220, 400, and 760 mg/kg/day for the females. In the high-dose group, body weight gain was statistically significantly reduced for males on days 4 and 7 and for females on day 1.

Male Fischer 344/N rats were dosed either by gavage with 2 to 200 mg/kg or in drinking water with 200 to 4000 ppm (23 to 369 mg/kg/day) ethyl acrylate (with 15 ppm 4-methoxyphenol) for 2 weeks (Frederick, Hazleton, and Frantz 1990). In the gavage study, in which the vehicle was corn oil and the animals were dosed once daily five times per week for 2 weeks, 10 and 4 animals per dose were used for histopathology and biochemistry, respectively. In the drinking water study, in which the animals were given dosing solutions at all times, 10 animals per dose were used for both histopathology and biochemistry.

"Primary compound-related histopathological changes were noted only in the forestomach" of the test animals. In the animals dosed by gavage, the following were observed in the forestomach: minimal diffuse epithelial hyperplasia in 2 animals of the 20-mg/kg group; mild diffuse epithelial hyperplasia in 1, 7, and 5 animals of the 20-, 50-, and 100-mg/kg groups, respectively; moderate diffuse epithelial hyperplasia in 5 and 3 animals of the 100- and 200-mg/kg groups, respectively; marked diffuse epithelial hyperplasia in 7 animals of the 200-mg/kg group; focal epithelial hyperplasia in 2 animals of the 200-mg/kg group; hyperkeratosis in 3, 8, 10, and 10 animals of the 20-, 50-, 100-, and 200-mg/kg groups, respectively; submucosal inflammation in 6 and 10 animals of the 100- and 200-mg/kg groups, respectively; submucosal edema in 2 and 9 animals of the 100- and 200-mg/kg groups, respectively; and ulcers and erosions of the epithelial layers in 6 animals of the 200-mg/kg group. In the glandular stomach, submucosal inflammation was observed in one and six animals of the 100- and 200-mg/kg groups, respectively, and submucosal edema seen in one animal of the 200-mg/kg group was viewed "as extensions of the main inflammatory process involving the forestomach." Two hours after the last dose, the forestomach of animals of the high-dose group had an increase in weight of 281% compared to control values; this increase was not seen in the glandular stomach. The NPSH content of the forestomach was significantly elevated in test animals compared to controls. However, the total NPSH content was rapidly depleted with a 200-mg/kg dose, whereas only a marginal change was seen with a 20-mg/kg dose.

In the animals dosed via the drinking water, again compound-related findings occurred only in the forestomach, but were generally less severe. The following were observed in the forestomach: minimal diffuse epithelial hyperplasia in 10, 1, and 2 animals of the 1000-, 2000-, and 4000-ppm groups, respectively; mild diffuse epithelial hyperplasia in 8 and 6 animals of the 2000- and 4000-ppm groups respectively; moderate diffuse epithelial hyperplasia in 1 animal of each the 2000- and

4000-ppm groups, respectively; marked diffuse epithelial hyperplasia in 1 animal of the 4000-ppm group; hyperkeratosis in 9 and 10 animals of the 2000- and 4000-ppm groups, respectively; submucosal inflammation in 1 and 2 animals of the 2000- and 4000-ppm groups, respectively; and focal epithelial hemorrhage in 1 animal of each the 2000- and 4000-ppm groups. A slight increase in forestomach weight was observed in the high-dose group, whereas the weight of the glandular stomach was similar to that of controls.

Inhalation

Crl:CD(SD)BR Sprague-Dawley-derived rats were exposed 6 hours per day, 5 days per week, for 2 weeks to aerosol concentrations of 4.9 to 949.6 μg/l of an acrylic polymer (not defined due to confidential business information status) that had a molecular weight of approximately 1,000,000 Da and that contained approximately 35% respirable (≤ 5 μ) dust (Rohm and Haas Co. 1984a). Groups of 8 male and 8 female rats were exposed to 4.9, 47.8, or 258.6 μg/l and a group of 16 male and 16 female rats was exposed to 949.6 μg/l of the acrylic polymer. The aerosol particle size distribution ranged from a mean mass median diameter (MMD) of 3.1 to 6.6 μm and a geometric standard deviation (GSD) of 3.0 to 3.7. A control group of 16 males and 16 females was exposed to air only. Half of the male and female animals of the control and high-dose groups were used as a 3-week recovery group. Body weights were measured weekly, feed consumption was determined for the periods days 1 to 3, 5 to 7, 7 to 8, and 9 to 10, and signs of toxicity were assessed before, during, and after each exposure. At the end of the 2 weeks of dosing or the 3-week recovery period, necropsy was performed and some tissues were collected for microscopic examination.

One or two animals of the control, 258.6-, and 949.9-μg/l groups had dry corneas, chromorhinorrhea, a "thriftless appearance," and alopecia, but persistent treatment-related signs of toxicity were not observed. Signs of toxicity were also not observed in animals of the 3-week recovery group. Dose-related differences in body weights and body weight gains were not observed between test and control animals. Overall feed consumption of the high-dose group was decreased compared to the controls. Treatment-related lesions were not observed at necropsy.

At microscopic examination of the lungs of all animals of the 258.6- and 949.6-μg/l groups, lesions were characterized by a multifocal or diffuse pneumonitis that consisted of proliferation of alveolar septal cells and macrophages and the infiltration of a few PMN leukocytes in the terminal bronchioles, alveolar ducts, and adjacent alveoli. The alterations in the animals of the 949.6-μg/l group were extensive, with mean severity scores of 2.4 for males and females and a diffuse distribution. The lesions in the 258.6-μg/l group were of lesser severity, with mean severity scores of 1.0 and 1.1 for the males and females, respectively, and a multifocal distribution. A similar response was observed in the lungs of animals of the 949.6-μg/l recovery group, with mean severity scores of 2.5 and 2.1 for males and females, respectively. Lesions were not observed in the lungs of the animals dosed with 4.9 or 47.8 μg/l of the acrylic polymer, and none of the control animals had pneumonitis. The minimum observed effect concentration was 258.6 μg/l and the maximum no-observed-effect concentration was 47.8 μg/l.

Groups of 40 Fischer 344 rats, 20 per sex, were exposed to 0.1, 1.0, or 10 mg/m^3 polyacrylate micronized dust or untreated air for 6 hours per day, 5 days per week for 19 exposures (Lomax, Nitschke, and Pugh 1991). The mass median aerodynamic diameter and the geometric standard deviation were approximately 5.3 to 6.1 μm and 2.4 to 2.7, respectively. Ten rats per sex per group were killed the day after the last exposure and the remaining 10 rats per sex per group were killed 60 days after the last exposure. Treatment-related effects were confined to the lungs; animals that were exposed to 10 mg/m^3 and killed the day after exposure had increased lung weight and inflammation in the alveolar ducts and alveoli. After the 60-day recovery period, the changes in the lungs of the animals of this group were generally not observed. The animals exposed to 0.1 and 1.0 mg/m^3 had minimal macrophage aggregates in the alveoli.

Acrylic Acid and Ethyl and Butyl Acrylate. "Strong, local irritation, resulting in irreversible changes in skin and eyes of rats, was noted after exposure to vapours in air. Five weeks' exposure to acrylic acid vapours at a concentration of 700 mg/m^3 (240 ppm) of air for 4 hours daily led to reduced body weight gain and an increased number of blood reticulocytes. Single and repeated doses caused injury to the gastric mucosa and inflammation of the upper respiratory tract" (IARC 1979).

Groups of five male and five female Fischer 344 rats and B6C3F$_1$ mice were exposed to 25, 75, or 225 ppm (0.074, 0.221, 0.662 mg/l) acrylic acid in air 6 hours per day, 5 days per week, for 2 weeks; a control group breathed untreated air (Miller et al. 1981). Animals were observed twice daily and body weights were determined on days 4, 7, 10, and 14. None of the animals died while on study. Rats and mice of the 225-ppm dose group had signs of nasal irritation by scratching at their noses. Mice of the 25- and 75-ppm groups and rats and mice of the 225-ppm groups had significantly lower body weight gains. Inflammatory and degenerative lesions of the nasal mucosa were observed in most control rats and rats of the 25- and 75-ppm groups, but more severe lesions of the nasal mucosa, including slight focal squamous metaplasia, were observed in rats of the 225-ppm group. In mice, concentration-dependent lesions of the nasal mucosa were observed; mice of the 225-ppm group had slight focal squamous metaplasia.

In inhalation studies, 6-hour exposures to 300 or 1500 ppm acrylic acid for 20 or 4 days, respectively, resulted in nasal irritation or discharge, lethargy, reduced body weight gain or body weight loss, and renal congestion (1500 ppm only); 4-hour exposures to 238 ppm for 35 days resulted in respiratory tract inflammation, reduced body weight gain, and alterations of renal function; 6-hour exposures to 5 or 25 ppm for 90 days had no effect; 6-hour exposure to 75 ppm for 90 days caused nasal lesions (Klimisch and Hellwig 1991).

Groups of 10 male and 10 female Fischer 344 rats and B6C3F$_1$ mice were exposed to 75, 150, or 300 ppm ethyl acrylate in air 6 hours per day, 5 days per week, for 1 month (a total of 22 exposures), while a control group breathed untreated air (Dow Chemical Co. 1979). All animals were observed daily for signs of toxicity. Body weights were determined twice weekly. Tissues from four male and four female rats and mice of the control and high-dose groups were examined microscopically. A statistically significant decrease was observed in mean body weight gain of male and female rats of the 150- and 300-ppm groups after 26 days. For mice, mean body weight gain was statistically significantly decreased for males of the 300-ppm group after 27 days and significantly increased for females of the 150-ppm group after 27 days and for males and females of the 75-ppm group. Mean relative kidney weights were statistically significantly increased for male rats of the 300-ppm group, female rats of the 150- and 300-ppm groups, and male rats of the 75-ppm group; the increases observed in the mid- and high-dose groups were considered possibly compound related, whereas the significance for the males of the 75-ppm group was uncertain. Mean absolute and relative liver weights were decreased as compared to controls; this effect was possibly compound-related. Lesions were not observed at microscopic examination.

Groups of 10 male and female Chinese hamsters and Sprague-Dawley rats, which were housed one animal and two to three animals per cage, respectively, during dosing, were exposed to 817 and 820 ppm butyl acrylate, respectively, for three 6-hour and one 5-hour exposure(s) (Engelhardt and Klimisch 1983). Signs of toxicity, including dyspnea, disequilibrium, and bloody discharge from the eyes and noses, were observed. Four male Chinese hamsters died.

Subchronic Toxicity

Dermal

Acrylic Acid. Groups of 30 outbred female ICR mice, inbred male C3H mice, and hybrid female B6C3F$_1$ mice were treated dermally three times per week for up to 13 weeks with 100 μl of 1% or 4% acrylic acid (containing 220 ppm maximum 4-methoxyphenol as an inhibitor) in acetone; corresponding controls were treated with vehicle only (McLaughlin et al. 1995). The test solutions were applied to a shaved site on the dorsal midline. Five animals per group were killed and necropsied 24 hours after dose 3, 6, 12, and 24, while the remainder were killed after dose 39.

Acrylic acid did not have a "consistent or remarkable effect on body weight" with any strain or dose. On microscopic examination, all animals treated with 1% acrylic acid, with the exception of 2 of 30 C3H mice and 1 of 30 B6C3F$_1$ mice, tolerated the dose. The majority of the animals (14 of 30 ICR mice, 21 of 30 C3H mice, and 21 of 30 B6C3F$_1$ mice) exceeded the maximum tolerated dose (MTD). The strain difference with respect to MTD was not significant. Upon gross examination at each week of the study, all animals exposed to 1% acrylic acid were classified as having tolerated the dose, whereas most animals exposed to 4% acrylic acid reached or exceeded MTD at some point. The total number of high-dose ICR, C3H, and B6C3F$_1$ animals that exceeded MTD at least once, based on gross observations, was 1, 21, and 18, respectively, and the number that reached MTD at least once was 23, 7, and 7, respectively. Compared to controls, incidence values for reaching or exceeding MTD were significantly increased for all strains exposed to 4% by week 2 and generally persisted until week 8. A strain-dependent relationship, in which a greater number of C3H animals exceeded MTD compared to ICR animals, was seen at week 3 and continued until week 8. After week 8, the animals appeared to adjust to the repeated exposure. Only poor to fair agreement between microscopic and gross findings was observed when using the MTD classification given at the week of necropsy, whereas fair agreement was found when analyzing and comparing the most severe gross MTD classification to microscopic findings.

Oral

Acrylic Acid and Methyl, Ethyl, and Butyl Acrylates. Groups of 15 male and 15 female Fischer 344 rats were given a dose of 83, 250, or 750 mg/kg acrylic acid in drinking water daily for 90 to 94 days (DePass et al. 1983). A control group was given untreated water. Body weights, feed consumption, and water consumption were determined weekly. Urinalysis was performed and clinical chemistry and hematology parameters were examined 2 weeks prior to study termination. Necropsy was performed on all animals, and selected tissues of animals of the control and high-dose group were examined microscopically.

None of the animals died during the study. Mean body weight gain, feed consumption, and water consumption were significantly reduced for animals of the high-dose group compared to control values. Body weight gain was reduced for animals of the mid-dose group, but the decrease was significant only for females at the end of the study. Water consumption was significantly decreased for all animals of the mid-dose group and males of the low-dose group. Differences in absolute and relative organ weights for animals of the high-dose group as compared to controls were observed; most of these differences were considered a result of decreased water and feed consumption. However, the increase in relative kidney and testes weights in male animals and the increase in absolute and relative kidney weights in female animals of the high- and mid-dose groups were considered treatment-related. Changes in clinical chemistry, hematology, and urinalysis parameters were observed; for animals of the high-dose group, an increase in blood urea nitrogen (BUN) in males and an increase in BUN and alkaline phosphatase in females were considered treatment-related. Gross and microscopic lesions were not observed.

Groups of 10 male and 10 female Wistar rats were given 150 or 375 mg/kg aqueous acrylic acid by gavage 5 days per week for 3 months; a control group was given water by gavage (Hellwig, Deckardt, and Freisberg 1993). Feed and water consumption and body weights were determined weekly. Animals were examined daily and palpated weekly. After 3 months, the

animals were killed and necropsied, and selected tissues were examined microscopically.

Body weight gains were slightly to moderately decreased for male rats of the high-dose group; body weight gains were also decreased for females during the first 3 weeks of the study. Tympanites of the gastrointestinal tract, often associated with cyanosis and dyspnea, were found in most animals as of week 3. Six males and nine females of the high-dose group and five males and five females of the low-dose group died during the study. In the animals of the high-dose group, irritation of the nonglandular and glandular stomach, elevation of the diaphragm, pulmonary edema/emphysema and alveolar hyperemia, dystelectases, catarrhal or catarrhal-purulent rhinitides, and necrotizing tubular nephrosis were observed. Similar but less severe lesions were observed in the low dose animals.

In a 90-day drinking water study using rats, the maximum no ill-effect dose of acrylic acid was at or slightly less than 0.083 g/kg/day (Dow Chemical Co. 1998). Study details were not provided. The authors estimated the minimal effect concentration to be 0.25 g/kg/day.

Methyl acrylate, $\leq$20 mg/kg, administered in the water was not toxic to rats (Rohm and Haas Co. 1983). Butyl acrylate, given in the drinking water or by gavage, also was not toxic.

Groups of 46 to 50 male F344 rats were dosed orally with 100 or 200 mg/kg ethyl acrylate (inhibited with 15 to 20 ppm HQMME) in 5 ml corn oil 5 days per week for 13 weeks; 55 control rats were given corn oil only (Ghanayem, Matthews, and Maronpot 1991). Twenty-four hours, 8 weeks, and 19 months after dosing, 10 to 11, 10, and the remaining 26 to 35 animals per group, respectively, were killed. Lesions were observed in the forestomach, but not in the glandular stomach or the liver. The forestomach of most animals of the low-dose group were thickened at the termination of dosing, and the incidence of mild to moderate hyperplasia was 100%. Animals of the high-dose group killed 24 hours after dosing had "randomly distributed focal and multifocal raised nodules that were the same color as unaffected mucosa"; two to five nodules were seen. The incidence of severe to extensive hyperplasia in the high dose animals killed 24 hours after dose termination was 100%. After an 8-week recovery period, no lesions were observed in animals of the low-dose group and occasionally "one or more punctate-white foci on the forestomach mucosa" were observed in the high-dose group. At this time, one low-dose and six high-dose animals had mild hyperplasia. After a 19-month recovery period, no lesions were observed except an occasional "more opaque stomach" in a high-dose animal. Two of 26 low-dose and 9 of 26 high-dose 19-month recovery animals had mild hyperplasia; 2 of 35 corresponding control animals had moderate to severe hyperplasia.

Inhalation

Acrylates Copolymer. The inhalation toxicity of Acrylates Copolymer was determined in a study using groups of 15 male and 15 female Crl:CD(SD)BR rats (WIL Research Laboratories, Inc. 1997). In this study, the polymer backbone was *n*-butyl acrylate, methyl methacrylate, and methacrylic acid (McEwen 1999). The animals were exposed via whole body inhalation 6 hours per day, 7 days per week, for 13 weeks to 1, 10, or 30 mg/m^3 of the Acrylates Copolymer formulation. (Particle size was 2.4, 2.4, and 2.5 μm, respectively; Lovelace Respiratory Research Institute 1998a.) Exposure concentrations of Acrylates Copolymer were measured by standard gravimetric methods and of the vehicle were measured using a total hydrocarbon analyzer or an infrared spectrophotometer. The measured exposure concentrations to the formulation were 1.14, 10.3, and 30.5 mg/m^3, respectively. The vehicle and polymer formulation contained 69% ethanol (16.2% solids by weight, viscosity 16 cPs, pH 8.4); residual monomer levels were 5 ppm *n*-butyl acrylate, 33 ppm methyl methacrylate, and 15.7 ppm methacrylic acid (McEwen 1999). The actual concentrations of polymer that the animals were exposed to were 0.185, 1.67, and 4.94 mg/m^3 (Lovelace Respiratory Research Institute 1998a; McEwen 1999). A vehicle-control group was exposed to 30 ppm ethanol and an untreated control group was exposed to filtered air. Exposure caging consisted of two cage batteries per group. Clinical observations were made twice daily. Body weights and feed consumption were measured weekly. Blood samples were taken from all animals at 4 and 13 weeks. Ocular examinations were conducted prior to the initiation of dosing and at the termination of dosing. Five males and five females per group were used as recovery groups and killed 4 weeks after the termination of dosing. All other animals were killed at the end of the dosing period.

None of the animals died during the study, and no test article-related lesions were observed. Body weights and feed consumption were generally similar for all groups. The mean body weights were significantly decreased for females of the high-dose groups during weeks 7 to 8 and males of the high-dose group during weeks 10 to 11. Males of the vehicle control group had a slight but significant increase in mean body weight during weeks 5 to 6. No exposure-related changes were observed in hematology or clinical chemistry parameters. No test article-related ophthalmological lesions were observed. At necropsy, no gross lesions were observed. A significant increase in mean absolute lung weights was observed in recovery females of the high-dose group; this increase was not observed in any other groups either at the termination of dosing or after the recovery period. At the termination of dosing, microscopic examination reported alveolar histiocytosis, characterized by focal accumulation of macrophages within the alveolar spaces, in 2, 3, 0, 2, and 9 males and 0, 2, 0, 1, and 7 females of the untreated-control, vehicle-control, 1-, 10-, and 30-mg/m^3 groups, respectively (10 animals per sex per group). In the high-dose animals, the foci of the alveolar macrophages were sometimes located in the subpleural areas of the lungs, but were more frequently located in the alveoli near the junction of the terminal bronchioles and alveolar ducts. In the other groups, the foci of histiocytosis were located near the pleural surface of the lungs and consisted of small aggregates (approximately 5 to 20) of macrophages

with a pale, basophlic to amphophilic staining cytoplasm. In selected recovery groups, histiocytosis was observed in 1, 1, and 4 males and 1, 0, and 5 females of the untreated-control, vehicle-control, and high-dose groups, respectively (5 animals per sex per group). The researchers stated that "the increase in alveolar histiocytosis (and increased lung weight) in the 30-mg/m^3 group was consistent with a normal, adaptive pulmonary response to an inhaled particulate matter." Alveolar histiocytosis "was not accompanied by any morphologic indicators of injury (i.e., macrophage necrosis, degenerative changes, inflammation, and/or hyperplastic or fibrotic responses)." Therefore, according to the researchers, this was a physiological rather than a pathological response and the no-observable-adverse-effect level (NOAEL) for the formulation containing Acrylates Copolymer was 30 mg/m^3 (corresponding to 4.94 mg/m^3 of the polymer).

A third party reviewer felt that the increase of and difference in alveolar histiocytosis in the high-dose animals indicated an adverse effect (Lovelace Respiratory Research Institute 1998b). The reviewer indicated that the NOAEL for the formulation was 10 mg/m^3 (corresponding to 1.67 mg/m^3 polymer). It was indicated that the "minimal severity of the lesions" and "their waning severity with 4 weeks recovery" indicated that "the particles have a relatively low pulmonary toxicity." The reviewer noted that there were pulmonary lymphoid and neutrophilic infiltrates suggesting "an occult respiratory infection"; such an infection could contribute to alveolar histiocytosis in control animals.

Groups of Crl:CD(SD)BR rats were exposed to an acrylic polymer 6 hours per day, 5 days per week, according to the schedule shown in Table 6 (Rohm and Haas Co. 1985).

The 4-week mean respirable concentrations (calculated from the total dust concentrations and the respirable fraction) were 7.2, 29.7, 51.7, and 94.1 mg/m^3 for groups 2 to 5, respectively, with MMD ranging from 4.4 to 5.4 μm and GSD from 2.6 to 2.7. The 13-week mean dust concentrations were 6.1, 22.1, and 52.4 mg/m^3 for groups 2 to 4, respectively, with MMD ranging from 4.8 to 5.2 μm and GSD from 2.7 to 2.9. A control group (group 1, subgroups A to D2), exposed to untreated air, followed the same schedule as groups 2 to 4, subgroups A to D2. The animals were examined and body weights were determined weekly for 19 weeks and then bimonthly; the animals were observed daily for signs of toxicity. Clinical chemistry, hematology, and microscopic evaluations were conducted on all animals necropsied after 4 and 13 weeks of exposure and after the 13- and 26-week recovery periods.

Signs of treatment-related toxicity were not observed for any of the animals exposed for 4 or 13 weeks. Differences in response

TABLE 6
Exposure regimen for inhalation toxicity study (Rohm and Haas Co. 1985)

Group	Subgroup	No. of animals	Target analytical concentration		Exposure duration (weeks)	Recovery period (weeks)	Necropsy interval (weeks)
			Total (mg/m^3)	Respirable (mg/m^3)			
2	A	10M/10F	17.0	5.0	4	0	4
	B	10M/10F			13	0	13
	C	10M/10F			13	13	26
	D1	10M/10F			13	26	39
	D2	8M/8F*			13	**	**
3	A	10M/10F	67.0	20.0	4	0	4
	B	10M/10F			13	0	13
	C	10M/10F			13	13	26
	D1	10M/10F			13	26	39
	D2	8M/8F*			13	**	**
4	A	10M/10F	167.0	50.0	4	0	4
	B	10M/10F			13	0	13
	C	10M/10F			13	13	26
	D1	10M/10F			13	26	39
	D2	8M/8F*			13	**	**
5	A1	10M/10F	250.0	87.5	4	0	4
	A2	10M/10F			4	13	17
	A3	10M/10F			4	26	30
	A4	18M/18F			4	**	**

*Extra animals included to compensate for unexpected mortality, for special or extra microscopic evaluation, or in the event more follow-up was desired.

**Killed without necropsy at week 49.

were not noted for any of the 13- or 26-week recovery animals. Deaths that occurred during the study were not considered dose-related. Statistically significant increases in body weight and body weight gain were observed for females of groups 4 and 5 and males of group 5 at different intervals, but these increases were not considered treatment-related. Treatment-related changes in clinical chemistry values were not observed. A statistically significant decrease in lymphocyte counts was observed for male and female group 4, subgroups B to D, animals, and the monocyte count for males and the segmented neutrophil count for females was significantly increased; these changes were consistent with an inflammatory response to the test substance. Other treatment-related changes in hematologic parameters were not observed. At ophthalmologic examination, treatment-related ocular lesions were not observed.

At necropsy, a statistically significant increase was reported in lung weights for males and females of groups 4A, 4B, 4C, and 5A1, males of groups 3B and 3D, and females of group 3C and in the lung-to-body weight ratio for males and females of groups 3D, 4B, 4C, 4D, and 5A1, males of groups 3B, 4A, and 5A3, and females of group 3C. At microscopic examination, dose-related bronchiolar-centric interstitial pneumonia was observed in two animals of group 2A, all animals of groups 3A, 4A, 5A1, in nearly all animals of groups 2B, 3B, and 4B, and in all but one animal of groups 2C, 2D, 3C, 3D, 4C, 4D, 5A2, and 5A3. Nodular histiocytosis, characterized by aggregates of large macrophages and an absence of necrosis or other inflammatory cells, and lymphoid hyperplasia, characterized by an increase in the number of lymphocytes and the size of the lymph nodes, was observed in the bronchial and thoracic lymph nodes; the incidence was greater in the animals exposed for 13 weeks than for those exposed for 4 weeks. Bronchiolarization of the alveoli, characterized by the presence of dark cuboidal, usually ciliated, epithelium in the alveoli near the terminal bronchioles, was reported for animals of groups 3B and 4B, with the incidence decreasing slightly in animals of groups 3C and 4C, and then increasing in animals of groups 3D, 4D, and 5A3 as compared to the incidence for groups 3C and 4C. Significant parenchymal cell necrosis and significant fibrosis were not observed.

In another inhalation toxicity study by Battelle (1987), groups of 70 male and 70 female Fischer 344 (CD) rats were exposed to 0.05, 0.2, 1, and 10 mg/m^3 of an acrylic acid polymer in an inhalation chamber 6 hours per day, 5 days per week, for 26 weeks for a total of 132 exposures (Battelle 1987). The polymer was comprised of acrylic acid, alkene-poly (alkenoate) and sodium acrylate (Procter and Gamble Co. 1987). Control groups of rats were exposed to a positive control, a nuisance dust, or untreated filtered air. The particle size distributions, as defined by mass median aerodynamic diameter (MMAD) and GSD, were similar and highly respirable for the test article and the controls (MMAD of 1.95 to 2.07). The mean chamber concentrations (and GSD) were 0.05 (0.01), 0.21 (0.04), 1.09 (0.17), and 9.68 (1.15) mg/m^3 as compared to the target concentrations of 0.05, 0.2, 1, and 10 mg/m^3.

TABLE 7
Exposure regimen for inhalation toxicity study (Battelle 1987)

Necropsy group	Exposure/recovery
1	20 exposures; 0/1-day recovery period
2	20 exposures; 60/61-day recovery period
3	64 exposures; 0/1-day recovery period
4	64 exposures; 89/90-day recovery period
5	132 exposures; 2/3-day recovery period
6	132 exposures; 89/90-day recovery period
7	132 exposures; 191/192-day recovery period

Animals were observed while in the exposure chambers and twice daily for signs of toxicity. Body weights and feed consumption were determined weekly. Ten animals per sex per group were killed according to the schedule shown in Table 7.

Ophthalmic examinations were performed on all animals 1 week prior to necropsy. One animal per sex per necropsy group was used for serology and all animals were used for hematology and clinical chemistry evaluation.

None of the animals died as a result of treatment during the study. Treatment-related physical changes were not observed in animals of any group, and no ophthalmic lesions were observed in any of the animals. Mean body weights of necropsy group 7 male rats exposed to 0.2, 1, or 10 mg/m^3 and female rats exposed to 10 mg/m^3 were statistically significantly less than control values during the last 90 days of recovery; the differences were not considered treatment-related. Absolute body weight gains of male rats of necropsy groups 2 and 7 that were exposed to 1 and 10 mg/m^3, respectively, female rats of necropsy group 3 that were exposed to 10 mg/m^3, and female rats of necropsy group 5 that were exposed to 0.05 and 1 mg/m^3 were significantly decreased. Absolute body weight gains of male rats at necropsy of necropsy group 3 that were exposed to 0.05 and 1 mg/m^3 were significantly increased compared to control values. The differences in absolute body weight gain were not considered treatment-related. Terminal body weights of males at necropsy of group 7 that were exposed to 0.2 and 10 mg/m^3 were significantly decreased compared to negative-controls. Significant differences in feed consumption were frequently observed between test and negative-control animals, but the overall pattern of feed consumption of test animals was not "remarkably different" from the controls.

Treatment-related changes in clinical chemistry parameters were not observed. Exposure to acrylic acid polymer produced concentration-dependent mild increases in the number of circulating mature neutrophils. Males of necropsy group 1 that were exposed to 1 mg/m^3, females of necropsy groups 1 and 5 that were exposed to 0.2 mg/m^3, and males and females of all necropsy groups except 4 and 2, respectively, that were exposed to 10 mg/m^3 had a significant increase in the number or segmented neutrophils. With the exception of the changes in the animals of the 0.2-mg/m^3 group, the changes were considered

treatment-related. For the animals of the 10-mg/m^3 group, the total number of leukocytes was also significantly increased when the neutrophil counts were increased.

A significant decrease in lung weight was observed for females of necropsy group 2 that were exposed to 0.05 mg/m^3. Absolute lung weight, the lung-to-body weight ratio, and the lung-to-brain weight ratio was significantly increased for male rats of necropsy group 6 exposed to 0.2 mg/m^3. Absolute lung weight was significantly increased in males and females of necropsy group 3 and in males of necropsy group 5 that were exposed to 1 mg/m^3. In the 10-mg/m^3 group, significant increases in absolute lung weight and lung-to-body weight ratio were observed for males and females of all necropsy groups. The changes observed for animals of the 1- and 10-mg/m^3 groups were considered treatment-related.

Mottled lungs were observed in one male of necropsy group 1, in all males and nine females of necropsy group 3 that were exposed to 1 mg/m^3, and in all animals exposed to 10 mg/m^3. Enlarged peribronchial and thymic lymph nodes were observed sporadically in rats exposed to acrylic acid polymer. Pulmonary inflammation was reported in animals of the 1 and 10 mg/m^3 groups. For the animals of the 1-mg/m^3 group, pulmonary inflammation was mostly mild in animals of necropsy group 1, nonexistent in animals of necropsy group 2, mostly mild to moderate in animals of necropsy groups 3 and 5, and mostly minimal in animals of necropsy groups 6 and 7. One and four males of necropsy groups 6 and 7, respectively, that were dosed with 1 mg/m^3 acrylic acid polymer had collagen associated with the few foci of inflammation; this collagen formation was minimal. For the animals of the 10 mg/m^3 group, the severity of pulmonary inflammation increased from mostly moderate after 20 exposures to mostly marked after 64 or 132 exposures. A reduction in inflammation and a more multifocal pattern was seen in the recovery groups. Collagen deposition occurred primarily in multifocal areas of inflammation along the periphery of the lungs. Two females of necropsy group 7 that were exposed to 10 mg/m^3 had alveolar/bronchiolar adenomas. Granulomatous inflammation in the thymic and/or peribronchial lymph nodes was seen in necropsy groups 4 to 6 animals exposed to 10 mg/m^3; these lesions were mostly minimal and did not increase in severity. Gross and microscopic lesions were also observed in the lungs of the positive-control group, but these lesions generally had patterns different than those of the test group. The researchers concluded that exposure-related effects occurred at all doses, but "due to the minimal nature of the pulmonary inflammation observed in the two lower exposure group, 0.05 and 0.2 mg/m^3 [acrylic acid copolymer] are considered to be no-adverse effect levels in this study" (Battelle 1987).

Acrylic Acid and Ethyl and Butyl Acrylates. Groups of 15 male and 15 female Fischer 344 rats and B6C3F$_1$ mice were exposed to 5, 25, or 75 ppm (0.015, 0.074, or 0.662 mg/l) acrylic acid in air for 6 hours per day, 5 days per week for 13 weeks; a control group breathed untreated air (Miller et al. 1981). All animals were observed twice daily. Body weights were measured weekly. The mean body weight gains of female mice of the 25- and 75-ppm dose groups were significantly decreased as compared to controls after 12 weeks. Focal degeneration of the olfactory epithelium of the nasal mucosa was observed in rats of the 75-ppm group and mice of all test groups.

Groups of 10 male and 10 female Sprague-Dawley rats were exposed to 23, 124, 242, or 626 ppm ethyl acrylate (measured dose) in air for 6 hours per exposure 58 times over a 12-week period; a control group breathed untreated air (BASF 1978a). The animals were checked daily for signs of toxicity. Body weights were measured weekly. Clinical chemistry and urinalysis were performed three times during the study. None of the animals of the 23-, 124-, or 242-ppm groups died, but all of the animals of the 626-ppm group died during the study. A decrease in body weight gains for animals of the 124-, 242-, and 626-ppm dose groups was considered treatment-related. Animals of the 242-ppm dose group had slight to severe irritation of the mucosa and slight dyspnea between exposures 3 and 9. Animals of the 626-ppm dose group had increasingly severe irritation of the mucosa and difficulty in breathing with gasping as of exposure 3. No compound-induced changes were observed during clinical chemistry or urinalysis. Increases in relative liver weights in females of the 124- and 242-ppm groups and in relative lung weights of females of the 124-ppm group and males and females of the 242-ppm groups were considered compound-related. At microscopic examination, dose-dependent lesions were observed in the area of the nasal mucosa and the olfactory areas in animals of the 242- and 626-ppm groups (BASF 1980).

Groups of 20 male and 20 female Sprague-Dawley rats were exposed to 21, 108, 211, or 546 ppm *n*-butyl acrylate (measured dose) in air for 6 hours per exposure 63 times over a 13-week period; a control group breathed untreated air (BASF 1978b). The animals were checked daily for signs of toxicity. Body weights were measured weekly. Clinical chemistry and urinalysis were performed three times during the study. None of the animals of the 21-, 108-, or 211-ppm groups died, but 16 males and 15 females of the 546-ppm group died during the study. A decrease in body weight gains for animals of the 211- and 546-ppm dose groups was significant and dose-dependent. All animals of the 211-ppm dose group had discharge from the eyes and nose during exposure; these animals recovered after each exposure. Animals of the 546-ppm dose group had pronounced discharge from the eyes and noses, which, until day 10, subsided after exposure; as of day 11, the animals did not recover and had dyspnea and bloody discharge from the eyes and nose. A number of clinical chemistry and hematology parameters were affected by the high dose. Increases were observed in the relative liver weights of females of all test groups, in the relative lung weights of males and females of the 546-ppm group, in the relative adrenal gland weights of males of the 211-ppm and males and females of the 546-ppm groups, and in the thyroid gland weights of females of the 546-ppm group. At microscopic examination, dose-dependent lesions were observed in the area

of the nasal mucosa and the olfactory area in animals of the 108-, 211-, and 546-ppm groups (BASF 1980).

Chronic Toxicity

Oral

Acrylic Acid and Ethyl Acrylate. Male and female Wistar rats were given 120, 800, 2000, or 5000 ppm acrylic acid in the drinking water; groups of 10 males and 10 females were dosed for 3 months and groups of 20 males and 20 females were dosed for 12 months (Hellwig, Deckardt, and Freisberg 1993). The control groups were given untreated water. Feed and water consumption and body weights were determined weekly for the first 3 months; feed and water consumption was then determined every 3 months and body weights were measured every 4 weeks. The animals were examined daily and palpated weekly. Blood samples were taken from 10 animals of each main group after 4, 12, 26, and 51 weeks. The animals were killed and necropsied at the end of the study. Gross lesions of all animals, the livers and kidneys of the animals given 2000 or 5000 ppm acrylic acid for 12 months, selected tissues of the animals given 2000 or 5000 ppm for 3 months, and selected tissues of all animals given acrylic acid for 12 months were examined microscopically.

Actual concentrations in the test solutions were 95% to 107%, 90% to 96%, 95% to 100%, and 94% to 100% of the target concentrations of 120, 800, 2000, and 5000 ppm, respectively, which corresponded to a daily mean intake of 9, 61, 140, and 331 mg/kg, respectively. A statistically significant decrease in water consumption was observed during most of the study for the animals given 5000 ppm for 12 months and until week 14 for animals given 2000 ppm for 12 months. None of the animals in the study died as a result of dosing. Treatment-related changes in clinical chemistry, hematology, or urinalysis parameters were not observed. Treatment-related lesions were also not observed. No significant differences in organ weights were observed between test animals dosed for 3 or 12 months and control animals.

In a 2-year study, groups of 25 male and 25 female Wistar rats were dosed with 6, 60, and 2000 ppm ethyl acrylate in drinking water; after 5 months, the 6- and 60-ppm doses were increased to 7 and 70 ppm, respectively (Borzelleca et al. 1964). Groups of two male and two female beagle dogs were dosed (also for 2 years) with 10, 100, and 1000 ppm ethyl acrylate dissolved in corn oil in gelatin capsules. The 1000-ppm ethyl acrylate capsules had an emetic effect. Reducing the dose to 500 ppm on day 2 resulted in vomiting in two dogs. Dosing for this group was discontinued for the week, the animals were given 300 ppm at week 2, and the dose was increased until it reached 1000 ppm at week 16. Feed and water consumption was determined at various intervals, and the animals were weighed regularly. Body weights were significantly decreased for male rats during year 1 and for female rats throughout the study. Decreased growth paralleled periods of decreased feed consumption. Water consumption was decreased for rats dosed with 2000 ppm. No compound-related lesions were observed for rats or dogs.

Inhalation

Groups of 60 male and 60 female F344 rats were exposed to 0.05, 0.2, or 0.8 mg/m^3 of respirable polyacrylate particles (not defined) (MMAD of 2 to 3 μ) for 24 months and a control group of 60 males and 60 females breathed untreated air (Institute for Polyacrylate Absorbents 1991). A subgroup of animals at each dose was used in a toxicokinetic study and exposed to radioactive material at 6, 12, and 20 months to determine the clearance kinetics. Necropsy of interim killed animals were performed after 6 and 12 months. Visible effects were not seen in animals of the low-dose group, and microscopic changes were not found at 6 and 12 months. One male and 3 females of the mid-dose group had nodules in the lungs and 7 males and 23 females of the high-dose group had pulmonary nodules; 1 female of the control group had pulmonary nodules. Nodules were not observed in animals at the 6- and 12-month necropsies. At 6 months, clearance of the radioactive material was altered at the doses where nodules formed. The researchers did not report that the incidence of pulmonary nodules was significant and considered it to be probably based on an irritant response involving altered clearance from the lungs.

Dermal Irritation

Acrylates Copolymer. The dermal irritation potential of Acrylates Copolymer (approximately 24% solids) was determined using three male and three female New Zealand white rabbits (Bushy Run Research Center 1993a). Acrylates Copolymer, 0.5 ml, was applied for 4 hours under an occlusive patch to intact skin on a clipped dorsal area on the trunk of each animal. The sites were scored 1 hour and 1, 2, 3, and 7 days after patch removal. Minor transient erythema was observed for three animals for <1 day and for two animals for <2 days, and minor transient edema was observed for one animal for <1 day.

Three white Vienna rabbits, two males and one female, were used to determine the dermal irritation potential of Acrylates Copolymer (BASF 1994c). One-half gram of the test material (supplied as a white powder and moistened with distilled water) was applied under a semiocclusive patch to intact skin on the back for 4 hours. The test site was scored for erythema and edema 1, 24, 48, and 72 hours, and 8 and 15 days after patch removal. The average score (24 to 72 hours) was 1.6/4 for erythema and 0.1/4 for edema. All three animals had very slight erythema and scaling on day 15. The researchers concluded that Acrylates Copolymer had "indication of an irritant property to the skin." However, the researchers stated that Acrylates Copolymer had adhesive effects upon moistening with water, making the test article difficult to remove from the skin. They stated that "signs of slight irritation have to be interpreted as artificial as sequela mechanically induced lesions of the superficial layers of the skin. Accordingly, the test substance cannot be considered 'irritant.'"

The dermal irritation potential of Acrylates Copolymer, 30% solids and pH 7 to 7.4, was determined in a Draize test using rabbits (BFGoodrich Specialty Chemicals 1997). Acrylates Copolymer was not a primary irritant.

In another Draize test using rabbits, a 25% solution of Acrylates Copolymer, 100% solids, in acetone also was not a primary irritant (BFGoodrich Specialty Chemicals 1997).

The dermal irritation potential of four Acrylates Copolymers was determined using New Zealand white rabbits according to Organization for Economic Cooperation and Development (OECD) guidelines (BFGoodrich Specialty Chemicals 1997). The test materials were applied for 4 hours to intact skin under semiocclusive patches. At most, the Acrylates Copolymers produced very slight erythema, with an "isolated incident" of very slight edema. Using the Draize scoring scale, three of the Acrylates Copolymers had PIIs of 0.0 and were nonirritating to rabbit skin. One Acrylates Copolymer had a PII of 0.5 and was a mild irritant.

Female New Zealand white rabbits were used to determine the dermal irritation potential of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) (MB Research Laboratories 1997). The test area, a 10 × 15-cm site on the dorsal area of the trunk, was clipped free of hair. Initially, one animal was dosed dermally for 4 hours with 0.5 ml Acrylates Copolymer under a semiocclusive patch; the test site was scored according to the methods of Draize 1, 24, 48, and 72 hours after patch removal. Subsequently, five animals were dosed dermally for 4 hours using semiocclusive patches, and the test sites were observed 1, 24, 48, and 72 hours and 7 days following dosing. The patches adhered to the skin of the animals and were not removable without causing damage to the skin; therefore, the perimeter of the test area was scored. With the exception of one animal that had a severe score at 72 hours the test article produced very slight to well-defined irritation through 72 hours. Very slight irritation was observed for one animal at day 7. (This was not the animal that had severe irritation at 72 hours.) This Acrylates Copolymer had a modified PII of 2.08. The researchers stated that "the elevated erythema scores [were] probably more a result of the animals effort to remove the test article rather than any irritating effect of the test article."

Ammonium Acrylates Copolymer. The dermal irritation potential of a mixture containing 30% Ammonium Acrylates Copolymer was determined using three rabbits (Allied Colloids 1997). The test material was applied under semiocclusive patches for 4 hours to a shaved dorsal area on the trunk of each animal. The test sites were scored 1, 24, 48, and 72 hours after patch removal. One animal had very slight erythema 1 and 48 hours after patch removal; the other two animals did not have an irritant response. Edema was not observed at any of the test sites. Ammonium Acrylates Copolymer was "practically nonirritant to rabbit skin."

Ethylene/Acrylic Acid Copolymer. An aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, was applied to rabbits in an open test (Union Carbide Chemical Co. 1998c). Study details were not provided. The authors stated that irritation was minor with a grade of 4.

Acrylates/VA Copolymer. New Zealand white rabbits, five males and one female, were used to determine the primary irritation potential of Acrylates/VA Copolymer solution (Bio/dynamics Inc. 1988a). One-half milliliter of undiluted solution was applied under occlusive patches to two intact shaved sites on the back of each animal for 4 hours. The sites were scored for erythema and edema according to the Draize scale 30 minutes and 24, 48, and 72 hours after patch removal; if signs of irritation were still apparent after 72 hours, the sites were observed 7, 10, and 14 days after dosing or until no evidence of irritation was present.

After 30 minutes, four animals had very slight to slight erythema with edema and two animals had moderate erythema with edema. The test sites of one animal had superficial necrosis after 24, 48, and 72 hours and 7 days and severe erythema with edema until day 7, the left test site of one animal had necrosis after 24, 48, and 72 hours, superficial necrosis after 7 and 10 days, severe erythema with edema until day 7, and severe erythema until day 10, and the left test site of a third animal had superficial dermatitis after 72 hours and 7 days and severe erythema on day 7. Desquamation was observed at the test sites of these animals on days 7 and 10. Signs of irritation were not seen on day 14. The researchers concluded that an Acrylates/VA Copolymer solution "produced moderate to severe but reversible dermal irritation."

Two male and four female New Zealand white rabbits were used to determine the dermal irritation potential of Vinyl Acetate/Maleate/Acrylate Copolymer solution (Bio/dynamics Inc. 1984c). One-half milliliter of the test material was applied undiluted to two clipped sites on the back under a semiocclusive patch for 4 hours and to two clipped sites under an occlusive patch for 24 hours. The sites were scored for irritation according to the Draize scale 30 minutes and 24, 48, and 72 hours after removal of the 4-hour semiocclusive patch and 30 minutes and 24 and 48 hours after removal of the 24-hour occlusive patch. If irritation was observed after 72 and 48 hours, respectively, the sites were observed on days 7, 10, and 14 or until no evidence of irritation was present.

Thirty minutes after removal of the 4-hour semiocclusive patch and the 24-hour occlusive patch, all animals had well-defined to severe erythema with edema. Epidermal tissue damage was observed at one or both 4-hour patch sites in four animals and at one or both 24-hour patch sites in three animals. Subepidermal damage was observed at both 24-hour patch sites in two animals. Very slight erythema was observed at the 4- and 24-hour patch sites through day 14 for all animals. The primary irritation index for the 24-hour exposure was 4.4.

Sodium Polyacrylate. Six albino rabbits were used to determine the irritation potential of Sodium Polyacrylate (Finnegan and Dienna 1953). Two milliliters of undiluted Sodium Polyacrylate was applied to the clipped back and sides of the animals once daily, 5 days per week for 4 weeks. Signs of irritation were not observed.

Acrylic Acid. Acrylic acid, 1% or 4% in acetone, was applied to the skin of groups of 30 female ICR, 30 male C3H,

and 30 female B6C3F$_1$ mice three times per week for 13 weeks (Tegeris et al. 1988). Control mice were dosed with acetone. Five mice per group were killed and necropsied after 1, 2, 4, and 8 weeks. Significant skin irritation, including desquamation, fissuring, and eschar, was observed in all three strains of mice treated with 4% acrylic acid. Proliferative, degenerative, and inflammatory changes in the epidermis and dermis were observed at microscopic examination of the skin of animals dosed with 4% acrylic acid. A low incidence of proliferative changes was observed in the animals dosed with 1%. No changes were observed in control animals.

Sensitization

Acrylates Copolymer. A Magnusson-Kligman maximization study was performed using albino guinea pigs to determine the sensitization potential of Acrylates Copolymer (approximately 25% solids; Amerchol 1997) (Pharmaco LSR 1993). A range-finding study was performed in which groups of two animals were dosed intradermally with 0.5%, 1.0%, or 5.0% *v/v* Acrylates Copolymer in propylene glycol. Extensive necrosis was observed 24 and 48 hours, but not 72 hours, after injection of 5.0% Acrylates Copolymer; local necrosis was produced by 0.5% and 1.0%. Also in a range-finding study, three male and three female animals were dosed dermally for 24 hours with 10%, 25%, 50% *v/v* and undiluted Acrylates Copolymer under an occlusive patch. Undiluted Acrylates Copolymer was nonirritating.

In the induction phase of the maximization study, a test group of 10 male and 10 female animals were dosed intradermally with 0.1 ml of 5% *v/v* Acrylates Copolymer (25% solids) and topically with undiluted Acrylates Copolymer (25% solids). After a 14-day nontreatment period, the animals were challenged with undiluted Acrylates Copolymer. An irritation control group of five male and five female animals were induced without test article and were challenged with undiluted Acrylates Copolymer. Acrylates Copolymer did not produce a sensitization reaction in any of the animals.

Female guinea pigs were used in a Magnusson-Kligman maximization test to determine the sensitization potential of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) (Unilever Research U.S. 1996). During induction, the intrascapular region of 20 animals was clipped free of hair, and intradermal injection of 25% Acrylates Copolymer (*w/v*) in distilled water with and without Freund's complete adjuvant (FCA) was given. (One test animal died prior to challenge; the reason was not test article related.) One week after intradermal injection, the test site was again clipped and an occlusive patch of undiluted Acrylates Copolymer was applied to the injection site for 48 hour. A control group of 10 animals was treated in a similar manner using distilled water. The challenge was conducted 14 days after the induction by applying an occlusive patch of 25% *w/v* Acrylates Copolymer in distilled water to the clipped left flank of test and control animals for 24 hours. The test sites were evaluated 24 and 48 hours after patch removal. Acrylates Copolymer was not a sensitizer in guinea pigs.

The sensitization potential of four Acrylates Copolymers was determined using groups of albino guinea pigs in Magnusson-Kligman maximization studies performed according to OECD guidelines (BFGoodrich Specialty Chemicals 1997). For three of the Acrylates Copolymers, groups of 20 test animals were dosed intradermally with 25% *w/v* test material in distilled water and topically with undiluted test material in the induction phase of the study. For one Acrylates Copolymer, the animals were challenged with 10% and 25% *v/v* test material, whereas for the other two Acrylates Copolymers, the animals were challenged with undiluted and 75% *v/v* test material in distilled water. For the fourth Acrylates Copolymer, a group of 20 test animals were dosed intradermally with 10% *w/v* test material in distilled water and topically with undiluted test material in the induction phase and challenged with undiluted and 75% *v/v* test material in distilled water. Control groups consisted of 10 animals. The Acrylates Copolymers did not produce a sensitization reaction in any of the animals.

Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively; CTFA 1999b) was evaluated for its sensitization potential in a Magnusson-Kligman maximization test (MB Research Laboratories 1999c). During induction, 10 male and 10 female Hartley albino guinea pigs were given three pairs of intradermal injections consisting of 50% Acrylates Copolymer in mineral oil, mineral oil, and/or FCA. One week after intradermal injection, an occlusive patch containing undiluted Acrylates Copolymer was applied for 48 hours to the test site, which was pretreated with sodium lauryl sulfate. A negative-control group of five males and five females was treated in a similar manner using vehicle only. The challenge was performed 2 weeks after induction by applying for 24 hours an occlusive patch containing undiluted test article to one flank and containing vehicle to the other flank of test and control animals. During induction, weak to moderate erythema was observed; none was observed at challenge. Two test animals had diarrhea and soiling of the anogenital area, whereas one had soiling only. The researchers concluded that Acrylates Copolymer had "a weak sensitizing potential" but "did not produce any sensitizing response."

The sensitization potential of Acrylates Copolymer was determined in a Buehler sensitization test using guinea pigs (Allied Colloids 1997). (Details were not given.) No positive reactions were observed during induction or challenge, and Acrylates Copolymer was not a sensitizer in guinea pigs.

Ocular Irritation

In Vivo

Acrylates Copolymer. Two male and two female New Zealand white rabbits were used to determine the ocular irritation potential of Acrylates Copolymer (approximately 24% solids) (Bushy Run Research Center 1993a). The test article, 0.1 ml, was instilled into the conjunctival sac of one eye of each

animal; the contralateral eye served as an untreated control. The eyes were examined 1 hour and 1, 2, 3, and 7 days after dosing. Minor to moderate conjunctival irritation was reported for all animals 1 hour after dosing. The maximum mean total score at 1 hour was 8.0/110. All eyes were normal within 2 to 3 days. Acrylates Copolymer was mildly irritating to rabbit eyes.

The ocular irritation potential of Acrylates Copolymer (supplied as a white powder) was determined using one male and two female white Vienna rabbits (BASF 1994d). Thirty-two milligrams of the test article was placed in the conjunctival sac of one eye of each animal and the eye was not washed; the contralateral eye served as an untreated control. The eyes were examined 1, 24, 48, and 72 hours after application. The average score (24 to 72 hours) was 0.0/4 for corneal opacity and chemosis, 0.0/2 for the iris, and 0.1/3 for conjunctivae redness. Acrylates Copolymer was not an ocular irritant.

Six New Zealand white rabbits were used to determine the ocular irritation potential of Acrylates Copolymer (containing 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively; CTFA 1999a) (MB Research Laboratories 1996b). One-tenth milliliter of the test article was placed in the conjunctival sac of the left eye, and the eye was not rinsed. The right eye served as a control. The eyes were examined for irritation 1 hours and 1, 2, 3, and 7 days after dosing. Corneal opacity, seen in four animals, and iritis, seen in three animals, cleared by day 7. Conjunctival irritation, which was observed in all animals, cleared in all but one animal by day 7. The researchers stated that Acrylates Copolymer was "an eye irritant but not corrosive."

The ocular irritation potential of Acrylates Copolymer, 30% solids and pH 7 to 7.4, was determined using rabbits (BFGoodrich Specialty Chemicals 1997). Study details were not reported, but the authors concluded that Acrylates Copolymer was not an ocular irritant.

The ocular irritation potential of a 15% solution of Acrylates Copolymer, 100% solids, in ammonia water, was determined according to the method of Carpenter and Smythe (BFGoodrich Specialty Chemicals 1997). Acrylates Copolymer was not an ocular irritant.

Using groups of three New Zealand white rabbits, the ocular irritation potential of four Acrylates Copolymers was determined according to OECD guidelines (BFGoodrich Specialty Chemicals 1997). The test materials were instilled into the conjunctival sac of one eye of each rabbit, and the eyes were not rinsed. The test materials produced minimal or minimal to moderate conjunctival irritation; the eyes appeared normal after 24 or 48 hours. Using the scoring of Kay and Calandra, the Acrylates Copolymers produced maximum group mean score of 2.7 to 5.3 and were minimal irritants.

The ocular irritation potential of Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively; CTFA 1999b) was determined using New Zealand white rabbits (MB Research Laboratories 1999d). Initially, 0.1 ml Acrylates Copolymer was instilled into the conjunctival sac of one male animal, and the eye was graded 1, 24, 48, and 72 hours after dosing. Subsequently, 0.1 ml was instilled into the eyes of four males and one female. Again, the eyes were evaluated 1, 24, 48, and 72 hours after dosing. No corneal opacity or iritis was observed. Conjunctival irritation, which was observed in all animals, cleared by 48 hours. The researchers stated that according to OECD guidelines, "the test article is an ocular irritant but not corrosive." According to the methods of Kay and Calandra, "the test article is minimally irritating."

Ammonium Acrylates Copolymer. The ocular irritation potential of a mixture containing 30% Ammonium Acrylates Copolymer was determined using three New Zealand white rabbits (Allied Colloids 1997). The eyes were examined 1, 24, 48, and 72 hours after instillation of the test article. Slight conjunctival redness and slight ocular discharge were observed for one animal 1 hour after instillation. Ammonium Acrylates Copolymer was "practically nonirritant to rabbit eyes."

Ethylene/Acrylic Acid Copolymer. In an ocular irritation study, an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer, 21.8% solids at pH 9.8, produced trace corneal injury (grade 2) in rabbit eyes (Union Carbide Chemical Co. 1998c). Study details were not provided.

Acrylates/VA Copolymer. Six male New Zealand white rabbits were used to determine the ocular irritation potential of Acrylates/VA Copolymer solution (Bio/dynamics Inc. 1988b). One-tenth milliliter of undiluted solution was placed in the lower conjunctival sac of the right eye of each animal. The eyes were not rinsed immediately after dosing but were rinsed after 24 hours to remove residual material. The contralateral eye served as a control. The eyes were scored for irritation according to the Draize method 1, 24, 48, and 72 hours and 7, 14, and 21 days after dosing. All animals had moderate to severe conjunctival irritation, corneal opacity and/or ulceration, and iridal damage or changes. Four animals had alopecia around the eye and one animal vocalized after application. Ocular irritation was observed for 7 days in five animals and for 14 days in one animal. The researchers stated that an Acrylates/VA Copolymer solution "produced severe but reversible ocular irritation."

Three male and three female New Zealand white rabbits were used to determine the ocular irritation potential of Vinyl Acetate/Maleate/Acrylate Copolymer solution (Bio/dynamics Inc. 1984d). One-tenth milliliter of undiluted solution was placed in the lower conjunctival sac of the right eye of each animal. The eyes were not rinsed immediately after dosing but were rinsed after 24 hours to remove residual material. The contralateral eye served as a negative control. The eyes were scored for irritation according to the Draize method after 1, 24, 48, and 72 hours and at 7, 14, and 21 days after dosing. All animals had moderate to severe conjunctival irritation and corneal opacity and/or ulceration. Two animals had iritic changes and four animals had desquamation on the outer eyelids and/or alopecia around the eye. Ocular irritation was observed for 7 days in all animals and for 14 days in four animals. The researchers stated that an

Vinyl Acetate/Maleate/Acrylate Copolymer solution "produced moderate to severe but reversible ocular irritation."

Sodium Polyacrylate. A Draize test was performed in which 0.1 cc of Sodium Polyacrylate was placed in the conjunctival sac of groups of rabbits; using groups of 10 animals, the eyes were not rinsed and using groups of three animals, the eyes were rinsed (Finnegan and Dienna 1953). Irritation was scored 1, 2, 3, 4, and 7 days after instillation. The greatest tolerated concentration was 13% to 20% for unrinsed eyes and 20% to 30% for rinsed eyes.

An irritant threshold test was performed in which Sodium Polyacrylate was placed in the conjunctival sac of groups of five rabbits, and the eyes were examined for edema, erythema, and increased secretions after 1 hour (Finnegan and Dienna 1953). The threshold concentration, i.e., the greatest concentration that did not produce irritation in three or more of the five animals, was 2%.

Acrylic Acid. A 1% acrylic acid solution caused significant injury to the rabbit eye (IARC 1979).

In Vitro

Acrylates Copolymer. Two chorioallantoic membrane vascular assays (CAMVAs) and two bovine corneal opacity and permeability (BCOP) tests were performed to determine the ocular irritation potential of Acrylates Copolymer (MB Research Laboratories 1996c, 1996d). In both CAMVAs, Acrylates Copolymer was a nonirritant and in both BCOPs it was a mild irritant.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Sodium Polyacrylate. The teratogenic potential of 4500- and 90,000-Da molecular weight Sodium Polyacrylate was evaluated using groups of Charles River CD rats that were dosed by gavage following a FDA Segment II protocol with some modifications (Nolen et al. 1989). Concentrations of 500, 1000, and 3000 mg/kg/day of the low-molecular-weight Sodium Polyacrylate (43.3% solids; 0.09% residual monomer) in demineralized, distilled water at a dose volume of 10 ml/kg/day and 125, 375, and 1125 mg/kg/day of the high-molecular-weight Sodium Polyacrylate (77.5% Sodium Polyacrylate; 3.3% free acrylic acid) in distilled water (*w/v*) were used. Vehicle-control groups were used with both Sodium Polyacrylates and an untreated-control group was used with the high-molecular-weight Sodium Polyacrylate. In the study using the low-molecular-weight Sodium Polyacrylate, 30 animals per group were dosed on days 6 to 15 of gestation and killed on day 19. In the study using the high-molecular-weight Sodium Polyacrylate, eight dams per group were dosed on days 6 to 13 of gestation and killed on day 13; the remaining 20 to 21 dams per group were dosed on days 6 to 15 of gestation and killed on day 19.

In the low-molecular-weight Sodium Polyacrylate study, two animals of the mid-dose group and one of the high-dose group died accidentally during the study. Significant differences in body weight gains and feed consumption were not observed. Dams of the high-dose group had soft or liquid stools. Effects on embryo viability and fetal growth were not observed, and significant differences in soft-tissue or skeletal abnormalities and variations were not seen between the treated and control groups.

In the high-molecular-weight Sodium Polyacrylate study, one dam of the mid-dose group and six dams of the high-dose group died during the study; three of the high-dose deaths were considered treatment-related, the others were accidental. Statistically significant differences from control values in maternal body weights and body weight gains during gestation were not observed. Changes in overall feed consumption during gestation were not seen; however, a decrease in feed consumption was observed for the high-dose animals on days 7 to 9 of gestation. Significant differences in reproductive and embryonic characteristics were not observed for the dams killed on day 13 or 19. The fetuses of the treated group were significantly longer and also somewhat heavier than the controls; this was not considered biologically significant. Significant differences in soft-tissue or skeletal abnormalities were not reported. Fetuses of both the control and test groups had some delayed skeletal ossification, but this was not considered a treatment-related effect.

Acrylic Acid. Groups of 10 male and 20 female Fischer 344 rats were given 83, 250, or 750 mg/kg acrylic acid in the drinking water daily, and the animals were mated after 13 weeks of dosing (DePass et al. 1983). The neonates, culled to litter size of 10 on day 5 of lactation, were weighed as litters on day 7 and individually on day 21. After weaning, five males and five females randomly selected from each group of the F_0 and F_1 generations were killed and necropsied.

For the F_0 generation, statistically significant decreases were observed in feed and water consumption and body weight gains for males and females of the high-dose group. Water consumption of males and body weight gains of females of the mid-dose group were significantly decreased. For males of the high-dose group, absolute liver weights were statistically significantly decreased and relative kidney weights and spleen and testes weights were statistically significantly increased. For female animals, absolute liver and spleen weights were statistically significantly decreased and relative kidney and brain weights were statistically significantly increased in the high-dose group and absolute kidney, relative kidney, and relative liver weights were statistically significantly increased in the mid-dose group. The researchers felt that most of the changes in organ weights were secondary effects of reduced body weight, with the exception of the increase in absolute and relative kidney weights in females.

Numerical, although not statistically significant, reductions in gestation index (89% for test animals, 100% for controls), number of live pups per litter (four for test animals, six for controls), and percentage of pups weaned (42% for test animals, 100% for controls) were observed in the high-dose group. Females of the high-dose group had a fertility index of 45%; however, the females of the control group had a relatively low fertility rate of 50%. The researchers noted that the control group was relatively atypical and the results of the high-dose group should be

interpreted cautiously. The researchers felt that a conclusion of no adverse effect at the mid or low dosages was correct; a number of the values observed for these groups were greater than those observed for control animals.

For the F_1 generation, the average body weights were statistically significantly decreased for neonates of the high-dose group as compared to those of the control group at days 7 and 21. At day 21, the absolute and relative liver weights and absolute kidney and heart weights were statistically significantly decreased and the relative brain weights were statistically significantly increased for male neonates of the high dose group. For females at day 21, absolute liver weights and absolute and relative spleen and body weights were statistically significantly decreased and relative brain weights were statistically significantly increased for neonates of the high-dose group and absolute liver and spleen weights were statistically significantly increased for neonates of the low-dose group. The researchers again felt that most of the changes in organ weights were due to decreased body weights, with the exception of the changes in weights of the liver and spleen.

Inhalation

Acrylic Acid and 2-Ethylhexyl, Methyl, Ethyl, Butyl, 2-Hydroxyethyl, and Hydroxypropyl Acrylate. In an inhalation study, gravid Sprague-Dawley rats were exposed to acrylic acid 6 hours per day on days 6 to 15 of gestation (Klimisch and Hellwig 1991). Groups of five animals were exposed to 225 or 450 ppm acrylic acid (analytical means of 217.6 and 438.9 ppm, respectively) in a dose range–finding study and groups of 30 animals were exposed to 40, 120, or 360 ppm (analytical means of 39.4, 114.0, 356.2 ppm, respectively) in the main study. (Particle size was not specified.) Control groups were used. The animals were killed on day 20 of gestation.

In the dose range–finding study, animals of both dose groups had signs of sensory irritation during dosing. Body weight gains and feed consumption of animals of the 450-ppm group were decreased throughout exposure. Maternal toxicity occurred at both concentrations, and was more pronounced at the higher dose.

In the main study, abnormal behavior was not noted in the 40- and 120-ppm dose groups, but signs of sensory irritation were observed for animals of the 360-ppm dose group. Body weights, body weight gains, and feed consumption were statistically significantly reduced for dams of the high-dose group throughout dosing. A significant decrease was observed in body weight minus uterine weight for animals of the mid- and high-dose groups. Acrylic acid was maternally toxic at doses of 120 and 360 ppm, and was possibly maternally toxic at a dose of 40 ppm acrylic acid. Acrylic acid was not teratogenic or embryotoxic.

Groups of 17 to 25 gravid Sprague-Dawley rats were exposed 6 hours per day on days 6 to 20 of gestation to acrylic acid or its esters via inhalation (Saillenfait et al. 1999). Exposure concentrations were 50 to 300 ppm acrylic acid (48.0 to 313.1 ppm actual), 25 to 200 ppm methyl acrylate (25.1 to 199.4 ppm actual), 25 to 200 ppm ethyl acrylate (25.0 to 202.0 ppm actual), 100 to 300 ppm *n*-butyl acrylate (103.3 to 302.5 ppm actual), 50 to 100 2-ethylhexyl acrylate (51.0 to 102.5 ppm actual), 1 to 10 ppm 2-hydroxyethyl acrylate (1.1 to 10.6 ppm actual); and 1 to 10 ppm hydroxypropyl acrylate (1.0 to 10.3 ppm actual). Controls were exposed to filtered room air. Airborne particles were measured with an Aerodynamic Particle Sizer, with a minimum detection limit of 0.5 μm; there was no difference in particle counts between clean filtered air (control) and vapor-laden air in the test chambers. (The particle sizes were not stated.) The animals were killed on day 21 of gestation.

No maternal deaths were observed in any test group. Reductions in maternal weight gain and feed consumption were observed at some doses with all test compounds. Decreased fetal body weights were observed with 300 ppm acrylic acid, 100 ppm methyl acrylate, 200 ppm ethyl acrylate, and 200 and 300 ppm butyl acrylate. No teratogenic or reproductive effects were seen with any of the test compounds.

Groups of 33 gravid Sprague Dawley rats were exposed to air with 50 or 150 ppm ethyl acrylate for 6 hours per day on days 6 to 15 of gestation; a control group was exposed to filtered air (Murray et al. 1981). All animals were observed daily for signs of toxicity. Maternal body weights were measured during gestation, and feed and water consumption was determined at 3-day intervals starting on day 6 of gestation. Maternal toxicity, as evidenced by decreased body weights and body weight gains, was observed in the 150-ppm dose group. Major malformations were observed in three neonates of the high-dose group; this was not statistically significant compared to controls and was not considered to be of toxicological significance. Ethyl acrylate was not embryotoxic or fetotoxic.

Gravid rats were exposed to $\leq$250 ppm *n*-butyl acrylate in an inhalation study (Rohm and Haas Co. 1983). High concentrations (135 and 250 ppm) had toxic effects on the dams and the fetuses, and the dams had signs of irritation. No toxic effects were seen with 25 ppm *n*-butyl acrylate.

Parenteral

Acrylic Acid and Methyl, Ethyl, Butyl, Isobutyl, and Isodecyl Methacrylate. Twenty-two groups of five gravid female Sprague-Dawley rats were dosed by IP injection on days 5, 10, and 15 of gestation with 0.13 to 0.44 ml/kg methyl, 0.12 to 0.41 ml/kg ethyl, 0.23 to 0.77 ml/kg *n*-butyl, 0.14 to 0.47 ml/kg isobutyl, and 0.25 to 0.82 isodecyl methacrylate monomers plus 0.0023 to 0.0075 ml/kg acrylic acid; the dose values were one-tenth, one-fifth, and one-third the LD_{50} (Singh, Lawrence, and Autian 1972). Groups of rats were given 0.82 ml/kg cottonseed oil, distilled water, or normal saline or were untreated and served as control groups. The dams were killed on day 20 of gestation.

Using a "pooled volume control," all three doses of ethyl methacrylate, the high doses of *n*-butyl methacrylate and isobutyl methacrylate, and the mid and high doses of isodecyl methacrylate significantly increased resorption. The incidence

of gross abnormalities was significantly increased in all dose groups, except the low-dose groups given methyl methacrylate and acrylic acid and the low- and mid-dose group given *n*-butyl methacrylate. The incidence of skeletal malformations was significantly increased in the acrylic acid high dose group.

Three groups of five gravid female rats were dosed by IP injection with 2.5, 4.7, or 8 mg/kg acrylic acid on days 5, 10, and 15 of gestation, while a control group was given vehicle (IARC 1979). Significant increases were observed in the number of "gross abnormalities" in the neonates of the mid- and high-dose groups and in skeletal abnormalities in the high-dose group as compared to controls. Embryotoxicity occurred in animals of the high-dose group.

On day 13 of gestation, the uterus of laparotomized gravid Sprague-Dawley rats was exposed, and each embryo in one uterine horn was given an intraamniotic injection of 10, 100, or 1000 μg/fetus acrylic acid in 0.9% saline (Slott and Hales 1985). The contralateral embryos were given an equivalent dose of saline. The uterus was repositioned. The dams were killed on day 20 of gestation, and the fetuses were examined. Acrylic acid was not significantly embryotoxic at doses of 10 or 100 μg/fetus, but 78% of the fetuses were resorbed with a dose of 1000 μg/fetus.

GENOTOXICITY

Acrylates Copolymer. An Ames test was performed to determine the mutagenic potential of Acrylates Copolymer (25% solids; Amerchol 1997) (Bushy Run Research Center 1993b). Acrylates Copolymer was assayed in duplicate at concentrations of 0.10 to 10 mg/plate using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 without and with metabolic activation. Negative and positive controls were used. Acrylates Copolymer was not mutagenic.

The mutagenic potential of Acrylates Copolymer was determined in an Ames test (BASF 1994e). Acrylates Copolymer was assayed in a standard plate test and a preincubation test at concentrations of 20 to 5000 μg/plate using *S. typhimurium* strains TA1535, TA100, TA1537, and TA98 with and without metabolic activation. Vehicle was used as a negative control. Acrylates Copolymer was not mutagenic.

Ammonium Acrylates Copolymer. The mutagenic potential of a mixture containing 30% Ammonium Acrylates Copolymer was determined in a modified Ames test using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* WP2uvrA (Allied Colloids 1997). Ammonium Acrylates Copolymer was not mutagenic.

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer. A microbial mutagen test was performed using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 to determine the mutagenic potential of 2-ethylhexyl acetate (Rohm and Haas Co. 1979). 2-Ethylhexyl acrylate in dimethylsulfoxide (DMSO) was tested at concentrations of 0.01 to 5.0 μl/plate with and without metabolic activation. DMSO alone was used as a negative control and 2-anthramine, 2-aminofluorene, and 2-acetaminofluorene were used as positive controls. A statistically significant increase in revertants per plate was observed with TA1535 with metabolic activation at the lowest concentration of 2-ethylhexyl acrylate tested. Negative results were obtained when the test was repeated with 0.0001 to 0.01 μl/plate. 2-Ethylhexyl acrylate was considered not mutagenic in this microbial mutagen test.

The mutagenic potential of 2-ethylhexyl acrylate was examined in an Ames test (Zeiger et al. 1985). Concentrations of 100 to 10,000 μg/plate were tested with and without metabolic activation using *S. typhimurium* strains TA100, TA1535, and TA98, and in strain TA1537, concentrations of 3.33 to 100 and 100 to 10,000 μg/plate were tested without and with metabolic activation, respectively. Negative and positive controls were used. 2-Ethylhexyl acrylate was not mutagenic.

2-Ethylhexyl acrylate was assayed in a mammalian cell transformation test using the fibroblastic cell line C3H 10T1/2, clone 8 cells. The results of the test were based on type III foci; i.e., piling of cells that are highly polar (elongated) and criss-crossing at the interfaces of the focus and the monolayer (Rohm and Haas Co. 1982). 2-Ethylhexyl acrylate was tested at concentrations of 1.0 to 30.0 nl/ml; concentrations were determined based on the results of a range-finding toxicity test. The vehicle, DMSO, was used as a negative control and DMBA was the positive control. 2-Ethylhexyl acrylate did not induce any type III foci and was considered negative in this mammalian cell transformation test.

The mutagenic potential of 2-ethylhexyl acrylate in acetone was evaluated in a mouse lymphoma forward mutation assay using L5178Y $TK^{+/-}$ cells with and without metabolic activation (Litton Bionetics, Inc. 1984). Vehicle was used as the negative control and ethylmethane sulfonate (EMS) and dimethylnitrosamine were used as the positive controls without and with metabolic activation, respectively. Multiple trials were performed without metabolic activation due to excessive toxicity and inconsistent results; doses of 1.95 to 1000 nl/ml were investigated, with concentrations up to 60 nl/ml giving usable results. Two trials were performed with metabolic activation, and concentrations of 7.810 to 150 nl/ml were tested. 2-Ethylhexyl acrylate was mutagenic in the presence of metabolic activation, inducing repeatable increases in the mutant frequency at the TK locus. Without metabolic activation, small but nonrepeatable increases in mutant frequency were observed with high toxicity.

The ability of 20 to 34 μg/ml 2-ethylhexyl acrylate to induce mutations, aberrations, and micronuclei was examined using L5178Y mouse lymphoma cells without metabolic activation (Dearfield et al. 1989). Testing was done in duplicate. 2-Ethylhexyl acrylate produced equivocal mutagenic responses for increased mutant frequency and induced aberrations; increases were not consistent, nor were they dose-dependent. The number of micronuclei was not increased by 2-ethylhexyl acrylate.

The mutagenic potential of 2-ethylhexyl acrylate in DMSO was evaluated in monolayer and suspension assays using

Chinese hamster ovary (CHO) cells (Moore et al. 1991). Two tests were performed for each assay type. 2-Ethylhexyl acrylate was tested at concentrations of 5 to 80 μg/ml in the monolayer assay and of 14 to 26 μg/ml in the suspension assay without metabolic activation. 2-Ethylhexyl acrylate did not induce a dose-related increase in hypoxanthine-guanine phosphoribosyltransferase (HGPRT) frequency in either type of assay.

A battery of three in vitro assays was performed using 2-ethylhexyl acrylate in DMSO (Bushy Run Research Center 1980). In a CHO assay, 2-ethylhexyl acrylate was tested at concentrations of 0.001% to 0.0000625% without metabolic activation and 0.0005% to 0.00003125% with metabolic activation. In a sister-chromatid exchange (SCE), concentrations of 0.001% to 0.00003125% and 0.001% to 0.0000625% were tested without and with metabolic activation, respectively. In an unscheduled DNA synthesis (UDS) assay, concentrations of 0.001% to 0.00001% were tested. Appropriate positive, negative, and solvent controls were used for each test. 2-Ethylhexyl acrylate was not mutagenic in the CHO assay. In the SCE assay, a weak response was observed with metabolic activation at doses of 0.0005% and 0.00025%. A weak non–dose-related effect was found in the UDS assay. 2-Ethylhexyl acrylate was a probable, but weak, mutagen in this battery of tests. The researchers stated "a pattern of mutagenic action in the SCE and UDS tests indicated the probable mutagenic potential of 2-ethylhexyl acrylate. The relatively low levels of genetic activity obtained with this sample also could be an indication of a mutagenically active contaminant contained in the test agent. This speculative possibility is appropriate to the low levels of activity observed and is consistent with the finding (in the literature) that hydroquinone (listed as one of the polymerization inhibitors used in this product) is mutagenic in the Ames test, in mouse bone marrow cells . . . , in *E. coli* and several plant systems." The researchers also stated that the lack of response in the CHO test "is probably an indication that 2-ethylhexyl acrylate was more adequately activated by the metabolic systems used in the other two tests than in the CHO test. A different lot of liver homogenate was used in the CHO Mutation test and the SCE test which may explain the difference in the results for these two tests both performed with CHO cells."

In an in vivo cytogenetic study, groups of 24 male CD-1 mice were given a single oral dose of and groups of eight animals were dosed daily for 5 days with 0.25, 1.0, or 2.5 g/kg 2-ethylhexyl acrylate in corn oil at a volume of 12 ml/kg/day (Rohm and Haas Co. 1984b). In the groups given the single dose, eight animals per group were killed 6, 24, and 48 hours after dosing and in the groups dosed for 5 days, the animals were killed 6 hours after the last dose; bone marrow slides were prepared. The animals were given 1 mg/kg colchicine 3 hours prior to being killed. Negative control (24 animals) were given vehicle only and a positive-control group (eight animals) was given a single IP dose of triethylene melamine. When compared to the negative controls, 2-ethylhexyl acrylate did not induce chromosomal aberrations in mouse bone marrow cells.

Sodium Polyacrylate. The mutagenic potential of Sodium Polyacrylate, 97.3% pure, was evaluated in an Ames test using *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with metabolic activation (Ishidate et al. 1984). Duplicate plates of six concentrations ≤8.0 mg/plate were examined. The results were negative.

A *Salmonella*/mammalian microsome plate incorporation assay was performed according to the methods of Maron and Ames (1983) using 0.05 to 20 μl/plate of 2000-Da molecular weight Sodium Polyacrylate (54% polymer prior to neutralization; 10% [*w/v*] sodium following neutralization) and 0.2 to 20 μl/plate 4500-Da molecular weight Sodium Polyacrylate (48% polymer; <0.02% residual starting material) with and without metabolic activation (Thompson, Aardema, and LeBoeuf 1989). Plating was done in triplicate. Vehicle alone was used as the negative control. Positive controls were sodium azide (TA1535; TA100), 9-aminocaridine (TA1537), and 2-nitrofluorene (TA1538; TA98) without metabolic activation and 2-aminoanthracene with metabolic activation. Neither of the Sodium Polyacrylates was mutagenic.

A L5178Y $TK^{+/-}$ mouse lymphoma assay was performed according to the methods of Clive and Spector (1975) and Clive et al. (1979) using 2.8 to 37 and 2.1 to 28 μl/ml of the 2000-Da molecular weight Sodium Polyacrylate without and with metabolic activation, respectively, and 7.5 to 75 and 3.2 to 32 μl/ml of the 4500-Da molecular weight Sodium Polyacrylate without and with metabolic activation, respectively (Thompson, Aardema, and LeBoeuf 1989). Plating was done in triplicate. Two solvents (not specified) were used as negative controls. Positive controls were EMS without metabolic activation and 7,12-dimethylbenz(a)anthracene (DMBA) with metabolic activation. Evidence of a mutagenic response was not observed with either of the Sodium Polyacrylates.

A chromosomal aberration test was performed using a Chinese hamster fibroblast cell line in which the cells were exposed to three doses ≤2.0 mg/ml of Sodium Polyacrylate, 97.3% pure, in physiological saline for 48 hours without metabolic activation (Ishidate et al. 1984). The results were negative.

An in vitro CHO cell cytogenetic assay was performed according to the methods of Natarajan et al. (1976) as modified by Thompson et al. (1984) using 43 to 77 μl/ml of 4500-Da molecular weight Sodium Polyacrylate without and with metabolic activation (Thompson, Aardema, and LeBoeuf 1989). Water and another negative control (not specified) were used. Positive controls were triethylene melamine without metabolic activation and cyclophosphamide with metabolic activation. Toxicity was not observed. Chromosome aberrations were not increased.

An UDS assay using primary cultures of rat hepatocytes was performed according to the methods of Williams (1977) and Williams, Bermudez, and Scaramuzzino (1977) as modified by Skare et al. (1986) using 0.005 to 5.0 μl/ml of 2000-Da molecular weight Sodium Polyacrylate and 0.2 to 20.0 μl/ml of the 4500-Da molecular weight Sodium Polyacrylate (Thompson, Aardema, and LeBoeuf 1989). DMSO was used as a negative

control and DMBA was used as a positive control. "Appreciable toxicity" was obtained with both Sodium Polyacrylates. Neither of the Sodium Polyacrylates induced UDS.

An in vivo mouse micronucleus assay was performed with 15 male and 15 female mice according to the methods of Matter and Schmid (1971) and Heddle (1973) as modified by Thompson, Aardema, and LeBoeuf (1989) using 13,850 mg/kg of 2000-Da molecular weight Sodium Polyacrylate (Thompson, Aardema, and LeBoeuf 1989). (The dose was expected to kill 10% of the animals within 72 hours.) Water was used as a negative control and mitomycin C was used as a positive control. Three females died. The number of micronuclei in polychromatic erythrocytes was not increased.

Acrylic Acid, Methyl, Ethyl, and Butyl Acrylate, and Methyl Methacrylate. A plate incorporation assay and a liquid preincubation assay were performed using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 without and with metabolic activation to determine the mutagenic potential of acrylic acid (Lijinsky and Andrews 1980). The maximum nontoxic dose tested was 1000 μg in the plate incorporation assay and 250 μg in the liquid preincubation assay. Appropriate positive controls were used. Acrylic acid was not mutagenic in either assay.

The mutagenic potential of 3.3 to 1000 μg/plate acrylic acid was determined using *S. typhimurium* strains TA100, TA1535, TA1537, and TA98 without and with metabolic activation (Zeiger et al. 1987). Acrylic acid was not mutagenic.

The mutagenic potential of acrylic acid was determined without and with metabolic activation in a plate incorporation assay using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (Cameron et al. 1991). Solvent (DMSO) and appropriate positive controls were used. Acrylic acid, $\leq$5000 μg/plate, was not mutagenic.

Methyl and ethyl acrylate were not mutagenic in an Ames test using *S. typhimurium* strains TA98, TA100, and TA1537 without metabolic activation (Ishidate, Sofuni, and Yoshikawa 1981).

Haworth et al. (1983) examined the mutagenic potential of ethyl acrylate and methacrylic acid in a *Salmonella*/mammalian microsome test. *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 were used without and with metabolic activation. Ethyl acrylate, tested at concentrations of 33 to 10,000 and 100 to 10,000 μg/plate in water and DMSO, respectively, and methacrylic acid, tested at concentrations of 33 to 4000 μg/plate in water, were not mutagenic.

A *Salmonella* microsome test was performed to determine the mutagenic potential of methyl, ethyl, and butyl acrylate and methyl, ethyl, and butyl methacrylate using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 (Waegemaekers and Benskin 1984). The ingredients were tested at concentration ranges of 40 to 2500, 30 to 2000, 30 to 2000, 40 to 10,000, 40 to 2500, and 40 to 2500 μg/plate, respectively, without and with metabolic activation, and none were mutagenic.

Methyl and butyl acrylate and methyl methacrylate were also tested without and with metabolic activation in a liquid incubation assay using *S. typhimurium* strain TA100 at concentrations of 60 to 6000, 15 to 1500, and 100 to 10,000 μg/2 ml, respectively (Waegemaekers and Bensink 1984). Again, these ingredients were not mutagenic.

In a reverse mutation assay spot test using *S. typhimurium* strains TA100, TA1535, TA1537, and TA98, 3 μmol/plate methyl acrylate was not mutagenic without or with metabolic activation (Florin et al. 1980). In another reverse mutation assay using these strains and strain TA1538, 590 μg/ml methyl acrylate (highest ineffective dose [HID]) was not mutagenic without or with metabolic activation.

Ethyl acrylate, 0.001 to 5.0 μl/plate, was tested for mutagenic potential using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Saccharomyces cerevisiae* strain D4 without and with metabolic activation (Industry Acrylate Testing Group (IATG) 1982). Ethyl acrylate was not mutagenic. Ethyl acrylate was also evaluated using a liquid suspension modification of the Ames test without and with metabolic activation. A concentration-dependent increase in revertants per survivors was observed using *S. typhimurium* TA100 in the presence of metabolic activation.

An enhancement assay was performed using *S. cerevisiae* strain D61.M to determine the ability of ethyl acrylate to induce chromosome loss (Zimmermann and Mohr 1992). Ethyl acrylate was tested by itself, in a cold shock regimen, and in combination with propionitrile (a positive control) at concentrations of 368 to 914, 230 to 1095, and 27.2 to 271.8 μg/ml, respectively. Ethyl acrylate alone induced numerous white resistant colonies, most of which were respiratory deficient. Using the cold shock regimen, "a strong increase in the frequencies of red and white resistant colonies was induced." With the addition of propionitrile, an induction of chromosome loss was seen. Ethyl acrylate induced chromosomal malsegregation and mitotic recombination.

The mutagenic potential of acrylic acid was determined in a mouse lymphoma assay using L5178Y $TK^{+/-}$ 3.7.C mouse lymphoma cells (Cameron et al. 1991). Solvent (DMSO) and appropriate positive controls were used. Acrylic acid, tested at concentrations of $\leq 5.44 \times 10^{-3}$ M without metabolic activation and $\leq 2.65 \times 10^{-2}$ M with metabolic activation, was mutagenic both without and with metabolic activation.

The genotoxicity of acrylic acid, methyl acrylate, and ethyl acrylate was studied using L5178Y mouse lymphoma cells with metabolic activation (Moore et al. 1988). Acrylic acid was tested at concentrations of 300 to 500 μg/ml, methyl acrylate was tested at concentrations of 16 to 24 μg/ml, and ethyl acrylate was tested at concentrations of 20 to 37.5 μg/ml. Acrylic acid, methyl acrylate, and ethyl acrylate were all mutagenic and clastogenic without metabolic activation.

A mouse lymphoma assay was performed to determine the mutagenic potential of ethyl acrylate (Litton Bionetics, Inc. 1980). Five trials were performed both without and with

metabolic activation. (Much toxicity was seen.) Without activation, concentrations of 1.56 to 60 nl/ml were tested; with activation, the test concentrations were 6.25 to 400 nl/ml. DMSO was used as the solvent. Ethyl acrylate was mutagenic at the TK locus without and with metabolic activation. "Without activation, the mutant frequency was elevated at 30 nl/ml and increased to about 7-fold over background for highly toxic treatments at 40 nl/ml. With activation, higher concentrations were required to achieve mutagenicity and high toxicity. The mutant frequency was first elevated at concentrations of 100–150 nl/ml and maximum increases of about 5 to 10 times the background were observed with highly toxic treatments at 200–300 nl/ml." Negative and positive controls generally gave expected results.

Ethyl acrylate in DMSO was tested in a L5178Y $TK^{+/-}$ mouse lymphoma cell forward mutation assay without metabolic activation (McGregor et al. 1988). Doses of 2.5 to 40 μg/ml were tested, and positive and negative controls were used. Ethyl acrylate induced significant increases in mutant fraction at doses of 20 μg/ml in one experiment and 40 μg/ml in another; relative total growth was 62% and 35%, respectively.

The mutagenic potential of methyl and ethyl acrylate was determined in a mouse lymphoma assay using L5178Y $TK^{+/-}$ 3.7.2 cells without metabolic activation (Moore et al. 1989). Methyl and ethyl acrylate were tested at concentrations of 16.0 to 24.0 and 20 to 37.5 μg/ml. For methyl acrylate, survival was 100%, 34%, 23%, and 16% with 0.0, 16.0, 22.0, and 24.0 μg/ml, respectively. For ethyl acrylate, survival was 100%, 60%, 40%, 32%, and 15% with 0.0, 20.0, 25.0, 30.0, and 37.5 μg/ml, respectively. For 0.0, 16.0, 22.0, and 24.0 μg/ml methyl acrylate, the total number of aberrations (100 cells scored) was 2, 30, 47, and 48, respectively, and the number of cells with aberrations was 2, 19, 26, and 28, respectively. For 20.0, 25.0, 30.0, and 37.5 μg/ml ethyl acrylate, the total number of aberrations was 3, 15, 41, 57, and 98 (50 cells analyzed), respectively, and the number of cells with aberrations was 3, 15, 24, 32, and 36, respectively. The TK mutant frequency, presented as small/large colony frequency, was 29/16, 147/37, 263/86, and 297/88 $\times 10^{-6}$ for 0.0, 16.0, 22.0, and 24.0 μg/ml methyl acrylate, respectively, and 148/37, 430/45, and 680/58 $\times 10^{-6}$ for 20.0, 30.0, and 37.5 μg/ml ethyl acrylate, respectively. With 0.0 and 25.0 μg/ml ethyl acrylate, colony sizing was not performed; the total mutant frequency was 61 and 331 $\times 10^{-6}$, respectively.

Dearfield et al. (1991) examined the mutagenic potential of ethyl acrylate and methyl methacrylate in DMSO without and with metabolic activation in a mouse lymphoma assay using L5178Y $TK^{+/-}$ 3.7.2C cells. Ethyl acrylate was mutagenic without metabolic activation, whereas methyl methacrylate was mutagenic with metabolic activation.

A mouse lymphoma assay to determine the mutagenic potential of ethyl acrylate was also performed by Ciaccio et al. (1998). Heterozygous L5178Y $TK^{+/-}$ mouse lymphoma cells were exposed to 10 to 40 μg/ml (0.1 to 0.4 mM) ethyl acrylate for 4 hours. Ethyl acrylate was positive without metabolic activation, with a concentration dependent increase in mutant frequency. The percentage of relative total growth (in both culture media and subsequent cloning efficiency in soft agar) was reduced approximately 50% and 80% with 20 and 30 μg/ml ethyl acrylate.

Ciaccio et al. (1998) also performed a NPSH (consisting largely of reduced GSH) assay, rhodamine 123 (Rh 123) assay, alkaline elution assay and apoptosis assessment, and pulsified-field gel electrophoresis (PFGE) detection of DNA double-strand breaks in mouse lymphoma cells. In the NPSH assay, cellular concentrations of NPSH were reduced by $\geq$50% with $\geq$20 μg/ml ethyl acrylate within 30 minutes, and at 4 hours, the cellular concentrations were reduced 70% to 90% with 10 to 40 μg/ml ethyl acrylate. In the Rh 123 assay, a 2-hour exposure did not reduce the mitochondrial Rh 123 uptake. Ethyl acrylate did induce a time- and concentration-dependent decrease in Rh 123 uptake after 4 + 0-hour or 4 + 2-hour exposure protocols. In the alkaline elution assay, 10 to 30 μg/ml ethyl acrylate caused low to moderate reductions in relative cell growth (RCG), but no change in the alkaline elution slope was seen. Marked cytotoxicity (80% to 87% reduction in RCG) was induced with 40 and 50 μg/ml ethyl acrylate, and the elution slope was three- to five-fold that of the vehicle control. In evaluating potential apoptotic oligonucleosomal DNA laddering effects and/or random smearing of DNA, "characteristic 180-bp DNA laddering effect below the random smearing of DNA, indicative of DNA double-strand breakage" was seen with 50 μg/ml ethyl acrylate, but not 10 or 20 μg/ml. With PFGE detection of DNA double-strand breaks, 50 μg/ml ethyl acrylate, which was cytotoxic, caused DNA double strand breaks in a range of sizes.

Acrylic acid was assayed in a CHO/HGPRT test using CHO K_1-BH_4 cells at concentrations of $\leq$1.9 and $\leq$2.8 μl/ml without and with metabolic activation, respectively (McCarthy et al. 1992). Acrylic acid was not mutagenic.

Methyl and ethyl acrylate were tested in a CHO assay examining the *hgprt* locus without metabolic activation (Moore et al. 1989). Doses of 14.0 to 18.0 and 21 to 24 μg/ml methyl and ethyl acrylate, respectively, were used. Total mutant frequencies were 17, 6, and 20 $\times 10^{-6}$ with 14, 16, and 18 μg/ml methyl acrylate, respectively, with survival of 53%, 22%, and 17%, respectively, and 9, 2, 21, and 1 $\times 10^{-6}$ for 21, 22, 23, and 24 μg/ml ethyl acrylate, respectively, with survival of 25%, 20%, 13%, and 8%, respectively.

The mutagenic potential of methyl and ethyl acrylate in DMSO was evaluated in a monolayer assay and of methyl acrylate in DMSO in a suspension assay using CHO cells (Moore et al. 1991). Two tests were performed for each assay type. Methyl and ethyl acrylate were tested at concentrations of 5 to 80 and 14 to 25 μg/ml, respectively, in the monolayer assay and methyl acrylate was tested at concentrations of 10 to 20.5 μg/ml in the suspension assay without metabolic activation. Methyl and ethyl acrylate did not induce a clear dose-related increase in HGPRT frequency.

A chromosomal aberration assay using Chinese hamster lung cells was also performed to determine the mutagenic potential

of methyl and ethyl acrylate (Ishidate, Sofuni, and Yoshikawa 1981). Both were mutagenic without metabolic activation. Methyl and ethyl acrylate had D_{20} values (the dose at which chromosomal aberrations were detected in 20% of metaphases) of 0.0065 and 0.0096 mg/ml, respectively.

Chromosome aberration tests were performed to examine the mutagenic potential of methyl acrylate (Sofuni et al. 1984a). Chinese hamster cells were exposed to 0.8 to 5.0 ml/h (60 to 378 ppm) gaseous methyl acrylate in distilled water for 1 hour with a 23-hour recovery and to 0.375 to 0.15 mg/ml liquid methyl acrylate for 24 or 48 hours with no recovery. In the gaseous phase, mutagenic effects were seen with 1.7 and 2.5 ml/h (128 and 189 ppm) methyl acrylate; the frequency of aberrant cells was 70% and 100%, respectively. In the liquid phase with a 24-hour exposure time, 0.075 and 0.15 mg/ml methyl acrylate were mutagenic, with an aberrant cell frequency of 18% and 98%. With a 48-hour exposure time in the liquid phase, a dose of 0.075 was "±," with 7% aberrant cells.

A AS52/XPRT assay using CHO cells was performed without metabolic activation to evaluate the mutagenic potential of methyl acrylate (Oberly et al. 1993). Methyl acrylate, tested at concentrations of 10 to 25 μg/ml, was not mutagenic in this assay.

Splenocytes from male C57BL/6 mice were used in an in vitro test to determine the effect of ethyl acrylate on SCE and chromosomal aberrations (Kligerman et al. 1991). The cells were treated for 4 hours with 10 to 80 and 10 to 30 μg/ml ethyl acrylate in DMSO. In order to expose blast-transformed (cycling) cells, the cultures were exposed to 1 to 20 μg/ml ethyl acrylate at 23 hours after culture initiation for 21 to 25 hours. Exposure of splenocytes in the G_0 phase to ethyl acrylate for 4 hours did not result in an increase in the frequency of SCEs or chromosomal aberrations. Ethyl acrylate was very toxic at concentrations $\geq$30 μg/ml. After blast transformation (G_1-S), exposure of splenocytes to 2 or 5 μg/ml resulted in an increase in the frequency of cells with chromatid-type aberrations and a slowing of the cell cycle. SCE frequency was increased in a nonsignificant manner. Ethyl acrylate, 10 μg/ml, was toxic.

The genotoxic potential of acrylic acid and *n*-butyl acrylate in DMSO was determined in UDS, micronucleus, and in vitro transformation assays using Syrian hamster embryo (SHE) fibroblasts without metabolic activation (Wiegand, Schiffmann, and Henschler 1989). Concentrations of 1 to 300 (acrylic acid) and 1 to 400 (*n*-butyl acrylate) μg/ml were used in the UDS assay, 0.5 to 10 μg/ml were used in the micronucleus assay, and 5 to 50 (acrylic acid) and 5 to 15 (*n*-butyl acrylate) μg/ml in the transformation assay. Appropriate positive controls were used. Acrylic acid and *n*-butyl acrylate were not genotoxic in these assays.

n-Butyl acrylate was tested for mutagenic potential without metabolic activation in an in vitro micronucleus test and a cell transformation assay using SHE cells (IARC 1999). Butyl acrylate was not mutagenic at a dose of 10 μg/ml (HID).

The mutagenic potential of acrylic acid was determined in vitro in cytogenetic and UDS assays (McCarthy et al. 1992). Acrylic acid was tested at concentrations of 2846 to 5000 and 1615 to 3769 nl/ml without and with metabolic activation, respectively, in the cytogenetic assay using CHO K1 cells and at concentrations of $\leq$0.6 μl/ml in the UDS assay using primary rat hepatocytes. Acrylic acid was mutagenic in the cytogenetic assay using CHO K1 cells and nonmutagenic in the UDS assay.

Methyl methacrylate was nonmutagenic without and with metabolic activation in a *Salmonella* assay (Zeiger et al. 1990). Methyl methacrylate was positive without and with metabolic activation in a chromosomal aberration assay and SCE assay, and was positive without metabolic activation in a mouse lymphoma assay.

The clastogenic potential of methyl acrylate was determined in vivo in a micronucleus test using male Balb C mice (Przybojewska et al. 1984). Four animals per group were given two IP doses, 24 hours apart, of 37.5 to 300 mg/kg methyl acrylate, and the animals were killed following the last dose. A negative and a positive control was used. At all doses tested, methyl acrylate significantly increased the percent of polychromatic erythrocytes with micronuclei (MPEs), and at all doses except the lowest, the ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs) was significantly decreased compared to the negative control. Methyl acrylate was clastogenic.

A micronucleus test was also performed using ddY mice that were exposed via inhalation to 1300 or 2100 ppm methyl acrylate for 3 hours (Sofuni et al. 1984b). In this study, methyl acrylate was not clastogenic.

Methyl acrylate was assayed in another in vivo micronucleus test using bone marrow cells from ddy mice dosed once orally with 250 mg/kg (IARC 1999). The results were negative.

The clastogenic potential of ethyl acrylate was determined in vivo in a micronucleus test using male Balb C mice (Przybojewska et al. 1984). Four animals per group were given two IP doses, 24 hours apart, of 112.5 to 1800 mg/kg ethyl acrylate, and the animals were killed following the last dose. (In the high-dose group, the dose was toxic to two animals; therefore, results from the high-dose group used two animals.) A negative and a positive control was used. At all doses except the lowest, ethyl acrylate significantly increased the percent MPEs. At all doses, the ratio of PCEs to NCEs was significantly decreased compared to the negative control. Ethyl acrylate was clastogenic.

Ashby, Richardson, and Tinwell (1989) performed four micronucleus assays using C57B16J Aplk or BALB/c mice to determine the mutagenic potential of ethyl acrylate (Ashby, Richardson, and Tinwell 1989). In the first assay, groups of five male and female C57B16 mice were given a single IP injection of 738 mg/kg ethyl acrylate in corn oil; sampling was done after 48 hours for one group of males and one group of females and after 72 hours for another group of males. In the second assay, 10 male C57B16 mice were given IP injections of 738 mg/kg in

distilled water at 0 and 24 hours, and sampling was done 6 hours later. In the third and fourth assays, groups of 10 male BALB/c mice were given two IP injections of 812 mg/kg, and sampling was done after 30 hours. Positive results were only observed in the third assay. A significant increase in MPEs was observed, due to two animals having "a marginally elevated MPE incidence," and the ratio of PCEs to NCEs was significantly different from controls. These results were not reproduced in the fourth assay. The researchers concluded that ethyl acrylate "is inactive as a micronucleus-inducing agent in bone marrow of both C57B1J and BALB/c mice."

Female homozygous Tg · AC transgenic mice were treated dermally on a shaved area of the back three times per week for 20 weeks with 200 μl of 60, 300, or 600 μM ethyl acrylate in acetone (Tice, Nylander-French, and French 1997). Positive controls were treated with 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and negative controls were treated with vehicle. Blood samples were collected from the tail at 4, 8, 12, 16, and 20 weeks; micronucleus effects were examined after 20 weeks while DNA migration was evaluated with each sample. After 20 weeks of dosing, the frequency of MPEs and NCEs was not increased in treated mice, nor was the percentage of PCEs altered. Additionally, the researchers determined the extent of DNA damage in peripheral blood leukocytes. Ethyl acrylate did not significantly alter the extent of DNA migration in leukocytes or the dispersion of migrating DNA among leukocytes.

The effect of ethyl acrylate on DNA damage in forestomach squamous epithelium was determined in an alkaline elution assay (Morimoto et al. 1990). No DNA damage was observed in male F344 rats given a single oral dose of 0.1% to 4.0% ethyl acrylate.

The effect of ethyl acrylate on chromosomal aberrations and SCEs was examined using groups of five male C57BL/6 mice that were dosed intraperitoneally with 125, 250, 500, or 1000 mg/kg ethyl acrylate in saline (Kligerman et al. 1991). Negative controls were dosed with saline and positive controls were dosed with 100 mg/kg acrylamide in saline. The spleens of the animals were removed 24 hours after dosing. Ethyl acrylate administration did not result in an increase in SCE frequency or percentage of cells with chromosomal aberrations in splenocytes. Also, ethyl acrylate did not slow the cell cycle in splenocytes.

Chromosomal aberration assays were performed using male and female Chinese hamsters and Sprague-Dawley rats to determine the effect of butyl acrylate on chromosomes (Engelhardt and Klimisch 1983). The hamsters and rats, which were housed one animal per cage and two to three animals per cage during dosing, respectively, were exposed to 817 and 820 ppm butyl acrylate, respectively, for three 6-hour and one 5-hour exposures. Butyl acrylate, although toxic to the animals, did not cause increased chromosomal aberrations in either species.

A chromosomal aberration assay was also performed using rat bone marrow cells to determine the mutagenic potential of *n*-butyl acrylate (IARC 1999). The animals were given one IP dose of 300 mg/kg. Butyl acrylate was mutagenic when given by IP administration.

The mutagenic potential of acrylic acid was determined in vivo in Drosophila sex-linked recessive lethal, cytogenetic, and mouse dominant lethal assays (McCarthy et al. 1992). Acrylic acid was tested at a concentration of 2%, given by feeding or injection, in the *Drosophila* sex-linked recessive assay, as a single dose of 100 to 1000 mg/kg by gavage or 2000 or 5000 ppm in the drinking water for 5 days in the cytogenetic assay using Sprague-Dawley rats, and as a single dose of 32 to 324 mg/kg or five daily doses of 16 to 162 mg/kg by gavage in the mouse dominant lethal assay using CD-1 mice. Acrylic acid was non-mutagenic in all assays.

In tests using *Drosophila melanogaster*, ethyl acrylate (inhibited) was not mutagenic following feeding of 40,000 ppm or injection of 20,000 ppm (Valencia et al. 1985).

Reactions of acrylic acid with 2′-deoxyadenosine, 2′-deoxycytidine, 2′-deoxyguanosine, and thymidine at pH 7.0 and 37°C for 40 days resulted in the formation of 2-carboxyethyl (CE) adducts via Michael addition (Segal et al. 1987). 1-CE-adenosine (1-CE-Ade), N^6-CE-Ade, 7-CE-guanine, and 3-CE-thymine were isolated after in vitro reaction of acrylic acid with calf thymus DNA at pH 7.0 and 37°C for 40 days.

CARCINOGENICITY

Dermal

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer. An 86.5% solution of 2-ethylhexyl acrylate in acetone was applied to the clipped dorsal skin of 40 mice throughout their lifetime (Rohm and Haas Co. 1983). Two test animals developed malignant skin carcinomas, and four had benign growths. One animal in the control group exposed to acetone only had a skin carcinoma.

A group of 40 male C3H/HeJ mice, housed 5 animals per cage, were dosed on a clipped area of the back three times per week with "one brushful" of 75% 2-ethylhexyl acrylate in acetone (approximate dose of 20 mg per application) (DePass, Maronpot, and Weil 1985). The dose was determined in a 2-week preliminary study and was the greatest concentration that "resulted neither in grossly observable irritation nor reduced weight gain." All animals were examined daily. Dosing resulted in two animals with squamous cell carcinomas and four with squamous cell papillomas on treated skin. The first tumor was observed after 11 months. A significant increase in the frequency of chronic nephritis was observed in treated animals compared to vehicle controls. The researchers stated that "treatment with EHA [2-ethylhexyl acrylate] may have exacerbated the onset and development of this condition which is normally seen in aged mice." 2-Ethylhexyl acrylate was "oncogenic."

The carcinogenic potential of 2.5%, 21%, 43%, and 86.5% 2-ethylhexyl acrylate in acetone was determined using groups of 80 male C3H mice (Wenzel-Hartung, Brune, and Klimisch 1989). Twenty-five microliters of the test article were applied to

a clipped area of the interscapular region of the animals three times per week throughout their lifetime, with the exception of the 43% concentration. For this concentration, application was discontinued after 24 weeks of dosing and the animals were observed until they died. Control groups were untreated or received applications of acetone only. All animals were observed twice daily for signs of toxicity. Body weights were measured weekly. A slight but statistically significant increase in body weights was observed for all test groups. All concentrations induced visible scale and/or eschar formation. Within 7 weeks after discontinuation of dosing with 43% 2-ethylhexyl acrylate, the skin appeared normal. The skin of the animals of the 2.5% group was normal after the 11th week of dosing. Application of 21% and 86.5% 2-ethylhexyl acrylate produced encrusted and keratinized nodules at the site of application. Hyperkeratosis and scabbing in the cutis, thickened and pigmented subcutaneous tissue, dermal hyperplasias, papillomas, and cornified squamous cell carcinomas, malignant melanomas, and fibrosarcomas were observed at microscopic examination in animals of the 21% and 86.5% dose groups. To a "small extent," the groups treated with 2.5% and 43% 2-ethylhexyl acrylate had hyperkeratosis and scabbing in the cutis. 2-Ethylhexyl acrylate had a "clearly carcinogenic effect" in the animals of the 21% and 86.5% dose groups. Skin tumor induction times were not significantly different between these groups. No neoplasias were seen in the animals of the 2.5% and 43% dose groups. The researchers stated that "the most essential finding of this study demonstrates that there is an association between severe skin-irritation symptoms and the occurrence of benign and malignant tumors."

The carcinogenic potential of 21.5%, 43%, and 85% (*w/w*) 2-ethylhexyl acrylate in acetone was determined in a 2-year study using groups of 80 male CRL:NMRI BR mice. In a preliminary study, NMRI mice were more resistant than C3H/HeJ mice to the irritant effects of 2-ethylhexyl acrylate (Mellert et al. 1994). The test substance was applied to the clipped interscapular area. Benzo[a]pyrene (B[a]P), 25 μl at a concentration of 0.015%, was used as a positive control. At 3 months, two animals per group were killed and skin from the test site was examined microscopically. After 7 months, the groups were divided into two subgroups; subgroup A continued the original treatment and subgroup B was untreated for 2 months and then received applications of 5 μg TPA in 0.1 ml acetone twice weekly for 20 weeks. Subgroup B animals with skin lesions that persisted during the nontreatment period (eight animals from the 21.5% group and three from the 85% group) were excluded from TPA treatment. Surviving animals in both subgroups were killed 2 years after the initiation of dosing. Body weights were determined weekly until week 14, and then monthly. All mice were examined daily for signs of toxicity, and skin effects and onset of tumors were recorded weekly.

Dosing with 2-ethylhexyl acrylate did not affect mean body weights. Mean survival was not affected by dosing with or without TPA. In the animals killed after 3 months, focal skin lesions were observed in one animal from each treated group; microscopy reported hyperkeratosis, hyperplasia (acanthosis), and increased numbers of macrophages. One animal of the high-dose group (as well as one positive-control animal) had ulceration and crust formation. No skin lesions were seen in the control animals. Animals of subgroup A had focal or multifocal skin lesions at the application site, the frequency of which was not dose-dependent. In the test groups, crust formation and ulcerations occurred to a slight or moderate degree; this was dose-related. No subgroup A animals developed skin tumors. Similar skin lesion and tumor results were observed in subgroup B. One squamous cell papilloma occurred at each dose in subgroup B. None of the animals of subgroup B excluded from TPA treatment developed skin tumors.

IARC determined that "there is inadequate evidence in humans" and "there is limited evidence in experimental animals for the carcinogenicity of ethylhexyl acrylate" (IARC 1994). The overall evaluation was "ethylhexyl acrylate is not classifiable as to its carcinogenicity to humans."

Acrylic Acid and Ethyl and Butyl Acrylates. Groups of 40 male C3H/HeJ mice were used to determine the carcinogenic potential of acrylic acid, butyl acrylate, and ethyl acrylate (DePass et al. 1984). Dermal applications of 25 μl of 1% acrylic acid, 1% butyl acrylate, or undiluted ethyl acrylate (doses of 0.20, 0.20, or 23 mg, respectively) were made to a clipped area on the back of each animal three times weekly throughout its lifespan. Negative (vehicle-acetone) and positive controls (vehicle-methycholanthrene) were used. The animals were housed in groups of five; animals of the ethyl acrylate test group were housed individually after 13 months because of early mortality. All animals were examined daily, and the onset and progress of neoplasms was recorded monthly. The dorsal skin and lesions from all animals that died were collected for microscopic examination. No skin irritation was observed during the study. No significant difference was found in survival time among the test and negative-control groups. Acrylic acid, butyl acrylate, and ethyl acrylate were not carcinogenic; one animal of the butyl acrylate group had a fibrosarcoma that appeared after 665 days of dosing. At microscopic examination, animals dosed with ethyl acrylate had epidermal necrosis (4), keratin necrosis (6), dermal fibrosis (6), hyperkeratosis (12), and dermatitis (5). One animal in each the of acrylic acid and butyl acrylate groups had epidermal hyperplasia.

The carcinogenic potential of acrylic acid was studied using groups of 30 female mice (Cote et al. 1986a, 1986b). Acrylic acid, 4% in acetone, was applied to dorsal skin three times per week for 1.5 years. A second group of mice was initiated with DMBA prior to application of acrylic acid. Acetone or DMBA followed by acetone were applied to control animals. Two squamous cell carcinomas were observed in the animals of the acrylic acid group, and one squamous cell carcinoma and three papillomas were observed in the DMBA/acrylic acid group. The researchers concluded that acrylic acid was a "complete although weak carcinogen."

The researchers reported that acrylic acid also produced an increase in leukemia, stating that the incidence of leukemia was 86% in test animals and 30% in controls. However, an independent review (Arthur D. Little, Inc. 1986) did not confirm the reported incidence. The independent reviewer stated that "although the numbers of lymphomas were elevated in one of the treatment groups, inconsistent patterns of tumor occurrence from organ to organ would strongly suggest that the lymphomas were not treatment related."

Groups of 50 C3H/HeN Hsd BR and Hsd:(ICR)BR mice were treated topically with 25 or 100 μl of 1% acrylic acid in acetone for 6 weeks or 21 months (Hoechst Celanese 1990). Negative-control groups were treated with acetone and positive control groups were treated with B[a]P. No definitive carcinogenic effect was observed in male and female ICR and male C3H mice; an increase in the frequency of lymphosarcomas was observed for female C3H mice. Acrylic acid was not carcinogenic.

Oral

Acrylic Acid and Ethyl Acrylate. Groups of 50 male and 50 female Wistar rats were given 120, 400, or 1200 ppm acrylic acid in the drinking water for 26 (males) or 28 (females) months (Hellwig, Deckardt, and Freisberg 1993). A control group was given untreated water. Feed and water consumption and body weights were determined weekly for the first 3 months; feed and water consumption was then determined every 3 months and body weights were measured every 4 week. The animals were examined daily and palpated weekly. Blood samples were taken from 10 males and 10 females per group after 12, 18, 24, 26, and 28 months. At study termination, the animals were killed and necropsied and selected tissues were examined microscopically.

The actual concentrations in the test solutions were 96% to 106%, 94% to 103%, and 92% to 102% of the target concentrations of 120, 400, and 1200 ppm, respectively, corresponding to a daily mean intake of approximately 8, 27, and 78 mg/kg acrylic acid, respectively. Significant differences in feed or water consumption or in body weights were not observed between the test and control animals. Clinical signs of toxicity were not observed, and differences in mortality were not observed between the test and control animals. Treatment-related changes in hematologic parameters were not found. Non-neoplastic tissue changes were similar to those of controls. A "slightly increased incidence in hepatocellular fatty deposits" in males of the high dose group could be treatment-related. The incidence and organ distribution of neoplasms did not differ between test and control animals. "No clear toxic or oncogenic effects" were found upon administration of 120 to 1200 ppm acrylic acid in the drinking water.

Groups of 50 male and 50 female F344N rats and B6C3F$_1$ mice were dosed by gavage with 100 or 200 mg/kg ethyl acrylate in corn oil five times per week for 103 weeks (NTP 1986). Control groups of 50 male and 50 female rats and mice were given corn oil by gavage. Survival was similar for test and control animals, and signs of systemic toxicity was not observed. Squamous cell papillomas and squamous cell careinomas of the nonglandular stomach occurred at the site of chemical deposition in both male and female rats and mice in a dose- and concentration-dependent manner. Ethyl acrylate also caused irritation of the gastric nonglandular stomach mucosa in male and female rats and mice. Ethyl acrylate was carcinogenic to F344/N rats and B6C3F$_1$ mice, causing squamous cell carcinomas in male rats and male mice, squamous cell papillomas in male and female rats and male mice, and squamous cell papillomas or carcinomas (combined) in male and female rats and mice.

Groups of 18 to 23 male F344 rats were dosed 5 days per week with 200 mg/kg ethyl acrylate in corn oil (dose volume of 5 ml/kg) for 6 or 12 months; a control group of 21 rats was dosed with corn oil for 12 months (Ghanayem et al. 1993). Five animals per group were killed 24 hours after dosing; the remaining animals of the low-dose group were killed 15 months and of the control and high-dose groups were killed 9 months after dose termination. All of the test animals killed 24 hours after dose termination had mucosal hyperplasia, but no squamous cell papillomas or carcinomas were observed. None of the 18 and 16, respectively, surviving 15-month and control recovery animals had any lesions, whereas 8 of 13 of the 12-month recovery animals had mucosal hyperplasia and 4 had squamous cell papillomas and carcinomas.

Inhalation

Methyl, Ethyl, and Butyl Acrylates. Groups of 86 male and 86 female Sprague-Dawley rats were exposed to air containing 15, 45, or 135 ppm methyl (58, 173, or 519 mg/m^3, respectively) or *n*-butyl acrylate (86, 258, or 773 mg/m^3, respectively) for 6 hours per day, 5 days per week for 2 years (Reininghaus et al. 1991). Control animals breathed untreated air. Animals exposed to *n*-butyl acrylate were observed for 6 months after the termination of dosing. Some animals of each group were killed after 12 and 18 months of dosing, and some of the animals exposed to *n*-butyl acrylate were killed after 24 months. A decrease in body weight gain was temporarily observed for animals of the 135-ppm methyl acrylate group. Local effects of irritation at the nasal mucosa were observed in the nasal turbinates. Dose-related atrophy of the neurogenic portion of the olfactory epithelium with proliferation of the reserve cells to a multilayered epithelium was reported. Regeneration was observed in the *n*-butyl acrylate recovery animals. Dose-related corneal opacity and ocular vascularization was observed with methyl acrylate and 135 ppm butyl acrylate.

Groups of 115 male and 115 female Fischer 344 rats and 105 male and 105 female B6C3F$_1$ mice were exposed 6 hours per day to air containing 25 or 75 ppm (0.10 or 0.31 mg/l, respectively) ethyl acrylate for 27 months or to 225 ppm (0.92 mg/l) for 6 months followed by a 21-month recovery period (Miller et al. 1985). Control groups of rats and mice were exposed to untreated air for 27 months. Some animals from each groups were killed for interim necropsy. The animals were observed daily for signs of toxicity. Body weights were initially determined

weekly, and were then determined biweekly or monthly. The mean body weight gains of rats and mice of the 75- and 225-ppm groups were statistically significantly decreased throughout the study; 225 ppm was determined to be in excess of the MTD based on the decreased weight gain. No other toxicologically significant changes were observed. In the test animals, tissues from 71 to 76 male and 70 to 78 female Fischer 344 rats and 69 to 75 male and 66 to 78 female B6C3F$_1$ mice were examined microscopically. No neoplasms were observed in rats or mice. In rats, concentration-dependent non-neoplastic lesions of the olfactory portion of the nasal mucosa were observed for test groups. In mice, lesions were concentration-dependent and consisted of replacement of the olfactory neuroepithelium by ciliated respiratory epithelium accompanied by submucosal glandular epithelium. In both rats and mice, only the areas of nasal mucosa normally lined by olfactory epithelium was altered.

Parenteral

Acrylic Acid. Groups of 30 female Hsd:(ICR)Br mice were dosed with 20 μmol (1.4 mg) acrylic acid in 0.05 ml trioctanoin or vehicle only subcutaneously into the left flank once weekly for 52 weeks; the animals were then observed for an additional 93 days (450 total days on study) (Segal et al. 1987). An untreated control group of 100 animals was observed for 450 days. Twenty-eight test and vehicle-control animals and 94 untreated controls survived until study termination. Two animals of the test group had sarcomas at the site of injection. None of the vehicle- or untreated-control animals had neoplasms.

IARC (1999) gave the following carcinogenic evaluations for acrylic acid, methyl acrylate, ethyl acrylate, and *n*-butyl acrylate. "No epidemiological data" and "no experimental data relevant to the carcinogenicity of acrylic acid were available"; "acrylic acid is not classifiable as to its carcinogenicity to humans." "No epidemiological data relevant to the carcinogenicity of methyl acrylate were available" and "there is inadequate evidence in experimental animals for the carcinogenicity of methyl acrylate"; "methyl acrylate is not classifiable as to its carcinogenicity in humans." "No epidemiological data relevant to the carcinogenicity of ethyl acrylate were available" and "there is sufficient evidence in experimental animals for the carcinogenicity of ethyl acrylate"; "ethyl acrylate is possibly carcinogenic to humans." "No epidemiological data relevant to the carcinogenicity of *n*-butyl acrylate were available" and "there is inadequate evidence in experimental animals for the carcinogenicity of *n*-butyl acrylate"; "*n*-butyl acrylate is not classifiable as to its carcinogenicity in humans."

IARC (1994) gave the following evaluation for methyl methacrylate: "There is inadequate evidence in humans for the carcinogenicity of methyl methacrylate. There is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals." Overall, "methyl methacrylate is not classifiable as to its carcinogenicity to humans."

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

Predictive

Acrylates Copolymer. A repeated insult patch test was completed using 47 subjects, 7 males and 40 females, to determine the irritation and sensitization potential of a 25% dilution of Acrylates Copolymer (supplied as a cloudy white liquid) using distilled water (percent solids not specified) (Consumer Product Testing Co. 1996). Semiocclusive patches containing approximately 0.2 ml of the test material were applied for 24 hours to the upper back of each subject three times per week for a total of 10 applications. The test sites were scored 24 to 48 hours after patch removal. Following a 14-day nontreatment period, a challenge patch was applied for 24 hours to the test site on the back and to a previously unpatched site on the volar forearm. The challenge sites were scored immediately and 24 hours after patch removal. Reactions were not observed during induction or at challenge, and Acrylates Copolymer was neither a dermal irritant nor a sensitizer.

An assay of the irritation and sensitization potential of Acrylates Copolymer, 30% solids and pH 7 to 7.4, and Acrylates Copolymer, 100% solids, as a 15% solution in ammonia water (pH 7.95) and as a 25% acetone solution, was completed using 49 patients (BFGoodrich Specialty Chemicals 1997). The test article was applied under an occlusive patch for 24 hours. The test site was scored for irritation upon patch removal and 3, 6, 10, and 14 days after application. After a 1-week nontreatment period, a challenge application was made and scored for the following 4 days. Acrylates Copolymer, 30% solids, was neither an irritant nor a sensitizer. Both Acrylates Copolymer, 100% solids, solutions did not produce an irritant response. The Acrylates Copolymer acetone solution produced a reaction upon challenge, but the ammonia water solution did not; the researchers stated that the reaction was probably due to the acetone.

Sodium Polyacrylate. The irritation and sensitization potential of Sodium Polyacrylate was determined using 50 subjects (Finnegan and Dienna 1953). A 1/4 inch square of cotton cloth was saturated with undiluted Sodium Polyacrylate, placed on the inner surface of the forearm, covered with aluminum foil, and held in place for 48 hours. The patch was then removed and the site was examined for irritation. Two weeks after patch application, the procedure was repeated on the opposite arm. Irritation and sensitization were not observed.

Provocative

Acrylates/VA Copolymer. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer. A total of 243 patients with a history of exposure to (meth)acrylates were patch tested with a (meth)acrylates series (Kanerva, Jolanki, and Estlander 1997). An occlusive patch containing 0.1% to 0.5% 2-ethylhexyl acrylate was applied to the back for 24 hours. None of the patients were sensitized by 2-ethylhexyl acrylate.

Ethyl Acrylate, Butyl Acrylate, and Methacrylate Monomers. Adams and Maibach (1985) reported on a 64-month study (during the years 1977 to 1983) involving 12 dermatologists that researched patient reactions to cosmetics. Of an estimated number of 281,100 patients seen, an estimated number of 13,216 patients had contact dermatitis and in 713 of those patients, it was related to cosmetics. Patch tests were performed according to the methods of the North American Contact Dermatitis Group (NACDG) on 56% of the subjects. There was one cutaneous reaction to unspecified methacrylate monomer and five to ethyl methacrylate.

Patch tests using the Finn-chamber method, which used nonocclusive tape and involved at least three readings, were performed to determine sensitization to acrylates (methyl methacrylate: 10% in petrolatum; remainder: 1% in petrolatum) (Kanerva, Estlander, and Jolanki 1988). Prior to 1982, testing was only done with methyl methacrylate; no patients were sensitized to this monomer. From 1982 to 1985, 12 of 22 patients did not react to (meth)acrylates, 10 had an irritation response to ethyl acrylate, 9 had irritation to butyl acrylate, and none reacted to methyl methacrylate. From 1985 to 1986, 12 of 24 patients did not react to (meth)acrylates, 6 had an irritation response to ethyl acrylate, and 2 had an irritation response to butyl acrylate.

In one case study, a patient was sensitized to a nail laquer that contained 9% methyl acrylate, and the patient had an allergic reaction when patch tested with 1.5% methyl acrylate in petrolatum (Kanerva et al. 1995). In another case study, a patient was sensitized to methyl acrylate from photobonded nail gel, methyl and ethyl methacrylate from nail liquid, and butyl methacrylate from nail hardener (Kanerva et al. 1996a). The patient did not react to patch testing with 0.1% 2-ethylhexyl acrylate or 0.1% to 1% methacrylic acid.

Workplace Exposure/Effects

The Finnish Register of Occupational Diseases reported that five of 815 cases of occupational contact urticaria (0.6%) were due to ethylhexyl acrylate (Kanerva et al. 1996b). All cases occurred in females.

Respiratory system observations, including pulmonary function testing (PFT) and chest x-rays, were made for 190 people who worked in the Spray Drier department from 1966 to 1983; these workers were exposed to a variety of acrylic polymer dusts as well as other materials (Rohm and Haas Co. 1984c). Twenty-five percent of the workers who had worked in this department had left before PFT was fully validated or x-rays were retained. The remainder of the plant workforce was used for the unexposed group. Chest x-rays were obtained for 109 exposed employees; controls were selected from the unexposed group by matching age, year hired, and smoking habit. The PFT results and the smoking habits, age, sex, race, and height were determined for 123 exposed employees; the latter four parameters and the prediction equations of Crapo, Morris, and Gardner (1981) were used to determine the predicted normal value for the forced vital capacity, the forced expiratory volume in the first second, and the forced expiratory flow rate over the middle half of the expirogram for each individual. Exposed employees did not have an excess of chest x-ray abnormalities, especially alterations suggestive of diffuse pulmonary fibrosis, and did not have an excess of PFT abnormality.

Threshold Limit Value

The threshold limit value–time weighted average (TLV-TWA) for Acrylic Acid is 10 ppm of contaminated air by volume at 25°C and 760 torr (American Conference of Governmental Industrial Hygienists [ACGIH] 1986) and 5.9 mg/m^3 in air (IARC 1999). The recommended TLVs for occupational exposure to methyl and ethyl acrylate in workplace air are 7 and 20 mg/m^3, respectively. The 8-hour TLV-TWA for occupational exposure to *n*-butyl acrylate in workplace air is 52 mg/m^3. Rohm and Haas Co. (1985) reported a TWA of 2 mg/m^3 for an acrylic polymer that had a molecular weight of approximately 1,000,000 and that contained approximately 35% respirable ($\leq 5\ \mu$) dust.

NTP REPORT ON CARCINOGENS

Ethyl Acrylate. In 1998, the Basic Acrylic Monomer Manufacturers, Inc., petitioned the NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee to delist ethyl acrylate from NTP's *Report on Carcinogens* based on the assumption that "significant human exposure is unlikely" (NTP 1998). Ethyl acrylate was first listed in the 5th Annual Report on Carcinogens as "reasonably anticipated to be a human carcinogen" based on the NTP gavage study. During the discussion, it was noted that ethyl acrylate was rapidly metabolized by carboxylesterases and by conjugation with GSH, and that it had a half-life in the rodent forestomach of 94 minutes. It was also noted that ethyl acrylate was mutagenic in some in vitro tests but was not genotoxic under in vivo physiological conditions, possibly due to its "rapid metabolism."

Mechanistic studies related to forestomach tumor response were conducted to examine the association of irritation and sustained cell proliferation. A dose of 200 mg/kg, which produced forestomach tumors in the NTP assay, induced "substantial cell proliferation" in the forestomach mucosa within hours of dosing.

"A premise of the petition [was] that humans would not ingest ethyl acrylate, rather inhalation and dermal would be the primary routes of human exposure, and, further, humans do not possess forestomachs." It was voted (7-2 and 6-1) that ethyl acrylate should be delisted from the *Report on Carcinogens*. Following further discussion of the proposal, it was voted that ethyl acrylate be delisted from the Report (8-2-2). One of the abstentions cited the reason that "there was important information on cell transformation" that were not accessible.

SUMMARY

Copolymers

This report reviews the safety of a large number of polymers that contain acrylic or methacrylic acid or one of their salts or

esters. Linear polymers of acrylic acid are produced by combining the monomer with a free-radical initiator, which is generally largely consumed by the reaction. However, some unreacted monomer and catalysts can remain. Additionally, hydroquinone and monomethyl ester of hydroquinone are often incorporated into acrylic acid and its esters as an inhibitor. 2-Ethylhexyl acrylate is a component of Acrylates/VA Copolymer.

One company reported that it manufactured Acrylates Copolymer and Ammonium Acrylates Copolymer using emulsion and solution polymerization. One company reported that it produces Acrylates Copolymer as 30% solids at a pH of 3.0 and Ammonium Acrylates Copolymer as a 30% solution in propylene glycol and water at a pH of 7.5.

Ten companies representing the majority of the production of polymers sold for cosmetic use indicated that residual acrylic acid concentrations in polymers are typically between 10 and 1000 ppm, with an upper limit of 1500 ppm.

One source reported Acrylates Copolymer can contain residual amounts of $\leq$20 ppm ethyl acrylate, methyl methacrylate, methacrylic acid, and acrylic acid; another source reported that three samples analyzed using GC contained <0.2 to 0.8 ppm acrylic acid, 0.8 to 2.6 ppm methyl methacrylate, and 1.3 to 3.9 ppm ethylene glycol dimethacrylate. Additionally, it was reported to CIR that two polymers, both defined as Acrylates Copolymer, contained different residual monomers; the first contained 36, 20, and 45 ppm *n*-butyl acrylate, methyl methacrylate, and methacrylic acid, respectively, and the second contained 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively. Acrylates/VA Copolymer can contain, as reported by two polymer producers, 100 to 1000 ppm residual 2-ethylhexyl acrylate. However, the 10 respondents of the survey described previously reported that they did not produce acrylate polymers with 2-ethylhexyl acrylate for use in the cosmetic industry. Using UV spectroscopy with a limit of detection of 300 mg/kg (ppm), acrylic acid was detected in Polyacrylic Acid at 195 nm. A 90,000-Da molecular weight sodium hydroxide–neutralized Polyacrylic Acid contained 77.5% Sodium Polyacrylate, 3.3% free acrylic acid, and 18.1% water, whereas a 4500-Da molecular weight compound contained 43.3% solids and 0.09% residual monomer.

The ingredients reviewed in this report have one or more of the following functions in cosmetic formulations: binder, film former, hair fixative, suspending agent, viscosity-increasing agent, emulsion stabilizer. Acrylates polymers used in final cosmetic products are typically used at concentrations of 2.5% to 6.0%, with a maximum of 7.5% to 25%, in binders, film formers, and fixatives and at a concentration of 0.5%, with a maximum of 2.0%, in viscosity-increasing agents, suspending agents, and emulsion stabilizers. It has been reported that Acrylates Copolymers is used at 3% to 22% and a mixture containing 30% Ammonium Acrylates Copolymer is used at 2% to 15%.

Polyacrylic Acid had an immunosuppressive effect on the response of mice to sheep red blood cells. Effects of Polyacrylic Acid–immunoglobulin G (PAIGP) complex on human polymorphonuclear leukocytes was examined; PAIGP stimulated chemiluminescence, released superoxide anion, and was a weak inducer of elastase release.

The following LD_{50} values were reported for Acrylates Copolymer: >16 g/kg (dermal, rabbits), >16 ml/kg (dermal), >9 g/kg (dermal), 9 g/kg (dermal, rats), >5.2 mg/l (rats). Ethylene/Acrylic Acid Copolymer had a low order of acute toxicity following dermal and oral administration to rats; the oral LD_{50} was >5 g/kg. The oral LD_{50} for rats of an ammonium salt of Ethylene/Acrylic Acid was 41.50 ml/kg. In an acute inhalation study, 0 of 6 rats exposed to an aqueous emulsion of the ammonium salt of Ethylene/Acrylic Acid polymer died; the IP LD_{50} for rats of the emulsion was 8.57 ml/kg. The dermal LD_{50} for rabbits and the oral LD_{50} for rats of Vinyl Acetate/Maleate/Acrylate Copolymer solution was >5 g/kg. For rats, the oral LD_{50} values of Polyacrylic Acid and Sodium Polyacrylate were 2.5 and >40 g/kg, respectively; and 0.34 and 2.59 ml/kg, respectively, for male rats. Copolymers of acrylic acid and *N*-vinyl pyrrolidone containing 25% to 45% and 69% to 70% acrylic acid were non- and slightly toxic, respectively. In a subchronic inhalation toxicity study of Acrylates Copolymer, alveolar histiocytosis was observed at a dose of 30 mg/m^3. Pulmonary lesions were observed in rats used in short-term and subchronic inhalation studies of acrylic acid polymers. In a chronic inhalation study of respirable polyacrylate particles, compound-related pulmonary lesions were not observed.

In dermal irritation studies using rabbits, Acrylates Copolymer was non- to mildly irritating. In one study, it produced signs of an irritant property. However, in a study in which the patches adhered to the skin, very slight to well-defined erythema, and severe erythema in one animal, were observed at 72 hours. A mixture containing 30% Ammonium Acrylates Copolymer was practically nonirritant, and an aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer produced minor irritation. Acrylates/VA Copolymer produced moderate to severe but reversible dermal irritation, Vinyl Acetate/Maleate/Acrylate Copolymer solution had a primary irritation index of 4.4. Sodium Polyacrylate did not produce irritation. Acrylates Copolymer was not a sensitizer to guinea pigs in maximization studies or a Buehler sensitization test. In ocular irritation studies using rabbits, Acrylates Copolymer was generally non- to mildly irritating. In two other studies, Acrylates Copolymer was an eye irritant but not corrosive. A mixture containing 30% Ammonium Acrylates Copolymer was practically nonirritating. An aqueous emulsion of the ammonium salt of an Ethylene/Acrylic Acid polymer produced trace corneal injury, Acrylates/VA Copolymer produced severe but reversible ocular irritation, and Vinyl Acetate/Maleate/Acrylate Copolymer solution produced moderate to severe but reversible ocular irritation. In a Draize test, the greatest tolerated concentration of Sodium Polyacrylate was 13% to 20% and 20% to 30% for unrinsed and rinsed eyes, respectively. In an irritant threshold test, the greatest concentration of Sodium Polyacrylate that did not produce irritation in three or more of five rabbits was 2%.

In in vitro studies, Acrylates Copolymer was non- to mildly irritating.

Reproductive effects were not observed in a study in which rats were dosed orally with 4500- or 90,000-Da molecular weight Sodium Polyacrylate.

Acrylates Copolymer was not mutagenic in Ames tests. A mixture containing 30% Ammonium Acrylates Copolymer was not mutagenic in a modified Ames test. Sodium Polyacrylate was not mutagenic in an Ames assay, a plate test, a mouse lymphoma assay, chromosomal aberration assays, a UDS assay, or an in vivo mouse micronucleus assay.

In clinical studies, Acrylates Copolymer and Sodium Polyacrylate did not produce irritation or sensitization. In examining the effects of workplace exposures, employees exposed to a variety of acrylic polymer dusts (as well as other materials) did not have an excess of chest x-ray abnormalities, especially those suggestive of diffuse pulmonary fibrosis, and they did not have an excess of PFT abnormality.

Monomers

Acrylic acid and methyl acrylate were administered dermally to rats and mice and to guinea pigs, respectively. Following dermal administration of acrylic acid, the radioactivity was recovered mostly in the skin trap, and then in expired carbon dioxide. Following dermal administration of methyl acrylate, radioactivity was found in the SC tissues and throughout the body. 2-Ethylhexyl acrylate, acrylic acid, methyl acrylate, ethyl acrylate, and butyl acrylate were administered orally to rats and/or mice. In most cases, the dose was generally excreted in expired air. When rats were exposed to acrylic acid via inhalation, most of the radioactivity was found in the head and snout, with relatively large amounts also being recovered in the upper respiratory tract. 2-Ethylhexyl acrylate and methyl and butyl acrylate were given intraperitoneally. Again, most of the dose was excreted in expired air.

The dermal LD_{50} of acrylic acid was 295 to 950 mg/kg for rabbits. The oral LD_{50} was 2100 to 3200 mg/kg for rabbits and for rats and 0.34 ml/kg for male rats. The oral LD_{50} of glacial acrylic acid was 193 to 350 mg/kg for rats. Acute oral administration of acrylic acid and methyl, ethyl, and butyl acrylate produced gastric lesions. The acute LC_{50} of acrylic acid was 3600 mg/m^3 for rats. Short-term oral administration of ethyl acrylate to rats produced gastric lesions, primarily in the forestomach. In short-term inhalation studies, nasal lesions were produced by acrylic acid but not ethyl acrylate. Butyl acrylate produced toxicity. In subchronic dermal studies using acrylic acid, 4% produced toxic effects in mice. Subchronic oral administration of acrylic acid, $\leq$750 mg/kg, also produced toxic effects, and $\leq$200 mg/kg ethyl acrylate produced lesions in the forestomachs of rats. Methyl and butyl acrylate were not toxic to rats when given orally. Rats and/or mice were exposed to acrylic acid and ethyl and butyl acrylate in subchronic inhalation studies; nasal lesions were observed. In chronic oral studies, acrylic acid given in drinking water did not produce lesions in rats and ethyl acrylate did not produce lesions in rats or dogs. Acrylic acid, 4%, was irritating to the skin of mice, and a 1% solution caused significant injury to the rabbit eye.

In oral and inhalation reproductive studies, acrylic acid was not teratogenic, and 2-ethylhexyl, methyl, ethyl, butyl, 2-hydroxyethyl, and hydroxypropyl acrylate were not teratogenic when administered via inhalation. In a reproductive study in which groups of gravid rats were dosed by IP injection with 0.002 to 0.008 ml/kg acrylic acid or 0.13 to 0.44 ml/kg methyl methacrylate, 0.12 to 0.41 ml/kg ethyl methacrylate, 0.23 to 0.76 ml/kg *n*-butyl methacrylate, 0.14 to 0.4 ml/kg isobutyl methacrylate, or 0.25 to 0.82 ml/kg isodecyl methacrylate monomers, the incidence of gross abnormalities significantly increased in all dose groups, except for dams of the acrylic acid and methyl methacrylate low-dose groups and of the *n*-butyl methacrylate low- and mid-dose groups. Also, the incidence of skeletal malformations was significantly increased in the acrylic acid high-dose group.

2-Ethylhexyl acrylate was not mutagenic in a microbial mutagen test, Ames test, mammalian cell transformation test, micronucleus test, monolayer or suspension assay, CHO assay, or in vivo cytogenetic assay; it was mutagenic in a mouse lymphoma forward mutation assay with metabolic activation, equivocally mutagenic in mutation and aberration assays, and weakly mutagenic in SCE and UDS assays. Acrylic acid was not mutagenic in plate incorporation, liquid preincubation, UDS, micronucleus, in vitro transformation, CHO/HGPRT, in vivo cytogenetic, *Drosophila* sex-linked recessive, or mouse dominant lethal assays. Acrylic acid was mutagenic in mouse lymphoma assays and in a CHO/HGPRT and in vitro cytogenetic assay. Methyl acrylate was not mutagenic in an Ames, *Salmonella*/microsome, spot, liquid incubation, monolayer, suspension, or AS52/XPRT assay; it was mutagenic in mouse lymphoma and chromosomal aberration assays. Methyl acrylate was positive in one and negative in two micronucleus tests. Ethyl acrylate was not mutagenic in an Ames, *Salmonella*/microsome, liquid incubation, monolayer, chromosomal aberration, SCE, or *Drosophila* assay; ethyl acrylate did induce chromosomal malsegregation and mitotic recombination using *S. cerevisiae*, and it was mutagenic in a mouse lymphoma and chromosomal aberration assay. Ethyl acrylate was positive in one and negative in one micronucleus assay. *n*-Butyl acrylate was not mutagenic in a *Salmonella*/microsome, liquid incubation, UDS, micronucleus, or in vitro transformation assay; it was nonmutagenic in one and mutagenic in another chromosomal aberration assay. Methacrylic acid was not mutagenic in a *Salmonella*/microsome test. Methyl methacrylate was not mutagenic in a *Salmonella*/microsome or liquid incubation assay; it was mutagenic in a chromosomal aberration, SCE, and mouse lymphoma assay. Ethyl and butyl methacrylates were not mutagenic in a *Salmonella*/microsome test.

2-Ethylhexyl acrylate was carcinogenic when applied dermally to mice; the carcinogenic response may be associated

with the severe skin irritation induced by the chemical. IARC determined that "there is inadequate evidence in humans" and "there is limited evidence in experimental animals for the carcinogenicity of ethylhexyl acrylate." In one study, 1% acrylic acid, undiluted ethyl acrylate, and 1% butyl acrylate were not carcinogenic. In another, 4% acrylic acid in acetone was a complete but weak carcinogen. Acrylic acid was not carcinogenic to rats when administered in the drinking water, but oral administration by gavage of ethyl acrylate in corn oil was carcinogenic to male and female rats and mice. Methyl, ethyl, and butyl acrylate were not carcinogenic in mice in inhalation studies, and acrylic acid was not carcinogenic when injected subcutaneously to mice.

IARC (1999) gave the following carcinogenic evaluations for acrylic acid, methyl, ethyl, and *n*-butyl acrylate, and methyl methacrylate: "no epidemiological data" and "no experimental data relevant to the carcinogenicity of acrylic acid were available"; "acrylic acid is not classifiable as to its carcinogenicity to humans." "No epidemiological data relevant to the carcinogenicity of methyl acrylate were available" and "there is inadequate evidence in experimental animals for the carcinogenicity of methyl acrylate"; "methyl acrylate is not classifiable as to its carcinogenicity in humans." "No epidemiological data relevant to the carcinogenicity of ethyl acrylate were available" and "there is sufficient evidence in experimental animals for the carcinogenicity of ethyl acrylate"; "ethyl acrylate is possibly carcinogenic to humans." "No epidemiological data relevant to the carcinogenicity of *n*-butyl acrylate were available" and "there is inadequate evidence in experimental animals for the carcinogenicity of *n*-butyl acrylate"; "*n*-butyl acrylate is not classifiable as to its carcinogenicity in humans." "There is inadequate evidence in humans for the carcinogenicity of methyl methacrylate. There is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals." Overall, "methyl methacrylate is not classifiable as to its carcinogenicity to humans." NTP has voted to delist ethyl acrylate from its *Report on Carcinogens*.

Case studies have been reported regarding sensitization reactions to methyl, ethyl, and butyl acrylate and ethyl methacrylate.

DISCUSSION

The CIR Expert Panel recognized that there are a large number of ingredients in this safety assessment and that these polymers are comprised of many different monomeric building blocks. Nonetheless, these polymers are uniformly large molecules and are produced in chemical reactions that leave very little residual monomer. The most recent information available indicates that, although residual acrylic acid may be as high as 1500 ppm, typical levels are 10 to 1000 ppm. The Panel was convinced that these low levels are routinely attained based on the information provided, which described significant odor if residual monomers are present. For these reasons, the Panel concluded that it is reasonable to consider these ingredients as a group.

Upon review of the available data, the Panel was primarily concerned with unreacted monomers and/or other residual chemicals such as plasticizers or catalysts. Irritation and sensitization tests on several of these polymers found very little irritation, suggesting that there are small enough levels of monomers, etc., so as not to cause irritation or sensitization. Because of the minimal irritation that was seen in some ingredients, the skin and ocular toxicity seen with Acrylates/VA Copolymer, and the strong irritancy exhibited by the monomers, it was concluded that a caveat regarding irritation should be included.

The principle concern regarding the use of these polymer ingredients is the presence of toxic residual monomers. In particular, although 2-ethylhexyl acrylate was not genotoxic, it was carcinogenic when applied at a concentration of 21% to the skin of C3H mice. Lower concentrations (2.5%) and stop-dose studies at high concentrations (43%) were not carcinogenic. 2-Ethylhexyl acrylate was not carcinogenic in studies using NMRI mice. If it is assumed that 2-ethylhexyl acrylate is present as a residual monomer at a concentration of 1000 ppm, it was reasoned that this could be compared to the 210,000 ppm (21%) used in the C3H mouse study discussed above, resulting in several orders of magnitude safety factor.

Whether in the mouse strain where an increase in carcinogenesis was seen or in the strain where no such effect was seen, there was evidence of severe dermal irritation in these 2-ethylhexyl acrylate studies. Although the Panel acknowledged that none of these copolymers in current use contains 2-ethylhexyl acrylate itself, its severe irritancy reinforced the Panel's concern about skin irritation.

Another concern regarding residual monomers was inhalation toxicity. Although the acrylic acid monomer is a nasal irritant, exposure to the monomer from use of these polymers in cosmetic formulations would always be less than the established TLVs for nasal irritation.

Although again recognizing that there is a huge variation in the mix of monomers used in the synthesis of these polymers, the Panel believes that they are similar in that the polymers, except for dermal irritation, are not significantly toxic, and residual monomer levels are kept as low as possible. Although the monomers may be toxic, the levels that would be found in cosmetic formulations are not considered to present a safety risk. Accordingly, these Acrylate Copolymers are considered safe for use in cosmetic formulations when formulated to avoid irritation.

CONCLUSION

On the basis of the available information, the CIR Expert Panel concludes that Acrylates Copolymer, Ammonium Acrylates Copolymer, Ammonium VA/Acrylates Copolymer, Sodium Acrylates Copolymer, Ethylene/Acrylic Acid Copolymer, Ethylene/Calcium Acrylate Copolymer, Ethylene/Magnesium Acrylate Copolymer, Ethylene/Sodium Acrylate Copolymer, Ethylene/Zinc Acrylate Copolymer, Ethylene/Acrylic Acid/VA

Copolymer, Acrylates/PVP Copolymer, Acrylates/VA Copolymer, Steareth-10 Allyl Ether/Acrylates Copolymer, Acrylates/Steareth-50 Acrylate Copolymer, Acrylates/Steareth-20 Methacrylate Copolymer, Acrylates/Ammonium Methacrylate Copolymer, Styrene/Acrylates Copolymer, Styrene/Acrylates/Ammonium Methacrylate Copolymer, Ammonium Styrene/Acrylates Copolymer, Sodium Styrene/Acrylates Copolymer, Acrylates/Hydroxyesters Acrylates Copolymer, Methacryloyl Ethyl Betaine/Acrylates Copolymer, Lauryl Acrylate/VA Copolymer, VA/Butyl Maleate/Isobornyl Acrylate Copolymer, Ethylene/Methacrylate Copolymer, Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer, Sodium Acrylates/Acrolein Copolymer, PVP/Dimethylaminoethylmethacrylate Copolymer, AMP-Acrylates Copolymer, Polyacrylic Acid, Ammonium Polyacrylate, Potassium Aluminum Polyacrylate, Potassium Polyacrylate, and Sodium Polyacrylate are safe for use in cosmetics when formulated to avoid skin irritation.

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Amended Final Report on the Safety Assessment of Ethyl Methacrylate[1]

Ethyl Methacrylate is a methacrylate ester used as a chemical additive in artificial fingernail enhancement products. These products may be applied by trained professionals or be provided directly to consumers with instructions for use. Ethyl Methacrylate readily polymerizes and rapidly reacts with multifunction methacrylates to form a highly cross-linked polymer. The oral LD_{50} of Ethyl Methacrylate for rats ranged from 12.7 to 18.14 g/kg. In acute studies with rats, hemoglobinuria and respiratory tract lesions were observed. Animal studies indicate that Ethyl Methacrylate is a skin irritant and sensitizer. In some cases the results were dependent on the vehicle. Evidence of embryotoxicity and teratogenicity were observed in rats injected intraperitoneally with 0.1223 to 0.4076 ml/kg Ethyl Methacrylate. Positive evidence of mutagenicity was observed in the L5178Y mouse lymphoma cell assay, but not in two Ames tests. Case reports cite examples of individuals suffering allergic contact dermatitis from exposure to Ethyl Methacrylate and related methacrylates, and some degree of cross-reactivity appears to exist between widely used acrylates and methacrylates. Information from several clinical registries of sensitization reactions to various agents reported that Ethyl Methacrylate is a sensitizer, but not a potent one. Because Ethyl Methacrylate monomer is short-lived in the normal course of using artificial fingernail-enhancement products, the primary hazard is expected to be inadvertant skin contact. In order to avoid sensitization, it is necessary to avoid skin contact. It is recommended that fingernail-enhancement products containing Ethyl Methacrylate include directions to avoid skin contact because of the sensitizing potential. Based on the available data on the formulation of nail products containing this ingredient, it is concluded that Ethyl Methacrylate is safe as used, when application is accompanied by directions for use as above.

INTRODUCTION

Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid used in artificial fingernail-enhancement products. A previous safety assessment of this ingredient (Andersen 1995) concluded that Ethyl Methacrylate was safe as used if skin contact was avoided. To emphasize this point, the discussion in that report included the recommendation that products containing Ethyl Methacrylate be applied only by trained individuals, and the statement that Ethyl Methacrylate should not be used in products intended for retail sale.

Since that report was published, a request was received from the Methacrylate Producers Association (MPA) to revise the Cosmetic Ingredient Review (CIR) conclusion to state that Ethyl Methacrylate is unsafe for use in cosmetics (MPA 1998). The MPA argued, in part, that use of Ethyl Methacrylate is accompanied by pretreatment of the nail with methacrylic acid, a known corrosive material. The sensitization potential of Ethyl Methacrylate and its ability to cross-sensitize to other methacrylates formed the other essential element in the argument that exposure to Ethyl Methacrylate was likely and would result in allergic reactions and cross-reactions. The request also extended to other methacrylates and methacrylic acid. These ingredients will be addressed separately by the CIR Expert Panel. It should be noted that the Consumer Product Safety Commission (CPSC) has proposed rulemaking to require child-resistant packaging for all household products containing 5% (by volume) or more of Methacrylic Acid (CPSC 1998).

Another group, the American Beauty Association (ABA) and its Nail Manufacturers' Council (NMC) disagreed, noting the procedures and practices of trained professionals in salons to assure safe use of artificial nail products, and supporting the conclusion that Ethyl Methacrylate is safe for use in cosmetics if skin contact is avoided (ABA 1998).

It was during the discussion of these issues that another group, the Retail Nail Association, Inc. (RNA) presented data on the use of Ethyl Methacrylate in nail products sold directly to consumers; that is, not applied by trained professionals (RNA 1999). This group argued that the conclusion as outlined above should be expanded in that "as used" clearly includes consumer purchase with the intent that the product be used outside of the context of a beauty salon and a trained professional.

Published data since the original report, as well as unpublished data included in the submissions of all three groups (MPA, ABA, and RNA) have been added to the report and form the basis for an amended conclusion regarding the safety of Ethyl Methacrylate in artificial fingernail enhancement products.

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Address correspondence to F. Alan Andersen, Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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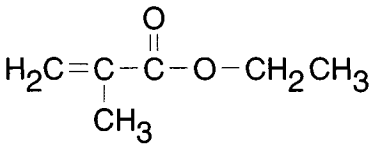
CHEMISTRY

Definition and Structure

Ethyl Methacrylate (CAS no. 97-63-2) is the ester of ethyl alcohol and methacrylic acid, which has the following chemical structure (Wenninger and McEwen 1997):



Other chemical names for Ethyl Methacrylate are Ethyl 2-Methyl-2-Propenoate; 2-Methyl-2-Propenoic Acid, Ethyl Ester; 2-Propenoic Acid, 2-Methyl-, Ethyl Ester; and Methyacrylic Acid, Ethyl Ester (Wenninger and McEwen 1997; RTECS 1992).

Properties

Ethyl Methacrylate is a colorless liquid with a melting point below −75°C, a boiling point of 119°C, and a specific gravity of 0.911 (Hawley 1971). It has a molecular weight of 114.14 Da (Environmental Protection Agency [EPA] 1986), a refractive index (*n*, 25/D) of 1.4116, and a flash point (OC) of 70°F (Hawley 1971). Ethyl Methacrylate has an acrid acrylate odor and is soluble in alcohol and ether (EPA 1985). Ethyl Methacrylate is readily polymerized (Hawley 1971), and is chemically reactive (Nemec and Kirch 1981).

Ethyl Methacrylate monomer is very hydrophobic and poorly "wets" the hydrophilic keratin surface of the nail plate, requiring the use of hydrophilic nail primers and additives to obtain sufficient adhesion (Schoon 1999b).

Curing of Salon Products

The extent of curing for two Ethyl Methacrylate–based fingernail formulations used by trained professionals in salons was determined over intervals ranging from 5 minutes to 24 hours. The formulations used were moderately cross-linked preparations that were cured in sample pans at body temperature (37°C). Differential scanning calorimetry was used to measure the exotherm created when unreacted monomer began to polymerize. Negative values were indicative of greater exotherm and, therefore, larger amounts of unreacted monomer. Additionally, the formulations were allowed to cure on fingernails at room temperature (28°C). Particles produced from filing the hardened formulations were analyzed after 45 and 90 minutes of aging, and fingernail clippings were evaluated after 45 minutes.

After 5 minutes of curing, both formulations had significant exotherm values (−44.93 J/g and −83.05 J/g) that were used as conservative estimates of the 50% monomer conversion value. Using these values, it was calculated that the relative percentage of unreacted monomer after 1 hour at 37°C was <1.0% for both formulations. The average residual monomer content for the fingernail filings was less than 2% at 45 minutes, and <1% at 90 minutes. The slower polymerization observed here was attributed to the cooler temperature (28°C) at which the formulations were allowed to cure. This was also observed with the fingernail clippings, in which <1% monomer was found in both clipping samples at 45 minutes (Schoon 1994a).

As a follow-up to this study, Schoon (1994b) measured the unreacted monomer content of the same two fingernail samples cured at 30°C. Both samples were cured in aluminum pans at 30°C, and exotherm measurements were taken at 5 minutes and 1 and 4 hours. Using the 5-minute exotherm values as the estimated 50% monomer conversion values, residual monomer content was calculated to be 0.6% at 1 hour. At 4 hours, the residual monomer content was below the limit of detection.

A profile of the cure temperature of the two Ethyl Methacrylate fingernail formulations was also conducted. Each formulation, stored at 23°C, was applied at 25°C to a fingernail fitted to precision fine wire thermocouples. Temperatures were recorded using an analog to digital data acquisition board, cold junction signal conditioner, and a 486/66-MHz computer. Immediately following the first bead application of both products at the dorsal tip of the nail, cooling was measured. When the formulations were applied directly over the thermocouple, the temperature dropped from 35.5°C to 29.2°C, which was attributed to the lower temperatures of the formulations. Two additional drops in temperature were observed when the second and third beads of each formulation were applied to the nail.

The temperature began to rise within 1 minute following the final bead application. This warming trend lasted for approximately 3 minutes for one formulation and an additional 20 seconds for the other formulation. Maximum exotherm temperatures of 41.8°C and 43.0°C were measured, which returned to a baseline temperature of 35.8°C. Five minutes after curing, the nail enhancements were filed, which produced a small amount of frictional heat. However, filing with a less abrasive "finishing" file produced an overall cooling effect, which the investigator attributed to lower generation of heat and higher thermal conductivity of the file. Temperatures returned to baseline values once the finishing process was completed.

The mean temperature over the 40-minute test period was 35.1°C and 35.2°C for the two formulations. The investigator noted that table lamps were not used during this experiment, but are commonly used during salon applications. Therefore, mean temperatures recorded in this study are probably lower than would occur under normal conditions of use (Schoon 1994c).

A comparison was made of properties of professional artificial fingernail products formulated with Ethyl Methacrylate versus methyl methacrylate (Schoon 1999a). Products formulated with methyl methacrylate were uniformly more resistant to bending, to deformation, and finally to breaking, compared to products formulated with Ethyl Methacrylate. It was also found that methyl methacrylate adheres less well to the nail plate compared to Ethyl Methacrylate products (used with a hydrophilic primer and additives), necessitating severe abrasion of the nail plate to achieve acceptable levels of adhesion of methyl methacrylate products.

Curing of Retail Products

The polymerization of Ethyl Methacrylate in home-use products has been described (Retail Nail Association 1999; Sauerhoff 1999). In one experiment, the applicator brush was dipped in liquid Ethyl Methacrylate monomer, excess monomer was removed, and then the applicator brush was touched to the polymer powder forming a ball, as would be done by a user. That mixture was placed on preweighed filter paper. Free monomer was absorbed by the filter paper from the uncured/curing ball for 2 minutes. Reweighing the filter paper determined that the mean (number of trials not stated) extractable monomer was 3.68%. This was extrapolated to a total of 22 mg of Ethyl Methacrylate available if a full set of 10 nails were completed. Further work was done to determine the available Ethyl Methacrylate monomer at 10 minutes after dipping the brush with monomer into the polymer powder. In this study, the ball of monomer/polymer was placed on a glass slide and allowed to cure for 10 minutes at 37°C. (*Note*: room temperature is usually considered to be 25°C.) The material was then extracted in 0.1 N NaCl containing 10 ppm N,N-Diethylhydroxylamine (DEHA) at 37°C for 8 hours and then analyzed by gas chromatography/mass spectroscopy. In 12 runs, the average Ethyl Methacrylate bound and not available for exposure was determined to be 99.83%. In a third study, a ball of monomer/polymer was formed and placed between two ZnSe crystals and compressed to form a thin film. Infrared (IR) scans at times from 0 to 5 minutes at 20°C and at 11.8 hours at 37°C were done. The signal corresponding to unsaturated Ethyl Methacrylate disappeared in the 11.8-hour run, indicating full polymerization.

Based on these data, an exposure assessment was done using the following parameters: product used once every 2 weeks; about 1.5 g total material used in an initial application; unlikely skin exposure; and exposure to Ethyl Methacrylate vapors equivalent to that found in salon worker breathing zones. In this scenario the only exposure is via inhalation and the lifetime average daily concentration is 0.0065 ppm. Comparing this to the 10-ppm limit extablished by Holland (NTIS 1994) gives over three orders of magnitude as a margin of safety (Sauerhoff 1999).

Method of Manufacture

Ethyl Methacrylate is formed by the reaction of methacrylic acid or methyl methacrylate with ethyl alcohol (Hawley 1971).

Analytical Methods

Gas chromatography (Black 1977) and glass-capillary gas chromatography combined with mass spectrometry (Horna, Taborsky, and Churacek 1986) can be used to identify Ethyl Methacrylate.

Impurities

Hydroquinone and the methyl ether of hydroquinone (as inhibitors) are typically found in commercial grades of Ethyl Methacrylate at concentrations ranging from 22 to 28 ppm and 15 to 20 ppm, respectively (EPA 1985; Nemec and Kirch 1981). The methacrylic acid content of Ethyl Methacrylate monomers is very low; analysis of commercially available Ethyl Methacrylate monomers reveals that the purity is >99%, with water being the highest of the impurities (Keystone Industries 1999).

USE

Cosmetic

Ethyl Methacrylate is used as a chemical additive in cosmetic formulations (Wenninger and McEwen 1997). Ethyl Methacrylate is a substitute for methyl methacrylate, the compound originally used in sculptured fingernail products. Action to remove fingernail products containing Methyl Methacrylate was taken by the Food and Drug Administration (FDA) in 1974 because of consumer complaints about onycholysis and fingernail dislocation and/or irritation (U.S. District Court Decision 1974).

Although this ingredient was not reported to the FDA as being used in 1994 (FDA 1994), representatives of the NMC reported that Ethyl Methacrylate is used in artificial fingernail-enhancement products, which are designed for application by trained individuals (Schoon 1994a). Recent information from manufacturers of home-use artificial nail products (RNA 1999) suggests that there is extensive use of such products by individual consumers. According to the RNA (1999), home-use artificial nail products are designed to minimize exposure to Ethyl Methacrylate during home, use by selecting rapidly polymerizing formulations and use of applicators that allow consumers to control the amount and extent of product applied to the nail.

Application by Trained Individuals

Typically, nail-enhancement products (artificial fingernails) are formed from two part formulations containing Ethyl Methacrylate as the major structural monomer and are cross-linked with one or more multifunctional methacrylates (Schoon 1994a). Typical instructions used by a nail technician to ensure that artificial fingernails are applied only to the hardened keratin of the nail plate are as follows:

- wash hands of salon patron and technician;
- after initially preparing nail for application, sanitize finger with antiseptic lotion or gel;
- apply nail primer to nail plate without touching the skin;
- fit form or tip around the nail plate;
- dip brush in monomer and then in polymer powder to obtain an aspirin size ball;
- place the small ball in the center of the still imaginary artificial nail (essentially on junction of nail form and nail plate);
- carefully pat material toward the cuticle and then toward the form edges without touching the skin;
- shape, contour, and finish application of the nail;
- wash hands.

The technique with which the mixed monomer and polymer is placed and spread is stated to be similar to instructions for use of similar materials by dental practitioners and for the fixation of internal orthopedic prostheses (ABA 1998).

Application by Retail Purchasers

Directions for use of home use artificial fingernails include the following examples of directions/warnings (RNA 1999):

- Use in a well ventilated area.
- Do not touch skin or cuticle during application.
- Avoid cuticle area.
- Brush product out to end of nail.
- Brush formula away from cuticle.
- Avoid cuticle area and brush out to end of nail to blend.
- If acrylic gets on cuticle, remove immediately.
- Discontinue use if redness or allergic symptoms occur.

In addition, the RNA (1999) provided examples of package warnings, including:

- Read all warnings and complete instructions before applying.
- Avoid inhalation.
- Avoid inhalation, ingestion, or prolonged contact with skin.
- Do not use on any nails that are infected, damaged, extremely thin, or weak.
- Do not apply to weak or damaged nails or if cuticle area is irritated or inflamed.
- Do not use if you are sensitive to acrylic products.
- Keep dust out of the eyes to prevent possible irritation. Get immediate medical help if irritation continues.
- In case of emergency, contact a physician immediately.
- Keep out of the reach of children.

These directions and warnings were considered by the RNA to be as complete as those provided to salon nail technicians.

Noncosmetic

Ethyl Methacrylate is used in the production of acrylic polymers for paints and coatings and in components for the automotive, aerospace, and furniture industries. It is also used by the dental industry for dentures, plates, and cements (EPA 1985; Freeman 1965). Contact lenses (Refojo 1979) and artificial fingernails (Lee and Orlowski 1976) are also produced with Ethyl Methacrylate.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Tanii and Hashimoto (1982) reported that the oral LD_{50} of Ethyl Methacrylate for mice was 68.64 mmol/kg (7.8 g/kg).

In another study, groups of 10 rats were administered Ethyl Methacrylate via stomach tube at doses ranging from 12.70 to 18.14 g/kg. The LD_{50} was between 12.70 and 14.51 g/kg. Two to 4 minutes following administration, the rats had an increased rate of respiration with lacrimation. After 15 to 40 minutes, they had motor weakness and their respiration decreased and breathing was irregular and labored. The frequency of defecation and urination were increased, blood was present in the urine, and reflex activity disappeared. The animals died in coma 1 to 1.5 hours following dosing. At necropsy, lesions were found primarily in the respiratory system. The lungs, trachea, and bronchi were markedly congested and edematous. The lungs were also spotted with areas of hemorrhage and emphysema. The thymus was swollen and congested. In the heart, the ventricles were well contracted and the auricles were dilated and filled with dark clotted blood. Blood was found in the dilated abdominal vessels. The greatly distended urinary bladder often contained bloody fluid and the mucosa had areas of hemorrhage, necrosis, and detachment. Congestion of the intestine and acute inflammation of the mucosa were also evident (Deichmann 1941).

The oral LD_{50} for rabbits was between 3.63 and 5.44 g/kg. Signs of toxicity were similar to those seen in the rats (Deichmann 1941).

Subcutaneous

Six of 10 rats died 8 to 18 hours following a single subcutaneous injection of 25 cc Ethyl Methacrylate. The animals had clinical signs of toxicity similar to that seen in the acute oral studies. A sudden increase in respiration was followed by reduced and labored respiration, the urine contained blood, and motor control and reflex activity were severely diminished. Lesions found at necropsy were the same as those found in the rats of the acute oral studies. The researchers noted that the LD_{50} dosage was greater for the subcutaneous study than for the oral study, suggesting that subcutaneous absorption was less rapid (Deichmann 1941).

Intraperitoneal

The intraperitoneal LD_{50} for rats was 1.2228 ml/kg (Singh, Lawrence, and Autian 1972).

Inhalation

The $LC_{50/24}$ for 10 Sprague-Dawley rats exposed to Ethyl Methacrylate in their air for 4 hours was 8300 ppm. During exposure, the behavior of the rats reflected irritation of the eyes, nose, and respiratory tract. The rats squinted, huddled, and had labored respiration. The investigators noted that death was predictable by the blanching of the pinnae and paws. Animals that survived the first 24 hours also survived the 14-day observation period. At necropsy, no gross abnormalities were found (Oberly and Tansy 1985).

Groups of two rats, one guinea pig, and one rabbit were exposed to 12.4, 15.0, and 17.7 mg/l Ethyl Methacrylate for 8 hours. Doses of 15.0 and 17.7 mg/l killed the rats within 3 to

4 hours, but did not kill either the rabbits or guinea pigs. None of the animals exposed to 12.4 mg/l Ethyl Methacrylate died. At necropsy, the lungs, trachea, and bronchi of the rats were markedly congested and edematous, and the lungs had areas of hemorrhage and emphysema. Pathological changes were also found in the thymus, heart, and abdomen. These changes were similar to those observed in the acute oral studies (Deichmann 1941).

Subchronic Toxicity

Intravenous

Because hemoglobinuria was observed in acute studies, a study was conducted to determine whether or not Ethyl Methacrylate caused an increase in blood and urine porphyrin concentrations. Five rabbits were injected with 2 cc/kg of Ethyl Methacrylate once a week for 3 weeks, and the blood and urine were analyzed before the first dose and after the last dose. Porphyrins were detected in both fluids; however, the individual porphyrins were not identified (Deichmann 1941).

Inhalation

A study conducted by Lawrence and Autian (1972) indicated that inhalation of Ethyl Methacrylate vapor affected drug metabolizing enzymes. Groups of 10 male ICR mice were exposed to 84.79 mg/l of Ethyl Methacrylate in their breathing air for 3.85, 7.70, and 19.25 minutes for 3 days. Sodium pentobarbital was administered 24 hours following the last Ethyl Methacrylate exposure and sleeping time was compared to that of a control group that was not exposed to Ethyl Methacrylate. Sleeping time increased with the duration of exposure. The mean sleeping time for the control mice was 50.63 minutes. For the mice in the low-, mid-, and high-dose groups, the sleeping times were 51.06, 53.93, and 94.93 minutes, respectively. The researchers stated that this dose-related increase was an indication that Ethyl Methacrylate can have an effect on drug metabolizing enzymes.

Dermal Irritation

The clipped skin of rabbits (number not stated) was treated with 10 cc/kg Ethyl Methacrylate. The animals were restrained under a hood in such a way that they were unable to inhale the evaporating material. Signs of irritation were observed at the site of exposure and the animals were inactive. The animals recovered within 1 hour (Deichmann 1941).

Sensitization and Cross-Reactivity

Ethyl Methacrylate was tested for sensitization potential in the guinea pig maximization test. Groups of 10 Duncan Hartley guinea pigs were administered three pairs of intradermal injections of 0.1 ml Freund's complete adjuvant (FCA), Ethyl Methacrylate in peanut oil, and Ethyl Methacrylate in FCA in their backs. The concentrations of Ethyl Methacrylate tested were 0.17, 0.50, and 1.50 M. On day 7, an occlusive patch containing 1 M Ethyl Methacrylate was applied to the site of the injections for 48 hours. After a 2-week nontreatment period, the right flank of each guinea pig was shaved and 3 M undiluted Ethyl Methacrylate was applied under occlusive patches for 24 hours. The sites were scored at 24 and 48 hours. On day 35, 3 M undiluted Ethyl Methacrylate was applied to the shaved left flank of each guinea pig and left uncovered. Readings were taken after 24 and 48 hours. A control group of six guinea pigs received the same treatment, except that only the vehicle was used in the applications.

No evidence of sensitization was observed in the guinea pigs induced with 0.17 M Ethyl Methacrylate. One guinea pig induced with 0.50 M Ethyl Methacrylate had evidence of sensitization after treatment on day 35 and one positive reaction was observed after both the 21- and 35-day treatments among the guinea pigs induced with 1.50 M Ethyl Methacrylate. When this experiment was repeated using a 0.5-M induction concentration on day 0, 1 of 10 guinea pigs reacted after both the 21- and 35-day applications (van der Walle et al. 1982).

Ethyl Methacrylate was also tested with FCA. Six guinea pigs were induced with intradermal injections of 5 × 0.5 M Ethyl Methacrylate in FCA and water on days 0, 2, 4, 7, and 9. On days 21 and 35, the shaved right and left flanks, respectively, were treated topically with 3 M undiluted Ethyl Methacrylate. The sites were left uncovered and readings were taken 24 and 48 hours following each of these treatments. Two of the six guinea pigs had positive reactions following both the 21- and 35-day treatments (van der Walle et al. 1982).

Chung and Giles (1977) conducted a study, the results of which suggested that the sensitization potential of Ethyl Methacrylate was dependent upon the vehicle of administration and that mutual cross-sensitivity exists between monomers of methacrylic acid. Guinea pigs were injected with 0.1 ml of FCA with heat-killed *Mycobacterium butyricum* into each foot pad (total volume 0.4 ml; total amount of *M. butyricum* 100 μg). One group of 25 animals was treated with topical applications of 0.03 ml of Ethyl Methacrylate in ethanol on days 0, 2, and 5. When the first challenge with 2% and 5% Ethyl Methacrylate in ethanol was administered on day 25, no sensitization was observed 72 hours following the challenge application. The animals received a second challenge on day 60 with either a topical dose of 10% Ethyl Methacrylate in olive oil or an intradermal dose of Ethyl Methacrylate in saline (0.01 and 0.1 μl/site). Ethyl Methacrylate in olive oil produced severe sensitization reactions. However, the intradermal dose of Ethyl Methacrylate in saline did not evoke any responses. A third challenge on day 122 with 0.4% and 2% Ethyl Methacrylate in olive oil caused sensitization within 72 hours. The researchers suggested that Ethyl Methacrylate in ethanol evaporated before it could elicit a response.

Another group of nine guinea pigs was initially treated with 0.0077 ml of Ethyl Methacrylate in olive oil on day 60 (as controls) and was challenged with 2% and 5% Ethyl Methacrylate in olive oil on day 95. Positive reactions were observed in all of the animals after 72 hours.

When the guinea pigs from both groups were challenged a second or fourth time with Ethyl Methacrylate and either 1% methyl methacrylate or 1% butyl methacrylate, strong cross-sensitivity was observed.

In another study, three guinea pigs sensitized to either 1 or 4 M Ethyl Methacrylate were tested for cross-reactivity with several acrylic monomers. The animals, sensitized in the Freund's adjuvant test or the guinea pig maximization test, were challenged on one flank with acrylates, methacrylates, diacrylates, and dimethacrylates (0.025 ml) 2 weeks after completing the tests. A second challenge with the monomers was conducted 2 weeks later on the other flank. Readings of the test sites were conducted 24 and 48 hours following application. After the last challenge to test cross-reactions, the guinea pigs were also challenged with Ethyl Methacrylate. Some of the animals had cross-reactions with acrylates, methacrylates, and dimethacrylates. However, these reactions were only to specific monomers and usually involved only one guinea pig. None of the guinea pigs reacted to the diacrylates (van der Walle and Bensink 1982).

Rustemeyer et al. (1998) recently investigated crossreactivity patterns of methacrylates. In a standard guinea pig maximization test, induction was done with 10% methyl methacrylate in water-FCA emulsion, 10% methyl methacrylate in corn oil, and a water-FCA emulsion in the neck region. Challenge was done with Finn chambers filled with 25 μl of 25% methyl methacrylate in corn oil. Open skin tests were made 2 weeks later with 25% and 50% methyl methacrylate in an ethanol/DMSO (40%) solution. A modification of this protocol with induction at day 0 with injections of 10% methyl methacrylate, 12% 2-hydroxyethyl methacrylate, 14% 2-hydroxypropyl methacrylate, or 20% ethylene glycol dimethacrylate into both flanks, the ears, and the neck was used in cross-reactivity tests. In the modified protocol, challenge was done at day 14 with open skin tests on clipped and shaved upper flanks with 25 μl of solution containing either 50% methyl methacrylate, 10% ethylene glycol dimethacrylate, 50% 2-hydroxyethyl methacrylate, or 50% 2-hydroxypropyl methacrylate. Challenge reactions were recorded after 6, 24, 48, and 72 hours as red (2), pink (1.5), pale pink (1), faintly pink (0.5), or negative (0). Table 1 gives the pattern of crossreactivity; each row shows the inducing chemical (crosshatched box) and the crossreactivity to that chemical for each of the other three (e.g., row 3 shows the reactions to methyl methacrylate, 2-hydroxyethyl methacrylate, and ethylene glycol dimethacrylate in animals sensitized to 2-hydroxypropyl methacrylate). The researchers concluded that crossreactions between methacrylates are most likely if there are similarities between size and polarity of the ester side chains.

A closed-patch method was used to study Ethyl Methacrylate sensitization in the guinea pig by North American Science Associates, Inc. (1998). Full strength Ethyl Methacrylate (0.3 ml) was applied to a nonwoven cotton disk in a Hill Top chamber, applied for 6 to 8 hours to the clipped left flank of 10 guinea pigs, and held in place with an elastic band. Observations were made 24 hours following the completion of exposure. Application was repeated 3 times each week for 3 weeks. Five guinea pigs treated similarly, but with sodium chloride in the patch, served as controls. Thirteen days after the final induction, the animals were challenged on the right flank using the same procedure as for induction. Observations were done 24, 48, and 72 hours after patch removal. One test animal had well-defined erythema and slight edema with induction patches 5 to 9. No other reactions were observed during induction. No evidence of sensitization was observed in that test animal or in any of the other test or control animals.

Photosensitivity

Deichmann (1941) speculated that edema and photosensitivity might occur in animals suffering from porphyrinuria or porphyrinemia when exposed to sunlight. In order to investigate this reaction, 0.5 cc Ethyl Methacrylate was applied to the skin of 10 rats six times a week for 20 weeks. Five rats were exposed daily to ultraviolet light from an Ashcraft ultraviolet generator

TABLE 1

Pattern of cross-reactivity of methacrylates in guinea pigs (Rustemeyer et al. 1998)

	Methyl methacrylate	2-Hydroxyethyl methacrylate	2-Hydroxypropyl methacrylate	Ethylene glycol dimethacrylate
Methyl methacrylate	—	Infrequent (9/16)[a] Weak (0.2)	Infrequent (5/15) Weak (0.0)	Frequent (18/21) Strong (1.1)
2-Hydroxyethyl methacrylate	Frequent (7/7) Strong (0.6)	—	Frequent (8/11) Strong (0.9)	Frequent (7/7) Strong (1.1)
2-Hydroxypropyl methacrylate	Intermediate (7/11) Weak (0.3)	Frequent (15/15) Strong (0.7)	—	Frequent (11/11) Strong (1.0)
Ethylene glycol dimethacrylate	Intermediate (8/11) Weak (0.2)	Infrequent (5/11) Weak (0.0)	Infrequent (2/11)[b] Weak (0.0)	—

[a]Animals with the strongest reactions to 2-hydroxyethyl methacrylate also showed the highest reactivity to 2-hydroxypropyl methacrylate.

[b]The two animals that reacted to 2-hydroxypropyl methacrylate also reacted to 2-hydroxyethyl methacrylate.

(Model 476) for 1 hour. Mild, transient irritation was the most severe reaction observed during the study.

Ocular Irritation

Two rabbits had 0.1 ml of undiluted Ethyl Methacrylate instilled into their right conjunctival sac. One eye was rinsed after 20 seconds, and the other eye was left unrinsed. The eyes were examined after 1 and 4 hours, and after 1, 2, 3, and 7 days. A small area of opacity was observed in the cornea of the unrinsed eye, which diminished through days 2 and 3. Discharge from the eye was severe 1 hour after treatment, moderate after 4 hours, and mild at 24 hours. The conjunctiva was slightly red and swollen through day 2. No effects were observed in the iris, and the cornea was transparent by day 7. Conjunctival irritation was milder in the rinsed eye. A small area of microscopic surface sheen observed in the test or control animals was seen in the cornea at day 1, and mild transient conjunctivitis was observed. No effects on the iris were found and all signs of irritation disappeared by day 3 (Haskell Laboratory for Toxicology and Industrial Medicine 1977).

Pharmacological Effects

Mir, Lawrence, and Autian (1973a) investigated the response of the isolated rabbit heart to Ethyl Methacrylate perfusion. The isolated hearts of rabbits were perfused with Ethyl Methacrylate at concentrations of 1:100,000, 1:10,000, and 1:1000 (*v/v*) in Locke's solution for 1 minute, followed by perfusion with Locke's solution only. Each concentration was tested five times and the heart rate, force of contraction, and coronary flow rate were quantified prior to perfusion and immediately after perfusion. Irreversible damage was reported if the cardiac parameters did not make a significant return to control levels of activity within 30 to 35 minutes. Ethyl Methacrylate, at a concentration of 1:1000, caused cardiac standstill.

A concentration of 1:10,000 reduced the cardiac rate by 17.8%, the force of contraction by 72.2%, and the coronary flow by 57.9%. These parameters were reduced by 5.8%, 19.8%, and 26.1%, respectively, at a 1:100,000 concentration. The effects of Ethyl Methacrylate on the isolated heart were irreversible at all three concentrations.

Ethyl Methacrylate was also tested using isolated guinea pig ileum. Actively contracting loops of ileum were isolated from guinea pigs and exposed to Ethyl Methacrylate at concentrations of 1:2000, 1:1000, and 1:500 (*v/v*) in Tyrode's solution. A force-displacement transducer electrically connected to a polygraph recorded changes in contractions when the ileum was exposed to Ethyl Methacrylate alone or in the presence of either acetylcholine (1:10,000,000) or barium chloride (3:100,000, *w/v*). Ethyl Methacrylate alone inhibited pendular movements and relaxation of the muscle, and a dose-response relationship was observed. The stimulant actions of acetylcholine and barium chloride were also antagonized by Ethyl Methacrylate in a dose-dependent fashion. These effects were reversed when the ileum was rinsed with fresh Tyrode's solution (Mir, Lawrence, and Autian 1973b).

Mir, Lawrence, and Autian (1974) also studied the effects of Ethyl Methacrylate on respiratory and cardiovascular function in dogs. Groups of three male mongrel dogs were anesthetized with sodium pentobarbital and were given intravenous doses of 0.0171, 0.0342, and 0.3684 ml/kg Ethyl Methacrylate. A pressure transducer was attached to the carotid artery to monitor the systemic blood pressure, and another transducer was attached to the trachea to record respiratory pressure changes. Four needle electrodes were placed subdermally into each limb of the dog to record the electrocardiogram.

Ethyl Methacrylate caused a biphasic response in the dogs' blood pressure. Blood pressure abruptly fell by 31.95% to 58.66% for 2 to 4 minutes, and then pressure slowly rose, reaching a plateau 7.21% to 24.74% above the control value lasting 10 to 15 minutes. The heart rate also decreased in a dose-dependent fashion, but was not of the same magnitude; there was a 11.13% to 25.11% decrease. Respiratory rate was increased by 34.10% to 146.41% for approximately 20 minutes. The electrocardiogram had the following dose-related changes: bradycardia, a reduction in the rate of impulse transmission through the A-V node, and indications of acute cardiac ischemia. The larger doses also caused premature ventricular contractions and incomplete A-V block (Mir, Lawrence, and Autian 1974).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Groups of five pregnant Sprague-Dawley rats were given 0.1223, 0.2446, and 0.4076 ml/kg Ethyl Methacrylate intraperitoneally on days 5, 10, and 15 of gestation. A control group of pregnant rats was left untreated. All of the rats were killed on day 20 of gestation and examined. The number of corpora lutea in the treatment groups ranged from 53 to 58, and 60 corpora lutea were in the control rats. Resorptions occurred only in the test animals; five resorptions occurred in the 0.1223 ml/kg group, six in the 0.2446 ml/kg group, and seven in the 0.4076 ml/kg group. Fewer fetuses were found in the test rats (42 to 51 fetuses) than in the control rats (59 fetuses). All of the fetuses in the experimental groups were alive, but the mean weights of the fetuses in the mid- and high-dose groups were significantly lower than that of the controls.

A significant number of gross abnormalities were found in the fetuses from the experimental groups. In the high-dose group, eight gross abnormalities were found: one hemangioma each of the hind leg and foreleg, three cases of hemangiomas of the shoulders, one case of twisted hind legs, one case of no tail, and one small fetus with a compact head and neck. Three of the 27 fetuses examined had elongated and fused ribs. In the mid-dose group, 5 hemangiomas of the neck were found, and 2 of the 26 fetuses examined had elongated and fused posterior ribs. Similar abnormalities were observed in the low-dose group. Two cases of hemangiomas on the shoulders were found, 1 fetus had twisted hind legs, and 1 fetus of the 25 examined had elongated

posterior ribs. No gross or skeletal abnormalities were found in the fetuses from the untreated control group. The researchers concluded that Ethyl Methacrylate produced significant embryopathic and teratogenic effects (Singh, Lawrence, and Autian 1972).

Saillenfait et al. (1999) studied the developmental toxicity of Ethyl Methacrylate in Sprague-Dawley rats. Mated females were randomly assigned to groups using a system stratified by body weight. Animals were housed separately and exposed to air containing Ethyl Methacrylate 6 h/day on days 6 through 20 of gestation. Ethyl Methacrylate was introduced by passing the exposure chamber air flow through the fritted disk of a heated bubbler containing Ethyl Methacrylate. Separate dosing groups of 0, 600, 1200, 1800, and 2400 ppm were studied.

No maternal deaths were observed during this study, although maternal weight gain was significantly reduced during the first half of exposures at the 1200- and 1800-ppm levels and over the entire period at the 2400-ppm level. There was a statistically significant dose dependent decrease in weight gain above 1200 ppm. Fetal body weight was significantly reduced in males in the 1200-ppm group, and in both sexes for all higher exposure groups. There was no significant effect on: (1) the mean number of implantations and live fetuses; (2) the frequency of non-live implants or resorptions; or (3) the fetal sex ratio. Although single cases of malformations were seen in all groups, there was no statistically significant differences between the control and the groups exposed to Ethyl Methacrylate.

GENOTOXICITY

Ethyl Methacrylate was evaluated at concentrations ranging from 33 to 10,000 μg/plate with the *Salmonella*/microsome test using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. Tests were conducted in triplicate both with and without activation with liver S9 from Aroclor-induced Sprague-Dawley rats and Syrian hamsters. Solvent and positive controls were also included with each trial. The positive controls used for tests without metabolic activation were sodium azide for strains TA100 and TA1535, 9-aminoacridine for TA1537, and 4-nitro-*o*-phenylenediamine for TA98. In tests with S9 activation, 2-aminoanthracene was used for all of the strains. Ethyl Methacrylate was negative in tests both with and without metabolic activation (Zeiger et al. 1987).

In another *Salmonella*/microsome test, Ethyl Methacrylate was tested at concentrations ranging from 40 to 2500 μg/plate using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. Metabolic activation was produced once with phenobarbital-induced S9 mix and once with Aroclor-1254–induced S9 mix. Two tests were conducted without metabolic activation. All of the tests were conducted in triplicate. In tests using phenobarbital-induced S9 mix, 2-aminoanthracene was the positive control for all of the strains. Benzo[a]pyrene was the positive control used to test strains TA98, TA100, and TA1538 with activation with Aroclor-induced S9 mix; no positive controls were used to test stains TA1535 and TA1537 in this system. The positive controls used for tests without activation were sodium azide for strains TA100 and TA1535, glycidyl methacrylate for TA1535, 9-aminoacridine for TA1537, and 4-nitro-*o*-phenylenediamine for TA98 and TA1538. Ethyl Methacrylate was negative both with and without phenobarbital or Aroclor-induced S9 mix (Waegemaekers and Bensink 1984).

Ethyl Methacrylate was tested in the L5178Y mouse lymphoma cell assay. L5178Y/TK$^{+/-}$ cells were treated with 900 to 2100 μg/ml of Ethyl Methacrylate without exogenous activation for 4 hours. 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 2 days and then cloned with and without trifluorothymidine (TFT) selection. Following an incubation period of 9 to 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% to 37%. A weak positive response was observed in cultures with 10% to 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 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).

CLINICAL ASSESSMENT OF SAFETY

Sensitization

Ethyl Methacrylate was tested on 542 dermatitis patients using either the A1-Test (Imeco Agency, Sweden) or the Finn Chamber method. Each subject was exposed for 48 hours to 1% Ethyl Methacrylate in petrolatum, and scoring was conducted at 48 and 96 hours. Only one subject developed signs of irritation. Four subjects who were sensitive to methyl methacrylate were also tested with Ethyl Methacrylate. No cross-reactions were observed (Maibach et al. 1978).

Koppula, Fellman, and Storrs (1995) presented the results of 23 patients with allergic contact dermatitis to acrylates seen in one clinic over a period of 10 years. Eleven of these patients had a history of exposure to artificial nails. Patch testing was conducted using 33 different acrylates, including Ethyl Methacrylate, but not all patients were tested with all acrylates. Positive reactions were seen with only 20 of the 33 tested. Of the 22 patients on whom Ethyl Methacrylate was tested, 14 were positive. Eleven of these 22 patients wore artificial nails; of these 11 patients wearing artificial nails, 7 had positive reactions.

TABLE 2
Rank order of positive patch test findings in all patients, including findings in wearers of artificial nails (Koppula, Fellman, and Storrs 1995)

	Positive results in all patients		Positive results in patients with artificial nails	
Acrylate tested	+ reactions/patients tested	%	+ reactions/nail patients tested	%
Ethyl acrylate	13/18	72	10/11	91
2-Hydroxyethyl methacrylate	10/14	71	8/10	80
Ethylene glycol dimethacrylate	11/16	69	6/10	60
Ethyl methacrylate	14/22	64	7/11	64
2-Hydroxyethyl acrylate	8/13	62	7/9	77
2-Hydroxypropyl methacrylate	8/13	62	5/9	55
Diethylene glycol dimethacrylate	8/14	57	6/9	67
2-Hydroxypropyl acrylate	6/13	46	5/10	50
Tetraethylene glycol dimethacrylate	6/14	43	3/9	33
Ethyl alpha cyanoacrylate	5/15	33	5/11	45
Trimethylol propane triacrylate	6/18	33	4/10	40
Methyl methacrylate	7/22	32	1/10	10
Triethylene glycol dimethacrylate	5/16	31	4/10	40
Triethylene glycol diacrylate	4/13	31	4/9	44
Pentaerythritol triacrylate	4/16	25	2/9	22
Urethane diacrylate	2/13	15	2/10	20
Tetrahydrofurfuryl methacrylate	2/13	15	1/7	14
1,4-Butanediol dimethacrylate	2/13	15	2/9	22
Butyl acrylate	2/15	13	2/10	20
N-Amylacrylate	2/16	13	2/11	18

Table 2 presents the results for all of the acrylates for which there were positive findings. Cross-reactivity of five patients in this group, who were allergic to ethyl alpha cyanoacrylate ("super glue"), was present for ethyl acrylate (5/5), Ethyl Methacrylate (5/5), 2- hydroxyethyl methacrylate (3/5), diethylene glycol dimethacrylate (2/5), ethylene glycol dimethacrylate (2/5), and trimethylol propane triacrylate (2/2). A short list of five relevant acrylates was identified to screen and diagnose patients allergic to acrylates used in artificial nails: ethyl acrylate, 2-hydroxyethyl acrylate, ethylene glycol dimethacrylate, ethyl alpha cyanoacrylate, and triethylene glycol diacrylate (Koppula, Fellman, and Storrs 1995).

In a review of 10 years (1985 to 1995) of patch testing with the (meth)acrylate series, Kanerva, Jolanki, and Estlander (1997) present the results from 275 patients with a history of exposure to (meth)acrylates. Occlusive patch testing was conducted using 31 (meth)acrylates applied to the back of each patient, with a patch time of 24 hour during the period from 1985 to 1988, and a patch time of 48 hour during the period from 1989 to 1995.

Of the 243 patients patch-tested with Ethyl Methacrylate, 18 had allergic reactions (7.4%). These 10-year data were also divided into two 5-year periods. For the early 5-year period, reported as 1985 to 1990, 124 patients were tested and 6 had allergic reactions (4.8%). For the later 5-year period, reported as 1991 to 1995, 119 patients were tested and 12 had allergic reactions (10.1%). These researchers concluded that compounds such as Ethyl Methacrylate that caused many positive occlusive patch test results "are obviously contact sensitizers in humans, or have a strong tendency to cross-react with sensitizers."

In a more recent summary of 15 years of experience of patch testing to (meth)acrylates, Tucker and Beck (1999) presented the results in 440 patients with a history of exposures to (meth)acrylates. In this population, 11 of 246 patients (4.5%) tested with Ethyl Methacrylate (patch-test concentration of 2%) had positive patch-test reactions. The most frequent positive test reactions were seen with 2-hydroxyethyl acrylate (9.6%), Ethyl Methacrylate was ranked 10th out of 30; the authors commented that the results of animal studies would have suggested a different rank order of sensitizing capacity than was actually seen.

A cumulative patch test was done on 10 adult volunteers with normal skin using Ethyl Methacrylate according to the methods of Jackson (1994). Preliminary patch testing was done with full strength Ethyl Methacrylate and the actual testing used open and semiocclusive patches, with positive and negative controls. No positive reactions occurred from exposure to Ethyl Methacrylate either during the induction or challenge phase of the test. Positive and negative controls produced the expected results. The investigator concluded that full strength Ethyl Methacrylate did not produce irritant contact dermatitis nor allergic contact dermatitis in individuals with normal skin (Jackson 1999a).

Repeat-insult patch testing was performed using 46 subjects (55 subjects were selected, but 9 dropped out for reasons reportedly unrelated to the use of the test materials) by the Consumer Product Testing Co. (1994). Two artificial nail products were tested, one with acrylic sculpture liquid and acrylic clear sculpture powder, the other with the same acrylic sculpture liquid, but with acrylic blush sculpture powder. In each case, the liquid was combined with the powder in a 1:1 proportion and brushed onto patches as a paste before it hardened. The material was allowed to volatilize before application to the skin, but the time was not recorded. The concentration of unreacted Ethyl Methacrylate was not determined. Semiocclusive patches with these materials were applied three times per week for a total of 10 applications. Subjects removed patches after 24 hours. Each site was evaluated immediately prior to reapplying a patch. Approximately 14 days after the 10th application, a challenge patch was applied to the original site on the back and to the volar forearm. These sites were evaluated at 24 and 48 hours. The treated areas were negative throughout the test interval.

In a recent commentary on the sensitization potential of methyl methacrylate and Ethyl Methacrylate, Jackson (1999b) concluded that both have the potential to cross-react with other methacrylates in sensitized individuals. Although the investigator stated that methyl methacrylate could produce irritant contact dermatitis and was a sensitizer, he went on to state that Ethyl Methacrylate had not been found to cause irritant contact dermatitis and was only a weak sensitizer. A practicing clinician specializing in nail disorders concluded, based on personal experience in a nail disorder clinical practice and the available published and unpublished data, that Ethyl Methacrylate was safe (NMC 1999).

Consumer Reporting

The experience of one manufacturer of retail artificial nail products who maintains a record of all consumer inquiries noted that the frequency of consumer contacts has increased in the period of 1995 to 1998 at a faster rate than has the total sales of products. As a result, the normalized frequency of consumer contacts per unit sold has more than tripled in that time period. Within this overall reporting, the frequency of reports of adverse events to the retail "kits" has decreased from 2.3 per 100,000 units in 1996 to 1.74 per 100,000 units sold in 1998. It was noted that allergy to Ethyl Methacrylate was not among the adverse events reported (Del Laboratories, Inc. 1999).

Case Reports

A number of case studies of allergic contact dermatitis caused by artificial fingernails containing Ethyl Methacrylate have been reported. The details of these studies are in Table 3. In addition, Mathias, Caldwell, and Maibach (1979) reported a case of a laboratory technician with allergic contact dermatitis associated with the use of 80% hydroxyethylmethacrylate in absolute alcohol as part of preparing samples for light microscopy. The patient exhibited cross-reactivity to methyl, ethyl, propyl, and isopropyl methacrylate, but not with butyl or isobutyl methacrylate. Casse et al. (1998) reported a case of depigmentation at the site on the back where positive reactions to occlusive patches containing Ethyl Methacrylate were placed.

Occupational Studies

Hiipakka and Samimi (1987) specifically studied nail sculptors for exposure to organic vapors and methacrylate dusts from acrylic fingernail extensions. Seventeen personal vapor samples were taken from nail salons and the mean time-weighted average concentration of Ethyl Methacrylate was 4.5 ppm. There is no threshold limit value (TLV) for Ethyl Methacrylate, but the researchers speculated that this concentration was probably below the expected threshold, as the TLV for methyl methacrylate is 100 ppm. Twenty sculptors completed self-administered symptom questionnaires, in which they consistently reported nasal and cutaneous irritation, drowsiness, dizzy spells, and trembling hands. These signs were reported more often by nail sculptors but were not statistically greater than that reported by matched controls. Throat irritation was the only statistically significant symptom.

Cases of contact dermatitis to anaerobic acrylic sealants also have been documented. Six workers who developed dermatitis after contact with various sealants in the work place were patch-tested with the sealants (0.1% to 1%), a standard patch test series, a plastic series, and a variety of acrylates. Each worker was exposed to the chemicals for 48 hours, and the sites were read at 48, 72, and 96 hours. The workers were positive for the sealants tested and negative for the standard and plastic series. Five of the workers had positive reactions to 10% Ethyl Methacrylate after 96 hours. These individuals also had sensitivity to 2% hydroxyethyl methacrylate, three were sensitive to 10% methyl methacrylate monomer and 1% ethylene glycol dimethacrylate, two were sensitive to 0.1% acrylic acid, and one had a reaction to 1% triethylene glycol dimethacrylate. A control group of 20 individuals were negative for all of the compounds tested (Condé-Salazar, Guimaraens, and Romero 1988).

Occupational contact dermatitis from acrylate- and methacrylate-based products was reported in workers exposed to anaerobic sealants (Kanerva, Estlander, and Jolanki 1989; Guerra et al. 1993), dental composite resins (Kanerva, Estlander, and Jolanki 1989), dental and medical protheses (Kanerva et al. 1993), sculptured fingernails (Taylor 1989; Tosti, Guerra, and Bardazzi 1992), printing materials (Calnan 1980), and plastic embedding media (Montgomery 1989).

Savonius et al. (1993) report that acrylates also have the potential to cause respiratory symptoms, most commonly asthma.

Industrial Hygiene Evaluations

At the request of the Springdale Ohio Health Department, the National Institute for Occupational Safety and Health (NIOSH) conducted an industrial hygiene evaluation of exposures to

TABLE 3
Case studies reporting allergic contact dermatitis associated with artificial fingernail use

Case study	Patch test	Results	Reference
A woman developed paronychial and eyelid dermatitis 2 days after new applications of nails. The components of the nail preparation were a clear liquid monomer, clear powder polymer, and white powder polymer.	An aluminum patch test using the components of the nail preparation and ethyl, methyl, and *N*-butyl methacrylate (5% in petrolatum and 1% in ethyl alcohol) were applied to the back.	The liquid monomer and all of the methacrylate esters produced erythema, papules, and vescicles at 48 and 96 hours.	Marks, Bishop, and Willis (1979)
A patient suffered from severe painful onychia and paronychia 3 weeks after applying nails containing Ethyl Methacrylate monomer and isobutyl methacrylate monomer.	Patch test with 1% Ethyl Methacrylate, 1% isobutyl methacrylate monomer, and methyl methacrylate monomer.	Strong positive reaction developed for all three monomers.	Fisher (1980)
A patient developed severe onychia and paronychia 4 weeks after applying nails containing Ethyl Methacrylate, tetrahydrofurfuryl methacrylate, and diethylene glycol dimethacrylate monomers.	Patch test with 1% of each monomer and methyl methacrylate monomer.	Strong positive reactions were caused by all four monomers.	Fisher (1980)
After 3 months of using nails containing Ethyl Methacrylate monomer and ethylene glycol dimethacrylate, a patient developed mild paronychia.	Patch tests with 1% and 5% of each monomer and methyl methacrylate monomer.	1% concentrations of all of the monomers caused faint positive reactions. Strong positive reactions occurred after testing with 5% concentrations.	Fisher (1980)
A woman working in the manufacture and application of sculptured nails developed allergic contact dermatitis on her hands.	Patch test with a standard series and with plastics and acrylates, including 10% Ethyl Methacrylate, 10% methyl methacrylate, and 2% hydroxy-ethyl methacrylate.	Positive reactons were present at 48 and 96 hours for the methacrylates tested, as well as nickel sulfate (2.5%), Prains (10%), and cavity primer (1% and 10%).	Condé-Salizar et al. (1986).
A 35-year-old male who worked with a series of (meth)acrylate resins developed lesions on the fingers and hands that progressed to severe pruritis, ruptured blisters, fissures, and hyperkeratosis.	Finn chamber tests of methyl methacrylate, urethane dimethacrylate, and ethylene glycol dimethacrylate; followed by tests of a range of methacrylate esters.	Positive reactions to hydroxyethyl methacrylate (+ at 0.5%; ++ at 1%) only. No reaction to Ethyl Methacrylate at 0.5%, 1%, or 5%.	Tobler, Wüthrich, and Freiburghaus (1990)
A 42-year-old woman developed chronic contact dermatitis from Ethyl Methacrylate in filings that fell on her left hand during sculpturing of not yet hardened material with the file in her right hand.	Patch tests were performed with the artificial nail material, Ethyl Methacrylate (1%), methyl methacrylate, Perubalsam, formaldehyde, etc.	The subject had a ++ reaction to the artificial nail material and Ethyl Methacrylate, a + reaction to Perubalsam and formaldehyde, but no reaction to methyl methacrylate.	Schubert, Linder, and Prater (1992)

(Continued on next page)

TABLE 3
Case studies reporting allergic contact dermatitis associated with artificial fingernail use *(Continued)*

Case study	Patch test	Results	Reference
A 46-year-old woman developed onycholisis of the fingernails and dermatitis of the fingers, dorsa of the hands, arms, upper trunk, and face 6 months after beginning regular application of sculptured fingernails.	Patch tests were performed using the components of the sculptured fingernails (Ethyl Methacrylate monomer liquid and polymethacrylate powder), the European standard series, and to a plastics and glue series.	The subject had positive reactions to patch test with 1% MEK Ethyl Methacrylate, 10% petrolatum polymer nail powder, and 1% petrolatum butyl methacrylate.	Fitzgerald and English (1994)
A 53-year-old woman presented with blisters, ethythema, and edema of the fingers and paraesthesia in several fingers. She had sculpted artificial nails applied for 2 years with no problem, but subsequently noticed an itch about 1 hour after application, proceeding to the above symptoms.	Finn chamber patch-testing was performed with the European standard series and an acrylate series that did not include Ethyl Methacrylate.	The woman had positive reactions only to 2% methyl methacrylate and 2% ethylene glycol dimethacrylate.	Freeman, Lee, and Gudmundsen (1995)
A 31-year-old woman with nail-fold dermatitis reported that she had herself applied artificial nails for the previous 18 months.	Finn chamber patch-testing was performed with the European standard series, an acrylate series that did not include Ethyl Methacrylate, and her own liquid monomer.	Strongly positive to 2% methyl methacrylate, her own liquid monomer at 1%, and to balsoam of Peru.	Freeman, Lee, and Gudmundsen (1995)
A 49-year-old woman presented with nail-fold and fingertip dermatitis. She had worked as a manicurist and nail artist for 6 years.	Finn chamber patch-testing was performed with the European standard series and an acrylate series that did not include Ethyl Methacrylate.	Strongly positive to 2% ethylene glycol methacrylate, fragrance mix, and formaldehyde.	Freeman, Lee, and Gudmundsen (1995)
A 46-year-old woman presented with dermatitis of the eyelids and neck, but no finger reactions. She worked as a manicurist and reported airborne powder that irritated her face and neck when she was working with artificial nails.	Finn chamber patch-testing was performed with the European standard series, an acrylate series that did not include Ethyl Methacrylate, and 15 common bases of medicaments and cosmetics.	Positive to 2% ethylene glycol methacrylate and strongly positive for nickel and cobalt.	Freeman, Lee, and Gudmundsen (1995)
A 38-year-old diabetic woman presented with eczematous plaques at infusion sites on the abdomen 4 months after beginning use of an infusion pump to deliver insulin.	Patch testing was done to the European standard series and an acrylate series.	Positive reactions were seen only to several of the chemicals in the acrylate series, including 2% methyl methacrylate and 2% Ethyl Methacrylate.	van den Hove et al. (1996)

chemicals used during the application of sculptured nails. Personal and air sampling was conducted at the nail salon for methyl methacrylate, Ethyl Methacrylate, acetone, and benzene. No methyl methacrylate or benzene vapors were found; Ethyl Methacrylate ranged from nondetected to 7 ppm; and acetone vapors ranged from 6 to 10 ppm. There was no provision for the mechanical introduction of outside air into the nail salon. Based on the measured concentrations of chemicals, no health hazard existed to either the workers in the nail salon or in nearby businesses. Recommendations were made to reduce the spread of chemical odors (NIOSH 1999).

At the request of the owner of a beauty salon, NIOSH conducted a health hazard evaluation of the facility. General air sampling for volatile organic chemicals, formaldehyde, and methacrylates; personal air sampling was done for methacrylates. Ethyl Methacrylate concentrations ranged from 10.3 to 14.1 mg/m^3. The combined time-weighted average concentration at table 1 was 10.7 mg/m^3 and 12.5 mg/m^3 at table 2. Short-term personal breathing zone air samples collected during the application of nails had concentrations of 128 mg/m^3 (7-minute sample) and 78.9 mg/m^3 (14-minute sample). Based on all test data, no health hazard was found. No provision had been made for the mechanical introduction of outside air into the nail salon and recommendations were made to install an outside air supply (NIOSH 1999).

Prompted by reports of occupational asthma in Colorado, NIOSH was asked to evaluate and develop control measures to reduce the risk to which nail salon technicians were exposed (Spencer et al. 1997). The study was conducted at a cosmetology school where the artificial nail products used had liquid and powder components consisting primarily of Ethyl Methacrylate, with trace concentrations of methyl methacrylate in both the liquid and powder. The primer was primarily methacrylic acid, again with traces of methyl methacrylate. The dehydrating liquid was primarily methyl ethyl ketone. Exposures to Ethyl Methacrylate and methyl methacrylate were quantified and used as an index of control. A commercially available downdraft manicure table, of a design similar to many of those that were available, was evaluated to determine its effectiveness. Based on leaks detected around the unit's charcoal filters, no indication when the filters needed to be replaced, and uneven and inadequate (velocity) airflow, the unit was not considered adequate. Modifications were made to increase the downdraft air volume from 0.03 m^3/s to 0.11 m^3/s, make the flow more uniform across the work area, replace the filters with an exhaust system, and place a baffle (rising to the height of the table at the client's side) around the downdraft area. The ventilation was turned off to simulate a nonventilated table.

Concentratons of Ethyl Methacrylate and methyl methacrylate were determined using a NIOSH-developed method. Air samples were collected for an entire school day (approximately 6 hours) at three locations: the nail technicians breathing zone; on the manicure table; and in the salon area at a distance of around 3 m from the table. Four nail technicians applied nails during the data gathering, over a period of several days. Methyl methacrylate was not detectable. Ethyl Methacrylate concentrations had a log-normal distribution and the geometric mean and geometric standard deviation were presented. Ethyl Methacrylate concentrations that were reported as nondetectable were considered to be at the detection limit of the NIOSH measurement technique (0.01 mg/sample). No differences were seen among the four nail technicians or between days of the week. Data gathered with the ventilation on were compared to data gathered with the ventilation off.

TABLE 4
Ethyl Methacrylate levels during application of artificial nails (Spencer et al. 1997)

Sample area	Unventilated	Ventilated
Nail technician (one set of nails)	8.7 ± 2.0	0.6 ± 2.3
Nail technician (entire day, approximately 6 hours)	9.4 ± 1.4	0.7 ± 2.0
Table	1.7 ± 1.2	0.4 ± 1.1
Away from table	0.4 ± 1.5	0.3 ± 1.1

The results of the study are presented in Table 4. The results were a statistically significant 10-fold reduction of Ethyl Methacrylate concentrations measured in the breathing zone when the modified ventilated table was used with the ventilation on. The reduction was essentially the same whether measurements were taken over the period of application of one set of nails or whether the samples were collected over an entire day. Statistically significant fourfold reductions at the level of the table when the ventilation was on were seen as well. No statistically significant difference was observed in concentrations at a distance 3 m away from the table when the ventilation was on.

No Occupational Safety and Health Administration (OSHA) requirements or NIOSH guides restrict occupational exposure to Ethyl Methacrylate. In a hazard-control announcement directed at nail salons, NIOSH cites the similarity of Ethyl Methacrylate to methyl methacrylate, which NIOSH says is considered harmful. The hazard control announcement describes the need for ventilated tables of adequate design, the need for closure of all dispenser bottles, and provides a list of seven changes in individual work habits that would lower exposures to airborne chemicals (NIOSH 1999).

In a report of the Dutch Expert Committee on Occupational Standards (National Technical Information Service [NTIS] 1994), the absence of human data was noted. The committee did conclude that the available animal data suggested a mode of action for Ethyl Methacrylate similar to methyl methacrylate. Accordingly, the health-based occupational exposure limit, 10 ppm, for methyl methacrylate was adopted for Ethyl Methacrylate.

SUMMARY

Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid and is used as the major structural monomer of commercial and retail artificial fingernail formulations that are cross-linked with one or more multifunctional methacrylates. Ethyl Methacrylate is used as a substitute for methyl methacrylate, after FDA acted to remove products containing methyl methacrylate from the market due to numerous consumer complaints about onycholysis and nail dislocation and/or irritation.

Instructions for use of both commercial and retail products stress the need to avoid contact with the skin and/or describe application techniques that minimize any potential skin contact.

Commercially available Ethyl Methacrylate monomer is over 99% in purity. In commercial fingernail formulations, the Ethyl Methacrylate monomer is rapidly polymerized. Approximately 50% of the polymerization occurs within 5 minutes, and <1% monomer is available after 1 hour. The monomer content detected in filings from these types of products was <2% after 45 minutes and <1% after 90 minutes.

In retail products, only approximately 4% of the Ethyl Methacrylate is available as monomer at the time it is applied. After 10 minutes over 99% is polymerized and not available for exposure. Full polymerization is demonstrated after 11 hours.

Ethyl Methacrylate monomer is hydrophobic and poorly "wets" the hard keratin surface of the nail plate, requiring use of hydrophilic nail primers and additives. As a result, with minimal pretreatment, Ethyl Methacrylate–based nail products had a better adhesion (compared to methyl methacrylate), allowing attachment to the nail plate with minimal or no abrasion.

The oral LD_{50} for rats ranged between 12.70 and 18.14 g/kg Ethyl Methacrylate. Hemoglobinuria and lesions in the respiratory system were observed. In an acute inhalation study, the $LC_{50/24}$ for rats was 8,300 ppm Ethyl Methacrylate, and ocular, nasal and respiratory tract irritation was observed. In another study, the lungs, trachea, and bronchi of the rats were markedly congested, edematous, and spotted. Hemorrhage and emphysema were also observed.

In subchronic studies, Ethyl Methacrylate increased the concentrations of blood and urinary porphyrins after intravenous administration to rabbits, and affected drug metabolizing enzymes in mice after inhalation exposure.

Ethyl Methacrylate was irritating to the skin of rabbits and sensitization reactions were observed in both the guinea pig maximization test and the Freund's complete adjuvant test. One study indicated that the sensitization potential of Ethyl Methacrylate was dependent upon the vehicle of administration. Full strength Ethyl Methacrylate produced neither irritant contact dermatitis nor allergic contact dermatitis in one occlusive patch study in guinea pigs. Mutual cross-sensitivity exists between monomers of methacrylic acid and a small degree of cross-reactivity occurs with other acrylic monomers. It has been postulated that cross-reactivity is most likely if there are similarities between size and polarity of the ester side chains.

Mild, transient irritation was the most severe reaction observed when rats were given topical applications of Ethyl Methacrylate and were irradiated with ultraviolet light for 1 hour. Ethyl Methacrylate also caused transient ocular irritation.

In a teratogenicity study, pregnant rats were injected intraperitoneally with 0.1223, 0.2446, and 0.4076 ml/kg of Ethyl Methacrylate. Evidence of embryotoxicity and teratogenic effects were observed in rats of all three dosage groups.

Ethyl Methacrylate was negative in two *Salmonella*/microsome tests both with and without metabolic activation. However, it was positive in the L5178Y mouse lymphoma cell assay.

In a clinical irritation study, 542 patients were exposed to 1% Ethyl Methacrylate for 48 hours. Only one subject developed signs of irritation.

Of 23 patients with allergic contact dermatitis to acrylates who had been evaluated over a 10-year period, a high percentage of all patients (64%) reacted to an Ethyl Methacrylate patch test, but the frequency was no different in a subset of patients who wore artificial nails. Of 275 patients with a history of exposure to (meth)acrylates who were patch-tested over a 10-year period, 18 of 243 had allergic reactions to Ethyl Methacrylate. For the second half of the 10-year period, the percentage of those tested who were positive was about 10%, compared with about 5% for the first 5 years. In another review of 440 patients with a history of exposure to (meth)acrylates who were patch tested over a 15-year period, 11 of 246 had positive reactions to an Ethyl Methacrylate patch test. In one cumulative patch test using 10 individuals, full strength Ethyl Methacrylate induced neither irritant contact dermatitis nor allergic contact dermatitis. A human repeat-insult patch test using 46 subjects in which partially cured material was used as the test substance produced similar negative results.

Both in animal studies and in clinical studies, there appears to be some degree of cross-reactivity between various methacrylates.

In several case studies, Ethyl Methacrylate and related methacrylates in artificial fingernails caused allergic contact dermatitis. Occupational contact dermatitis from acrylates and methacrylates has been observed in individuals exposed to sealants, dental resins, protheses, and plastic embedding media, as well as those handling artificial nails.

Consumer complaints to manufacturers of artificial nail products have not included reports of sensitization.

Occupational studies have found concentrations of Ethyl Methacrylate to be lower than established threshold limit values for methyl methacrylate, but have recommended that steps be taken to provide adequate ventilation.

DISCUSSION

The sensitization and cross- or co-reactivity potential of Ethyl Methacrylate was of concern to the Expert Panel. Some animal studies indicated that Ethyl Methacrylate is a strong sensitizer.

However, clinical data presented a different picture. In one study that presented 10 years' accumulated data of patch testing with the (meth)acrylate series, 18 of 243 patients had positive test results with Ethyl Methacrylate. In another study that presented 15 years' accumulated patch testing with the (meth)acrylate series, 11 of 246 patients had positive test results with Ethyl Methacrylate. In another comparison, positive patch-test reactions to Ethyl Methacrylate were no more frequent in individuals with allergic contact dermatitis to acrylates who wore artificial nails than were positive reactions to Ethyl Methacrylate in the entire population of individuals with allergic contact dermatitis to acrylates.

Further, the CIR Expert Panel recognized that Ethyl Methacrylate is used as the major structural monomer of artificial fingernail formulations that are cross-linked with one or more multifunctional methacrylates. For both commercial and retail products, due to the nature of these types of formulations, Ethyl Methacrylate monomer is entrapped quickly and very little free monomer is available even during filing of the fingernails. The Panel also considered available information suggesting that hydrophobic Ethyl Methacrylate monomer would not penetrate the hydrophilic keratin substructure of the nail plate, supporting the view that penetration of the nail bed would not be a route of exposure.

Combining the frequency with which allergic contact dermatitis reactions to Ethyl Methacrylate appear with the small likelihood that Ethyl Methacrylate monomer will be available to expose a user, the CIR Expert Panel concluded that, although individuals can become sensitized to Ethyl Methacrylate, the risk of that happening as a result of the use of artificial nail products is low. In order to minimize any exposure to the free monomer, the Expert Panel recommends that commercial fingernail enhancement products containing Ethyl Methacrylate be applied by trained individuals and that skin contact be avoided. Accordingly, the Panel believes that directions for use should be provided that alert users to the need to avoid skin contact because of the possibility of an allergic reaction.

Regarding the consequences of cross- or co-reactivity, a concern about methyl methacrylate was raised. Medical implants are of particular concern in this regard because of the use of methyl methacrylate as a bone cement and the possibility that an individual sensitized to Ethyl Methacrylate might then have an allergic reaction to the bone cement in a necessary medical procedure. Comment was provided both by an individual with experience in the manufacture of implants (Blessing 1999) and a physician with experience in the implantation of such devices (Booth 1999). In both cases, the strong assertion was made that there are no data supporting any sensitization reactions in patients receiving implants cemented with methyl methacrylate. Booth (1999) went on to assert that, even were such sensitization to occur, there are uncemented alternatives that would not expose the patient to methyl methacrylate. In a similar analysis, Hume (1999) concluded that sensitization to methyl methacrylate is not a clinical issue, and that uncemented alternatives exist against the hypothetical possibility that methyl methacrylate sensitization would occur. The Panel considered that this potential adverse consequence of cross-reactivity of Ethyl Methacrylate and methyl methacrylate is not an actual concern. Potential respiratory problems caused by the inhalation of Ethyl Methacrylate particles produced from filing of artificial fingernails was also discussed. Because this type of particulate matter is usually large enough to be seen and is not likely to be airborne for extended periods of time, Ethyl Methacrylate is not expected to cause respiratory problems.

The Expert Panel also discussed the teratogenic effects observed in a study with rats. They agreed that the study was a poor indicator of developmental toxicity because the route of exposure was intraperitoneal. Additional studies are not required because exposure to the monomer is expected to be low and because cutaneous absorption of this material is low. Negative mutagenicity results also alleviated the Expert Panel's concerns.

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.

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Final Report on Ethyl Methacrylate[1]

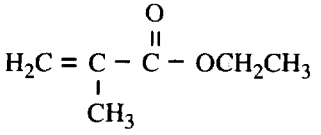
Abstract: Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid used as the major structural monomer of artificial fingernail formulations that are cross-linked with one or more multifunctional methacrylates. Ethyl methacrylate monomer is polymerized rapidly and very little free monomer is available even during filing of the fingernails. The oral LD_{50} for rats ranged from 12.7 to 18.14 g/kg, with lesions in the respiratory system and hemoglobinuria observed in treated animals. Ocular, nasal, and respiratory tract irritation was observed in acute inhalation tests using rats. Very little toxicity was seen in subchronic studies using rabbits. Ethyl Methacrylate caused irritation and vehicle dependent sensitization in animals, but no photosensitization. Evidence of embryotoxic and teratogenic effects were observed in pregnant rats after intraperitoneal injection of Ethyl Methacrylate at a range of concentrations. Both positive and negative mutagenicity test data were found. Clinical testing showed little evidence of irritation, although case studies report allergic contact dermatitis as a result of exposure to Ethyl Methacrylate and related methacrylates with application of artificial fingernails. Occupational contact dermatitis from acrylates and methacrylates are also reported, with some evidence for cross-reactivity between the two chemical classes. Based on the sensitizing potential of this ingredient the CIR Expert Panel recommended that fingernail enhancement formulations with Ethyl Methacrylate be applied only by trained individuals and that the ingredient not be used in products intended for retail sale (currently, these products are believed to be sold only for application by a trained individual). Because of the low likelihood of significant exposure if such formulations are applied properly, the Expert Panel concluded that the ingredient is safe as used, with the caveat that skin contact should be avoided.
Key Words: Ethyl methacrylate—Embryotoxic effect—Teratogenic effect.

Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid used in artificial fingernail enhancement products. The safety data on this ingredient are presented in this report.

CHEMISTRY

Definition and Structure

Ethyl Methacrylate (CAS No. 97-63-2) is the ester of ethyl alcohol and methacrylic acid, which has the following chemical structure (Nikitakis et al., 1991):



[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.

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Other chemical names for Ethyl Methacrylate are Ethyl 2-Methyl-2-Propenoate; 2-Methyl-2-Propenoic Acid, Ethyl Ester; 2-Propenoic Acid, 2-Methyl-, Ethyl Ester; and Methacrylic Acid, Ethyl Ester (Nikitakis et al., 1991; RTECS, 1992).

Properties

Ethyl Methacrylate is a colorless liquid with a melting point below −75°C, a boiling point of 119°C, and a specific gravity of 0.911 (Hawley, 1971). It has a molecular weight of 114.14 (EPA, 1986), a refractive index (n 25/D) of 1.4116, and a flash point (OC) of 70°F (Hawley, 1971). Ethyl Methacrylate has an acrid acrylate odor and is soluble in alcohol and ether (EPA, 1985).

Ethyl Methacrylate is readily polymerized (Hawley, 1971), and is chemically reactive (Nemec and Kirch, 1981).

The extent of curing for two Ethyl Methacrylate–based commercial fingernail formulations was determined over intervals ranging from 5 min to 24 h. The formulations used were moderately cross-linked preparations that were cured in sample pans at body temperature (37°C). Differential scanning calorimetry was used to measure the exotherm created when unreacted monomer began to polymerize. Negative values were indicative of greater exotherm, and therefore larger amounts of unreacted monomer. Additionally, the formulations were allowed to cure on fingernails at room temperature (28°C) and particles produced from filing the hardened formulations were analyzed after 45 and 90 min of aging, and fingernail clippings were evaluated after 45 min.

After 5 min of curing, both formulations had significant exotherm values (−44.93 J/g and −83.05 J/g) that were used as conservative estimates of the 50% monomer conversion value. Using these values, it was calculated that the relative percentage of unreacted monomer after 1 hr at 37°C was <1.0% for both formulations. The average residual monomer content for the fingernail filings was <2% at 45 min, and <1% at 90 min. The slower polymerization observed here was attributed to the cooler temperature (28°C) at which the formulations were allowed to cure. This was also observed with the fingernail clippings, in which <1% monomer was found in both clipping samples at 45 min (Schoon, 1994*a*).

As a follow up to this study, Schoon (1994*b*) measured the unreacted monomer content of the same two fingernail samples cured at 30°C. Both samples were cured in aluminum pans at 30°C, and exotherm measurements were taken at 5 min and 1 and 4 h. Using the 5-min exotherm values as the estimated 50% monomer conversion values, residual monomer content was calculated to be 0.6% at 1 h. At 4 h, the residual monomer content fell below detection levels.

A profile of the cure temperature of the two Ethyl Methacrylate fingernail formulations was also conducted. Each formulation, stored at 23°C, was applied at 25°C to a fingernail fitted to precision fine wire thermocouples. Temperatures were recorded using an analog-to-digital data acquisition board, cold junction signal conditioner, and a 486/66 MHz computer. Immediately following the first

bead application of both products at the dorsal tip of the nail, cooling was measured. When the formulations were applied directly over the thermocouple, the temperature dropped from 35.5 to 29.2°C, which was attributed to the lower temperatures of the formulations. Two additional drops in temperature were observed when the second and third beads of each formulation were applied to the nail.

The temperature began to rise within 1 min following the final bead application. This warming trend lasted for ~3 min for one formulation and an additional 20 s for the other formulation. Maximum exotherm temperatures of 41.8 and 43.0°C were measured, which returned to a baseline temperature of 35.8°C. Five minutes after curing, the nail enhancements were filed, which produced a small amount of frictional heat. However, filing with a less abrasive "finishing" file produced an overall cooling effect, which the investigator attributed to lower generation of heat and higher thermal conductivity of the file. Temperatures returned to baseline levels once the finishing process was completed.

The mean temperature over the 40-min test period was 35.1 and 35.2°C for the two formulations. The investigator noted that table lamps were not used during this experiment, but are commonly used during salon applications. Therefore, mean temperatures recorded in this study are probably lower than would occur under normal conditions of use (Schoon, 1994*c*).

Method of Manufacture

Ethyl Methacrylate is formed by the reaction of methacrylic acid or methyl methacrylate with ethyl alcohol (Hawley, 1971).

Analytical Methods

Gas chromatography (Black, 1977) and glass capillary gas chromatography combined with mass spectrometry (Horna et al., 1986) may be used to identify Ethyl Methacrylate.

Impurities

Hydroquinone and the methyl ester of hydroquinone (as inhibitors) are typically found in commercial grades of Ethyl Methacrylate at concentrations ranging from 22 to 28 ppm and 15–20 ppm, respectively (EPA, 1985; Nemec and Kirch, 1981).

USE

Cosmetic

Ethyl Methacrylate is used as a chemical additive in cosmetic formulations (Wenninger and McEwen, 1992). Although this ingredient was not reported to the FDA as being used in 1994 (FDA, 1994), representatives of the Nail Manufactur-

ers Council reported that Ethyl Methacrylate is used in artificial fingernail enhancement products which are designed for application by trained individuals (Schoon, 1994*a*).

Typically, artificial fingernails are formed from two part formulations containing Ethyl Methacrylate as the major structural monomer and are crosslinked with one or more multifunctional methacrylates (Schoon, 1994*a*).

Ethyl Methacrylate is a substitute for methyl methacrylate, the compound originally used in sculptured fingernail products. Methyl Methacrylate was banned from use in fingernail products by the U.S. Food and Drug Administration in 1974 because of consumer complaints about onycholysis and fingernail dislocation and/or irritation (U.S. District Court Decision, 1974).

Noncosmetic

Ethyl Methacrylate is used in the production of acrylic polymers for paints and coatings and in components for the automotive, aerospace, and furniture industries. It is also used by the dental industry for dentures, plates, and cements (EPA, 1985; Freeman, 1965). Contact lenses (Refojo, 1979) and artificial fingernails (Lee and Orlowski, 1976) are also produced with Ethyl Methacrylate.

BIOLOGICAL PROPERTIES

Pharmacological Effects

Mir et al. (1973*a*) investigated the response of the isolated rabbit heart to Ethyl Methacrylate perfusion. The isolated hearts of rabbits were perfused with Ethyl Methacrylate at concentrations of 1:100,000, 1:10,000, and 1:1,000 (v/v) in Locke's solution for 1 min, followed by perfusion with Locke's solution only. Each concentration was tested five times and the heart rate, force of contraction, and coronary flow rate were quantified prior to perfusion and immediately after perfusion. Irreversible damage was reported if the cardiac parameters did not make a significant return to control levels of activity within 30–35 min. Ethyl Methacrylate, at a concentration of 1:1,000, caused cardiac standstill. A concentration of 1:10,000 reduced the cardiac rate by 17.8%, the force of contraction by 72.2%, and the coronary flow by 57.9%. These parameters were reduced by 5.8, 19.8, and 26.1%, respectively, at a 1:100,000 concentration. The effects of Ethyl Methacrylate on the isolated heart were irreversible at all three concentrations.

Ethyl Methacrylate was also tested using isolated guinea pig ileum. Actively contracting loops of ileum were isolated from guinea pigs and exposed to Ethyl Methacrylate at concentrations of 1:2,000, 1:1,000, and 1:500 (v/v) in Tyrode's solution. A force–displacement transducer electrically connected to a polygraph recorded changes in contractions when the ileum was exposed to Ethyl Methacrylate alone or in the presence of either acetylcholine (1:10,000,000) or barium chloride [3:100,000 (w/v)]. Ethyl Methacrylate alone inhibited pendular movements and relaxation of the muscle, and a dose–response relation was observed. The stimulant actions of acetylcholine and barium chloride were also antagonized

by Ethyl Methacrylate in a dose-dependent fashion. These effects were reversed when the ileum was rinsed with fresh Tyrode's solution (Mir et al., 1973*b*).

The effects of Ethyl Methacrylate on respiratory and cardiovascular function was studied in dogs. Groups of three male mongrel dogs were anesthetized with sodium pentobarbital and were given intravenous doses of 0.0171, 0.0342, and 0.3684 ml/kg Ethyl Methacrylate. A pressure transducer was attached to the carotid artery to monitor the systemic blood pressure, and another transducer was attached to the trachea to record respiratory pressure changes. Four needle electrodes were placed subdermally into each limb of the dog to record the electrocardiogram.

Ethyl Methacrylate caused a biphasic response in the blood pressure. Blood pressure abruptly fell by 31.95–58.66% for 2–4 min, and then pressure slowly rose, reaching a plateau 7.21–24.74% above the control value lasting 10–15 min. The heart rate also decreased in a dose-dependent fashion, but was not of the same magnitude; there was a 11.13–25.11% decrease. Respiratory rate was increased by 34.10–146.41% for ~20 min. The electrocardiogram had the following dose-related changes: bradycardia, a reduction in the rate of impulse transmission through the A-V node, and indications of acute cardiac ischemia. The larger doses also caused premature ventricular contractions and incomplete A-V block (Mir et al., 1974).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Tanii and Hashimoto (1982) reported that the oral LD_{50} of Ethyl Methacrylate for mice was 68.64 mmol/kg (7.8 g/kg).

In another study, groups of 10 rats were administered Ethyl Methacrylate via stomach tube at doses ranging from 12.70–18.14 g/kg. The LD_{50} was between 12.70 and 14.51 g/kg. Two to four minutes following administration, the rats had an increased rate of respiration with lacrimation. After 15–40 min, they had motor weakness and their respiration decreased and breathing was irregular and labored. There was increased defecation and urination, blood was present in the urine, and reflex activity disappeared. The animals died in coma 1–1.5 h following dosing. At necropsy, lesions were found primarily in the respiratory system. The lungs, trachea, and bronchi were markedly congested and edematous. The lungs were also spotted with areas of hemorrhage and emphysema. The thymus gland was swollen and congested. The ventricles were well contracted and the auricles were dilated and filled with dark, clotted blood. Fluid blood was found in the dilated abdominal vessels. The greatly distended urinary bladder often contained blood and areas of hemorrhage, necrosis, and detachment of the mucosa. Congestion of the intestine and acute inflammation of the mucosa were also evident (Deichmann, 1941).

The oral LD_{50} for rabbits was between 3.63 and 5.44 g/kg. Signs of toxicity were similar to those seen in the rats (Deichmann, 1941).

Subcutaneous

Six of 10 rats died 8–18 h following a single subcutaneous injection of 25 cc Ethyl Methacrylate. The animals had clinical signs of toxicity similar to those seen in the acute oral studies. A sudden increase in respiration was followed by reduced and labored respiration, the urine contained blood, and motor control and reflex activity were severely diminished. Lesions found at necropsy were the same as those found in the rats of the acute oral studies. The researchers noted that the LD_{50} dosage was greater for the subcutaneous study than for the oral study, suggesting that subcutaneous absorption was less rapid (Deichmann, 1941).

Intraperitoneal

The intraperitoneal LD_{50} for rats was 1.2228 ml/kg (Singh et al., 1972).

Inhalation

The $LC_{50/24}$ for 10 Sprague–Dawley rats exposed to Ethyl Methacrylate in their air for 4 h was 8,300 ppm. During exposure, the behavior of the rats reflected irritation of the eyes, nose, and respiratory tract. The rats squinted, huddled, and had labored respiration. The investigations noted that death was predictable by the blanching of the pinnae and paws. Animals that survived the first 24 h also survived the 14-day observation period. At necropsy, no gross abnormalities were found (Oberly and Tansy, 1985).

Groups of two rats, one guinea pig, and one rabbit were exposed to 12.4, 15.0, and 17.7 mg/L Ethyl Methacrylate for 8 h. Doses of 15.0 and 17.7 mg/L killed the rats within 3–4 h, but did not kill either the rabbits or guinea pigs. None of the animals exposed to 12.4 mg/L Ethyl Methacrylate died. At necropsy, the lungs, trachea, and bronchi of the rats were markedly congested and edematous, and the lungs had areas of hemorrhage and emphysema. Pathologic changes were also found in the thymus, heart, and abdomen. These changes were similar to those observed in the acute oral studies (Deichmann, 1941).

Subchronic Toxicity

Intravenous

Because hemoglobinuria was observed in acute studies, a study was conducted to determine whether or not Ethyl Methacrylate caused an increase in blood and urine porphyrin concentrations. Five rabbits were injected with 2 cc/kg of Ethyl Methacrylate once a week for 3 weeks, and the blood and urine were analyzed before the first dose and after the last dose. Porphyrins were detected in both fluids; however, the individual porphyrins were not identified (Deichmann, 1941).

Inhalation

A study conducted by Lawrence and Autian (1972) indicated that inhalation of Ethyl Methacrylate vapor affected drug metabolizing enzymes. Groups of ten male ICR mice were exposed to 84.79 mg/L of Ethyl Methacrylate in their breath-

ing air for 3.85, 7.70, and 19.25 min for 3 days. Sodium pentobarbital was administered 24 h following the last Ethyl Methacrylate exposure and sleeping time was compared with that of a control group which was not exposed to Ethyl Methacrylate. Sleeping time increased with the duration of exposure. The mean sleeping time for the control rats was 50.63 min, and for the rats in the low, mid, and high dosage groups the sleeping times was 51.06, 53.93, and 94.93 min, respectively. The researchers stated that this dose-related increase was an indication that Ethyl Methacrylate can have an effect on drug metabolizing enzymes.

Dermal Irritation

The clipped skin of rabbits (number not stated) was treated with 10 cc/kg Ethyl Methacrylate. The animals were restrained under a hood in such a way that they were unable to inhale the evaporating material. Signs of irritation were observed at the site of exposure and the animals were inactive. The animals recovered within 1 h (Deichmann, 1941).

Sensitization and Cross-Sensitivity

Ethyl Methacrylate was tested for sensitization potential in the guinea pig maximization test. Groups of ten Duncan Hartley guinea pigs were administered three pairs of intradermal injections of 0.1 ml Freund's complete adjuvant (FCA), Ethyl Methacrylate in peanut oil, and Ethyl Methacrylate in FCA in their backs. The concentrations of Ethyl Methacrylate tested were 0.17, 0.50, and 1.50 *M*. On day 7, an occlusive patch containing 1 *M* Ethyl Methacrylate was applied to the site of the injections for 48 h. After a 2-week non-treatment period, the right flank of each guinea pig was shaved and 3 *M* undiluted Ethyl Methacrylate was applied under occlusive patches for 24 h. The sites were scored at 24 and 48 h. On day 35, 3 *M* undiluted Ethyl Methacrylate was applied to the shaved left flank of each guinea pig and left uncovered. Readings were taken after 24 and 48 h. A control group of six guinea pigs received the same treatment, except that only the vehicle was used in the applications.

There was no evidence of sensitization in the guinea pigs induced with 0.17 *M* Ethyl Methacrylate. One guinea pig induced with 0.50 *M* Ethyl Methacrylate had evidence of sensitization after treatment on day 35 and one positive reaction was observed after both the 21- and 35-day treatments among the guinea pigs induced with 1.50 *M* Ethyl Methacrylate. When this experiment was repeated using a 0.5 *M* induction concentration on day 0, one of 10 guinea pigs reacted after both the 21- and 35-day applications (Van Der Walle et al., 1982).

Ethyl Methacrylate was also tested with Freund's complete adjuvant. Six guinea pigs were induced with intradermal injections of 5 × 0.5 *M* Ethyl Methacrylate in FCA and water on days 0, 2, 4, 7, and 9. On days 21 and 35, the shaved right and left flanks, respectively, were treated topically with 3 *M* undiluted Ethyl Methacrylate. The sites were left uncovered and readings were taken 24 and 48 h following each of these treatments. Two of the six guinea pigs had positive reactions following both the 21- and 35-day treatments (Van Der Walle et al., 1982).

Chung and Giles (1977) conducted a study that suggested the sensitization potential of Ethyl Methacrylate was dependent upon the vehicle of administration and that mutual cross-sensitivity exists between monomers of methacrylic acid. Guinea pigs were injected with 0.1 ml of Freund's complete adjuvant with heat-killed *Mycobacterium butyricum* into each foot pad (total volume 0.4 ml; total amount of *M. butyricum* 100 μg). One group of 25 animals was treated with topical applications of 0.03 ml of Ethyl Methacrylate in ethanol on days 0, 2, and 5. When the first challenge with 2 and 5% Ethyl Methacrylate in ethanol was administered on day 25, no sensitization was observed 72 h following the challenge application. The animals received a second challenge on day 60 with either a topical dose of 10% Ethyl Methacrylate in olive oil or an intradermal dose of Ethyl Methacrylate in saline (0.01 and 0.1 μl/site). The Ethyl Methacrylate in olive oil produced severe sensitization reactions. However, the intradermal dose of Ethyl Methacrylate in saline did not evoke any responses. A third challenge on day 122 with 0.4 and 2% Ethyl Methacrylate in olive oil caused sensitization within 72 h. The researchers suggested that Ethyl Methacrylate in ethanol evaporated before it could elicit a response.

Another group of nine guinea pigs was initially treated with 0.0077 ml of Ethyl Methacrylate in olive oil on day 60 (as controls) and was challenged with 2 and 5% Ethyl Methacrylate in olive oil on day 95. Positive reactions were observed in all of the animals after 72 h.

When the guinea pigs from both groups were challenged a second or fourth time with Ethyl Methacrylate and either 1% methyl methacrylate or 1% butyl methacrylate, strong cross-sensitivity was observed.

In another study, three guinea pigs sensitized to either 1 or 4 *M* Ethyl Methacrylate were tested for cross-reactivity with several acrylic monomers. The animals, sensitized in the Freund's Adjuvant Test or the Guinea Pig Maximization Test, were challenged on one flank with acrylates, methacrylates, diacrylates, and dimethacrylates (0.025 ml) 2 weeks after completing the tests. A second challenge with the monomers was conducted 2 weeks later on the other flank. Readings of the test sites were conducted 24 and 48 h following application. After the last challenge to test cross reactions, the guinea pigs were also challenged with Ethyl Methacrylate. Some of the animals had cross-reactions with acrylates, methacrylates, and dimethacrylates. However, these reactions were only to specific monomers and usually involved only one guinea pig. None of the guinea pigs reacted to the diacrylates (Van Der Walle and Bensink, 1982).

Photosensitivity

Deichmann (1941) speculated that edema and photosensitivity might occur in animals suffering from porphyrinuria or porphyrinemia when exposed to sunlight. In order to investigate this reaction, 0.5 cc Ethyl Methacrylate was applied to the skin of 10 rats six times a week for 20 weeks. Five rats were exposed daily to ultraviolet light from an Ashcraft ultraviolet generator (Model 476) for 1 h. Mild, transient irritation was the most severe reaction observed during the study.

Ocular Irritation

Two rabbits had 0.1 ml of undiluted Ethyl Methacrylate instilled into their right conjunctival sac. One rabbit's eye was rinsed after 20 s, and the other rabbit's eye was left unrinsed. The eyes were examined after 1 and 4 h, and after 1, 2, 3, and 7 days. A small area of opacity was observed in the cornea of the unrinsed eye, which diminished through days 2 and 3. Discharge from the eye was severe 1 h after treatment, moderate after 4 h, and mild at 24 h. The conjunctiva was slightly red and swollen through day 2. No effects were observed in the iris, and the cornea was transparent by day 7. Conjunctival irritation was milder in the rinsed eye. A small area of microscopic surface sheen was seen in the cornea at day 1, and mild transient conjunctivitis was observed. No effects on the iris were found and all signs of irritation disappeared by day 3 (Haskell Laboratory for Toxicology and Industrial Medicine, 1977).

REPRODUCTION AND DEVELOPMENTAL TOXICITY

Groups of five pregnant Sprague–Dawley rats were given 0.1223, 0.2446, and 0.4076 ml/kg Ethyl Methacrylate intraperitoneally on days 5, 10, and 15 of gestation. A control group of pregnant rats was left untreated. All of the rats were killed on day 20 of gestation and examined for evidence of embryonic–fetal toxicity and teratogenic effects. The number of corpora lutea in the treatment groups ranged from 53 to 58, and there were 60 corpora lutea in the control group. Resorptions occurred only in the test animals; five resorptions occurred in the 0.1223 ml/kg group, six in the 0.2446 ml/kg group, and seven in the 0.4076 ml/kg group. There were fewer fetuses in the test groups (42–51 fetuses) than in the control group (59 fetuses). All of the fetuses in the experimental groups were alive, but the mean weights of the fetuses in the mid- and high-dosage groups were significantly lower than that of the controls.

A significant number of gross abnormalities were found in the fetuses from the experimental groups. In the high-dosage group, eight gross abnormalities were found: one hemangioma each of the hind leg and foreleg, three cases of hemangiomas of the shoulders, one case of twisted hind legs, one case of no tail, and one fetus was very small with a compact head and neck. Three of the 27 fetuses examined had elongated and fused ribs. In the mid-dose group, five hemangiomas of the neck were found, and two of the 26 fetuses examined had elongated and fused posterior ribs. Similar abnormalities were observed in the low-dosage group. Two cases of hemangiomas on the shoulders were found, one fetus had twisted hind legs, and one fetus of the 25 examined had elongated posterior ribs. No gross or skeletal abnormalities were found in the fetuses from the untreated control group. The researchers concluded that Ethyl Methacrylate produced significant embryopathic and teratogenic effects (Singh et al., 1972).

MUTAGENICITY

Ethyl Methacrylate was evaluated at concentrations ranging from 33 to 10,000 μg/plate with the *Salmonella*/microsome test using *Salmonella typhimurium*

strains TA98, TA100, TA1535, and TA1537. Tests were conducted in triplicate both with and without activation with liver S9 from Aroclor-induced Sprague–Dawley rats and Syrian hamsters. Solvent and positive controls were also included with each trial. The positive controls used for tests without metabolic activation were sodium azide for strains TA100 and TA1535, 9-aminoacridine for TA1537, and 4-nitro-*o*-phenylenediamine for TA98. In tests with S9 activation, 2-aminoanthracene was used for all of the strains. Ethyl Methacrylate was negative in tests both with and without metabolic activation (Zeiger et al., 1987).

In another *Salmonella*/microsome test, Ethyl Methacrylate was tested at concentrations ranging from 40 to 2,500 μg/plate using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. Metabolic activation was produced once with phenobarbital-induced S9 mix and once with Aroclor-1254–induced S9 mix. Two tests were conducted without metabolic activation. All of the tests were conducted in triplicate. In tests using phenobarbital-induced S9 mix, 2-aminoanthracene was the positive control for all of the strains. Benz[*a*]pyrene was the positive control used to test strains TA98, TA100, and TA1538 with activation with Aroclor-induced S9 mix; no positive controls were used to test strains TA1535 and TA37 in this system. The positive controls used for tests without activation were sodium azide for strains TA100 and TA1535, glycidyl methacrylate for TA1535, 9-aminoacridine for TA1537, and 4-nitro-*o*-phenylenediamine for TA98 and TA1538. Ethyl Methacrylate was negative both with and without phenobarbital or Aroclor-induced S9 mix (Waegemaekers and Bensink, 1984).

Ethyl Methacrylate was tested in the L5178Y mouse lymphoma cell assay. L5178Y/TK$^{+/-}$ cells were treated with 900–2,100 μg/ml of Ethyl Methacrylate without exogenous activation for 4 h. Control cells were treated with the solvent (dimethyl sulfoxide) 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 2 days and then cloned with and without trifluorothymidine (TFT) selection. Following an incubation period of 9–11 days, the colonies were counted and sized. Cytotoxicity was only observed at concentrations >1,000 μg/ml. Toxicity plateaued at concentrations >1,500 μg/ml, where survival fluctuated from 2 to 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 1,626 μg/ml (16% survival); Ethyl Methacrylate induced 83 mutants/10^6 survivors and 11 aberrations/200 cells. Some of the cultures with <10% survival had mutation frequencies three time greater than background. The colony size distribution was difficult to determine; however, the authors did note that cultures with mutation frequencies of 200 mutants/10^6 survivors (<10% survival) had an induction of primarily small colonies. The authors suggested that the genotoxicity of Ethyl Methacrylate was likely due to a clastogenic mechanism (Moore et al., 1988).

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Cross-Reactivity

Ethyl Methacrylate was tested on 542 dermatitis patients using either the A1-Test (Imeco Agency, Sweden) or the Finn Chamber method. Each subject was

TABLE 1. *Case studies of contact dermatitis caused by artificial fingernails*

Case study	Patch test	Results	Reference
A woman developed paronychial and eyelid dermatitis 2 days after new application of nails. The components of the nail preparation were a clear liquid monomer, clear powder polymer, and white powder polymer	An aluminum patch test using the components of the nail preparation and ethyl, methyl, and *N*-butyl methacrylate (5% in petrolatum and 1% in ethyl alcohol) were applied to the back	The liquid monomer and all of the methacrylate esters caused erythema, papules, and vesicles at 48 and 96 h	Marks et al. (1979)
A patient suffered from severe painful onychia and paronychia 3 weeks after applying nails containing Ethyl Methacrylate monomer and isobutyl methacrylate monomer	Patch tests with 1% Ethyl Methacrylate, 1% isobutyl methacrylate monomer, and methyl methacrylate monomer	Strong positive reaction developed for all three monomers	Fisher (1980)
A patient developed severe onychia and paronychia 4 weeks after applying nails containing Ethyl Methacrylate, tetrahydrofurfuryl methacrylate, and diethylene glycol dimethacrylate monomers	Patch tests with 1% of each monomer and methyl methacrylate monomer	Strong positive reactions were caused by all four monomers	Fisher (1980)
After 3 months of using nails containing Ethyl Methacrylate monomer and ethylene glycol dimethacrylate, a patient developed mild paronychia	Patch tests with 1 and 5% of each monomer and methyl methacrylate monomer	1% concentrations of all of the monomers caused faint positive reactions. Strong positive reactions occurred after testing with 5% concentrations	Fisher (1980)
A woman working in the manufacture and application of sculptured nails developed allergic contact dermatitis on her hands	Patch tests with a standard series and with plastics and acrylates, including 10% Ethyl Methacrylate, 10% methyl methacrylate, and 2% hydroxyethyl methacrylate	Positive reactions were present at 48 and 96 h for the methacrylates tested, as well as nickel sulfate (2.5%), Prains (10%), and cavity primer (1 & 10%)	Condé-Salazar et al. (1986)

TABLE 1. *Continued*

Case study	Patch test	Results	Reference
A 46-year-old woman developed onycholysis of the fingernails and dermatitis of the fingers, dorsa of the hands, arms, upper trunk, and face 6 months after beginning regular application of sculpture fingernails	Patch tests were performed using the components of the sculptured fingernails (Ethyl Methacrylate monomer liquid and polymethacrylate powder), the European standard series, and to a plastics and glue series	The subject had positive reactions to patch tests with 1% MEK Ethyl Methacrylate, 10% pet. polymer nail powder, and 1% pet. butyl methacrylate.	Fitzgerald and English (1994)

exposed for 48 h to 1% Ethyl Methacrylate in petrolatum, and scoring was conducted at 48 and 96 h. Only one subject developed signs of irritation. Four subjects who were sensitive to methyl methacrylate were also tested with Ethyl Methacrylate. No cross reactions were observed (Maibach et al., 1978).

Patients with acrylate allergies were patch tested with 35 acrylates, including 2% Ethyl Methacrylate in petrolatum. Fourteen of 22 patients had positive reactions to Ethyl Methacrylate. Eleven of these patients had occupational exposure to artificial fingernails and, among this subgroup, seven patients had positive reactions (Koppula et al., unpublished observations).

A number of case studies of allergic contact dermatitis caused by artificial fingernails containing Ethyl Methacrylate have been reported. The details of these studies are in Table 1. In all six patients reported sensitized to methacrylates in sculptured nails, cross-reactivity with other methacrylate monomers was seen.

Cases of contact dermatitis to anaerobic acrylic sealants have also been documented. Six workers who developed dermatitis after contact with various sealants in the work place were patch tested with the sealants (0.1–1%), a standard patch test series, a plastic series, and a variety of acrylates. Each worker was exposed to the chemicals for 48 h, and the sites were read at 48, 72, and 96 h. The workers were positive for the sealants tested and negative for the standard and plastic series. Five of the workers had positive reactions to 10% Ethyl Methacrylate after 96 h. These individuals also had sensitivity to 2% hydroxyethyl methacrylate, three were sensitive to 10% methyl methacrylate monomer and 1% ethylene glycol dimethacrylate, two were sensitive to 0.1% acrylic acid, and one had a reaction to 1% triethylene glycol dimethacrylate. A control group of 20 individuals was negative for all of the compounds tested (Condé-Salazar et al., 1988).

Occupational Exposure

Occupational contact dermatitis from acrylate- and methacrylate-based products was reported in workers exposed to anaerobic sealants (Kanerva et al., 1989; Guerra et al., 1993), dental composite resins (Kanerva et al., 1989), dental and medical prostheses (Kanerva et al., 1993), sculptured fingernails (Taylor, 1989;

Tosti et al., 1992), printing materials (Calnan, 1980), and plastic embedding media (Montgomery, 1989).

Savonius et al. (1993) report that acrylates also have the potential to cause respiratory symptoms, most commonly asthma.

Hiipakka and Samimi (1987) specifically studied nail sculptors for exposure to organic vapors and methacrylate dusts from acrylic fingernail extensions. Seventeen personal vapor samples were taken from nail salons and the mean time-weighted average concentration of Ethyl Methacrylate was 4.5 ppm. There is no threshold limit value (TLV) for Ethyl Methacrylate, but the authors speculated that this concentration was probably below the expected threshold, as the TLV for methyl methacrylate is 100 ppm. Twenty sculptors completed self-administered symptom questionnaires, in which they consistently reported nasal and cutaneous irritation, drowsiness, dizzy spells, and trembling hands. These signs were reported more often by nail sculptors but were not statistically greater than that reported by matched controls. Throat irritation was the only statistically significant symptom.

SUMMARY

Ethyl Methacrylate is the ester of ethyl alcohol and methacrylic acid and is used as the major structural monomer of artificial fingernail formulations which are cross-linked with one or more multifunctional methacrylates. Ethyl Methacrylate is used as a substitute for methyl methacrylate, which was banned from use in fingernail products in 1974 by the U.S. Food and Drug Administration due to numerous consumer complaints about onycholysis and nail dislocation and/or irritation.

In commercial fingernail formulations, Ethyl Methacrylate monomer is rapidly polymerized. Approximately 50% of the polymerization occurs within 5 min, and <1% monomer is available after 1 h. The monomer content detected in filings from these types of products was <2% after 45 min, and <1% after 90 min.

The oral LD_{50} for rats ranged between 12.70 and 18.14 g/kg Ethyl Methacrylate. Hemoglobinuria and lesions in the respiratory system were observed. In an acute inhalation study, the $LC_{50/24}$ for rats was 8,300 ppm Ethyl Methacrylate, and ocular, nasal, and respiratory tract irritation was observed. In another study, the lungs, trachea, and bronchi of the rats were markedly congested, edematous, and spotted. Hemorrhage and emphysema were also observed.

In subchronic studies, Ethyl Methacrylate increased the concentrations of blood and urinary porphyrins after intravenous administration in rabbits, and affected drug-metabolizing enzymes in mice after inhalation exposure.

Ethyl Methacrylate was irritating to the skin of rabbits and sensitization reactions were observed in both the guinea pig maximization test and the Freund's complete adjuvant test. One study indicated that the sensitization potential of Ethyl Methacrylate was dependent upon the vehicle of administration. Strong sensitization was observed in guinea pigs when olive oil was the vehicle, but no sensitization occurred when ethanol was used. Mutual cross-sensitivity exists between monomers of methacrylic acid and a small degree of cross-reactivity occurs with other acrylic monomers.

Mild, transient irritation was the most severe reaction observed when rats were given topical applications of Ethyl Methacrylate and were irradiated with UV light for 1 h. Ethyl Methacrylate also caused transient ocular irritation.

In a teratogenicity study, pregnant rats were injected intraperitoneally with 0.1223, 0.2446, and 0.4076 ml/kg of Ethyl Methacrylate. Evidence of embryotoxicity and teratogenic effects were observed in all three dosage groups.

Ethyl Methacrylate was negative in two *Salmonella*/microsome tests both with and without metabolic activation. However, it was positive in the L5178Y mouse lymphoma cell assay.

In a clinical irritation study, 542 patients were exposed to 1% Ethyl Methacrylate for 48 h. Only one subject developed signs of irritation. In several case studies, Ethyl Methacrylate and related methacrylates in artificial fingernails caused allergic contact dermatitis. Occupational contact dermatitis from acrylates and methacrylates has been observed in individuals exposed to sealants, dental resins, prostheses, and plastic embedding media, as well as those handling artificial nails. There appears to be some degree of cross-reactivity between the acrylates and methacrylates.

DISCUSSION

The sensitization and cross- or co-reactivity potential of Ethyl Methacrylate was of concern to the Expert Panel. Some animal studies indicate that Ethyl Methacrylate is a strong sensitizer. Although one study in humans indicated a lack of sensitizing potential, it was noted that the concentration tested (1%) was below the concentration typically used in patch tests (2%). Incidence data are not available because acrylates and methacrylates are not regularly used in clinical patch testing.

Ethyl Methacrylate is used as the major structural monomer of artificial fingernail formulations which are crosslinked with one or more multifunctional methacrylates. Due to the nature of these types of formulations, the monomer is entrapped quickly and very little free monomer is available even during filing of the fingernails. In order to minimize any exposure to the free monomer, the Expert Panel recommends that fingernail enhancement products containing Ethyl Methacrylate be applied only by trained individuals and that skin contact be avoided. Ethyl Methacrylate should not be used in products intended for retail sale.

Concern regarding the potential respiratory problems caused by the inhalation of Ethyl Methacrylate particles produced from filing of artificial fingernails was also discussed. Since this type of particulate matter is usually large enough to be seen and is not likely to be airborne for extended periods of time, Ethyl Methacrylate is not expected to cause respiratory problems.

The Expert Panel also discussed the teratogenic effects observed in a study with rats. They agreed that the study was a poor indicator of developmental toxicity because the route of exposure was intraperitoneal. Additional studies are not required because exposure to the monomer is expected to be low and because cutaneous absorption of this material is low. Negative mutagenicity results also alleviated the Expert Panel's concerns.

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. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate.

Acknowledgment: Susan N. J. Pang, former Scientific Analyst and Writer prepared this report.

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Safety Assessment of Cross-Linked Alkyl Acrylates as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review (CIR) Expert Panel assessed the safety of cross-linked alkyl acrylates as used in cosmetics. The 23 cross-linked alkyl acrylates included in this safety assessment are reported to function as absorbents, film formers, emulsion stabilizers, viscosity increasing agents, suspending agents, binders, and/or skin-conditioning agents. The Panel reviewed available animal and clinical data, as well as information from previous CIR reports on monomer components. Because data were not available for the individual ingredients, and because residual monomer may be present, the Panel extrapolated from previous reports to support safety. The Panel concluded that cross-linked alkyl acrylates are safe in the present practices of use and concentration, provided that they are not polymerized in benzene. For those ingredients polymerized in benzene, the data available were insufficient to make a determination of safety. A risk assessment for the amount of benzene present would be needed.

Keywords

cross-linked alkyl amides, safety, cosmetics

Introduction

This draft final report includes information relevant to the safety of 23 cross-linked alkyl acrylates as used in cosmetic formulations. These cross-linked polymers consist of comonomers of at least 1 of the following: acrylic acid, sodium acrylate, methacrylic acid, or alkyl acrylate that share chemical properties, including a general lack of chemical reactivity. The ingredients included in this group are:

Acrylates/C10-30 alkyl acrylate cross polymer
Acrylates/C12-13 alkyl methacrylates/methoxyethyl acrylate cross polymer
Acrylates cross polymer
Acrylates/ethylhexyl acrylate cross polymer
Acrylates/ethylhexyl acrylate/glycidyl methacrylate cross polymer
Acrylates/PEG-4 dimethacrylate cross polymer
Acrylates/Steareth-20 methacrylate cross polymer
Acrylates/vinyl isodecanoate cross polymer
Acrylates/vinyl neodecanoate cross polymer
Allyl methacrylate/glycol dimethacrylate cross polymer
Allyl methacrylates cross polymer
Butyl acrylate/glycol dimethacrylate cross polymer
C8-22 alkyl acrylates/methacrylic acid cross polymer
Glycol dimethacrylate/vinyl alcohol cross polymer
Lauryl methacrylate/glycol dimethacrylate cross polymerr
Lauryl methacrylate/sodium methacrylate cross polymer
Methacrylic acid/PEG-6 methacrylate/PEG-6 dimethacrylate cross polymer
PEG/PPG-5/2 methacrylate/methacrylic acid cross polymer
Potassium acrylates/C10-30 alkyl acrylate cross polymer
Sodium acrylates cross polymer 2
Sodium acrylates/C10-30 alkyl acrylate cross polymer
Sodium acrylates/vinyl isodecanoate cross polymer
Stearyl/lauryl methacrylate cross polymer

These ingredients are reported to function in cosmetics as absorbents, film formers, emulsion stabilizers, viscosity increasing agents, suspending agents, binders, or skin-conditioning agents.

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In 2002, the Cosmetic Ingredient Review (CIR) published the Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients.[1] The Panel concluded that those ingredients were safe for use in cosmetics when formulated to avoid skin irritation. While copolymers are polymers synthesized from 2 or more different monomers, cross polymers are polymers that are cross-linked (ie, individual polymer chains are connected by bridging molecules [cross-linking agents]). Cross-linked polymers are generally less chemically reactive and less soluble (if not totally insoluble) than their respective non-cross-linked counterparts.

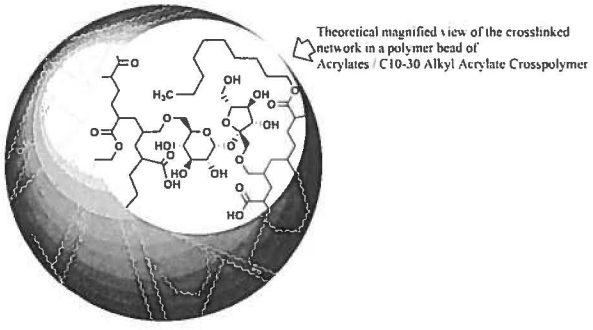
A CIR report on another family of polymers is also available. In 1982, the CIR published the Final Report on the Safety Assessment of Carbomers-934, -910, -934P, 940, -941, and -962, in which it was concluded that carbomers are safe as used.[2] That conclusion was reaffirmed in 2003.[3] A carbomer is a homopolymer of acrylic acid cross-linked with an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene.[4]

Due to the paucity of published safety and toxicity data on these ingredients, this report includes summary information included in technical data sheets, ingredient specification sheets, and material safety data sheets (MSDSs); this information is identified as such.

Chemistry

Definition and Structure

Cross-linked alkyl acrylates are cross-linked polymers in which the comonomers consist of at least 1 of the following: acrylic acid, sodium acrylate, methacrylic acid, or alkyl acrylate. Whereas polymers consisting purely of acrylic acid are often referred to as "carbomers," copolymers comprised of mixtures of acrylic acid and alkyl acrylate monomers may sometimes be referred to as "alkyl carbomers." In that vein, most of the ingredients in this report could be classified as *cross-linked* alkyl carbomers. For example, dodecyl (C12 alkyl) acrylate, acrylic acid, and methacrylic acid could be copolymerized and cross-linked with diallyl sucrose to form an acrylates/C10-30 alkyl acrylate cross polymer with the internal structure.



Accordingly, although all of the monomers and cross-linking agents may be the same, 2 polymers with very different physical properties may share the same name under INCI conventions. The definitions and structures of the ingredients included in this review are provided in Table 1.

Physical and Chemical Properties

The available physical and chemical property information is provided in Table 2. The properties of a single ingredient, such as the above cross polymer, can vary from a highly swellable, soft material to an unswellable, very hard material because of the multitude of possible reaction conditions and the methods involved in the manufacture of these polymers. The nature of these ingredients is highly dependent on the identity of the alcohol radicals of these acrylate esters (eg, the stearyl and lauryl groups of stearyl/lauryl methacrylate cross polymer).[5] Acrylate cross polymers that correspond to 1 INCI name often have many trade names, and production processes may vary for different trade name products bearing the same INCI name. Since the products may have different properties, the trade name is included in parenthesis when available.

The polymers in this group share a general lack of chemical reactivity that renders them nearly impervious to degradation. These ingredients are essentially insensitive to solar ultraviolet light (UV) degradation, as the primary UV absorption of acrylics is at a lower wavelength.

Method of Manufacture

Cross-linked alkyl acrylates are typically produced via free radical, head-to-tail chain-propagation polymerization.[5] The most common method is the emulsion method, but bulk and solution methods are also used. The marked variability in the identity of monomers and cross-linking agents, the ratio of comonomers, the order of addition of comonomers, the level of cross-linking, and other reaction conditions in the polymerization process can significantly alter the polymeric structure and properties of the product.[6] Additionally, postsynthesis, mechanical processing of these products can also significantly affect the consistency of these ingredients. These variables will likely differ from vendor to vendor, and possibly even from batch to batch.

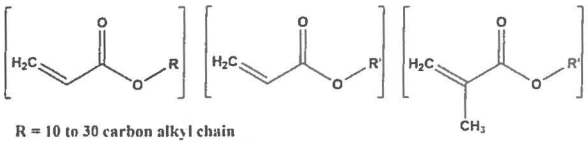
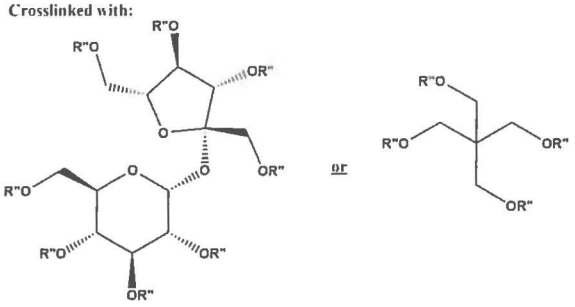
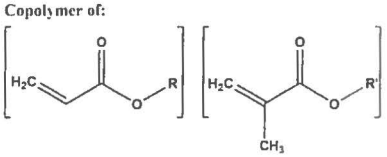
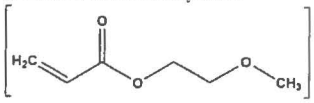
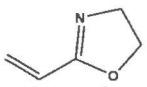
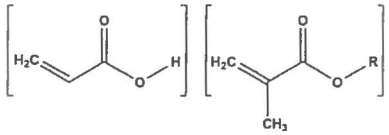
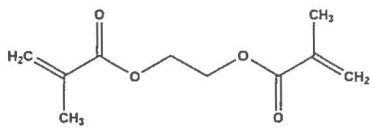
Table 3a lists the monomers used to create these cross polymers (based on INCI definition), and Table 3b names the cross-linking compounds and initiators used.[4]

Acrylates/C10-30 alkyl acrylate cross polymer. According to a trade product technical data sheet, acrylates/C10-30 alkyl acrylate cross polymer (as Pemulen) is polymerized in an ethyl acetate–cyclohexane mixture.[7] Another source reports that acrylates/C10-30 alkyl acrylate cross polymer may be polymerized in benzene.[8] A third supplier reports that acrylates/C10-30 alkyl acrylate cross polymer is polymerized in n-hexane.[9]

Acrylates/steareth-20 methacrylate cross polymer. Acrylates/steareth-20 methacrylate cross polymer (as Aculyn 88 polymer) is manufactured by an emulsion polymerization process.[10]

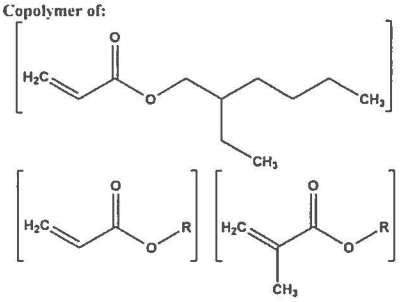
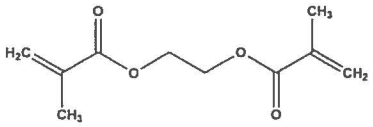
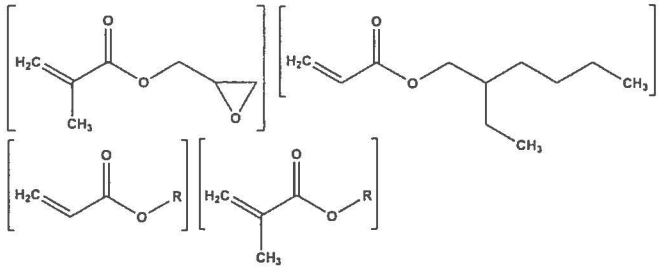
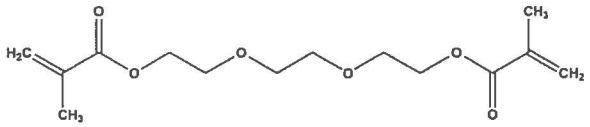
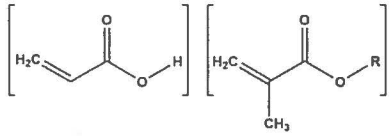
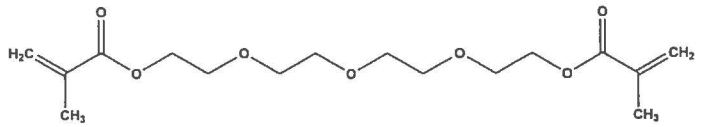
Acrylates/vinyl isodecanoate cross polymer. Acrylates/vinyl isodecanoate cross polymer (as Stabylen 30) is produced synthetically by a free radical polymerization.[11]

Table 1. Definitions, Functions, and Structures.[a]

Ingredient/CAS Number	Definition/Structure	Reported Function(s)
Acrylates/C10-30 alkyl acrylate cross polymer	A copolymer of C10-30 alkyl acrylate and 1 or more monomers of acrylic acid, methacrylic acid or 1 of their simple[b] esters cross-linked with an allyl (2-propenyl) ether of sucrose or an allyl ether of pentaerythritol Copolymer of:  R = 10 to 30 carbon alkyl chain R' = hydrogen or a "simple" alkyl chain Crosslinked with:  R" = hydrogen or 2-propenyl, wherein at least two R" groups are 2-propenyl	Emulsion stabilizer; viscosity increasing agent—aq; viscosity increasing agent—nonaq
Acrylates/C12-13 alkyl methacrylates/ methoxyethyl acrylate cross polymer	A copolymer of C12-13 alkyl methacrylates, methoxyethyl acrylate, and 1 or more monomers of acrylic acid, methacrylic acid, or 1 of their simple esters, cross-linked with vinyloxazoline Copolymer of:  R = hydrogen or a "simple" alkyl chain R' = a 12 or 13 carbon alkyl chain  Crosslinked with:  vinyloxazoline	Hair fixative
Acrylates cross polymer 26794-61-6 (when R is butyl) 74464-10-1 (when R is isobutyl)	A copolymer of acrylic acid, methacrylic acid, or 1 of its simple esters, cross-linked with glycol dimethacrylate Copolymer of:  R = hydrogen or a "simple" alkyl chain Crosslinked with: 	Absorbent

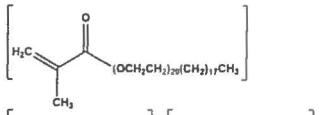
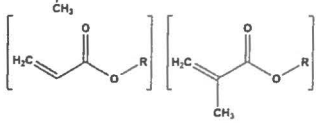
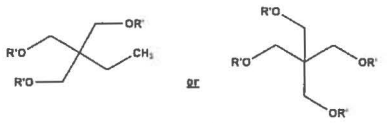
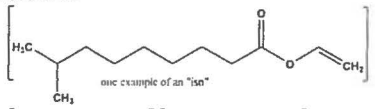
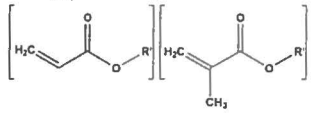
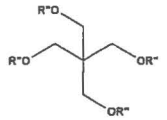
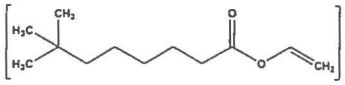
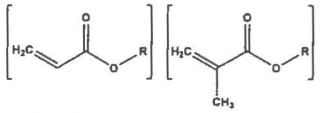
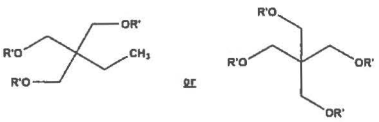
(continued)

Table 1. (continued)

Ingredient/CAS Number	Definition/Structure	Reported Function(s)
Acrylates/ethylhexyl acrylate cross polymer	A copolymer of 2 ethylhexylacrylate and 1 or more monomers of acrylic acid, methacrylic acid, or 1 of their simple esters, cross-linked with ethylene glycol dimethacrylate Copolymer of:  R = hydrogen or a "simple" alkyl chain Crosslinked with: 	Binder
Acrylates/ethylhexyl acrylate/glycidyl methacrylate cross polymer	A copolymer of 2-ethylhexyl acrylate, glycidyl methacrylate, and 1 or more monomers consisting of acrylic acid, methacrylic acid, or 1 of their simple esters, cross-linked with triethylene glycol dimethacrylate Copolymer of:  R = hydrogen or a "simple" alkyl chain Crosslinked with: 	Film former
Acrylates/PEG-4 dimethacrylate cross polymer 50657-38-0	A copolymer of 1 or more monomers of acrylic acid, methacrylic acid, or 1 of their simple esters cross-linked by PEG-4 dimethacrylate Copolymer of:  R = hydrogen or a "simple" alkyl chain Crosslinked with: 	Film former

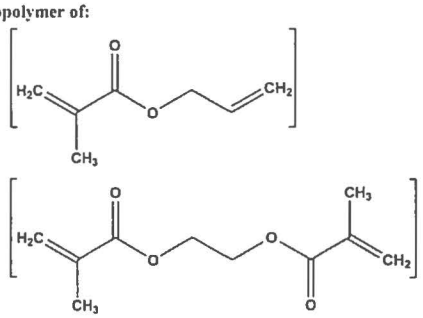
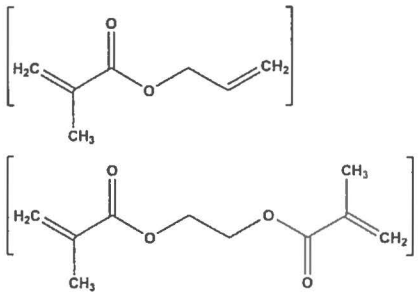
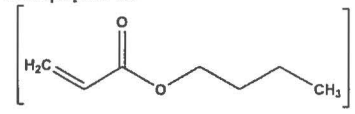
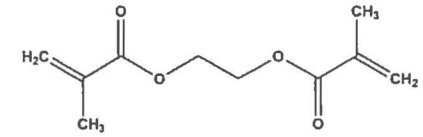
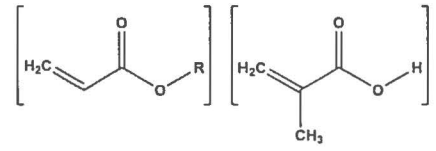
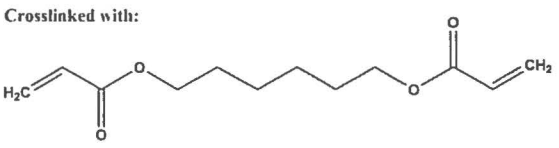
(continued)

Table 1. (continued)

Ingredient/CAS Number	Definition/Structure	Reported Function(s)
Acrylates/Steareth-20 methacrylate cross polymer	A copolymer of steareth-20 methacrylate and 1 or more monomers consisting of acrylic acid, methacrylic acid, or 1 of their simple esters, cross-linked with an allyl ether of pentaerythritol or an allyl ether of trimethylolpropane Copolymer of:   R = hydrogen or a "simple" alkyl chain Crosslinked with:  R' = hydrogen or 2-propenyl, wherein at least two R' groups are 2-propenyl	Film former; suspending agent—nonsurfactant
Acrylates/vinyl isodecanoate cross polymer	A copolymer of the ester of vinyl isodecanoate and 1 or more monomers of acrylic acid, methacrylic acid, or 1 of their simple esters cross-linked with polyalkenyl polyether Copolymer of:   R = isododecyl (branched, 12 carbon chain) R' = hydrogen or a "simple" alkyl chain Crosslinked with a "polyalkenyl polyether." One example of such could be:  R" = hydrogen or 2-propenyl, wherein at least two R" groups are 2-propenyl	Emulsion stabilizer; suspending agent—nonsurfactant; viscosity increasing agent—aq
Acrylates/vinyl neodecanoate cross polymer	A copolymer of vinyl neodecanoate and 1 or more monomers of acrylic acid, methacrylic acid, or 1 of their simple esters cross-linked with an allyl ether of trimethylolpropane or pentaerythritol Copolymer of:   R = hydrogen or a "simple" alkyl chain Crosslinked with:  R' = hydrogen or 2-propenyl, wherein at least two R' groups are 2-propenyl	Emulsion stabilizer; film former; viscosity increasing agent—aq

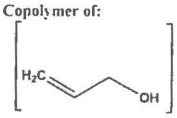
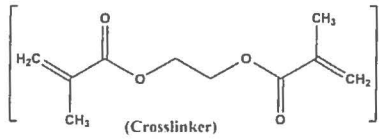
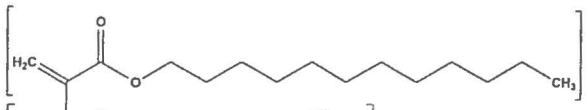
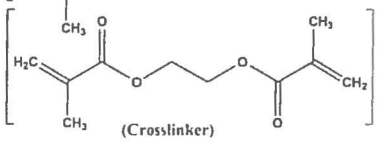
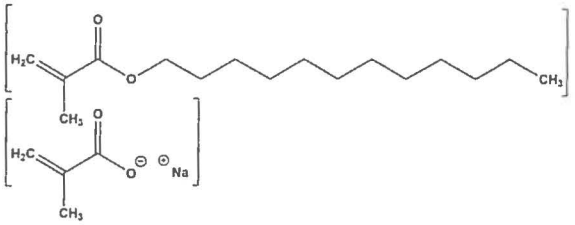
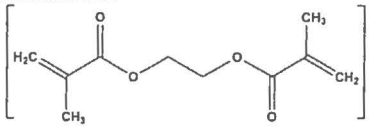
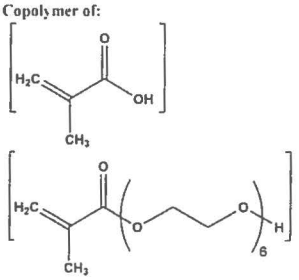
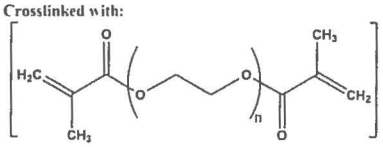
(continued)

Table 1. (continued)

Ingredient/CAS Number	Definition/Structure	Reported Function(s)
Allyl methacrylate/glycol dimethacrylate cross polymer 779327-42-3	A highly cross-linked polymer of allyl methacrylate and ethylene glycol dimethacrylate (diisopropyl peroxydicarbonate initiated) **Copolymer of:**  **Both of which can function as crosslinking agents**	Oral care agent; skin protectant; skin-conditioning agent—emollient; skin-conditioning agent—misc
Allyl methacrylates cross polymer 182212-41-5	A copolymer of allyl methacrylate cross-linked with ethylene glycol dimethacrylate **Copolymer of:**  **Both of which can function as crosslinking agents**	Emulsion stabilizer; opacifying agents; viscosity increasing agent—nonaq
Butyl acrylate/glycol dimethacrylate cross polymer	A homopolymer of butyl acrylate cross-linked with ethylene glycol dimethacrylate **Homopolymer of:**  **Crosslinked with:** 	Absorbent; film former
C8-22 alkyl acrylates/ methacrylic acid cross polymer	A copolymer of C8-22 alkyl acrylate and methacrylic acid cross-linked with hexanediol diacrylate **Copolymer of:**  **R = C8-22 alkyl chain** **Crosslinked with:** 	Film former; hair fixative; hair waving/ straightening agent

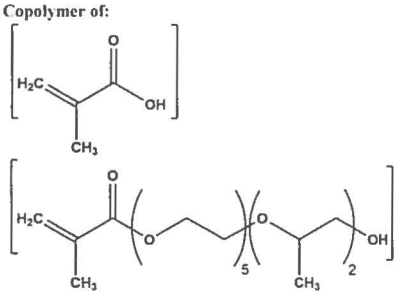
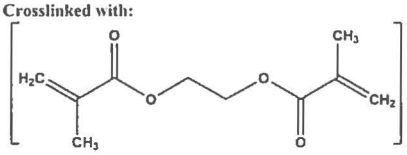
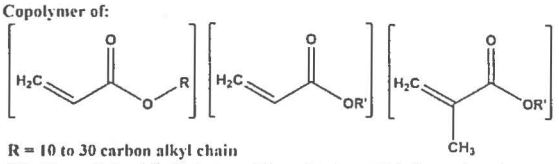
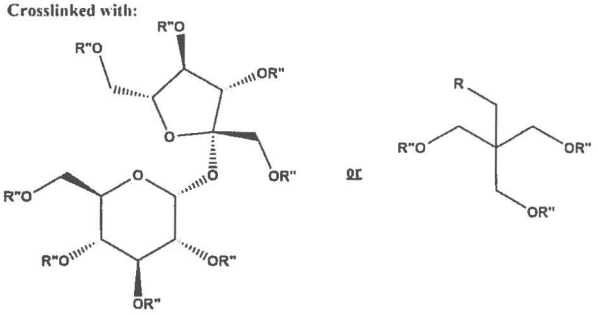
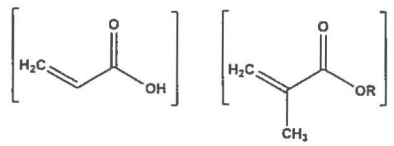
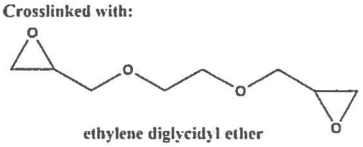
(continued)

Table 1. (continued)

Ingredient/CAS Number	Definition/Structure	Reported Function(s)
Glycol dimethacrylate/vinyl alcohol cross polymer	Vinyl alcohol and ethylene glycol dimethacrylate Copolymer of:   (Crosslinker)	Film former
Lauryl methacrylate/glycol dimethacrylate cross polymer	A cross-linked copolymer of lauryl methacrylate and ethylene glycol dimethacrylate monomers Copolymer of:   (Crosslinker)	Film former; hair fixative
Lauryl methacrylate/sodium methacrylate cross polymer	A copolymer of lauryl methacrylate and sodium methacrylate cross-linked with ethylene glycol dimethacrylate. Copolymer of:  Crosslinked with: 	Slip modifier; surface modifier
Methacrylic acid/PEG-6 methacrylate/PEG-6 dimethacrylate cross polymer	a copolymer of methacrylic acid and PEG-6 methacrylate cross-linked with polyethylene glycol dimethacrylate Copolymer of:  Crosslinked with:  wherein "n" is variable	Film former

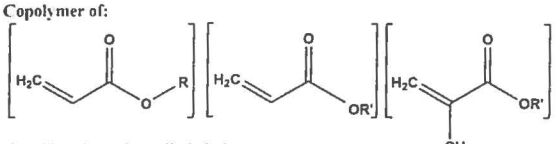
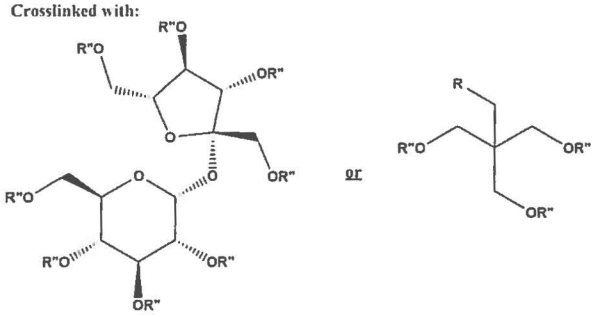
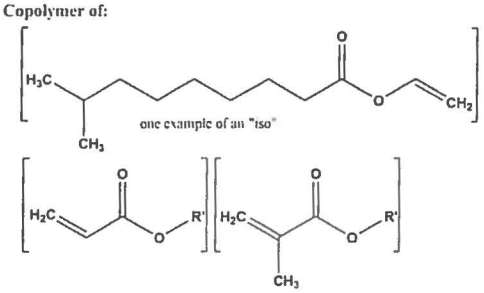
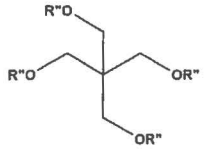
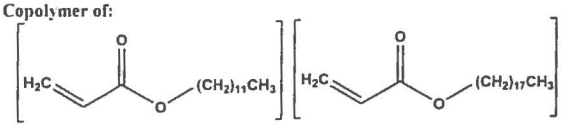
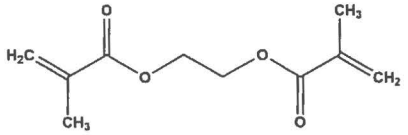
(continued)

Table 1. (continued)

Ingredient/CAS Number	Definition/Structure	Reported Function(s)
PEG/PPG-5/2 methacrylate/ methacrylic acid cross polymer	A copolymer of methacrylic acid and polyethylene glycol, polypropylene glycol methacrylate containing an average of 5 moles of ethylene oxide and 2 moles of propylene oxide, cross-linked with ethylene glycol dimethacrylate **Copolymer of:**  **Crosslinked with:** 	Film former
Potassium acrylates/C10-30 alkyl acrylate cross polymer	The potassium salt of acrylates/C10-30 alkyl acrylate cross polymer **Copolymer of:**  **R = 10 to 30 carbon alkyl chain** **R' = H or a "simple" alkyl group (the potassium salt is formed post-polymerization)** **Crosslinked with:**  **R" = hydrogen or 2-propenyl, wherein at least two R" groups are 2-propenyl**	Film former
Sodium acrylates cross polymer-2	The sodium salt of a copolymer of acrylic acid, methacrylic acid, or 1 or more of its simple esters, cross-linked with ethylene diglycidyl ether **Copolymer of:**  **R = H or a "simple" alkyl group (the sodium salt is formed post-polymerization)** **Crosslinked with:**  **ethylene diglycidyl ether**	Absorbent

(continued)

Table 1. (continued)

Ingredient/CAS Number	Definition/Structure	Reported Function(s)
Sodium acrylates/C10-30 alkyl acrylate cross polymer	The sodium salt of acrylates/C10-30 alkyl acrylate cross polymer Copolymer of:  R = 10 to 30 carbon alkyl chain R' = H or a "simple" alkyl group (the sodium salt is formed post-polymerization) Crosslinked with:  R" = hydrogen or 2-propenyl, wherein at least two R" groups are 2-propenyl	Film former
Sodium acrylates/vinyl isodecanoate cross polymer	The sodium salt of acrylates/vinyl isodecanoate cross polymer. Copolymer of:  R = isododecyl (branched, 12 carbon chain) R' = H or a "simple" alkyl group (the sodium salt is formed post-polymerization) Crosslinked with a "polyalkenyl polyether." One example of such could be:  R" = hydrogen or 2-propenyl, wherein at least two R" groups are 2-propenyl	Emulsion stabilizer; suspending agent—nonsurfactant; viscosity increasing agent—aq
Stearyl/lauryl methacrylate cross polymer	A copolymer of lauryl methacrylate and stearyl methacrylate cross-linked with ethylene glycol dimethacrylate Copolymer of:  Crosslinked with: 	Skin-conditioning agent—misc

Abbreviations: aq, aqueous; misc, miscellaneous.
[a]References.[4,8,48]
[b]According to the International Cosmetic Ingredient Dictionary and Handbook nomenclature conventions, "simple," as used herein, is "described as simple alkyls ranging from C1 to C4 (linear or branched)."

Table 2. Chemical and Physical Properties.

Property	Description	Reference
Acrylates/C10-30 alkyl acrylate cross polymer		
Appearance	White powder;	13-19
Odor	Slightly acetic	13-19
Activity, as supplied	Approximately 100% active	8
Molecular weight	>500 000 Da	8
Solubility	swells in water	39
pH	~2.5-3 at 1% in water[39]	
Heavy metals content	10 ppm (max), under all trade names	13-19
Specific gravity	1.4 (at 20°C)	39
Particle size (as tested by 1 source)	2-7 μm	23
Bulk density	<0.24 kg/L; <2 lb/gal	39
Acrylates cross polymer		
Particle size (as tested by 1 source)	18-22 μm	24
Heavy metal content	Lead, 10 ppm (max) arsenic, 2 ppm (max)	25
Acrylates/Steareth-20 methacrylate cross polymer		
Appearance (Aculyn 88 polymer)	Milk-white fluid	10
Solids content (Aculyn 88 polymer)	28.0%-30.0% by weight	10
Heavy metal content (Aculyn 88 polymer)	Iron, 1.028 ppm zinc, 0.082 ppm	
pH (Aculyn 88 polymer)	3.30-4.30	10
Acrylates/vinyl isodecanoate cross polymer		
Molecular weight	24 400 Da (average; <1% by weight is <1000 Da)	11
Acrylates/vinyl neodecanoate cross polymer		
Appearance (Aculyn 38 polymer)	Milk-white fluid	12
Solids content (Aculyn 38 polymer)	28.0%-30.0% by weight	12
Activity, as supplied	29% solids in 71% water	26
Heavy metal content (Aculyn 38 polymer)	Copper, 0.2 ppm iron, 0.5 ppm zinc, 1.2 ppm	12
pH (as Aculyn 38 polymer)	2.10-3.20	12
Allyl methacrylates cross polymer		
Appearance	Fine white powder	49,50
Solubility	Insoluble	49,50
Refractive index	1.517-1.519	49
	1.511-1.513	50
Particle size (by laser diffraction)	5-15 μm	49
	15-25 μm	50
Bulk density	0.03 g/cc	49,50
Water adsorption	Oleophilic (hydrophobic) dual: hydrophilic and oleophilic	50
Sodium acrylates cross polymer-2		
Appearance	White powder	28
Odor	Odorless	41
Solubility	Swells in water	41
pH	6-8	41
Particle size	Approx. 20 μm	28
Bulk density	0.75-0.95 g/ml	41
Stability	Stable at room temperature	41

Acrylates/vinyl neodecanoate cross polymer. Acrylates/vinyl neodecanoate cross polymer (as Aculyn 38 polymer) is manufactured by an emulsion polymerization process.[12]

Impurities and Residual Monomer or Solvent

Acrylates/C10-30 alkyl acrylate cross polymer. According to product specification sheets from 1 company, acrylates/C10-30 alkyl acrylate cross polymer can contain (total) residual solvent (ethyl acetate + cyclohexane) at a maximum of 0.45% (Carbopol 1382; Carbopol Ultrez 20; Carbopol Ultrez 21)[13-15] or 0.5% (Pemulen TR1; Pemulen TR2; Carbopol ETD 2020).[16-18] Another supplier, who uses n-hexane as a solvent, reported that the maximum residual solvent in the polymer is 0.2% n-hexane.[9]

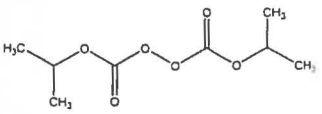
As Carbopol 1342, the product specifications state that acrylates/C10-30 alkyl acrylate cross polymer can contain 0.5%

Table 3a. Monomers Used to Create Cross-Linked Alkyl Acrylates.

Acrylic acid
Acrylic acid, simple esters (simple alkyls ranging from C1 to C4, linear or branched, ie, methyl, ethyl, propyl, and butyl esters, including branched versions: isopropyl, isobutyl, sec-butyl, and tert-butyl esters)
Butyl acrylate
C8-22 alkyl acrylate
2-Ethylhexyl acrylate
Glycidyl methacrylate
Lauryl methacrylate
Methacrylic acid
Methacrylic acid, simple esters (simple alkyls ranging from C1 to C4, linear or branched, ie, methyl, ethyl, propyl, and butyl esters, including branched versions: isopropyl, isobutyl, sec-butyl, and tert-butyl esters)
PEG-6 methacrylate
PEG/PPG-5/2
Sodium methacrylate
Steareth-20 methacrylate
Stearyl methacrylate
Vinyl alcohol
Vinyl isodecanoate, ester of
Vinyl neodecanoate

Table 3b. Cross-Linkers and Initiators Used in Manufacture of Acrylate cross polymers.

Allyl methacrylate
Ethylene diglycidyl ether
Glycol dimethacrylate
Hexanediol diacrylate
PEG-4 dimethacrylate
Pentaerythritol, allyl ether
Polyalkenyl polyether
Polyethylene glycol dimethacrylate
Sucrose, allyl ether
Triethylene glycol dimethacrylate
Trimethylolpropane, allyl ether
Diisopropyl peroxydicarbonate (initiator)



(max) residual benzene.[19] A supplier reported that analysis of 40 lots of Carbopol 1342 indicated that the average level of benzene was 0.25%, and the level ranged from 0.04% to 0.41% benzene.[20] (According to the European Commission Cosmetics Directive, benzene cannot be present as a constituent of other substances, or in mixtures, in concentrations equal to, or greater than 0.1% by weight.[21] As another point of reference, US Pharmacopeia limits for benzene for several carbomers manufactured with benzene range from 0.01% to 0.5%.[22])

One source stated that residual monomer content of acrylates/C10-30 alkyl acrylate cross polymer (trade name not provided) is typically less than 0.25% acrylic acid and less than 0.5% residual ester (C10-30 alkyl acrylate),[8] while another stated that acrylic acid monomer content is <0.1%.[23]

Acrylates cross polymer. One source reported that acrylates cross polymer contained <0.005% methyl methacrylate and <0.005% butyl acrylate,[24] and another reported 0.005% (max) of methyl methacrylate, ethylene methacrylate, and isobutyl methacrylate, and that acrylates cross polymer did not contain residual solvents or preservatives.[25]

Acrylates/steareth-20 methacrylate cross polymer. The composition of acrylates/steareth-20 methacrylate cross polymer (as Aculyn 88 polymer) is stated as 28.0% to 30.0% acrylates/steareth-20 methacrylate cross polymer, <0.01% residual monomer, 70.0% to 72.0% solvent (water), and 0.195% (max) sodium benzoate.[10] According to actual analytical specifications, the amount of residual ethyl acrylate present is ≤0.0001%.

Acrylates/vinyl isodecanoate cross polymer. The residual acrylic acid monomer content of acrylates/vinyl isodecanoate cross polymer (Stabylen 30) is reported to be <0.05% by weight.[11]

Acrylates/vinyl neodecanoate cross polymer. The composition of acrylates/vinyl neodecanoate cross polymer (as Aculyn 38 polymer) is stated as 28.0% to 30.0% acrylates/vinyl neodecanoate cross polymer, <0.1% residual monomer, and 70.0% to 72.0% solvent (water).[12] According to actual analytical specifications, the amount of residual ethyl acrylate present was ≤0.0001%.

Another source reported the residual monomer level of acrylates/vinyl neodecanoate cross polymer is <0.01%.[26]

Lauryl methacrylate/glycol dimethacrylate cross polymer. The residual monomer levels of lauryl methacrylate/glycol dimethacrylate cross polymer are <0.01% lauryl methacrylate and <0.01 ppm ethylene glycol dimethacrylate.[27] Lauryl methacrylate/glycol dimethacrylate cross polymer has a residual solvent level of ≤0.1% isopropanol. The ingredient can contain up to 2% adsorbed water.

Sodium acrylates cross polymer 2. The maximum amount of residual monomer content in sodium acrylates cross polymer 2 (Aqua Keep 10SH-NFC) is 0.02%.[28]

Use

Cosmetic

Cross-linked alkyl acrylates are reported to function as absorbents, film formers, emulsion stabilizers, viscosity increasing agents, suspending agents, binders, and/or skin-conditioning agents in cosmetic formulations.[4] Acrylates/C10-30 alkyl acrylate cross polymer functions as a primary emulsifier in oil-in-water emulsions.[7] Voluntary Cosmetic Registration Program data obtained in 2011,[29] and the concentration of use information received in response to a survey conducted by the Personal Care Products Council,[30] indicates that 11 of the 23 cross-linked alkyl acrylates named in this report currently are used

in cosmetic formulations. Acrylates/C10-30 alkyl acrylate cross polymer has the greatest number of uses, with 1,696 reported; 1,365 of those uses are in leave-on products. Acrylates cross polymer, acrylates/vinyl isodecanoate cross polymer, acrylates/vinyl neodecanoate cross polymer, allyl methacrylates cross polymer, lauryl methacrylate/glycol dimethacrylate cross polymer, lauryl methacrylate/sodium methacrylate cross polymer, and sodium acrylates/C10-30 alkyl acrylate cross polymer are all used in less than 75 formulations.

Some acrylates/C10-30 alkyl acrylate cross polymers are polymerized in benzene; the highest reported concentrations of use of this ingredient when polymerized in benzene are 0.4% and 1.1% for leave-on and rinse-off products, respectively.[31] The use concentrations for acrylates/C10-30 alkyl acrylate cross polymer not polymerized in benzene are up to 5% in leave-on and rinse-off products; 5% is the highest rinse-off concentration of use of the cross-linked alkyl acrylates. The highest concentration of use reported in leave-on cross-linked alkyl acrylates is 6% acrylates/ethylhexyl acrylate cross polymer.[30] Frequency and concentration of use data are provided in Table 4a. The ingredients not reported to be used are listed in Table 4b.

Products containing some cross-linked alkyl acrylates may be applied to baby skin, used near the eye area or mucous membranes, or could possibly be ingested or inhaled. In practice, 95% to 99% of the particles released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to 110 μm range.[32,33] Therefore, most particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal region and would not be respirable to any appreciable level.[34,35] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic diameters in the range considered to be respirable.[35] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

All of the ingredients included in this review, with the exception of acrylates/C12-13 alkyl methacrylates methoxyethyl acrylate cross polymer and methacrylic acid/PEG-6 methacrylate/PEG-6 dimethacrylate cross polymer, are listed in the European Union inventory of cosmetic ingredients.[36] The 2 ingredients that are not included in the European Union inventory are in the process of being named and will be added once that process is complete.[37]

Noncosmetic

Acrylic ester polymers are used in coatings, textiles, adhesives, and paper manufacture.[5]

Toxicokinetics

Published toxicokinetics, absorption, distribution, metabolism, and excretion data were not found for the cross polymers. Large polymeric structures, however, such as cross-linked alkyl acrylates, generally are not absorbed through the skin. Toxicokinetics data on some of the monomers are provided in Table 5.

Effect on Skin Permeation

Acrylates/C10-30 alkyl acrylate cross polymer. A topical formulation vehicle that included acrylates/C10-30 alkyl acrylate cross polymer (Pemulen TR-2), in combination with PEG 400 and carbomer, reduced the permeation of *N,N*-diethyl-*m*-toluamide through skin.[38] Evaluations were made in vitro using excised rat skin and in vivo using Beagle dogs.

Toxicological Studies

To aid in the evaluation of the safety of these cross polymers, Table 5 provides a brief summary of relevant data on a number of monomer components. (This summary is not intended to be an all-encompassing review of these monomers.)

Single-Dose (Acute) Toxicity

Dermal

Acrylates/C10-30 alkyl acrylate *cross polymer.* According to an industry MSDS, the dermal LD_{50} of acrylates/C10-30 alkyl acrylate cross polymer (as Pemulen TR1) in rabbits is >2.0 g/kg.[39]

Acrylates/vinyl neodecanoate *cross polymer.* The dermal LD_{50} of acrylates/vinyl neodecanoate cross polymer (as Aculyn 38 polymer) in rabbits is >5.0 g/kg.[12]

Oral

Acrylates/C10-30 alkyl acrylate *cross polymer.* According to an industry MSDS, the oral LD_{50} of acrylates/C10-30 alkyl acrylate cross polymer (as Pemulen TR1) in rats is >10 g/kg.[39] Another source provided information from an MSDS, stating that the oral LD_{50} in rats is >2 g/kg.[23]

Acrylates/vinyl isodecanoate *cross polymer.* The oral LD_{50} acrylates/vinyl isodecanoate cross polymer (as Stabylen 30) in rats is >2 g/kg body weight.[40]

Acrylates/vinyl neodecanoate *cross polymer.* The oral LD_{50} of acrylates/vinyl neodecanoate cross polymer (as Aculyn 38 polymer) in rats is >5.0 g/kg.[12]

Sodium acrylates cross polymer 2. According to an industry MSDS, the oral LD_{50} of sodium acrylates cross polymer 2 (as Aqua Keep 10SH-NFC) in rats is >2 g/kg.[41]

Inhalation

Acrylates/vinyl neodecanoate *cross polymers.* The inhalation LC_{50} of acrylates/vinyl neodecanoate cross polymer (as Aculyn 38 polymer) in rats is >16.34 mg/L air (1 hour).[12]

Repeated Dose Toxicity

Inhalation

Acrylates/C10-30 alkyl acrylate *cross polymer.* In an industry MSDS for acrylates/C10-30 alkyl acrylate cross polymers (as Pemulen TR-1), a 2-year inhalation study in which rats were exposed to a respirable, water-absorbent sodium polyacrylate dust is described under toxicological information. Lung effects such as

Table 4a. Frequency and Concentration of Use According to Duration and Type of Exposure.

	# of Uses[29]	Concentration of Use (%)[30]		# of Uses[29]	Concentration of Use (%)[30]	# of Uses[29]	Concentration of Use (%)[30]
	Acrylates/C10-30 Alkyl Acrylate Cross Polymer			Acrylates Cross Polymer		Acrylates/Ethylhexyl Acrylate Cross Polymer	
Totals[a]	**1696**	**0.0002-5** (not Polymerized in Benzene[30])	**0.05-1.1** (Polymerized in Benzene[31])	**2**	**0.1-4**	**NR**	**4-6**
Duration of use							
Leave-on	*1365*	*0.0002-5*	*0.05-0.4*	*2*	*0.1-4*	*NR*	*4-6*
Rinse off	*313*	*0.002-5*	*0.2-1.1*	*NR*	*0.3-0.8*	*NR*	*NR*
Diluted for (bath) use	*18*	*1*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type							
Eye area	132	0.003-2	NR	NR	0.8	NR	6
Incidental ingestion	3	0.5	NR	NR	4	NR	NR
Incidental inhalation—sprays	70[b,c]	0.03-2	NR	NR	NR	NR	NR
Incidental inhalation—powders	6	0.0002-0.1	NR	NR	2	NR	NR
Dermal contact	1591	0.0002-5	0.05-1.1	2	0.1-4	NR	4-6
Deodorant (underarm)	1	0.001	NR	NR	NR	NR	NR
Hair—non-coloring	77	0.1-2	0.2	NR	NR	NR	NR
Hair—coloring	11	0.4-5	NR	NR	NR	NR	NR
Nail	9	0.1-1	NR	NR	NR	NR	NR
Mucous membrane	111	0.002-3	NR	NR	4	NR	NR
Baby products	10	0.2	NR	NR	NR	NR	NR

	Acrylates/Steareth-20 Methacrylate Cross Polymer		Acrylates/Vinyl Isodecanoate Cross Polymer		Acrylates/Vinyl Neodecanoate Cross Polymer	
Totals[a]	**NR**	**0.1-2**	**33**	**0.2-0.5**	**10**	**2**
Duration of use						
Leave-on	*NR*	*0.1-2*	*25*	*0.3-0.5*	*4*	*NR*
Rinse off	*NR*	*1*	*8*	*0.2-0.5*	*4*	*2*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*2*	*2*
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—sprays	NR	NR	NR	0.4	NR	NR
Incidental inhalation—powders	NR	NR	NR	NR	NR	NR
Dermal contact	NR	0.1-1	33	0.2-0.5	10	2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—non-coloring	NR	2	NR	NR	NR	NR
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	1	NR	NR	6	2
Baby products	NR	NR	NR	NR	NR	NR

	Allyl Methacrylates Cross Polymer		Lauryl Methacrylate/Glycol Dimethacrylate Cross Polymer		Lauryl Methacrylate/Sodium Methacrylate Cross Polymer	
Totals[a]	**48**	**0.003-2**	**63**	**0.06-3**	**1**	**0.004-4**
Duration of use						
Leave-on	*44*	*0.003-2*	*56*	*0.06-3*	*1*	*0.1-4*
Rinse off	*4*	*0.1*	*7*	*0.2-3*	*NR*	*0.004-0.1*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye area	4	0.003-0.8	9	0.1-3	NR	NR
Incidental ingestion	16	0.04-0.2	8	0.06-2	NR	NR
Incidental inhalation—sprays	2[c]	NR	1[b]	0.3	NR	NR

(continued)

Table 4a. (continued)

	# of Uses[29]	Concentration of Use (%)[30]	# of Uses[29]	Concentration of Use (%)[30]	# of Uses[29]	Concentration of Use (%)[30]
	Allyl Methacrylates Cross Polymer		Lauryl Methacrylate/Glycol Dimethacrylate Cross Polymer		Lauryl Methacrylate/Sodium Methacrylate Cross Polymer	
Totals[a]	**48**	**0.003-2**	**63**	**0.06-3**	**1**	**0.004-4**
Incidental inhalation—powders	2	0.3-0.8	8	0.1-1	NR	NR
Dermal contact	31	0.003-2	53	0.06-3	1	0.004-4
Deodorant (underarm)	NR	NR	1	0.3	NR	NR
Hair—non-coloring	NR	NR	NR	NR	NR	NR
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR
Mucous membrane	16	0.04-0.2	8	0.06-2	NR	NR
Baby products	NR	NR	NR	NR	NR	NR
	Sodium Acrylates/C10-30 Alkyl Acrylate Cross Polymer		Sodium Acrylates Cross Polymer-2			
Totals[a]	**6**	**NR**	**NR**	**0.8**		
Duration of use						
Leave-on	*6*	*NR*	*NR*	*0.8*		
Rinse off	*NR*	*NR*	*NR*	*NR*		
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*		
Exposure type						
Eye area	NR	NR	NR	NR		
Incidental ingestion	NR	NR	NR	NR		
Incidental inhalation—sprays	1	NR	NR	NR		
Incidental inhalation—powders	NR	NR	NR	NR		
Dermal contact	6	NR	NR	0.8		
Deodorant (underarm)	NR	NR	NR	NR		
Hair—non-coloring	NR	NR	NR	NR		
Hair—coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous membrane	NR	NR	NR	NR		
Baby products	NR	NR	NR	NR		

Abbreviation: NR, no reported uses.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.
[b]Includes deodorants, in that it is not known whether or not the product is a spray.
[c]Includes suntan products, in that it is not known whether or not the reported product is a spray.

inflammation, hyperplasia, and tumors were observed.[39] There were no observed adverse effects at exposures of 0.05 mg/m^3.

Reproductive and Developmental Toxicity

Published reproductive and developmental toxicity data were not found. Reproductive and developmental toxicity data on some of the monomers are provided in Table 5.

Genotoxicity

Genotoxicity data on some of the monomers are provided in Table 5.

Acrylates/C10-30 *alkyl acrylate cross polymer.* Acrylates/C10-30 alkyl acrylate cross polymer, tested at 156 to 500 µg/plate in dimethyl sulfoxide, was not mutagenic in an Ames assay with *Salmonella typhimurium* TA98 and TA100.[23] It is not stated directly, but it appears that the studies were performed with and without metabolic activation.

Acrylates/Steareth-20 *methacrylate cross polymer.* The acrylic copolymer of acrylates/steareth-20 methacrylate cross polymer (as Aculyn 88 polymer) was not mutagenic in an Ames test, with or without metabolic activation.[10] (Study performed using good laboratory practices [GLP]; details not provided.)

Acrylates/*vinyl neodecanoate cross polymer.* The acrylic copolymer of acrylates/vinyl neodecanoate cross polymer (as Aculyn 38 polymer) was not mutagenic in an Ames test, with or without metabolic activation.[12] (GLP study; details not provided).

Sodium *acrylates cross polymer* 2. According to an industry MSDS, sodium acrylates cross polymer 2 (as Aqua Keep 10SH-NFC) was negative in an Ames test using *S typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2uvrA.[41]

Table 4b. Ingredients Not Reported to be Used.

Acrylates/C12-13 alkyl methacrylates/methoxyethyl acrylate cross polymer
Acrylates/ethylhexyl acrylate/glycidyl methacrylate cross polymer
Acrylates/PEG-4 dimethacrylate cross polymer
Allyl methacrylate/glycol dimethacrylate cross polymer
Butyl acrylate/glycol dimethacrylate cross polymer
C8-22 alkyl acrylates/methacrylic acid cross polymer
Glycol dimethacrylate/vinyl alcohol cross polymer
Methacrylic acid/PEG-6 methacrylate/PEG-6 dimethacrylate cross polymer
PEG/PPG-5/2 methacrylate/methacrylic acid cross polymer
Potassium acrylates/C10-30 alkyl acrylate cross polymer
Sodium acrylates/vinyl isodecanoate cross polymer
Stearyl/lauryl methacrylate cross polymer

Carcinogenicity

Published carcinogenicity studies were not found. Carcinogenicity data on some of the monomers are provided in Table 5.

Irritation and Sensitization

Irritation and sensitization data on some of the monomers are provided in Table 5.

Skin Irritation and Sensitization

Dermal irritation and sensitization studies, using alternative methods and nonhuman and human test populations, are presented in Table 6.

In an alternative method study, acrylates/vinyl neodecanoate cross polymer was predicted to be a nonirritant. The nonhuman studies reported no to slight irritation with undiluted and weak sensitization with 2% aq, acrylates/C10-30 alkyl acrylate cross polymer, no irritation with acrylates cross polymer at 30% in olive oil, and no irritation or sensitization with sodium acrylates cross polymer 2 (concentration not specified). Mostly, human testing with undiluted acrylates/C10-30 alkyl acrylate cross polymer, acrylates cross polymer, and acrylates/ethylhexyl acrylate cross polymer, up to 2.5% aq acrylates/vinyl isodecanoate cross polymer, 1% aq dilutions of formulations containing 2% acrylates/vinyl neodecanoate cross polymer, and formulations containing up to 2.6% lauryl methacrylate/glycol dimethacrylate cross polymers do not indicate any dermal irritation or sensitization. The only exception was a weak irritant response noted during an intensified Shelanski human repeated insult patch test (HRIPT) with undiluted acrylates/C10-30 alkyl acrylate cross polymer.

Ocular Irritation

Alternative studies

Acrylates/vinyl isodecanoate *cross polymer.* The EYE-TEX alternative method was used to predict the in vivo ocular irritation classification of acrylates/vinyl isodecanoate cross polymer (as Stabylen 30).[40] The results obtained in a standard volume–response study using samples of ≤100 µl test material corresponded to a Draize ocular irritation classification of nonirritant.

Lauryl methacrylate/glycol dimethacrylate *cross polymer.* The EpiOcular Human Cell Construct (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide [MTT] assay), was used to assess the potential ocular irritation of a face powder containing 1% lauryl methacrylate/glycol dimethacrylate cross polymer.[42] The ET_{50} (duration of exposure resulting in a 50% decrease in MTT conversion) of the test material was >1,440 minutes, which was the maximum exposure time. (As a reference point, the ET_{50} of the positive control, 0.3% Triton X-100, was 16.3 minutes.)

Nonhuman

Acrylates/C10-30 alkyl acrylate *cross polymer.* The ocular irritation potential of acrylates/C10-30 alkyl acrylate cross polymer (as Carbopol ETD) was evaluated using groups of 3 albino rabbits.[43] The test material, undiluted and as a 1% neutralized solution (pH 6.9-7.0), was instilled into the conjunctival sac of 1 eye of each rabbit per group; the contralateral eyes served as a control. The eyes were not rinsed. The undiluted test material produced slight to moderate corneal and conjunctival irritation which cleared by day 7. Slight iridal and conjunctival irritation was observed with the 1% solution. All signs of irritation cleared within 72 hours.

In other studies using the same procedure, the ocular irritation potential of acrylates/C10-30 alkyl acrylate cross polymer (as Carbopol Ultrez 20 and Carbopol Ultrez 21) was evaluated using groups of 3 rabbits.[44,45] The test material was evaluated undiluted and as a 5% dilution in distilled water. The undiluted test material produced moderate corneal irritation and conjunctival irritation which cleared by day 21. (The maximum mean score [MMS] was 37.7/110.) Moderate conjunctival irritation (MMS 9.3/110) was observed with the 5% solution, which was classified as a minimal irritant.

The ocular irritation potential of acrylates/C10-30 alkyl acrylate cross polymer (as Pemulen) was evaluated by instilling 0.021 g of the test article into the conjunctival sac of 1 eye of 9 New Zealand White rabbits.[46] The contralateral eyes were untreated and served as the control. At 30 seconds postinstillation, both eyes of 3 rabbits were rinsed; the eyes of the other 6 rabbits were not rinsed. The eyes were examined for irritation for up to 72 hours following dosing. "Significant" ocular irritation was observed in 3 of the 6 unrinsed eyes. At 24 hours after instillation, corneal opacity was observed in 3 and iritis in 1 unrinsed eye; minimal conjunctivitis was seen in all 6 unrinsed eyes. These observations were resolved by 72 hours. "Less severe responses" were observed in the rinsed eyes. Iritis was observed in 1 and conjunctivitis in 3 of the rinsed eyes at 24 hours after dosing. At 48 hours after dosing, conjunctivitis was observed in 1 rinsed eye. Based on the observations made for

Table 5. Relevant Summary Information on Component Monomers.

Monomer Component	Parameter Evaluated	Outcome	Reference
Acrylic acid	Toxicokinetics	Dermal: radioactivity was recovered mostly in the skin trap, and then in expired CO_2	1
		Oral: in numerous studies using rats, the dose was primarily excreted in expired air in most cases; elimination was generally rapid; uptake and elimination appeared to be biphasic; absorption and excretion were also rapid in mice	
		Inhalation: rats were exposed to acrylic acid via inhalation; most of the radioactivity was found in the head and snout, with relatively large amounts also recovered in the upper respiratory tract	
	Toxicological studies	Single dose—dermal: LD_{50}—295-950 mg/kg in rabbits	1
		Oral: LD_{50}—2,100-3,200 mg/kg in rabbits and rats; produced gastric lesions	
		Inhalation: LC_{50}—3,600 mg/m^3 in rats	
		Repeated dose—dermal: 4% produced toxic effects in mice in a 13-week study	1
		Oral: toxic effects were observed in rats in a 90-day drinking water study with doses of $\leq$750 mg/kg and in a 90-day gavage study in rats doses with 150 or 375 mg/kg; stomach lesions were not observed with up to 500 ppm in a 12-month drinking study with rats	
		Inhalation: nasal irritation and/or lesions were observed in rats and/or mice exposed to 1500 ppm for 4-day up to 225 ppm for 2-week, 300 ppm for 20-day, and 75 ppm for 13-week	
	Reproductive and developmental toxicity	Oral: did not produce teratogenic effects in rats, NOAEL of 250 mg/kg; did affect body weights and some organ weights in the parental animals	1
		Inhalation: not teratogenic or embryotoxic in rats at concentrations up to 120 ppm; did produce maternal toxicity at concentrations of 120 ppm and greater	
	Genotoxicity	Genotoxic in mouse lymphoma assays, and in an in vitro cytogenetic assay; not genotoxic or mutagenic in Ames tests, unscheduled DNA synthesis (UDS) assay, micronucleus assay, in vivo transformation assay, Chinese hamster ovary (CHO)/HGPRT, in vivo cytogenetic assay, Drosophila test, or mouse dominant lethal assay	1
	Carcinogenicity	Dermal: in 1 study, 4% in acetone was a complete but weak carcinogen in mice; in another, 1% was not carcinogenic in mice	1, 68
		Oral: not carcinogenic in rats when given in drinking water at up to 1200 ppm	
		Parenteral: not carcinogenic when 1.4 mg was injected subcutaneously (sc) to mice	
		IARC evaluation: no epidemiological data relevant to carcinogenicity were available; no experimental data relevant to carcinogenicity were available; *not classifiable as to its carcinogenicity to humans (group 3)*	
	Irritation and sensitization	Skin: 4% was irritating to the skin of mice	1
		Mucosal: a 1% solution caused significant injury to the rabbit eye	
Methyl acrylate	Toxicokinetics	Dermal: in guinea pigs exposed dermally to methyl [2,3-^{14}C]acrylate, radioactivity was seen in the sc tissues and throughout the body	69
		Oral: the dose was primarily excreted in expired air; elimination was rapid (rats)	
	Toxicological studies	Single dose—oral: produced gastric lesions when given inhibited with 200 ppm hydroquinone monomethyl ether (HQMME)	1
		Repeated dose—oral: not toxic when given orally to rats (details not provided)	1
	Reproductive and developmental toxicity	Inhalation: up to 200 ppm did not produce teratogenic or reproductive effects in rats	1
	Genotoxicity	Genotoxic in mouse lymphoma and chromosomal aberration assays; positive in 1 and negative in 2 micronucleus tests; not mutagenic or genotoxic in an Ames, *Salmonella*/microsome, liquid incubation, monolayer, suspension, or AS52/XRPT assay	1
	Carcinogenicity	Inhalation: up to 135 ppm was not carcinogenic to rats	1
		IARC evaluation: no epidemiological data relevant to the carcinogenicity; *inadequate evidence* in experimental animals; *not classifiable as to its carcinogenicity to humans (group 3)*	69
Ethyl acrylate	Toxicokinetics	Oral: the dose was primarily excreted in expired air; elimination was rapid (rats)	1

(continued)

Table 5. (continued)

Monomer Component	Parameter Evaluated	Outcome	Reference
	Toxicological studies	Single dose—oral: produced gastric lesions when given inhibited with 15 to 20 ppm HQMME	1
		Repeated dose—oral: a 2-week study in rats with dosing via gavage or drinking water—gastric lesions were observed, primarily in the forestomach., at doses of 20 to 100 mg/kg given buy gavage and at concentrations1000 to 4000 ppm in drinking water; in a 13-week gavage study, doses of ≤200 mg/kg produced lesions in the forestomach of rats; stomach lesions were not observed at concentrations up to 2000 ppm in a 2-year drinking study with rats or up to 1000 ppm in a 2-year capsule study with dogs	1
		Inhalation: no nasal lesions were observed with up to 300 ppm in a 1-month study using rats and mice; nasal lesions were observed at concentrations of ≥242 ppm in rats in a 12-week study	
	Reproductive and developmental toxicity	Inhalation: up to 200 ppm was not embryotoxic or fetotoxic in rats; maternal toxicity observed with 150 ppm	1
	Genotoxicity	Genotoxic in a mouse lymphoma and chromosomal aberration assay; induced chromosomal malsegregation and mitotic recombination using *Salmonella cerevisiae*; positive in 1 and negative in 1 micronucleus assay; not mutagenic or genotoxic in an Ames, *Salmonella*/microsome, liquid incubation, monolayer, chromosomal, sister chromatid exchange (SCE), or Drosophila assay	1
	Carcinogenicity	Dermal: tested undiluted, not carcinogenic to mice	1
		Oral: in corn oil, carcinogenic in male and female rats and mice at 100 and 200 mg/kg	70
		Inhalation: up to 225 ppm was not carcinogenic in mice or rats	
		IARC evaluation: no epidemiological data relevant to the carcinogenicity; *sufficient evidence* in experimental animals; *possibly carcinogenic to humans (group 2B)*	
Butyl acrylate	Toxicokinetics	Oral: the dose was primarily excreted in expired air (rats)	1
	Toxicological studies	Single dose—oral: produced gastric lesions when given inhibited with 10 to 55 HQMME	1
		Repeated dose—oral: not toxic when given orally to rats (details not provided)	1
		Inhalation: toxicity was observed in rats and hamsters upon three 6-hour exposures to 820 and 817 ppm, respectively; nasal lesions were observed in rats exposed to concentrations ≥108 ppm in a 13-week study	
	Reproductive and developmental toxicity	Inhalation: no toxic effects were seen with 25 ppm; high concentrations had toxic effects on the fetuses and dams	1
	Genotoxicity	positive in 1 and negative in 1 chromosomal aberration assay; not mutagenic or genotoxic in an Ames, *Salmonella*/microsome, liquid incubation, UDS, micronucleus, or in vitro transformation assay	1
	Carcinogenicity	Dermal: 1% was not carcinogenic in mice	1
		Inhalation: up to 135 ppm was not carcinogenic to rats	71
		IARC evaluation: no epidemiological data relevant to the carcinogenicity; *inadequate evidence* in experimental animals; *not classifiable as to its carcinogenicity to humans (group 3)*	
2-Ethylhexyl acrylate	Toxicokinetics	Oral: the dose was primarily excreted in expired air; elimination was rapid (rats)	1
	Reproductive and developmental toxicity	Inhalation: up to 100 ppm did not produce teratogenic or reproductive effects in rats	1
	Genotoxicity	Genotoxic in a mouse lymphoma forward mutation assay with metabolic activation; equivocally genotoxic in mutation and aberrations assays; weakly mutagenic in SCE and UDS assays; not mutagenic or genotoxic in a microbial mutagen test, Ames test, mammalian cell transformation assay, micronucleus test, monolayer or suspension assay, CHO assay, or in vivo cytogenic assay	1
	Carcinogenicity	Dermal: carcinogenic at a dose of ≥21% when applied to mice—the carcinogenic response may have been associated with the severe skin irritation induced by the chemical	1 72

(continued)

Table 5. (continued)

Monomer Component	Parameter Evaluated	Outcome	Reference
		Tested by skin application in 3 experiments in mice; it increased the incidence of squamous-cell carcinomas of the skin in 2 experiments and of malignant melanomas in 1 experiment; in the third experiment, in a different strain of mice, no increase skin tumor incidence was seen with or without subsequent application of 12-0-tetradecanoylphorbol 13-acetate	
		IARC evaluation: *inadequate evidence* in humans for carcinogenicity; *limited evidence* in experimental animals; *not classifiable as to its carcinogenicity to humans (group 3)*	
	Irritation and sensitization	Dermal—nonhuman: sensitization was observed when guinea pigs were treated with 2-ethylhexyl acrylate in Freund complete adjuvant	72
		Human: in a provocative test with 243 patients with a history of exposure to (meth)acrylates, none of the patients were sensitized with patches containing 0.1% to 0.5% 2-ethylhexyl acrylate	1
Polyacrylic acid	Animal toxicology	Single dose—oral: LD_{50}—2500 mg/kg in rats	1
	CIR conclusion (2002)	*Safe as used when formulated to avoid skin irritation*	1
Sodium polyacrylate	Animal toxicology	Single dose—oral: LD_{50}—>40 g/kg in rats for a 15% solution	1
	Reproductive and developmental toxicity	Oral: up to 3000 mg/kg/d low-molecular weight and up to 1125 mg/kg/d high-molecular weight did not cause reproductive effects in rats	1
	Genotoxicity	Not genotoxic in an Ames assay, a plate test, a mouse lymphoma assay, chromosomal aberration assays, a UDS assay, or an in vivo mouse micronucleus assay	1
	Irritation and sensitization	Dermal—nonhuman: not an irritant to rabbit skin when applied undiluted	1
		Human: not an irritant or sensitizer (concentration not given)	
		Ocular: the greatest tolerated concentrations were 13% to 20% for unrinsed and 20% to 30% for rinsed rabbit eyes; in an irritant-threshold test, 2% was the greatest concentration that did not produce irritation in rabbit eyes	
	CIR conclusion (2002)	*Safe as used when formulated to avoid skin irritation*	1
Methacrylic acid	Toxicokinetics	Readily absorbed through the mucous membranes of the lungs and gastrointestinal tract of and the skin, and is readily distributed to all major tissues	73
	Animal toxicology	Single dose—dermal: reported LD_{50} values ranged from 500 to 1243 mg/kg for rabbits	73
		Oral: reported LD_{50} values ranged from 827 to 1600 mg/kg for mice, 277 to 2260 mg/kg for rats, and 280 to 1200 mg/kg for rabbits	
		Inhalation: reported LC_{50} values were 3657 ppm in mice, 1350 ppm/4 h in rats, and 2522 ppm/1 h in rabbits	
		Repeated dose—oral: no signs of toxicity in a short-term study	73
		Inhalation: nose and eye irritation and weight loss in rats with 5 exposures to 1300 ppm; only renal congestion in rats with 20 exposures to 300 ppm; in a 2-week study, repeated doses of ≥100 ppm caused reactions in rats, ≥500 ppm caused reactions in mice, and 1000 ppm killed all rats and mice; in a 90-day study, respiratory effects were seen in rats and mice exposed to 300 ppm—cytomegaly of renal tubular epithelium was observed in >50% of test male mice	
	Reproductive and developmental toxicity	Inhalation: no reproductive or developmental effects at concentrations up to 300 ppm	73
		In vitro: adverse effects were seen with exposure of rat embryos to ≥129 μg/ml	
	Genotoxicity	Positive in a DNA cell-binding assay; negative in an Ames test	73
	Carcinogenicity	It was reported that IARC reviewed methacrylic acid, but did not prepare a monograph because inadequate data were available	73
	Irritation and sensitization	Dermal—nonhuman: corrosive to rabbit and guinea pig skin; in a guinea pig maximization study, it was difficult to determine if observed reactions were hypersensitivity or irritation; guinea pigs were not sensitized in 3 other studies	73
		Mucosal: caused severe corneal, iridal, and conjunctival effects in rabbits in 1 study; in an inhalation study, 56 916 ppm was corrosive to rabbit eyes	
	Clinical use	Negative results were reported in a number of patch tests of patients allergic to methyl methacrylate and to workers exposed to acrylates	73

(continued)

Table 5. (continued)

Monomer Component	Parameter Evaluated	Outcome	Reference
	Discussion items	The Panel was concerned with the extreme corrosivity; a presentation demonstrated that a trained professional could apply the acid to the nail without exposure to the skin, but this could not be demonstrated for retail consumers; due to concerns that inhalation could affect the respiratory tract, and the nail technician could be subjected to increased exposure in a commercial setting, the NIOSH-recommended exposure limit of 20 ppm as a time-weighted average concentration should not be exceeded; the Consumer Product Safety Commission rule requires child-resistant packaging for liquid household products containing >5% methacrylic acid (wt to vol)	73
	CIR conclusion (2005)	*Safe as used as a nail primer by trained professionals; insufficient data for retail use by consumers*	73
Methyl methacrylate	Toxicokinetics	Can be absorbed through the skin of humans	74
	Animal toxicology	Repeated dose—oral: chronic exposure to ≤400 ppm did not cause tumors in hamsters or rats	75
	Genotoxicity	Genotoxic in a chromosomal aberration, SCE, and mouse lymphoma assay; not mutagenic in a *Salmonella*/microsome or liquid incubation assay	1
	Carcinogenicity	Oral: not carcinogenic in a drinking study using rats Inhalation: up to 400 ppm was not carcinogenic in mice or rats IARC evaluation: *inadequate evidence* in humans for carcinogenicity; *evidence suggesting lack of carcinogenicity* in experimental animals; *not classifiable as to its carcinogenicity in humans (group 3)*	74,75
	Irritation and sensitization	Dermal—nonhuman: sensitizing at 25% in guinea pigs; minimum induction concentration was 1 M; was a weak contact allergen in a local lymph node assay Human: the frequency of positive reactions among all patients to methyl methacrylate was 7/22; the frequency of positive reactions among patients with artificial nails was 1/10	76
Ethyl methacrylate	Genotoxicity	Not mutagenic in a *Salmonella*/microsome assay; genotoxicity in a mouse lymphoma cell assay was considered likely due to a clastogenic mechanism	1
	Irritation and sensitization	Dermal—human: the frequency of positive reactions among all patients tested was 14/22; the frequency of positive reactions among patients with artificial nails was 7/11 (64%),	76
	Discussion items	(This ingredient was reviewed for its use nail enhancement products.) The Panel was concerned with the strong sensitization and cross- or coreactivity potential of methacrylates; however, data were submitted that indicated there would be little monomer available for exposure to the skin; genotoxicity data indicated the some methacrylates could produce chromosome damage; the Panel restricted methacrylates to the nail, and they must not come in contact with skin; initial concern that exotherms created from the rapid polymerization of the monomers could damage the nail were alleviated	75
	CIR conclusion (2005)	*Safe as used in nail enhancement products when skin contact is avoided; products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates*	75
Butyl methacrylate	Animal toxicology	Single dose—dermal: 10 cc/kg did not cause mortality in rabbits, but acute dermal irritation was reported; 1 LD_{50} value of >2000 mg/kg in rabbits was reported; the LD_{50} in guinea pigs was >20 ml/kg Oral: reported oral LD_{50} values in rats ranged from >2000 to >20 000 mg/kg Inhalation: reported LC_{50} value was 28 469 mg/m^3 rats Repeated dose—oral: in rats, the NOELS were 20 mg/kg/d in a 28-day study, 30 (males) and 300 (females) mg/kg/d in a 45-day study, and <30 (males) and 30 (females) mg/kg/d in a 50-day study Inhalation: caused upper airway irritation in a 28-day study in rats—the NOEL was 1801 mg/m^3	75 75
	Reproductive and developmental toxicity	Oral: a decrease in corpora lutea and implantations was reported in rats; the parental NOAELs were 1000 and 300 mg/kg/d for males and females, respectively Inhalation: threshold concentration for embryotoxic and teratogenic effects in rats was 0.1 mg/m^3; slight fetotoxicity was reported in rats exposed to ≤1200 ppm on days 6 to 20 of gestation	75

(continued)

Table 5. (continued)

Monomer Component	Parameter Evaluated	Outcome	Reference
	Genotoxicity	Not mutagenic in multiple Ames tests with or without metabolic activation; was mutagenic to *Salmonella typhimurium* TA1538 with metabolic activation in 1 study	75
	Irritation and sensitization	Dermal—nonhuman: a very strong sensitizer in 1 study using guinea pigs; considered a moderate sensitizer in another study using guinea pigs; in a few studies, a sensitization reaction was not produced Human: 1% caused 1 positive reaction in 12 patients in a Draize contact sensitization study; in provocative testing, 1% elicited positive reactions to patch tests Ocular: mildly irritating to rabbit eyes	75
	Discussion items	(This ingredient was reviewed for its use nail enhancement products.) The Panel was concerned with the strong sensitization and cross- or coreactivity potential of methacrylates; however, data were submitted that indicated there would be little monomer available for exposure to the skin; genotoxicity data indicated the some methacrylates could produce chromosome damage; the Panel restricted methacrylates to the nail, and they must not come in contact with skin; initial concern that exotherms created from the rapid polymerization of the monomers could damage the nail were alleviated.	75
	CIR conclusion (2005)	*Safe as used in nail enhancement products when skin contact is avoided; products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates*	75
Isobutyl methacrylate	Animal toxicology	Single dose—dermal: the reported dermal LD_{50} was >20 ml/kg in guinea pigs Oral: reported LD_{50} values in rats ranged from >5,000 to 12,800 mg/kg Inhalation: 50% of mice died after exposure to 29.74 mg/L for 289 minutes; was considered a toxic (but not highly toxic) substance by inhalation exposure	75
	Genotoxicity	Not mutagenic in multiple Ames tests with or without metabolic activation	75
	Irritation and sensitization	Dermal—human: 1% caused no positive reaction in 11 patients in a contact sensitization study; in provocative testing, 1% elicited positive reactions to patch tests Ocular: mildly irritating to rabbit eyes	75
	Discussion Items	(This ingredient was reviewed for its use nail enhancement products.) The Panel was concerned with the strong sensitization and cross- or coreactivity potential of methacrylates; however, data were submitted that indicated there would be little monomer available for exposure to the skin; genotoxicity data indicated the some methacrylates could produce chromosome damage; the Panel restricted methacrylates to the nail, and they must not come in contact with skin; initial concern that exotherms created from the rapid polymerization of the monomers could damage the nail were alleviated.	75
	CIR conclusion (2005)	*Safe as used in nail enhancement products when skin contact is avoided; products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates*	75
Lauryl methacrylate	Animal toxicology	Single dose—oral: no rats dosed with ≤21.5 ml/kg C12 to C18 methacrylate monomers died Inhalation: the RD_{50} was 3,900 mg/m^3 in mice	75
		Repeated dose—inhalation: not toxic to rats in a 20-day study	75
	Irritation and sensitization	Dermal—nonhuman: strong sensitizer in guinea pigs	75
	Discussion items	(This ingredient was reviewed for its use nail enhancement products.) The Panel was concerned with the strong sensitization and cross- or coreactivity potential of methacrylates; however, data were submitted that indicated there would be little monomer available for exposure to the skin; genotoxicity data indicated the some methacrylates could produce chromosome damage; the Panel restricted methacrylates to the nail, and they must not come in contact with skin; initial concern that exotherms created from the rapid polymerization of the monomers could damage the nail were alleviated.	75
	CIR conclusion (2005)	*Safe as used in nail enhancement products when skin contact is avoided; products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates*	75

(continued)

Table 5. (continued)

Monomer Component	Parameter Evaluated	Outcome	Reference
PEG-4 dimethacrylate	Animal toxicology	Single dose—dermal: the LD_{50} was >3 g/kg in rats Oral: LD_{50} was >5,000 mg/kg in rats	75
	Genotoxicity	Not mutagenic in multiple Ames tests with or without metabolic activation; weakly positive in a mouse lymphoma cell assay with metabolic activation	75
	Carcinogenicity	Dermal: no increase in skin or visceral tumors in an 80-week study with 25 mg given twice weekly	75
	Irritation and sensitization	Dermal—nonhuman: moderate sensitizer in guinea pigs; not a sensitizer in 1 study Ocular: minimally irritating to rabbit eyes	75
	Discussion items	(This ingredient was reviewed for its use nail enhancement products.) The Panel was concerned with the strong sensitization and cross- or coreactivity potential of methacrylates; however, data were submitted that indicated there would be little monomer available for exposure to the skin; genotoxicity data indicated the some methacrylates could produce chromosome damage; the Panel restricted methacrylates to the nail, and they must not come in contact with skin; initial concern that exotherms created from the rapid polymerization of the monomers could damage the nail were alleviated.	75
	CIR conclusion (2005)	*Safe as used in nail enhancement products when skin contact is avoided; products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates*	75

Abbreviations: CIR, Cosmetic Ingredient Review; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health.

the unrinsed eyes, the authors stated that this product was considered a borderline irritant.

Acrylates *cross polymer*. The ocular irritation potential of acrylates cross polymer was evaluated by instilling 0.1 ml of the test material, at a concentration of 50% in olive oil, into the conjunctival sac of 1 eye of 3 Japanese white rabbits.[24] The Draize score was 1.3. (Additional details were not provided.)

Sodium acrylates *cross* polymer 2. According to an industry MSDS, sodium acrylates cross polymer 2 (as Aqua Keep 10SH-NFC) is not an ocular irritant in rabbits.[41]

Clinical Assessment of Safety

Risk Assessment

Conservative risk assessments were submitted by the Personal Care Products Council's CIR Science and Support Committee (SSC) and by the CIR to address the carcinogenic endpoint for benzene, because it may be used as a solvent in the manufacture of acrylates/C10-30 alkyl acrylates cross polymer. Both assessments assumed the highest reported concentration of residual benzene in acrylates/C10-30 alkyl acrylates cross polymer used as a raw ingredient, the highest reported use concentration in a leave-on product of the raw ingredient polymerized in benzene, 10% evaporation of the residual benzene during manufacturing of the product, 10% benzene absorbed from the product through the skin, and the reported 50th and 95th percentiles of the amount of product used daily.

CIR SSC Risk Assessment[31]

The assumptions used to calculate CIR SSC's example exposure assessment were:

- 50th percentile use =7.63 g body lotion used/use day
- 95th percentile use =16.83 g body lotion used/use day
- 0.4% acrylates/C10-30 alkyl acrylate cross polymer in body lotion
- 0.41% benzene in acrylates/C10-30 alkyl acrylate cross polymer
- 10% benzene absorbed percutaneously

Estimated Exposure

0.41% benzene in raw material × 0.4% acrylates/C10-30 alkyl acrylates cross polymer in a body product
= 0.00164% benzene in the product

50th 7.63 g body product used/day × 0.00164%
= 0.000125 g/d
= 125 μg/d

absorb 10% × 125 μg/d
= 12.5 μg/d

95th 16.83 g body product used/d 0.00164%
= 0.000276 g/d
= 276 μg/d

absorb 10% × 276 μg/d
= 27.6 μg/d

The SSC Comparison to Risk Level

The Environmental Protection Agency (EPA) drinking water concentration associated with 10^6 cancer risk is 1 and 10 μg/L.[47] Assuming consumption of 2 L of water each day, this results in a value of 2 to 20 μg/d. The estimated exposure from the use of a leave-on body product at the 50th percentile, assuming the greatest concentration of acrylates/C10-30 alkyl acrylates cross polymer polymerized in benzene, is in within

Table 6. Dermal Irritation and Sensitization: Alternative, Nonhuman, and Human.

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
Alternative studies					
Acrylates/vinyl isodecanoate cross polymer					
As Stabylen 30 (tradename)			SKIN-TEX method; standard volume-response study using ≤100 ml samples	Nonirritant (predicted classification)	40
Nonhuman					
Acrylates/C10-30 alkyl acrylate cross polymer					
As Pemulen (trade name)	0.5 g undiluted	6 NZW rabbits	Semi-occlusive; abraded and nonabraded sites; 24 hours application	PII 0.42/8—negligible irritation potential very slight erythema was observed at 1 hour; no irritation observed at 72 hours	46
As Carbopol ETD (trade name)	0.5 g undiluted	3 rabbits	Semi-occlusive patch; nonabraded skin; 4 hours application	PII 0.0-1.5; non- to slight irritant very slight erythema and edema	43
	0.5 ml of a 1% neutralized solution			PII 0.0-0.1; non- to very slight irritant	
As Carbopol Ultrez-21 (trade name)	0.5 g, moistened with 0.5 ml water	3 rabbits	Semi-occlusive patch; nonabraded skin; 4 hours application	PII 0.3—produced slight irritation	44
As Carbopol Ultrez-20 (trade name)	0.5 g, moistened with 0.5 ml water	3 rabbits	Semi-occlusive patch; nonabraded skin; 4 hours application	PII 0.3—produced slight irritation	45
Acrylates/C10-30 alkyl acrylate cross polymer	2% aq	5 guinea pigs	Maximization (split adjuvant) test (details not provided)	Weak sensitizer	23
Acrylates cross polymer					
Acrylates cross polymer	30% in olive oil	3 rabbits	open application of 0.1 ml to a 2.5 cm × 2.5 cm site; 1 time daily for 4 days	No irritation	24
Sodium acrylates cross polymer 2					
As Aqua Keep 10SH-NFC (tradename)	Not stated	Rabbits Guinea pigs	Information provided in an industry MSDS	Not an irritant Not a sensitizer	41
Human					
Acrylates/C10-30 alkyl acrylate cross polymer					
Acrylates/C10-30 alkyl acrylate cross polymer	15 µl of 2% aq dilution	20 patients	Single 24-hour occlusive patch	24 hours: ± response in 3/20 patients 84 hours: ± response in 1/20 patients (results were based on Japanese criteria)	23
As Carbopol ETD (tradename)	Undiluted (>97.5%)[51]	100 patients	Material was applied to a 2 cm × 2 cm pad; patch was applied for 4 consecutive days during weeks 1 to 3; challenge was performed after 1 week and included 4 applications	Not an irritant or sensitizer	43
As Carbopol Ultrez 21 (tradename)	150 mg of a 10% dilution	111 patients	Test material was applied to a 2 cm × 2 cm pad; patch was applied for 4 consecutive days during weeks 1 to 3; challenge was performed after 1 week and included 4 applications	Not an irritant or sensitizer	44
As Carbopol Ultrez 20 (tradename)	150 mg of a 10% dilution	111 patients	Test material was applied to a 2 cm × 2 cm pad; patch was applied for 4 consecutive days during weeks 1 to 3;	Not an irritant or sensitizer	45

(continued)

Table 6. (continued)

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
			challenge was performed after 1 week and included 4 applications		
As Pemulen (tradename)	Undiluted (97.5%)[51]	54 patients	"Intensified" Shelanski HRIPT; test material was applied to a 1″ × 1″ patch	Weak irritant response; not a sensitizer During induction, faint or moderate erythema was observed once for 9 patients and twice for 2 patients; at challenge, faint erythema was observed once for 3 patients	46
Body lotion with 0.15% acrylates/C10-30 alkyl acrylate cross polymer	0.2 g	107 patients	Test material was applied to a 1″ × 1″ absorbent pad and allowed to volatize for several minutes; semi-occlusive patch; 24 hours applications made 3 times/wk for 3 weeks; challenge was applied after 2 weeks	not a dermal irritant or sensitizer	52
Crème with 0.60% acrylates/ C10-30 alkyl acrylate cross polymer	0.2 g	51 patients	Test material was applied to a 1″ × 1″ absorbent pad and allowed to volatize for several minutes; semi-occlusive patch; 24 hours semi-occlusive patches applied 3 times/ wk for 3 weeks; challenge was applied after 2 weeks	Not a dermal irritant or sensitizer	53
Acrylates cross polymer					
Acrylates cross polymer	15 μl; 30% in olive oil	20 patients	Single 24-hour occlusive patch	Not an irritant according to Japanese criteria	24
Eye lotion with 0.75% acrylates cross polymer	Undiluted	46 patients	HRIPT with occlusive patch	Not an irritant or sensitizer	54
Skin cleanser with 0.8% acrylates cross polymer	1% aq dilution	60 patients	HRIPT with occlusive patch	Not an irritant or sensitizer	54
Lipstick with 4% acrylates cross polymer	0.2 g	85 patients	HRIPT with occlusive patch	Not an irritant or sensitizer	55
Acrylates/ethylhexyl acrylate cross polymer					
Facial sunscreen with 6.8565% acrylates/ethylhexyl acrylate cross polymer	Undiluted	600 patients	Modified Draize RIPT with ten 48-hour induction patches using 0.5 in square occlusive patches; the first challenge was applied after a 2-week non-treatment period; an additional challenge application was made 1 week after the first challenge application	No evidence of primary irritation, skin fatigue, or sensitization	56
Acrylates/Steareth-20 methacrylate cross polymer					
The acrylic copolymer of Aculyn 88 Polymer (trade name)	Not stated	Not stated	21-day cumulative irritation study (GCP)	No irritation or sensitization	10
The acrylic copolymer of Aculyn 88 Polymer (trade name)	Not stated	Not stated	HRIPT (GCP)	No irritation or sensitization	10
Acrylates/vinyl isodecanoate cross polymer					
As Stabylen 30 (trade name)	0.5%-2.5% aq	25 patients	Kligman test (additional details were not provided)	Not an irritant or sensitizer	40
Acrylates/vinyl neodecanoate cross polymer					
The acrylic copolymer of Aculyn 38 Polymer (trade name)	Not stated	Not stated	21-day cumulative irritation study (GCP)	At most, a mild irritant with unformulated polymer and under worse-case conditions	12
The acrylic copolymer of Aculyn 38 Polymer (trade name)	Not stated	Not stated	HRIPT (GCP)	Not an irritant or sensitizer	12
	1% aq dilution	108 patients		Not an irritant or sensitizer	57

(continued)

Table 6. (continued)

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
Bath crème with 2% acrylates/ vinyl neodecanoate cross polymer			HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)		
Bath crème with 2% acrylates/ vinyl neodecanoate cross polymer	1% aq dilution	109 patients	HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	58
Bubble bath with 2% acrylates/ vinyl neodecanoate cross polymer	1% aq dilution	108 patients	HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	59
Bath gel with 2% acrylates/vinyl neodecanoate cross polymer	1% aq dilution	108 patients	HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	60
Bath product with 2% acrylates/ vinyl neodecanoate cross polymer	1% aq dilution	106 patients	HRIPT; 24-hour occlusive patches applied 3 times/week for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	61
Bath foam with 2% acrylates/ vinyl neodecanoate cross polymer	1% aq dilution	106 patients	HRIPT; 24-hour occlusive patches applied 3 times/week for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	62
Bath foam with 2% acrylates/ vinyl neodecanoate cross polymer	1% aq dilution	106 patients (same patients as above)	HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	63
Bath foam with 2% acrylates/ vinyl neodecanoate cross polymer	1% aq dilution	106 patients (same patients as above)	HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	64
Bubble bath with 2% acrylates/ vinyl neodecanoate cross polymer	1% aq dilution	107 patients	HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 2-week nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	65
Lauryl methacrylate/glycol dimethacrylate cross polymer					
Face powder with 1% lauryl methacrylate/glycol dimethacrylate cross polymer	0.2 g	104 patients	HRIPT; 24-hour occlusive patches applied 3 times/wk for 3 weeks; 24-hour challenge after a 10- to 15-day nontreatment period (size of patch was not provided)	Not an irritant or sensitizer	66
exfoliator cream with 2.6% lauryl methacrylate/glycol dimethacrylate cross polymer	0.2 g	619 patients	HRIPT with ten 24 hours occlusive applications of a ¾″ × ¾″ patch; 24-hour challenge after a 2-week nontreatment period; rechallenge was performed on 2 patients using semi-occlusive and open repetitive application	Not an irritant or sensitizer After challenge, 1 patient had moderate (at 24 hours) and mild (at 72 hours) erythema and edema, and 1 patient had barely perceptible erythema at 72 hours; these results were not reproducible at rechallenge	67

Abbreviations: NZW, New Zealand White; HRIPT, human repeated insult patch test.

the range associated with a 10^6 cancer risk, while use at the 95th percentile is just above the range associated with a 10^6 risk. The SSC noted that significant volatilization of benzene would occur during the manufacture of the finished product because the temperatures reached during processing are at or near the boiling point of benzene (80.1°C). They indicated that assuming that only 10% of the residual benzene is volatilized during product manufacture, would yield an exposure within the range associated with a 10^{-6} risk for use of a body lotion at the 95th percentile.

CIR's Risk Assessment

The EPA presents the oral slope factor for benzene as a range, based on the assumption that benzene is 100% absorbed after oral exposure. Specifically, the slope factor ranges from 1.5×10^{-5} to 5.5×10^{-5} $(\mu g/kg/d)^{-1}$. The EPA drinking water concentration range (1-10 μg/L) representing a 10^{-6} lifetime cancer risk was calculated from the slope factor range, rounding down the lowest concentration of the range to 1 μg/L and rounding up the highest concentration to 10 μg/L.

General Equation

- [%] benzene in acrylates/C10-30 alkyl acrylates crosspolymer × [%] acrylates/C10-30 alkyl acrylates crosspolymer in body lotion × [g/d] body lotion × [%] benzene absorbed percutaneously × $[kg]^{-1}$ body weight × 10^6 [μg/g] conversion factor × slope factor $[\mu g/kg/d]^{-1}$ =Cancer Risk Estimate [unitless]

Using the EPA's highest cancer slope factor in the range (5.5×10^{-5} $[\mu g/kg/d]^{-1}$) in accordance with the EPA risk assessment guidelines yields an upper bound lifetime cancer risk estimate of 2.2×10^{-5}, assuming the 95th percentile product use and 70 kg body weight:

Upper Bound Risk for 95th Percentile Exposure

- $0.41\% \times 0.4\% \times 16.83\ g/d \times 10\% \times 1/70[kg]^{-1} \times 10^6\ \mu g/g \times 5.5 \times 10^{-5}[\mu g/kg/d]^{-1} = 2.17 \times 10^{-5}$

This estimate (2.2×10^{-5}) is 22 times higher than the upper bound risk estimate considered to be de minimis (10^{-6}).

Assuming that 10% of the benzene evaporates during the product manufacturing process reduces the upper bound estimate to 2×10^{-5} ($2.17 \times 10^{-5} \times 90\% = 1.95 \times 10^{-5}$), which is still about 20 times higher than 10^{-6}.

Using the EPA's lowest cancer slope factor in their range (1.5×10^{-5} $[\mu g/kg/d]^{-1}$), assuming 50th percentile product use, 10% percutaneous absorption, and 10% evaporation during the manufacturing process yields upper bound cancer risk estimates that still exceed 10^{-6} by 2- to 3-fold:

Upper Bound Risk for 50th Percentile Exposure

- $0.41\% \times 0.4\% \times 7.63\ g/d \times 10\% \times 1/70[kg]^{-1} \times 10^6\ \mu g/g \times 1.5 \times 10^{-5}\ [\mu g/kg/d]^{-1} \times 90\% = 2.41 \times 10^{-6}$

The SSC reported that the cancer risk would $<10^{-6}$, by comparing the estimated daily absorbed dose of benzene from the product to drinking water concentrations that EPA suggests represents a 10^{-6} lifetime risk. However, CIR calculated upper bound lifetime cancer risk estimates up to 20-fold greater than 10^{-6}, based on EPA's cancer slope factors for benzene.

Industrial Exposure Limits

According to an industry MSDS, no exposure limits have been established for acrylates/C10-30 alkyl acrylate cross polymer.[39] The industry-recommended permissible exposure limits for respirable polyacrylate dusts is 0.05 mg/m^3. Breathing of dust may cause coughing, mucous production, and shortness of breath. According to an industry MSDS, the exposure limit for respirable sodium acrylates cross polymer 2 dust (particle size <10 μm) is 0.05 mg/m^3.[41]

Summary

The cross-linked alkyl acrylates are cross-linked polymers and are very large molecules that consist of comonomers of acrylic acid, sodium acrylate, methacrylic acid, and/or alkyl acrylate, and they share chemical properties, including a general lack of chemical reactivity. Cross-linked alkyl acrylates are typically produced via free radical, head-to tail chain-propagation polymerization. Ethyl acetate + cyclohexane, water, n-hexane, and benzene are all named as solvents. Because of the manner in which these polymers are created and the mixture of monomers and cross-linking agents that can be used, 2 polymers that have the same INCI name can have very different physical consistencies. Small amounts of residual monomer and/or solvent may be present in the raw ingredients.

Cross-linked alkyl acrylates are reported to function in cosmetic formulations as absorbents, film formers, emulsion stabilizers, viscosity increasing agents, suspending agents, binders, and/or skin-conditioning agents. In 2011, it was reported that acrylates/C10-30 alkyl acrylate cross polymer was used in 1,696 cosmetic formulations; 1,365 of those uses are in leave-on products, and the reported concentration of use in these leave-on products is up to 5%. According to industry data, acrylates/ethylhexyl acrylate cross polymer had the highest concentration of use in a leave-on product at 6%; the highest concentration of use reported in rinse-off products was 5% acrylates/C10-30 alkyl acrylate cross polymer.

Toxicokinetic data were not found in the published literature. Little toxicity data were available; the acute dermal and oral toxicity data that were found indicated that these ingredients are not very toxic. The little genotoxicity data that were

available reported negative results in Ames tests. Carcinogenicity data were not found in the published literature for the polymers, but data were available for the monomers.

In an alternative method study, acrylates/vinyl neodecanoate cross polymer was predicted to be a nonirritant. The nonhuman studies reported no to slight irritation with undiluted and weak sensitization with 2% aq, acrylates/C10-30 alkyl acrylate cross polymer, no irritation with acrylates cross polymer at 30% in olive oil, and no irritation or sensitization with sodium acrylates cross polymer 2 (concentration not specified). Mostly, human testing with undiluted acrylates/C10-30 alkyl acrylate cross polymer, acrylates cross polymer, and acrylates/ethylhexyl acrylate cross polymer, up to 2.5% aq acrylates/vinyl isodecanoate cross polymer, 1% aq dilutions of formulations containing 2% acrylates/vinyl neodecanoate cross polymer, and formulations containing up to 2.6% lauryl methacrylate/glycol dimethacrylate cross polymers do not indicate any dermal irritation or sensitization. The only exception was a weak irritant response noted during an intensified Shelanski HRIPT with undiluted acrylates/C10-30 alkyl acrylate cross polymer.

Alternative test methods for ocular irritation indicated that acrylates/vinyl isodecanoate cross polymer and a formulation containing 1% lauryl methacrylate/glycol dimethacrylate cross polymer are not likely ocular irritants. In studies using rabbits, undiluted acrylates/C10-30 alkyl acrylate cross polymer produced minimal to moderate irritation, and it was considered a borderline irritant in unrinsed rabbit eyes. Acrylates cross polymer, at 50% in olive oil, and sodium acrylates cross polymer 2 did not appear to be ocular irritants in rabbit eyes.

Two different risk assessments evaluating the carcinogenic endpoint for benzene that may be present in acrylates/ C10-30 alkyl acrylates cross polymer resulted in different lifetime risk. One found that the risk was within the range associated with a 10^6 cancer risk, while the other reported a 20-fold greater risk.

Discussion

Few published data were available on the cross-linked alkyl acrylates. The CIR Expert Panel was provided with some summary information on the monomers for their use in evaluating these cross polymers.

The Panel noted that these cross-linked alkyl acrylates are macromolecules that are not expected to pass through the stratum corneum of the skin, so significant dermal absorption is not expected. Therefore, topically applied cosmetics are not expected to result in systemic or reproductive and developmental toxicity or to have genotoxic or carcinogenic effects upon use.

The Panel noted that cosmetic products containing these ingredients are reportedly used around the eyes, on the lips, and on other mucous membranes. Thus, cross-linked alkyl acrylates could be absorbed systemically through the relatively moist, thin stratum cornea of the conjunctiva, lips, and other mucous membranes, and through ingestion when applied to the lips. However, the Panel noted that any absorption through healthy intact mucous membranes is likely to be not significant, primarily because of the relatively large molecular sizes. Furthermore, the chemically inert nature of the polymers precludes degradation to smaller absorbable species. Absorption of the polymers and their residual monomers in cosmetic products also would be limited after application to the lips or eye area based on the relatively small fractions of the applied products that might be inadvertently ingested or make direct contact with the conjunctiva.

The Panel addressed the concern of residual monomer or solvent that might be present in the cross polymers. In most cases, taking into consideration the low amount of residual monomer in the cross polymers and the low use concentration of the polymers themselves, the Panel was not concerned that the presence of residual monomer would result in adverse effects. However, the use of benzene as a solvent is an exception and did cause concern. It cannot be predicted with certainty what quantity of benzene would be volatilized/leached from acrylates/C10-30 alkyl acrylates cross polymer during manufacture, formulation, or use. While some benzene is inevitably volatilized during manufacture, some benzene may be trapped in the polymer matrix and may leach out during formulation and use, but there is no way of knowing how much (or if *any*) benzene would leach out without appropriate data from a representative product formulation.

Conservative risk assessments were submitted by industry and by the CIR to address the carcinogenic endpoint for benzene, because it may be used as a solvent in the manufacture of acrylates/C10-30 alkyl acrylates cross polymer. Both assessments assumed the highest reported concentration of residual benzene in acrylates/C10-30 alkyl acrylates cross polymer used as a raw ingredient, the highest reported use concentration in a leave-on product of the raw ingredient polymerized in benzene, 10% evaporation of the residual benzene during manufacturing of the product, 10% benzene absorbed from the product through the skin, and the reported 95th percentile of the amount of product used daily. Industry reported that the cancer risk would $<10^{-6}$, by comparing the estimated daily absorbed dose of benzene from the product to drinking water concentrations that EPA suggests represents a 10^{-6} lifetime risk. However, CIR calculated upper bound lifetime cancer risk estimates up to 20-fold greater than 10^{-6}, based on EPA's cancer slope factors for benzene. Given the uncertainty of the assumptions used in the risk assessment, the Panel was not comfortable with using a risk assessment in evaluating the carcinogenic endpoint. Therefore, the Panel found the data insufficient to conclude that the residual benzene levels are safe.

Because these ingredients can be used in products that may be aerosolized, including sprays and powders, the Panel discussed the issue of potential inhalation toxicity. The limited data available from an acute exposure study suggested little potential for pulmonary overload or other respiratory effects at relevant doses. The Panel considered other data available to characterize the potential for cross-linked alkyl acrylates to cause systemic toxicity, irritation, sensitization, or other effects. They noted the lack of systemic toxicity at high doses

in several acute oral exposure studies, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, and the absence of genotoxicity in Ames tests. In addition, these ingredients are macromolecules, insoluble in water, and chemically inert under physiological conditions or conditions of use, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract. Further, these ingredients are reportedly used at concentrations ≤4% in cosmetic products that may be aerosolized. The Panel noted that 95% to 99% of particles produced in cosmetic aerosols would not be respirable to any appreciable extent. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information indicates that inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

Conclusion

The CIR Expert Panel concluded that the cross-linked alkyl acrylates listed below are safe in the present practices of use and concentration described in this safety assessment, except when they are polymerized in benzene. Acrylates/C10-30 alkyl acrylate cross polymer may be polymerized in benzene, and the available data are insufficient to make a determination of safety for this cross-linked alkyl acrylate when it is polymerized in benzene.

Acrylates/C10-30 alkyl acrylate cross polymer
Acrylates/C12-13 alkyl methacrylates/methoxyethyl acrylate cross polymer*
Acrylates cross polymer
Acrylates/ethylhexyl acrylate cross polymer
Acrylates/ethylhexyl acrylate/glycidyl methacrylate cross polymer*
Acrylates/PEG-4 dimethacrylate cross polymer*
Acrylates/Steareth-20 methacrylate cross polymer
Acrylates/vinyl isodecanoate cross polymer
Acrylates/vinyl neodecanoate cross polymer
Allyl methacrylate/glycol dimethacrylate cross polymer*
Allyl methacrylates cross polymer
Butyl acrylate/glycol dimethacrylate cross polymer*
C8-22 alkyl acrylates/methacrylic acid cross polymer*
Glycol dimethacrylate/vinyl alcohol cross polymer*
Lauryl methacrylate/glycol dimethacrylate cross polymer
Lauryl methacrylate/sodium methacrylate cross polymer
Methacrylic acid/PEG-6 methacrylate/PEG-6 dimethacrylate cross polymer*
PEG/PPG-5/2 methacrylate/methacrylic acid cross polymer*
Potassium acrylates/C10-30 alkyl acrylate cross polymer*
Sodium acrylates cross polymer 2
Sodium acrylates/C10-30 alkyl acrylate cross polymer
Sodium acrylates/vinyl isodecanoate cross polymer*
Stearyl/lauryl methacrylate cross polymer*

*Were the ingredients not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contributions

Fiume, M. contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted manuscript; Heldreth, B. contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript; Boyer, I. contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript; Gill, L., Andersen, F. Alan, Bergfeld, W., Belsito, D. Hill, R., Klaassen, C., Liebler, D., Marks, J., Shank, R., Slaga, T., and Snyder, P. contributed to analysis and interpretation, contributed to conception and design, and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Final Report of the Cosmetic Ingredient Review Expert Panel Safety Assessment of Polymethyl Methacrylate (PMMA), Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer

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Abstract

Polymethyl methacrylate (PMMA) and related cosmetic ingredients methyl methacrylate crosspolymer and methyl methacrylate/glycol dimethacrylate crosspolymer are polymers that function as film formers and viscosity-increasing agents in cosmetics. The Food and Drug Administration (FDA) determination of safety of PMMA use in several medical devices, which included human and animal safety data, was used as the basis of safety of PMMA and related polymers in cosmetics by the Cosmetic Ingredient Review (CIR) Expert Panel. The PMMA used in cosmetics is substantially the same as in medical devices. The Panel concluded that these ingredients are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

Keywords

cosmetics, methyl methacrylate/glycol dimethacrylate crosspolymer, polymethyl methacrylate, safety

Introduction

This is the final report of the safety assessment of polymethyl methacrylate (PMMA) as used in cosmetics by Cosmetic Ingredient Review (CIR). Based on chemical similarity, the CIR considers that 2 other cosmetic ingredients should be considered in this safety assessment: methyl methacrylate crosspolymer and methyl methacrylate/glycol.

Polymethyl methacrylate is the polymer of methyl methacrylate (MMA). In commercial medical devices, PMMA is available in its components for mixing and formation in situ or preformed into beads or other shapes. Polymethyl methacrylate produced for cosmetics is similar to the PMMA in certain medical device categories in that it is already formed into beads or powder. The safety information for those medical devices has been provided to the Food and Drug Administration (FDA) in medical device applications of PMMA in intraocular lenses (IOLs), bone cement, dental fillers, and dermal fillers. The FDA has found those data to be adequate and has determined the safety (and efficacy) of PMMA for use in these devices. Several of these devices have been approved as implants, resulting in systemic exposures that far exceed that expected for PMMA use in cosmetics.

The CIR considers that the assessment of PMMA safety as used in medical devices by the FDA provides the basis to establish the safety of PMMA in cosmetics because the PMMA is substantially the same as that used in approved medical devices and is used in a manner that presents less exposure risk. Given the chemical similarity, it follows that such data could be extrapolated to support the safety of methyl methacrylate crosspolymer and methyl methacrylate/glycol dimethacrylate crosspolymer.

Below is a summary of the information available from the FDA to assess the safe use of PMMA, methyl methacrylate crosspolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer in cosmetics as well as supplemental information from the cosmetic industry.

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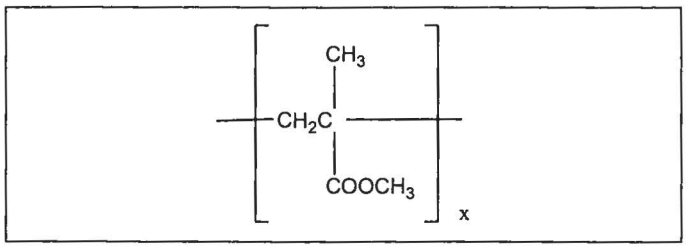

Figure 1. The monomer structure of PMMA.[30] PMMA indicates polymethyl methacrylate.

Chemical Description

Polymethyl methacrylate (CAS No. 9011-14-7) is the polymer of methyl methacrylate that conforms to the formula in Figure 1.[1] Its chemical class is synthetic polymers and it functions as a film former and it has only synthetic sources. Another technical name is 2-propenoic acid, 2-methyl, methyl ester, homopolymer.

Methyl methacrylate crosspolymer (CAS No. 25777-71-3) is a copolymer of methyl methacrylate crosslinked with glycol dimethacrylate (Figure 2). Its chemical class is synthetic polymers and it functions as a film former and a viscosity-increasing agent—nonaqueous. It has only synthetic sources. Other technical names include:

- methyl 2-methyl-2-propenoate, polymer with 2-methyl-2-propenoic acid, 1,2-ethanediyl ester;
- 2-methyl-2-propenoic acid, 1,2-ethanediyl ester, polymer with methyl 2-methyl-2-propenoate; and
- 2-propenoic acid, 2-methyl, 1,2-ethanediyl ester, polymer with methyl 2-methyl-2-propenoate.

The International Nomenclature of Cosmetic Ingredients (INCI) defines methyl methacrylate/glycol dimethacrylate crosspolymer (no CAS No.) as a cross-linked copolymer of methyl methacrylate and ethylene glycol dimethacrylate monomers (Figure 2). Its chemical class is synthetic polymers and it functions as a film former.

Material Characterization

Data provided by industry include a sufficient description of PMMA to conclude that it is similar to the PMMA medical devices approved by the FDA. Table 1 compares the physical properties of PMMA beads used in cosmetics and dermal fillers.

Polymethyl methacrylate. Ingredients in this safety assessment are polymers. In a linear polymer (eg, PMMA), the structural units are connected in a long, linear chain arrangement and thus need to be only bifunctional, that is, have 2 bonding sites. When the structural unit is trifunctional (3 bonding sites) and is polymerized, a nonlinear branched polymer results. Ethylene, styrene, and ethylene glycol are examples of bifunctional monomers, while glycerin and divinyl benzene are both polyfunctional. A crosspolymer has multiple polymer chains that are linked together with a compound called a crosslinking agent (eg, methyl methacrylate crosspolymer and methyl methacrylate/glycol dimethacrylate crosspolymer). Polymers containing a single repeating unit, such as PMMA, are called homopolymers. Polymers containing 2 or more different structural units (monomers), such as phenol-formaldehyde resin, are called copolymers. Polymers can be classified as either addition polymers or condensation polymers. An addition polymer is one in which the molecular formula of the repeating structural unit is identical to that of the monomer, for example, polyethylene and polystyrene. A condensation polymer is one in which the repeating structural unit contains fewer atoms than that of the monomer or monomers because of the splitting of water or some other substance, for example, polyesters and polycarbonates. Accordingly, PMMA is an addition type of homopolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer is an addition type of copolymer.

A comparison of PMMA beads used in dermal fillers with different sources revealed a wide variation in quality and conformity.[6] One source reported size ranges from 30 to 50 μm with negligible small sizes. The surfaces were smooth with scant, if any, sediment. The beads from another source were characterized as having a wide variety of particle sizes (0.2-70 μm), with

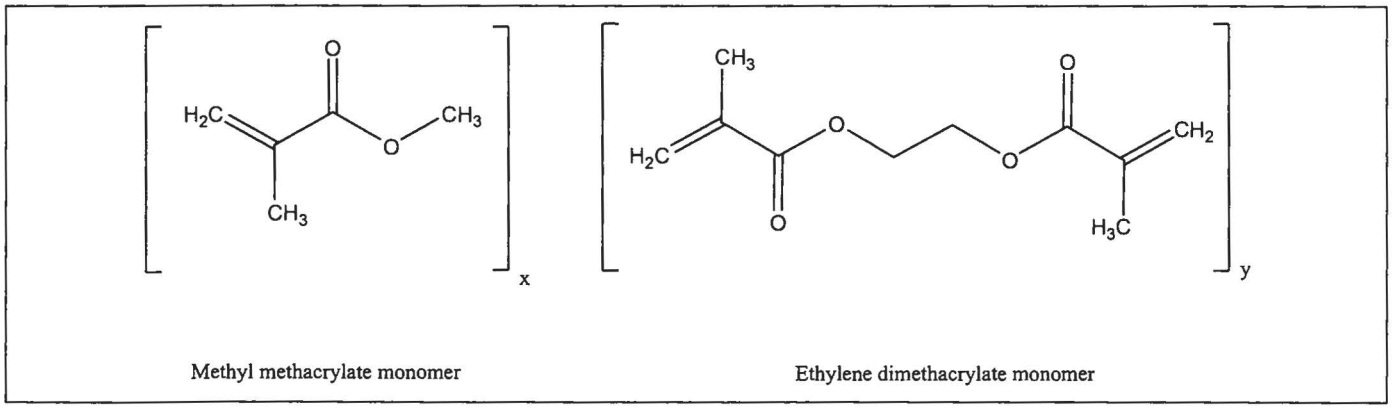

Figure 2. Methyl methacrylate monomers and ethylene dimethacrylate monomers are polymerized to make up methyl methacrylate/glycol dimethacrylate crosspolymer and methyl methacrylate crosspolymer—more detailed structures are not available because the connectivity is not given and the values for x and y are not known.

Table 1. Comparison of PMMA Beads Used in Cosmetic and Dermal Fillers

Property	Cosmetics	Dermal Fillers
Form	Beads	Beads
Appearance	Fine white powder	Fine white powder
Diameter (μm)	5-10, 6-10, 6.5-10.5, 5-16[2]; 4-8, 6-10, 20[3]; <2-35[4]; 4.5-8.5[5,6]; 60-80[7]	30-50[8]; .2-70[8]; 30-42[9]; 4-40[10]; 4.3-72[10]; 30-42[9]
Molecular weight of monomer	PMMA—88.11	PMMA—88.11
Molecular weight of polymer (d)	> 250,000[7]	Not available
Residual monomer (ppm)	< 100, < 50, < 10[2]; < 20 on surface, < 100 total[2]; < 100[2,11,6]	10.3 μg/kg[2,10]

some oversized and very small spheres. Some of the particles were not round and/or were conjoined.

The molecular weight of the PMMA monomer is 88.11. Polymethyl methacrylate made by emulsion polymerization can have a molecular weight of several million. The glass transition temperature (Tg), where the polymer changes between the crystal state and glass state, of PMMA is 105°C. Polymethyl methacrylate is rigid at room temperature and is highly stable.[12] The surface of PMMA is dominated by methyl ester groups and when exposed to water demonstrate no detectable surface restructuring.[13] Visible light transmits through PMMA up to 92% and transmits into the ultraviolet range. Emulsion-made polymers of methacrylates that are copolymers (mixed with other polymer components) have physical properties that vary widely depending on the composition and morphology of the emulsion particles.[14]

Polymethyl Methacrylate in Cosmetics. The PMMA used in cosmetics are in the form of fine powders or beads.[2] The diameter of the beads supplied to cosmetic companies were reported to be 5 to 10 μm, 6 to 10 μm, 6.5 to 10.5 μm, 5 to 16 μm, or having an average diameter of 6 μm, depending on product. One product information sheet for PMMA for cosmetic use identified the form as highly porous spherical beads. Size range and tolerance, porosity, or any chemical property information were not provided.[15] Another product information[3] sheet described the PMMA product (for use in cosmetics) as low-micron materials with an appearance of white fine powders with an average particle size of 4 to 8 μm. At 10% in water, the pH is 5.0 to 8.0 and the oil absorbance is 64 mL/100 g.

A product information sheet of several PMMA bead products (for use in cosmetics) described the products as a white fine powder.[11] Diameters were reported to be 4 to 8, 6 to 10, or 20 μm with a pH in the range of 5.0 to 8.0. The oil absorbance ranges from 64 to 73 mL/100 g.

An analysis of the diameters of beads in a sample of PMMA (for use in cosmetics) shows a peak at just under 5 μm with the highest range of ~3.5 to 10 μm.[4] The entire bead diameter size range is < 2 to ~35 μm.

Another analysis of PMMA beads confirms that the sample is a white powder with an average particle size of 6.3 μm (specifications 4.5-8.5 μm), a pH of 6.5 (5-8), 0.07% residue at ignition (≤0.1%), and 0.4% loss on drying (≤2%).[5]

In artificial nail-enhancement products, the molecular weights of PMMA particles are, >250 000 Da.[7] The particle size ranges between 60 and 80 μm.

Methyl Methacrylate Crosspolymer

On a product data sheet, methyl methacrylate crosspolymer beads have an average size of 8 μm and the spheres are hollow.[16]

Methyl methacrylate crosspolymer products are also described as a white fine powder with diameters reported to be 8.5, 4 to 8, or 6 to 10 μm.[17] The pH ranges from 5.0 to 8.0 and the oil absorbance is from 70 to 75 mL/100 g with one reported to be 170.

Methods of Manufacture

Industry has stated that the manufacturing process for PMMA beads used in medical devices and cosmetic products is the same. The only difference is the size of the PMMA spheres, which are provided according to the specifications of the purchaser.

Polymethyl methacrylate beads or powders in cosmetics are precipitated out from a polymerization reaction.[2] The average bead size can be controlled within the 4 to 50 μm specifications. Furthermore, the chemical resistance and the compositions of submicron polymers can be altered.[16]

Polymethyl methacrylate can be polymerized, then crushed and pelletized.[18] Suspension and bulk polymerization are generally used for injection molding and extrusion applications. Variation in the diameter of commercial PMMA beads was achieved by changing the time the stabilizing agent was added to the reaction; delay in the addition of the stabilizing agent resulted in larger beads.

Several methods of PMMA manufacture have been described.[14] Bulk casting employs a mold of glass to create sheets, rods, and blocks. Suspension and bulk polymerization are generally used for injection molding and extrusion applications. Suspension polymerization uses beads of the monomer to form beads of the polymer that may be used as produced or extruded to yield pellets. Continuous bulk polymerization can be carried out using PMMA as both the reactant and the solvent. Emulsion polymerization is used to create submicron-sized (50-1000 nm) particles in an aqueous medium, which has the advantages of easy heat dispersion, low polymerization medium viscosity, ability to achieve high-molecular weight, and high monomer conversion.[14]

Table 2. Methods of Physical and Chemical Analysis of PMMA Used as a Bone Cement[23]

Characterization	Suggested Testing	Examples of Testing Methods
Mixing and application	Mix liquid and powder components	ASTM F451-95; ISO 5833-92
	Dough time	ASTM F451-95; ISO 5833-92
	Setting time	ASTM F451-95; ISO 5833-92
	Viscosity: pre-dough stage extrusion	ASTM F451-95; ISO 5833-92
	Dough stage extrusion	ASTM F451-95; ISO 5833-92
Chemical composition	Ingredients: chemical formula, structure, additives, etc	Liquid-NMR, FTIR, HPLC/MS
	Type of radiopacifier	TGA/gross pyrolysis
	Purity or trace elements	ICP/MS, GC/FTIR/MS, titration
	Residue low-mw molecules	GC, HPLC/GPC, liquid-NMR
	Leachables (ie, low MW molecules)	GC, HPLC/GPC
Molecular weight and polymer structure	MW by viscosity flow	Viscosity measurements (ie, solution)
	MW: polydispersity, M_n, M_w	GPC with refractive index detector using polystyrene as standard material
	Branched, linear, or cross-linked	Solubility, swelling, liquid NMR
	% Crystallinity, if applicable	X-ray diffraction, DSC
	Crystallization temperature, if applicable	DSC, DMA
	Glass transition temperature (Tg), if applicable	DSC, DMA
Physical properties	Powder's morphology, size characterization, and dispersion of polymer and additives	Light microscopy, SEM of powder and cured cement
	Porosity characterization	Scanning acoustical microscopy of bulk cement (ie, SLAM, C-SAM) and serial sectioning of the cured cement
	Dimensional changes during curing (shrinkage)	Volume measurement
	% Water absorption (swelling)	Saturation testing
	Aging due to fluid absorption and polymerization	Mechanical testing
Stability of components	Change in monomer viscosity due to artificial aging	ASTM 451-95
	Change in benzoyl peroxide levels	Titration method, FTIR, GC
Thermal properties	Maximum polymerization temperature	ASTM F451-95; ISO 5833-92

Abbreviations: TM, American Standard for Testing Materials; C-SAM, C-mode scanning acoustical microscopy; MDA, dynamic mechanical analysis; DSC, differential scanning calorimetry; FTIR, Fourier transform infrared; GC, Gas chromatography; GPC, gel permeation chromatography; HPLC, High performance liquid chromatography; ICP, Inductively coupled plasma; ISO, International Standards Organization; MS, mass spectroscopy; MW, molecular weight; NMR, nuclear magnetic resonance; SEM, scanning electron microscope; SLAM, scanning laser acoustical microscopy; TGA, thermogravimetric analysis.

In nail products, polymer powders are made from methyl or ethyl methacrylate or their copolymers.[7]

The methods of manufacture, where available, are included with the description of the FDA-approved medical devices below. Manufacture of PMMA for medical devices requires compliance with good manufacturing practices.[19]

Analytical Methods

To test for residual monomer, beads of PMMA for cosmetics are soaked in methanol with supersonic dispersion. The sample is then centrifuged, and the solution on the upper side is analyzed by high-pressure liquid chromatography.[20] A fluorine limit test is used to test for the fluorine, and a lead limit test is used to test for lead contained in a sample of PMMA.[21]

During manufacture, infrared spectroscopy is used to monitor the polymerization of MMA to PMMA.[22] Table 2 shows the methods of physical and chemical analysis of PMMA used as bone cement.

Raman spectroscopic identification was used to identify PMMA IOLs implanted in human eyes.[24]

The amount of the residual monomer MMA on PMMA denture material was measured by removing the monomer with tetrahydrofuran and analyzing using HPLC.[25] A light microscopic technique with polarized light was used to measure the thickness of the unpolymerized surface layer of PMMA.

Impurities

The monomer levels in PMMA used in cosmetics were reported as <100, <50, and <10 ppm, depending on the product.[2] One supplier reported a monomer level of <20 ppm on the surface and <100 ppm total. Analysis showed <5 ppm on the surface and <25 ppm total.

The Nail Manufacturers Council reported that the residual monomer is typically <1.5%; averages of 0.7% and 1.2% have been reported.[7]

The PMMA in an eyebrow pencil contained <20 ppm monomer.[26]

A 2-year-old PMMA sample was found to have <1 ppm arsenic and <10 ppm heavy metal (specifications were <3 ppm and <10 ppm, respectively). The surface had <5 ppm residual monomer and there was <25 ppm total, below specifications of <20 ppm and <100 ppm.[5]

A supplier reported that residual MMA in methyl methacrylate crosspolymer is similar to that of PMMA, <100 ppm.[2]

Cosmetic Use

According to information supplied to the FDA by industry as part of the Voluntary Cosmetic Registration Program (VCRP), PMMA was used in a total of 892 cosmetic products (Table 3).[29] Use concentrations ranged from 0.01% to 45%, according to a survey of current use concentrations conducted by the Personal Care Products Council (Council).[30] Polymethyl methacrylate was reported to be used in 304 eye products, 369 makeup products (including 60 lipsticks), and 198 other types of leave-on products.

Methyl methacrylate crosspolymer was reported to be used in 144 cosmetic products at 0.1% to 14%. Methyl methacrylate crosspolymer was used in 15 eye products, 79 makeup products (including 15 lipsticks), and 47 other types of leave-on products. It was used in at least 1 spray product.

Methyl methacrylate/glycol dimethacrylate crosspolymer was reported to be used in 7 leave-on cosmetic products at 0.1% to 3%.

The number of uses within concentration ranges as reported by Health Canada is presented in Table 4.

A product data sheet stated that PMMA beads are used as a delivery system in cosmetic applications, commonly for sodium hyaluronate, folic acid, vitamin E, Fomblin, and a-hydroxy acid. The beads may also be used to deliver colorants. The beads provide a ball-bearing effect that contributes to product feel.[15]

Both PMMA and methyl methacrylate crosspolymer are used in color sprays. For ingredients used in cosmetic sprays and aerosols, it is important to consider inhalation safety. Safety of inhaled aerosols depends on the ingredient, the concentration, the duration of the exposure, and where they are deposited within the respiratory system.[30] The site of deposition is associated most with the particle size and density of the particle being inhaled.

Absorption of gases and vapors by inhalation is determined by the partitioning of the compound between the blood and the gas phase along with its solubility and tissue reactivity. The important characteristics that affect absorption after exposure to aerosols are the aerosol size and water solubility of any chemical present in the aerosol. In general, the smaller the particle, the further the particle will deposit into the respiratory tree and the greater the impact on the respiratory system.

The parameter most closely associated with this regional deposition is the aerodynamic diameter, d_a, defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question. In humans, particles with an aerodynamic diameter of ≤ 10 μm are respirable. Particles with a d_a from 0.1 to 10 μm settle in the upper respiratory tract and particles with a d_a <0.1 μm settle in the lower respiratory tract.[32,33] Nanoparticles have the potential to deliver high amounts of particulates to the lung.[34]

As noted earlier, PMMA is supplied as a fine powder with an average particle size between 4 and 8 μm, in the respirable size range. The current technology for producing cosmetic aerosols for the mixture of all ingredients cannot deliver particles that small. Particle diameters of 60 to 80 μm and ≥ 80 μm have been reported for anhydrous hair sprays and pump hairsprays, respectively.[35] In practice, aerosols should have at least 99% of their particle diameters in the 10 to 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm.[36] Therefore, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

A search of the Environmental Working Group's database of cosmetic ingredients revealed 4 uses of PMMA in nail glues that were not reported to the FDA or the Council.[37] Additional input from the Personal Care Products Council (Council) and the Nail Manufacturer's Council revealed that the PMMA was used in final form in nail glues and was not mixed in situ, as with bone cement.[38]

In artificial nail-enhancement systems, PMMA is used as an inert carrier for the curing agent, benzoyl peroxide (BPO), and FD&C and D&C coloring agents.[7] It also serves as a thickening agent for placement and shaping of liquid and powder slurry on the nail plate in nail products. Polymethyl methacrylate beads are a reinforcing agent to prevent crack propagation in the cured polymer matrix.

Polymethyl Methacrylate Use in Medical Devices

The FDA has considered the safety of PMMA when approving medical devices made of this material.

Intraocular lenses (ie, Tecnis, Advanced Medical Optics, Inc., Irvine, CA and SENSAR Soft Acrylic UV Light-absorbing Posterior Chamber Intraocular Lens, Allergan, Inc., Santa Ana, CA) are made of PMMA. Premarket applications have been approved since 1976.[39,40]

Polymethyl methacrylate bone cement has been approved by the FDA as a class II (special controls) medical device that requires premarket notification and adherence to standards. The FDA-cleared bone cements have been marketed since 1999.[41,42]

Polymethyl methacrylate beads are incorporated into collagen as dermal fillers (ie, Artecoll PMMA/Collagen Implant, Artes Medical, Inc., San Diego, CA and Artefill, Artes Medical, Inc., San Diego, CA). A premarket application was approved in 2006.[43,44]

Temporary (provisional) PMMA crown and bridge materials (ie, Artegral ImCrown, Merz Dental, Lutjenberg, Germany) have been cleared for marketing since before 1976 and comply with class II special controls.[45]

Polymethyl methacrylate membranes also have been used in dialyzers for hemodialysis.[46,47] Polymethyl methacrylate has been used in other medical applications.[48-62]

Safety Data Submitted to the FDA on PMMA Medical Devices

The FDA has reviewed extensive data on several medical devices; that review was considered to support the safety of use of PMMA and the associated ingredients in cosmetics. Data on the safety of implanted PMMA obviates the need for absorption, distribution, metabolism, and excretion (ADME) or

Table 3. Cosmetic Product Uses and Concentrations for PMMA, Methyl Methacrylate Crosspolymer, and Methyl Methacrylate/Glycol Dimethacrylate Crosspolymer

Product Category (Total Products in Category—FDA 2008)	2008 Uses (FDA 2010)[27]	2009 Concentrations (%) Council 2009)[28]
Polymethyl methacrylate		
Bath products		
Soaps and detergents (1329)	2	6
Eye products		
Eyebrow pencil (153)	13	5-15
Eyeliner (834)	59	0.1-17
Shadow (1343)	173	5-45
Lotion (260)	20	0.5-3
Makeup remover (133)	–	–
Mascara (528)	9	0.5-2
Other (412)	30	0.9[a]
Fragrance products		
Colognes and toilet waters (1426)	–	15
Perfumes (742)	2	20
Powders (237)	2	10
Other (641)	3	0.5-11
Noncoloring hair care products		
Rinses (34)	2	0.3
34 Tonics, dressings, etc (1321)	–	1
Hair-coloring products		
Tints (6)	–	2
Color sprays/aerosol (7)	1	–
Makeup		
Blushers (471)	70	0.1-16
Face powders (724)	91	2-30
Foundations (624)	99	3-25
Lipstick (2045)	60	3-20
Makeup bases (126)	13	1-26
Rouges (107)	9	–
Fixatives (49)	14	5
Other (536)	13	2-23
Nail care products		
Polish and enamel (351)	2	0.7-20
Other (137)	12	30
Personal hygiene products		
Underarm deodorants (623)	–	4
Shaving products		
Aftershave lotions (381)	4	0.4-2
Shaving cream (128)	2	–
Other (126)	3	–
Skin care products		
Cleansing creams, lotions, liquids, and pads (1528)	2	–
Face and neck creams, lotions, etc (1652)	62	1-16
Body and hand creams, lotions, etc (1875)	17	0.3-5
Moisturizers (2750)	50	0.3-3
Night creams, lotions, powder and sprays (386)	15	0.2-2
Paste masks/mud packs (462)	2	0.5-2
Fresheners (267)	2	–
Other (1446)	27	0.2-3
Suntan products		
Suntan gels, creams, liquids, and sprays (106)	3	0.01-15
Indoor tanning preparations (247)	1	–
Other (61)	3	3
Total uses/ranges for PMMA	892	0.01-30
Methyl methacrylate crosspolymer		
Eye products		
Eyebrow pencil (153)	–	10
Eyeliner (834)	1	10
Shadow (1343)	7	1-10
Lotion (260)	3	0.5
Mascara (528)	1	1-2
Other (412)	3	–
Fragrance products		
Powders (237)	1	8
Noncoloring hair care products		
Sprays/aerosol fixatives (321)	–	0.1
Makeup		
Blushers (471)	6	0.8-1
Face powders (724)	16	0.5-12
Foundations (624)	33	0.5-10
Lipstick (2045)	15	1-10
Makeup bases (126)	–	4
Fixatives (49)	4	–
Other (536)	5	4-10
Nail care products		
Basecoats and undercoats (69)	–	1
Nail polish and enamel (351)	1	–
Personal hygiene products		
Underarm deodorants (623)	–	0.9
Shaving products		
Other (126)	1	–
Skin care products		–
Skin cleansing creams, lotions, liquids, and pads (1528)	1	–
Face and neck creams, lotions, etc (1652)	13	1-3
Body and hand creams, lotions, etc (1875)	3	0.1-0.5
Moisturizers (2750)	17	0.8-3
Night creams, lotions, powder, and sprays (386)	5	–
Fresheners (267)	1	0.6
Other (1446)	5	3-14
Suntan products		
Indoor tanning preparations (247)	2	–
Total uses/ranges for methyl methacrylate crosspolymer	144	0.1-14
Methyl methacrylate/glycol dimethacrylate crosspolymer		
Fragrance products		
Powders (237)	–	3
Makeup		
Other (536)	4	0.6
Skin care products		–
Face and neck creams, lotions, etc (1652)	–	0.1-0.2
Moisturizers (2750)	1	0.5
Paste masks/mud packs (462)	–	0.1
Other (1446)	2	–
Total uses/ranges for Methyl methacrylate/glycol dimethacrylate crosspolymer	7	0.1-3

Abbreviations: FDA, Food and Drug Administration; PMMA, polymethyl methacrylate.

[a] 0.9% in an eye makeup fixative.

Table 4. Use and Concentration of Use Reported by Health Canada[31]

	Range							
Ingredient Name	>30%-100%	>10%-30%	>3%-10%	>1%-3%	>0.3%-1%	>0.1%-0.3%	0.1% or Less	Total
Polymethyl methacrylate	57	180	543	595	542	143	156	2216
Methyl methacrylate crosspolymer	6	41	154	185	106	19	15	526
Methyl methacrylate /glycol dimethacrylate crosspolymer	0	0	5	17	16	9	8	55

other safety data. Relevant safety issues, such as microbial adhesion and monomer issues, have been addressed by the FDA in the course of its safety review.

Intraocular Lenses

Intraocular lenses are considered permanent implants. They replace the natural occluded lens following lens removal in cataract surgery. A battery of in vivo and in vitro acute and chronic toxicity tests established the biocompatibility of the PMMA IOL material. Based on these studies and data from chemistry and engineering analyses, the suitability of the material for use as IOL material was established. Physiochemical tests include tests for exhaustive extraction, leachables, hydrolytic stability, photostability against ultraviolet and visible irradiation, stability against neodymium yttrium-aluminum-garnet (Nd-YAG) laser exposure, and insoluble inorganics. The FDA also requires biocompatibility testing according to the FDA-modified use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation, and Testing for blood-contacting, long-term devices.[63] Biological testing must conform to International Standard ISO-10993-5, Biological Evaluation of Medical Devices Part 5: Tests for in vitro cytotoxicity.[64] Testing for effects on cell growth and cell damage, genotoxicity, local effects after implantation, and sensitization potential is required.

Postoperative follow-up of patients (n = 335) implanted with acrylic IOLs with PMMA haptics (SENSAR Soft Acrylic UV Light-Absorbing Posterior Chamber Intraocular Lens, Model AR40) implants was performed for 12 months. The FDA concluded that the clinical performance of the IOL compared favorably with 1983 historical data including adverse events reported to the FDA.[40]

Nonclinical and clinical testing of PMMA IOLs was conducted (Model AC21B Ultraviolet-Absorbing PMMA Anterior Chamber Intraocular Lens). Patients (n = 722) were followed for 12 to 24 months. No adverse events were reported. A battery of in vivo and in vitro and chronic toxicity tests established biocompatibility in this application.[65]

Manufacturing information on PMMA was provided to the FDA. Quality control procedures, purity, and other tests are required. The FDA requires that <1% free monomer be present in the PMMA used in IOLs (Don Calogero, personal communication, September 2009).

Bone Cement

The FDA has issued a class II special controls guidance document for PMMA bone cement for the allowance of new commercial bone cement products to be deemed "substantially equivalent to legally marketed predicate devices."[23] The guidance stipulates that the cement be PMMA. The FDA also requires biocompatibility testing according to the FDA-modified Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation, and Testing for blood-contacting, long-term devices.[66] The ISO standard also states that the identified risks of bone cement implantation syndrome, polymerization setting problems, loosening or migration of the device, infection and fever, adverse tissue reaction, pain and/or loss of function, and revision be mitigated by material and performance characterization (physical and chemical characterization, mechanical testing, shelf-life, product expiration dating, and storage conditions), sterility, and labeling. Bone cement labeling must include cautions about inhalation of monomer vapors, exothermic reaction, inadequate fixation, and the dissolving of rubber or latex gloves or tissue during mixing and setting. None of these possible adverse events pertain to cosmetic use since PMMA used in cosmetics is used only in its final, fully polymerized form.

The FDA has approved a number of PMMA bone cements for market, including Cemex ISOPLASTIC Bone Cement, SmartSet GH Gentamicin, Cobalt HV Bone Cement, Spine-Fix Biomimetic Bone Cement, and SmartSet MV Bone Cement.[65,23,67-70]

Polymethyl methacrylate bone cement consists of methyl methacrylate (97.4% w/w) added to *N,N*-dimethyl-*para*-toluidine (2.6% w/w) and hydroquinone (75 ± 15 ppm). This is then added to PMMA (15% w/w) and methyl methacrylate-styrene copolymer (75% w/w) with barium sulfate USP (10% w/w) to make the cement radiopaque.[71]

Polymethyl methacrylate bone cement is polymerized by radical-initiated addition reaction. The 2 components are a powder containing prepolymerized beads of PMMA (or PMMA/styrene copolymer) and a liquid containing MMA monomers. The BPO initiator is incorporated into the powder, and the chemical activator is incorporated into the liquid. Peroxide cleavage and polymerization begins when the 2 are mixed. Growing polymer chains encapsulate the PMMA beads. The liquid-to-powder ratio affects the strength of the cement and temperature. The initiator-to-activator ratio affects

polymerization times. Polymethyl methacrylate beads act as heat sinks; their concentration and size affect overall temperature and setting times but have little impact on strength.[57]

Artecoll Dermal Filler

Safety and effectiveness data for approval by the FDA of Artecoll, a dermal filler made up of collagen and PMMA beads, are summarized in the summary of safety and effectiveness (SSE).[10]

Testing for cytotoxicity was done according to the ISO-10993-5 guidelines.[64] There was no evidence of cell toxicity observed. Artecoll was found to be less cytotoxic than a grade 2 (mild reactivity) material.

Testing for mutagenicity was done in a reverse mutation assay. Artecoll was nonmutagenic to *Salmonella typhimurium* and *Escherichia coli*.

A guinea pig (n = 10) maximization test was performed. Artecoll did not cause a delayed dermal contact sensitization reaction.

Artecoll was studied in implantation studies in rabbits and did not cause a significant reaction compared to controls. Microscopic evaluation found the test substance to be nonirritating. Implantation studies of cross-linked collagen, hyaluronic acid, silicone oil, PMMA microspheres (4-40 μm), PMMA microspheres in hyaluronic acid (40 μm), polylactic acid microspheres (40 μm), dextran microspheres (40 μm), trisacryl-gelatin microspheres, silicone particles, ZrO-coated parrolytic carbon beads (212-500 μm) suspended in 3% β-glucan and polyacrylamide were also done in humans or mice. Polymethyl methacrylate microspheres were well tolerated and stable over 9 months.

Phagocytosis of PMMA microspheres (4.3-72 μm) was determined by incubation with U-937 macrophage, XS 106, and SX 52 Langerhans cells as well as HaCaT keratinocytes. U-937 macrophages, keratinocytes, and Langerhans cells phagocytosized PMMA microspheres <20 μm; larger microspheres were not ingested. There was no tumor necrosis factor-alpha (TNF-α) secreted.

The FDA concluded that PMMA microspheres are safe and approved for dermal implantation due to the above data and the evidence that MMA has been removed by the bead processing (use could result in dose of MMA of 10.3 μg/kg).[10]

The PMMA beads range in size from 30 to 42 μm.[9]

The trade name for this product in the United States is now Artefil.[72] Artecoll is the name used outside the United States.

Dental Material

The FDA has issued a class II special controls guidance document for PMMA provisional dental crowns and bridges for new commercial dental material products to be deemed substantially equivalent to legally marketed predicate devices. Manufacturers are required to test for mechanical failure; toxicity and adverse tissue reaction, and identification of improper use. Physical properties to be tested are compressive strength (MPa), flexural strength (MPa), elastic modulus (GPs), intensity (mW/cm^2) for curing (for photo-initiated resins), wavelength (nm) for curing (for photo-initiated resins), depth of cure (mm; for photo-initiated resins), filler particle size distribution (μ), surface hardness (KHN), radiopacity (mm of Al), water sorption ($\mu g/mm^3$), solubility ($\mu g/mm^3$), release profile ($\mu g/mm^3$; if the device contains a releasable agent such as fluoride or nitrate ions), working time (seconds), curing time (seconds; for photo-initiated resins), and setting time (minutes). Biocompatibility is tested according to ISO-10993-5.[45,64,73]

Nonmedical Device Assessment

Acute Oral Toxicity

Polymethyl methacrylate (500 mg/kg in water and carboxymethylcellulose) was orally administered to male ICO:OF1 IFFA CREDO mice (n = 6) after overnight fasting.[74] The mice were observed for 8 days then necropsied. In the first 24 hours, the mice had short time periods of prostration and diarrhea. From day 2 on, there were no clinical signs and all mice survived the observation period. The necropsies were unremarkable.

Ocular Irritation

In an ocular irritation study of a PMMA (0.1 mL; 4.5-8.5 μm) sample using New Zealand rabbits (n = 6), the test sample was placed in the right eye and the untreated left eye was the control.[75] After 24 hours, the eyes were rinsed with sterile water and scored. There were slight signs of irritation on the conjunctiva (redness, swelling, and lacrimation) at 24 hours. Only lacrimation was observed at 48 hours. At 72 hours, 3 of the 6 had recovered and all had recovered by 96 hours. The general behavior of the rabbits was not modified by the test substance. The mean ocular irritation scores were 6.7, 3.7, 1.0, 0, and 0 at 24, 48, 72, and 96 hours, respectively. The authors concluded that PMMA is a slight ocular irritant.

Dermal Irritancy

A dermal patch test was performed on a PMMA (0.5 mL) sample using male New Zealand rabbits (n = 6).[76] The test material was applied to the intact and scarified clipped skin and was left for 24 hours. There was no edema up to 72 hours after patch removal. Five of the rabbits had slight redness on both application sites. The primary irritation score was 0.46 and PMMA was rated a nonirritant.

Clinical Assessment of Safety

A modified Draize human repeat insult patch test (HRIPT) was conducted on the bulk material of a brow pencil (9.723% PMMA) diluted to 70% in water. The test material was applied to the upper arm of the participants (n = 52) and removed after 24 hours under semiocclusion for 9 consecutive applications. The challenge application was applied after a 2-week rest. No skin reactivity was observed in any test participant during

sensitization. The authors[26] concluded that there was no indication of cumulative skin irritation or sensitization of PMMA at 6.8%.

An HRIPT was conducted on a mascara (0.2 g) containing methyl methacrylate crosspolymer (2.0%).[77] The test material was applied to the backs of the participants (n = 106). There was no dermal reactivity during induction or challenge.

In an EpiOcular test of a mascara containing methyl methacrylate crosspolymer (2.0%) diluted to 20% in distilled water, tissue was exposed to the test material for 20 minutes, 1 hour, and 4 hours.[78] The Draize ocular irritation score of 100% methyl methacrylate crosspolymer was calculated to be 0 and classified as nonirritating.

Monomer Sensitivity

After the polymerization process, there is the possibility of unreacted monomer being present within and on the final product. The monomer has been examined and some of the data considered are summarized here.[79] Methyl methacrylate is the residual monomer from the polymerization process in making PMMA. Methyl methacrylate was found to be sensitizing at 25% in guinea pigs.[80] The minimum induction concentration in a guinea pig maximization test was 1 mol/L (100 and 120 ppm).[81] In a local lymph node assay, MMA had an EC3 (stimulation index [SI] of 3 relative to concurrent vehicle-treated controls) of 60% w/v in acetone and 90% w/v in olive oil. Methyl methacrylate was rated as a weak contact allergen.[82]

Sensitization data also were reviewed in the safety assessment of ethyl methacrylate used in the formulation of artificial nail-enhancement products. Ethyl methacrylate was found to be "... safe as used when application is accompanied by directions to avoid skin contact because of the sensitizing potential of ethyl methacrylate."[79] The frequency of positive reactions among all patients tested with ethyl methacrylate was 14 (64%) of 22. The frequency of positive reactions among patients with artificial nails was 7 (64%) of 11, suggesting that the use of artificial nail-enhancement products presented no additional risk. More to the point of considering the potential sensitization of the MMA monomer, the frequency of positive reactions to MMA among all patients was 7 (32%) of 22 and among patients with artificial nails was 1 (10%) of 10. Combining the low frequency of sensitization to MMA with the low level of the monomer in PMMA, the risk of sensitization may be considered low.

Cross- or co-reactivity of ethyl methacrylate and MMA was another concern addressed in the safety assessment of ethyl methacrylate, specifically because of the use of MMA in PMMA bone cements and the possibility that an individual sensitized to ethyl methacrylate might then have an allergic reaction to the bone cement in a necessary medical procedure. The Panel concluded that there were no data supporting any sensitization reactions in patients receiving implants cemented with MMA and that adverse consequences of cross-reactivity of ethyl methacrylate and MMA are not a concern.

Summary

The FDA has already reviewed the safety of PMMA for the use in several medical devices that are implanted into the human body, (IOLs, bone cement, dental fillers, and dermal fillers) that result in far greater systematic exposure than any use in cosmetics. Presuming that the PMMA used in cosmetics is not substantially different (eg, same or lower monomer levels) from PMMA used in medical devices, then the data available to the FDA in support of medical device safety have relevance to safety in cosmetics.

These ingredients are polymers with synthetic sources that are used as film formers, viscosity-increasing agents, binders, and emulsion stabilizers. Commonly used analytical techniques can determine monomer and polymer levels.

The impurity of concern is the monomer MMA. Analysis of PMMA beads used in cosmetic formulations found MMA to be present at <100 ppm. Arsenic and heavy metals are found at low levels.

Polymethyl methacrylate is reported to be used in 892 cosmetic products at 0.01% to 45%; methyl methacrylate crosspolymer in 144 cosmetic products at 0.1% to 14%; and methyl methacrylate/glycol dimethacrylate crosspolymer in 7 products at 0.1% to 3%.

Safety data for use of PMMA in IOLs included monomer levels (< 1%), other leachables, hydrolytic stability, photostability, biocompatibility, in vitro cytotoxicity, local effects at site of implantation, cell damage, genotoxicity, and sensitization. Extensive postimplantation follow-up did not uncover any material-related safety concerns.

Safety data for use of PMMA in bone cements reviewed by the FDA included monomer levels, polymer setting process, and biocompatibility. Other safety data developed for bone cements related to polymerization at the site of use were not relevant to cosmetic use where PMMA is used in its fully polymerized form.

Of the medical devices, the safety data for dermal fillers may be the most relevant to cosmetic use because both use PMMA beads. The FDA reviewed cytotoxicity, mutagenicity, sensitization, irritation, biocompatibility, and TNF-α stimulation data, leading to the approval of dermal fillers with PMMA in the market.

While biocompatibility testing of PMMA in dental material was required by the FDA to support that approval, most of the data requirements related to physical performance.

Additional data indicated that PMMA was not orally toxic to mice at 500 mg/kg. Polymethyl methacrylate was mildly irritating in an eye test and was not a dermal irritant to rabbits. Polymethyl methacrylate was not irritating or sensitizing at 6.8% in an HRIPT test using 52 participants. The same result was obtained in another HRIPT test of PMMA at 2.0% using 106 participants. In an EpiOcular test, PMMA had a Draize ocular irritation score of 0.

Methyl methacrylate, the monomer of PMMA, was sensitizing at 25% in guinea pigs. Methyl methacrylate was a weak contact allergen in a local lymph node assay (LLNA); MMA had an

EC3 of 60% w/v in acetone and 90% w/v in olive oil. Ethyl methacrylate was sensitizing in 64% of participants tested.

Discussion

The CIR Expert Panel used a different approach (compared to past safety assessments) to the assessment of PMMA, methyl methacrylate crosspolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer. The FDA had already reviewed the safety of PMMA for use in several medical devices that are implanted into the human body (IOLs, bone cement, dental fillers, and dermal fillers), which result in far greater systemic exposure than any use in cosmetics. The Panel considered that the PMMA used in cosmetics to be substantially the same as PMMA used in medical devices. Thus, the data available to the FDA in support of medical device safety has relevance to cosmetics. Data made available by industry confirmed that there are no significant differences in the material or in the monomer levels that may be related to PMMA and the other ingredients used in cosmetic products.

The CIR Expert Panel saw no need to review systemic toxicity data on PMMA and related polymers applied to the skin as the safety of this route of exposure can be extrapolated from data on use of these polymers as medical devices, which had already been reviewed and found safe by the FDA. Several of these devices have been approved as implants, resulting in systemic exposures that far exceed the exposure expected for PMMA use in cosmetics.

Polymethyl methacrylate-based cosmetic ingredients are large molecules and remain in particulate form (dispersed) in final preparations and thus will not likely cross the stratum corneum to induce systemic toxicity.

While the residual monomer methyl methacrylate (MMA) has the potential to induce sensitization, the levels in these ingredients were reported to be well below the levels that would induce sensitization to MMA, thus resolving the Panel's concern about sensitization.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure, and their site of deposition within the respiratory system. In practice, aerosols should have at least 99% of their particle diameters in the 10 to 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm. Particles with an aerodynamic diameter of $\leq$10μm are respirable. The smallest diameter of PMMA in cosmetics is 4 μm. However, in aerosols, the particles will not be isolated but in formulation, so the aerosol spray containing PMMA will be of a diameter that will not be respirable. In the absence of inhalation toxicity data, the Panel determined that PMMA and the associated ingredients can be used safely in hair sprays, because the product particle size is not respirable.

Conclusion

Polymethyl methacrylate, methyl methacrylate crosspolymer, and methyl methacrylate/glycol dimethacrylate crosspolymer are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

Author's Note

The 2009 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, MD, FACP; Donald V. Belsito, MD; Curtis D. Klaassen, PhD; Daniel C. Liebler, PhD; Ronald A. Hill, PhD; James G. Marks Jr, MD; Ronald C. Shank, PhD; Thomas J. Slaga, PhD; and Paul W. Snyder, DVM, PhD. The CIR Director is F. Alan Andersen, PhD. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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8

Final Report on the Safety Assessment of Carbomers-934, -910, -934P, -940, -941, and -962

The Carbomers are synthetic, high molecular weight, nonlinear polymers of acrylic acid, cross-linked with a polyalkenyl polyether. The Carbomer polymers are used in cosmetics and emulsifying agents at concentrations up to 50%.

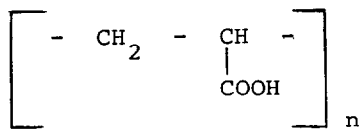
Acute oral animal studies showed that Carbomers-910, -934, -934P, -940, and -941 have low toxicities when ingested. Rabbits showed minimal skin irritation and zero to moderate eye irritation when tested with Carbomers-910 and -934. Subchronic feeding of rats and dogs with Carbomer-934 in the diet resulted in lower than normal body weights, but no pathological changes were observed. Dogs chronically fed Carbomer-934P manifested gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver.

Clinical studies with Carbomers showed that these polymers have low potential for skin irritation and sensitization at concentrations up to 100%. Carbomer-934 demonstrated low potential for phototoxicity and photocontact allergenicity.

On the basis of the available information presented and as qualified in the report, it is concluded that the Carbomers are safe as cosmetic ingredients.

CHEMICAL AND PHYSICAL PROPERTIES

The Carbomer resins (-910, -934, -934P, -940, -941, and -962) are synthetic, high molecular weight, nonlinear polymers of acrylic acid cross-linked with a polyalkenyl polyether. They are chemically similar to each other, differing only in ascending molecular weights (which range from Carbomer-910 to Carbomer-962). They contain between 98.7% and 99.9% acrylic acid. When dried at 80°C for one hour, they contain not less than 56.0% and not more than 68.0% carboxylic acid (−COOH) groups.[1-5] The general structural formula is:[6]



Carbomer-934 is reported to be a polymer of acrylic acid cross-linked with alkyl-sucrose: $CH_2 = CHCH_2$-O-sucrose.[6] Carbomer-934P is the pharmaceutical grade of Carbomer-934.[2] Carbomer-962 is the ammonium salt of Carbomer-941 and contains about 20% NH_3.[7] The exact compositions of the Carbomer polymers are proprietary information.[7]

Carbomers-910 and -962 are two new cosmetic ingredients, and they are not listed in the 1977 *CTFA Cosmetic Ingredient Dictionary*.[2] Carbomers-960 and -961, formerly used in cosmetics, are no longer produced.[8]

The Carbomers are white, fluffy powders with a slight characteristic odor.[5] They are highly ionic and slightly acidic; they are largely insoluble in water and in the majority of common solvents.[3,4] When neutralized with alkaline hydroxides or with amines, they dissolve in water, alcohol, and glycerin.[5] Molecular weights for Carbomers-934, -940, and -941 range from approximately 500,000 to 4,000,000.[9]

The Carbomer polymers are hygroscopic in nature. Because of their ability to absorb and retain water, these polymers swell to many times their original volume. Such swollen particles remain discrete in various mucilaginous or colloidal dispersions. Although swelling is inherently caused by their hydrophilic nature, "maximum volume swell" does not occur in water until the polymers are converted to partial organic or inorganic salts. The increased volume is stable at all pH levels and increases as neutralization increases. Maximum volume occurs at 50–90% neutralization, with a neutralization of 75% normally occurring at pH 7.0.[4]

The finely divided, free-flowing Carbomer powders readily disperse in water to yield a low viscosity acid solution. When neutralized, the solution is transformed into a clear, stable gel. In acidic aqueous media (pH 3.5–4.0), the Carbomers yield dispersions of low to moderate viscosity. Between pH 5.0 and 10.0, the polymers reach their optimal viscosity when they set into an emollient gel. At pH levels above 10, the gel structure collapses and viscosity drops.[10] Carbomer dispersions show increased viscosity with increasing concentration of the polymer. Viscosity may be decreased by adding NaCl to the dispersion.[11]

Cahen et al.[10] reported that " . . . Carboxy vinyl polymer . . . does not form a gel in the acid medium of the stomach, whereas in alkaline medium, gel formation gradually occurs."

Chemical and physical properties of the Carbomers are presented in Table 1.[1,5,7,10,12] Additional data relating to the chemical and physical properties of these polymers are reported elsewhere in the literature.[13-29]

Reactivity

Carbomer-934, -940, and -941 gels undergo oxidative degradation when they are exposed to sunlight. The reaction is known to be catalyzed by trace metals; however, no information on the degradation products has been reported. UV absorbers can be incorporated into Carbomer gels to prevent metal-catalyzed depolymerization which in turn can cause loss of viscosity and emulsion stability.[30-32]

Carbomers may react with amines to form thick and stable emulsions of oils in water.[3]

TABLE 1. Chemical and Physical Properties.[a]

Properties	*Carbomer-910*	*Carbomer-934*	*Carbomer-934P*	*Carbomer-940*	*Carbomer-941*	*Carbomer-962*	*Carbomer (unspec.)*
Loss on Drying (Maximum) (%)	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Viscosity (0.5% aqueous) (CPS)		30,500–39,000	29,400–39,400	40,000–60,000	4,000 min.–11,000 max.		
Viscosity of Neutralized Solution at 25°C: (CPS)							
a. 0.2% Solution		2,000–5,450		15,000–30,000	2,500–6,400		
b. 0.5% Solution		26,500–39,500		45,000–70,000	5,400–11,400		10,000
c. 1.0% Solution							30,000
Clarity of Neutralized Solution				80.0% min.			
Specific Gravity							1.41
pH of 0.5% Solution at 25°C							2.7–3.3
pH of a 1% Water Solution							3.0
Equivalent Weight							71–80
Viscosity of Neutralized Solution containing 2.50 g Carbomer in 500 ml of Water (CPS)							not less than 30,000 and not more than 40,000
Equilibrium Moisture Content at Room Temperature and 50 percent Relative Humidity							8.0%
Bulk Density (lbs./cubic foot)							13
Moisture Content (%)							2.0 max.
Carbon (%)							47.0–50.8
Hydrogen (%)							5.0–6.2
Residue on Ignition (%)							0.1

[a]Data from Refs. 1, 5, 7, 10, and 12.

Methods of Manufacture and Impurities

The Carbomer polymers are manufactured by reflux polymerization of acrylic acid in an inert solvent in the presence of a catalyst; in doing this, a closed system, free of oxygen and water, is used.[9] Details of the manufacturing process are proprietary information.[7]

Impurities for each of the Carbomers are presented in Table 2.[7] The Panel calls attention to the presence of benzene as an impurity in Carbomers and recommends that every effort be made to reduce it to the lowest possible value. Benzene is a known toxic agent and human epidemiological evidence strongly suggests that it is a leukemogenic agent as well.[33-39]

PURPOSE AND FREQUENCY OF USE IN COSMETICS

The Carbomer polymers are supplied as free-flowing powders, but in cosmetic preparations they are frequently used in their neutralized form—that is, as a gel. (In a few preparations, such as aerosol formulations and shaving creams, they are used in the unneutralized form.) The Carbomers are normally used in cosmetics between a pH of 6.0 and 9.0.[9]

The Carbomers are used as thickening, suspending, dispersing, and emulsifying agents.[3,4,9,12,32,33] They are widely used to provide emulsion stability[4,28,29] and rheologic control.[4]

FDA product formulation data are presented in Table 3. These data show that the various Carbomers may be used up to a concentration of 50 percent.[41] However, one industry source reports that in cosmetics, Carbomers are normally used at concentrations below 1.0%. When Carbomers are used in unneutralized form, however, their concentration may be as high as 2.0%.[9]

TABLE 2. Impurities.[a]

Ingredient	Impurities	Typical values
Carbomers-910, -934, -940 and -941	Water	<0.5%
	Benzene	1,800 ppm (5,000 ppm max.)
	Propionic Acid	1,200 ppm
	Acetic Acid	600 ppm
	Acrylic Acid	80 ppm
	Heavy Metals	10 ppm maximum
	Iron	1 ppm
	Arsenic	<1 ppm
	Lead	<0.3 ppm
Carbomer-934P	Same as above except for:	
	Benzene	<100 ppm (100 ppm max.)
Carbomer-962	Water	<0.5%
	Benzene	1,300 ppm (4,000 ppm max.)
	Propionic Acid	1,000 ppm
	Acetic Acid	500 ppm
	Acrylic Acid	60 ppm
	Heavy Metals	10 ppm maximum
	Iron	1 ppm
	Arsenic	<1 ppm
	Lead	<0.3 ppm

[a]Data from Ref. 7.

TABLE 3. Product Formulation Data.[a]

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Carbomer-934		
Lotions, oils, powders, and creams	>0.1–1	4
	≤0.1	1
Other bath preparations	>10–25	1
	>1–5	2
	>0.1–1	2
Eyeliner	>0.1–1	5
Eyeshadow	>0.1–1	20
Mascara	≤0.1	1
Perfumes	>0.1–1	9
Sachets	>0.1–1	10
	≤0.1	1
Other fragrance preparations	>0.1–1	5
Hair conditioners	>0.1–1	3
Permanent waves	>0.1–1	1
Shampoos (noncoloring)	≤0.1	1
Tonics, dressing, and other hair grooming aids	>1–5	1
	>0.1–1	7
Wave sets	>0.1–1	1
Other hair preparations	>1–5	1
	>0.1–1	3
Hair dyes and colors (all types requiring caution statement and patch test)	>0.1–1	1
Other hair coloring preparations	>0.1–1	1
Blushers (all types)	>1–5	4
	>0.1–1	10
Foundations	>1–5	1
	>0.1–1	12
Makeup bases	>0.1–1	2
	≤0.1	2
Rouges	>10–25	1
	>0.1–1	5
Makeup fixatives	≤0.1	1
Other makeup preparations	>0.1–1	2
Cuticle softeners	>0.1–1	3
Dentifrices (aerosol, liquid, pastes, and powders)	>0.1–1	1
Bath soaps and detergents	>0.1–1	1
Deodorants (underarm)	>0.1–1	1
	≤0.1	1
Other personal cleanliness products	>0.1–1	1
Aftershave lotions	>0.1–1	8
Beard softeners	>0.1–1	1
Shaving cream (aerosol, brushless, and lather)	>0.1–1	4
Other shaving preparations	>0.1–1	2
	≤0.1	1
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>1–5	2
	>0.1–1	29
	≤0.1	9
Face, body, and hand (excluding shaving preparations)	>1–5	2
	>0.1–1	68
	≤0.1	18

TABLE 3. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Moisturizing	>1–5	3
	>0.1–1	123
	≤0.1	21
Night	>1–5	1
	>0.1–1	16
	≤0.1	3
Paste masks (mud packs)	≤0.1	7
Wrinkle smoothing (removers)	>0.1–1	4
Other skin care preparations	>1–5	1
	>0.1–1	7
	≤0.1	2
Suntan gels, creams, and liquids	>1–5	1
	>0.1–1	14
	≤0.1	1
	Total	477
Carbomer-934P		
Other bath preparations	>0.1–1	1
Moisturizing	>0.1–1	2
Night	>0.1–1	1
	Total	4
Carbomer-940		
Eyeliner	≤0.1	1
Eyeshadow	>0.1–1	2
Eye makeup remover	>0.1–1	1
Mascara	>0.1–1	1
Other eye makeup preparations	>0.1–1	1
Colognes and toilet waters	>1–5	4
	>0.1–1	12
Perfumes	>0.1–1	1
Sachets	>0.1–1	4
Other fragrance preparations	>1–5	6
	>0.1–1	14
	≤0.1	1
Hair conditioners	>1–5	1
	>0.1–1	4
Tonics, dressing, and other hair grooming aids	>1–5	3
	>0.1–1	15
	≤0.1	2
Wave sets	>1–5	2
	>0.1–1	37
	≤0.1	2
Other hair preparations	>0.1–1	3
Blushers (all types)	>1–5	3
	>0.1–1	27
Foundations	>0.1–1	6
Leg and body paints	>1–5	1
Makeup bases	>0.1–1	1
Rouges	>0.1–1	9
Other makeup preparations	>1–5	4
	>0.1–1	8
Cuticle softeners	>0.1–1	1
	≤0.1	1
Other personal cleanliness products	>0.1–1	1

TABLE 3. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Aftershave lotions	>1-5	1
	>0.1-1	8
Cleansing (cold creams,	>1-5	3
cleansing lotions, liquids,	>0.1-1	18
and pads)	≤0.1	7
Face, body, and hand	>1-5	1
(excluding shaving	>0.1-1	31
preparations)	≤0.1	10
Foot powders and sprays	>0.1-1	1
Moisturizing	>10-25	1
	>1-5	1
	>0.1-1	37
	≤0.1	7
Night	>1-5	2
	>0.1-1	23
Paste masks (mud packs)	>0.1-1	8
	≤0.1	2
Skin fresheners	>0.1-1	6
	≤0.1	3
Wrinkle smoothing (removers)	>0.1-1	1
Other skin care preparations	>0.1-1	18
	≤0.1	1
Suntan gels, creams, and	>1-5	1
liquids	>0.1-1	7
Indoor tanning preparations	>0.1-1	2
Other suntan preparations	>0.1-1	3
	Total	382
Carbomer-941		
Bubble baths	>0.1-1	2
	≤0.1	1
Other bath preparations	>0.1-1	1
Eyeshadow	≤0.1	1
Eye lotion	>0.1-1	1
Eye makeup remover	≤0.1	1
Colognes and toilet waters	>0.1-1	8
Perfumes	>1-5	1
	>0.1-1	2
	≤0.1	1
Sachets	>5-10	2
	>0.1-1	10
Other fragrance	>1-5	1
preparations	>0.1-1	12
	≤0.1	8
Hair conditioners	>0.1-1	1
Tonics, dressing, and other	>0.1-1	2
hair grooming aids	≤0.1	1
Wave sets	>0.1-1	1
Other hair preparations	>0.1-1	4
Blushers (all types)	>0.1-1	1
	≤0.1	1
Lipsticks	>0.1-1	1
Makeup bases	>0.1-1	1
	≤0.1	1
Other makeup preparations	>0.1-1	3
Cuticle softeners	>0.1-1	3

TABLE 3. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Nail creams and lotions	≤0.1	1
Other manicuring preparations	>25-50	1
Aftershave lotions	>0.1-1	5
	≤0.1	3
Other shaving preparation products	>0.1-1	2
	≤0.1	1
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>0.1-1	13
	≤0.1	11
Face, body, and hand (excluding shaving preparations)	>1-5	1
	>0.1-1	23
	≤0.1	20
Moisturizing	>0.1-1	31
	≤0.1	20
Night	≤0.1	3
Skin fresheners	>0.1-1	3
	≤0.1	3
Other skin preparations	>10-25	1
	>0.1-1	4
	≤0.1	1
Suntan gels, creams, and liquids	>0.1-1	1
	≤0.1	1
	Total	221

[a]Data from Ref. 41.

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations (21 CFR 720.4). Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the concentration reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Carbomers can be applied to or come in contact with skin, eyes, mucous membranes, respiratory epithelium, hair, and nails; small amounts are likely to be ingested from dentifrices (Carbomer-934) and lipsticks (Carbomer-941). Product formulations containing one or more of these ingredients may be used from once a week up to several times per day. Many of the products may be expected to remain in contact with the body for as little as a few minutes to as much as a few days. Over the course of several years, each product could be applied hundreds of times.[41]

Non-cosmetic Uses

Pharmaceutical Uses: Carbomer polymers are used in pharmaceutical products as thickening,[3,12,42,43] suspending,[3,5,12,43-47] dispersing,[3] and emulsifying

agents.[3,5,12] They are also used to control the release of medicaments from time-release tablets or from entrapped systems,[48-52] as bulking agents in laxatives,[12] and as bases or vehicles for jellies, ointments, and pastes.[53-57] Spermicidal jellies and ointments formulated in a Carbomer-934 base are particularly effective on human sperm in vitro,[58] and are nonirritating to the vaginal mucosa of rats.[59] Various jellies formulated with Carbomer-934 and -940 are nonirritating to the rabbit eye and skin.[56] Carbomer-934 is currently used in oral pharmaceutical preparations under an over-the-counter label.[12]

Chemical and Industrial Specialities: Carbomers are used in wallpaper removers, waxes, polishes, paints, waterproof and oilproof coatings, emulsion-based lubricants, and printing inks. In latexes, tape adhesives, and solvents Carbomers function as thickeners. In creosote, tars, and asphalts they are used as emulsifiers. They are also employed in suspensions of glass fibers, graphite, powdered metals, and in forming gels with hydrocarbons.[3,12,43]

Additional data relating to the noncosmetic use of the Carbomer polymers are reported elsewhere in the literature.[60-66]

BIOLOGICAL PROPERTIES

General Effects

Carbomer as a Bulk Laxative in Animals: Carbomer-934 was reported by Cahen et al.[10] to have a significant laxative effect on rats, guinea pigs, and dogs. The nature of its laxative activity was essentially different from that of cathartics or saline purgatives and more comparable to the activity of bulk laxatives. In contrast to other hydrophilic laxatives like methylcellulose, Carbomer-934 exhibited a swelling action 20 times its bulk in intestinal fluid and no action in gastric juice. The minimum effective dose for laxative activity in rats was 0.4 g/kg; the laxative effect of this disappeared after 72 hours.

Effect of Carbomer on the Growth and Metabolic Activities of *Aspergillus Niger:* Addition of 0.3% (w/v) Carbomer-934 to fermentation media "enhanced the metabolic activities" of *Aspergillus niger*. Increases in cellular growth, potassium transport, amylase production, and respiration rate were observed; more specifically, the last of these was increased by as much as 200%.[67,68] However, the addition of 0.3% (w/v) Carbomer-934 to growth media did not alter the respiratory quotient or the overall enzyme system for respiration.[69]

Effect of Carbomer on Viral Reverse Transcriptase: De Clercq and Claes[70] reported that Carbomer-934 has a stimulatory effect on the activity of RNA-dependent DNA polymerase (reverse transcriptase) in the Moloney strain of Murine Leukemia Virus (M-MuLV). The addition of Carbomer-934 to a standard in-vitro RNA-dependent DNA polymerase assay mixture containing the M-MuLV virus resulted in a significant increase in both the rate and extent of DNA synthesis. The stimulatory effect was found to be dose-dependent; a "maximum response" was obtained at a concentration of 160 μg Carbomer-934/ml saline.

Bloemers and Van der Horst[71] showed that Carbomer-934 had an inhibitory effect on reverse transcriptase activity in both Rauscher Murine Leukemia Virus (R-MuLV) and Avian Myoblastosis Virus (AMV). When synthetic

poly(A)* templates were used, 50 to 500 μg Carbomer-934/ml saline was strongly inhibitory to R-MuLV reverse transcriptase activity. Employing both synthetic poly(A) and poly(C)† templates, investigators observed strong inhibition of AMV enzyme activity at concentrations of 100–300 μg/ml. The endogenous activity of R-MuLV reverse transcriptase was slightly stimulated at 1 and 5 μg/ml, but concentrations ranging from 5 to 100 μg/ml were inhibitory. According to the authors, "The observed competitive inhibition seems a logical result, because a negatively charged polymer-like Carbopol could be expected to mimic nucleic acids and, thus, to interfere with the binding of the template to the enzyme."[71]

Kumar[72] confirmed Bloemers and Van der Horst's work[71] regarding Carbomer-934's inhibition of reverse transcriptase. Further, he also showed that it was possible to use these inhibitory activities to differentiate viral reverse transcriptase from such closely related enzymes as mammalian r-DNA polymerase.

Effect of Carbomer on the Resistance of Mice to Viral Infection: De Clercq and Luczak[6] reported that intraperitoneal administration of Carbomer-934 imparts to mice a resistance to vaccinia and herpes simplex (Type 1) viral infections. When Carbomer-934 was injected intraperitoneally into mice at a dose of 80 mg/kg four days before intravenous vaccinia virus challenge, the number of pox lesions was significantly reduced relative to the number of such lesions in the controls. However, when Carbomer-934 was injected intramuscularly at a dose of 80 mg/kg four days before vaccinia virus innoculation, the polymer was not effective in reducing pox lesions. An intraperitoneal dose of 100 mg/kg (0.8 mg/mouse) one or four days before intranasal herpes simplex (Type 1) virus challenge significantly reduced mortality caused by viral encephalitis. An intramuscular dose of 100 mg/kg one or four days before virus innoculation, however, failed to confer any significant protection. When female mice were injected intraperitoneally with the polymer at 100 mg/kg (2 mg/mouse), a low titer interferon response was generated. The investigators postulated that the antiviral effects that Carbomer-934 did manifest were brought about by activation of peritoneal macrophages and/or interferon production. Since Carbomer-934 was only effective against viral infection when it was injected intraperitoneally (vs. intramuscularly), the possibility that this compound acted by directly inactivating the virus was dismissed.

Animal Toxicology

General Studies

Acute toxicity: oral

Acute oral studies with rats, guinea pigs, mice, and dogs showed that Carbomers-910, -934, -940, and -941, have low toxicity when ingested. Results of these studies are presented in Table 4.[10,73-80]

Acute toxicity: inhalation

Carbomer-910: Three groups of albino rats (five males and females/group) were exposed to Carbomer-910 dust for four hours at chamber concentrations of

*poly(A) = poly(adenyl acid)
†poly(C) = poly(cytidylic acid)

TABLE 4. Acute Oral Toxicity.[a]

Carbomer	*Concentration (%)*	*Dose and/or amounts administered (g/kg)*	*No. and type of animal*	*No. of animals per dose level*	*Observations and/or comments*	*LD50 (g/kg)*	*Ref.*
-910	30 w/v susp. in corn oil	4.556, 6.834, 10.250, 15.380	16 albino rats	4	Hypoactivity at all dose levels; diarrhea, labored breathing, muscular weakness, rhinitis at 10.250 and 15.380 g/kg. Two out of 4 and 4/4 rats died at 10.250 and 15.380 g/kg, respectively. Gross necropsy of 6 that died revealed pale livers, kidneys and spleens; test material present in stomach and blood noted in GI tract. Body weight gains of 10 survivors w/in normal limits.	10.250 ± 1.203	81
-934	20 in aq. susp.	5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0	80 albino rats	10	All animals survived 14-day observation period in good health.	>40 > 8 (ingred.)	74
-934	20 in aq. susp.	50	10 albino rats	10	All animals survived w/out showing evidence of pharmacological disturbance.	>50 >10 (ingred.)	75
-934 Sample A	25 w/v susp. in corn oil	4.556, 6.834, 10.250	12 albino rats	4	At 10.250 g/kg, 2/4 rats died; all other animals survived w/no pathologic alterations noted. Necropsy of 2 that died revealed hemorrhages in GI tract. Reactions at 10.250 g/kg included hypoactivity, labored breathing, muscular weakness, hemorrhagic rhinitis.	10.250	76

TABLE 4. (Continued.)

Carbomer	Concentration (%)	Dose and/or amounts administered (g/kg)	No. and type of animal	No. of animals per dose level	Observations and/or comments	LD50 (g/kg)	Ref.
-934 Sample B	25 w/v susp. in corn oil	4.556, 6.834, 10.250	12 albino rats	4	At 10.250 g/kg, 4/4 rats died; all other animals survived w/no pathologic alterations noted. Necropsy of 4 that died revealed hemorrhages in GI tract, hardened test material noted in stomach. Reactions at 10.250 g/kg included hypoactivity, labored breathing, muscular weakness, ataxia, prostration, tremors.	8.370	76
-934	7.5 in aq. sol'n	–	230 rats	–		4.1	10
-934	–	–	rats	–		4.3	77
-934	0.20 in formulation	30 of form.	10 rats	10	No deaths or toxic signs reported for the skin moisturizer formulation as tested.	>30 (form.) >.06 (ingred.)	78
-934	0.20 in formulation	25 of form.	10 rats	–	No deaths or toxic signs reported for the skin moisturizer formulation as tested.	>25 (form.) >.05 (ingred.)	78

-934	20 in aq. susp.	5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0	80 albino guinea pigs	10	All animals survived 14-day observation period in good health.	>40 >10 (ingred.)	74
-934	20 in aq. susp.	50	10 albino guinea pigs	10	All animals survived w/out showing evidence of pharmacological disturbance.	>50 >10 (ingred.)	75
-934	7.5 in aq. sol'n	–	124 guinea pigs	–	–	2.5	10
-934	–	–	guinea pigs	–	–	2.5	77
-934	10.0 in aq. sol'n	–	266 albino mice	–	–	4.55	77
-934	–	–	mice	–	–	4.6	77
-934	–	2.24, 4.0, 4.8, 6.0, 8.0, respectively; mixed w/food in ratio 1:10.	16 dogs	2, 5, 2, 5, 2, respectively	Anorexia, vomiting observed 6–24 hrs following Carbomer administration; no relationship between dose and effect noted. No fatalities observed even at highest dose.	–	10
-940	1.0 or 2.5 in aq. sol'n	0.625 max. dose	10 albino rats	–	No deaths.	>0.625	79
-941	1.0 or 2.0 in aq. susp.	0.1, 0.5, 1.0	10 albino rats	10	No deaths during 14-day observation period.	>1.0	80

[a]Data from Refs. 10 and 74–81.

1.01, 1.82, or 5.86 mg/l air.[81] Analysis of the Carbomer particles revealed that 83.4% were 10 microns or less in diameter; particles less than 10 microns were considered respirable. One male and one female rat from the low-dose group, three males and two females from the middle-dose group, and all rats from the high-dose group died during the 14-day observation period. The average two-week body weight gains of all animals were within normal limits. Moreover, "No gross tissue changes attributable to the effects of the test material were observed at necropsy of any of the rats that survived to termination of the study. Gross tissue changes found at necropsy of rats that died during the experiment were considered normal postmortem alterations." Under conditions of this test, the acute LC50 was determined to be 1.71 mg/l air.[81]

Acute toxicity: dermal

Carbomer-910: Carbomer-910 was applied to the skin of four albino rats, two with abraded skin and two with intact skin, at a dose of 3.0 g/kg. The test material was premoistened with water and then held in place for 24 hours by an impervious wrapping. At the end of this period, the wrapping and the residual test material were removed and the animals observed thereafter for 14 days. "No unusual behavioral or systemic reactions" or signs of skin irritation were observed. Under these test conditions, the dermal LD50 was determined to be >3.0 g/kg.[73]

Carbomer-934: A skin moisturizer containing 0.20% Carbomer-934 was tested for acute dermal toxicity in eight albino rabbits (4M, 4F) weighing 2.3 to 2.8 kg. A single 10 g/kg was topically applied to abraded and intact skin. No treatment-related deaths or toxic signs were reported. The acute dermal LD50 and MLD of the skin moisturizer formulation were considered to be >10 g/kg.[78]

Acute toxicity: intravenous administration

Carbomer-934: Three groups of albino rabbits (3 animals/group) were given intravenous injections of either 1%, 2%, or 3% Carbomer-934 in aqueous solution at doses of 5 ml/kg; no deaths resulted.[74]

Skin irritation

Carbomer-910: Using the procedures of the Federal Hazardous Substances Act (FHSA), investigators evaluated the skin irritation potential of 100% Carbomer-910 in six albino rabbits. The test material, 0.5 g moistened with 0.5 ml water, was applied to abraded and intact skin under an impervious wrapping for 24 hours. Erythema was observed at all test sites (abraded and intact) at 24 hours, but by the end of 72 hours this was reduced to barely perceptible erythema at three sites (two abraded and one intact). Slight edema was noted in three rabbits on both abraded and intact skin at 24 hours, but not at 72 hours. A score of 1.3 out of a possible 8.0 was assigned to the polymer. The investigators concluded that Carbomer-910 is not an "irritant" as defined in the FHSA.[81]

Carbomer-934: By means of the Draize procedure,[82] two samples (A and B) of 100% Carbomer-934 were tested for primary skin irritation. Each test sample of 0.5 g was premoistened with water and applied for 24 hours under an impervious wrapping to the abraded and intact skin of six albino rabbits. Three of six animals tested with Sample A showed barely perceptible erythema of the abraded skin at 24 hours, whereas, two of six animals showed the same response on intact skin. Of the six rabbits tested with Sample B, two showed barely perceptible erythema

on both abraded and intact skin at 24 hours. All the tested animals were negative for edema at 24 hours and for edema and erythema at 72 hours. Primary irritation scores for both test materials were 0.2, indicating minimal irritation.[83]

By means of the Draize method, a skin moisturizer formulation containing 0.2% Carbomer-934 was tested for primary skin irritation in 12 rabbits. The animals were exposed to 0.5 g of the moisturizer under occlusive patches for 24 hours. The formulation elicited mild skin irritation with Primary Irritation Indices (PIIs) ranging from 0.5 to 0.9 out of a possible score of 8.0.[78]

Eye irritation

In studies conducted on rabbits, Carbomers-910, -934, -934P, -941, and/or their salts caused zero to moderate eye irritation at concentrations of 0.20%–100%. Results of the various tests are summarized in Table 5, while details of the individual studies are presented in the discussion that follows.[73,78,79,83-91] Since Carbomers are hydroscopic gel-forming polymers, one would expect them to draw water from the eye tissue in such a way as to result in some irritation.[4]

Carbomer-910: Through the use of the FHSA procedures, the eye irritation potential of 100% Carbomer-910 resin was evaluated in six rabbits. At one hour, Carbomer-910 formed a thick gel in the eyes, so that a valid evaluation of the cornea was precluded. Corneal injury was noted in the eyes of two animals at 24 hours and in one at 48 hours. Irritation was noted in the iris of each animal at one hour, of two animals at 24 hours, and of one at 48 hours. Although irritation of the conjunctiva was observed in each animal at 1, 24, and 48 hours, this had cleared by 72 hours. At the one-hour reading, the highest score obtained was 17 out of 110 points. On the basis of these results, Carbomer-910 was classified as an eye "irritant" as defined in the FHSA.[81]

Carbomer-934: Using a modified Draize procedure, investigators tested each of two samples (A and B) of 100% Carbomer-934 resin for eye irritation in six rabbits. Both samples formed a gelatinous film over the cornea, so that no valid one-hour readings of corneal injury could be made. At 24 hours, three rabbits manifested corneal injury caused by Sample A while one animal displayed corneal injury caused by Sample B. Corneal injury persisted through the 14-day observation period in two animals tested with Sample A, while no injury was apparent at the 3-, 7-, or 14-day readings of rabbits tested with Sample B. Sample A produced slight to moderate irritation in the iris and conjunctiva of each animal at one hour and in five of six animals at 24 hours; at 72 hours, no irritation was observed. By 24 hours, sample B had caused slight to moderate irritation in the iris of three animals and moderate irritation in the conjunctiva of two animals; no evidence of irritation was noted at 72 hours. Sample A was considered to be "moderately irritating," insofar as it elicited a score of 15.7 points out of a possible 110. With a score of 7.0 points, Sample B was rated as "minimally irritating."[83]

The following salts at 0.5% in aqueous solution were each tested for eye irritation potential in six rabbits:

(1) Sodium salt of Carbomer-934: pH 7.0;
(2) Sodium salt of Carbomer-934: pH 8.0;
(3) Sodium dodecylamine salt of Carbomer-934: pH 6.8;
(4) Sodium dodecylamine salt of Carbomer-934: pH 7.0;
(5) Sodium dodecylamine salt of Carbomer-934: pH 8.2.

TABLE 5. Eye Irritation.[a]

Carbomer	Concentration (%)	No. of rabbits	Procedure	Conclusion	Ref.
1. *-910*	100	6	FHSA	"irritant"	73
2. *-934*					
Sample A	100	6	Draize	"moderately irritating"	83
Sample B	100	6	Draize	"minimally irritating"	
3a. *-934*					84
sodium salt: pH 7.0	0.5 in aq. sol'n	6	–	mild irritant	
sodium salt: pH 8.0	0.5 in aq. sol'n	6	–	mild irritant	
sodium dodecylamine salt: pH 6.8	0.5 in aq. sol'n	6	–	mild irritant	
sodium dodecylamine salt: pH 7.0	0.5 in aq. sol'n	6	–	mild irritant	
sodium dodecylamine salt: pH 8.2	0.5 in aq. sol'n	6	–	mild irritant	
b. sodium salt: pH 7.0	0.5 in aq. sol'n	1	–	mild irritant	84
sodium salt: pH 8.0	0.5 in aq. sol'n	1	–	mild irritant	
sodium dodecylamine salt: pH 6.8	0.5 in aq. sol'n	1	–	mild irritant	
sodium dodecylamine salt: pH 7.0	0.5 in aq. sol'n	1	–	mild irritant	
sodium dodecylamine salt: pH 8.2	0.5 in aq. sol'n	1	–	mild irritant	
4. *-934*					
sodium PEG-15-Cocamine	0.5 by wt in aq. gel	9	–	". . . no . . . detectable evidence of eye injury . . ."	86
5. *-934*	2.0 in TEA	9	–	". . . may possess very mild irritant properties"	87

6.	*-934 and -934P*					
	-934 neutralized w/TEA-pH 7.0	1.0 in gel	6	FHSA	". . . cannot be considered . . . a mild or severe eye irritation hazard"	88, 89
	-934 neutralized w/NaOH-pH 7.0	1.0 in gel	6	FHSA	". . . cannot be considered . . . a mild or severe eye irritation hazard"	
	-934 P neutralized w/NaOH-pH 7.0	1.0 in gel	6	FHSA	". . . cannot be considered . . . a mild or severe eye irritation hazard"	
	-934					
7a.	skin moisturizer formulation	0.20 in formulation	9	Draize modification	formulation "minimally irritating"	78, 90–91
b.	skin moisturizer formulation	0.20 in formulation	9	Draize modification	formulation "minimally irritating"	
8.	*-940*					
	-940	1.0 in aq. sol'n	6	Draize	minimally irritating	79
	monoisopropanolamine salt	0.4 and 1.0 in aq. sol'n, resp.	6 and 3, resp.	Draize	minimally irritating	
	sodium salt	0.4, and 1.0 in sol'n, resp.	6 and 3, resp.	Draize	minimally irritating	
9.	*-940*					
	di-(2-ethylhexyl)amine salt	1.0 in aq. susp.	10	–	". . . no . . . detectable evidence of eye injury . . ."	86
10.	*-941*					
	-941	1.0 in aq. susp.	4	–	Practically nonirritating	85
	sodium salt	1.0 in aq. susp.	4	–	Practically nonirritating	
	monoisopropylamine salt	1.0 in aq. susp.	4	–	Practically nonirritating	

[a]Data from Refs. 73, 78, 79, and 83–91.

Quantities varying from 0.01 to 1.0 ml were instilled into the eyes in a single application. Slight corneal injury and slight to severe hyperemia of the conjunctiva and sclera were frequently noted 24 hours after instillation; however, by 72 hours there was complete recovery in most of the eyes so affected. In a second test, each of the five Carbomer-934 salts (0.1 ml) was instilled into the eye of one rabbit every day for five days. Again, corneal injury and hyperemia of the conjunctiva and sclera were frequently observed, with most symptoms disappearing 72 hours after the final treatment. The investigators concluded that "Any of these compounds at 0.5% aqueous solutions, if accidentally introduced into the eyes of workmen, may produce mild irritation."[84]

An aqueous gel containing 0.5% by weight sodium-PEG-15 Cocamine salt of Carbomer-934 was instilled into the right eye of each of nine albino rabbits. Eyes were examined at one-half hour and 24 hours post-instillation. The results indicated that "in no instance was there any detectable evidence of eye injury . . . "[86]

A triethanolamine solution containing 2.0% Carbomer-934 was instilled into one eye of each of nine albino rabbits. Twenty-four hours later, seven animals showed corneal epithelial damage, while two animals showed no eye injury. Seventy-two hours after instillation, only one of the original seven affected eyes still manifested corneal damage. The investigators concluded that Carbomer-934 ". . . may possess very mild irritant properties"; however, they also stated that "Reservation may be placed on that conclusion in the absence of eye irritation testing with triethanolamine as a control."[87]

According to the method outlined in *Principles and Procedures for Evaluating the Toxicity of Household Substances,*[89] a 1.0% gel of each of the following materials (neutralized to pH 7.0) was tested for eye irritation potential in six albino rabbits:

(1) Carbomer-934: neutralized with triethanolamine (TEA);
(2) Carbomer-934: neutralized with sodium hydroxide (NaOH);
(3) Carbomer-934P: neutralized with sodium hydroxide (NaOH).

Carbomer-934 neutralized with TEA caused superficial corneal damage in one of six rabbits 24 hours after instillation; however, at the 48-hour reading, this eye had cleared, and it remained clear 72-hours post-instillation. At 48 hours, Carbomer-934 neutralized with NaOH caused conjunctivitis and slight dullness of the cornea in one of the six rabbits that were tested; at 72 hours these changes had disappeared. Carbomer-934P neutralized with NaOH produced no corneal damage. According to the investigators, "These tests must be considered negative since only one of the six rabbits tested by exposure to any test compound demonstrated any reaction. Accordingly, under the provisions . . . of the Hazardous Substances Labelling Act, these materials . . . cannot be considered as constituting a mild or severe eye irritation hazard."[88]

Through the use of a modified Draize procedure, a skin moisturizer containing 0.20% Carbomer-934 was tested for eye irritation potential in nine rabbits.[90] While six of the rabbit eyes remained unwashed, three of them were washed 30 seconds after instillation of the test material. Generally, irritation was characterized by mild conjunctivitis and mild irititis, though the level of irritation was lower in the washed eyes; all eyes were normal by 72 hours. According to the classification system of Kay and Calandra,[91] the moisturizer formulation was considered "minimally irritating."[78] In a second test, a new group of nine rabbits

displayed responses similar to those of the first when they were exposed to the same formulation and concentration.[78,90-91]

Carbomer-940: Aqueous solutions of Carbomer-940 (1.0%), the monoisopropanolamine salt of Carbomer-940 (0.4% and 1.0%), and the sodium salt of Carbomer-940 (0.4% and 1.0%) were tested for eye irritation potential in 24 rabbits. Approximately 1 ml of each test substance was introduced into the conjunctival sac; the eyes were then scored by the Draize method (max. score = 110). At the one-hour reading, minimal eye irritation was observed in all animals for all three test substances; the maximum score in any instance was 4.0. The incidence of irritation was reduced to half the animals at 24 hours (max. score = 2.0) and to one animal at 48 hours (score = 2.0). At 72 hours post-instillation, scores for each test material were 0. The investigators considered Carbomer-940 and its sodium and monoisopropanolamine salts to be at most minimally irritating.[79]

An aqueous suspension containing 1.0 percent by weight di-(2-ethylhexyl) amine salt of Carbomer-940 was instilled into the right eye of each of ten albino rabbits. Observations for eye irritation were made at one and 24 hours. "In no instance was there any detectable evidence of eye injury . . . ".[86]

Carbomer-941: Aqueous solutions containing 1.0% by weight Carbomer-941, sodium salt of Carbomer-941, or monoisopropylamine salt of Carbomer-941 were tested for eye irritation potential. Each test material was instilled into the right eye of each of four albino rabbits by a single application. Seven of the 12 animals that were tested reacted immediately showing redness of the conjunctiva; there was no reaction on the part of five rabbits. Of the seven rabbits showing immediate eye reactions, one rabbit showed irritation to the Carbomer-941 solution, two to the solution containing the sodium salt of Carbomer-941, and four to the solution containing the monoisopropylamine salt of Carbomer-941. No irritation was observed for any of the test materials on Days 1, 2, or 3 post-instillation.[85]

Subchronic toxicity

Carbomer-934: Five groups of rats (eight rats/group) were administered Carbomer-934 in the diet for 49 days at daily doses of either 0.055, 0.133, 0.3, 0.95, or 5.0 g/kg. Animals receiving 5.0 g/kg daily showed a significant reduction in body weight; however, when the Carbomer-934 was withdrawn from their diet on Day 30, their weights increased normally. No deaths occurred at any of the dose levels.[10]

Carbomer-934P: For 21 days, male and female albino rats were fed Carbomer-934P at dietary levels of either 0% (10 rats) or 5.0% (20 rats). Male rats consumed less food and gained less body weight than did controls. With regard to females, food consumption and weight gains were comparable to those of controls. No abnormal reactions or deaths occurred during the study.[92]

Four groups of rats (30 animals/group) were fed Carbomer-934P at dietary levels of either 0%, 0.2%, 1.0%, or 5.0% for 90 days. Rats to which doses of less than 5.0% were administered showed no ill effects, but the growth of those on 5.0% was stunted. No differences were observed between test and control animals with respect to hematology, blood chemistry, urinalyses, or gross pathology. In rats on the highest dose, absolute liver weights and liver to body and brain weight ratios were reduced; however, this reduction was not accompanied by gross or microscopic pathologic changes. Other organ-weight data revealed no significant differences between treated and untreated animals.[93]

Four groups of beagle dogs (eight animals/group) were fed Carbomer-934P at dietary levels of either 0%, 0.2%, 1.0%, or 5.0% for 90 days. No significant differences between treated and control animals were observed with respect to mortality, food consumption, behavior, chemistry, urinalyses, liver-function tests (for bromosulfophthalein retention), organ weights, organ-to-body and brain-weight ratios, gross pathology, or histopathology. Animals receiving less than 5.0% Carbomer-934P gained weight normally; however, those receiving 5.0% had retarded growth. Although erythrocyte counts, hemoglobin concentrations, and hematocrit values of the high-dose group were also lowered, the values remained within normal limits. Hematologic values of dogs receiving 0.2% and 1.0% were comparable to those of controls.[94]

Chronic toxicity

Carbomer-934: For five days a week over periods of up to 32 months (960 days), dogs received Carbomer-934, in the diets, at doses of either 0, 0.1, 0.5, or 1.0 g/kg. Gross and microscopic examination of tissues revealed no abnormalities. Body and organ weights were also normal. The blood of treated animals showed no deviation from that of controls with regard to complete blood count (CBC), hematocrit, or alkali reserve. Some of the dogs receiving 0.1 g/kg daily for four and one-half months were mated successfully, and the pups born to them were normal.[10]

Carbomer-934P: Carbomer-934P was fed at dietary levels of 0%, 0.1%, 0.5%, and 5.0% to groups of 50, 100, 100, and 100 albino rats, respectively, for six and one-half months. Whereas growth patterns of animals receiving concentrations less than 5.0% were normal, the rats which received 5.0% manifested reduced body weights. (This weight depression, however, was not statistically confirmed.) No significant differences were noted between treated and control animals with respect to food consumption, behavior, or mortality. Hematologic studies, blood chemistries, and urinalyses of the 5% group were also comparable to those of controls. Gonad weights, gonad-to-body weight ratios, and gonad-to-brain weight ratios of females in the 5.0% group were elevated, as were heart weights, heart-to-body weight ratios, and heart-to-brain weight ratios of females in the 0.50% and 5.0% groups. Heart weights and heart-to-brain weight ratios among males in the 5.0% group were lowered, while liver-to-body weight ratios of females receiving 0.1% were elevated. Organ weights and ratios of all other test animals were normal. Gross and microscopic pathological findings of all treated animals were comparable to those of controls.[95]

Beagle dogs were orally administered gelatin capsules containing Carbomer-934P for seven days a week over a period of six and one-half months (200 days). Doses of 0, 0.1, 0.5, and 1.0 g/kg were given to 6, 12, 12, and 12 dogs, respectively. No significant differences were observed between treated and control animals with respect to body weight, food consumption, mortality, behavior, hematology, blood chemistries, urinalyses, or organ weights. Most animals receiving 0.5 and 1.0 g/kg showed gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver. There were no other pathological findings.[96]

Clinical Assessment of Safety

Primary Skin Irritation and Sensitization Studies: Clinical studies with Carbomer-934 and its various salts showed that these polymers have low poten-

tial for skin irritation and sensitization at concentrations of 0.5%, 5.0%, 10.0%, and 100%. When tested at 1.0% concentration, Carbomers-940, -941, and their various salts also showed low potential for human skin irritation and sensitization. Further, clinical studies with formulations containing up to 0.25% Carbomer-934 demonstrated that the products have low potential for both skin irritation and sensitization. These tests are individually discussed below; results are summarized in Table 6.

Carbomer-934: Carbomer-934 was applied daily for five days to skin on the backs of 200 human subjects, half of them men and half women; the polymer was put on each subject in two different forms—as a dry resin and as a 10% aqueous solution under occlusive patches. After a three-week rest period, the material was reapplied to the backs of the same subjects for one 48-hour period. None of the test individuals exhibited any evidence of skin irritation or sensitization. The same lot of Carbomer-934 was applied as a dry resin under occlusive patches to the backs of 50 human subjects (25 males and 25 females) for a 24-hour period, every other day, for 15 applications (30 days). After a three-week rest period, the polymer was reapplied for one 48-hour period. No evidence of skin irritation or sensitization was observed.[74]

In a repeated insult patch test, Carbomer-934 was applied as a dry resin to skin on the backs of 50 human subjects (25 males and 25 females) for 24 hours, every other day, for 15 applications (30 days). After a three-week rest period, the polymer was reapplied to the backs for one 48-hour period. No evidence of skin irritation or sensitization was observed.[75]

In a repeated insult patch test, Carbomer-934 was applied as a dry resin and as a 10% (w/v) aqueous solution to skin on the backs of 50 human subjects (25 males and 25 females). Each test material was applied every other day for a total of 15 applications (30 days). Following a two-week rest period, all subjects were given a single challenge application. Forty-eight of the 50 subjects tested with the dry resin showed no irritation reaction (scores = 0), while two individuals scored single 1+ reactions. No reactions occurred in any subject as a result of the challenge application. Of the 50 subjects tested with 10% (w/v) Carbomer-934, 44 showed no irritation reaction, while six individuals showed at most only 1+ reactions. One of the 50 subjects showed a 1+ reaction as a result of the challenge application. In this study, the investigators concluded that Carbomer-934 demonstrated a low potential for primary skin irritation and sensitization.[97]

The following salts at 0.5% in aqueous solution were tested for human skin sensitization potential:

(1) Sodium salt of Carbomer-934: pH 8.0;
(2) Sodium dodecylamine salt of Carbomer-934: pH 6.8;
(3) Sodium dodecylamine salt of Carbomer-934: pH 7.0;
(4) Sodium dodecylamine salt of Carbomer-934: pH 8.2.

Sixty-five subjects (28 males and 37 females) ranging in age from five months to 86 years were selected for study; 50 of these subjects were white and 14 were black. After being applied in a single drop to the previously cleaned skin, each test material was covered with a patch. Every site was inspected daily, and a new drop of test solution was applied each day for 15 days. After a one-week rest, test substances were reapplied for a single 24-hour period. Daily inspections made through the 27th day revealed no reactions to any of the test materials.[101]

The sodium PEG-15 Cocamine salt of Carbomer-934 was tested for skin irrita-

TABLE 6. Human Skin Irritation and Sensitization Studies.[a]

Carbomer	*Conc. (%)*	*Method applied to skin*	*No. of subjects*	*Conclusion/Comments*	*Ref.*
-934	100 (dry resin)	Applied to skin daily for 5 days; occlusive patches; reapplied for 48 hrs. after 3-wk rest	200	No skin irritation or sensitization	74
-934	10 in aq. sol'n.	Applied to skin daily for 5 days; occlusive patches; reapplied for 48 hrs. after 3-wk rest	200	No skin irritation or sensitization	74
-934	100 (dry resin)	Applied to skin every other day for 30 days; occlusive patches; re-applied for 48 hrs. after 3-wk rest	50	No skin irritation or sensitization	74
-934	100 (dry resin)	Applied to skin every other day for 30 days; reapplied for 48 hrs. after 3-wk rest	50	No skin irritation or sensitization	75
-934	100 (dry resin)	Applied to skin every other day for 30 days; challenge after 2-wk rest	50	2/50 showed single 1+ reactions for skin irritation; no sensitization observed	97
-934	10 in aq. sol'n.	Applied to skin every other day for 30 days; challenge after 2-wk rest	50	6/50 showed at most only two 1+ reactions for skin irritation; 1/50 showed single 1+ reaction to challenge. In this study, the polymer demonstrated a low potential for primary skin irritation and sensitization.	97
-934 Sodium salt pH 8.0	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80

Sodium dodecyl-amine salt pH 6.8	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80
Sodium dodecyl-amine salt pH 7.0	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80
Sodium dodecyl-amine salt pH 8.2	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80
-934					
Sodium PEG-15 Cocamine salt	0.5 in aq. gel	Applied to skin daily for 14 days; reapplied for 24 hrs. after 6 days rest	50	No visible reactions; however, 2/50 complained of itching. Investigators concluded that the polymer was neither a primary skin irritant nor a sensitizer.	86
-934					
Sample A	5 in aq. gel	Applied to skin every other day for total of 9 induction patches; reapplied for 24 hrs after 2-wk rest	50	2/50 demonstrated single 2.0± skin irritation reactions (max. score = 8.0); no sensitization observed. Investigators concluded that material was neither a primary skin irritant nor sensitizer.	98
Sample B	5 in aq. gel	Applied to skin every other day for total of 9 induction patches; reapplied for 24 hrs after 2-wk rest	50	4/50 demonstrated a total of five skin irritation reactions: 3 reactions were 1.0± and 2 reactions were 2.0± (max. score = 8.0): no sensitization observed. Investigators concluded that material was neither a primary skin irritant nor sensitizer.	98
-934	0.20 in skin moisturizer	Applied to skin daily for 10 days (Kligman and Wooding, 1967)	10	No instances of primary irritation observed	78
-934	0.20 in skin moisturizer	Applied to skin 3 times a day for 28 days	30	No instances of skin irritation or sensitization were observed; however, investigators concluded that formulation has a low potential for both skin irritation and sensitization.	78

TABLE 6. (Continued.)

Carbomer	*Conc. (%)*	*Method applied to skin*	*No. of subjects*	*Conclusion/Comments*	*Ref.*
-934	0.20 in perfumed skin moisturizer	Applied to skin 3 times a day for 28 days	50	1/50 demonstrated a minimal facial erythema on day 28. Investigators concluded that formulation has low potential for skin irritation and sensitization.	78
-934	0.25 in perfumed skin moisturizer	Applied to skin 3 times a day for 28 days	50	No observed reactions. Investigators concluded that formulation has a low potential for skin irritation and sensitization.	78
-934	0.20 in non-perfumed skin moisturizer	Applied to skin 3 times a day for 28 days	50	2/50 reacted with doubtful to minimal erythema. Investigators concluded that formulation has low potential for skin irritation and sensitization.	78
-934	0.15 in moisturizing lotion	Applied to skin every other day for 3 wks; challenge after 2-wk rest (Draize, 1959)	94	The formulation elicited "little or no primary irritation" and no sensitization.	99
-934	0.20 in non-perfumed skin moisturizer	Kligman Maximization Procedure (Kligman, 1966)	25	Most subjects showed slight erythema at challenge, but investigators attributed this to sodium lauryl sulfate. Investigators concluded that formulation was unlikely to present risk of contact sensitization. Repeat of test with a second group showed similar results.	78
-934	0.25 in skin moisturizer	Kligman modified Maximization Procedure (Kligman and Epstein, 1975)	25	No observed reactions. Investigators concluded that formulation was unlikely to present a risk of contact sensitization.	78
-940	1 in aq. gel	Applied to skin essentially every other day for 15 days; 24-hr challenge after 1-wk rest.	68	No skin irritation or sensitization.	81

Sodium salt	1 in aq. gel	Applied to skin essentially every other day for 15 days; 24-hr challenge after 1-wk rest.	68	No skin irritation or sensitization.	81
Monoisopropanolamine salt	1 in aq. gel	Applied to skin essentially every other day for 15 days; 24-hr challenge after 1-wk rest	68	No skin irritation or sensitization.	81
-941	1 in aq. sol'n.	Applied to skin daily for 15 days; occlusive patches; reapplied for 24 hrs following 1 wk rest.	58	No skin irritation or sensitization.	100
Sodium salt	1 in aq. sol'n.	Applied to skin daily for 15 days; occlusive patches; reapplied for 24 hrs following 1 wk rest.	58	No skin irritation or sensitization.	100
Monoisopropanolamine salt	1 in aq. sol'n.	Applied to skin daily for 15 days; occlusive patches; reapplied for 24 hrs following 1 wk rest.	58	No skin irritation or sensitization.	100

[a]Data from Refs. 74, 75, 78, 80, 81, 86, and 97–100.

tion and sensitization on 50 white human subjects, 38 of them males and 12 females, aged 20–79. An aqueous gel containing 0.5% of the test material was applied to the arm of each subject daily for 14 days. After a six-day rest, the investigators reapplied the test material for a single 24-hour period. The sites were examined on four subsequent days. There were no visible reactions to any of the applications; however, on days six through ten, two subjects complained of itching at the test sites. The investigators concluded that the test material was neither a primary skin irritant nor a sensitizer.[86]

In a repeated insult patch test, two samples (A and B) of 5.0% Carbomer-934 in deionized water were evaluated for their skin irritation and sensitization potential on 50 human subjects. The test population ranged in age from 18 to 47 and consisted of 29 males (28 whites and 1 black), and 21 females (19 whites and 2 Asians). Each test material was applied to the skin for 24 hours on Monday, Wednesday, and Thursday for a total of nine induction patches. After the ninth patch, a rest period of two weeks elapsed before a single 24-hour challenge patch was applied. Of the 50 subjects tested with Sample A, 48 showed no irritation, while two demonstrated single 2.0± reactions (max. score = 8.0). Thus, the overall incidence of irritation reaction during the nine induction patches on 50 subjects was 2/450 or 0.4 percent. Forty-six of the 50 subjects tested with Sample B showed no irritation, while four individuals demonstrated a total of five reactions. Of these five reactions on the skin of four reactors, three were 1.0± and two were 2.0± (max. score = 8.0). Thus, the overall incidence of irritation reaction during the nine induction patches on 50 subjects was 5/450 or 1.1%. In no subject was there evidence of skin sensitization to either sample. On the basis of the "incidence" and "severity" of the reactions to these repeated tests, the investigators concluded that the test materials were neither primary skin irritants nor sensitizers.[98]

The procedure of Kligman and Wooding[102] was used on 10 normal, adult subjects to test a skin moisturizer containing 0.20 percent Carbomer-934 for skin irritation potential. Approximately 0.3 ml of undiluted moisturizer was applied every day for 10 days under an occlusive patch. No instances of primary irritation were observed.[78]

In a safety-in-use study, a skin moisturizer containing 0.20% Carbomer-934 was tested on 30 adult women for its skin irritation and sensitization potential. Three times a day for 28 days, the undiluted product was applied to facial and periorbital areas. Examinations were conducted at 14 and 28 days for facial, periorbital, conjunctival, and mucous membrane irritation. Occlusive patches were applied pre- and post-treatment. No instances of skin irritation or sensitization were observed in any of the test subjects. The investigators concluded that the formulation has a low potential for skin irritation and sensitization "under conditions of normal intended use."[78]

In a second safety-in-use study, three groups of 50 adult women were tested with either a perfumed skin moisturizer which contained 0.20% or 0.25% Carbomer-934, or a nonperfumed variation of the moisturizer which contained 0.20% Carbomer-934. Three times a day for 28 days, the undiluted products were applied to facial and periorbital areas. Occlusive patches were applied pre- and post-treatment. No instances of mucous membrane, periorbital, or conjunctival inflammation were observed. There were no instances of facial erythema, except in one subject to whom the perfumed formulation containing 0.20% Carbomer-934 had been applied; this individual demonstrated a minimal facial

erythema on Day 28. Of the 150 subjects tested, only two on the nonperfumed formulation reacted to the post-study patches, one with minimal (1+) erythema at 24 and 48 hours, and one with doubtful (±) erythema at 24 hours. The investigators concluded that the formulations have low potential for irritation and sensitization "under conditions of normal intended use."[78]

By means of a modified version of the repeated insult test of Draize,[90] a moisturizing lotion containing 0.15% Carbomer-934 was tested for its skin irritation and sensitization potential. Of the 112 adult men and women selected for study, only 94 completed the program. The 18 panelists who left the evaluation protocol did so for causes unrelated to reactions to the test material. A patch containing 0.2 g of the lotion was applied to the back of each panelist for 24 hours on Monday, Wednesday, and Friday for three consecutive weeks. Duplicate challenge applications of the test material were made two weeks after the final serial applications, one patch to the original site and one to an adjacent site. The test sites were scored just prior to the patch applications on the second through the ninth visits and on the tenth visit. The challenge application sites were scored at 48 and 96 hours after application. The moisturizing lotion elicited "little or no primary irritation" and no sensitization.[99]

Using the Kligman Maximization Procedure,[103] investigators tested an undiluted, nonperfumed skin moisturizer containing 0.20% Carbomer-934 for its sensitization potential on 25 human subjects. At challenge, most subjects showed slight erythema, a phenomenon which the investigators attributed to sodium lauryl sulfate. Four cases of definite erythema (±) were observed at 48 hours, but only one was still evident at 72 hours. The investigators did not consider these four reactions to be the result of contact sensitization. On the basis of the maximization grading scale, the moisturizer formulation was rated the lowest grade (i.e., Grade 1, a weak potential sensitizer) and was considered "unlikely to present a risk of contact sensitization under conditions of normal intended use."[78] In a second test, a second group of 25 subjects displayed similar responses when they were exposed to the same formulation and concentration.[78,103]

Through the use of Kligman's modified Maximization Procedure,[104] an undiluted skin moisturizer containing 0.25% Carbomer-934 was tested for its sensitization potential on 25 human subjects. No reactions were observed in any of the test subjects. On the basis of the maximization grading scale, the moisturizer formulation was rated the lowest grade (i.e., Grade 1, a weak potential sensitizer) and was considered "unlikely to present a risk of contact sensitization under conditions of normal intended use."[78]

Carbomer-940: Aqueous gels containing 1.0% Carbomer-940, 1.0% sodium salt of Carbomer-940, and 1.0% monoisopropanolamine salt of Carbomer-940 were applied, under occlusive patches, to the skin of 68 subjects. The test population consisted of 36 men and 32 women ranging in age from 18 to 80; nine of the subjects were black and 59 were white. On Days 2, 3, 5, 7, 11, and 15, the patches were removed and new test material was reapplied. After a one-week rest period, the materials were reapplied for 24 hours. No skin irritation or sensitization was observed for any of the test materials.[81]

An aqueous suspension containing 1.0 percent by weight di-(2-ethylhexyl)-amine salt of Carbomer-940 was tested on 50 white subjects (38 men and 12 women) aged 20–79. The test material was applied daily to the arm for 14 days. Following a six-day rest period, the material was reapplied for 24 hours, and the sites examined on the four subsequent days. Two subjects complained of itching

at the test site on Days 6, 7, 8, 9, and 10; however, no visible evidence of irritation or sensitization could be detected.[86]

Carbomer-941: Aqueous solutions of 1.0% Carbomer-941, 1.0% sodium salt of Carbomer-941, and 1.0% monoisopropanolamine salt of Carbomer-941 were tested on 58 hospitalized subjects (32 men and 26 women) aged 18–78. A drop of each test material was applied daily, under occlusive patches, to the skin of the chest for a total of 15 applications. After a one-week rest period, the test materials were reapplied for one 24-hour period. (The study was discontinued on six subjects because they were discharged from the hospital.) No primary skin irritation or sensitization was observed in any subject for any of the test materials.[100]

Photo-Testing

Carbomer-934: A skin moisturizer containing 0.25% Carbomer-934 was tested for phototoxicity on ten normal adult subjects. The material was applied (5 $\mu l/cm^2$) undiluted under occlusive patches and after 6 and 24 hours of contact, the sites irradiated with a solar simulator. No instances of phototoxicity were observed. The investigators concluded that this formulation "is unlikely to present a risk of phototoxicity under conditions of normal intended use."[78]

Twenty-five normal, adult subjects were tested with a skin moisturizer containing 0.25% Carbomer-934 for photo-contact allergenicity. During the induction period, the material was applied (5 $\mu l/cm^2$) under occlusive patches for 24 hours and then irradiated with a solar simulator; this procedure was repeated twice a week until there was a total of six exposures for each subject. A challenge was performed ten days after the last induction exposure. No instances of photo-contact allergenicity were observed. The investigators concluded that the formulation has "a low potential for photo-contact allergenicity under conditions of normal intended use."[78]

Miscellaneous Studies

Carbomer-934: Carbomer-934 was clinically tested as a bulk laxative over a period of several months. Hospitalized patients given tablets of the polymer showed no deleterious effects.[12]

SUMMARY

The Carbomers are synthetic, high molecular weight, nonlinear polymers of acrylic acid, cross-linked with a polyalkenyl polyether. These polymers are hygroscopic and, when exposed to sunlight, they undergo oxidative degradation. Reported impurities for the Carbomer resins include water, benzene, propionic acid, acetic acid, acrylic acid, heavy metals, iron, arsenic, and lead. The Panel calls attention to the presence of benzene as an impurity in Carbomers and recommends that every effort be made to reduce it to the lowest possible value.

Although supplied as free flowing powders, the Carbomer polymers are frequently used in cosmetic preparations as gels. They function as thickening, suspending, dispersing, and emulsifying agents, and they are also used to provide emulsion stability and rheologic control. Concentrations in cosmetic formulations are reported to vary between $\leq 0.1\%$ and 50%, with most formulations containing concentrations below 1.0%. Products incorporating these polymers are applied to or come in contact with skin, eyes, mucous membranes,

respiratory epithelium, hair and nails; small amounts of Carbomers are likely to be ingested in dentifrices and lipsticks.

Acute oral studies with rats, guinea pigs, mice, and dogs showed that Carbomers-910, -934, -940, and -941 have low toxicities when ingested. The inhalation LC50 of Carbomer-910 in albino rats was 1.71 mg/l. The dermal LD50 of rats exposed to Carbomer-910 was > 3.0 g/kg. No mortalities occurred in rabbits injected intravenously with 1%, 2%, or 3% Carbomer-934 in aqueous solution at a dose of 5 ml/kg. Rabbits showed minimal skin irritation when tested with 100% Carbomer-910 or -934, and zero to moderate eye irritation when tested with Carbomers-910, -934, -934P, -940, -941, and/or their various salts at concentrations of 0.20–100%.

Subchronic feeding of rats with doses up to 5.0 g/kg/day Carbomer-934 (49 days) and of rats and dogs with up to 5.0% Carbomer-934P in the diet (21 and/or 90 days) resulted in lower than normal body weights. In rats fed Carbomer-934P at dietary levels of 5.0% for 90 days, absolute liver weights and liver to body and brain weight ratios were reduced, but no pathological changes were observed.

When dogs were chronically fed up to 1.0 g/kg/day Carbomer-934 (32 months) or -934P (six and one-half months), and when rats chronically received less than 5.0% Carbomer-934P in their diet (six and one-half months), there was no significant effect on body weight, food consumption, mortality, behavior, or blood chemistries. Hematology, gross pathology, histology, and urinalyses of treated animals were comparable to those of controls. Rats fed Carbomer-934P at dietary levels of 0.1%, 0.5%, or 5.0% for six and one-half months exhibited various organ weight changes. Dogs fed 0.5 or 1.0 g/kg/day Carbomer-934P for six and one-half months manifested gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver.

Clinical studies with Carbomer-934 and its various salts showed that these polymers have low potential for skin irritation and sensitization at concentrations of 0.5%, 5.0%, 10.0%, and 100%. When tested on humans at 1.0% concentration, Carbomers-940, -941, and their various salts also demonstrated low potential for skin irritation and sensitization. Further, formulations containing up to 0.25% Carbomer-934 demonstrated low potential for human skin irritation, sensitization, phototoxicity, and photo-contact allergenicity.

The following data were not available for Carbomers-910, -934, -934P, -940, -941, or -962: (1) exact structural composition; (2) details of manufacturing process; (3) analytical methods; (4) potential interactions with other ingredients; (5) absorption; (6) metabolism; (7) excretion; (8) teratogenesis; (9) mutagenesis; and (10) carcinogenesis.

Clinical data for assessing the skin irritation and sensitization potential of Carbomer-940 and -941 were limited to studies in which concentrations of only 1.0% were tested. Clinical data for assessing phototoxicity and photo-contact allergenicity were limited to formulation studies in which concentrations of only 0.25% Carbomer-934 were tested. No clinical studies were reported for Carbomers-910, -934P, or -962.

CONCLUSION

On the basis of the available information presented in this report, and as the information is qualified in the summary, the Panel concludes that the Carbomers are safe as cosmetic ingredients in the present practices of use and concentration.

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ACRYLATES COPOLYMERS – ORIGINAL REVIEW

April 3-4, 1997

Special presentations to the Panel on … and on Acrylate Copolymers (by Dr. Ian Cottrell) were made during the closed session. Dr. Bergfeld thanked Dr. McEwen for making arrangements for these presentations. She remarked that the Panel found the information relating to … acrylate copolymers in cosmetic products very helpful.

June 5, 1997

At the June 5, 1997 Team meetings, informal data requests on this group of ingredients were made by both the Belsito and Schroeter Teams. The combined list of data requested from industry is included below:

1. Current concentration of use data
2. (Chemical properties and method of manufacture; including impurities data, especially unreacted monomers, precursors, catalysts, plasticizers, etc.
3. Dependent on the amount of unreacted monomer, etc., dermal reproductive/developmental toxicity data may be needed
4. Ocular irritation data at concentration of use, if available
5. Skin irritation and sensitization data on Acrylates Copolymer and/or Styrene Acrylates at concentrations of use
6. Two genotoxicity studies, one using a mammalian system, on Acrylates Copolymer of Styrene Acrylates Copolymer and on Acrylates/VA Copolymer; if positive, a two-year dermal carcinogenicity assay performed using NTP methods is needed

In response to the above data requests, the following types of studies were received prior to (but after meeting materials had been mailed) the present meeting: impurities analysis, acute oral toxicity, acute inhalation toxicity, dermal irritation, ocular irritation, repeated insult patch test, and Ames mutagenicity test. Having briefly reviewed these studies for the first time on the preceding day, the Panel noted that data on Acrylates/VA Copolymer are needed for each type of study in the list of informal data requests. The Panel also noted that the amount of methyl methacrylate in Acrylates Copolymer is of concern, and that additional studies may be needed.

The Panel voted unanimously in favor of tabling the Draft Report on Acrylates Copolymer until the December 8-9, 1997 Panel meeting. This action was based on the fact that the Panel did not have an opportunity to review the large submission of new data prior to the present meeting.

December 8-9, 1997

Dr. Belsito said that a significant amount of information was received in response to the informal data requests issued at the June 5-6, 1997 Panel meeting. However, skin irritation data on the Acrylates/VA Copolymer were not included in the submission. Dr. Belsito noted that data already included in the CIR Draft Report indicate that this ingredient was quite irritating to the skin, perhaps, primarily, because it appeared to have been used full-strength. Dr. Belsito said that the data also indicate that Acrylates/VA Copolymer is extremely toxic to the eye.

Dr. Belsito noted that his Team determined that the available data are still insufficient for evaluating the safety of this group of ingredients, and that the following data are needed: (1) Current concentration of use data, especially on the Acrylates/VA Copolymer, (2) Impurities data, including precursors, catalysts, and plasticizers, and other ingredients, (3) Skin irritation data, at the concentration of use, on the Acrylates/VA Copolymer, and (4) Ocular irritation data, at the concentration of use, on the Acrylates/VA Copolymer, if available.

Dr. McEwen said that the Panel has reviewed irritating chemicals before, and has not frequently expressed the need for data at a concentration that is less than irritating. However, he noted that the Panel has stated than an ingredient cannot be irritating in formulation, and did not see why the Panel could not address Acrylates/VA Copolymer in a similar manner.

Dr. Schroeter said that his Team recognized that industry is eliminating the unreacted monomer from Acrylates/VA Copolymer, and, if this is the case, then the need for data becomes much less demanding in terms of irritation and sensitization. Thus, Dr. Schroeter's Team asserted that the Acrylates Copolymer ingredient family is safe as used.

Dr. Belsito said that, typically, when the Panel has used the terminology safe as used, the function of the ingredient and its use concentration range have been known, and the ingredient was not irritating or sensitizing or was not sufficiently absorbed within the use concentration range. Dr. Belsito said that the Panel does not know the use concentration range for Acrylates/VA Copolymer in cosmetics and does not have data indicating the concentration of Acrylates/VA Copolymer that does not cause skin irritation. Dr. Belsito also said that data in the Draft Report indicate that Acrylates/VA Copolymer is corrosive when placed on the skin. Thus, even though Acrylates/VA Copolymer is low in unreacted monomer, it can be extremely irritating.

Dr. Bailey made comments relating to the issue of composition and impurities (monomers and other contaminants that may be present). Initially, he referred to a risk assessment on acrylamide and the polyacrylamides that was done in Sweden. He said that he was somewhat hesitant to mention this because he was unsure of its relevance. However, he said that in understanding that acrylic acid can be derived from acrylamide, the risk assessment is relevant and also points to some of the other issues relative to styrene residues etc. in setting a specification. A fairly detailed risk assessment on acrylamide and polyacrylamides was conducted

in Sweden. Basically, it is a worst case risk assessment where the investigators considered exposure not only from one product, but from all products that an individual may be using at any given time. Dr. Bailey noted that a risk of 2×10^{-3}, which is fairly significant if one accepts it, was determined.

Dr. Bailey noted that in the risk assessment mentioned above, the investigators are assuming a level at a specification of 0.01% of residues of acrylamide in the polymer. Thus, he said that the Panel may wish to consider not only the issue of acrylamide residues, but also styrene and other contaminants that could be present. Dr. Bailey recalled that data from either one or two companies are represented in the risk assessment, and that whether of not the data are representative of what is on the market is questionable.

Dr. Bailey added that, in his opinion, the available data in the CIR report are fairly incomplete in terms of providing the Panel with what it needs to know about contaminant residues.

Dr. Shank noted that the Acrylates/VA Copolymer is not being used in cosmetics.

Dr. Bergfeld said that it could be stated in the report discussion that the data are insufficient for evaluating the safety of Acrylates/VA Copolymer in cosmetics.

Dr. McEwen said that the Panel has data on VA Copolymer, and that these data indicate that this ingredient is severely irritating, but that the irritation is reversible.

Dr. Belsito recalled that at the June 5-6, 1997 Panel meeting, a variety of impurities was requested, and that the only information received was on the level of monomer impurities. He wanted to know if the Panel is now concluding that the remainder of the information is no longer needed.

Dr. McEwen noted that mutagenicity data, reproductive toxicity data, and other toxicity data are available on acrylates other than Acrylates Copolymer.

Dr. Belsito reiterated that his Team concluded that the available data are insufficient for determining safety and that the following data are needed:

1. Current concentration of use data, especially on the Acrylates/VA Copolymer
2. Impurities data, including precursors, catalysts, and plasticizers, and other ingredients
3. Skin irritation data at the concentration of use on the Acrylates/VA Copolymer
4. Ocular irritation data at the concentration of use on the Acrylates/VA Copolymer, if available.

Dr. Belsito said that a modification of this conclusion would be a statement to the effect that these ingredients are safe for use in cosmetic products, if formulated to avoid irritant levels of the Acrylate Copolymers.

Ms. Fise wanted to know how the issue of impurities would be dealt with.

Dr. Belsito said that one would assume that the Panel does not need to be concerned about impurities, based on the other toxicology data that are available.

Dr. Shank said that if the Panel is willing to use the available data on several, but not all, of the ingredients, then the Panel has sufficient toxicological data to indicate that the ingredients are not a toxicological problem, whether or not impurities are present.

Dr. Slaga said that it could still be emphasized in the report discussion that impurities (any of the catalysts, initiators, monomers etc.) should be kept at a minimum.

Dr. Belsito wanted to know if the information on levels of the monomer, received from Chemir Polytech Laboratories, should be included in the report discussion. This would be done to indicate that the level of monomer present is very small, and would provide further support for a safe as used conclusion.

Dr. Slaga said that limiting levels of the monomer should not be the only concern, because in order to reduce levels of the monomer, the levels of catalyst and initiators have to be increased to make sure that the reaction goes to completion. Therefore, all of the impurities related to leftover monomers, catalysts, and initiators have to be kept at a minimum.

Dr. Bailey said that if the Panel's conclusion on the safety of the Acrylates Copolymer ingredient family is premised on a limited amount of data indicating that some manufacturers are taking steps to produce a product that is freer of contaminants, then this should be captured in the report discussion and, possibly, in the conclusion.

Dr. McEwen did not see the need for inclusion of such a statement in the report conclusion. He said that it is understood that a manufacturer is going to produce an ingredient that is as free of impurities as possible.

Ms. Fise said that if this is the case, why doesn't industry supply the data.

Dr. Bailey noted that one company has stated that residues of the monomer are present at concentrations of $\leq$ 20 ppm. He said that perhaps, either in the report discussion or conclusion (or in both), it should be stated that the initiators, plasticizers, etc. should be kept at a minimum, since no data are available on this.

Based on the Panel's discussion, Dr. Belsito proposed the following conclusion for the Acrylates Copolymer ingredient family: Safe for use in cosmetics when the concentration of copolymer is adjusted (or designed) to minimize irritation and when the level of unreacted monomers, catalysts, and other impurities are kept at a minimum.

Dr. Shank wanted to know what the minimum is.

Dr. Belsito said that this information was requested from industry, but was not received.

Dr. Slaga said that it would be better if the Panel could establish specific restrictions on impurities, but this is not possible.

Dr. Shank said that the issue of impurities should be handled in the report discussion, but not in the conclusion.

Drs. Shank and Slaga agreed that a statement to the effect that impurities should be kept at a level that is as low as analytically possible should be included in the report.

Dr. Carlton noted that Acrylates/VA Copolymer is a very irritating substance when undiluted, and that the Panel needs data indicating the concentrations at which skin irritation is not observed. He favored issuing a Tentative Report with an insufficient data conclusion, with the data needed to complete the safety assessment listed in the report discussion.

Dr. Belsito said that the issue now is how the Panel should deal with unreacted monomer and catalysts.

Dr. Shank said that the Panel has dealt with this issue through its review of a variety of toxicological tests that yielded negative results for the ingredients tested. He said that if levels of impurities were a problem, this would have been evident in test results.

Dr. Bergfeld said that the preceding statement by Dr. Shank should be included in the report discussion.

The Panel voted unanimously in favor of issuing a Tentative Report with the following conclusion: Based on the available data, the Acrylates Copolymer group of ingredients is safe for use in cosmetics when formulated to avoid skin irritation. The ingredients included in this group are:

Acrylates Copolymer
Ammonium Acrylates Copolymer
Ammonium VA/Acrylates Copolymer
Sodium Acrylates Copolymer,
Ethylene/Acrylic Acid Copolymer,
Ethylene/Calcium Acrylate Copolymer,
Ethylene/Magnesium Acrylate Copolymer,
Ethylene/Sodium Acrylate Copolymer,
Ethylene/Zinc Acrylate Copolymer,
Ethylene/Acrylic Acid/VA Copolymer,
Acrylates/PVP Copolymer,
Acrylates/VA Copolymer, Steareth-10 Allyl Ether/Acrylates Copolymer,
Acrylates/Steareth-50 Acrylate Copolymer,
Acrylates/Steareth-20 Methacrylate Copolymer,
Acrylates/Ammonium Methacrylate Copolymer, Styrene/Acrylates Copolymer,
Styrene/Acrylates/Ammonium Methacrylate Copolymer,
Ammonium Styrene/Acrylates Copolymer,
Sodium Styrene/Acrylates Copolymer,
Acrylates/Hydroxyesters Acrylates Copolymer,
Methacryloyl Ethyl Betaine/Acrylates Copolymer,
Lauryl Acrylate/VA Copolymer,
VA/Butyl Maleate/Isobornyl Acrylate Copolymer,
Ethylene/Methacrylate Copolymer,
Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer,
Sodium Acrylates/Acrolein Copolymer,
PVP/Dimethylaminoethylmethacrylate Copolymer, AMP-Acrylates Copolymer,
Polyacrylic Acid, Ammonium Polyacrylate,
Potassium Aluminum Polyacrylate,
Potassium Polyacrylate,
Sodium Polyacrylate

Dr. Bergfeld said that a report discussion addressing the issues discussed during the open session, skin irritation and impurities, will be developed.

At Dr. Bergfeld's request, Dr. Bailey agreed to make the report that he mentioned earlier (risk assessment on acrylamide and polyacrylamides) available to the Panel.

May 18-19, 1998

Dr. Belsito recalled that at the December 8-9, 1997 Panel meeting, the Panel concluded that these ingredients are safe for use in cosmetics when formulated to avoid skin irritation. He also noted that during the public comment period for the Tentative Report, several submissions on mutagenicity and carcinogenicity testing were received. Dr. Belsito said that the study on the dermal oncogenicity of 2-ethyl- hexyl acrylate (one of the monomer units of Acrylates VA Copolymer) that was received was perhaps of most concern to the Panel. In that study, 43% and 83% concentrations of this chemical induced skin cancer. However, in reviewing the document, the Belsito Team concluded that the most likely mechanism for this finding was the chronic, very intense irritation of the skin. This opinion was based on the fact that when the 43% treatment group was discontinued after 24 weeks and the animals were observed throughout their lifetime, there was no evidence of skin cancer. Furthermore, Dr. Belsito noted that an additional group in this study was dosed with 2.5% 2-ethylhexyl acrylate, and that there was no evidence of skin cancer at this concentration.

In addition to the above comments, Dr. Belsito said that in a presentation to the Panel that was made by Dr. Ian Cottrell, it was stated that the acrylates are polymerized, virtually to 100%. Referring to information in the CIR report, he also noted that acrylate copolymers would typically contain ≤ 20 ppm of unreacted monomer, which is well below the 2.5% dose that was found to be safe in the above study. After considering the dermal carcinogenicity study as well as the presentation to the Panel that had been made by Dr. Ian Cottrell, Dr. Belsito's Team determined that a conclusion of safe for use in cosmetics, with a restriction of ≤ 20 ppm unreacted monomer, could be issued.

Dr. Schroeter noted that members of his Team disagreed, stating that it cannot be concluded that the Acrylates Copolymer group of ingredients is safe because of the data discussed by Dr. Belsito. He added that the 2-ethylhexyl ester is difficult to quantify, and that his Team expressed concern over its presence. Furthermore, Dr. Schroeter said that there are no available data that could be used to arrive at a safe concentration for this impurity.

Dr. Slaga said that there was some concern that the 21% dose of 2-ethylhexyl acrylate induced a higher incidence of carcinoma than did the 86.5% dose in the dermal carcinogenicity study. Based on these results, he noted that the Schroeter Team was unable to establish a safe concentration.

Dr. Belsito said that there were four test groups in the dermal carcinogenicity study (2.5, 21, 43, and 86.5% 2-ethylhexyl acrylate, respectively). He recalled that the group dosed with 43% 2-ethylhexyl acrylate was dropped from the study after 24 weeks and subsequently reverted back to normal. Furthermore, the 21% dose group that was allowed to continue beyond the 24 weeks also had carcinomas.

Dr. Shank said that the test results make it difficult for one to conclude that 2.5% 2-ethylhexyl acrylate is a safe concentration.

Dr. McEwen disagreed. He said that if one looks closely at the dermal carcinogenicity data, these data are indicative of a physical irritation phenomenon. Dr. McEwen proposed that the reason why 43% 2-ethylhexyl acrylate did not cause skin tumors is because dosing was discontinued before the skin irritation progressed to tumor stages. He also asked the Panel to review the changes in the skin that were observed prior to tumor formation, which included not only hyperkeratosis, but other types of lesions.

Regarding the skin changes noted prior to discontinuation of treatment with 43% 2-ethylhexyl acrylate, Dr. Slaga said that limited application of almost any carcinogen will cause these changes, regardless of whether it is genotoxic or irritating.

Dr. McEwen noted that the 43% concentration was applied for 24 weeks and that 2.5% was applied for a lifetime. Comparatively speaking, he said that the mice tested with the 43% concentration over a period of 24 weeks received the higher dose.

Dr. Slaga emphasized that 20 carcinomas were reported for the group that received 21% 2-ethylhexyl acrylate, versus 14 carcinomas for the group that received 86.5% 2-ethylhexyl acrylate. With this in mind, he said that the Schroeter Team did not know how to judge these results in terms of establishing a threshold concentration for the induction of skin tumors.

Dr. Shank said that irritation is one possible explanation for the results of the dermal carcinogenicity study, but is not the only explanation.

Dr. McEwen said that irritation (erythema) was not the only skin effect noted; trauma was also observed.

Dr. Belsito wanted to know whether the reduction in carcinoma incidence at the highest concentration tested (86.5% 2-ethylhexyl acrylate) was suggestive of the fact that it was so irritating that it was actually toxic.

Dr. Slaga said that it was not possible to determine a dose response in the study. Furthermore, he said that if the results at the highest test concentration (reduction in carcinoma incidence noted) were indicative of a toxic effect, then there could be a lower dose that could yield more tumors.

Dr. Belsito noted that the limitation established by his Team, ≤ 20 ppm of unreacted monomer, is much lower than the 2.5% concentration of 2-ethylhexyl acrylate that did not cause skin tumors in the dermal carcinogenicity study.

Dr. Slaga wanted to know the origin of the ≤ 20 ppm limitation.

Dr. Belsito recalled that Dr. Ian Cottrell had indicated in his presentation to the Panel that industry allows the polymerization reaction to progress to nearly 100%, primarily because the monomers have an unwanted odor. Dr. Belsito also referred to the following statement in the impurities section of the Acrylates Copolymer Draft Report: A company reported that in its production of Acrylates Copolymer, it controls impurities in the form of residual, unreacted monomer (i.e. ethyl acrylate, methyl methacrylate, methacrylic acid, and acrylic acid) to ≤ 20 ppm.

Dr. McEwen said that ≤ 20 ppm unreacted monomer is not an industry standard, but is a limitation that the Panel could propose and announce to the public for comment.

Dr. Shank said that this limitation is acceptable only if there are data to substantiate that ≤ 20 ppm is well below toxic levels for the monomer, and that the Panel does not have these data. He also said that ≤ 20 ppm monomer is based on what industry says that it has achieved, and not on safety.

Dr. Shank said that he does not know the mechanism of action of the carcinogen and cannot rely on the negative results for 2.5% 2-ethylhexyl acrylate in the dermal carcinogenicity study. He also said that the mechanism of action proposed by Dr. McEwen is plausible, but that there are others as well.

Dr. McEwen said that the no-effect-level is 2500 ppm.

Dr. Shank said that when one is dealing with a carcinogen and there is a no-effect-level in an eighty-mouse study (80 mice at that one level), it cannot be said that level is a level that has been proven to be safe.

Dr. Belsito said that a number of negative mutagenicity studies, with the exception of the mouse lymphoma assay, are included in the Draft Report on Acrylates Copolymer. He also noted that oral carcinogenicity studies on acrylic acid and ethyl acrylate were negative, and that the dermal carcinogenicity study on 2-ethylhexyl acrylate was the only study in the Draft Report over which his Team had expressed concern.

Dr. Shank said that his Team had no concerns about the safety of acrylic acid, but that the safety of 2-ethylhexyl acrylate is definitely a concern.

Dr. Klaassen noted that at a concentration of 2500 ppm, 2-ethylhexyl acrylate was not carcinogenic in mice (group of 80). However, at higher concentrations, carcinomas were observed. He asked for any suggestions as to what could be done in order to establish an acceptable limitation.

Dr. Shank said that if it could be established that 2-ethylhexyl acrylate is carcinogenic through irritation only, then a threshold could be argued.

Dr. Klaassen wanted to know how suitable the ATGC transgenic mouse is for determining promoters.

Dr. Slaga said that this strain is good for promoters, but not as good for complete carcinogens.

Dr. Bailey said that in a situation such as this, FDA would typically do a quantitative risk assessment to actually extrapolate from the available data to a risk, and determine whether or not that risk is acceptable.

Dr. McEwen said that the problem with doing a risk assessment is making a determination as to the method of action of the purported carcinogen. He also said that if the Panel believes that the method of action is a physical phenomenon, then a threshold-type risk assessment should be performed. If it is not believed to be a physical phenomenon, then an EPA-type risk assessment should be performed.

Dr. McEwen also said that the concern that he would have is that the Panel does not seem to be comfortable with the proposition that the method of action in the dermal carcinogenicity study on 2-ethylhexyl acrylate is a physical phenomenon, and, therefore, is being forced into doing a risk assessment based on data that are not believed to show a genotoxic carcinogen.

Dr. Belsito asked Dr. Shank if a negative genotoxicity study on 2-ethylhexyl acrylate would increase his comfort level.

Dr. Shank said that if it could be established that there is no basis for genotoxicity, he would feel more comfortable. He also indicated that he has not concluded that 2-ethylhexyl acrylate is unsafe, but that the Panel does not have sufficient data for concluding that it is safe.

Dr. Shank also said that after paying close attention to the monomer issue and reviewing the available data more closely, he concluded that of the 34 ingredients that are being reviewed in the Draft Report on Acrylates Copolymer, a reasonable amount of data are available on only four ingredients. Furthermore, he said that he does not favor including all 34 ingredients in one report or agree that the data that are available on four ingredients can be used to sufficiently evaluate the safety of all 34. Dr. Shank recommended that a decision be made as to which ingredients should remain in the present safety assessment, and that the Panel should be very careful in determining exactly which data on these compounds are needed.

The Panel voted in favor of tabling the Draft Report on Acrylates Copolymer. Drs. Belsito and Carlton voted against the motion to table.

Dr. Shank noted that the report is being tabled such that 34 ingredients can be placed into groups and the Panel can determine how much information is actually available. He said that the Panel will find that there are data only on the following three ingredients: Acrylates Copolymer, Polyacrylic Acid, Sodium Polyacrylate. Additionally, Dr. Shank noted that the Panel has fairly good impurities data on these ingredients and that this is not the case for the remaining 31 ingredients. He suggested requesting impurities data (unreacted copolymers included) on each ingredient for which no impurities data have been made available.

Dr. Shank indicated that he is not in favor of regrouping the 34 ingredients in the safety assessment and creating individual group reports, but wants to analyze the group of 34 ingredients differently, compared to what has been done in the past.

Dr. Belsito asked if Dr. Shank wants, e.g., all of the information on Acrylates Copolymer grouped within the document.

Dr. Shank said that, at least, the information should be looked at in that way, even if there is no physical grouping of information within the document.

Dr. Andersen said that the types of data available on each ingredient will be listed in a table.

Dr. Bergfeld asked what should be done concerning the issue of 2-ethylhexyl acrylate carcinogenicity.

Dr. Schroeter said that as justification for tabling the report, he had suggested that a risk assessment be done on 2-ethylhexyl acrylate. He also said that if there are individuals or groups that have information that would assist the Panel in making a decision, then such information should be made available.

In light of the Panel's discussion, Dr. Bergfeld noted that, possibly, a risk assessment will be done and that the Panel will again request information on the safety of these polymers from industry. She also suggested that the Panel discussion that led to the decision to do a risk assessment should be captured in the minutes.

Concerning Acrylates/VA Copolymer, Dr. Shank said that, perhaps, 2-ethylhexyl acrylate is not present in the finished product and that industry may be able to prove this. In other words, it may be that 2-ethylhexyl acrylate is not included in the chemical process of synthesizing a copolymer. Dr. Shank noted that the name, Acrylates/VA Copolymer has the name of the carcinogen in it, and that the Panel has asked for but not received information on this compound. He said that without any information, one has to assume, based on the name, that unreacted carcinogen is present.

Dr. Belsito noted that Acrylates/VA Copolymer is a copolymer of vinyl acetate and 2-ethylhexyl acrylate copolymer. He said that the reason why he originally wanted information on Acrylates/VA Copolymer is because, in irritation studies, it was the most irritating. At a concentration of 100%, it was extremely corrosive to skin. Dr. Belsito also noted that this same effect was reported in the dermal carcinogenicity study on 2-ethylhexyl acrylate.

Dr. Ian Cottrell said that most of the polymers don't contain 2-ethylhexyl acrylate. He wanted to know if the Panel is only concerned about this monomer.

In response to Dr. Bergfeld's request, Dr. Cottrell agreed to supply data on some of the polymers indicating that 2-ethylhexyl acrylate is not present. He said that he could supply the Panel with a package of information on the polymers with which he is familiar within four to six weeks.

Dr. Bailey said that if the Panel is going to invite an expert to discuss the mechanism (mechanism for 2-ethylhexyl acrylate-induced dermal carcinogenicity) issue, it is his recommendation that the Panel be involved in the selection of this person such that there will be an independent opinion. Dr. Bailey recommended that the scientist be from academia.

Dr. Slaga said that mutagenicity data on 2-ethylhexyl acrylate would be helpful.

Dr. McEwen wanted to know the types of mutagenicity studies that would be sufficient.

Dr. Shank said that the usual mutagenicity profile (2 mutagenicity assays, one in a mammalian system) that has been requested in the past for other compounds would be sufficient.

Dr. Bergfeld confirmed that mutagenicity data will be requested in order to resolve the issue of mechanism (i.e., is the mechanism for 2-ethylhexyl acrylate-induced dermal carcinogenicity related to genotoxicity or irritation?).

Dr. Bronaugh made a comment relating to the family of acrylates being reviewed. He said that he recently noticed that there is an acrylamide sodium acrylate copolymer that is used in some products according to FDA's voluntary reporting system. Dr. Bronaugh wanted to know if this compound should be included in the family of acrylates that is being reviewed.

Dr. Bergfeld said that Dr. Belsito's Team had considered the addition of this ingredient.

Dr. Belsito said that the Panel was appreciative of the FDA submission on the risk assessment of acrylamide monomer and polyacrylamide. He also said that his Team specifically wanted to be assured that there no polyacrylamides would be included in the family of ingredients being reviewed, because the polyacrylamides would need to be addressed on a very specific basis. Dr. Belsito added that based on the risk assessment that was received from FDA, his Team was very specific to exclude any of the polyacrylamides from the safety assessment of the Acrylates Copolymer ingredient family.

Dr. Bronaugh noted that the ingredient that he was referring to is not a polyacrylamide. It is an acrylamide sodium acrylate copolymer.

Dr. Belsito said that the reason for concern over polyacrylamide is the presence of acrylamide monomer, which could be present in acrylamide sodium acrylate copolymer. Therefore, any copolymer with acrylamide would be removed from the Acrylates Copolymer ingredient family and reviewed specifically.

Ms. Fise asked if acrylamides are on the CIR priority list as a separate group, and when the Panel might be expected to review this group.

Dr. Andersen said that the Panel has completed the safety assessment on polyacrylamide, and FDA's risk assessment was not part of that evaluation. Therefore, Dr. Andersen said that he would like to use these data to reopen the Panel's discussion on Polyacrylamide.

Dr. Bergfeld asked Dr. Andersen to comment on how the Panel will proceed with its review of the Acrylates Copolymer ingredient family at the next Panel meeting.

Dr. Andersen said that the CIR staff will present a description of the data included in the Draft Report, as a function of each ingredient (i.e., how much data are actually available on each ingredient) in tabular form. He also said that the CIR staff will also attempt, with assistance as needed, to perform a risk assessment and present that analysis to the Panel. As recommended by Dr. Bailey, Dr. Andersen noted that outside academic assistance will be utilized, as needed, in order to complete the risk assessment. He added that exposure assessment is going to be part of any risk assessment, and that the information on monomer residues may be accessible only from industry. Therefore, there are some limits in terms of how this information can be factored in.

Dr. Andersen also stated that a number of possibilities was presented to industry as ways of helping to resolve the issue of potential 2-ethylhexyl acrylate-induced dermal carcinogenicity, which included the conduct of genotoxicity tests. The genotoxicity tests normally described by the Panel would include at least one in a mammalian system, and, in this case, the goal is to characterize the genotoxicity potential of 2-ethylhexyl acrylate. Dr. Andersen noted that another possibility was a description of the chemistry of copolymers containing 2-ethylhexyl acrylate, with a goal of showing that there may actually be no monomer left in the final material.

Dr. Andersen stated that his comments (stated immediately above) relate to possibilities that industry may consider as ways of assisting in the resolution of the issue of potential 2-ethylhexyl acrylate-induced dermal carcinogenicity.

Dr. Shank wanted to know which ingredient will be evaluated in the risk assessment, 2-ethylhexyl acrylate (monomer) or Acrylates/VA Copolymer.

Dr. Andersen said that the risk assessment will be done on the monomer, with some assumptions that may have to be made, if actual values are not available, on how much of that compound is actually going to be in a cosmetic formulation and how much of that cosmetic formulation is going to contact the user's skin.

Dr. Bergfeld said that if the polymerization is complete and there is no residue left, then the Panel's data needs would be greatly reduced.

Dr. Shank wanted to know if there is any information on how free the monomer is to migrate from the polymer into the skin. He also wanted to know if one should assume that all of the monomer is going to migrate out.

Dr. Cottrell said that one cannot assume that all of the monomer is going to migrate from the polymer. He added that it may only be used at a very small percentage in the final formulation that contacts the skin. Dr. Cottrell also noted that much skin irritation data is available on Acrylates Copolymer, and that he is willing to provide the Panel with these data.

Noting that many ingredients are being reviewed in the present report, Dr. Slaga said that, in the future, it may be a good idea to break any large group of ingredients down into smaller groups. He said that this would make the review process a lot easier.

In summary, the Panel asked for a risk assessment based on the carcinogenic potential of 2-ethylhexyl acrylate, one of the monomers used to create one of the copolymers in the Acrylates Copolymer ingredient family. The concern could be resolved if it were understood that the mechanism of action in the dermal carcinogenicity study is likely physical (e.g. genotoxicity tests in bacterial and mammalian systems are negative). Additional information on the specific copolymers that could contain 2-ethylhexyl acrylate as a monomer was also requested from industry, along with any other information on monomer residues that would help make the report more complete.

Furthermore, as stated earlier, the Panel voted in favor of tabling the Draft Report on Acrylates Copolymer. Drs. Belsito and Carlton voted against the motion to table.

June 14-15, 1999

Dr. Belsito noted that, at the December 8-9, 1997 Panel meeting, the Panel concluded that these ingredients are safe for use in cosmetics when formulated to avoid skin irritation. He also mentioned that the following two caveats are included in the report discussion: (1) The levels of unreacted monomer should be kept at a minimum, consistent with good manufacturing practices and (2) Based on the information that was provided, hydroquinone is completely removed before the acrylates are used in the production of a cosmetic product.

Dr. Schroeter said that his Team expressed concern about the following two issues relating to acrylates copolymer: (1) the cocarcinogenicity of 2-ethylhexyl acrylate, one of the monomers in Acrylates /VA Copolymer - Dr. Schroeter said that 2-ethylhexyl acrylate does have carcinogenic activity, and, therefore, may be unsafe. (2) the carcinogenicity of acrylic acid, which is a monomer in many of the copolymers. There is a concern that acrylic acid is unsafe based on the data that have been supplied. 1% acrylic acid showed no significant effect, while 4% acrylic acid induced two tumors in 30 animals. Acrylic acid is said to be found in Sodium Polyacrylate at concentrations almost as high as 4%. Furthermore, according to an IARC report on acrylic acid that the Panel has not seen, it is possible that this chemical may be a human carcinogen.

Dr. Schroeter said that in light of the absence of data from IARC and the other data that are in question, perhaps the Panel should table the review of this ingredient group, pending the Panel's review of the IARC report on acrylic acid.

Dr. McEwen recalled that, on the preceding day, the Panel was informed that acrylic acid has been classified as a category III chemical, meaning that IARC was unable to arrive at a conclusion on its carcinogenicity, not that there was evidence that acrylic acid might be a carcinogen.

The Panel voted in favor of tabling the report on Acrylates Copolymer. Drs. Slaga and Shank opposed the motion to table.

Mr. McLaughlin made the following comments: IARC completed its review on acrylic acid, ethyl acrylate and ethylhexyl acrylate last year. Additional data are included in the EPA IRIS report (acrylic acid reviewed), which will be provided. ECETOC (European Chemical Council) completed a review on acrylic acid as well, and this will be provided along with all relevant data addressing genotoxicity and carcinogenicity. A large body of data from the mouse lymphoma assay exists. Information will be provided on monomers in this assay, including those that have been tested in product studies and shown to be negative for carcinogenicity.

Dr. Belsito wanted to know why the mutagenicity of 2-ethylhexyl acrylate is still an issue. He thought that this issue had been resolved by the Panel's suggestion that the weak mutagenic effect reported was probably due to an irritant effect of the chemical. He recalled that, except for the mouse lymphoma assay, the mutagenicity data were relatively clean. He also recalled that 43% ethylhexyl acrylate induced excess irritation in mice to the point where application was discontinued, and that the mice went on to heal without the subsequent development of tumors.

Dr. Slaga recalled that 2.5% ethylhexyl acrylate was also positive (an irritant).

Dr. Shank noted that there is a possibility that 2-ethylhexyl acrylate is a weak mutagen, and that the Panel has not seen the genotoxicity data on this chemical. He acknowledged that there is no evidence that 2-ethylhexyl acrylate is a strong mutagen, but also said that if there is any doubt surrounding the mutagenicity data, one cannot say that the mutagenicity data exclude a possible genotoxic mechanism. Therefore, the Panel has to be confident that the chemical is carcinogenic only because it is an irritant.

Dr. Klaassen said that he is not concerned about the mutagenicity of 2-ethylhexyl acrylate. However, he noted that an IARC document on acrylic acid has just been reviewed, and that the CIR report could possibly be made stronger by including studies from the IARC report.

Dr. Shank said that, at this point, it would be very difficult to develop a report discussion that explains why the Panel is saying that chemicals that cause skin cancer (acrylic acid, ethyl acrylate, and 2-ethylhexyl acrylate) are safe as used. He also noted that the Panel has not had an opportunity to review the mutagenicity data.

Dr. Bailey said that it would be reasonable for the Panel to request any additional data on residues of these monomers in the ingredients being reviewed. He recalled from yesterday's Team discussions that the data submitted thus far are not really reflective of what is actually in the material, and that such data exist. He said that the Panel would benefit from asking for these data again.

Dr. Andersen said that the fact that the discussion of this ingredient report was tabled will be included in the announcement of the results of this meeting. It will be explained that the basis for tabling was to allow receipt of additional data that may in-clude an IARC report, other industry data on genotoxicity, and, at Dr. Bailey's request, a request for any additional information on monomer residues that may be present in any of the copolymers that are being considered will be added to the list.

Dr. Bailey requested that any data on monomer residues should be on cosmetic grade materials.

As noted earlier, the Panel voted in favor of tabling the report on the Acrylates Copolymer ingredient family, pending the Panel's review of the IARC report on acrylic acid. Assuming that the IARC report may be a lengthy document, Dr. Belsito requested that this document be mailed to Panel members as soon as it is received, rather than holding it until the mail date for meeting materials.

December 20-21, 1999

Dr. Bergfeld thanked Dr. Clay Frederick, Basic Acrylic Monomer Manufacturers, for assisting the Panel with its review of the Acrylates Copolymer ingredient family.

Dr. Belsito recalled that a Tentative Report with a conclusion indicating that these ingredients are safe for use in cosmetics when formulated to avoid skin irritation was issued two years ago. He also said that over the past two years, the Panel has struggled with reports on the carcinogenic potential of 2-ethylhexyl acrylate, which is said to be a trace component of one of the acrylate copolymers that is being reviewed.

Dr. Belsito noted that the Panel recently received information on the extreme sensitivity, but lack of specificity, of the mouse lymphoma assay for genotoxicity and also received another report (Mellert et al., 1994) on the carcinogenicity of 2-ethylhexyl acrylate in different mouse strains (C3H and NMRI). In the latter strain, in spite of some irritation that was observed, the induction of carcinogenicity was not observed. Carcinogenicity was induced in the C3H strain.

Dr. Belsito said that the Panel has also had an opportunity to review risk assessment data based on use concentrations of the Acrylate Copolymers in cosmetics, working under the assumption by the Panel that monomer will be present in amounts < 1,000

ppm. He also recalled that the concentration that induced skin cancer, even when assuming that this was an effect of 2-ethylhexyl acrylate in that solution, was 210,000 ppm. Dr. Belsito said that this concentration is 210-fold higher than any amount of monomer that would be expected, even if it were used in pure form in a cosmetic product. Thus, Dr. Belsito concluded that based on the animal and clinical data included in the CIR report, all of the Acrylates Copolymer included in this review are safe as used when formulated to avoid irritation.

The Panel voted unanimously in favor of issuing a Final Report with the conclusion stated in the preceding paragraph.

Dr. Schroeter confirmed that Dr. Belsito's comments will be included in the report discussion. These relate to the reasoning behind the Panel's evaluation of the carcinogenicity of Acrylates Copolymer.

RE-REVIEW OF ETHYL METHACRYLATE

September 10-11, 1998

Dr. Andersen … noted that CIR received a request from the Meth Producers Association. This group is asking that the Expert Panel re-review its report on Ethyl Methacrylate, taking into consideration the conclusions included in the submission by the Methacrylate Producers Association, and issue a revised conclusion indicating that Ethyl Methacrylate is unsafe for use in cosmetics. The Methacrylate Producers Association is also requesting that the Panel make a similar statement regarding the use of methyl methacrylate in cosmetic formulations. These requests will also be addressed by the Panel at a future date.

December 2-3, 1998

Dr. Bergfeld also announced that presentations on … ethyl methacrylate will be made at today's meeting.

Methacrylate Producers Association
(William Barbour, ICI Acrylics
Dr. Craig Farr, ELF Atochem N.A.
Dr. James McLaughlin, Rohm & Haas)

Commenting on the Ethyl Methacrylate report on the meeting agenda, the Methacrylate Producers Association stated that its members are sufficiently concerned about the adverse effects of Methacrylic Acid and the various Methacrylate esters in their monomeric form that they have decided not to sell these ingredients to the purchasers known to use them in artificial nails. They emphasized the adverse reactions that can be associated with exposure to Methacrylic Acid, Methyl Methacrylate, and Ethyl Methacrylate contained in the published reports provided to the CIR Expert Panel. They provided new information suggesting that these ingredients are readily available at beauty supply businesses and described the labels and the chemical analysis of the contents of samples obtained therefrom.

American Beauty Association
(Eric Schwartz, OPI Products
Doug Schoon, Creative Nail Designs
Dr. Edward Jackson, Jackson Research Assoc.)

Also commenting on the Ethyl Methacrylate report, the American Beauty Association described the activities of its Nail Manufacturers Council, which has taken extensive steps to educate individuals who apply artificial nails regarding the steps necessary to ensure safe use. They reiterated information provided to the Panel regarding the actual process of applying the nails, arguing that the recommended technique assures that Methacrylic Acid will only be applied to the center of the nail and spread carefully from there. Arguing, that the exposures known to cause injury appear to be accidental, they support child-proof caps on this material. With respect to Ethyl Methacrylate, it was noted that only a small quantity of monomer is actually used and that most of the material applied to the nail is powdered polymer. As in previous submissions to the Panel, it was noted that the amount of free monomer decreased with time. Given all the information, it was argued that the CIR Expert Panel's conclusion that artificial nails should not be sold in retail stores, but that they could be safely used by trained professionals was still the correct conclusion. There was unequivocal support for eliminating the use of Methyl Methacrylate in artificial nail products; numerous efforts of the nail manufacturers to support State legislative and regulatory efforts to remove these products from the marketplace were cited.

Panel Deliberations

Presentations on Ethyl Methacrylate by the Methacrylate Producers Association and the American Beauty Association are summarized earlier in the minutes (pages 5-7).

Dr. Schroeter asked Dr. Bailey to state FDA's position on the regulation of methyl methacrylate. Dr. Bailey's comments are summarized below:

In the 1970's, FDA received numerous complaints of injuries arising from nail extension products containing methyl methacrylate. In response to this, the agency seized these products and took action to remove them from the market. FDA's action was challenged in court and FDA won the decision that products containing methyl methacrylate were adulterated under the law. Thus, the agency position at that time was that methyl methacrylate was a harmful ingredient and its use in finished products would not be allowed. This was a court action relating to specific products under specific circumstances, but, it does not constitute a regulation that says any future use is prohibited.

One of the reasons why the court action was not captured in a regulation is that industry was not using methyl methacrylate. At the time, it did not seem necessary to develop a regulation. FDA's position today remains that methyl methacrylate is a harmful

ingredient and should not be used in products. FDA may consider capturing this statement in a regulation, because methyl methacrylate seems to be making its way back into the marketplace. FDA has been monitoring this by working with the states to see exactly what they are doing and to help support their actions.

Dr. McEwen said that in order for FDA to take action, the product in question must fall within FDA's ability to regulate. Therefore, some type of claim must be made on the product label or in the advertisement for the product, indicating that the product is either, e.g., a food, drug, medical device, or dietary supplement.

Dr. Bailey said that If a product containing methyl methacrylate has liquid nail monomer printed on the label, then it falls within FDA's legal authority and FDA can take action. However, he also said that if methyl methacrylate monomer purchased from an industrial supplier (e.g., in a 5 gallon container) is being diverted in the string of commerce, then this becomes a very different issue, one that FDA will have to attack differently in terms of public health issues.

Dr. Bailey stated that it is important to note that it is of concern that there seems to be a tendency on the part of salons to sell products (directly to consumers) that are not intended to be sold to consumers. With this in mind, he said that every effort that the trade association can make to ensure that this does not happen is extremely important.

Dr. McEwen wanted to know if the nail industry is making certain that the products that are supplied to the salons are labeled in such a way that retail sale would be illegal.

Mr. Schoon, with Creative Nail Designs, noted that "For Professional Use Only" is prominently displayed on the product label. He also said that there are 8-page MSDS sheets for each product.

Dr. Belsito wanted to know the source of the nail industry's methacrylates, given the fact that the Methacrylate Producers Association no longer sells methacrylates to the nail industry. He also wanted to know if the nail industry reanalyzes the products in order to be sure of their content.

Mr. Schoon said that Creative Nail Designs has a quality control department, which includes an analytical laboratory with strict quality control standards, that is regularly audited.

Mr. Schwartz, with OPI Products, said that certificates of analysis are received from the vendor.

Dr. Belsito recalled that when Dr. Kanerva analyzed dental acrylates, he found that, in many cases, what was present was far from what was labeled on the MSDS sheets. He emphasized that the acrylates analyzed were acrylates that were produced by large, respectable corporations world-wide.

Mr. Schoon noted that OPI Products has developed a methyl methacrylate detection kit (color test). He said that any nail technician can take a small amount of monomer and place it in the kit. Within a few minutes, the color change determines whether or not the material contains methyl methacrylate.

Dr. Bailey wanted to know if "Not For Retail Sale" also appears on the label of products for professional use.

Mr. Schoon indicated that this language does not appear on the product label.

Dr. Bailey wanted to know if the nail industry has any information on the incidence of sensitization reactions in nail salon workers.

Mr. Schwartz said that the results of his company's review indicated no nail technicians with sensitization reactions.

Dr. McEwen suggested that the Panel consider the applicability of its actions on Chlorhexidine earlier today to its present review on Ethyl Methacrylate.

Dr. Bergfeld recalled the Panel's actions on Chlorhexidine as follows: (1) letter to the editor of the *International Journal of Toxicology*), (2) letter to FDA concerning continued updates and (3) reporting of Panel's actions on CTFA, CIR, and FDA homepages.

Dr. Bergfeld stated that Dr. McEwen's suggestion would be addressed during the following full Panel discussion.

Dr. Schroeter noted that, recently, the issue of Ethyl Methacrylate safety was brought to the Panel's attention by the Methacrylate Producer's Association. He said that in a letter from this group, it was recommended that the Panel rescind its Final Report on Ethyl Methacrylate (issued in 1994) and that the Panel was also encouraged to advise the public of the unsafe status of other methacrylates.

Dr. Schroeter said that his Team concluded that the Panel's 1994 safety assessment on Ethyl Methacrylate remains valid. With this in mind, he said that a position statement by the CIR Expert Panel and a letter to the editor of the *International Journal of Toxicology* publicizing this statement would be appropriate.

Dr. Schroeter noted that his Team had also reviewed the Methacrylate Producers Association's concern about the safety of other methacrylates (butyl and lauryl methacrylate) and methacrylic acid. He said that although butyl and lauryl methacrylate are not listed in the International Cosmetic Ingredient Dictionary and Handbook, these ingredients probably are being used. With this in mind, Dr. Schroeter said that his team recommended that butyl methacrylate, lauryl methacrylate, and methacrylic acid be prioritized for review by the Panel. Furthermore, he stated that his Team is also concerned about methyl methacrylate and its

misuse. Dr. Schroeter then recommended that the Panel table the issue of reconsideration of its 1994 Final Report conclusion on Ethyl Methacrylate until the Panel has had an opportunity to review other information on methacrylates in the published literature.

Dr. Bergfeld said that Dr. Schroeter's motion is to table the issue of reconsideration of the Panel's 1994 Final Report conclusion on Ethyl Methacrylate until the next Panel meeting, allowing time for the consideration of all available data.

The Panel voted in favor of the preceding motion. Dr. Belsito was opposed to the motion.

Dr. Schroeter noted that the Panel had just agreed with the following proposal: The issue that was proposed by the Methacrylate Producers Association and rebutted by the American Beauty Association will be tabled for review at the March 3-4, 1999 Panel meeting, pending documentation that is appropriate for making a decision.

Dr. Bergfeld interpreted Dr. Schroeter's comments to mean that CIR will seek out the literature (unpublished data) to go forward with the accumulation of data that are needed in order for the Panel to reexamine the issues, specifically, sensitization and any other health hazards that may arise during cosmetic use.

Dr. Schroeter said that the main issue is the safety of Ethyl Methacrylate and methacrylic acid, and that he does not think that the Panel needs to review all of the literature on lauryl and butyl methacrylate at this time. However, he said that the Panel needs to make a decision as to whether lauryl and butyl methacrylate need to be prioritized for review at a later date.

Dr. Belsito did not understand which information that is relevant to the review of Ethyl Methacrylate, other than that already made available to the Panel, could possibly be needed at this point, considering that new ingredients are not being recommended for addition to this review. Thus, he offered a new motion that the Panel prioritize methacrylic acid, methyl methacrylate, butyl methacrylate, and lauryl methacrylate for review at the next Panel meeting.

The Panel voted in favor of Dr. Belsito's motion in the preceding paragraph. Drs. Schroeter, Shank, and Slaga abstained.

Dr. Andersen said that if the Panel is to initiate a review of these ingredients, then it is not possible for such a review to be ready by March, because of the time needed to gather data.

Dr. Bergfeld said that the safety issues relate to the sensitization potential of methyl methacrylate and the corrosive or irritation potential of methacrylic acid.

It was suggested that it would be of value for the CIR Expert Panel to make a statement (on an interim basis) that the "For Professional Use Only" products containing Ethyl Methacrylate not be sold at retail. This action would reemphasize the conclusion that the Panel has already issued on Ethyl Methacrylate, and could be carried out in the form of a letter to FDA or a statement at the website.

The Panel voted unanimously in favor of the proposal to submit a letter to FDA reemphasizing the Panel's conclusion on Ethyl Methacrylate.

Dr. McEwen said that the letter could also contain a statement indicating that there will also be a review of the other methacrylate esters and methacrylic acid.

Dr. Andersen summarized his understanding by stating that there is sufficient concern about the safety of methacrylic acid, methyl methacrylate, lauryl methacrylate, and butyl methacrylate, such that the Panel has decided to initiate a safety assessment of these ingredients.

Dr. Bergfeld confirmed with the Panel that the letter to FDA will be placed on various websites (e.g., American Academy of Dermatology and North American Contact Dermatitis Group) after appropriate review.

Dr. Bailey expressed concern over communication of the Panel's conclusion regarding professional versus consumer use. He noted that past conclusions (e.g., conclusion on AHAs) issued by the Panel have contained the restriction that products containing the ingredient in question should only be applied by trained professionals. With this in mind, he said that the Panel needs to determine whether this caveat, which is critical, should be included in the discussion or conclusion of the Ethyl Methacrylate report. He recalled that limited information is provided at the website; i.e., the report conclusion, but not the discussion, is provided. Dr. Bailey said that if the report discussion is an important part of what the Panel is trying to communicate to the cosmetics industry, then there needs to be a strong effort to disseminate all of the information to everyone who may be affected by the conclusion.

Dr. Bergfeld recommended further discussion of FDA's purported ban on the use of methyl methacrylate at the March 3-4, 1999 Panel meeting, considering that there is no official ban on the use of this ingredient in cosmetics. She said that FDA's position needs to be clarified.

March 3-4, 1999

Presentations on Ethyl Methacrylate will be given by the Retail Nail Association and the Nail Manufacturers Group at this meeting.

Dr. Bergfeld asked Dr. Andersen to inform the audience of the status of the CIR Report on Ethyl Methacrylate and introduce the individuals who are scheduled to make presentations. Dr. Andersen's comments are included below.

Ethyl Methacrylate had been assessed by the CIR Expert Panel, and, last Fall, the Panel received a petition from the Methacrylate Producers Association arguing that there were safety data relating to the use of Ethyl Methacrylate, methacrylic acid, and other methacrylates that suggested that they were inappropriate for use in consumer products. This petition was discussed at the last CIR Expert Panel meeting along with material that was provided by the Nail Manufacturers Council. In the original review, the Nail Manufacturers Council had been quite active in providing information to the CIR Expert Panel. This group came back with additional information for the Panel's deliberations relative to the Methacrylate Producers' petition. Since the last Panel meeting, the CIR Staff was charged with searching the published literature to find out what other new information might be available. This was done and the information was provided to the Expert Panel at this meeting. In addition, another group (the Retail Nail Association) provided information to the CIR Expert Panel that documented the retail sale of nail products containing Ethyl Methacrylate. Prior to this, this information was not available to the CIR Expert Panel.

Presently, CIR essentially has a problem with the following three facets: (1) The Methacrylate Producers have taken a position relative to their concerns about safety. (2) The Nail Manufacturers Council has taken the position that the report on Ethyl Methacrylate, as written by CIR, does not need to be changed. (3) The Retail Nail Association has taken the position that the discussion that contains an admonition that these products are not appropriate for retail use needs to be changed.

Dr. Andersen announced that the first presentation would be given by the Retail Nail Association to provide its perspective on the data. Dr. Steven Weisman, with The Weinberg Group, will be making the presentation. Larry Steffier, representing the Retail Nail Association and serving as Director of Chemical Operations at Keystone Industries, will be available for questions. Dr. Weisman's presentation (copies distributed) is included at the end of the minutes.

The presentations by the Nail Manufacturers Council are summarized below. Dr. Andersen announced that this group presentation will be made by Eric Schwartz (with American Beauty Association), Dr. Edward Jackson, and Doug Schoon (with Creative Nail Design, Inc.).

Presentation by Eric Schwartz - American Beauty Association

Last December, we made a submission that included a variety of materials. Dr. Jackson reviewed the literature that is available on Ethyl Methacrylate and we also summarized the adverse incident information that is available at FDA and in our professional database, finding that the levels are very favorable. Yesterday, in addition to the materials that we had filed earlier, we filed a short cover note and six exhibits. The first attachment is an expert opinion from Dr. Richard Scherr that relates to these issues. The second item is some new patch test data that were produced by Dr. Jackson at our request. The third item is an article, reviewing some of the available literature that Dr. Jackson prepared for the journal. The fourth item is an update on Consumer Product Safety Commission activities concerning child-proof packages and an examination of the toxicology of these products at the same time. The fifth item is a mailing that was distributed to all of our 50 member companies, reminding them of the importance of keeping these products in the professional channel and urging them to upgrade their labeling to make sure that this is more likely. The sixth item is a brief commentary on the NIOSH document . The levels of exposure there were relatively low. However, according to NIOSH, there is room for improvement in terms of

work practices and ventilation to keep exposure even lower.

Dr. Edward Jackson

I am going to limit my comments exclusively to the sensitization potential of Ethyl Methacrylate. I'd like to begin by saying that predisposition to allergic reactions is indeed an issue with cemented in prostheses (regardless of the cause of that sensitivity), so much so that the orthopedic surgeon does not assess the patient's potential sensitivity or allergy to the prosthesis and/or cement. However, the anesthesiologist routinely does. Prostheses that can be used with or without cement are available. If the Panel believes that there is a possible acrylic sensitization potential issue regarding the use of methacrylates in orthopedic surgery, then I think that the Panel needs to return to the CIR report on Ethyl Methacrylate that was published in 1995, which demonstrated that Ethyl Methacrylate is a weak sensitizer.

Orthopedic prostheses are not the only uses of methacrylates. We have to look at the dental community, and there has been a balancing of relative risks. This has been addressed in depth in the dental industry because dentists routinely mix methacrylate powder and liquid and apply it directly to the gingiva. The clinical experience of methacrylates is over 30 years old. Many of these are approved by FDA. In fact, all of them are.

The CIR report that was published in 1995 contains eight guinea pig sensitization studies. Two were negative, four showed that Ethyl Methacrylate had some potential for sensitization, and two were literally positive. In the cross sensitization data, one study was positive and one was negative for cross sensitization potential of Ethyl Methacrylate. This is obviously a set of mixed results. A ninth guinea pig sensitization test was conducted by the Nail Manufacturers Council and was found to be negative. Obviously,

human data does tend to supersede animal data. The prognostic test done by Maibach (included in 1995 CIR report on Ethyl Methacrylate) on Ethyl Methacrylate was negative. There were four published reports at that time showing six cases of Ethyl Methacrylate sensitization. There have been two or three more since then. Diagnostically, the study by Koppula that was reviewed in the CIR report showed that there was some potential for sensitization by Ethyl Methacrylate.

The Nail Manufacturers Council commissioned my company to conduct another prognostic patch test. This is a cumulative patch test that is modified in two essential ways. It reduces the exposure from 21 to a lesser number, because this has been statistically validated in the literature in more than one publication. We also added a rest period, which gives us the allergic contact dermatitis phase. So, we demonstrated in ten individuals that 100% full-strength Ethyl Methacrylate applied directly to the skin under open and semiocclusive patches did not produce either irritant or allergic contact dermatitis. Dr. Richard Scherr has reviewed all of these data, and, in his letter, arrives at the same conclusion that was reached by the CIR Expert Panel. This is also the same conclusion that I now can draw from our testing of Ethyl Methacrylate. The conclusion is that Ethyl Methacrylate is a weak sensitizer.

Before I conclude, I would like to clarify one very important physical difference between Ethyl Methacrylate and methyl methacrylate. It is simply that one carbon does make a difference. I would reference simply ethyl alcohol and methyl alcohol, one which we ingest with great gusto and, the other, of course, can be lethal.

Mr. Doug Schoon

The Nail Manufacturers Council has made recommendations to place a **NOT FOR RETAIL SALE** sticker on their products. Creative Nail Design, Inc. and OPI Products have agreed to do this. Between my company, Creative Nail Design, Inc., and Eric Schwartz's company, OPI Products, we make up nearly 50% or more of the professional nail industry.

Ethyl Methacrylate and methyl methacrylate are very different monomers, and we continue to support the FDA's contention that methyl methacrylate is not a suitable monomer for our industry. [Mr. Schoon distributed copies of a report detailing the physical differences between Ethyl Methacrylate and methyl methacrylate based artificial nail products. He noted that methyl methacrylate has been mentioned during the Panel's discussions on Ethyl Methacrylate.]

Dr. Bergfeld read the Panel's conclusion on Ethyl Methacrylate, published in 1995, 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. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate. She then noted that the Panel has the following options at this point: (1) Reconsider the conclusion, (2) Reconfirm the conclusion , or (3) Table to consider other issues.

Dr. Andersen said that the two words "as used" in the 1995 conclusion now have a different meaning because "as used" now encompasses retail use. He said that the Panel needs to determine whether the terminology "as used" should be corrected.

Dr. Bergfeld said that the conclusion could remain the same, but that the report discussion should be revised to reflect retail use.

Dr. McEwen noted that it was learned during Team meetings on the preceding day that there are products in which Ethyl Methacrylate and methyl methacrylate are combined. Therefore, it should be clearly stated in the report addendum that the safety of Ethyl Methacrylate only is being evaluated. The fact that skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate should be emphasized as well. Dr. McEwen also said that the human data should be placed in perspective. In two studies using normal volunteers (46 and 10 subjects, respectively), Ethyl Methacrylate did not induce sensitization. In another study, Ethyl Methacrylate induced skin irritation in one of 542 dermatitis patients. Patients with a history of exposure to Ethyl Methacrylate were also tested. Of the 243 who were tested with Ethyl Methacrylate, only 18 responded. Finally, 14 of 22 individuals with acrylate allergies at the time of study initiation were found to be sensitive to Ethyl Methacrylate in the study. Dr. McEwen noted that in all of these studies, individuals were subjected to rigorous exposures to Ethyl Methacrylate, not the same types of exposure that one would expect even from a sloppy person applying Ethyl Methacrylate.

Dr. McEwen added that the results of adverse reactions reports are fairly consistent. Complaints from individuals involved with the production of Ethyl Methacrylate products for retail sale are in the neighborhood of 2.5 to 3 per million complaints. Data on nail product use from FDA's voluntary reporting program indicate two complaints per million (consumer use) and three complaints per million (professional use). Dr. McEwen said that these results indicate that nail products are relatively well accepted by the public in terms of health risks. Furthermore, FDA's harm data on all nail products did not indicate reactions from these types of products.

Dr. Belsito said that the Final Report on Ethyl Methacrylate has to be amended because use of this ingredient in retail products was determined after the Final Report was published in 1995, and that the Panel needs to determine whether or not its original conclusion should be changed based on this information.

Dr. Schroeter recalled that new information on Ethyl Methacrylate has been made available since the Final Report was published in 1995, and that this information pertains to home use. He also noted that it has been suspected that methyl methacrylate was not present in the mixtures evaluated, but that the Panel now knows decisively that it is not present. Concerning the sensitization potential of Ethyl Methacrylate, Dr. Schroeter noted that though it is classified as a strong sensitizer in the report discussion, the

data that have been received are not supportive of this classification. However, the cross sensitization potential of Ethyl Methacrylate is questionable and must be taken into consideration.

Dr. Schroeter also said that he is concerned about the restriction by professionals. He expressed concern over whether the Panel should be given guidelines related to safety (in terms of cautiously used products) rather than designating who should be making the applications. Dr. Schroeter then recommended that all of the data received since the Final Report was issued in 1995 should be incorporated into the Final Report and, after this has been done, that the document should be reconsidered for amendment at the next Panel meeting.

Dr. Bergfeld confirmed that Dr. Schroeter is in favor of tabling the report on Ethyl Methacrylate, with the understanding that the document will be amended.

Dr. McEwen said that the Nail Manufacturers Council has asked (considering all of the information that has been submitted) if there is any reason why the Panel's conclusion should be changed on the basis of professional product use.

Dr. Belsito said that the basic question now relates to whether the Panel stands by its decision relating to salon use and if this decision can be generalized to retail use. Ms. Fise wanted to know whether the Panel has ruled on the petition that was submitted by the Methacrylate Producers Association.

Dr. Bergfeld noted that, in response to the petition, the review of methyl methacrylate was tabled and that this ingredient has been added to the CIR priority list for review in the near future.

Dr. Andersen recalled that part of the petition called for rescinding the Panel's conclusion on Ethyl Methacrylate. He also said that if the Panel addresses Dr. Belsito's question (on preceding page), then the Panel will be effectively addressing that portion of the petition. Furthermore, if the Panel were to reconfirm the appropriateness of the professional use, CIR would be obliged to communicate this decision to the Methacrylate Producers Association. Likewise, any decision regarding retail use would also be communicated.

Dr. Klaassen said that confirmation of the Panel's earlier conclusion on Ethyl Methacrylate at today's meeting would mean that it is alright for anyone to use Ethyl Methacrylate for cosmetic purposes.

Dr. Schroeter disagreed with Dr. Klaassen's account. He said that any future decision on Ethyl Methacrylate by the Panel will be based on any amendments to the Final Report and a revised report discussion.

Dr. McEwen said that how Ethyl Methacrylate is used in retail products can be clarified in the report discussion.

Dr. Klaassen indicated that he would vote against any motion to reconfirm the Panel's earlier conclusion on the safety of Ethyl Methacrylate. He said that the appropriateness of placing on the market a weak sensitizer that may later alter the options of a person's health care (e.g., hip replacement surgery, i.v. infusiions, etc.) is questionable.

Dr. Schroeter said that Dr. Klaassen's concern relates to the potential for an increasing incidence of sensitization in the population that would endanger the population's safety in terms of other products. He also understood Dr. Klaassen's comments to mean that if the Panel had data supporting this concern, then the Panel's earlier conclusion would be considered invalid. Dr. Schroeter said that he does not think that data supporting this concern are in place. However, he wanted to know if Dr. Klaassen's concern could be addressed by either conducting some type of study or by identifying studies that are already in the literature.

Dr. Klaassen said that if Ethyl Methacrylate is known to be a weak sensitizer (meaning that some individuals do become sensitized to this ingredient) and this chemical is used on a patient at some time in the future, problems could develop. In other words, if an individual becomes sensitized to Ethyl Methacrylate and needs to have hip replacement surgery or a pacemaker implanted in the future, that individual's options for health care are limited.

Dr. Andersen indicated that the Panel is not suggesting anything about the safety of combination products that would consist of Ethyl Methacrylate + methyl methacrylate. He also suggested that this point should be captured as part of today's Panel discussion.

Dr. Bailey stated that if Ethyl Methacrylate is allowed for retail sale, then the number of individuals who become sensitized to Ethyl Methacrylate in the future may increase. Dr. Bailey asked that the Panel consider this possibility in its safety assessment.

Dr. McEwen disagreed. He said that there are millions of individuals who are exposed and have been exposed continuously to acrylates, and the issue of sensitization has not become a big public health concern for these individuals.

Dr. Bergfeld called for the vote for reconfirmation of the Panel's earlier conclusion on Ethyl Methacrylate that was published in 1995, which 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. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate. She reminded the Panel that this conclusion now includes salon and retail use.

The Panel voted against the motion to reconfirm the Panel's earlier conclusion. Drs. Carlton and Slaga were in favor of the motion.

The Panel voted in favor of the motion to table. The initial vote resulted in a tie, and Dr. Bergfeld's vote was needed. Drs. Belsito, Klaassen, and Carlton voted against the motion.

Dr. Bergfeld noted that the Final Report, with discussion, conclusion, and amendments, has been tabled until the next meeting for continuation of today's discussion. She said that the report is being referred to Teams.

June 14-15, 1999

In a presentation to the Panel, Mr. Eric Schwartz, Chairman, Safety and Standards Committee - Nail Manufacturers Council of the American Beauty Association, said that the data, literature, expert opinions, and experience reports compellingly establish that Ethyl Methacrylate is safe as used in nail care products. He also indicated that the goal of his organization today is to complete the record so that the Panel may confidently reaffirm the safety of Ethyl Methacrylate in nail care products. Mr. Schwartz recalled that analyses (by Dr. Robert Booth and Edith Blessing) stating that there is no reasonable basis to suspect that methyl methacrylate used as a liquid monomer in bone cement systems or exposure to Ethyl Methacrylate in artificial systems creates any impediment to joint implants were submitted along with a letter, dated May 17, 1999. He announced that Mrs. Blessing will make a presentation concerning this issue to the Panel. Mrs. Blessings presentation will be followed by presentations, on behalf of the Retail Nail Association, by Dr. Eric Hume (orthopaedic surgeon) and Dr. Mitch Sauerhoff (with Sauerhoff & Associates). Mrs. Blessing's presentation is included below:

I appear before you today on behalf of the Nail Manufacturers Council to explain the basis of my opinion that sensitization to methyl methacrylate is not a limiting factor

from the use of bone cement. In all of these years of professional knowledge of bone cement, I never learned or heard any evidence that a bone cement was rejected due to allergenic reactions to methyl methacrylate. Therefore, despite the very widespread use of methyl methacrylate in the United States, sensitization to the compound has never been reported as causing a problem with the use of bone cement. Based upon this experience, my review of the literature, and my knowledge of joint implant procedures, I conclude that methyl methacrylate sensitization is not a contributing factor in the use of bone cement in implant procedures.

Let me elaborate on the basis of my opinion. I will first discuss my experience with bone cement and then turn to my review of the literature. As for my background, I came to the United States from Germany in 1950 with a degree in chemistry from the Technical University. I later received an M.S. degree in chemistry from the University of Delaware. I retired from Wella in 1998 (22 years of service) as Associate Director of Regulatory Affairs. Thereafter, I have continued working as a consultant on matters related to orthopedic products and as a translator of scientific, technical, and medical literature. Wella has a formal reporting method for adverse reactions to its products in its regulatory compliance division, and I had access to these reports for my annual report to the FDA. In summary, I have spent 20 years in a position in which it was my job to know and continuously monitor the effects of bone cement, to alert operating room personnel to these effects, and to communicate with such personnel and other interested persons, including the FDA, regarding the safe and efficacious use of bone cement. In those years, I never read any paper, saw any report, or heard any comment indicating that sensitization to methyl methacrylate had actually caused rejection of an implant. Experience, therefore, indicates that sensitization to methyl methacrylate is not a problem with joint implants.

I have reviewed the available literature up to the present date using the National Library of Medicine system. The search included information on the allergenicity of methyl methacrylate and related acrylic and methacrylic esters. One-hundred sixty publications and abstracts were reviewed. I also reviewed two existing comprehensive books on bone cements. These books contain information on a number of American as well as European bone cements, some of which contain methyl methacrylate. Neither book mentioned implant failure because of the fallacy of the methyl methacrylate. The literature reviews did not reveal any references concerning difficulties or problems with joint implants as a result of sensitization to methyl methacrylate. Therefore, a patient previously sensitized to this compound still remains a good candidate for a cemented implant. The fact that there is no evidence that sensitization to methyl methacrylate is a problem for joint implants is not surprising.

There is a fundamental difference between the application of methyl methacrylate to the skin and the use of bone cement in an orthopedic patient. In this regard, I would just like to briefly review the history of this very remarkable product called methyl methacrylate, a material that you are all familiar with as plexiglass or lucite. As far back as 1902, a scientist found that by polymerizing a monomeric substance called methyl methacrylate, a clear licite polymer could be obtained. Starting in 1959, various hip prostheses containing polymethyl methacrylate were implanted. Today, we have the advantage that the long history and very high volume of use of methyl methacrylate throughout our society has led to the accumulation of much safety and compatability data. This level of use has also created a very large population of people who have been exposed to the monomer (as well as numerous surgeons, other operating room personnel, and several living patients associated with the use of bone cement) without any evidence that a pre-existing condition of sensitivity to the monomer would make it inadvisable to implant the joint prosthesis.

During the operation for implantation of a joint prosthesis, the patient is shielded from the monomer. In a joint implant, the bony bed of the recipient reacts to the thermal injury of the compound, which the body is able to heal. It can also rid itself of the very small amount of the main monomer that assists in the hardening of cement. The lungs and the metabolic pathways are able to take care of that. Thus, any monomer getting into the blood stream is caught and exhaled through the lungs. The body, via the Kreb's

cycle, can also break down the methyl methacrylate in a pathway that involves transesterification and eventual breakdown to inoccuous products. Patients are not exposed to the potential dermal effects associated with exposure to methyl methacrylate because the skin is never brought in contact with the monomer.

In summary, the implantation of joint prostheses with and without bone cement is now a mature technique, and it is already used on millions of patients. It is highly improbable that we will now see reports of rejection of a cemented implant because of the sensitivity to methyl methacrylate as a constituent of bone cement. This view, of course, has been brought out to you by two very experienced and renowned orthopedic surgeons whose letters you should have before you. They, like numerous domestic and international colleagues, have massive evidence to that effect.

To reiterate, there have been no reports of any medical problems with implant patients who may have been previously sensitized to methyl methacrylate or related acrylates or methacrylic esters. There is no reason to believe that this may occur in the future. [End of Mrs. Blessing's presentation]

Dr. Bailey wanted to know whether Mrs. Blessing was saying that implant rejection in patients previously sensitized to methyl methacrylate is not observed because the technique is such that there is no exposure, and, therefore, no reaction to methyl methacrylate from bone cement during surgery, or if she was saying that people are not sensitized to methyl methacrylate. In other words, did she mean that implants may be provided to sensitized individuals, but that the technique for doing this is such that it doesn't elicit that response?

Dr. Blessing said that she would not be able to say with 100% certainty that either statement is correct. However, she said that because of the irritating effect of the monomer, it is in the interest of the patient, the hospital, and the orthopedic surgeon to protect the patient from any cutaneous irritation or sensitization effect of the monomer.

Dr. Hume (orthopedic surgeon) made the following comments: The patients are exposed to large amounts of the monomer because, when the cement is inserted, it is a very liquid mixture. The cement is inserted in liquid form because the intrusion of the cement into the bony surfaces is desired. So, a high surface area, low viscosity cement is used. There are many situations where patients have multiple exposures to methyl methacrylate over the years. This refers to a situation in which patients have a mechanical failure of the implant and have monomer re-implanted in the same location. The other situation, which is extremely common, is when the patient gets a second knee, or has hip replacement surgery after knee replacement surgery, or has shoulder replacement surgery after hip and knee replacement surgeries. Patients may be subjected to as many as eight isolated situations in which they are exposed to the monomer at relatively high dosages. The dosages can be identified by blood and exhalation levels.

Dr. McEwen said that the fact that this is a medical device means that adverse reactions are required to be reported to FDA, and anything that is unusual is required to be followed up to find the cause. Furthermore, he said that if there were adverse reactions to these products that were caused by sensitization, we all would have expected, over the years that these have been used, that this would have been publicized by now. Dr. McEwen said that the issue that was raised by the Panel, methacrylate-sensitive patients not being able to have hip replacement surgery, is certainly not an issue now based on what is currently being done.

The presentation by Dr. Eric Hume (orthopedic surgeon), on behalf of the Retail Nail Association, is included below:

There is a huge experience among orthopedic surgeons with use of the acrylic cements. Over the past three decades in the United States, methyl methacrylate has been the material, along with the polyethylene bearing, that has made joint replacement the success that we enjoy today. Large numbers of people (in the operating room and on my staff) plus my patients have multiple exposures to methyl methacrylate day after day (several times a day) over many years. With this huge volume of experience, if allergic responses were an issue, with the millions of exposures over 30 to 40 years, we would indeed be seeing allergic responses, but we do not. At the present, cement is still the standard of care in knee replacement because, mechanically, the cement is loaded in such a way that the cement works very well. Concerning the hip, the mechanics of the shear loading across the cement is the basis for moving in the direction of "cementless" devices. We can do a "cementless" implant in any situation, but we are just learning the mechanics of when cement devices are important and when "cementless" devices are important. [End of Dr. Hume's presentation]

Dr. Carlton wanted to know if there are any reports of sensitization in workers.

Dr. Hume said that he does not see sensitization reactions to methyl methacrylate in the operating room; however, there is a problem with sensitization reactions to latex. He said that his workers who are exposed to methyl methacrylate and latex with the same frequency develop latex allergies, but do not develop acrylic allergies.

Dr. Bergfeld asked Dr. Hume to review the rejection phenomenon associated with total hip replacement surgery.

Dr. Hume said that rejection is probably a poor word, and that it has been used too generally. When he started in orthopedics in 1978, it was thought that there was a chemical response, not an allergic response. In fact, there was a term, coined cement disease, that was popular through the early and middle 1980's. Dr. Hume said that it is now known that the foreign body response is to polyethylene, not methyl methacrylate. The response is actually a giant-cell foreign body response a (not a true allergic response).

Dr. Bailey made the following comments concerning methyl methacrylate in artificial nail products: In the 1970's, when FDA initially took action against methyl methacrylate, we had clear reactions. This was not a situation that required a lot of

investigation. We were seeing reports of fairly serious adverse reactions to methyl methacrylate and pulled it off of the market through a court action. So, it hasn't been on the market to a large degree since then, and you are giving a clear picture of its benefit in joint replacement. If methyl methacrylate were to enter the market again, would we see sensitization and would it become an issue for you as surgeons in joint replacement surgery?

Dr. Hume said that the majority of his joint replacement patients receive one exposure, but also noted that many of his patients have artificial nails. He also indicated that he typically performs six to eight joint replacements per week, meaning that he has six to eight exposures to methyl methacrylate monomer through his gloves, plus inhalation exposure. Many of his patients have multiple exposures (i.e., multiple hip or knee replacement surgeries). He added that the American Academy of Orthopedic Surgery issues monographs, and that there is a hip-knee replacement monograph as well as a chapter on acrylics. One of the paragraphs in the chapter on acrylics indicates that allergic responses to acrylics have not been reported in orthopedic surgery and are not an issue.

Dr. Carlton asked Dr. Hume whether he has any data indicating that any of his patients have become sensitized.

Dr. Hume said that he has not seen any evidence of clinical sensitization. In other words, no observations have been made that would warrant patch testing for sensitivity.

Dr. Mitch Sauerhoff's presentation, on behalf of the Retail Nail Association, is included below:

I am going to discuss "Product Chemistry of Artificial Nail-Care Products; Exposure Assessment of Ethyl Methacrylate; and Sensitization to the Use of Methyl Methacrylate in Biomedical Materials". [Copies of transparencies presented are included at the end of the minutes.] This summary presentation captures information that has been provided to CIR. Ethyl Methacrylate has been used in artificial nail care products for over 20 years. In 1994, CIR concluded that Ethyl Methacrylate is safe, however, concern was expressed over the home use of nail products containing Ethyl Methacrylate, based on its sensitization potential. Methyl methacrylate is structurally similar to Ethyl Methacrylate and is used widely in a variety of biomedical applications. CIR expressed concern regarding the sensitization potential of methyl methacrylate as a result of Ethyl Methacrylate exposure. In addition, CIR has expressed concern that sensitization to methyl methacrylate could have adverse medical consequences and/or limit treatment options. You have heard that this is not the case.

My objectives are as follows: (1) present information on the chemistry of Ethyl Methacrylate-containing artificial nail care products, (2) assess Ethyl Methacrylate exposure to artificial nail care product consumers for both dermal contact and inhalation, (3) compare exposure assessment with industry's recognized safe levels of exposure, and (4) determine if cross sensitization between Ethyl Methacrylate and methyl methacrylate is a medical concern.

I have never used retail nail care products, but I am told by industry experts that they consist of a two-component system, an Ethyl Methacrylate monomer and a poly Ethyl Methacrylate polymer. 0.6 g of Ethyl Methacrylate is used per application. Ethyl Methacrylate is a liquid and the polymer is a powder. They are mixed together during the application. This mixing causes a rapid polymerization of the Ethyl Methacrylate. This is documented in three independent tests included in the report that you have. The conclusion is that the rapid polymerization of the Ethyl Methacrylate results in a consequential potential for skin contact or inhalation.

The exposure assessment for home use nail care products will be covered next. The product is designed to be applied to the nail. I have already noted the rapid polymerization. An additional feature to this assessment is the lack of complaints and/or insurance claims regarding allergic reactions. With the widespread use of these products, if there were complaints or problems, the companies manufacturing these products would certainly know about them.

I thought about a calculation of potential inhalation exposure to home use nail care products, in fact, similar to the way that EPA calculates a lifetime average daily dose. The calculations show that the exposure is very, very low, on the order of 0.0065 ppm. I have used conservative assumptions in calculating that exposure, concluding that the potential for exposure to Ethyl Methacrylate is negligible. Because the question, negligible to what, arises, it is helpful to compare this exposure to recognized industry or governmental standards. In the case of Ethyl Methacrylate, there are no EPA or OSHA standards. One U.S. manufacturer has established, as an in house value, 50 ppm as a time-weighted-average TLV and 75 ppm as a ceiling limit for Ethyl Methacrylate. In Holland, a TLV of 10 ppm that has been established. Comparing the 0.0065 ppm with the available standards of exposure, we find that there is over three orders of magnitude between this value and the 10 ppm TLV.

I also reviewed the literature and spent a significant amount of time trying to identify potential adverse reactions resulting from the use of methyl methacrylate, which is used in biomedical applications. The orthopedic elements of this have been covered very well. Methyl methacrylate is used in other biomedical materials in dentistry as well as in orthopedics. However, after reviewing numerous abstracts, I determined that there are no documented cases showing adverse reactions to biomedical materials containing methyl methacrylate.

I would like to close with a couple of comments reiterating points that I have made. Product chemistry is a key element here. The rapid polymerization documents the lack of availability of Ethyl Methacrylate. If you subscribe to the adage that the dose makes the poison, in essence, there is no dose. The home use exposures are well below recognized standards of exposure in industry as well as the baseline for safety that was established by CIR in 1994. The best evidence is that Ethyl Methacrylate, as used in nail

product formulations, is not a sensitizer. The labels for these home use products contain warning statements and use instructions to preclude significant exposure. It is clearly my opinion that the scientific evidence supports the safety of home use formulations containing Ethyl Methacrylate. [End of Dr. Sauerhoff's presentation]

Dr. Belsito said that it is known that methacrylates can penetrate through gloves and wanted to know if there is any available information on the ability of these chemicals to penetrate through the nail plate.

Doug Schoon, with American Beauty Association (ABA), said that his group has done studies showing that the combination of the viscosity and the rapid polymerization prevents penetration of the product. He also said that ABA will submit a letter containing this statement along with supporting data.

Dr. Bergfeld asked that this information be incorporated into the CIR report on Ethyl Methacrylate once it has been received.

Dr. Belsito wanted to know if Ethyl Methacrylate contains any methacrylic acid. He recalled that CIR received information indicating that Acrylates Copolymer contains 3% acrylic acid during the Panel's review of the Acrylates Copolymer ingredient family.

Larry Steffier, with Keystone Industries, stated that his company manufactures monomers and polymers. He said that based on GC, mass spectrometry, and specifications by the major manufacturers around the world, the level of methacrylic acid typically is below 10 ppm.

Dr. McEwen asked that this information be submitted in the form of a letter.

Dr. Bergfeld thanked the speakers for their presentations on methacrylates, and announced that the Panel would now begin its discussion of the CIR report on Ethyl Methacrylate.

Dr. Schroeter noted that the Methacrylate Producers Association, the American Beauty Association, and the Retail Nail Association provided a significant amount of data that have alerted the Panel to the fact that changes to the CIR Final Report on Ethyl Methacrylate need to be made, if for no other reason than to address retail nail products containing Ethyl Methacrylate. Based on the presentations made this morning, Dr. Schroeter noted that the Panel has been reassured relative to safety concerns that the Panel has addressed in previous reviews. Dr. Schroeter then said that in light of all of the information provided, his Team determined that there is no reason to change the Panel's final conclusion on Ethyl Methacrylate, which 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. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate. Dr. Schroeter added that Ethyl Methacrylate has a relatively low degree of sensitization.

The Panel voted unanimously in favor of reaffirming its conclusion on the safety of Ethyl Methacrylate that is stated in the preceding paragraph.

Dr. Schroeter indicated that the present report discussion needs to be revised, taking into consideration that nail products containing Ethyl Methacrylate are available for retail sale and that the report discussion states that Ethyl Methacrylate should not be used in products intended for retail sale.

Dr. Schroeter also communicated his Team's concern over the sensitization potential of Ethyl Methacrylate, though it is low, and recommended the following changes in the report discussion (last sentence of 4th paragraph and first sentence of 5th paragraph) to reflect this: In order to minimize any exposure to the free monomer, the Expert Panel recommends that commercial fingernail enhancement products containing Ethyl Methacrylate be applied by trained individuals to avoid skin contact so as to reduce possible allergic reactions (paragraph 4) - Likewise, individuals using retail products at home should be provided with instructions adequate to insure that skin contact does not occur so as to reduce possible allergic reactions (paragraph 5).

Dr. Belsito said that the statement relating to the sensitization potential of Ethyl Methacrylate in the report conclusion is not adequate, and recommended that the conclusion be revised to state that the ingredient is safe as used when the product is labeled to indicate that skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate. The old 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. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate.

Dr. McEwen noted that the term labeled or labeling implies some type of regulatory status and did not favor the use of either term in the report conclusion. He requested that the term should be replaced with language indicating that instructions will be provided.

Dr. Andersen recommended that language in the report conclusion on AHAs (i.e., when application is accompanied by directions for....) be incorporated into the Ethyl Methacrylate report.

The Panel unanimously approved the following modified 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. [This action was necessary because the Panel had voted to reaffirm its original conclusion on Ethyl Methacrylate earlier in the minutes.]

Dr. Belsito stated that the Panel has been informed that information from two letters (relative to nail penetration and methacrylic acid or acrylic acid content, respectively) that are forthcoming will be included in the Ethyl Methacrylate report.

A representative of the Methacrylate Producers Association added that in addition to information on methacrylic acid or acrylic acid content, information on the amount of residual methyl methacrylate in the formulation of Ethyl Methacrylate or, in fact, any other monomers, should also be included. He said that methyl methacrylate may be a contaminant of Ethyl Methacrylate, and that he will provide CIR with information on the content of methyl methacrylate or any other monomer in Ethyl Methacrylate.

Dr. Andersen said that new information regarding various surveys of patch test results has been included in the Ethyl Methacrylate report. He also said that the results of Team discussions on the preceding day seem to support the classification of Ethyl Methacrylate as a weak sensitizer, and that it would be the Panel's intention to so characterize these results in the report discussion prior to announcement of the tentative revised conclusion.

Dr. Bergfeld wanted to know exactly how the insert that was provided by Drs. Storrs and Kanerva will be used.

Dr. Andersen noted that the surveys of patch test results (in CIR report) that he was referring to are the data provided by Drs. Storrs and Kanerva. He indicated that the data received yesterday (from Tucker and Beck experience on the 15-year study of patch testing of methacrylates) will also be added. He also said that the characterization of all of these data in the report discussion will be that Ethyl Methacrylate is a weak sensitizer

December 20-21, 1999

The Panel voted unanimously in favor of issuing a 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.

ORIGINAL REVIEW OF ETHYL METHACRYLATE

May 1993

Dr. Bergfeld noted that a clastogenic assay and irritation and sensitization data were requested informally, but that no data were received. The Panel has to determine whether or not an Insufficient Data Announcement should be issued or if the Panel has enough information in order to reach a conclusion.

Dr. Belsito said that his Team expressed very strong concern about the sensitization potential of Ethyl Methacrylate. This ingredient is a strong sensitizer in guinea pigs. Another basis for Dr. Belsito's concern results from his experience with patch testing patients with Ethyl Methacrylate and the cross reactivity of the methacrylates. He concluded that this ingredient could be banned from use in cosmetics based on its substantial ability to induce sensitization.

Dr. Bergfeld reminded Dr. Belsito that the only human studies that are documented in the Draft Tentative report are those involving patients with dermatitis.

Dr. Belsito then noted that his Team members had determined that additional human sensitization studies are needed.

Dr. Belsito reiterated that he is still considering the idea of banning Ethyl Methacrylate and not requesting additional information, based on the guinea pig sensitization study and cross reactivity with other methacrylates, particularly methyl methacrylate. Methyl methacrylate is still the principal bone cement that is used for any type of joint replacement surgery. Thus, an entire population is being placed at risk with respect to being sensitized to this material.

Dr. Schroeter stated that his Team shares some of the same concerns that were expressed by Dr. Belsito's Team. Additionally, there is concern about teratogenicity. Based on teratogenicity data, Dr. Schroeter said that Ethyl Methacrylate would have to be declared unsafe. Furthermore, if this is true, then the issue of dermal sensitization is irrelevant.

Dr. Schroeter's Team agreed that Ethyl Methacrylate is a sensitizer, but that the extent of its sensitization potential is questionable. Dr. Schroeter expressed uncertainty as to whether his Team would ban the ingredient based on the sensitization data included in the report. He said that Ethyl Methacrylate is an ingredient in nail polish and that there is limited exposure to the skin. Thus, the sensitization data in the report is not as relevant as the teratogenicity data.

Concerning the teratogenicity data, Dr. Shank noted that only one study is included in the report and that all three doses tested resulted in significant teratogenic effects.

Dr. Bergfeld asked if there would be any need to repeat the study or use another animal model.

Dr. Schroeter expressed concern about dermal absorption.

Dr. Shank said that Ethyl Methacrylate is used only in nail polish. Therefore, how much is going to be absorbed may be a real question. He was not convinced that applying a formulation to the fingernail precludes absorption. Data would be needed in order

to prove that. If there is no absorption after application to the fingernail, then there is no need to worry about sensitization or teratogenicity.

Dr. Bergfeld asked if Dr. Shank was referring to absorption through the plate, through the skin surrounding the nail, or just skin absorption studies.

Dr. Shank said that he was probably referring to absorption through the nail itself.

Dr. Bergfeld noted that nail polish comes in contact with skin around the nail.

Dr. McEwen said that the Panel must keep in mind that the teratogenicity study involves i.p. injection. Furthermore, based on a safety factor calculation incorporating the classical safety factors used by regulatory agencies, it would be sufficient in this case to say that dermal application of Ethyl Methacrylate is safe.

Mr. Eiermann said that polymerization of Ethyl Methacrylate occurs. Thus, a very small amount of residual Ethyl Methacrylate remains. Most of the Ethyl Methacrylate polymerizes rather quickly on the nail. Furthermore, FDA has said that Ethyl Methacrylate can be safely used if applied with a nail shield. In other words, the surrounding cuticle (area around the nail) should be covered.

Dr. Carlton mentioned that the teratogenicity study is not a good study. Ethyl Methacrylate was injected intraperitoneally, only five animals were used, and there were very few fetuses. The designation of a lesion as a hemangioma immediately places the study in question. Hemangiomas are not observations that one would think about in terms of teratogenesis.

Dr. Slaga acknowledged that there are some inconsistencies in the teratogenicity study. However, considering the number of fetuses that were examined, there are some clear effects that warrant further investigation. Dr. Slaga also noted that Ethyl Methacrylate polymerizes and that very little breakdown or dermal absorption is going to occur. How one would test this chemical dermally is questionable. (i.e. Should the pure chemical or the polymer be tested?)

The Panel agreed that a dermal teratogenicity study would not be requested.

Dr. Belsito surmised that the polymerized form of Ethyl Methacrylate would not be dermally absorbed, thus, dismissing any teratogenic effects. However, positive sensitization data remain; 100% of the guinea pigs tested were sensitized. Dr. Belsito asked the Panel if any additional data would be needed in order for Ethyl Methacrylate to be declared unsafe, based on its capability of inducing sensitization.

Dr. Slaga said that additional data would not be needed in order for the Panel to declare Ethyl Methacrylate unsafe.

Dr. Schroeter recalled that all nine guinea pigs were sensitized in the study; Ethyl Methacrylate is a sensitizer. However, when one examines the human study involving 542 dermatitis patients (included in Draft Tentative report), one sees a sensitization rate of 1.0%. He then questioned banning Ethyl Methacrylate, in that there is a 1.0% sensitization risk within a population.

Dr. Belsito mentioned that in this human study, one subject had skin irritation and four subjects were sensitized. In clarifying this study, he said that 541 patients were being evaluated for allergic contact dermatitis. Methacrylates, particularly in Scandinavia (where the study was done), are not widely used in cosmetics. Therefore, the 1.0% rate is a factor of exposure, whereas, exposure to methylchloroisothiazolinone and to Bronopol was much higher because these products were actually used in cosmetic formulations in this country and in Europe. Dr. Belsito also said that, in his estimation, one would see a very high sensitization rate if a human sensitization study on Ethyl Methacrylate were conducted.

Dr. Bergfeld said that the Panel has the option of either restricting the use of Ethyl Methacrylate only to nail products (shield used during application), or restricting the use concentration.

Dr. Belsito said that the leading cause of eyelid dermatitis in women is toluenesulfonamide resin in nail polish, in terms of allergenicity. So restricting the use of this ingredient to nail polish is not going to prevent the incidence of sensitization. The product is largely used in nail sculpting, which is done with cyanoacrylates. Each time the nail is buffed, the polymer will be "powderized" and the powder is going to come in contact with the skin and induce sensitization. It was once thought that individuals would not react to cyanoacrylate because it polymerized so quickly.

Dr. Carlton asked if Dr. Belsito was suggesting that sensitization reactions in humans may be due to the Ethyl Methacrylate polymer. He noted that the Panel has information indicating that, perhaps, very small amounts of free Ethyl Methacrylate may be present in the polymer. Dr. Carlton also wanted to know if that small amount is adequate for inducing sensitization.

Dr. Belsito said that the small amount is adequate for inducing sensitization. In fact, there are individuals who object to standard screening panels that contain any of the acrylates, acrylates and methacrylates included, because of the risk of sensitization just in doing standard patch testing.

Given Dr. Belsito's response, Dr. Carlton wanted to know if it would be considered unethical to request a human sensitization study on Ethyl Methacrylate.

Dr. Belsito said that this type of study could be done because test subjects are always made aware of any implications associated with being tested. Therefore, ethically, this type of testing could be done. Dr. Belsito said that he would not want to conduct such a study because he is convinced that, in so doing, a large percentage of the subjects tested would become sensitized.

Dr. Carlton wanted to know if the Panel should have human sensitization data before making a decision to ban Ethyl Methacrylate.

Dr. Belsito said that if the Panel feels that the sensitization study involving nine guinea pigs is insufficient, then additional guinea pig sensitization data should be requested.

Dr. Bergfeld recalled from the CIR Final Report on Chloroacetamide that the Panel concluded that Chloroacetamide is unsafe for use as a cosmetic ingredient. This conclusion is based on the decision that this ingredient was a potential human sensitizer at use concentrations. The Panel's final conclusion on Chloroacetamide is as follows: Based upon the data included in this report and the reconfirmation that Chloroacetamide is a potential human sensitizer at use concentrations, the Expert Panel concludes that Chloroacetamide is unsafe for use as a cosmetic ingredient.

Dr. McEwen said that the test that he thought the Panel was asking for could easily be done by testing the product (nail polish) with Ethyl Methacrylate in it, as it is formulated. In his opinion, this is the key information that is missing that would allow the Panel to have some sense that Ethyl Methacrylate is acceptable, even when its sensitization potential is taken into consideration.

Dr. Shank said if Ethyl Methacrylate is not declared unsafe based on its sensitization potential, then a good teratogenicity bioassay needs to be requested.

Dr. Bergfeld said that the Panel needs to focus first on clarifying the sensitization potential of Ethyl Methacrylate, and this would entail doing some type of study. A human sensitization study, rather than an animal study, has been suggested.

Dr. Belsito said that if industry wants to test Ethyl Methacrylate as it is used, then the concentration that is used should be incorporated into a petrolatum type of vehicle.

Dr. Bergfeld said that the Panel would request a human irritation and sensitization study; the standard number of subjects has been 150. The comment was made that pulverized nail polish in petrolatum should be tested. Additionally, the test should be a 48 h patch test, with readings at 72 and 96 h.

Dr. Bergfeld then mentioned that the issue of teratogenicity needed to be addressed.

Dr. Carlton said that if Ethyl Methacrylate is a sensitizer in humans, the Panel will probably ban this ingredient, and an additional teratogenicity study will not be needed.

The Panel voted in favor of issuing an Insufficient Data Announcement that contains the following data requests: (1) Human irritation and sensitization using a dry powdered formulation and (2) Teratogenicity data.* [* Because of the possibility that this material will be a potent irritant, the CIR Expert Panel would want to review any data on human irritation and sensitization before any teratogenicity testing is undertaken.]

November 22-23, 1999

Dr. Schroeter stated that the Panel issued an Insufficient Data Announcement on Ethyl Methacrylate at the May 1993 Expert Panel meeting. The data requested in this announcement are as follows:

(1) Human irritation and sensitization using a dry powdered formulation*
(2) teratogenicity data

* Because of the possibility that this material will be a potent irritant, the CIR Expert Panel would want to review any data on human irritation and sensitization before any teratogenicity testing is undertaken.

He noted that Ethyl Methacrylate is used mostly in nail sculpting, and, for this reason, it is to be tested as a dry powdered formulation in the human skin irritation and sensitization study. He also said that a considerable amount of irritation of the respiratory tract and sensitization is observed in manicurists. Dr. Schroeter noted that there is also concern about the teratogenic potential of Ethyl Methacrylate, and that the Expert Panel noted that the available study is a poor indicator of teratogenicity because intraperitoneal injection was the route of exposure. It was concluded that an oral or dermal teratogenicity study should be a better indicator of teratogenic potential. Dr. Schroeter's Team concluded that the data in the report on Ethyl Methacrylate are insufficient for determining whether or not this ingredient is safe for use in cosmetics.

Dr. Belsito said that his Team had also concluded that the data on Ethyl Methacrylate are insufficient. However, in his opinion, Ethyl Methacrylate is unsafe just based upon the high rate of sensitization in guinea pigs and cross reactivity with methyl methacrylate (the major bone cement that is being used in orthopedic surgery). With this in mind, an individual may become sensitized to methacrylate and then not be able to have hip replacement surgery. Dr. Belsito said that even in the absence of human tests, there is sufficient data available to declare Ethyl Methacrylate unsafe.

Dr. Schroeter agreed that Ethyl Methacrylate is a significant sensitizer.

Dr. Bergfeld noted that the Expert Panel had declared Chloroacetamide, a cosmetic preservative, unsafe based on its sensitization potential. She stated the Panel's conclusion on this ingredient as follows: Based on the data included in this report and the reconfirmation that Chloroacetamide is a potential human sensitizer at use concentrations, the Expert Panel concludes that Chloroacetamide is unsafe for use as a cosmetic ingredient.

Dr. Schroeter agreed with Dr. Belsito, in that Ethyl Methacrylate could be declared unsafe based on the guinea pig sensitization and cross sensitivity data included in the CIR report. He also thought that the Panel's concern about the teratogenicity of Ethyl Methacrylate should be addressed in the discussion section of the report.

Dr. Bergfeld was concerned that the latest publication on methacrylate cross reactivity that is included in the CIR report is dated 1978. She asked Dr. Belsito if the North American Contact Dermatitis Group has more recent information.

Dr. Belsito said that Ethyl Methacrylate is not included on the North American Contact Dermatitis Group standard tray because there is a great debate as to whether one should routinely apply methacrylates to a patient, unless one absolutely believes that the patient has an allergy that is related to this ingredient.

Dr. Belsito moved that the Panel declare Ethyl Methacrylate unsafe based on the high rate of sensitization in the guinea pig studies and the potential for cross reactivity across a broad group of methacrylates.

Dr. Schroeter said that he would second the motion, with the caveat that the Panel would see the report discussion (to be developed) before voting on the conclusion that has been proposed.

Dr. Bergfeld noted that the motion had not been seconded by Dr. Schroeter because a caveat had been added. She then said that Dr. Schroeter's caveat may actually be a suggestion to table the report on Ethyl Methacrylate and develop a report discussion which serves as the basis for a conclusion of unsafe.

Dr. Belsito noted that Lassie Konerva, expert on the cross reactivity of methacrylates, would be attending the December 1993 American Academy of Dermatology meeting in Washington D.C. He said that he could possibly contact Dr. Konerva and ask him to bring any information that he has on sensitization rates in Finland, particularly data on cross reactivity in humans.

Dr. Bergfeld suggested that the CIR report on Ethyl Methacrylate be tabled, pending sensitization and cross reactivity data on Ethyl Methacrylate from Dr. Lassie Konerva.

The Panel voted in favor of tabling the document until the next Panel meeting

February-March 1, 1994

The Panel was also reminded that representatives of the Nail Manufacturers Council and Creative Nail Design would be making presentations on Ethyl Methacrylate during the public session on the following day. The information presented will be supportive of the company's suggestion that the sensitization potential of Ethyl Methacrylate is not a major concern. Dr. McEwen noted that Ethyl Methacrylate is not used in any retail products and, therefore, the focus of the presentations will be on occupational exposure.

Presentation by Doug Schoon, consultant to the Nail Manufacturers Council

Initially, a presentation on Ethyl Methacrylate was given by Mr. Doug Schoon, consultant to the Nail Manufacturers Council. Excerpts from this presentation are as follows:

Although it is clear that Methyl Methacrylate is a strong sensitizer, it may be that Ethyl Methacrylate is quite a bit lower in sensitization potential. There are no hard data to support this, but the process of accumulating these data is in progress. Based on insurance claims, complaints received on hot lines, and based on personal interviews with individuals over the last five years, this information supports the fact that Ethyl Methacrylate has low sensitization potential. Part of the reason is in the way that the products are formulated. The issue here is whether we are cross-sensitizing to methyl methacrylate, but if you look at the methyl methacrylate type bone cements, you typically end up with 2 or 3% unreacted monomer, and that can be problematic. However, because we are looking at highly cross-linked systems, the molecular weight of a bone cement might be on the order of a quarter of a million, whereas, the molecular weights of these materials that we are looking at are many millions, maybe even tens of millions, which means trifunctional and difunctional cross-linking agents. Because the recent trend in the industry is using faster setting products, higher molecular weight materials, we expect to exceed the highest polymerization level that bone cement would achieve in several days, but will reach that point within several hours. With bone cements, the maximum cross-link density is usually reached in 18 h. This has been confirmed using differential scanning calorimetry. Many studies have been done using this method to verify that the unreacted monomer content is well below 0.5%, and, within 24 h, it drops to below the detection limits for that method.

The problem of sensitization reactions to nail products is not so much due to presence of the monomer. When nail technicians work, if they are not trained and licensed, they tend to brush Ethyl Methacrylate across the cuticle. This prolongs the repeated contact.

We would like to receive input from the Panel as to what should be studied and the types of information the Panel wants. Obviously, we would like to examine the percentage of people who have been sensitized and the likelihood of cross-sensitization

to methyl methacrylate. A few studies suggest that this is possible, but, we want to determine whether or not this is a probable occurrence. It may also be that sensitivity to Ethyl Methacrylate is permanent. There are cases in which individuals who had been sensitized to Ethyl Methacrylate products and, after several years, discovered that they were no longer sensitive after product use had been resumed. This was true especially for technicians who returned to a nail practitioning group that actually used the procedures and the recommendations that the Nail Manufacturers Council and each of the individual manufacturers suggest.

It may be possible to examine some case studies to determine whether there is a problem with individuals becoming cross-sensitized to bone cements. Based on the new technology (the better balance between the catalyst and activators, better linking agents, third generation monomers that are known to be of low sensitivity and low reactivity to the skin, and faster set times that allow the products to adhere to the nail, cure up, and reach low residual monomer very quickly), the incidence of sensitization has been drastically reduced.

Dr. Bergfeld asked Mr. Schoon if he was speaking on behalf of the nail industry when he made a pledge to do whatever is necessary in order to clarify Ethyl Methacrylate induced sensitization.

Mr. Schoon stated that, as a consultant to the Nail Manufacturers Council, he feels that industry wants to cooperate.

Dr. McEwen asked Mr. Schoon to comment on potential alternatives to using Ethyl Methacrylate.

Mr. Schoon said that there are no alternatives that he is aware of.

Dr. Belsito asked if the typical nail product consists of Ethyl Methacrylate as a monofunctional acrylate combined with di- and tri-functional acrylates. In other words, Ethyl Methacrylate is one component of a multicomponent product.

Mr. Schoon agreed and added that the di- and tri-functional products are

usually fairly high in molecular weight, and the feeling is that they are less likely to penetrate the skin.

Dr. Bergfeld recalled that Mr. Schoon had stated earlier that if nail technicians were trained properly, the sensitization rate in clients would probably be reduced.

Mr. Schoon agreed that the source of the problem is nail technicians who don't understand that the product should not come in contact with the cuticle.

Ms. Fise asked Mr. Schoon if he shares Dr. McEwen's assessment that nail products containing Ethyl Methacrylate cannot be purchased by the consumer.

Mr. Schoon said that he agreed with Dr. McEwen's assessment. Furthermore, he said that his industry is very careful to make sure that these products are for professional use only, and a statement to this effect appears on the label.

In response to Dr. Bergfeld's question, Mr. Schoon noted that the sensitization rate in nail technicians is surprisingly low. Usually, sensitization reactions in this group result from either their tendency to brush the brush that was immersed in the product with the fingertips or direct contact with a wet product container.

Dr. Bailey wanted to know if a monitoring system exists whereby feedback concerning sensitization can be obtained from trained technicians.

Mr. Schoon said that hotlines exist. He noted that the complaints on Ethyl Methacrylate-based materials are exceedingly low compared to some of the other complaints that have been received. In general, sensitization is in the lower quarter of complaints.

Ms. Fise asked Mr. Schoon if he would ever recommend use of products containing Ethyl Methacrylate by the consumer.

Mr. Schoon said that these products should not be used without proper training and education. He also said that he would not venture to guess whether or not the consumer could ever be trained to use these products or whether or not the products could ever be made safe enough for the consumer to use.

Dr. Shank wanted to know how nail products containing Ethyl Methacrylate are applied.

Mr. Schoon said that the natural nail can either be overlaid with a thin layer of a liquid and powder mixture that hardens very quickly or an ABS type tip can be glued with cyanoacrylate onto the nail. The nail can then be shaped and an overlay can be performed on the shaped nail.

A second presentation was made by Mr. Jim Nordstrom, Vice President of the Nail Manufacturers Council:

The companies represented by the Nail Manufacturers Council are companies that manufacture products for the salon. Within the last year or two, we have seen the emergence of a few retail companies that are offering products in this category to the retail trade. However, these companies are not part of our group or industry. Our industry has been in existence for approximately 20 years. As an aside, forty-six states currently have licensing in place. Typically, there are two components to licensing, a cosmetology license and a license specifically for manicurists. This requires 350 to 500 hours of education and passing a state board.

Two weeks in advance of this meeting records from my company (Creative Nail Design) and from one other company were obtained. If these two companies were viewed as one large company, we feel that this would translate into 50% market share of

the Ethyl Methacrylate monomer-polymer based systems market. Based on company records, we determined allergic reaction and skin sensitivity rates of 0.000315%. This figure is based on an extrapolation of data (supplied by Creative Nail Design and a competitor) from telephone conversations (hotlines), insurance records, and written complaints. Additionally, based on the number of products that we sell, we estimate that the number of wearers in the United States is approximately 7 million. The number of wearers outside of the United States is approximately 1 million.

Another important point that I wish to make is that in going through initial records and data, we found that there was a disproportionate number of reported cases in Los Angeles county and New York City, compared to a national average. Typically, this is due to a high incidence of unlicensed manicurists performing services. New York state passed licensing requirements just last year and is in the process of having those implemented.

On behalf of the Nail Manufacturers Council (57 members), we are willing to cooperate 100% with the recommendations of the Panel.

Ms. Fise expressed concern over the emerging retail products.

Mr. Nordstrom said that some retail products have emerged into the marketplace; many companies are involved.

Dr. Bailey said that if the number of complaints (2200 per 7.7 million units, based on company data) for Ethyl Methacrylate products is normalized, the result is approximately 300 per million units used. He noted that this rate is considered to be high and is approximately ten times that observed in the voluntary reporting program for high incidence products such as home permanents (between 30 and 40 per million units distributed).

EXPERT PANEL'S DELIBERATIONS ON ETHYL METHACRYLATE

Dr. Schroeter noted that his Team had reviewed the data, submitted by Dr. Lasse Kanerva, that were accumulated at a patch test clinic in Finland from 1985 to 1989 and concluded that Ethyl Methacrylate sensitization in the general population is relatively low. He also said that appropriate application of hair products containing Ethyl Methacrylate, together with the fact that this ingredient is slowly or poorly absorbed, further reduce the risk of sensitization. Dr. Schroeter's Team agreed that the sensitization potential of Ethyl Methacrylate and the lack of teratogenicity data should be addressed in the report discussion.

Dr. Schroeter also noted that protection of the consumer is the Panel's concern. The Panel has the responsibility of indicating that Ethyl Methacrylate is a strong sensitizer and that utmost care should be taken in minimizing skin contact.

Ms. Fise agreed that protection of the consumer is the ultimate goal and that the Panel can protect the consumer by very affirmatively stating that the consumer should not be applying nail products containing Ethyl Methacrylate.

Dr. McEwen proposed that it could be stated in the report conclusion that, for the consumer, these products should not be used where skin contact is likely. Additionally, the report discussion could contain significant information on use of Ethyl Methacrylate in professional products and the need for proper training in their use.

Regarding the sensitization data from Finland that were submitted by Dr. Lasse Kanerva, Dr. Belsito noted that one of the problems associated with examining incidence rates for acrylate sensitization is that there is great concern among individuals who patch test that sensitization can occur during the course of patch testing. Therefore, patch testing with acrylates is not routinely done. Furthermore, Dr. Kanerva's data have to be evaluated from the standpoint that 124 patients, each with an allergy, were using acrylates and the percentage of those patients who ended up being allergic. From this standpoint, a significant percentage of the patients exposed to acrylates developed allergy. Dr. Belsito also noted that, in his opinion, the reason why more allergic reactions are not observed is because exposure is limited.

Dr. Belsito recalled that acrylate allergies were a major problem in plastics, aerospace, and automobile industries, and that a large proportion of the work with acrylates has become automated because of problems with sensitization. He acknowledged that there probably aren't any good data on the incidence of Ethyl Methacrylate sensitization, but also recognized the very strong sensitization data on this ingredient in guinea pigs.

Dr. Belsito also indicated his concern about the cross-reactivity of Ethyl Methacrylate with a major bone cement and the very high number of consumer complaints. On the latter concern, he noted that many of the observed acrylate allergies are small patchy rashes around the periungual area and some patchy rashes on the face and neck. Furthermore, patients may not associate this rash with their use of nail products, because it develops days after exposure and not immediately after exposure. With this in mind, Dr. Belsito said that it seems as though the degree of Ethyl Methacrylate sensitization is not known. He then reiterated that studies involving guinea pigs suggest a high degree of sensitization and that Ethyl Methacrylate is capable of cross-reacting with other methacrylates. Therefore, there is still reason for concern about Ethyl Methacrylate-induced sensitization.

Dr. Schroeter noted that in addition to information on the sensitization potential of Ethyl Methacrylate, the issues of cross-reactivity and teratogenicity (lack of data) should be mentioned in the report discussion.

Dr. Andersen agreed that it could be stated in the report discussion that teratogenicity data are not needed because of low exposure to Ethyl Methacrylate and its low absorption potential. However, he noted that it was unclear to him exactly what should be discussed in terms of cross-reactivity.

Dr. Schroeter said that it is known that cross-reactive sensitization is associated with ethyl, methyl, and butyl methacrylates and that a statement to the effect that this is of concern should be included in the report discussion.

Dr. Belsito said that there is definite cross-reactivity, and that this should be discussed as potential cross-reactivity or co-reactivity from co-exposure to the acrylates.

Dr. Carlton mentioned that representatives of the nail industry emphasized in their presentation that Ethyl Methacrylate is mixed with other acrylates (polyfunctional) and that it is rapidly used up in the reaction mixture. Therefore, the Panel should emphasize that there is probably no Ethyl Methacrylate monomer left in the product to induce sensitization. How nail products containing Ethyl Methacrylate are used and how rapidly the monomer is used up in formulation should be mentioned in the report discussion.

Dr. Belsito expressed concern over the production of powder during the process of filing, buffing, or wrapping the nails after product application.

Mr. Schoon agreed that powders are generated and stated that dust masks should be worn by technicians. He also said that the monomer on the nail is not completely hardened when filing and shaping of the nail is begun. However, a significant portion of the cross-linking has occurred, and the monomer is not believed to be leachable at this point. The monomer is pretty much trapped in the matrix because of the three dimensional network that has been set up.

Dr. Belsito recalled that he has observed positive patch test reactions to the dust from nail wraps in patients and positive reactions to cyanoacrylates. He also noted that he has observed positive reactions to the dust of cyanoacrylate glues that presumably are very rapidly polymerized.

Mr. Schoon noted that cyanoacrylates are linear monomers that are not cross-linked, and that Dr. Belsito's concern relating to their sensitization potential is well taken. He then explained that, with Ethyl Methacrylate, the network that is set up makes it very difficult for the monomer to escape.

Dr. Carlton asked Mr. Schoon if he could supply the Panel with data substantiating the rapid polymerization and extinction of the monomer.

Mr. Schoon said that the Panel can be supplied with these data.

Dr. Belsito noted that the Panel also needs data on the amount of unreacted Ethyl Methacrylate monomer, and said that he would feel more comfortable if the Panel could receive verification of Dr. Bailey's earlier comments. Dr. Bailey had noted that the number of consumer complaints on nail products containing Ethyl Methacrylate is greater than what is observed for high incidence products, such as home permanents, in the voluntary program.

Dr. Belsito also requested from the nail industry information on the incidence of consumer complaints on nail products containing Ethyl Methacrylate before and after the implementation of state regulations. These data would give some indication of the impact of regulations requiring that cosmetologists be trained on reducing the improper application of these products. It was requested that the data be presented on a state-by-state basis. However, in response to Mr. Nordstrom's suggestion, Dr. Belsito agreed that a comparison between New York City and Chicago would be acceptable. Dr. Belsito also wanted to know whether there has been a change, over time, with respect to the number of consumer complaints on Ethyl Methacrylate-containing nail products that have been reported to FDA.

Drs. Bergfeld and Andersen suggested that the Panel delay the issuance of a Tentative Report on Ethyl Methacrylate until the May 23-24, 1994 Panel meeting, by which time the data promised by the Nail Manufacturers Council will have been received and incorporated into the Draft Report.

Dr. McEwen asserted that the Panel has sufficient information for arriving at a conclusion on Ethyl Methacrylate and that the information that is anticipated is not directly related to the conclusion, but simply supports it.

Ms. Fise stated her preference for a conclusion on Ethyl Methacrylate that is very explicit. Specifically, it should be stated in the conclusion that this ingredient is safe for use only in products that are sold to and applied by trained professionals.

With the exception of one abstention (Dr. Belsito), the Panel approved the following conclusion on Ethyl Methacrylate: 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 by trained individuals. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate.

Dr. Bergfeld noted that the report on Ethyl Methacrylate would be submitted to the Panel for a mail review. The Panel needs to review the report discussion, the substance of which was mentioned during the Panel's deliberations.

It was also noted by Dr. Andersen that an article, entitled Widespread Contact Dermatitis From Sculptured Nails, appeared in **Contact Dermatitis**, Volume 30 (1994), and may raise concerns because of the implication of the title. The term, widespread in the title means over large parts of the body, as opposed to frequent occurrences of adverse effects. This article was mentioned because it is current and the Panel will be discussing Ethyl Methacrylate at this meeting.

Dr. Schroeter read the following conclusion on Ethyl Methacrylate that was drafted by the Expert Panel: 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 by trained individuals. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate. He then proposed deleting the last sentence in the first paragraph of the discussion, which reads as follows: Ethyl Methacrylate should not be used in products intended for retail sale. This statement should be deleted because, in Dr. Schroeter's opinion, it is not the Panel's intent to dictate how products are to be sold, but only to recommend that the products should be applied by trained individuals.

Dr. Belsito said that his Team is of the opinion that the data included in the Draft Report are insufficient for determining whether or not Ethyl Methacrylate is safe. Furthermore, in order for this position to be changed, The Belsito Team would have to be convinced that when products containing Ethyl Methacrylate are applied by trained individuals, one does not see the high incidence of sensitization that appears to occur when these products are applied by untrained individuals. Dr. Belsito said that the types of data that would be needed in order for his Team to feel more comfortable with approving Ethyl Methacrylate, with the restrictions stated in the report conclusion, are: (1) the sensitization rate in Chicago, Illinois, where products containing Ethyl Methacrylate are regulated, versus the sensitization rate in New York, where these products most recently have become regulated and (2) longitudinal data from Chicago, Illinois, where the rate actually decreased over time following the passage of legislation relating to the licensing of cosmetologists. Dr. Belsito noted that these data were promised at the last Expert Panel meeting.

Dr. Andersen noted that the conclusion that was read by Dr. Schroeter at the beginning of the discussion was approved by the Panel at the last meeting.

Dr. Belsito said that the conclusion was made, taking into consideration data that were promised, and these data still have not been received.

Dr. Schroeter noted that at the time that the Panel developed its conclusion and asked for additional data to provide justification for the product being applied by trained personnel, there was a higher incidence of contact allergy in the population, as estimated. Since that time, this has been corrected to the extent that the incidence is now very low. Taking this into consideration, it is questionable whether the comparison between New York and Chicago would yield a statistically significant difference. He also said that if the statement (in report conclusion) to the effect that Ethyl Methacrylate is safe as used by trained individuals is to remain in the conclusion, there should be more information to justify that this practice would result in a lower incidence of sensitization.

Mr. Schoon, with Creative Nail Design, said that he did not have the data that the Panel had requested because the period of time since New York and Illinois became licensed has been too short, and because the magnitude of the effort (response to Panel's request) would have taken more time. Such an effort could probably be completed after a year or two of data collection. However, he suggested that the revised data submitted to the Panel would show that Ethyl Methacrylate is much less likely to cause sensitization than previously believed. He apologized for the error that was made in the original calculation.

Concerning the FDA data on consumer complaints, Mr. Schoon said that he had reviewed the injury reports that were submitted by consumers during the years 1987 to 1993. He noted that quite a few of the reports are not in any way related to Ethyl Methacrylate.

Dr. Schroeter recommended that the phrase, safe as used by trained individuals, be changed to safe as used in the report conclusion, considering that the data, promised by the nail industry, that may have supported the former conclusion do not exist.

Given Dr. Schroeter's proposed change in the conclusion, Dr. Belsito wanted to know how the issue of uncured monomer, which may come in contact with the skin, existing for 5 min should be dealt with. He also wanted to know how one could justify classifying a compound that yielded positive results in a guinea pig maximization test as safe as used without restricting it to retail sale.

Dr. Schroeter said that Dr. Belsito's concern seems to be that the technician would begin to file the nails at a time before there is a critical reduction in the monomer, which would not produce an adverse effect.

Mr. Schoon said that after the chemicals are mixed, by the time the point at which the nail technician can begin to shape the nail with a file is reached, essentially less than 1% monomer is present.

Dr. Belsito said that less than 1% monomer is present because multifunctional acrylates are in the formulation.

Mr. Schoon said that the Ethyl Methacrylate nail products are never formulated without trifunctional crosslinks; at least, this has been the case for the last ten years.

Dr. Schroeter said that the fact that Ethyl Methacrylate is formulated with trifunctional crosslinks should be mentioned in the report discussion.

Dr. Carlton wanted to know if Ethyl Methacrylate is considered safe for use by untrained individuals, and if this is not the case, why the phrase safe as used by trained individuals should be deleted from the conclusion.

Drs. Belsito and Schroeter agreed that the Panel does not have data indicating that Ethyl Methacrylate is safe as used by untrained individuals.

Dr. Schroeter said that the Panel can only suspect that products containing Ethyl Methacrylate will be safe if applied correctly, and, therefore, that they are probably safer if applied by trained individuals. He also said that the phrase, safe as used by trained individuals, should be deleted because the Panel does not have data that support this conclusion.

Dr. Andersen recalled that, at the last Panel meeting, Mr. Schoon indicated that there may be some products containing Ethyl Methacrylate that are being sold directly to consumers for their own use. He also said that his concern is that he can interpret the report discussion to mean that the Panel expects that the vast majority of exclusive use of these products is through professional application, and understand that the conclusion, safe as used, relates to that professional application.

Dr. Schroeter agreed with Dr. Andersen's interpretation of the discussion and conclusion.

Dr. Bergfeld noted that Dr. Schroeter had proposed deleting the reference to trained individuals from the conclusion, and was concerned that use by trained individuals would not be addressed anywhere in the report.

Dr. Schroeter said that though the reference to use by trained individuals was being deleted from the conclusion, the following statement relative to this concern is included in the discussion: In order to minimize any exposure to the free monomer, the Expert Panel recommends that fingernail enhancement products containing Ethyl Methacrylate be applied only by trained individuals and that skin contact be avoided.

Dr. Gettings suggested that the fact that Ethyl Methacrylate is formulated with multifunctional acrylate monomers should be included in the discussion as well as in the text.

Dr. Bergfeld noted that a motion to accept the existing discussion, with an additional statement that Ethyl Methacrylate products are formulated with multifunctional monomers, and to delete the phrase, safe as used by trained individuals, from the conclusion had been made. The revised 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. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate.

With the exception of Drs. Belsito and Klaassen, all were in favor of the motion.

Dr. Andersen noted that the report on Ethyl Methacrylate would be issued as a Tentative Report and that there would be a 90-day comment period. He also said that there is no indication that additional data will be received from the industry or any other interested party

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Dr. Belsito stated that he continues to be bothered by the sensitization potential of Ethyl Methacrylate. This level of concern is based, in part, on Dr. Bailey's comments to the effect that the incidence of consumer-generated reports of sensitization reactions is quite high compared to other data reported to FDA, and the fact that information indicating that products containing Ethyl Methacrylate are designed for professional use is included in the report text. Dr. Belsito noted that though it is stated in the CIR report that Ethyl Methacrylate is used in artificial fingernail enhancement products designed for application by trained individuals, the Panel elected not to include this restriction in the report conclusion. In his opinion, this restriction should have been incorporated into the conclusion. Furthermore, Dr. Belsito stated that he would not be comfortable with the use of products containing Ethyl Methacrylate, even by trained individuals, and that he did not think that any concentration of Ethyl Methacrylate is safe for use by the consumer. The fact that the sensitizing potential of Ethyl Methacrylate is great and the fact that this ingredient has the potential for cross-reactivity with other acrylates were also noted.

Ms. Fise stated that it is the Panel's responsibility to review the safety of cosmetic ingredients for consumers. She also noted that it is essentially stated in the report discussion that the Panel does not want the ordinary consumer to buy and use products containing Ethyl Methacrylate from the shelf, and this should be reflected in the conclusion.

The Panel voted in favor of issuing a Final Report on Ethyl Methacrylate. The report 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. Skin contact should be avoided because of the sensitizing potential of Ethyl Methacrylate.

Dr. Belsito voted against the motion.

June 2011 Meeting – Belsito Team

DR. BELSITO: Okay. So, we're going back now to acrylates crosspolymers, is that correct? Okay. So, the title has now been generalized to crosslinked alkyl acrylates. In March, insufficient data asking for impurities with a focus on residual benzene. Those have been provided and incorporated into the report. The panel -- so, basically that's what we're looking at. We have, just to remind you, the highest concentration -- at least, this is my scribble -- 6 percent leave-on n-hexane at.2 and benzene at.5 percent were the maxes that I scribbled down. So, assuming that Curt and Paul and Dan are okay with those levels, safe as used for this acrylate copolymer group.

DR. BERGFELD: Before you go there, could I have you remind me about how you felt about the human sensitization, irritation? Are you using -- trying to look at this particular document, how it's arranged? But anything but particle size or size of molecule? There's not a lot here.

DR. BELSITO: You mean because of the acrylic component to them or what?

DR. BERGFELD: Yeah. Well, and just the fact that there's little information on it.

DR. BELSITO: It's Table 5. There's quite a bit of information in Table 5.

DR. BERGFELD: Non-human.

DR. BELSITO: No irritation, no sensitization. I mean, it's only summarized in two short lines in the text, but the table has quite a bit of data.

DR. BERGFELD: Yeah, you're right. It is.

MS. FIUME: I did just want to point out

so it's not missed, on Panel Book page 49, the calculation for the amount of benzene that could be in cosmetic formulations has an extra zero after the decimal point. It's actually.03 percent, not.003.

DR. BELSITO: What line is this, Monice?

MS. FIUME: Fourth line from the bottom, very left.

DR. BELSITO: Okay, 0.03, not --

MS. FIUME: Yes.

DR. SNYDER: I had a question. Are we okay with that language, that last sentence there? That care should be taken to minimize the amount of residual benzene?

DR. BELSITO: Why? What is your concern with that?

DR. SNYDER: I mean, I think we could -- I think because it is such a significant toxicant that we probably should be a little bit more --

DR. BERGFELD: Specific --

DR. SNYDER: -- specific as to what we mean by minimize. I mean, it --

DR. LIEBLER: Well, I think you just said in the sentence prior to that, such a trace amount presents no safety issues.

DR. BERGFELD: Why don't you just end there?

DR. LIEBLER: I would recommend deleting the last sentence.

DR. KLAASSEN: I would, too. It kind of sounds the opposite.

DR. BELSITO: Yeah, so --

DR. EISENMANN: But did you catch it's 03 not 003. That's --

DR. BELSITO: .03 percent.

DR. EISENMANN: Right.

DR. BELSITO: You're okay with that?

DR. SNYDER: I'm asking that also, I guess. As to what level -- if we're comfortable with that level.

DR. KLAASSEN: Well, one thing with benzene is that we know it's a human carcinogen. And thus, people get very excited about it. But the amount of benzene that it takes to be a human carcinogen actually is very high. So, I have no concern with this concentration in this compound or class of compounds.

DR. BELSITO: Okay.

DR. LIEBLER: I agree.

DR. BELSITO: Okie-doke. So, safe as used.

DR. SNYDER: Monice, had a comment on Table 6. When you compile the tables like this, which are highly informative, like on Page 71? If you look under acrylic acid, under toxicological studies, there's an inhalation study there that says lesions were observed in rats and mice in 4-day, 2-week, 20-day, and 13-week studies. But there's no dose information. And particularly if we could just at least have the doses that were tested, and if there was any way to calculate an NOAEL. And the same thing down on methyl methacrylate, toxicological studies: Single dose, oral, produced gastric lesions, but there's no indication of what doses to give us some idea. And likewise, even in the negative studies, like the repro studies, did not produce teratogenic or reproductive effects in rats. But I'd like to really know the doses that they tested.

MS. FIUME: Can I ask, if there's multiple studies, do you want me to just pick the one that had the lowest or -- you know, that was most representative for that amount? How do you want that handled?

DR. SNYDER: Certainly a study that could derive an NOAEL is the most -- going to be the most informative.

DR. BRESLAWEC: Keeping in mind that these are components, not the actual ingredients that we're talking about.

DR. EISENMANN: I have one thing in the discussion. This sentence, "The panel indicated that competence in these assumptions would be bolstered by data from well-conducted absorption penetration studies on, for example," and it continues. I don't remember you guys saying that, and these things are -- I am -- it's in the second paragraph, last -- or the third paragraph, actually, the last sentence.

DR. LIEBLER: "The panel indicated that confidence in these assumptions would be bolstered," that sentence?

DR. EISENMANN: Yes.

DR. LIEBLER: Yeah, I flagged that, also. And I asked whether it suggests that we want or expect to see these data.

DR. EISENMANN: I mean --

DR. LIEBLER: That was my question.

DR. EISENMANN: These are -- they're just so large. At least the ones that you have in the molecular weight information are just so large that I don't know why you would need any information at all.

DR. LIEBLER: I agree with that view.

MS. FIUME: So just delete that sentence?

DR. LIEBLER: Yes, right?

MR. DEMARIA: Anything else?

DR. SNYDER: I have just a kind of global editorial thing. That in all of these reports, when we talk about the ingredients and their use in cosmetics, we use various terms like are used, "may function as," "can function as." And I think what we're really talking about, "as they're reportedly used," because that's what it's based on, correct?

DR. BRESLAWEC: Right. We've tried to standardize that language. And instead of saying "used as," we're trying to say, "reported to function as." So that's the language we're trying to move toward.

DR. SNYDER: Yeah, because it is a reported use to us and that's what we base all of our conclusions on. So I think it's really important that we are accurate on what it is. Not that they can or may or --

DR. BELSITO: I'd like the "reported to function as." Comments? Monice, you have everything you need from us for this one?

MS. FIUME: Yes, thank you.

DR. BELSITO: Okay.

DR. BERGFELD: The only passing comment is on page 7, where you -- alternative studies. Under mucosal irritation, there you have a bunch of eye studies. They're a little bit tough to pull out, if you're just looking for eye. And in other documents, it was non-human eye or eye toxicity. I'm not sure what you're going to do about that, but this is inconsistent now with several documents.

MS. FIUME: So you're looking for eye.

DR. BERGFELD: And frequently look for eye, because of irritation.

MS. FIUME: So you would prefer the term "ocular" versus "mucosal?"

DR. BERGFELD: No. I prefer "eye" appear somewhere in the title so I can find it. That's basically what I'm saying.

DR. BRESLAWEC: Got it. What we occasionally come up with is that we have more headings than text, and then we go through this heading removal exercise. And I think this is a victim -- fell victim to that.

Marks Team

Next is the Pink Book, acrylic crosspolymers or crosslinked alkyl acrylates. In March of this year, the panel issued an insufficient data announcement asking for impurities particularly focusing on residual benzene. Data has been provided and it's found in the report. Ron or Tom? How do you feel?

DR. SHANK: On page 49 of the book, page 9 of the report near the very bottom, it says that in worst case for benzene concentrations 0.003 percent, that's not correct. There is one too many zeros. So multiply that by 10 and it's 0.03 percent. And I calculated that if the maximum concentration of the polymer in a cosmetic formulation is 6 percent, for every gram of formulation would produce three- tenths of a milligram of benzene. And the EPA water standard for benzene is a maximum of 5 micrograms per liter, so this works out that an adult would be exposed to 10 micrograms per liter in drinking water as a maximum. The cosmetic concentration would be 30 times above that. So I think we need to say something about limiting the benzene concentration in the polymer.

DR. BRESLAWEC: Dr. Loretz, do you want to comment on that? There is some discussion about how it's lodged in and that the 6-percent concentration actually could be more like 1 percent.

DR. LORETZ: I think this is the supplier that provided information suggesting that the maximum concentration that they were aware of in use was less than that, so this is the worst case in the course of the study minus the zero. So I think this is the highest concentration and higher than you would see, and then they've raised the issue of benzene when you mix it, et cetera, as it's volatile and expect to get some amount although we don't have anything.

DR. SHANK: I did a calculation based on 1 gram of cosmetic applied to the skin, that a concentration limit for benzene of 0.016 percent would be the same exposure as the EPA drinking water standard just as a reference. What we want to say is up to everybody. That would be 167 PPM in the cosmetic formulation. In the polymer, pardon me.

DR. MARKS: And the benzene is the only issue at this point with the safety of these ingredients. Ron, how would you work that in the conclusion then? I am presenting it so I'm going to ask you have you figured out how you'd like to work this?

DR. SHANK: No, I have not.

DR. MARKS: It obviously would be safe as used as long as the crosslinked alkyl acrylates have less than X- amount of benzene impurity or something to that effect. Is that what you were thinking, Ron, the way we'd do this, that we would in the conclusion state that we want a maximum amount of benzene impurity in it?

DR. SHANK: I was trying to find out in other ingredients we have reviewed. Have we asked this question before, a limitation on the amount of free benzene in an ingredient? Unfortunately, my access to the website doesn't work again, so I tried to do it through the compendium and I couldn't find anything, fortunately, the compendium we have online. So perhaps we have already asked this question about free benzene in other ingredients and refer to that. Otherwise we'll have to discuss what basis we want to -- I just took the EPA drinking water standard because it was an easy number to find, but maybe there's a better way to do this.

MS. FIUME: I have a question per the discussions. Last night I pulled up the NIOSH and the OSHA limitations, but if we were to use EPA drinking water, in the discussion we currently say that we don't really expect it to absorb so the rationale for using the discussion of using an oral limitation versus something else, what type of wording would you want for something like that?

DR. SHANK: If the benzene in the ingredient polymer is free, then it will be absorbed through the skin. So that's why using an oral -- the polymer stays behind, but the benzene would be absorbed into the blood.

DR. SLAGA: In the past we always discussed the level of impurity is the word to make sure that benzene between 5 or less. Wouldn't just be as easy based on your calculation?

DR. SHANK: Putting 5 percent I think is too high.

DR. MARKS: Right.

DR. SHANK: Because.6 percent of 6 percent is 300 micrograms of benzene per gram of formulation. You can check my calculations. So 1 gram of formulation would give 300 micrograms of benzene. Two liters of drinking water at the maximum EPA limit would give you 10 micrograms of benzene. So 1 gram of cosmetic formulation at 6 percent polymer content would be 30 times above the EPA water standard.

DR. MARKS: That's assuming you only apply 1 gram.

DR. SHANK: Yes.

DR. MARKS: In a normal application if you're doing total body it would be 30 grams.

DR. LORETZ: It would depend on the product type, too.

DR. MARKS: Exactly. It could be significantly more than just 1 gram applied. Again, on page 49, you took one of the zeros for a final level of 0.03 percent of benzene? Is that what you said, Ron?

DR. SHANK: Yes.

DR. MARKS: Such trace amounts presents no safety issues. You want that sentence struck obviously.

DR. SHANK: Yes, please.

DR. MARKS: And now the question is such trace amounts may present a safety issue might be the better way of doing it since you have the EPA level. The panel did caution that care should be taken to minimize the amount of residual benzene. We're sort of addressing it with that but we haven't set a level.

DR. SLAGA: What level would you suggest?

DR. SHANK: As a starter for discussion tomorrow I guess, that application of the formulation would provide no more than 10 micrograms of benzene. That would be equivalent to 2 liters of drinking water. That's the rationale. I'm sure the others will find that worthy of comment.

DR. BRESLAWEC: And that is based on the EPA drinking water standard?

DR. SHANK: This is the EPA drinking water standard and that standard is a maximum concentration of 5 micrograms of benzene per liter of water assuming an adult drinks 2 liters of water a day.

DR. BRESLAWEC: I'm sorry. Could you repeat that definition?

DR. SHANK: The EPA standard is a maximum concentration of benzene in drinking water of 5 micrograms of benzene per liter, and the assumption is that an adult would drink 2 liters of water a day. So the total exposure would be 10 - 15 micrograms per day of benzene.

MS. FIUME: Dr. Shank, out of my own curiosity, I've gotten lost in the numbers. That's my own fault. The California Prop 65 limits, are they higher or lower than the EPA that was listed in the text?

DR. SHANK: They would not be higher. If anything, they would be lower.

MS. FIUME: They would be lower. There is 6.4 micrograms per day.

DR. SHANK: So that would be lower.

DR. MARKS: So one part would be in the discussion we're explaining the rationale based on the EPA 2 liters of water adjusted daily in that total of 10 micrograms of benzene. The other is going to be how we word the conclusion that these crosslinked alkyl acrylates are safe as used as long as the limit of benzene is no greater than 10 micrograms total daily exposure or something like that. How do you like that, Ron or Tom?

DR. SLAGA: That sounds good.

DR. SHANK: The rationale is the EPA drinking water standard. I should know this. The Prop 65 limit is 6 micrograms.

MS. FIUME: 6.4 micrograms per day orally.

DR. SHANK: Oral?

MS. FIUME: Yes. That's actually in there.

DR. SHANK: Does that mean if a cosmetic formulation has 10 that it can't be sold in California which is 10 percent of the U.S. population?

DR. SLAGA: They probably use more cosmetics out there.

DR. MARKS: What was California?

MS. FIUME: 6.4 micrograms per day for oral exposure and 13 for inhalation.

DR. SHANK: I don't know that I would recommend using the California Prop 65. I won't comment further. I wouldn't use that as the standard.

MS. FIUME: I would imagine that suppliers have had to do something because the European limits are very different. There are different limits for the amount of residual benzene based on where they're supplying to. Europe has a level of.1 so certainly they can't use that in their jurisdiction.

DR. SHANK: .1 microgram?

MS. FIUME: .1 percent.

DR. LORETZ: .1 percent.

DR. SHANK: .1 percent.

DR. SLAGA: That adds up to impurities?

DR. LORETZ: They showed that the loss they looked at, it range and I think the highest was.41 and that some fall well below that.

MS. FIUME: I tried to find what Europe's rationale was for the limit and I wasn't able to find it to really pinpoint what they were basing their number on.

DR. LORETZ: We would assume that somebody selling it in California is aware of that and in compliance with Prop 65 but we don't have any more information.

DR. MARKS: So you don't have a problem, Ron, with saying we're going to limit it to 10 even though California has 6.4?

MS. FIUME: Actually in the memo it does say that formulators that sell products in California must comply with California's Prop 65 which limits benzene exposure from a product to 6.4 micrograms per day for oral exposure. So the information that did come from industry does state that they are aware of what California's limit is and that they have to comply.

DR. MARKS: I would say we go to 6.4.

DR. SLAGA: It's easier for the formula based on the lowest.

DR. MARKS: Yes.

DR. SLAGA: You don't have to mention California.

DR. SHANK: You'd have to mention why is it 6. --

DR. SLAGA: That's true.

MS. FIUME: Provide it just in case you --

DR. MARKS: Then we get into we think that EPA is better than the California Prop 65. I don't know. I just see that if I were a formulator a conflict when I look at the CIR recommendation of 10, although maybe that happens all the time. I'm not sure. We can certainly leave it at 10. You're our California representative here, Dr. Shank. So it's going to be safe?

DR. SLAGA: Industry will probably try to keep it below Proposition 65, I'd guess.

MS. FIUME: Because there's multiple solvents.

DR. BRESLAWEC: And that.1 percent, how does that compare to the 10 micrograms per day?

DR. MARKS: Let me see. I think I'm the one proposing, so tomorrow I'm going to move that we issue a tentative report on the crosslinked.

MS. FIUME: Insufficient?

DR. MARKS: Yes. It was insufficient. So a tentative report on -- yes, I know the subject says tentative report, but actually it's what we're moving. A tentative report on crosslinked alkyl acrylates as safe as used as long as the benzene impurity limit is no greater than 10 micrograms of benzene total exposure daily or daily total exposure. Does that sound like the way to handle it?

DR. SLAGA: Total from all sources or cosmetics?

DR. MARKS: We say there that in cosmetics safe for cosmetics. So you think somebody would interpret the conclusion total or should we be more specific and say 10 micrograms of total exposure? Now you get into all the other issues we have like the phthalates in nail. We limited in the nail cosmetic but we're not limiting it to all phthalate exposure from --

DR. SLAGA: Any source.

DR. MARKS: Yes.

DR. SHANK: I haven't reviewed the EPA document for some time, but I would be -- I'm fairly sure that they considered other sources of exposure because it's an additive to gasoline. People who pump gasoline are exposed by inhalation to benzene. There are several sources of benzene in the environment and I'm pretty sure the EPA water standard took that into account. So I would put the benzene limitation as 10 micrograms per cosmetic exposure or however you word that.

DR. MARKS: Personal care product.

DR. SHANK: Personal care product.

DR. MARKS: Personal care product exposure.

DR. LORETZ: That's a little complicated as to you don't know if -- still in theory so if you're putting in your five and he's putting his five, it gets challenging that way.

DR. MARKS: Another nuance.

MS. FIUME: And that will be in the conclusion and not just the discussion?

DR. SHANK: It would have to be in the discussion to say how we arrived at that number.

DR. MARKS: But the conclusion would limit.

DR. SHANK: The limit would be in the conclusion, yes.

DR. MARKS: Right.

DR. SHANK: Is there some way to scan previous documents to see if we've asked this question about limited benzene before?

DR. LORETZ: There's one coming up on today's agenda that refers to benzene free.

DR. SHANK: For benzyl alcohol?

DR. LORETZ: It must be in that.

DR. BRESLAWEC: I'm not particularly aware that we've limited it per product exposure before. I think, and I honestly can't say this with 100 percent certainty, but I think it's always been concentration in the ingredient because we're looking at an ingredient and not the product.

DR. MARKS: Right.

DR. BRESLAWEC: So I would urge you to characterize it in a way that focuses on the level of impurity in the ingredient rather than in the product.

DR. SLAGA: In this specific ingredient.

DR. MARKS: This is for the specific ingredient.

DR. SLAGA: Not in personal care products.

MS. FIUME: But I think it was just PEG alkyl ethers that there was concern over some of the residual solvents or residual components. In the discussion it was worded a certain way without specifics, but I would have to go back and look at it because I want to think it was the alkyl PEG ethers that addressed that. Same type of concept.

DR. MARKS: What do we do with heavy metals, aflatoxins and that sort of thing? We don't do limits do we?

DR. BRESLAWEC: We have in the past.

DR. SLAGA: We have a boilerplate.

DR. MARKS: Right. A boilerplate.

DR. BRESLAWEC: But it's based on the ingredient.

DR. MARKS: Right.

MS. BECKER: Dr. Marks? It's in the silylate report in the report on toluene. The CIR Expert Panel has stated that all cosmetic ingredients should be benzene free.

DR. BRESLAWEC: But there was a comment from industry where they questioned where CIR had stated that, so that's an issue we need to address.

MS. BECKER: I can go get my computer and pull it up.

DR. BRESLAWEC: Let's do that.

DR. SHANK: It's hard to say because I based my calculations on 1 gram, but that was arbitrary, so I guess it depends on what the product is and how much is applied to the skin. So how do you set a limit on the concentration in the ingredient based on the maximum amount you apply to the skin and what would that be? I have no idea.

DR. BRESLAWEC: I think you can help us on that.

DR. MARKS: Because here we have -- I mean there's a lot of leave-on use. For the C-10 to 30 acrylates there are over 1,300 leave-on products.

MS. FIUME: Another complicating factor and I think Linda was alluding to this earlier is that from that manufacturer under that trade name they state that they're aware of it being used at a maximum of 1 percent, but the problem is we don't have the concentration of use breakdown by trade name, it's by INCI name. So they may only be using it at 1 percent and we're using it at 6 percent as the worst-case scenario, so it also complicates what is actually being put in. In one of my reports there's actually a calculation of how much is exposed based on product type. I don't know if this is helpful, but in the TEA report a company actually came up with an exposure of consumers. It's on page 6 of the report.

DR. SHANK: Of the report. Yes?

MS. FIUME: And then on page 6, the third full paragraph down, it --

DR. SLAGA: What page, ma'am?

MS. FIUME: Page 6 of the report, which is Panel Book page 25, and that's TEA.

DR. MARKS: It's a different book.

MS. FIUME: Yes.

DR. MARKS: TEA.

DR. SLAGA: Yes, I have that.

MS. FIUME: I don't know if that's helpful at all.

DR. SHANK: So there is some kind of algorithm to use?

MS. FIUME: That was submitted to us. And I know calculations have been done for things like the diluted products, how much is actually exposed per day, but I don't know of any other products if there's been calculations as to what type of product, how much exposure actually occurs per day.

DR. MARKS: I think we saw that with the RFL presentations on fragrance exposure and they did it with various product categories.

DR. LORETZ: And we've published. There are a lot of publications.

MS. FIUME: It sounds familiar because I know the diluted ones, if that would be referred to more often in the report. Yes, that calculation actually came from an OECD SIDS document that was their calculation that was included in their report.

DR. SHANK: Okay.

DR. LORETZ: I know the Expert Panel has used the Prop 65 levels before. I guess this one's just more complicated because if you take the worst case then you start getting into a different --

DR. MARKS: Here we go. On toluene it says that was the question actually I was going to ask, and I don't know whether it can be answered, can these acrylics be manufactured free of benzene?

DR. LORETZ: I think benzene is just way of making it. It's not necessarily a common way. It's just one way.

DR. MARKS: So if it isn't a common way then to me the way to solve it would be that we recommend there be no benzene.

DR. LORETZ: I think it's a certain product type that some people find have some benefits.

DR. SHANK: I'm perfectly happy with this. What year was this written? Back in the day.

DR. MARKS: Do you want to read it? I like the second sentence under the discussion I guess it is or the summary.

DR. SHANK: This is on the toluene document in the 1980s I guess, "One possible impurity, benzene, is a carcinogen. Therefore, cosmetic products formulated with toluene should be benzene free." That's the best way for us to go if that doesn't cripple the manufacturer if there are other solvents that can be used.

DR. MARKS: Is there anybody from -- of course that's not going to influence our decision on safety other than to say is that an issue with the manufacturer.

DR. LORETZ: I think what the manufacturer said is that is an issue, that they do sell that product and that product has value, so I guess that's why they -- you know, we think it would be a safety assessment on the benzene levels rather than just a flat-out ban.

MR. LABA: Dennis Laba from Presperse. Presperse represents one manufacturer that makes products. These products were originally precipitated in benzene and they have been moving more and more environmentally friendly solvents and toxicity safe solvents. But the whole industry has not moved as fast as the manufacturers though these other products have been available. People who have been using these for years have not changed all of their products over to the other ones. There is one particular manufacturer that has most of the market and they would probably be the ones most upset about that, saying that there can't be any benzene, but the alternatives are out there certainly.

DR. SHANK: Thank you.

DR. SLAGA: Let's proceed then.

DR. SHANK: So the precedent if the benzene document is that we say benzene free.

DR. BRESLAWEC: The toluene, yes.

DR. SHANK: Toluene document. Thank you.

DR. MARKS: I like safe. And then in the discussion because that's the way it is in the toluene document, in the discussion we say that it's benzene free, that we're concerned about benzene and unless there's an alternative way of arriving at a safe limit which we've discussed, it doesn't sound like that's going to be easy.

DR. LORETZ: I guess I have some real concerns about benzene free because that implies a zero tolerance which, I mean, when you look at like traces in things that are like in Annex 2 in Europe, I mean, they, you know, qualify that as a good manufacturing practice, et cetera. It's not a true zero. So, but to me benzene free taken literally is a true zero which is --

DR. SHANK: The original toluene document is dated 1987, so that must have gone through re-review. So if we could find the re-review to see -- because I'm sure we've handled this before.

DR. MARKS: So we're back to safe, and then in the conclusion do we mention there it should be benzene free or should we put that in the discussion? Because in the toluene document it's in the discussion, is it not?

DR. SLAGA: Not in the conclusion.

DR. MARKS: Right.

DR. SLAGA: We ought to be consistent depending on what the re-review was.

DR. MARKS: Then the question also there is do we want to as you suggested what may create heartburn, but from a safety point of view do we want to be benzene free? Because obviously what we've struggled is if we don't say it's benzene free, what is the limit we're going to set?

DR. SLAGA: In the original discussion we were talking about benzene that's trapped.

DR. BRESLAWEC: I think that was a misunderstanding on my part.

DR. SLAGA: I'm sorry. We'd have to have had some kind of linkage wouldn't we to keep it --

DR. SHANK: It's a polymer so it could be physically trapped, not chemically trapped.

DR. LORETZ: I think benzene is referred to a monomer at some point in here and that's not correct.

DR. SLAGA: I think in reality we're worried about the total exposure of benzene so maybe we're going into cosmetic and looking for environmentally safe alternative solvents here, then it seems to me that's as good a case.

DR. LORETZ: While that may be the ideal, does it make sense if your product is in compliance with Prop 65 and you specify that that's what you recognize is your safe level?

DR. SLAGA: That means that we would be going beyond Proposition 65.

DR. LORETZ: Right.

DR. SLAGA: We can't say we're excepting Prop 65.

DR. SHANK: Another way is to take the EPA water standard for a total exposure of 10 and that cosmetic personal product care use should contribute no more than half of that, so that would be 5 micrograms?

DR. BRESLAWEC: At what level?

DR. SLAGA: That's getting a little wishy.

DR. SHANK: Somebody else try it.

DR. SLAGA: This is toluene sulfonamide formaldehyde residue and that was straight toluene in that one.

DR. SHANK: Yes.

DR. LORETZ: I think for consistency I'm concerned about again setting a zero standard because we're going risk based throughout and not just benzene.

MS. FIUME: I'm trying to think about in the past with the wording where is a maximum is allowed per day, but you could have multiple exposures how we've worded it in the conclusion. Peppermint oil might be one because I think peppermint oil didn't have a maximum that should be allowed per day and I don't know if the discussion handled that at all or not.

DR. SHANK: What was it called?

DR. MARKS: That was a sensitivity issue.

MS. FIUME: Peppermint oil.

DR. MARKS: Let me see. I'm trying to think. Again, I come back to the phthalates because there was the concern that nail polish would add to the total burden of phthalates, but I think we just did a safe because our margin of safety calculation with that showed that it would be --

DR. SLAGA: Wouldn't have been very large.

DR. MARKS: -- a very small contribution by nail. Whereas this potentially --

DR. SLAGA: We've added significant with our approval.

DR. MARKS: Yes. This with your calculation, Ron, would give a significant amount of exposure.

DR. LORETZ: Would you maybe then be going to ask industry for more information on use levels and risk to defend the risk assessment?

DR. SHANK: It's a genotoxic carcinogen.

DR. MARKS: The way we could proceed is to with the benzene free and that goes out as a tentative report which means industry can react to it. And if they can show us some margin-of-safety calculation that is reassuring -- we're obviously struggling with coming up with establishing a limit. Maybe industry could suggest a limit.

DR. SLAGA: We'll have the discussion tomorrow.

DR. SHANK: The limit on aflatoxin is a lot more potent carcinogen than benzene by far. That limitation is based on the fact that in certain things you can't get it any lower so you just have to live with it. Even FDA allows it in food at a certain level because it's associated with the use of peanuts. You can't get it to zero. But here if it's used a solvent, you can get it to zero by not using it as a solvent.

DR. SLAGA: Let's go with benzene free because at least we have the toluene document to base it on.

DR. LORETZ: I guess I'm still struggling with the free and that meaning zero and that being kind of a scary precedent. Would it maybe make more sense or would it be just as well to say benzene should not be used as a solvent and then leave open the door for industry to come back with some kind of a risk assessment to defend it?

DR. MARKS: If they don't use it as a solvent, there won't be any benzene. Correct?

DR. SLAGA: Yes.

DR. LORETZ: I guess I'm struggling again with the zero because benzene free to me is too absolute.

DR. BRESLAWEC: Perhaps we can say something alone the lines of benzene no higher than a safe level as determined by a risk assessment and then expect the risk assessment to come in from industry to provide a level that the panel would consider safe at its next deliberation. Bart Heldreth is here.

DR. SHANK: Benzene in crosslinked polymer.

DR. MARKS: Alkyl acrylates.

DR. SHANK: Alkyl acrylates. Is the benzene that's a solvent physically trapped in the polymer so that it can't be absorbed?

DR. HELDRETH: That potentially could be the case. We don't have any data from industry saying that they used it as a solvent and during the crosslinking it got trapped in there. Potentially, sure. Anytime you do crosslinking you could trap the solvent or anything else that's in the solution inside small spaces inside the polymer. Whether that's the case here we don't know. The other thing, once you have a polymer, especially a crosslinked polymer, there's also the possibility of the solvent absorbing into the polymer even though it didn't get tracked on crosslinking and residing in there and even upon heating and doing lyophilization to try to get things out of there, it could stay in there a little longer than you would expect. Whether that's the case here, though, we don't have any data on that, but there is that potential.

DR. SHANK: Thank you. I guess we can say in the discussion that benzene should not be used as a solvent. Then the question is what do you put in the conclusion.

DR. MARKS: If we do what you suggest, it was a draft tentative report, we could issue a tentative report with insufficient and out concern about benzene and let industry come back and provide sufficient information to declare it safe. That would be another tact, move forward with a formal insufficient report.

DR. SHANK: Could you go sufficient for a crosspolymer that is made without benzene and insufficient for a crosspolymer that is made with benzene?

DR. MARKS: That's another option.

DR. SHANK: Because if a lot of this product is made without benzene, it seems unfair to put it all into insufficient.

DR. BRESLAWEC: I think there's only one

39 polymer that we have data on.

DR. SHANK: We've never done that before, split it.

DR. BRESLAWEC: You're making a distinction on the method of manufacture rather than levels of something in the ingredients.

DR. MARKS: Ron, we've been struggling here. We've only gotten to the third ingredient. The first two we did not reopen, HC Red No. 1 and the glutaral. Where we're struggling with the crosslinked alkyl acrylates is the benzene impurity, benzene using a solvent. If we go on page 49, Ron pointed out that the actual calculation there in the next to the last paragraph should be 0.03 percent of benzene in cosmetic formulations. Is that correct, Ron?

DR. SHANK: Yes.

DR. HILL: Is that by the California numbers?

DR. MARKS: No.

DR. SHANK: It's based on industry data and it was calculated --

DR. HILL: Five times formula 6.

DR. SHANK: Right.

DR. HILL: There it is.

DR. MARKS: Ron further calculated that if we had the maximum concentration and we applied 1 gram of a cosmetic ingredient, all the benzene in this polymer was released and that would be equivalent of 300 micrograms. Did I recall that correctly?

DR. SHANK: Correct.

DR. MARKS: Which is 30 times -- in the EPA and drinking 2 liters of water a day. So assuming all this benzene is absorbed or even a large portion of it, we've exceeded the EPA limits for exposure to benzene systemically. So we're struggling on in the one case trying to set a limit based on the EPA drinking water or the California Prop or going back to a 1987 report on toluene which in the discussion it was stated that toluene should be benzene free. So we're exploring the idea of having this document saying safe but in the discussion put benzene free. That gets into the issues that some of these products apparently are now made without benzene as a solvent. Should we go that strict and say benzene free or should we try and establish some sort of a limit and what is that limit going to be? Do we move forward by issuing a tentative report splitting out these product whether they have benzene or not benzene and safe for benzene free, obviously insufficient for benzene containing or just go to an insufficient tentative report? So that's sort of where we were and we're struggling with how to present this tomorrow. Does that pretty much summarize where we are?

DR. SHANK: Yes.

MS. FIUME: As a suggestion, if somehow the discussion or the risk assessment can be written in giving industry the option to either bring in information or send information with a safe as used conclusion and then the comments came in, as long as it didn't become more restrictive, that wording in the discussion can change based on the industry comments and it could still go as a final report next time as long as it didn't change the conclusion and the main point of the discussion. Not that that's a reason to do it one way or the other, but that is a consideration as you write the conclusion as to the next step of the report.

DR. MARKS: Tom and Ron, do you think there is a safe limit that benzene could be used or exposure? It seems like there is since the EPA has set a safe limit. So I guess, yes, you could put safe and then the challenge will be somehow crafting a way of setting that limit. What you're doing is helping facilitate so the next time if there are any changes you can move right on to a final. I'm not quite so sure that procedurally that's -- even though that's expeditious, I'm not sure it sends the right message that it's safe, but we really have concerns.

MS. FIUME: I was thinking is that we have items that are sensitizers. We don't set a limit. It's formulated so that they're not sensitizing, so if it was formulated so that the amount of benzene isn't above safe limits, because when I searched benzene using our SciFinder and you hit regulations, there are so many different numbers. There was page after page after page. So I think trying to find a specific number is going to be difficult.

DR. BRESLAWEC: You could specify in the discussion which standard and you could say to the EPA standard.

DR. SHANK: You can't formulated to be non- carcinogenic.

DR. MARKS: Here are some more complications. We don't get hell from the re-review. It doesn't mention benzene in the re-review Lillian tells us.

DR. SLAGA: We didn't re-review it did we?

DR. SHANK: Toluene.

DR. MARKS: Toluene.

DR. BRESLAWEC: There should have been probably two by now.

DR. MARKS: Which year is this?

MS. BECKER: This is 2005.

DR. MARKS: So it's the most recent one.

DR. SLAGA: We didn't re-review it. We didn't reopen it did we?

MS. BECKER: No.

DR. SLAGA: So that's the reason.

DR. SHANK: We agreed with the benzene

free.

DR. MARKS: Right.

DR. SLAGA: I think we ought to use that. Don't you?

DR. MARKS: Obviously industry didn't have a problem with benzene free.

DR. HILL: Yes, but the catch to that there's no such thing as benzene-free toluene. What you're really dealing with is a detection limit issue and now with the mass specs available I think that would be way down there compared to whatever year that was sent. There's no such thing as benzene-free toluene.

DR. SLAGA: Approaching benzene free.

DR. BRESLAWEC: I actually think that it might be worth asking FDA whether FDA has a benzene limit.

MS. DEWAN: Not that I'm aware of as far as know.

DR. HILL: And these California standards are for ingestion. Right?

MS. FIUME: One is oral and one is inhaled.

DR. HILL: Inhalation and oral, but we don't have any dermal.

DR. MARKS: No, and one of the problems we have with that, Ron, is that when Ron Shank was calculating, he was using an EPA standard with a 10. With California Prop 65 the limit is 6.5 for oral exposure. So it's actually lower.

DR. HILL: 6.5.

DR. MARKS: Yes, 6.5.

DR. HILL: That's practically nothing. It's about the same.

DR. SLAGA: And we're assuming that it all gets absorbed.

DR. MARKS: I shouldn't have written this many notes over here because I still have to make a motion tomorrow and I'm not sure what motion I'm going to make.

DR. HILL: In the EU the raw material has to be.1 percent or less. Do I remember that correctly?

DR. MARKS: Yes.

DR. BRESLAWEC: To me it seems as if you are lacking data to make a decision.

DR. MARKS: I wait.

MS. FIUME: Actually that's not raw material. It's mixtures I think so that it should be final product.

DR. MARKS: Right.

DR. HILL: In the final product makes your point. Is that right? I don't trust my memory.

MS. FIUME: A constituent of other substances or in mixtures. So that would be final product. Correct?

DR. HILL: My impression was it was in

47 the raw material.

DR. LORETZ: That was my understanding as well.

DR. HILL: Again, lots of water has flowed under the bridge.

DR. MARKS: I don't know how that is calculating now.

DR. LORETZ: That sounds fine in the final product.

DR. HILL: The final product?

DR. LORETZ: No, I said that sounds fine in the final product.

DR. HILL: Yes.

MS. FIUME: Other directive. As a constituent of other substances or in mixtures in concentrations equal to or greater than 0.1 percent by weight.

DR. MARKS: That seems like a higher limit than micrograms of drinking water. Options? We can't take this. We've got to move it forward.

DR. SLAGA: No, we have to move it forward.

DR. MARKS: So the next is, and we've already had a draft, we had the insufficient data announcement, so we're into a tentative report and the options there are safe, insufficient, unsafe. We aren't at unsafe. That's for sure. So do we do safe and address the benzene impurity in the discussion? Or do we put insufficient and ask industry to help us reach a margin of safety?

DR. HILL: My impression is that if the EU sets the standard which again I interpret to be a raw material number, that it's possible to achieve that and that maybe people are formulating with a less-expensive grade, we've talked about and that maybe better grades either because it's not pulverized in benzene in the first place or because it's processed more to get rid of the benzene more thoroughly, then it's available to them. But I also realize whenever you say somebody has to reformulate a product that's a big deal.

DR. SLAGA: There are a number of products that don't use benzene as a solvent.

DR. HILL: That's what I'm saying. They use either hexane/ethyl acetate or something unspecified.

DR. MARKS: We could do the safe and in the discussion mention that a number of products do not use benzene. The ones who use the benzene, the panel is concerned about its toxicity and then elaborate on that. Then if we can get a margin of safety in and have a suggested limit it would be good, but we could certainly reference the California Prop and the EPA. So that might be another way of handling it. I know that gets to what you said in terms of let's do safe and move forward, but that would be another way of handling it.

DR. SLAGA: We're discussing all the possibilities.

MS. FIUME: That's right, and there are at least four solvents that are available for that one ingredient which is the one trade name.

DR. MARKS: Tom, how do you want to proceed?

DR. SLAGA: I would go with that. I definitely don't want to table it.

DR. MARKS: No.

DR. SLAGA: And I'm just thinking what the other group would do. None of them would say it's safe too.

DR. MARKS: I think we'll find out tomorrow when I make our team's move and our team needs to feel comfortable with that. It is a little bit different knowing that we really feel it's safe when it's benzene free. That's the easiest way of looking at it.

DR. SLAGA: When benzene is not used as

a solvent.

DR. MARKS: Right.

DR. SHANK: I'm not at ease calling it safe if our calculations are that it can contain levels of benzene that have been found in excess of several regulatory bodies' standards. So I don't like saying it's safe alone unless it's qualified. Polymers made with solvents other than benzene are safe, and then in the discussion say
why we say that. If you're going go safe I'd put in there for those polymers that are not made with benzene. That's not saying benzene free or anything.

DR. HILL: To me that seems overly restrictive given the fact, although I'm not thoroughly familiar with what happens to small, small amounts of benzene when it gets into the skin or an even smaller amount if it entered the nasopharyngeal region than was suggested, I would think those kinds of levels if we were within the European limits of.1 percent and then formulate it a maximum of 6 percent if we're going to put it way down in the levels of benzene, I wouldn't think anything systemic would be any problem. Are there any dermal carcinogenesis sorts of things that one needs to worry about with that small an amount of benzene?

DR. SLAGA: It's extremely weak activity.

DR. HILL: I used to wash my hands in it.

DR. SHANK: I don't think that's the problem. I think the problem is setting the concentration limit in personal care products.

DR. HILL: Right. I know. I get that.

DR. SHANK: Finding the number.

DR. HILL: We don't have the information that lets us do that.

DR. SHANK: That's correct.

DR. MARKS: So we could go forward with insufficient.

DR. HILL: Insufficient with anything with benzene in it?

DR. MARKS: Just insufficient. We keep coming back to saying either there is no benzene or there is a benzene limit and we have a problem with finding what the benzene limit is and determining that.

DR. LORETZ: You're not comfortable with splitting them into insufficient for the benzene and asking for further information and safe for the others?

DR. MARKS: We could say, yes, the conclusion could be safe and as we've done -- this would be the first we've had the same ingredient and said they're safe when they're done one way and insufficient in another way. We've done that for ingredients within groups where there are different ingredients, some are safe and some are insufficient.

DR. HILL: But I'm thinking why not?

DR. MARKS: Yes, that's an interesting -- precedent setting, but maybe that's the way it should be.

DR. SHANK: I favor that. Safe for rinse-off, safe for leave-ons when the polymer is made with solvents other than benzene, insufficient for leave-on when the polymer is made with benzene.

DR. SLAGA: That could start a discussion tomorrow.

DR. SHANK: That will start a discussion.

DR. HILL: It sure will. Were there any concerns about the residual ester monomers at.5 percent when we're talking alkyl acrylates? I'm looking at page 3 at the bottom. Did anybody have any concerns related to those? I'm looking at Panel Book page 43, which is draft report page 3, talking about.5 percent residual ester in the C-10 and C-30 alkyl acrylates. So in formulation that would be again down in the.03 percent range or something like that, but we are talking alkyl acrylates.

DR. SHANK: I think our only concern was acrylic acid itself and the concentration is below our concern.

DR. HILL: Okay.

DR. SHANK: The larger ones were not our concern.

DR. HILL: I was thinking that the esters might be more problematic than the acids. I don't know that for a fact, but that was my sense is the esters could be thermally absorbed. I'm not sure how much the acid would penetrate past upper stratum corneum, but the esters might. I think defenses such as glutathione would take this out pretty effectively, but I wondered if anybody else even thought about that. And I'm guessing it was thought about -- it wasn't this that was the original review, but the other alkyl acrylate polymers there was discussion of monomers. We don't have that report, but I at least glanced at it.

DR. MARKS: I'm going to summarize where I think we are, and Tom, Ron and Ron just be sure I'm on the same page with you. Tomorrow I'll move that we issue a tentative report on the crosslinked alkyl acrylates, that they're safe, but they're insufficient for leave-on products having benzene impurities.

DR. LORETZ: You don't want to say polymerized with benzene just for clarity?

DR. MARKS: No, I think benzene impurity.

DR. HILL: Yes, because in principle that's the only place it could come from, but it would be good either way.

DR. MARKS: Safe, however insufficient.

DR. HILL: I suppose it's polymerized in the other solvent, but then recrystallized with benzene and you'd have the possibility of getting the benzene active. I don't know anybody would do that, but then I've done a lot of crystallization in my life and sometimes --

DR. MARKS: Leave-ons having benzene impurities. That can be refined, but does that catch it?

DR. SHANK: Yes. That's okay. I can be wordsmithed.

DR. MARKS: Then the insufficient data is we need a margin-of-safe calculation with a limit and establish a limit so if industry came back and showed us a margin of safety with establishing a limit for benzene impurity on a leave-on then we'd feel comfortable. Does that capture it? Do you think this is going to make an interesting discussion on the conclusion in this tentative report and then of course the discussion is going to go all around what we just talked about, the EPA limits, the California Prop 65, the European and all that and their concern that benzene is a carcinogen. Does that sound good?

DR. SHANK: I'm going to change my flight tomorrow.

DR. MARKS: We haven't even gotten to the formaldehydes.

DR. BRESLAWEC: Apparently the other group is still on formaldehydes.

DR. MARKS: Who knows? Maybe ours will go quicker. At any rate, are there any other discussions? Safe, however insufficient data for leave-ons having benzene impurities and that's how we're going to deal with the benzene impurity and deal with that the industry can help us with this. Ron Shank? Be prepared tomorrow. I'm going to say, Ron, would you make comments on this?

Full Panel

Thank you. Unanimous. Then we're skipping the next ingredient and going on to the crosslinked alkyl acrylates and that is Dr. Marks again.

DR. MARKS: So, in March of this year's meeting, the panel issued an insufficient data announcement asking for impurity data and what we were concerned about was benzene as the impurity in these crosslink alkyl acrylates, which are 23 compounds, and we had extensive discussion on how to deal with this benzene impurity, whether or not we should try and set limits to what should be in a cosmetic product and where would those limits be derived from. Would it be from the California Prop 65 limits? Would it be EPA drinking water limits of benzene? And how we finally ended up is feeling, since a number of these crosslink alkyl acrylates are -- benzene is not used in the manufacturing process, we felt that a reasonable conclusion would be safe, however insufficient data for leave-ons having benzene impurity within it.

DR. BERGFELD: And that's a motion?

DR. MARKS: That's a motion. I'm sure there will be discussion.

DR. BERGFELD: Discussion? Belsito response?

DR. BELSITO: Yeah, we, in the draft discussion, in the third -- fourth paragraph, the next to the last sentence, it says, "For example, a worse case for benzene as an impurity would be 0.5 max times 6 percent maximum use concentration in the ingredient for a final level of 0.03 percent in a cosmetic formulation. Such a trace amount presents no safety issue," and then just deleted that last sentence. So, the feeling of my panel members was that 0.03 percent did not represent a safety issue.

DR. MARKS: So, Ron Shank actually did the calculations on this comparing it to the EPA water level of 10 microns -- I'll tell you what, Ron, why don't you go through your calculations with the 10 micrograms if you drank 2 liters of water -- and then he calculated in a cosmetic ingredient that you could apply 1 gram and get a third of that potentially.

DR. SHANK: Right. I took the maximum concentration of a polymer in cosmetics is 6 percent and 1 gram of that cosmetic applied, which would give 60 micrograms of the polymer. If that's a half percent benzene, that would produce 300 micrograms of benzene per gram of formula -- formulation. That 300 micrograms is 30 times higher than the EPA maximum benzene drinking water standard of 5 micrograms per liter. Assuming an adult drinks 2 liters, that would be 10 micrograms of benzene per day. The cosmetic formulation would provide 300 micrograms per day. So, the benzene concentration is too high. And that's for one gram of cosmetic applied to the skin.

DR. BELSITO: I mean, we obviously had concerns with benzene as did you. I mean, I don't really have a problem with your conclusion. I mean, that's what we're all trying to get at is the restriction of benzene. So, I mean --

DR. LIEBLER: So, I think the calculation's valid. The question I have is, drinking water, obviously you're ingesting it and that means you're ingesting all the benzene in the calculation in the drinking water side. With a cosmetic ingredient you're applying an ingredient, and the question remains, how much of that ingredient -- of the benzene in that ingredient would actually be absorbed. And, you know, you would certainly be losing it -- if it's there, you'd be losing it to evaporation as well as absorbing whatever you could absorb. So, I mean, the difference you point out is high, except that the amount that you'd actually get into the body would be much lower -- lower fraction of what's presented to the body.

DR. SHANK: But you have to know how much.

DR. MARKS: And that's what we struggle with, and that's only one gram, Dan. If we applied this total body to an adult it would be 30 grams, and there are some baby products here, so if you did total body application, it could be not 300 in an adult, but exposure to 30 times that and then we don't know what percentage of that -- I agree, that's why we struggle trying to figure out how we could set a limit. And then we ended up with insufficient for leave-on just because we couldn't determine the limit and we didn't know how much absorption would occur. And we even asked the manufacturers how much benzene would be free within these acrylate ingredients and we couldn't come up with an answer to that.

DR. LIEBLER: It's insufficient for leave-on at a given concentration of benzene? Is that what you said?

DR. MARKS: Yes, insufficient data for leave-ons having benzene impurity within it. We're told that a number of these acryl acrylates are actually manufactured without benzene, so.

DR. SLAGA: As a solvent.

DR. MARKS: Yeah, as a solvent, so it would -- if it's not manufactured with benzene as a solvent, then it's a nonissue. It's only those ones in which benzene is a solvent.

DR. BELSITO: So, you need to be careful how you craft that because what you're saying is that it's -- the data are sufficient to support the safety for leave-on and rinse-off products, however, the assumption is that the leave-on products will not be manufactured with the use -- or however you want to say it -- of benzene.

DR. MARKS: Yeah, that's correct, Don. That's essentially it. However, insufficient data for leave-ons having benzene impurity.

DR. BRONAUGH: Could I just add that 1 gram of product probably, you know, that would cover 1,000 square centimeters of a baby. You couldn't get much more than one gram on --

DR. SHANK: It's still, at this concentration of a half a percent, it's still more benzene for a baby than would be allowed if the baby had that benzene in drinking water.

DR. BERGFELD: You're going out as insufficient in the leave-ons, did you want to modify?

DR. BELSITO: Only if the product is manufactured with benzene.

DR. MARKS: Correct.

DR. BERGFELD: Is there another way of stating that where it would be fine or safe if benzene-free leave- ons, but unsafe or insufficient for those who contain benzene?

DR. MARKS: That's exactly what we said.

DR. BELSITO: Have we ever set a limit for benzene?

DR. MARKS: Well, we tried doing that, Don, and if we can -- you know, as this goes out, issuing a tentative report, one of the data needs we would want for the insufficient data is establish a limit. We struggled with that so we would ask industry to help us with establishing a limit and a margin of safety calculation.

DR. BERGFELD: Would you restate your motion then again and --

DR. MARKS: We would move to issue a tentative report on these ingredients, and I have noted that there are 23 of them, that they're safe; however, insufficient data for leave-ons having benzene impurity.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Second. Any further discussion?

DR. BELSITO: Yeah, what we would need would be, as Jim said, for -- they may be safe if they have a benzene impurity, but what is the level and what's the margin of safety?

DR. BERGFELD: All right. Calling the question then, all those in favor of this motion? Approved, thank you.

DR. MARKS: And let me just reference one thing we did consider and look at was the 1987 report on toluene and actually in that conclusion it was that that ingredient would be benzene free, but we decided not to go to that extent that it had to be benzene free.

DR. BERGFELD: Any other points that need to be made at this time?

DR. KLAASSEN: Yes, I think it's very important that we don't say something like that, that it -- and if we said that for toluene before we should all be spanked.

DR. MARKS: Well, you can review the report. We pulled it up yesterday.

DR. KLAASSEN: I believe you, but we made a mistake.

DR. BELSITO: Last comment was we were asked whether if other chain length molecular weight acrylate crosspolymers came on could we do like what we did with PEGs and just say safe if they're used in the same way? And our group felt we could not, we would like to see each individually.

Going on to the next Green Book, and that's the acrylate crosspolymers, Dr. Marks presenting.

DR. MARKS: A scientific literature

review for these cosmetic ingredients were issued in December of last year. Our team reviewed the available data. This is the first time we saw it, and we moved to issue a tentative report that these ingredients are safe as used in cosmetics.

DR. BERGFELD: Second or comments?

DR. BELSITO: Comment?

DR. BERGFELD: Yes, go ahead.

DR. BELSITO: We were struck on page 3 or Panel Book page 9 by the benzine impurities in carbachol 1342. The specifications state that it can contain 0.5 percent max of residual benzine. Monice was nice enough to pull a material safety data sheet on carbachol 1342, and it indicates that to -- it can be produced at 0.1 percent maximum as benzine -- as required by Canada, the EU, and Korea with no further information there. But this is only from one manufacturer.

So, we had actually thought that we would like to go insufficient on these acrylate crosspolymers at this time to get clarification regarding the level of benzine. Dr. Bailey had

indicated that that was perhaps an old manufacturing method that was no longer applicable to the current way that these cross-linked acrylate polymers are produced. But this is the first time we're seeing it. So, we would like to go insufficient for impurities, specifically benzine.

DR. BERGFELD: Tom?

DR. SLAGA: I agree that would be worthwhile doing.

DR. MARKS: I withdraw our team's motion. And we'll second the motion of Dr. Belsito's team.

DR. BERGFELD: To go insufficient? John Bailey?

DR. BAILEY: Why can't we go with Monice's find on the MSDS sheet, which was.01 percent, right?

DR. BELSITO: 0.1.

DR. BAILEY: 0.1.

MS. FIUME: For the EU. It didn't give for the U.S. For the U.S., the main impurity

specification says.5 max with a footnote from EU, Canada, and Korea. So that.5 max is sort of hanging out there in the air, unless it's addressed in a different manner.

DR. BAILEY: But if the panel issues a tentative report that restricts benzine impurities to 0.1 percent, then it's not hanging in the air anymore.

DR. BELSITO: You know, we certainly could do that. I mean, the highest level of use is 6 percent in an eye care product. So that's the highest. So, I don't -- I'm not a benzine toxicologist, so I throw that out. So.1 percent benzine in the product, maximum use at 6 percent is -- does anyone perceive that that would be a problem?

If not, then hopefully we can get the data to support that and we can go ahead with the safe as used conclusion.

DR. BERGFELD: Ron Hill?

DR. HILL: Yes, I wanted to raise one more while we were on the subject of impurities.

On same page of the book, under impurities. The last sentence in the first section says the residual monomer content of acrylates, blah, blah, blah, blah, is typically less than 2,500 ppm acrylic acid and 500 ppm residual ester. So, it has the word "typically." And I had a note that I wrote here that said, we really need this information for all the acrylates because acrylate esters are not something we want to be having dermally absorbed in high concentrations, I think. And we didn't really have that.

So, from -- I wondered if anybody else had that same concern.

DR. MARKS: I thought we had addressed that. We were going to address it in a discussion, we didn't get to editorial comments. But the -- would be monomer impurities, and that they've been addressed in previous CIR reports.

DR. HILL: Okay, I think that's the way it was dealt with, yes. I just --

DR. MARKS: So that was going to be in the discussion. But if we still go back to how

are we going to move forward, and the -- Don, you made the motion to insufficient. Do we want to change that? Our team made a motion to safe. Do we want to do a safe with a limit of benzine?

DR. BELSITO: I think --

DR. BERGFELD: Either way, you have to withdraw the motion.

DR. BELSITO: I didn't make the motion.

DR. BERGFELD: Yes, you did. Insufficient was the motion. And Jim was seconding it.

DR. BELSITO: Okay.

DR. BERGFELD: No one seconded his --

DR. BELSITO: No, Dr. Marks' initial motion was safe as used.

DR. BERGFELD: Nobody seconded.

DR. BELSITO: Oh, okay. Someone seconded mine?

DR. MARKS: Yes, I did.

DR. BELSITO: Oh, good. Okay.

(Laughter) Whoa, okay. So, again, I throw it -- it's not my area of

expertise. I'm telling you that they -- in Europe, they can limit to 0.1. We don't have any information as to how they came up with that magic number, though the maximum concentration of use is limited here, 6 percent in eye products.

So those of you who know about benzine toxicity, if you're prepared to do the math today and sign off on it, I'm comfortable with it. In terms of skin sensitization, yadda, yadda, yadda, I'm comfortable. I can't comment on benzine toxicity at that level.

DR. SLAGA: Can't we --

DR. BERGFELD: Tom.

DR. SLAGA: -- look at the data, continue with this motion but get the European data -- the EU data and look at why they came up with.1?

I mean, first thought -- you know, 6 percent of.1 is very, very small and more likely

would have no carcinogenic or any other effect. But they probably already made the calculation. And why don't we just look at it?

DR. BELSITO: So, do you want to go safe as used when benzine impurity in the material is less than.1, or do you want to go insufficient --

DR. SLAGA: Insufficient until we get comparison --

DR. BELSITO: I'm fine --

DR. SLAGA: -- and see what kind of calculations they made.

DR. BELSITO: I'm fine either way. I think there are probably no safety issues, so delaying the final on this report -- I think, don't think --

DR. SLAGA: Right --

DR. BELSITO: -- it's going to be a big deal.

DR. BERGFELD: Ron Shank?

DR. SHANK: So, your motion is --

DR. BELSITO: Insufficient for impurities, specifically benzine.

DR. SHANK: -- insufficient for -- and what do you want? Is --

DR. BELSITO: I want to know what --

DR. SHANK: How much is in there or how much --

DR. BELSITO: How much is in there, and I want some benzine toxicity brought in. I want information as to why the Europeans decided to regulate it at.1. Where they got that information that allowed them to set that limit.

DR. SHANK: Okay.

DR. BERGFELD: Ron Hill, okay? Dan?

DR. LIEBLER: Yes, I like that approach.

DR. BERGFELD: Paul? Curt?

DR. KLAASSEN: Yes.

DR. BERGFELD: How about John Bailey?

DR. BAILEY: You know, I hate to continue this on for another meeting, but I think it's a reasonable request and we'll certainly do our best to get the information.

DR. BERGFELD: Thank you. So, we have a motion. We had a second. Any other discussion?

Seeing none -- yes, Monice.

MS. FIUME: I just want to clarify. So it's an insufficient data announcement --

DR. BELSITO: Right.

DR. BERGFELD: Call for the question. All those in favor, raise your hands. Thank you, unanimous.

Anything else? Hearing nothing else, the next one we're looking at would be acrylate cross-polymers. Now, you were going to hand out a hard copy of something that you had e-mailed to us, is that correct, Monice?

MS. FIUME: Yeah. Table 1 was corrected. There was a structure that was missing, and there was a structure that was incorrect. We've just redone the entire table. You might --

DR. BELSITO: Sure.

MS. FIUME: And then also -- sorry.

DR. BELSITO: I looked at this.

MS. FIUME: I have about 16 of these. Does anyone else need a copy? And then for you, Dr. Belsito. I updated the data profile. The one in the bag matched what came in with wave 2. They're sort of hard to see, but the X is in red.

DR. BELSITO: Yes, yes.

MS. FIUME: Here's the updated information for wave 2.

DR. BELSITO: Right, which is mainly all dermal, and a --

MS. FIUME: Little bit monomer.

DR. BELSITO: -- little bit of monomer content.

MS. FIUME: I only made one -- I have a couple of copies if anyone else would like one.

DR. BELSITO: Okay. And when I looked at the changes in table 1, they didn't really seem -- I mean, it was just really more editorial corrections than anything of substance. Is that a good, correct assumption?

MS. FIUME: Look at the -- the one structure was incorrect, and my structure was missing. But it was more substance. We were e-mailing it to Dr. Liebler electronically, so I wanted to make sure you were included.

DR. BELSITO: Oh, thank you. Okay, so the acrylate cross-polymers -- this is the first time we're looking at the report. We've previously looked at acrylate copolymers and found them to be safe as used when formulated to avoid skin irritation. The cross-polymers theoretically should be even safer, because they're going to be even larger molecules with less chance of penetration and less reactive monomer content, and the cross-polymers we're looking at probably number about 20. They're listed on page 1 of the book or page 7 of the Panel Book.

And beyond that, I really had no substantive comments. I was comfortable with the report. I thought it was very well put together. We got a whole wave of second data dealing with skin irritation and sensitization, and that was

all negative. So, I really had no comments on this report. I love that little circular structure, the theoretical magnified view of the cross-linked --

MS. FIUME: (inaudible) having a chemist on (inaudible).

DR. LIEBLER: We did that.

DR. BELSITO: I don't have a clue how you would do that, but I thought it was phenomenal.

DR. LIEBLER: Yeah, I wanted to also second that, because I think that was a very effective way to portray the chemical nature of these above and beyond just the structure that would be on the table, and it worked very nicely also in the silylates report as well. So, this is a nice innovation. It really helps to bring the chemistry to the non-chemist audience I think better, so nice idea.

DR. SNYDER: Can I add one question on the impurities on page 3?

DR. KLAASSEN: Yes, the benzene?

DR. SNYDER: Yeah, the benzene. So, we recognize that a product can -- one product does have residual benzene, and we do have leave-on in the baby/infant use, so is that an issue?

DR. BELSITO: Where are you, Paul, on --

DR. SNYDER: Carbopol 1342, the product specification states that the acrylates C10 to C30 -- acrylate cross-polymer continue --

DR. BELSITO: 0.5 percent max.

MR. SNYDER: Okay.

MS. FIUME: And the baby product is.2 percent use.

DR. BELSITO: Okay.

MS. FIUME: In that entire product, leave-on is.0002 to 5 percent. But the baby product is.2.

DR. BELSITO: Okay.

DR. SNYDER: All right.

DR. BELSITO: Is that okay?

DR. SNYDER: Yeah, I mean, I just wanted to point it out and make sure that we considered it. I mean, is there anything in the manufacture

that other ones would contain higher levels than that?

MS. FIUME: I haven't included anything that I either found through industry or MSDS that had residual levels, and that's why I broke it out by trade name, because they did have different amounts. Even though it was the same ingredient, the trade names did have different specifications.

DR. KLAASSEN: Well, where did you find this up to 5 percent?

DR. BELSITO: 0.5.

DR. KLAASSEN: Did you say 5 percent someplace else?

MS. FIUME: Oh, the max leave-on use is percent.

DR. KLAASSEN: Oh, the max leave-on use, okay, not the amount of benzene.

DR. BELSITO: No. Well, is this something that we need to put into the discussion?

DR. SNYDER: I think so.

DR. KLAASSEN: Yes.

DR. SNYDER: I think so.

DR. KLAASSEN: Yes, I noted it also.

DR. BELSITO: And how would you address that?

DR. SNYDER: That we noted it in the method of manufacture that benzene can be an impurity in that process based on the information that we have that it's at a low level in the product and at the low exposure rates that is not a concern, I guess, or something along that line saying --

DR. BELSITO: Well, how specific do you want to be about not a concern? I mean, so we're saying -- are we saying it shouldn't contain more than 0.5 crystal benzene?

DR. SNYDER: Well, I actually queried to say should we limit the amount of benzene. I don't know what we've done in -- with been benzene in other reports, because I have that tagged as have we limited benzene in other --

DR. BELSITO: I don't remember ever specifically discussing a limit on benzene. I don't.

MS. FIUME: Yeah, I can't recall off the top of my head.

DR. SNYDER: I don't recall it either. I'm checking the report on sodium dodecylbenzenesulfonate to see if we did anything. You know, up above there it said that when they make these cross-polymers, they can make them in apple acetate cycle hexane mixture or may also be polymerized in benzene. So, some of them might not have any.

DR. ANDERSEN: When I think a question that while wouldn't specifically be directed but the producer of the material should be aware that the question has come up, and while 0.5 percent may be the maximum, what's the normal expected level, and if that is what I would think would be significantly lower than that they just put a max to cover the possibility, then that gives some more information.

DR. BELSITO: Well, I guess, you know, if we're going to -- I mean, we obviously -- the issue is raised. We obviously feel it needs to go

in the discussion. I think from my point of view, and again this is not my area of expertise -- benzene toxicity applied to the skin. If we're going to say that it shouldn't contain more than 0.5 percent, it would seem to me that we would have to have a rationale as to why it couldn't, why we're limiting it at 0.5, because maybe it could be 1 percent, you know? Maybe it could be 2.5.

So, I guess the question becomes we're obviously concerned that at some point benzene could be an issue. But what's that point, and since we can either table it to get to that point, give a specific -- and that's not going to happen -- or if we say, you know, safe as used in the current yadda, yadda, yadda, does that mean that the assumption is it won't contain more than 0.5 percent benzene max? I mean, we don't have all of the manufacturers here.

MS. FIUME: I found what I could find on the internet.

DR. BELSITO: Right.

DR. ANDERSEN: Yeah. Perhaps we could provide some additional clarification on this. This is a report from 15 years ago. Benzene is an industrial solvent for purposes of polymerization and is, you know, somewhat old style, so let us see if we can provide some guidance. But we were also aware of the report that they have established a maximum for this particular grade of 0.5 percent, but that seems like a lot.

DR. KLAASSEN: Yeah, it might not even be used anymore.

DR. BELSITO: Okay, so then looking at these acrylate cross-polymers, I mean, essentially safe as used but we need to deal with this benzene in some fashion, and so do we table it to hear back from industry about current methods of manufacture? Does a "safe as used" -- does that mean that we're assuming there would be no more than 0.5 percent benzene? Because if we start getting into specifics in the discussion about that, then I think we need to justify why we put that limit, and we don't have the data to do that.

DR. SNYDER: Well, benzene is not an insignificant toxicant.

DR. BELSITO: Right.

DR. SNYDER: I mean it's -- and so -- I mean, I think that we have information that it is an impurity, and in one product it can -- you know, they say it maxes at.05 percent. But, again, we also have --

DR. BELSITO: 0.5.

DR. SNYDER: 0.5 percent. And we also have information, though, that it is used in a polymerization, or has been historically used in a polymerization. So, I think this --

DR. BELSITO: Then maybe we should table it and hear what industry has to say about current methods of manufacture? I mean, because that's -- I mean, basically if there's no benzene or if every product on the market is less than 0.5 percent, we're comfortable going ahead with "safe as is," is that correct?

DR. SNYDER: Correct.

DR. KLAASSEN: Right.

DR. BELSITO: But right now we don't know that. We have one company saying their max is 0.5, but we don't know who the manufacturers are, and we're not prepared to do a risk assessment on benzene.

DR. KLAASSEN: I suggest we wait for this information.

DR. SNYDER: I concur.

DR. ANDERSEN: There's two ways of waiting -- passively waiting and aggressively waiting. (Laughter) The aggressive stance would be to issue an insufficient data announcement to -- for clarification of benzene levels in these products period. We just -- that's what you need to know.

DR. BELSITO: I'm an aggressive guy. Let's go with that if you're comfortable. I mean, insufficient, further information on levels of benzene.

DR. ANDERSEN: I mean, it's -- you would expect that you will get a response. So, it's not like it's sending it to insufficient limbo, and

once you have the information, you can easily issue the safety assessment as a tentative the next time we meet.

DR. KLAASSEN: Fine.

DR. BELSITO: I like that better than tabling, yeah. Puts a time limit on it. Okay, good.

So, then, Dan, you comfortable with that?

DR. LIEBLER: Yeah, I am.

DR. BELSITO: We're going to go insufficient, further information about levels of benzene and the acrylate cross-polymers. Otherwise, once we get that if the information is less than.5 percent, we'll go ahead with the safe as used.

DR. SNYDER: I have another question. So, the inhalation data. So, we go through our respiratory boilerplate, and I quite didn't know how to correlate with -- we have known industrial exposure limits. So, it is respirable, and so how does -- it comes up in another report, too, where

we actually have inhalation data where they actually dosed animals and it was -- it did have an effect. And so the use of the boilerplate usually says "in the absence of data," but could -- we have data that says it is respirable -- I'm kind of conflicted there as to what does that -- how are we dealing with that or --

DR. ANDERSEN: I think, Paul, the issue of respirable/not respirable really relates more to the class of products called cosmetics. As aerosols are produced in the cosmetics industry, they are not blockbuster particles but they're bigger than what's respirable in general, and we simply capture that. I don't have any question that the technology exists to make smaller particles, which would be respirable, but you aren't going to find it in cosmetics. And so there's been limits established for respiratory levels, and that's fine. They wouldn't have been needed for cosmetics.

DR. BELSITO: Okay.

DR. SNYDER: I have one editorial

suggestion on report page 2 right under the virtual -- well, virtual molecule structure. It says, "Due to the multitude of possible reaction conditions" -- this is under chemistry and structure, a definition and structure -- "Due to multitude of possible reaction conditions and methods, the properties of a single ingredient" blah-blah-blah. And then the sentence -- two sentences after that, "Nonetheless, the polymers in this group share the same lack of chemical activity." These are really discussions of properties. So, they should be moved down under "Physical and Chemical Properties." And I actually reworded the sentence about the polymers having a lack of chemical reactivity to read, "The polymers in this group share a general lack of chemical reactivity that renders them nearly impervious to degradation." So, this is very clearly outlined in my annotated version.

DR. BELSITO: Anything else?

DR. ANDERSEN: No.

DR. BELSITO: Okay, so we're going

"Insufficient, for further information" on the benzene content, residual benzene content.

DR. MARKS: "After penetration" -- delete. Okay. Acrylate Cross Polymers.

Let's go to acrylate cross polymers, Green Book, titled "Crosslinked Alkyl Acrylates." And then we got another electronic transmission of changes in the Table 1, "Definitions, Functions, Structures."

This is the first time we've seen this report, the first time for us to review these cosmetic ingredients. So we have the draft report in front of us.

And I'll ask the old team, Tom and Ron, are there any needs from your vantage point? And, also -- I think I have that.

MS. FIUME: Okay.

DR. MARKS: I printed it out. Thanks.

MS. FIUME: I will give you this. This is just the updated data profile. The red is what was new.

DR. MARKS: Oh, okay. Thank you.

DR. SHANK: I have no data needs.

DR. SLAGA: Same here. It's a very

stable -- probably even more so than the original document on just the (inaudible).

DR. MARKS: So we would issue a tentative report "safe?"

DR. SLAGA: Yep.

DR. SHANK: Right.

DR. MARKS: I saw no issues. And -- okay. Safe. Shall we move on without Ron Hill being here?

DR. SHANK: (Inaudible).

DR. MARKS: Yes, I agree. This would actually be good armor in warfare?

DR. SHANK: Yes -- oh.

DR. MARKS: So one thing I highlighted on page 74, it is used in baby products. There's no -- again, it doesn't raise any issues from that point of view. It's used in baby lotions, oils, powders and creams. That -- still -- safe.

DR. SHANK: Well, I think in the "Discussion," we should have discussion that the monomers could be impurities, but the monomers have already been reviewed by the panel? And we

should wait for Dr. Hill?

DR. MARKS: Yes -- will do. They've already been addressed in previous CIR reports.

And, obviously, they were addressed as being safe, or else we would be concerned about the monomers' being present.

DR. SHANK: Well, the maximum use-concentration --

DR. MARKS: Right.

DR. SHANK: -- for the polymers is (inaudible). So the un-reacted monomer's going to be small.

DR. MARKS: Right. So, Ron, we've already decided that we have enough data, and we can issue a tentative report with a "safe" conclusion. And this is for the crosslinked --

DR. HILL: Yes.

DR. MARKS: -- alkyl acrylates. But we didn't want to finalize that until we got your input. We didn't want you to be surprised tomorrow when I moved to make this --

DR. HILL: No, I think that's where I

came to. I'm just trying to remember if there were any --

DR. MARKS: Monomer impurities are addressed in previous -- so that would be in the discussion. Yes.

DR. HILL: I think most of my things in here were all editorial. So --

DR. MARKS: Okay.

DR. BERGFELD: May I ask a question? Some of the special tox studies were not here. If you're using the monomer studies, is that adequate? The genotox, the reproductive? You know, there's nothing on this group, crosslinked acrylates.

DR. SHANK: These won't be absorbed.

DR. BERGFELD: So they won't be absorbed. So that's -- you don't need that.

So you'll put that in the discussion, as well?

DR. MARKS: Yes.

DR. BERGFELD: Okay. So they've very big.

DR. HILL: Who was the report writer here?

MS. FIUME: I am.

DR. HILL: Okay. Yes, I have quite a bit of -- it falls in the category of editorial things. But in the structures table, and --

MS. FIUME: Oh, I just gave you a new structures table --

DR. HILL: You gave me a new --

MS. FIUME: -- that has a corrected structure, and one that was missing.

DR. HILL: Well, there are quite a few places where I made notations concerning the structures. And it doesn't affect anything in terms of conclusion. And it's probably, in many cases, traceable to dictionary errors. But -- so --

DR. MARKS: Okay. So tomorrow I'll move to issue a tentative report with a "safe as used" conclusion. And the discussion will say that these ingredients are not absorbed, hence the lack of some of the data points needed. And that the

monomer impurities have been addressed in previous CIR reports.

DR. HILL: The only other question I had was will Table 5 -- it is intended that Table 5 will be maintained in the final report? I'm hoping yes.

MS. FIUME: Yes, Table 5 will replace that "Dermal Irritation and Sensitization" -- the text will be replaced by Table 5.

DR. HILL: Okay. But Table 5 is planned for the final report?

MS. FIUME: Yes.

DR. HILL: Yes? Great.

POLYMETHYL METHACRYLATE (PMMA) REPORT

June 28-29, 2010

The CIR Expert Panel utilized data from FDA approvals of PMMA medical devices including: intraocular lenses (IOLs), bone cement, dental fillers, and dermal fillers. Available data on PMMA used in cosmetics demonstrated the equivalence to that used in devices. The Panel deleted Sodium polymethacrylate from the report because it is not a methyl methacrylate polymer.

The CIR Expert Panel concluded that these three ingredients are safe in the practices of use and concentration as given in the safety assessment.

April 5-6, 2010

A new approach was used in the assessment of the safety of PMMA. PMMA is used in several implanted medical devices that have been approved by the Food and Drug Administration (FDA) including: intraocular lenses (IOLs), bone cement, dental fillers, and dermal fillers. Because FDA has examined these devices for safety far beyond the risks posed by use in cosmetic applications, the CIR Expert Panel concluded that FDA's approval is sufficient for a conclusion of safety for cosmetic uses.

The CIR Expert Panel had sought better characterizations of the PMMA used in cosmetics. These data were received and were consistent with those data available that characterized the PMMA approved by FDA (the data on which was a primary basis for this safety assessment). The Panel asked that additional information about the characterization of the PMMA material as used in devices be included.

The CIR Expert Panel concluded that these ingredients are safe in the practices of use and concentration as given in the safety assessment.

December 7-8, 2009

The CIR Expert Panel agreed that the approach taken by CIR to evaluate these ingredients was acceptable, but determined that certain additional data are needed. Additional data needs include evaluation of:

- Level of monomer in methyl methacrylate/glycol dimethacrylate crosspolymer

In addition, CIR staff will gather relevant data on methyl methacrylate sensitization for incorporation into the draft report.