Safety Assessment of
Styrene and Vinyl-type Styrene Copolymers as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	May 16, 2014
Panel Date:	June 9-10, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, 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 Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 16, 2014
Subject: Draft Report on Styrene and Vinyl-type Styrene Copolymers

A Scientific Literature Review (SLR) was issued on February 21, 2014. In response, safety test data and comments from the Personal Care Products Council (Council) were received during the 60-day comment period. All comments have been addressed. Use concentration data received from the Council were included prior to announcement of the SLR.

Also included in this package for your review is the Draft Report on Styrene and Vinyl-type Styrene Copolymers, the CIR report history, Literature search strategy, Ingredient Data profile, 2014 FDA VCRP data, Comments from the Council (pcpc1 pdf file), use concentration data (data 1 pdf file), safety test data on various styrene acrylates/copolymer trade name materials (data 2 pdf file), Final report on PVP/VA copolymer (data 3 pdf file), Re-review on PVP/VA copolymer (data 4 pdf file – See pages 55-59), and Final report on acrylates copolymer (data 5 pdf file). Additional safety test data received in response to the SLR announcement will be included in the wave 2 data submission.

Please note that data on trade name materials containing styrene/acrylates copolymer at concentrations ranging from 26-28% to 86-90% (lowest and highest concentration range for copolymer in trade name materials, respectively) are included in this safety assessment. Information on their composition is included in the section on Composition/Impurities. Safety test data including data on the trade name materials, data on unnamed compositionally-similar trade name materials, and on a trade name material (i.e., SunSpheres™) for which the chemical name is not stated have been added to the report. Details relating to the test protocol and animal strains tested are not included in the study summaries. Safety test data submitted on OPULYN™ PQG Opacifier were not added to the safety assessment, because the CAS number for the ethalkonium chloride acrylate/HEMA/styrene copolymer (26010-51-5) in this trade name material does not appear to be valid for styrene/acrylates copolymer.

After reviewing the composition data on styrene/acrylates copolymer trade name materials, the Panel should identify which, if any, of the trade name materials and relevant associated safety test data should remain in this safety assessment. Data from the selected studies will be added to the next version of this safety assessment.

It should be noted that this safety assessment also includes data on monomers such as styrene, which is present in all of the ingredients reviewed in the safety assessment, and 1,3-butadiene. The need for safety test data on other component monomers comprising these ingredients in this safety assessment will be determined, if necessary.

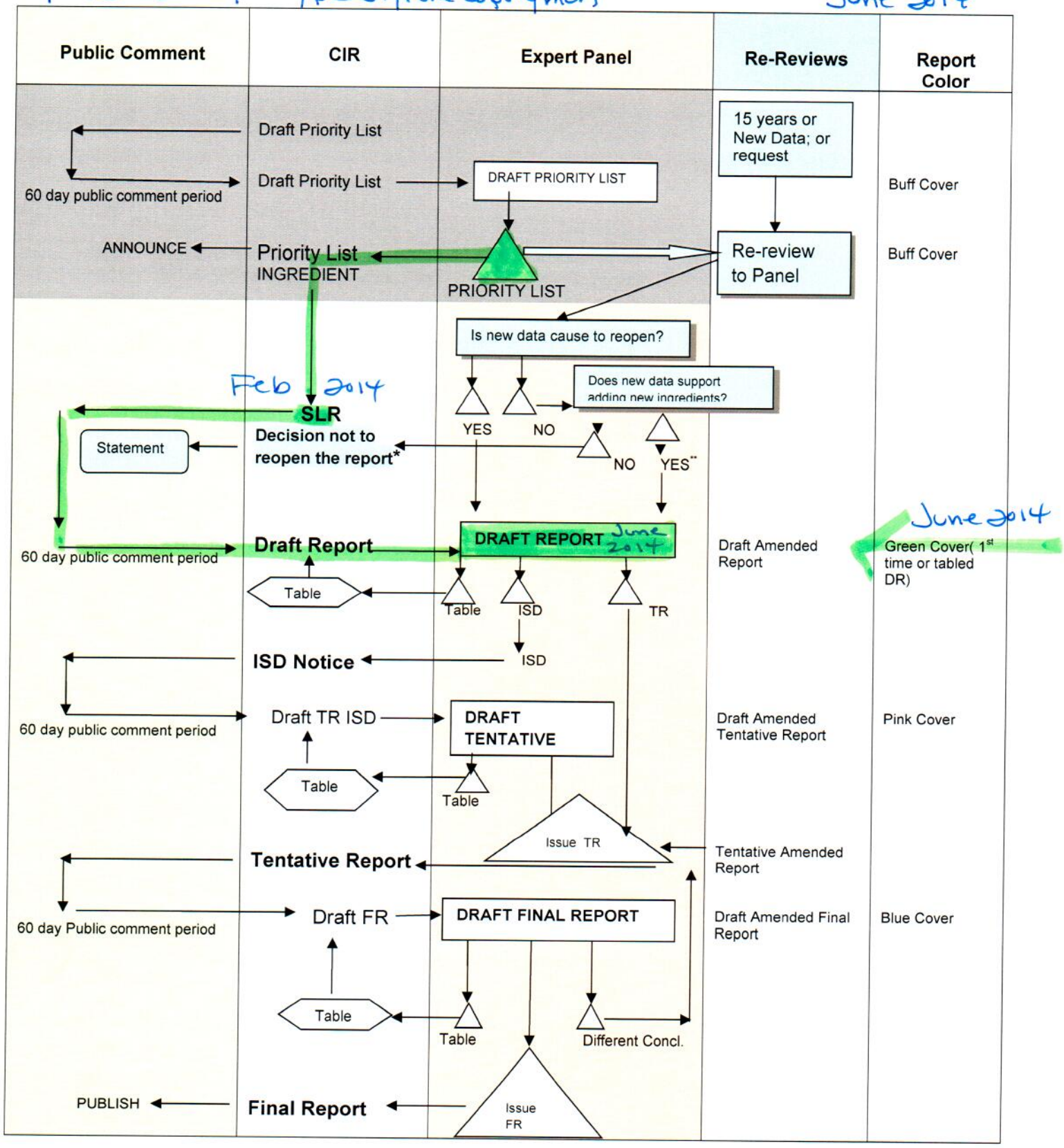
Ultimately, after reviewing the available data, the Panel needs to determine whether an insufficient data announcement or tentative report with a safe as used, safe with qualifications, or unsafe conclusion should be issued.

1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

SAFETY ASSESSMENT FLOW CHART

Styrene and Vinyl-type Styrene Copolymers

June 2014



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

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CIR History of:

Styrene and Vinyl-type Styrene Copolymers

A Scientific Literature Review (SLR) Notice was announced on February 21, 2014. Comments and safety test data were received during the 60-day comment period. Use concentration data were received prior to issuance of the SLR.

Draft Report, Belsito and Marks Teams/Panel: June 9-10, 2014

Use concentration data and safety test data received from the Council have been incorporated. Comments received from the Council have been addressed. Additional safety test data received will be included in the wave 2 data submission.

Styrene and Vinyl-type Styrene Copolymers Check List for June, 2014. Analyst – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Ethylene/Propylene/Styrene Copolymer																				
Butylene/Ethylene/Styrene Copolymer																				
Acrylates/Ethylhexyl Acrylate/Styrene Copolymer																				
Butyl Acrylate/Styrene Copolymer																				
C4-6 Olefin/Styrene Copolymer																				
C5-6 Olefin/Styrene Copolymer																				
Hydrogenated Butadiene/ Isoprene/Styrene Copolymer																				
Hydrogenated Butylene/ Ethylene/Styrene Copolymer																				
Hydrogenated Ethylene/ Propylene/Styrene Copolymer																				
Hydrogenated Styrene/Butadiene Copolymer																				
Hydrogenated Styrene/Isoprene Copolymer																				
Isobutylene/Styrene Copolymer																				
Methacrylic Acid/Styrene/VP Copolymer																				
Methylstyrene/Vinyltoluene Copolymer																				
Polystyrene																		X	X	
Polystyrene/Hydrogenated Polyisopentene Copolymer																				
Sodium Methacrylate/Styrene Copolymer																				
Sodium Styrene/Acrylates Copolymer																				
Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer																				
Styrene/Acrylates Copolymer				X		X	X				X	X	X	X		X		X		X
Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer																				
Styrene/Butadiene Copolymer																			X	
Styrene/Isoprene Copolymer																				

Styrene and Vinyl-type Styrene Copolymers Check List for June, 2014. Analyst – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Styrene/Methylstyrene Copolymer																				
Styrene/Stearyl Methacrylate Crosspolymer																				
Styrene/VA Copolymer																				
Styrene/VP Copolymer																				
Polyacrylate											X							X	X	
Polyacrylate-2																				
Polyacrylate-5																				
Polyacrylate-12																				
Polyacrylate-15																				
Polyacrylate-16																				
Polyacrylate-18																				
Polyacrylate-21																				
Polyacrylate-30																				

Search Strategy – Styrene and Vinyl-type Styrene Copolymers

12/12-13/13 Search-Pubmed name +CAS; SeardchScifinder name; 0 = nothing or nothing useful

List of Ingredients:

1. Ethylene/Propylene/Styrene Copolymer (0;0)
2. Butylene/Ethylene/Styrene Copolymer (0;0)
3. Acrylates/Ethylhexyl Acrylate/Styrene Copolymer (0;0)
4. Butyl Acrylate/Styrene Copolymer (0;0)
5. C4-6 Olefin/Styrene Copolymer (0;0)
6. C5-6 Olefin/Styrene Copolymer (0;0)
7. Hydrogenated Butadiene/ Isoprene/Styrene Copolymer (0;0)
8. Hydrogenated Butylene/ Ethylene/Styrene Copolymer (0;0)
9. Hydrogenated Ethylene/ Propylene/Styrene Copolymer (0;0)
10. Hydrogenated Styrene/Butadiene Copolymer (0;0)
11. Hydrogenated Styrene/Isoprene Copolymer (0;0)
12. Isobutylene/Styrene Copolymer (16;2)
13. Methacrylic Acid/Styrene/VP Copolymer (0;0)
14. Methylstyrene/Vinyltoluene Copolymer (0;0)
15. Polystyrene (28;0)
16. Polystyrene/Hydrogenated Polyisopentene Copolymer (0;0)
17. Sodium Methacrylate/Styrene Copolymer (0;0)
18. Sodium Styrene/Acrylates Copolymer (0;0)
19. Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer (0;0)
20. Styrene/Acrylates Copolymer (9;0)
21. Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer (0;0)
22. Styrene/Butadiene Copolymer (0;2)
23. Styrene/Isoprene Copolymer (0;0)
24. Styrene/Methylstyrene Copolymer (0;0)
25. Styrene/Stearyl Methacrylate Crosspolymer (0;0)
26. Styrene/VA Copolymer (0;0)
27. Styrene/VP Copolymer (0;0)
28. Polyacrylate-2 (1;1)
29. Polyacrylate-5 (0;0)
30. Polyacrylate-12 (0;0)
31. Polyacrylate-15 (0;0)
32. Polyacrylate-16 (0;0)
33. Polyacrylate-18 (0;0)
34. Polyacrylate-21 (0;0)
35. Polyacrylate-30(0;0)

Safety Assessment of Styrene and Vinyl-type Styrene Copolymers as Used in Cosmetics

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INTRODUCTION

This report presents information relevant to evaluating the safety of styrene and vinyl-type styrene copolymers as used in cosmetics. Film former is the most frequent function reported for these ingredients. Other common functions included opacifying agent and viscosity agent.

Very limited safety test data on the styrene and vinyl-type styrene copolymers reviewed in this safety assessment were found in the published literature. This safety assessment also includes data on monomers such as styrene, which is present in all of the ingredients reviewed in the safety assessment, and 1,3-butadiene.

In the absence of data on most of the copolymers, it should also be noted that the Cosmetic Ingredient Review (CIR) Expert Panel has evaluated the safety of polyvinyl pyrollidone (PVP)/vinyl acetate (VA) copolymer (also known as VP/VA copolymer) and concluded that this ingredient is safe as a cosmetic ingredient under present conditions of concentration and use.[1] Data from this safety assessment may be useful because of monomer overlap with styrene/VA copolymer and styrene/VP copolymer. Additionally, in another safety assessment, the CIR Expert Panel concluded that acrylate copolymers are safe for use in cosmetic formulations when formulated to avoid irritation.[2,3] The Panel also stated that, although the monomers comprising the acrylate copolymers may be toxic, the levels that would be found in cosmetic formulations are not considered to present a safety risk. Data from this safety assessment may also be useful because of monomer overlap between the acrylate copolymers and ingredients in the current safety assessment. For example, acrylic acid and methacrylic acid are components of acrylates copolymer and ammonium acrylates copolymer (both in acrylate copolymers safety assessment) and of sodium styrene/acrylates copolymer and acrylates/ethylhexyl acrylate/styrene copolymer (both in current safety assessment). Similarly, 2-ethylhexyl acrylate is a component of acrylates/VA copolymer (in acrylate copolymers safety assessment) and of polyacrylate-21 (in current safety assessment).

CHEMISTRY

Definition and Structure

Polystyrene is the polymerization product of vinylbenzene (a.k.a. styrene). The other ingredients in this report are all vinyl-type copolymers with vinylbenzene. The term “vinyl-type copolymers” means that all of the monomers, utilized to make these polymer ingredients, have in common an ethylene unit whose pi electrons are directly involved in the polymerization process. Typically, a catalyst is utilized to initiate the polymerization.[4] There is a large multitude of relevant initiating catalysts, ranging from UV light to Ziegler-Natta-type catalysts, which can result in a variety of differences in the characteristics (e.g. crystallinity and resultant hardness) of the copolymer formed. The synthesis of these ingredients is typically carried out in one or more organic solvents, with one or more catalysts.

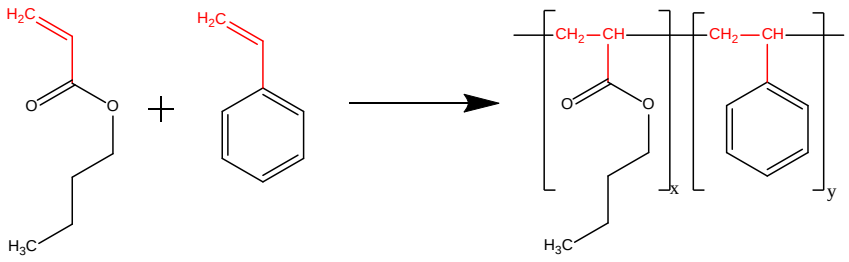


Figure 1. Butylacrylate/Styrene Copolymer

These ingredients are high molecular weight, large molecular volume, inert polymers. While not truly soluble, these ingredients may be swellable in certain organic solvents.

The molecular structures and definitions of styrene and vinyl-type styrene copolymers are presented in Table 1.[5]

Physical and Chemical Properties

Polystyrene

Properties of polystyrene are presented in Table 2.[6,7,8] Some of the properties include physical state (colorless solid in various forms), molecular mass (10,000 to 300,000), relative density (1.04 to 1.13), melting point (240°C), flash point (345 to 360°C), and auto-ignition temperature (427°C).

The thermal degradation of high impact polystyrene to styrene and other thermal degradation products occurred at a temperature of 250°C.[9] Reportedly, the principal limitations of polystyrene in industry are brittleness, inability to withstand the temperature of boiling water, and poor oil resistance.[10] Thus, polystyrene is often modified, e.g., by copolymerization with acrylonitrile and/or butadiene. Regarding this process, the most common styrene polymers are poly(acrylonitrile-butadiene-styrene and styrene-butadiene.

Styrene

Styrene is a component of each styrene and vinyl-type styrene copolymer reviewed in this safety assessment. The vinyl group of styrene is reactive, and styrene polymerizes at a significant rate at room temperature.[11] Polymerization proceeds more rapidly at elevated temperatures or in the presence of many commonly available reagents. Commercially available grades of styrene contain an inhibitor of styrene polymerization (e.g., 4-tertiary-butylcatechol). Additionally, upon exposure to light and air, styrene undergoes polymerization and oxidation, with the formation of peroxides.[7] Additional properties of styrene are presented in Table 3.[7]

Styrene-Butadiene Copolymer

Properties of styrene-butadiene copolymer are presented in Table 4.[8]

1,3-Butadiene

Properties of 1,3-butadiene are presented in Table 5.[12]

Composition/Impurities

Polystyrene

Polystyrene is available in the United States in a variety of grades, and the following are considered major grades:[8] crystalline or straight polystyrene, (2) impact-modified grades, which typically contain approximately 5% polybutadiene elastomer, and (3) expandable beads, which contain a small amount of *n*-pentane entrapped in each globule.

During the early years of polystyrene production, the residual monomer content was as high as 2%, and, at the beginning of the 1960's, it was approximately 1%.[13] Since that time, polystyrene grades with concentrations of ≤ 500 ppm residual styrene, have been developed.

Styrene/Acrylates Coplymer

Composition/impurities data on styrene/acrylates copolymer trade name materials are presented below.

Sunspheres™ LCG Polymer (pH: 6.50-7.50) has the following composition: styrene/acrylates copolymer (up to 28%), individual residual monomers (< 100 ppm maximum; for styrene, butyl methacrylate, and methyl methacrylate), aqua ammonia (up to 0.1%), water (up to 74%), and mixture of 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1) (up to 23 ppm).[14] The results of a metals analysis indicated the presence of copper at a concentration of 0.7 ppm.

Composition data on Sunspheres™ Powder include: styrene/acrylates copolymer (up to 90%), individual residual monomers (≤ 100 ppm maximum; for styrene, butyl methacrylate, and methyl methacrylate), fatty acid ethoxylate (up to 11%), related reaction products (up to 2%), and water (up to 3%). The results of a metals analysis indicated the presence of iron at a concentration of 2 ppm. Byproducts and impurities were listed as follows: 1,4-dioxane (1.23 ppm), toluene (< 0.05 ppm), 2-methyl-4-isothiazolin-3-one (5 ppm), and diethylene glycol (64 ppm).[15]

OPULYN™ 302B Opacifier (molecular weight: > 1,000,000) has the following composition: styrene/acrylic copolymers (up to 41%), individual residual monomers (< 500 ppm maximum), styrene (≤ 50 ppm), water (up to 61%), and benzoic acid (up to 0.5%).[16] The results of a metals analysis indicated the presence of iron (2,153 ppb) and magnesium (1,735 ppb).

Composition data on ACUDYNE™ Shine Polymer (pH of 3-5) include: styrene/acrylates copolymer (up to 41%), individual residual monomers (< 100 ppm; for styrene, butyl acrylate, and 2-ethyl hexyl acrylate), water (up to 61%), and benzoic acid (up to 0.75%).[17] The results of a heavy metals analysis indicated the presence of chromium (70 ppb), iron (333-1996 ppb), and nickel (92 ppb).

SunSpheres™ PGL Polymer (pH of 6.5-7.5) has the following composition: styrene/acrylates copolymer (up to 26%), residual monomers (< 100 ppm; for styrene, butyl methacrylate, and methyl methacrylate), aqua ammonia (up to 0.1%), pentylene glycol (up to 6%), and water (up to 69%).[18] The results of a heavy metals analysis indicated the presence of iron (1 ppm).

OPULYN™ 301 Opacifier (molecular weight: > 1,000,000; pH of 2.05-2.50) has the following composition: styrene/acrylic copolymer (up to 41%), water (up to 61%), residual monomers (< 500 ppm), and styrene (≤ 20 ppm).[19] Heavy metals were not detected.

Composition data on ACUDYNE™ Bold Polymer (pH of 3-5) include: styrene/acrylates copolymer (up to 41%), individual residual monomers (< 100 ppm; for styrene, butyl acrylate, 2-ethyl hexyl acrylate), water (up to 61%), and benzoic acid (up to 0.75%).[20] The results of a heavy metals analysis indicated the presence of chromium (82 ppb), iron (2,270 ppb), and nickel (173 ppb).

Styrene-Butadiene Copolymer

The following styrene-butadiene copolymers are available in the United States: (1) styrene-butadiene elastomers (commonly called SBR, or styrene-butadiene rubber), (2) styrene block polymers with butadiene, and (3) styrene-butadiene copolymer latexes. Dry SBR (produced by emulsion polymerization) contains styrene units (23% to 25%) and butadiene units (75% to 77%) on a polymer basis. When produced via solution polymerization, the composition of dry SBR varies; however, typical grades contain styrene units (~ 10% to 25%) and butadiene units (75% to 90%). Styrene block polymers with butadiene are available with a styrene content of 25% to 50%, and the most widely used grades contain 30% styrene units.

Methods of Production

Polystyrene

Polystyrene is produced from styrene by mass, solution, suspension, or emulsion polymerization processes.[10] Polystyrene resins are typically produced by a modified mass polymerization process in a continuous manner.[8] The liquid styrene monomer is diluted with a relatively small amount of a diluent, e.g., 5% to 15% of ethylbenzene. In some cases, more diluent is used, and the process may then be called a solution process. The heated mixture of styrene, solvent, and initiator is reacted at 120°C to 160°C. Unreacted monomer and solvent are removed after polymerization is complete.

Styrene/Butadiene Copolymer

Dry SBR is produced via an emulsion polymerization (cold or hot) or solution polymerization process.[8] Composition data on styrene/butadiene copolymer resulting from either process are presented in the Composition/Impurities section.

The following components (in parts per 100 monomer) comprise a typical recipe for SBR produced by cold emulsion polymerization:[8] butadiene (70), styrene (30), water (180), fatty acid soap (2.25), disproportioned rosin soap (2.25), potassium chloride (0.3), potassium hydroxide (0.3), *tert*-dodecyl mercaptan (0.23), sodium formaldehyde β-naphthalene sulfonate (0.04), sodium formaldehyde sulphoxylate (0.04), *para*-methane hydroperoxide (0.04), tetrasodium ethylenediaminetetraacetate (0.025), and ferrous sulfate heptahydrate.

A typical recipe (component data in parts per 100 monomer) for SBR produced by hot emulsion polymerization is as follows:[8] butadiene (75), styrene (25), water (180), fatty acid or rosin soap (5), *n*-dodecyl mercaptan (0.5), and potassium persulfate (0.3).

Recipes for SBR produced by solution polymerization are said to vary greatly, and depend upon the properties desired.[8] SBR is vulcanized (typically 1.5 to 2.0 parts sulfur per 100 parts of polymer are used). Furthermore, accelerators, antioxidants, activators, fillers (e.g., carbon black), and softeners may be used, depending on the properties of the finished rubber that are desired. SBR is also extended with aromatic and naphthenic oils to improve handling and processing.

Styrene block copolymers with butadiene are typically produced by anionic solution polymerization with *sec*-butyllithium or *n*-butyllithium in a solvent such as cyclohexane, isopentane, *n*-hexane, or mixtures.[8] The styrene is homopolymerized, followed by the addition of butadiene; more styrene is then added. The polymer is coagulated from the solution with water. Styrene block polymers are usually compounded with fillers, extenders oils, and, sometimes, other polymers (e.g., polyindene or polystyrene).

USE

Cosmetic

Styrene and vinyl-type styrene copolymers function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products.[5]

Information on the use of these ingredients as a function of product type was supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP).[21] The highest use frequency was reported for ethylene/propylene/styrene copolymer, followed by butylene/ethylene/styrene copolymer. The Personal Care Products Council conducted a survey of ingredient use concentrations in 2013-2014, and maximum use concentrations ranging from 0.000038% (styrene/VP copolymer) to 36.5% (polystyrene) were reported.[22] The highest maximum reported use concentrations for rinse-off and leave on products were 36.5% (polystyrene) and 35% (styrene/acrylates copolymer), respectively. Ingredient frequency of use and concentration data are presented in Table 6.

Cosmetic products containing styrene and vinyl-type styrene copolymers may be applied to the skin and hair or, incidentally, these products may come in contact with the eyes. Products containing this ingredient may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

The following ingredients are used in products that are sprayed (maximum concentrations reported): hair sprays (styrene/acrylates copolymer [0.35%,]; styrene/VP copolymer [0.12%, in pump spray]), suntan sprays (styrene/acrylates copolymer [3.5%]), and body and hand sprays (ethylene/propylene/styrene copolymer [0.5%]). Additionally, isobutylene/styrene copolymer is used in face powders at a maximum concentration of 1%. Because styrene/acrylates copolymer, styrene/VP copolymer, and ethylene/propylene/styrene copolymer are used in products that are sprayed and isobutylene/styrene copolymer is used in face powders they could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[23,24,23,25] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[23,24]

Noncosmetic

Polystyrene

Polystyrene is used as a plasticizer in the bottled water industry, and studies have shown that styrene leaches continuously from polystyrene bottles.[26] The skin adhesive layer of a pressure ulcer preventive dressing may contain styrene block copolymer as an adhesive compound.[27] Polystyrene foam is widely used for thermal insulation.[10]

Additionally, polystyrene may be safely used as a component of articles intended for use in contact with food. For this purpose, polystyrene shall contain not more than 1 weight percent of total residual styrene monomer.[28] The exception to this limit relates to use in contact with fatty foods, whereas such polystyrene basic polymers shall contain not more than 0.5 weight percent of total residual styrene monomer.

Styrene

Styrene is listed among the synthetic flavoring substances and adjuvants that may be safely used in food.[29] It should be used in the minimum quantity required to produce the intended effect, and, otherwise, in accordance with all principles of good manufacturing practice.

Styrene/Butadiene Copolymer

Butadiene-styrene rubber (styrene/butadiene copolymer) is included on the list of FDA-approved direct food additives.[30]

TOXICOKINETICS

The sources of study summaries in this section are the 2002 IARC monograph on styrene,[31] the 2012 IARC monograph on 1,3-butadiene,[12] and the 1984 NTP report on the toxicology and carcinogenesis of 1,3-butadiene.[32]

Styrene

Nine male volunteers were exposed for 10 to 30 minutes by dipping one hand in liquid styrene. Urine and breath were sampled periodically for metabolites (mandelic and phenylglyoxylic acids) and styrene analyses respectively. The results obtained show that the rate of absorption of styrene through the skin was very low, averaging 1 ± 0.5 $\mu g/cm^2$/minute.[31,33]

A field study comparing the urinary excretion of styrene metabolites in 4 groups of workers who performed the same task, but wore different protective equipment, was performed.[31] It was concluded that the percutaneous absorption of styrene was not an important contribution to the body burden.

Several studies have suggested that styrene accumulates in the subcutaneous fat.[31] However, based on the measurement of urinary metabolites, there was no styrene accumulation in workers exposed to 37 ppm (160 mg/m^3) styrene in air during the work week.

Styrene is primarily metabolized to styrene 7,8-oxide by cytochrome P450 (CYP) enzymes.[31] Epoxide hydrolase metabolizes the oxide to phenylethylene glycol, and then to mandelic, phenylglyoxylic, and benzoic acids. Additional routes of metabolism include ring hydroxylation, but this appears to be a minor pathway in humans. Another pathway is the conversion of styrene to 1- and 2-phenylethanol, which is further metabolized to phenylacetaldehyde, phenylacetic acid, phenylaceturic acid, and hippuric acid. Styrene 7,8-oxide may also be metabolized by conjugation with glutathione to form mercapturic acids. This pathway, considered a minor pathway in humans, amounts to < 1% mercapturic acids.

Small amounts of styrene (0.7% to 4.4%) are exhaled unchanged.[31] This finding has been confirmed in additional studes in which 0.7% to 2.2% of the amount of inhaled styrene was found unchanged in the exhaled breath of 4 subjects exposed to 50 ppm [213 mg/m^3) styrene in air for 2 h. Small amounts of styrene are also excreted unmetabolized in the urine.

The pharmacokinetics of inhaled styrene (80 ppm [341 mg/m^3]) was studied using 4 volunteers.[31] Calculated half-life values of 0.6 h and 13.0 h for the 2 phases of elimination were reported. In a study of blood styrene concentrations in 76 exposed workers at the end of their work shift and in the morning thereafter, the elimination half-life was 3.9 h.

1,3-Butadiene and Styrene

Nine minutes after rabbits were exposed to 1,3-butadiene at concentrations of 250,000 ppm in air, the test chemical was found in the femoral artery at a concentration of 0.26 mg/ml and in the femoral vein at a concentration of 0.18 mg/ml.[32]

Mice and rats were exposed (dynamic flow exposure: 2 h [mice] and 4 h [rats]) to butadiene or styrene vapors.[32,34] The number, strain, and sex of the animals tested were not specified. LC_{50} values were: 270 mg/liter (butadiene [mice]), 285 mg/liter (butadiene [rats]), 21 mg/liter (styrene [mice]), and 11.8 mg/liter (styrene [rats]). The concentratons of butadiene and styrene in tissues at the LC_{50} exposure concentration were determined by gas liquid chromatography. Various tissues

from rats were analyzed, but only brain tissue from mice was analyzed. Mean concentrations in tissues from rats are included below:

- 50.8 mg butadiene/100g brain (10 tests)
- 25 mg styrene/100g brain (7 tests)
- 51.4 mg butadiene/100g liver (10 tests)
- 20 mg styrene/100g liver (7 tests)
- 36.3 mg butadiene/100g kidney (7 tests)
- 14.7 mg styrene/100g kidney (7 tests)
- 45 mg butadiene/100g spleen (7 tests)
- 19.1 mg styrene/100 g spleen (7 tests)
- 152.1 mg butadiene/100g perinephric fat (7 tests)
- 132.8 mg styrene/100g perinephric fat (7 tests)

Mean concentrations in brain tissue from mice were 54.4 mg butadiene/100cc brain (10 tests) and 18.02 mg styrene/100cc brain (7 tests). In a subsequent experiment series (rats, same procedure), mean concentrations in the brain and liver were determined at various times for up to 90 minutes after removal from the chamber. By 90 minutes, mean tissue concentrations were:[32,34]

- 0 to traces of butadiene/100cc brain (4 tests)
- traces to 4.4 mg styrene/100 cc brain (4 tests)
- 0 to traces of butadiene/100cc liver (4 tests)
- 5.2 to 11 mg styrene/100cc liver (4 tests)

The first step in butadiene metabolism involves cytochrome P450 (CYP)-mediated oxidation to epoxybutene.[12] At low concentrations of butadiene, metabolism via CYP2E1 predominates. Epoxybutene may be metabolized by conjugation with glutathione (GSH), mediated by glutathione S-transferase (GST), or by hydrolysis, catalyzed by epoxide hydrolase. Epoxybutene may also be oxidized to multiple diastereomers of diepoxybutane. Dihydroxybutene formed by hydrolysis of epoxybutene may be oxidized to epoxybutanediol. The latter epoxides are also detoxified by GST or EH. The partial hydrolysis of diepoxybutane also produces epoxybutanediol.

TOXICOLOGY

Acute Inhalation Toxicity

Styrene/Acrylates Copolymer

In an acute inhalation toxicity study on Sunspheres™ Powder, an LC_{50} of > 5.3 mg/L was reported. The test protocol was not provided.[15]

An acute inhalation LC_{50} (4 h) value of > 5.11 mg/L air was reported for ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer.[17,20] The test protocol was not described. The animal species was not stated, but it was noted that no clinical signs or mortalities were observed.

Acute Oral Toxicity

Styrene/Acrylates Copolymer

In an acute oral toxicity study on a product (unnamed, but compositionally similar to SunSpheres™ LCG Polymer) involving rats, an LD_{50} of > 5 g/kg (non-toxic) was reported. The test protocol was not stated.[14]

An LD_{50} of > 5 g/kg (non-toxic) was reported for a product (unnamed, but compositionally similar to Sunspheres™ Powder) in an acute oral toxicity study involving rats. The test protocol was not stated.[15]

OPULYN™ 302B Opacifier was evaluated in an acute oral toxicity study involving rats, and an LD_{50} of > 5 ml/kg was reported. The test protocol was not stated.[16]

An LD_{50} of > 5 g/kg (non-toxic) was reported for certain polymers (unnamed, but compositionally similar to ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer) in acute oral toxicity studies (animal species not stated).[17,20] The test protocol was not stated.

In an acute oral toxicity study on a product (unnamed, but compositionally similar to SunSpheres™ PGL Polymer) involving rats, an LD_{50} of > 5 g/kg (non-toxic) was reported.[18] The test protocol was not stated.

Acrylic co-polymers (unnamed, but compositionally similar to OPULYN™ 301 Opacifier) were evaluated in an acute oral toxicity study involving rats, and an LD_{50} of > 5 g/kg was reported. The test protocol was not stated.[19]

Acute Dermal Toxicity

In an acute dermal toxicity study on a product (unnamed, but compositionally similar to SunSpheres™ LCG Polymer) involving rabbits, an LD_{50} of > 5 g/kg (non-toxic) was reported. The test protocol was not stated.[14]

An LD_{50} of > 5 g/kg (non-toxic) was reported for a product (unnamed, but compositionally similar to Sunspheres™ Powder) in an acute dermal toxicity study involving rabbits. The test protocol was not stated.[15]

OPULYN™ 302B Opacifier was evaluated in an acute dermal toxicity study involving rats, and an LD_{50} of > 5 g/kg was reported. The test protocol was not stated.[16]

An LD_{50} of > 5 g/kg (non-toxic) was reported for certain polymers (unnamed, but compositionally similar to ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer) in acute dermal toxicity studies (animal species not stated).[17,20] The test protocol was not stated.

In an acute dermal toxicity study on a product (unnamed, but compositionally similar to SunSpheres™ PGL Polymer) involving rabbits, an LD_{50} of > 5 g/kg (non-toxic) was reported.[18] The test protocol was not stated.

Acrylic co-polymers (unnamed, but compositionally similar to OPULYN™ 301 Opacifier) were evaluated in an acute dermal toxicity study involving rats, and an LD_{50} of > 2 g/kg was reported. The test protocol was not stated.[19]

Repeated Dose Toxicity

Inhalation

Polyacrylate

Polyacrylate, a polymer of acrylic acid and sodium acrylate, was tested in a repeated dose toxicity study involving groups of Fischer 344 rats (ages and number per group not specified).[35] It was noted that the large particle size of polyacrylate used in manufacturing makes this material non-respirable, i.e., less than 1% of received material is < 40 microns. The particle size used in this study was reduced (by milling) to make it highly respirable in test animals (mass mean aerodynamic diameter [MMAD] = 1.95 to 2.07 microns). Four groups of animals were exposed to concentrations of 0.05, 0.2, 1, and 10 mg/m^3, respectively, 5 days per week (6 h/day) for up to 26 consecutive weeks. The control group was exposed to filtered room air. No adverse effects were observed at concentrations of 0.05 and 0.2 mg/m^3. Mild to moderate pulmonary inflammation, which resolved during the recovery period, was observed in the 1.0 mg/m^3 exposure group. Exposure to 10 mg/m^3 (at this concentration, threshold for clearing inhaled test material from the lungs was exceeded) caused adverse pulmonary effects (marked inflammation and benign alveolar/bronchiolar adenoma) that are not relevant to subthreshold exposure concentrations. Inflammation decreased during the recovery period. The authors stated that these results support the inhalation safety of the polyacrylate material under both occupational and consumer exposure conditions. The 0.05 and 0.2 mg/m^3 concentrations were considered no-adverse-effect levels.

Three groups of 120 F344 rats (60 males, 60 females/group) were exposed for 24 months to respirable polyacrylate particles (MMAD ≈ 2 to 3 microns) at concentrations of 0.05, 0.2, and 0.8 mg/m^3, respectively.[36] Gross necropsy was performed at 6, 12, and 24 months. Gross necropsy results at 24 months indicated no visible effects in males or females exposed to 0.05 mg/m^3. Lung nodules were observed in 1 male and 3 females exposed to 0.2 mg/m^3. The numbers of pulmonary nodules were even higher in the 0.8 mg/m^3 exposure group (7 males and 23 females with nodules). Only one animal (1 female) in the air-exposed control group had a pulmonary nodule. Interim necropsy results at 6 and 12 months

indicated the absence of nodule formation in all exposure groups. The authors noted that characterization of the nodules was not possible, and it was determined that conclusions regarding the lung nodule incidence and its significance (if any) in this study could not be made.

Styrene/Acrylates Copolymer

ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were evaluated in a 2-week aerosol (nose only) exposure study involving rats.[17,20] The test protocol was not stated. There were no signs of clinical toxicity at any administered dose. The no-observed-effect-concentration (NOEC) was 10.8 mg polymer solids/m^3, based on slight irritant effects in the lungs at a concentration of 100 mg/m^3.

In a 13-week aerosol (nose only) study on ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer involving rats, the no-observable adverse-effect level (NOAEL) for changes in the lung (and related lymph nodes) was 8.3 mg/m^3.[17,20]

Oral

Styrene

The Environmental Protection Agency (EPA) has established a reference dose for chronic oral exposure (RfD) to styrene of 1 mg/kg/day, based on effects on red blood cells and the liver.[37] The RfD is based on the assumption that thresholds exist for certain toxic effects, such as cellular necrosis. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Ocular Irritation

1,3-Butadiene

Workers exposed to 1,3-butadiene at concentrations of 8,000 ppm for 8 hours complained of eye irritation and blurred vision.[38]

Styrene/Acrylates Copolymer

SunSpheres™ (chemical name not stated) was non-irritating to the eyes of rabbits in an ocular irritation study. The test protocol was not stated.[14,18] These data are included in an industry data submission on SunSpheres™ LCG Polymer and SunSpheres™ PGL Polymer, for use in evaluating the safety of these trade name materials.

Sunspheres™ Powder was classified as minimally irritating to the eyes of rabbits.[15] The test protocol was not stated. In another ocular irritation study involving rabbits, a product (unnamed, but compositionally similar to Sunspheres™ Powder) was classified as non-irritating. The test protocol was not stated.[15]

In an ocular irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-iritant. The test protocol was not stated.[16]

The ocular irritation potential of ACUDYNE™ Shine Polymer was evaluated in the bovine corneal opacity and permeability test *in vitro*. The test protocol was not stated. Results were negative.[17]

Acrylic co-polymers (unnamed, but compositionally similar to OPULYN™ 301 Opacifier) were classified as non-irritants in an ocular irritation study involving rabbits. The test protocol was not stated.[19]

ACUDYNE™ Bold Polymer was classified as a non-irritant in the bovine corneal opacity and permeability test *in vitro*.[20] The test protocol was not stated.

Skin Irritation

Styrene/Acrylates Copolymer

In a skin irritation study involving rabbits, SunSpheres™ (chemical name not stated) was classified as a non-irritant. The test protocol was not stated.[14,18] These data are included in an industry data submission on SunSpheres™ LCG Polymer and SunSpheres™ PGL Polymer for use in evaluating the safety of these trade name materials.

A product (unnamed, but compositionally similar to Sunspheres™ Powder) was classified as a non-irritant in a skin irritation study involving rabbits. The test protocol was not stated.[15]

In a skin irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-iritant. The test protocol was not stated.[16]

The skin irritation potential of ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer was evaluated in the EpiDermal *in vitro* assay.[17,20] The test protocol was not stated. Results were negative.

Acrylic co-polymers (unnamed, but compositionally similar to OPULYN™ 301 Opacifier) were classified as non-irritants in a skin irritation study involving rabbits. The test protocol was not stated.[19]

Skin Irritation and Sensitization

Animal

Styrene and Methylstyrene

The skin sensitization potential of styrene was evaluated in the guinea pig maximization test (15 guinea pigs).[39] Details relating to the test protocol were not included. The test procedure involved intradermal injections of 10% (w/v) styrene, topical application of 20% (w/v) styrene, and challenge with 2% (w/v) styrene in acetone. Skin sensitization was not observed in any of the animals tested. Methylstyrene was also evaluated in a maximization test involving 15 guinea pigs, and the procedure involved intradermal injections of 2.5% (w/v) methylstyrene, topical application of 5% (w/v) methylstyrene, and challenge with 0.5% (w/v) methylstyrene in acetone. The results were also negative.

Human

Styrene/Acrylates Copolymer

SunSpheres™ (chemical name not stated) was classified as non-irritating and non-sensitizing in a human repeated insult patch test (HRIPT). The test protocol was not stated.[14,15,18] These data are included in industry data submissions on SunSpheres™ LCG Polymer, SunSpheres™ powder, and SunSpheres™ PGL Polymer for use in evaluating the safety of these trade name materials.

In a 21-day cumulative skin irritation study, OPULYN™ 302B Opacifier was classified as non-irritating and non-sensitizing. The test protocol was not stated.[16]

OPULYN™ 301 Opacifier was also classified as non-irritating and non-sensitizing in a 21-day cumulative irritation study. The test protocol was not stated.[19]

Styrene and Methylstyrene

Styrene (5% w/v in petrolatum) was evaluated in a skin sensitization study involving 303 patients (diagnoses not stated).[39] Details relating to the test procedure were not provided. Negative results were reported for all patients. Negative results for methylstyrene (1% w/v in ethanol) in these patients were also reported.

In Vitro

Styrene/Acrylates Copolymer

ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were classified as a non-sensitizers in the mouse local lymph node assay.[17,20] The test protocol was not stated.

Phototoxicity and Phoallergenicity

Styrene/Acrylates Copolymer

SunSpheres™ (chemical name not stated) was classified as non-phototoxic and there was no evidence of photosensitivity. The test protocol was not stated.[14,15,18] These data are included in an industry data submission on SunSpheres™ LCG Polymer, SunSpheres™ Powder, and SunSpheres™ PGL Polymer for use in evaluating the safety of these trade name materials.

Case Reports

Polystyrene

A 10-year-old boy had a history of cushion styrofoam beads embedded in the right ear. Styrofoam is polystyrene foam.[40] Attempts to remove the bead caused it to lodge further, and the bead became deeply embedded and occluded the right auditory canal. The spraying of ethyl chloride into the distal ear canal resulted in dissolution of the first bead and then a second bead. Subsequent complete and uncomplicated recovery of the boy was reported. It was noted that the small residue of dissolved Styrofoam that remained after the procedure did not appear to have caused toxic effects.

Styrene and Methylstyrene

A 40-year-old man with a history of bronchitis and contact allergy to styrene cross-reacted when patch-tested with 3- and 4-vinytoluene (also known as 3- and 4-methylstyrene, respectively).[39] The vinyltoluene compounds were patch-tested at concentrations equimolar to 0.1% w/v styrene. The patient also had a positive reaction to styrene (0.1% and 5% v/v in methy ethyl ketone).

In a subsequent case report, the same patient cross-reacted when patch tested with 2-, 3-, and 4-vinyltoluene (2-, 3-, and 4-methylstyrene, respectively) and to the metabolites styrene epoxide and 4-vinylphenol (4-hydroxystyrene).[41] It is assumed that styrene is a prohapten metabolized in the skin by aryl hydrocarbon hydroxylase (AHH) to styrene epoxide, which acts as a true hapten.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Styrene

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel concluded that styrene does not cause developmental or reproductive toxicity in experimental animals.[42] In developmental toxicity studies in rats and rabbits, the highest exposure concentrations tested (600 ppm by inhalation or 300 mg/kg body weight/day by oral dosing) did not have any observable adverse effects on fetuses. The effects of styrene exposure on reproduction and post-natal development were assessed in 2 multigeneration studies involving rats. Neither study produced results indicating a styrene-induced reproductive effect, even at the highest concentrations administered. However, in one of the studies, there was decreased birth weight and delays in the postnatal development of pups from parents exposed (by inhalation) to 500 ppm styrene. This concentration of styrene also caused a significantly reduced body weight gain in the dams. Thus, the NTP-CERHR Expert Panel concluded that it was not possible to separate the observed effects in the offspring from the effects on maternal weight. Inhalation exposure to 500 ppm styrene did not cause developmental neurotoxicity.

In the second multigeneration study, styrene was administered at concentrations up to 250 ppm in drinking water (estimated intake = 18 mg/kg body weight/day (for males) and 23 mg/kg body weight/day (for females). Results indicated no

treatment-related effects on maternal food consumption or weight gain, and no significant developmental effects on the pups. The NTP-CERHR Expert Panel considered these data to be relevant for the assessment of potential human hazard.

The NTP-CERHR Expert Panel determined that there was insufficient information available to arrive at conclusions about reproductive and developmental outcomes from studies of humans exposed to styrene. Studies performed in occupational settings suggest that the exposure of women to styrene is associated with slightly increased levels of prolactin in blood serum and possible depletion of peripheral blood dopamine metabolizing activities, when compared to levels in women not occupationally exposed to styrene. The Panel determined that the clinical relevance of these effects is uncertain for the following 2 reasons: (1) the average elevation in prolactin concentrations in blood serum was small and within the normal range of blood serum values and (2) menstrual function and other reproductive endpoints were not evaluated in these studies.[42]

1,3-Butadiene

According to the 1984 NTP report on the toxicology and carcinogenesis of 1,3-butadiene,[32] the fertility of rats was not severely impaired when they were exposed (inhalation) to 1,3-butadiene at concentrations of 600-6,700 ppm for 7.5 hours per day, 6 days per week, for 8 months; however, the decreased fecundity observed may have been related to exposure. No evidence of degenerative testicular changes in males was seen, and all embryos appeared normal at necropsy.

When female rats were exposed (inhalation) to 1,3-butadiene for 4 months at 45 ppm, increased embryonic mortality and teratogenesis were reported.

Pregnant female Sprague-Dawley rats exposed (inhalation) to 1,3-butadiene at concentrations of 0, 200, 1,000, or 8,000 ppm for 6 hours per day during days 6-25 of gestation showed embryonic growth retardation and slight embryo-mortality at all concentrations. At the highest exposure concentration, evidence of teratogenicity (major fetal defects such as cardiovascular, sternebral, and thoracic abnormalities) was seen.[32]

GENOTOXICITY

Bacterial Cells

Polystyrene

The genotoxicity of polystyrene was evaluated in the Ames test using the following *Salmonella typhimurium* strains, with and without metabolic activation: TA97, TA98, TA100, and TA1535.[43] Concentrations of the test substance were not stated; however, at least 5 concentrations were tested. Methyl ethyl ketone served as the vehicle and the control. Polystyrene was not genotoxic with or without metabolic activation in any of the bacterial strains tested. The positive controls in experiments without metabolic activation were: 2-nitrofluorene, 4-nitro-o-phenylenediamine, sodium azide, 9-aminoacridine, mitomycin C, and methyl methanesulfonate. The positive control for the metabolic activation experiments was 2-aminoanthracene. Results for the vehicle control or positive controls were not stated.

Polyacrylate

The genotoxicity of polyacrylate (polymer of acrylic acid and sodium acrylate) was evaluated in the following assays:[35] Ames *Salmonella* assay, unscheduled DNA synthesis assay (rat hepatocytes), the mouse lymphoma mammalian cell assay, and the *in vivo* cytogenetics assay (rat bone marrow cells). Neither the test concentrations nor details relating to the test protocols were stated. However, it was stated that polyacrylate was not genotoxic in any of the assays.

Styrene/Acrylates Copolymer

In the Ames test, SunSpheres™ (chemical name not stated) was non-genotoxic with and without metabolic activation. The test protocol was not stated.[14,15,18] These data are included in an industry data submission on SunSpheres™ LCG Polymer, SunSpheres™ Powder, and SunSpheres™ PGL Polymer for use in evaluating the safety of these trade name materials.

OPULYN™ 302B Opacifier was not genotoxic in the Ames test, with or without metabolic activation. The test protocol was not stated.[16]

In the Ames test, ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were not genotoxic.[17,20] The test protocol was not stated. These polymers also were not genotoxic in the chromosomal aberrations test *in vitro* (test protocol not stated).[17,20]

OPULYN™ 301 Opacifier was not genotoxic in the Ames test, with or without metabolic activation. The test protocol was not stated.[19]

Mammalian Cells

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was not genotoxic in the *in vitro* cytogenetic assay, with or without metabolic activation. The test protocol was not stated.[16]

OPULYN™ 301 Opacifier also was not genotoxic in the in vitro cytogenetic assay, with or without metabolic activation. The test protocol was not stated.[19]

CARCINOGENICITY

Animal

Polystyrene

The carcinogenicity of the following different physical forms of polystyrene was evaluated using groups of Wistar rats: smooth discs (47 rats); perforated discs (51 rats); rods, spheres, and fibers (40 rats), and powder (number of rats not stated).[8,44] Following subcutaneous (s.c.) implantation of each type, sarcoma incidences at the implantation site were as follows: 37 of 47 rats (78.7%), 25 of 51 rats (49%), and 15 of 40 rats (37.5%). Sarcomas were not observed in rats implanted with the powder.

In another study, discs (1.25 cm diameter x 0.026 mm thick) and perforated discs (central hole, 6 mm) of polystyrene were implanted s.c. into Wistar rats (from 3 different laboratory sources).[8,45] Differences in the incidence of local sarcomas (8% to 48%) were found, depending on the animal strain. Wistar rats from one of the laboratory sources were the most sensitive. No appreciable differences were found between implanted discs that were perforated and unperforated.

Regarding the preceding 2 studies, the International Agency for Research on Cancer noted in its 1979 monograph that these results point to the need for further investigations regarding polystyrene.[8]

Styrene

A National Toxicology Program (NTP) carcinogenicity bioassay on styrene was performed using Fischer 344 rats and B6C3F1 mice (groups of 50 males and 50 females per species).[46] Groups of 40 males and 40 females per species served as vehicle controls. Styrene was administered (by gavage, 5 days/week) to 3 groups of rats at doses of 500 mg/kg/day (low dose), 1,000 mg/kg/day (medium dose), and 2,000 mg/kg/day (high dose), respectively. The 2 groups of mice received doses of 150 mg/kg/day (low dose) and 300 mg/kg/day (high dose), respectively. The dosing period was 78 weeks (followed by 27 weeks of observation) for rats in both high and medium dose groups, 103 weeks (followed by 1-week observation period) for low dose rats, and 78 weeks (followed by 13 weeks of observation) for all mice.

In male mice, there was a significant positive association between the dose of styrene administered and the incidences of a combination of adenomas and carcinomas of the lung. It was noted that this finding was supported by the results of a high dose-to-control Fischer exact test. However, the variation of the incidence of these neoplasms in historical control male mice at the test laboratory did not permit a firm conclusion of carcinogenicity. When dosed groups were compared to vehicle controls, there was no significant difference between tumor incidence at any other site in male mice, or at any site in rats or female mice. The authors noted that the findings of an increased incidence of a combination of adenomas and carcinomas of the lung provided suggestive evidence for the carcinogenicity of styrene in male B6C3F1 mice. However, it was concluded that, under the conditions of this bioassay, no convincing evidence for the carcinogenicity of styrene was found in Fischer 344 rats or in B6C3F1 mice of either sex.[46]

1,3-Butadiene

NTP inhalation carcinogenicity studies on 1,3-butadiene was performed. Groups of 50 male and female B6C3F$_1$ mice were exposed to air containing 625 ppm or 1,250 ppm 1,3-butadiene 5 days per week (6 h/day).[32] Chamber controls were air-exposed. The exposure period in these studies was to have been 103 weeks, but study termination was at week 60 or week 61 because of rapidly declining survival, primarily due to neoplasia. Significantly increased incidences of neoplasms at multiple sites were observed in mice exposed to 1,3-butadiene. It was concluded that there was clear evidence of carcinogenicity for 1,3-butadiene in male and female B6C3F$_1$ mice, based on the following results: increased incidences and early induction of hemangiosarcomas of the heart, malignant lymphomas, alveolar/bronchiolar adenomas and carcinomas, and papillomas of the stomach in male and females, and increased incidences and early induction of acinar cell carcinomas of the mammary gland, granulosa cell tumors of the ovary, and hepatocellular adenomas and adenomas or carcinomas (combined) in female mice. Exposure to 1,3-butadiene was also associated with nonneoplastic lesions in the respiratory epithelium, liver necrosis, and testicular or ovarian atrophy.

Groups of 70 male and 70 female B6C3F$_1$ mice were exposed to air containing 0, 6.25, 20,625, or 200 ppm 1,3-butadiene for 6 hours per day, 5 days per week for up to 2 years; groups of 90 male and 90 female B6C3F$_1$mice were exposed to 625 ppm 1,3-butadiene on the same schedule.[47] Up to 10 animals from each group were examined after 9 and 15 months of exposure. Two-year survival was decreased for males and females exposed to concentrations of 20ppm or above, primarily due to the development of chemical-related malignant neoplasms. No female mice exposed to 200 or 625 ppm or males exposed to 625 ppm survived to the end of the studies (males: 35/50, 39/50, 24/50, 22/50, 4/50, 0/70*;* females: 37/50, 33/50, 24/50, 11/50, 0/50,0/70). At 9 months, decreases in erythrocyte counts, hemoglobin concentration, and packed red cell volume were observed in male mice exposed to 62.5 ppm or above and in female mice exposed to 200 ppm or 625 ppm. At 15 months, these changes were observed in female mice exposed to 625 ppm.

Exposure of mice to 1,3-butadiene induced benign and malignant neoplasms at multiple sites. Statistically significant increases in the incidences of neoplasms at one or more sites were seen at concentrations of 20 ppm and higher in males and 6.25 ppm and higher in females. There was no exposure level in this study at which a significant carcinogenic response was not observed. Statistically significant increases occurred in the incidences of malignant lymphoma; histiocytic sarcoma; cardiac hemangiosarcoma; harderian gland adenoma; hepatocellular adenoma and carcinoma; alveolarbronchiolar adenoma and carcinoma; mammary gland carcinoma, adenoacanthoma, and malignant mixed tumor (females only); benign and malignant ovarian granulosa cell tumor; and forestomach squamous cell papilloma and carcinoma. Lymphocytic-lymphomas appeared as early as week 23 and were the principal cause of death of male and female mice exposed to 625 ppm 1,3-butadiene. The early and extensive development of lethal lymphocytic lymphomas in mice exposed to 625 ppm resulted in a reduced number of mice at risk for neoplasms developing later atother sites. Exposure-response relationships for 1,3-butadiene- induced neoplasms were more clearly characterized at concentrations below 625 ppm and after adjustment for intercurrent mortality.

When compared to the first NTP carcinogenicity study on 1,3-butadiene summarized in this section, this study provides a better characterization of the concentration-dependent responses for 1,3-induced neoplasms and nonneoplastic lesions. This study also confirmed the clear evidence of carcinogenicity of 1,3-butadiene in male B6C3F$_1$ mice, based on increased incidences of neo-plasms in the hematopoietic system, heart, lung, forestomach, liver, harderian gland, preputial gland, brain, and kidney. There was clear evidence of carcinogenicity of 1,3-butadiene in female B6C3F$_1$ mice, based on increased incidences of neoplasms in the hematopoietic system, heart, lung, forestomach, liver, harderian gland, ovary, and mammary gland. It was also noted that low incidences of intestinal carcinomas in male mice, Zymbal's gland carcinomas in male and female mice, and renal tubule adenomas and skin sarcomas in female mice may also have been related to 1,3-butadiene exposure.

Human

Styrene

According to the NTP, styrene is reasonably anticipated to be a human carcinogen and was first listed in the NTP's *Twelfth Report on Carcinogens* in 2011.[48] This categorization is based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting data on mechanisms of carcinogenesis. The limited evidence of the carcinogenicity of styrene in humans is based on studies of workers exposed to styrene that showed: (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers. Causality was not established

in these studies, because the possibility that the results were due to chance or was confounded by exposure to other carcinogenic chemicals could not be completely ruled out. However, NTP noted that a causal relationship between styrene exposure and cancer in humans is credible and is supported by the finding of DNA adducts and chromosomal aberrations in lymphocytes from styrene-exposed workers. Most of the evidence of styrene carcinogenicity in humans comes from occupational cohort studies in two major industries: the reinforced plastics industry and the styrene-butadiene rubber industry. The NTP's analyses of data from the latter industry are included in the section on Styrene/Butadiene Copolymer below.

A committee of the National Research Council (NRC) will conduct a scientific peer review of the styrene assessment presented in the National Toxicology Program (NTP) *12th Report on Carcinogens* (RoC).[49] The committee will identify and evaluate relevant, publicly available, peer-reviewed literature, with particular emphasis on literature published since June 10, 2011, the release date of the 12th RoC. The committee will apply independently the NTP's established RoC listing criteria to the scientific evidence from studies in humans, experimental animals, and other studies relevant to mechanisms of carcinogenesis and make independent level-of-evidence determinations with respect to the human and animal studies. Ultimately, an independent listing recommendation for styrene, along with the scientific justification for this recommendation, will be made. This project is sponsored by the Department of Health and Human Services, and the approximate start date was September 10, 2012. A final report will be issued at the end of the project in approximately 24 months.

The International Agency for Research on Cancer (IARC) has classified styrene as possibly carcinogenic to humans (Group 2B).[31] The Working Group found limited evidence in humans and limited evidence in experimental animals for carcinogenicity. Evidence from mechanistic studies did not contribute to their overall classification decision.

The United States Environmental Protection Agency (EPA) has classified styrene as a Group C carcinogen, a possible human carcinogen.[50]

1,3-Butadiene

EPA has concluded that 1,3-butadiene is carcinogenic to humans by inhalation exposure.[51] The unit cancer risk estimate is 0.08/ppm, based primarily on linear modeling and extrapolation of human data. This incorporates an adjustment factor of 2 to address concerns for sensitive populations. The corresponding estimate of the chronic exposure level of 1,3-butadiene resulting in extra cancer risk of 10^{-6} (i.e., 1 in a million) is 0.01 ppb.

IARC has classified 1,3-butadiene as a Group 2A carcinogen, a probable human carcinogen.[52] However the following revised evaluation is published in the 2012 IARC monograph on 1,3-butadiene:[12] "There is sufficient evidence in humans for the carcinogenicity of 1,3-butadiene. 1,3-Butadiene causes cancer of the hematolymphatic organs. There is sufficient evidence for the carcinogenicity of 1,3-butadiene in experimental animals…. There is strong evidence that the carcinogenicity of 1,3-butadiene in humans operates by a genotoxic mechanism that involves formation of reactive epoxides, the interaction of these direct-acting mutagenic epoxides with DNA, and resultant mutagenicity. The metabolic pathways for 1,3-butadiene in experimental animals have also been demonstrated in humans. 1,3-Butadiene is carcinogenic to humans."

Styrene/Butadiene Copolymer

IARC has determined that epidemiological information on styrene-butadiene copolymer workers, which suggest elevated risk for lymphato-hematopoietic malignancies, clearly requires elucidation by further studies.[8]

Multi-plant cohort studies of male styrene-butadiene rubber workers have been performed.[53,54] These workers had significantly increased cancer risks, including risks of non-Hodgkin's lymphoma (NHL), NHL-chronic lymphocytic leukemia (NHL-CLL), and leukemia (overall and specific types) among subgroups of workers (1) with a long duration of employment (> 10 years), (2) with a long time since the first exposure (20 to 29 years or ≥ 30 years), (3) in specific job categories, or (4) with the highest levels of cumulative exposure to styrene.

In an effort to elucidate the effects of styrene from those of butadiene, internal analyses were performed for quartiles of cumulative exposure or exposure to periodic spikes of high styrene concentrations (styrene peaks, defined as ≥ 50 ppm) involving the following statistical models: (1) styrene exposure only and (2) styrene and butadiene exposure. The number of cases at each exposure level was small, and this limited the power to detect statistically significant risk estimates. No trend analyses were reported. The internal analyses suggested an exposure-response relationship between styrene exposure and NHL and NHL-CLL combined. It was noted that the relative risk of NHL or NHL-CLL increased with increasing levels of cumulative exposure to styrene, and was not attenuated by control for butadiene exposure. However, the relative risk

reached statistical significance only for the highest styrene exposure level in the styrene-only model, and only for NHL-CLL combined. Exposure to butadiene was not associated with risk of NHL or NHL-CLL. The association observed between styrene exposure and leukemia relates to analyses of cancer among workers exposed to styrene peaks. The relative risk of leukemia increased with increasing numbers of styrene peaks in both chemical models, and was significantly elevated at the 2 highest styrene exposure levels when the models were controlled for butadiene exposure. The relative risk of leukemia also increased with increasing cumulative styrene exposure, but the response was attenuated by control for butadiene exposure.[53,54]

Polyacrylate

A cross-sectional respiratory survey of workers (164 workers: 153 men, 11 women; average age = 28.4 years) exposed to polyacrylate dust was performed to assess possible respiratory effects.[55] The site of the survey was a plant in Calvert City, Kentucky that manufactured high molecular weight polyacrylate products. The average number of years of worker employment at the plant was 20.7 years. There was no evidence of excess risk of lung cancer or chest x-ray abnormalities in exposed workers. However, there were exposure-related decrements in lung function.

It should be noted that polyacrylates are included on the 2013 list of substances that have been nominated to the National Toxicology Program's *Report on Carcinogens* (RoC), but have not yet been approved for formal review.[56]

OTHER EFFECTS

Hormonal Activity

Polystyrene

Two studies evaluating the estrogenic activity of polystyrene are available from the National Technical Information Service, and have been ordered.

SUMMARY

The safety of styrene and vinyl-type styrene copolymers as used in cosmetics is evaluated in this safety assessment. These ingredients function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products. Very limited safety test data on the styrene and vinyl-type styrene copolymers reviewed in this safety assessment were found in the published literature. However, data on monomers, styrene and 1,3-butadiene, are included.

Information on the use of these ingredients as a function of product type was supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2013. The highest use frequency was reported for ethylene/propylene/styrene copolymer, followed by butylene/ethylene/styrene copolymer. The Personal Care Products Council conducted a survey of ingredient use concentrations in 2013-2014, and maximum use concentrations ranging from 0.000038% (styrene/VP copolymer) to 36.5% (polystyrene) were reported. The highest maximum reported use concentrations for rinse-off and leave-on products were 36.5% (polystyrene) and 35% (styrene/acrylates copolymer), respectively.

Polystyrene grades with low concentrations, ≤ 500 ppm residual styrene, have been developed.

The absorption of styrene was low (averaging 1 μg/cm^2/minute) in human volunteers exposed by placing one hand in liquid styrene for 10 to 30 minutes. The percutaneous absorption of styrene was not an important contribution to the body burden in a field study comparing the urinary excretion of styrene metabolites in 4 groups of workers, all performing the same task, but wearing different protective equipment. It was concluded that. Styrene is primarily metabolized to styrene 7,8-oxide by cytochrome P450 enzymes.

Nine minutes after rabbits were exposed to 1,3-butadiene at concentrations of 250,000 ppm, the test chemical was found in the femoral artery at a concentration of 0.26 mg/ml and in the femoral vein at a concentration of 0.18 mg/ml. Following 1 h of exposure to 130,000 ppm 1,3-butadiene in rats, the chemical was detected in the brain and liver. At 2 h post-exposure to the same concentration (rats), 1,3-butadiene was detected in the perirenal fat, liver, brain, spleen, and kidneys. The first step in butadiene metabolism involves cytochrome P450-mediated oxygen to epoxybutene.

Polyacrylate, a polymer of acrylic acid and sodium acrylate, was tested in a repeated dose inhalation toxicity study involving groups of Fischer 344 rats. Regarding the test material as received (considered non-respirable), less than 1% was < 40 microns. The particle size used in this study was reduced to make it highly respirable in test animals (mass mean aerodynamic diameter [MMAD] = 1.95 to 2.07 microns). The animals were exposed to polyacrylate at concentrations of 0.05, 0.2, 1, and 10 mg/m^3. Mild to moderate pulmonary inflammation and benign alveolar/bronchiolar adenomas were reported, and the 0.05 and 0.2 mg/m^3 concentrations were considered no-adverse-effect levels.

EPA has estimated the safe dose of styrene for human oral exposure during a lifetime to be 1 mg/kg-day.

Workers exposed to 1,3-butadiene at concentrations of 8,000 ppm for 8 hours complained of eye irritation and blurred vision.

In the maximization test, sensitization was not observed in 15 guinea pigs challenged with 2% (w/v) styrene in acetone. Results were also negative for sensitization in 303 patients tested with 5% (w/v) styrene in petrolatum.

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel concluded that styrene does not cause developmental or reproductive toxicity in experimental animals. The highest doses/exposure concentrations in developmental toxicity studies (rats and rabbits) evaluated were 600 ppm (inhalation) or 300 mg/kg body weight/day by oral dosing. The NTP-CERHR Expert Panel determined that there was insufficient information available to arrive at conclusions on reproductive and developmental outcomes from studies of humans exposed (occupational exposure) to styrene.

The fertility of rats was not severely impaired when they were exposed to 1,3-butadiene at concentrations of 600-6,700 ppm for 8 months (6 days/week). However, it was noted that the decreased fecundity observed may have been exposure-related. There was no evidence of degenerative testicular changes in males. The results of other studies indicated increased embryonic mortality and teratogenesis at exposure concentrations as low as 45 ppm (4-month exposure) and embryonic growth retardation and embryo mortality at exposure concentrations ranging from 200 ppm to 8,000 ppm. Teratogenicity was observed only at the highest concentration of 8,000 ppm.

Polystyrene was not genotoxic with or without metabolic activation in the Ames test. Polyacrylate was not genotoxic in the following tests: Ames test, unscheduled DNA synthesis assay (rat hepatocytes), mouse lymphoma mammalian cell assay, and the *in vivo* cytogenetics assay (rat bone marrow cells).

The subcutaneous implantation of various physical forms of polystyrene produced sarcomas in rats. In an NTP oral carcinogenicity bioassay on styrene, it was concluded that there was no convincing evidence of carcinogencity in rats or mice receiving doses up to 2,000 mg/kg. for 78 or 103 weeks (rats) or 78 weeks (mice). However, the NTP has concluded that styrene is reasonably anticipated to be a human carcinogen based on the results of occupational cohort studies. The Environmental Protection Agency and the International Agency for Research on Cancer have also classified styrene as possibly carcinogenic to humans. A committee of the National Research Council will conduct a scientific peer review of the styrene assessment presented in the NTP 12^{th} Report on Carcinogens.

In NTP inhalation carcinogenicity studies, 1,3-butadiene was carcinogenic in $B6C3F_1$ mice at concentrations up to 1,250 ppm. Inhalation exposure was also associated with non-neoplastic lesions in the respiratory epithelium, liver necrosis, and testicular or ovarian atrophy. It should be noted that the Environmental Protection Agency and the International Agency for Research on Cancer have concluded that 1,3-butadiene is carcinogenic in humans by inhalation exposure.

The International Agency for Research on Cancer has determined that epidemiological information on styrene-butadiene copolymer workers, which indicates lymphato-hematopoietic malignancies, clearly requires elucidation by further studies.

A cross-sectional respiratory survey of workers (164 workers: 153 men, 11 women; average age = 28.4 years) exposed to polyacrylate dust was performed to assess possible respiratory effects. There was no evidence of an excess risk of lung cancer or chest x-ray abnormalities in exposed workers. However, there were exposure-related decrements in lung function.

Polyacrylates are included on the 2013 list of substances that have been nominated to the National Toxicology Program's Report on Carcinogens, but have not yet been approved for formal review.

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[5]

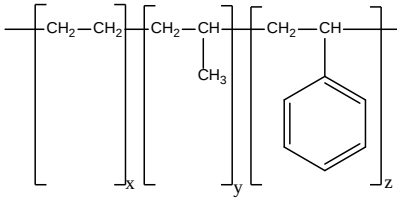
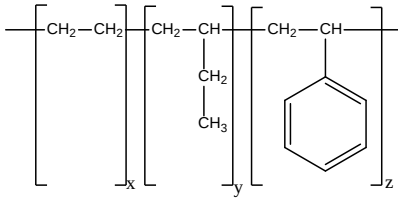
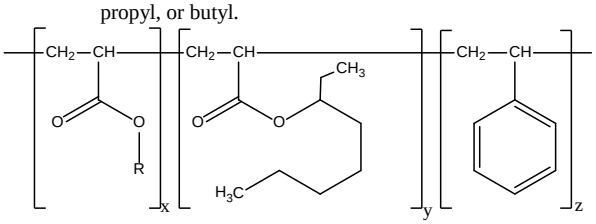
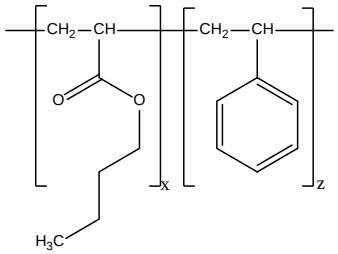
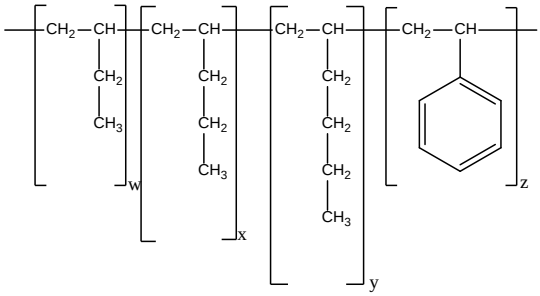
Ingredient CAS No.	Definition	Function(s)
Ethylene/Propylene/Styrene Copolymer 68648-89-5	Ethylene/Propylene/Styrene Copolymer is a polymer of ethylene, propylene and styrene monomers that has been terminated by hydrogenation. 	Viscosity increasing agent-nonaqueous
Butylene/Ethylene/Styrene Copolymer 66070-58-4	Butylene/Ethylene/Styrene Copolymer is a polymer of butylene, ethylene and styrene monomers terminated by hydrogenation. 	Viscosity increasing agent-nonaqueous
Acrylates/Ethylhexyl Acrylate/Styrene Copolymer	Acrylates/Ethylhexyl Acrylate/Styrene Copolymer is a copolymer of ethylhexyl acrylate, styrene and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters. wherein R is hydrogen, methyl, ethyl, propyl, or butyl. 	Film formers
Butyl Acrylate/Styrene Copolymer	Butyl Acrylate/Styrene Copolymer is a copolymer of butyl acrylate and styrene monomers. 	Film formers
C4-6 Olefin/Styrene Copolymer	C4-6 Olefin/Styrene Copolymer is a copolymer of C4-6 olefins and styrene monomers. 	Epilating agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[5]

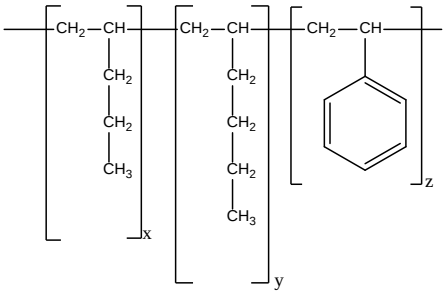
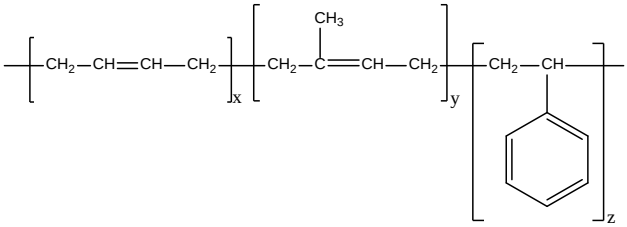
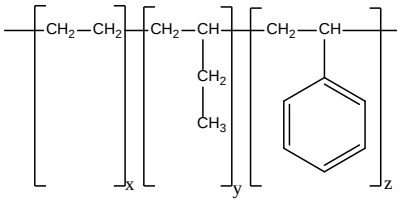
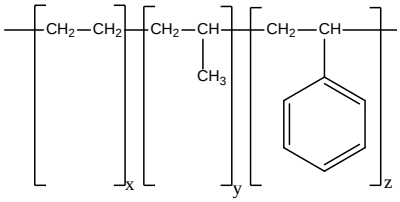
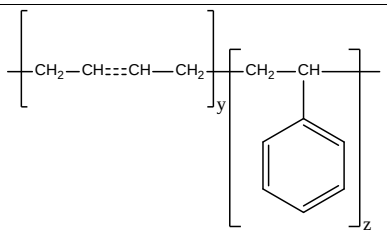
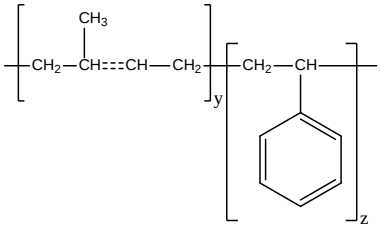
Ingredient CAS No.	Definition	Function(s)
C5-6 Olefin/Styrene Copolymer	C5-6 Olefin/Styrene Copolymer is the copolymer of C5-6 olefins and styrene monomers. 	Epilating agents
Hydrogenated Butadiene/ Isoprene/Styrene Copolymer 132778-07-5	Hydrogenated Butadiene/Isoprene/Styrene Copolymer is the end-product of the controlled hydrogenation of a block copolymer composed of 1,3-butadiene, isoprene and styrene monomers. 	Film formers
Hydrogenated Butylene/ Ethylene/Styrene Copolymer	Hydrogenated Butylene/Ethylene/Styrene Copolymer is a polymer of butylene, ethylene and styrene that has been hydrogenated. 	Viscosity increasing agents-nonaqueous
Hydrogenated Ethylene/ Propylene/Styrene Copolymer	Hydrogenated Ethylene/Propylene/Styrene Copolymer is a polymer of ethylene, propylene and styrene that has been hydrogenated. 	Viscosity increasing agents-nonaqueous
Hydrogenated Styrene/Butadiene Copolymer 66070-58-4	Hydrogenated Styrene/Butadiene Copolymer is the hydrogenated polymer of styrene and 1,4-butadiene. 	Film formers; viscosity increasing agents-nonaqueous
Hydrogenated Styrene/Isoprene Copolymer 68648-89-5	Hydrogenated Styrene/Isoprene Copolymer is the end product of the controlled hydrogenation of Styrene/Isoprene Copolymer. 	Viscosity increasing agents-nonaqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[5]

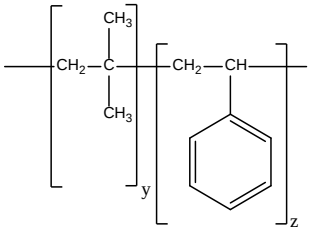
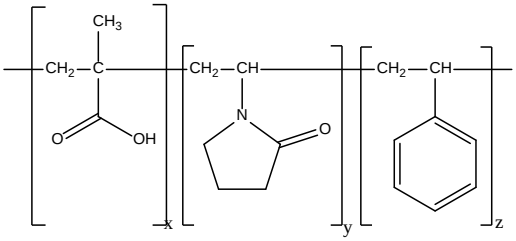
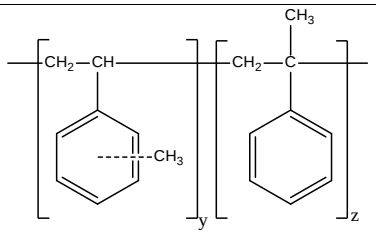
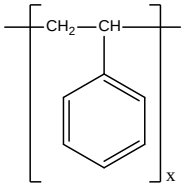
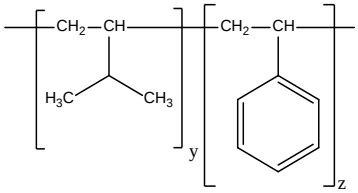
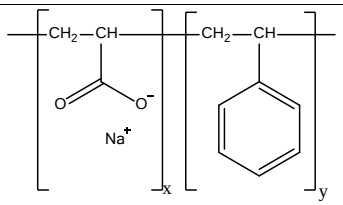
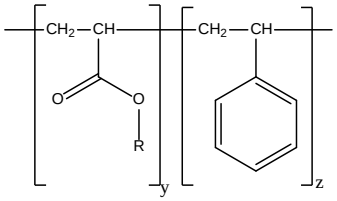
Ingredient CAS No.	Definition		Function(s)
Isobutylene/Styrene Copolymer 9011-12-5	Isobutylene/Styrene Copolymer is a copolymer of isobutylene and styrene monomers.		Film formers
Methacrylic Acid/Styrene/VP Copolymer 27554-92-3	Methacrylic Acid/Styrene/VP Copolymer is a copolymer of styrene, methacrylic acid and vinyl pyrrolidone.		Opacifying agents
Methylstyrene/Vinyltoluene Copolymer 9017-27-0	Methylstyrene/Vinyltoluene Copolymer is the polymer of methylstyrene and vinyltoluene monomers.		Viscosity increasing agents-nonaqueous
Polystyrene 9003-53-6	Polystyrene is the polymer that conforms to the formula. *Polystyrene is the homo-polymer formed from the polymerization of vinylbenzene.*		Film formers; viscosity increasing agents-nonaqueous
Polystyrene/Hydrogenated Polyisopentene Copolymer	Polystyrene/Hydrogenated Polyisopentene Copolymer is a copolymer of polystyrene and hydrogenated polyisopentene.		Not reported
Sodium Methacrylate/Styrene Copolymer 33970-45-5	Sodium Methacrylate/Styrene Copolymer is a copolymer of sodium methacrylate and styrene monomers.		Opacifying agents
Sodium Styrene/Acrylates Copolymer 9010-92-8	Sodium Styrene/Acrylates Copolymer is the sodium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters.	 wherein R is a lone pair of electrons with a sodium cation, methyl, ethyl, propyl, or butyl.	Film formers; viscosity increasing agents-aqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[5]

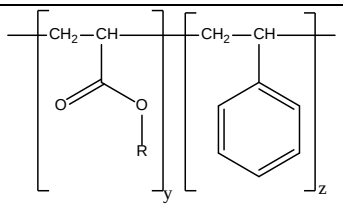
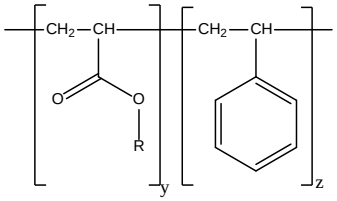
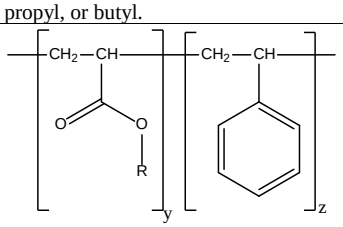
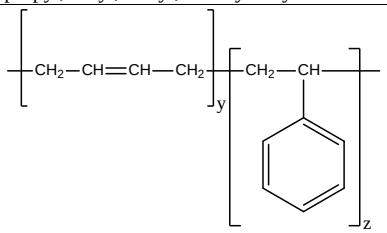
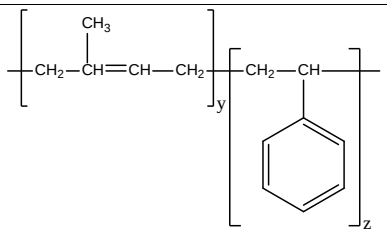
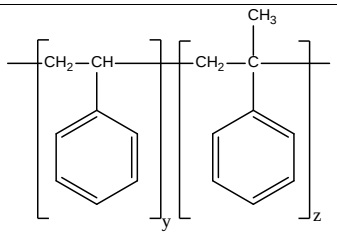
Ingredient CAS No.	Definition		Function(s)
Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer is the sodium salt of Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	 wherein R is a lone pair of electrons with a sodium cation, methyl, ethyl, propyl, butyl, lauryl, or ethylhexyl.	Film formers
Styrene/Acrylates Copolymer 25034-86-0 25085-34-1 9010-92-8	Styrene/Acrylates Copolymer is a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters.	 wherein R is hydrogen, methyl, ethyl, propyl, or butyl.	Film formers; opacifying agents
Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer is a coplymer of styrene, acrylates, ethylhexyl acrylate and lauryl acrylate.	 wherein R is a hydrogen, methyl, ethyl, propyl, butyl, lauryl, or ethylhexyl.	Film formers
Styrene/Butadiene Copolymer 9003-55-8	Styrene/Butadiene Copolymer is a copolymer of styrene and butadiene monomers.		Opacifying agents
Styrene/Isoprene Copolymer 25038-32-8	Styrene/Isoprene Copolymer is a copolymer of styrene and isoprene monomers.		Film formers; opacifying agents
Styrene/Methylstyrene Copolymer 37218-15-8 9011-11-4	Styrene/Methylstyrene Copolymer is a copolymer of styrene and methyl styrene monomers.		Binders; depilating agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[5]

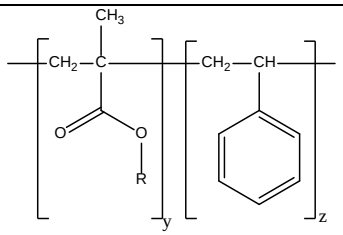
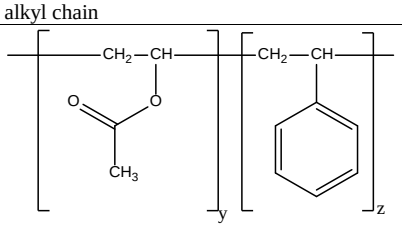
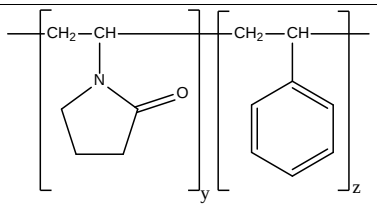
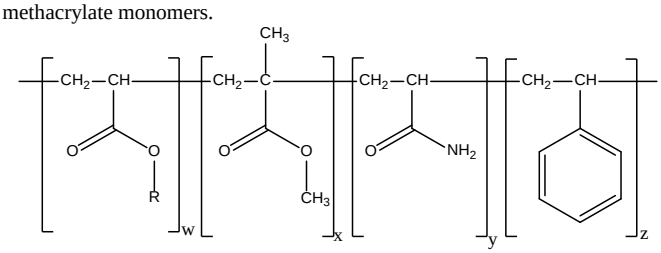
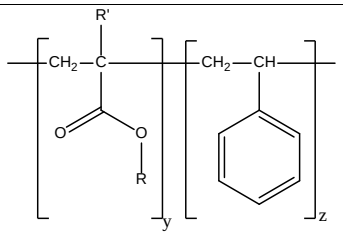
Ingredient CAS No.	Definition		Function(s)
Styrene/Stearyl Methacrylate Crosspolymer 91838-84-5	Styrene/Stearyl Methacrylate Crosspolymer is a copolymer of styrene and stearyl methacrylate monomers crosslinked with divinylbenzene.	 wherein R is an eighteen carbon, saturated alkyl chain	Absorbents; skin-conditioning agents-miscellaneous
Styrene/VA Copolymer	Styrene/VA Copolymer is a copolymer of styrene and vinyl acetate monomers.		Film formers;opacifying agents
Styrene/VP Copolymer 25086-29-7	Styrene/VP Copolymer is a copolymer prepared from vinylpyrrolidone and styrene monomers.		Film formers
Polyacrylate-2 31759-42-9	Polyacrylate-2 is a copolymer of styrene, acrylamide, octyl acrylate and methyl methacrylate monomers.		Film formers
Polyacrylate-5	Polyacrylate-5 is a copolymer of styrene, ethylhexyl acrylate, hydroxyethyl acrylate, and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters.	 wherein R is a hydrogen, methyl, ethyl, propyl, butyl, hydroxyethyl, or ethylhexyl. wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, ethyl, propyl, or butyl, R' may also me methyl.	Film formers

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[5]

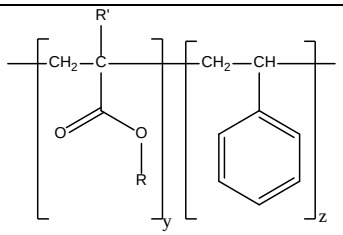
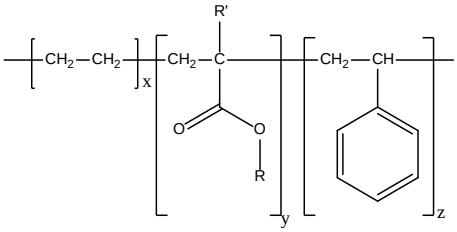
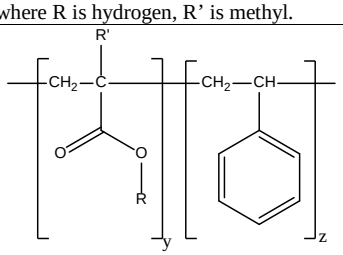
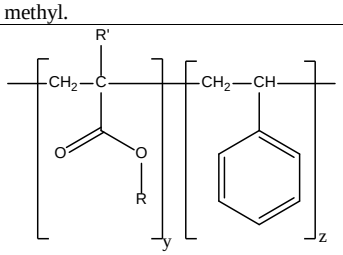
Ingredient CAS No.	Definition		Function(s)
Polyacrylate-12	Polyacrylate-12 is a copolymer of C3-11 acrylate, styrene, methacrylic Acid and acetoacetoxyethyl methacrylate monomers.	 wherein R is a hydrogen, methyl, an alkyl chain from 3 to 11 carbons in length methyl, or acetoacetoxyethyl wherein R' is hydrogen, or in the cases where R is methyl, or acetoacetoxyethyl, R' is methyl.	Film formers; nail conditioning agents
Polyacrylate-15 67892-91-5	Polyacrylate-15 is a copolymer of n-butyl acrylate, ethyl acrylate, methyl methacrylate, ethylene, methacrylic acid and styrene monomers	 wherein R is a hydrogen, methyl, ethyl , or butyl wherein R' is hydrogen, or in the case where R is hydrogen, R' is methyl.	Film formers; hair fixatives
Polyacrylate-16 67952-78-7	Polyacrylate-16 is a copolymer of n-butyl acrylate, diethylaminoethyl methacrylate, ethyl acrylate, methacrylic acid, hydroxypropyl methacrylate, methyl methacrylate and styrene monomers.	 wherein R is a hydrogen, methyl, diethylaminoethyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, diethylaminoethyl, or hydroxypropyl, R' is methyl.	Film formers; hair fixatives
Polyacrylate-18	Polyacrylate-18 is a copolymer of n-butyl acrylate, ethyl acrylate, methacrylic acid, hydroxypropyl methacrylate and styrene monomers,	 wherein R is a hydrogen, ethyl, butyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, butyl, or hydroxypropyl, R' is methyl.	Film formers; hair fixatives

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[5]

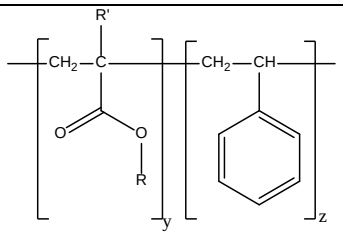
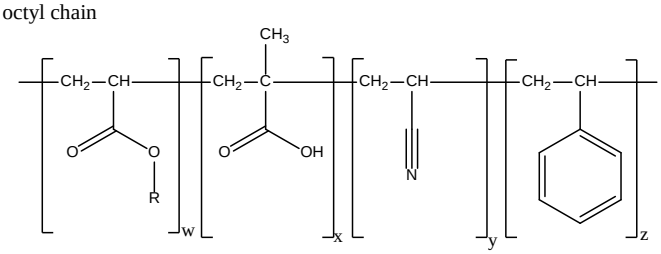
Ingredient CAS No.	Definition		Function(s)
Polyacrylate-21	Polyacrylate-21 is a copolymer of 2-ethylhexyl acrylate, butyl methacrylate, methacrylic acid, methyl methacrylate, hydroxypropyl methacrylate and styrene.		Binders; film formers; hair fixatives
Polyacrylate-30	Polyacrylate-30 is a copolymer of acrylonitrile, methacrylic acid, octyl acrylate, and styrene. wherein R is a hydrogen, methyl, butyl, ethylhexyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, butyl, or hydroxypropyl, R' is methyl. wherein R is an octyl chain		Nail conditioning agents

Table 2. Properties of Polystyrene.[6,7,8]

Form	Transparent, hard solid; water-clear solid plastic
Molecular Mass	10,000 to 300,000
Density	1.04-1.065 (amorphous); 1.111 (crystalline)
Stability	Yellows on exposure to light
Solubility	Soluble in ethylbenzene, methyl isobutyl ketone, tetrahydrofuran, benzene, toluene, methylene chloride, and pyridine
Melting Point	240°C
Softening Temperature	Begins to soften at ≈ 85°C
Flash Point	345°C to 360°C
Auto-ignition Temperature	427°C
Refractive Index	1.591
Spectroscopy Data	λ_{max} at 260 nm, 215 nm, 194 nm abd 80 nm

Table 3. Properties of Styrene.[7]

Form	Colorless to yellowish, very refractive oily liquid
Density	0.9059
Solubility	Soluble in alcohol, ether, methanol, acetone, and carbon disulfide; sparingly soluble in water
Melting Point	30.6°
Boiling Point	145° to 146°
Flash point (closed cup)	31°C
Refractive Index	1.5463

Table 4. Properties of Styrene/Butadiene Copolymer.[8]

Form	Amorphous solid
Density	0.933
Refractive Index	1.5345
Melting Point	-59 to -64°C

Table 5. Properties of 1,3-Butadiene.[12]

Form	Colorless gas
Relative Molecular Mass	54.09
Solubility	Sparingly soluble in water (1 g/L at 20°C); slightly soluble in ethanol and methanol; soluble in benzene, carbon tetrachloride, and diethyl ether

Table 6. Frequency and Concentration of Use According to Duration and Type of Exposure.[21,22]

	Ethylene/Propylene/Styrene Copolymer		**Butylene/Ethylene/Styrene Copolymer**		**Butyl Acrylate/Styrene Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	16	0.075-2.3	19	0.01-0.25	NR	NR
Incidental Ingestion	324	6-8.2	314	1-8.2	NR	NR
Incidental Inhalation- Sprays	32	0.5	29	1.9**	NR	NR
Incidental Inhalation- Powders	27	0.17-3.9*	25	0.008-0.84*	NR	NR
Dermal Contact	72	0.075-3.9	70	0.008-1.9	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	1-2	2	NR	NR	0.25
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	2	3-5.7	2	0.18-1.9	NR	NR
Mucous Membrane	328	6-8.2	318	0.11-8.2	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
Duration of Use						
Leave-On	408	0.075-8.2	395	0.008-8.2	NR	NR
Rinse off	5	0.18	5	0.11-0.95	NR	0.25
Diluted for (bath) Use	NR	NR	NR	0.95	NR	NR
Totals/Conc. Range	413	0.075-8.2	400	0.008-8.2	NR	0.25
	Hydrogenated Butylene/Ethylene/Styrene Copolymer		**Hydrogenated Ethylene/Propylene/Styrene Copolymer**		**Hydrogenated Styrene/Butadiene Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	NR	NR	1	2	NR	2.3
Incidental Ingestion	7	NR	7	NR	8	0.33-18.7
Incidental Inhalation- Sprays	4**	NR	4**	NR	2**	NR
Incidental Inhalation- Powders	4*	NR	4*	NR	1	4*
Dermal Contact	7	10	8	1.5-4.4	2	2.3-4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	NR	8	NR	3	2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	7	NR	8	0.33-18.7
Baby Products	NR	NR	NR	NR	NR	NR
Duration of Use						
Leave-On	19	NR	20	1.5-4.4	13	0.33-18.7
Rinse off	3	10	3	NR	NR	2
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Totals/Conc. Range	22	10	23	1.5-4.4	13	0.33-18.7
	Hydrogenated Styrene/Isoprene Copolymer		**Isobutylene/Styrene Copolymer**		**Methylstyrene/Vinyltoluene Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	25	NR	NR	NR	NR	NR
Incidental Ingestion	30	2.5-3	NR	NR	2	NR
Incidental Inhalation- Sprays	2	4**	NR	NR	NR	NR
Incidental Inhalation- Powders	5	3*	1	1	NR	NR
Dermal Contact	45	0.89-4	1	1	NR	0.58
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	4.2	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	30	2.5-3	NR	NR	2	NR
Baby Products	3	NR	NR	NR	NR	NR
Duration of Use						
Leave-On	78	0.89-4	1	1	2	0.58
Rinse off	NR	4.2	NR	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Totals/Conc. Range	78	0.89-4.2	1	1	2	0.58

Table 6. Frequency and Concentration of Use According to Duration and Type of Exposure.[21,22]

	Polystyrene		**Polystyrene/Hydrogenated Polyisopentene Copolymer**		**Sodium Styrene/Acrylates Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	2	NR	7	0.15-1.2	NR	NR
Incidental Ingestion	NR	NR	NR	0.05	NR	NR
Incidental Inhalation- Sprays	5	0.4**	2**	NR	4**	NR
Incidental Inhalation- Powders	4	0.08-0.4*	2**	NR	4*	NR
Dermal Contact	10	0.08-36.5	16	0.0002-1.2	22	NR
Deodorant (underarm)	NR	NR	NR	NR	13	NR
Hair - Non-Coloring	9	0.4	NR	NR	3	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.49
Mucous Membrane	2	NR	NR	0.05	2	NR
Baby Products	NR	NR	NR	NR	NR	NR
Duration of Use						
Leave-On	16	0.08-0.4	13	0.015-1.2	19	0.49
Rinse off	3	36.5	3	0.0002	4	NR
Diluted for (bath) Use	NR	NR	NR	NR	2	NR
Totals/Conc. Range	19	0.08-36.5	16	0.0002-1.2	25	0.49
	Styrene/Acrylates Copolymer		**Styrene/Butadiene Copolymer**		**Styrene/VP Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	11	0.36-15	NR	NR	NR	0.2-0.4
Incidental Ingestion	3	0.13	NR	NR	1	NR
Incidental Inhalation- Sprays	34	0.35-3.5	NR	NR	22	0.12
Incidental Inhalation- Powders	21	0.8-14.8*	NR	NR	6	0.12-0.2*
Dermal Contact	201	0.028-17.7	8	NR	18	0.000038-0.4
Deodorant (underarm)	2	0.4	NR	NR	NR	NR
Hair - Non-Coloring	8	0.2-1	1	NR	36	0.032-1
Hair-Coloring	NR	0.04-12	NR	NR	25	0.04-0.7
Nail	57	0.52-35	NR	NR	2	NR
Mucous Membrane	133	0.04-7.7	8	NR	6	0.057
Baby Products	2	0.2	NR	NR	NR	NR
Duration of Use						
Leave-On	121	0.028-35	NR	NR	30	0.000038-0.4
Rinse off	135	0.04-12	9	NR	52	0.021-1
Diluted for (bath) Use	16	0.2-0.4	NR	NR	NR	NR
Totals/Conc. Range	272	0.028-35	9	NR	82	0.000038-1
	Polyacrylate-5		**Polyacrylate-15**		**Polyacrylate-16**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	NR	NR	NR	NR	4	1-4.5
Incidental Ingestion	2	NR	NR	NR	NR	11.3
Incidental Inhalation- Sprays	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Powders	NR	NR	NR	0.38*	NR	NR
Dermal Contact	NR	NR	NR	0.38	4	1-4.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	22	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	NR	NR	NR	11.3
Baby Products	NR	NR	NR	NR	NR	NR
Duration of Use						
Leave-On	3	NR	NR	0.38	4	1-11.3
Rinse off	NR	NR	22	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Totals/Conc. Range	3	NR	22	0.38	4	1-11.3

Table 6. Frequency and Concentration of Use According to Duration and Type of Exposure.[21,22]

	Polyacrylate-21	
	# of Uses	Conc. (%)
Exposure Type		
Eye Area	NR	0.9
Incidental Ingestion	NR	NR
Incidental Inhalation-Sprays	NR	NR
Incidental Inhalation -Powders	NR	0.7
Dermal Contact	NR	0.7-0.9
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR
Duration of Use		
Leave-On	NR	0.7-0.9
Rinse off	NR	NR
Diluted for (bath) Use	NR	NR
Totals*/Conc. Range	NR	0.7-0.9

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
*It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
**It is possible that this product may be a spray, but it is not specified whether the reported use is a spray.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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2014 FDA VCRP Data

Polystyrene

03C - Eye Shadow	2
05C - Hair Straighteners	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	3
05I - Other Hair Preparations	8
07A - Blushers (all types)	1
07E - Lipstick	2
07I - Other Makeup Preparations	1
10E - Other Personal Cleanliness Products	2
12D - Body and Hand (exc shave)	2
12F - Moisturizing	2
Total	**24**

Butylene/Ethylene/Styrene Copolymer

03B - Eyeliner	1
03C - Eye Shadow	2
03D - Eye Lotion	1
03F - Mascara	12
03G - Other Eye Makeup Preparations	2
04B - Perfumes	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
07A - Blushers (all types)	1
07C - Foundations	3
07E - Lipstick	362
07I - Other Makeup Preparations	27
08B - Cuticle Softeners	1
10A - Bath Soaps and Detergents	2
10E - Other Personal Cleanliness Products	1
11E - Shaving Cream	1
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	3
12F - Moisturizing	7
12J - Other Skin Care Preps	2
13B - Indoor Tanning Preparations	1
Total	**435**

Ethylene/Propylene/Styrene Copolymer

03B - Eyeliner	1
03C - Eye Shadow	1
03D - Eye Lotion	1
03F - Mascara	11
03G - Other Eye Makeup Preparations	2
04B - Perfumes	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
07A - Blushers (all types)	1
07C - Foundations	3

07E - Lipstick	371
07I - Other Makeup Preparations	26
08B - Cuticle Softeners	1
10A - Bath Soaps and Detergents	2
10E - Other Personal Cleanliness Products	1
11E - Shaving Cream	1
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	3
12F - Moisturizing	8
12J - Other Skin Care Preps	2
13B - Indoor Tanning Preparations	1
Total	**442**

Hydrogenated Butylene/ Ethylene/Styrene Copolymer

05C - Hair Straighteners	2
05I - Other Hair Preparations	6
07E - Lipstick	7
07I - Other Makeup Preparations	1
12D - Body and Hand (exc shave)	2
12F - Moisturizing	2
12J - Other Skin Care Preps	1
Total	**21**

Hydrogenated Ethylene/ Propylene/Styrene Copolymer

03C - Eye Shadow	1
05C - Hair Straighteners	2
05I - Other Hair Preparations	6
07A - Blushers (all types)	1
07E - Lipstick	7
12D - Body and Hand (exc shave)	2
12F - Moisturizing	2
12J - Other Skin Care Preps	1
Total	**22**

Hydrogenated Styrene/Butadiene Copolymer

03C - Eye Shadow	2
05C - Hair Straighteners	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
05I - Other Hair Preparations	2
07E - Lipstick	16
07I - Other Makeup Preparations	2
12F - Moisturizing	1
Total	**25**

Hydrogenated Styrene/Isoprene Copolymer

01B - Baby Lotions, Oils, Powders, and Creams	3

03C - Eye Shadow	49
03G - Other Eye Makeup Preparations	1
05C - Hair Straighteners	1
05I - Other Hair Preparations	2
07C - Foundations	1
07E - Lipstick	46
07I - Other Makeup Preparations	13
12C - Face and Neck (exc shave)	2
12F - Moisturizing	2
12J - Other Skin Care Preps	1
Total	**121**

Isobutylene/Styrene Copolymer

07B - Face Powders	1
Total	**1**

Methylstyrene/Vinyltoluene Copolymer

07E - Lipstick	2
Total	**2**

Polystyrene/Hydrogenated Polyisopentene Copolymer

12A - Cleansing	2
12C - Face and Neck (exc shave)	1
12F - Moisturizing	1
12J - Other Skin Care Preps	2
Total	**6**

Sodium Styrene/Acrylates Copolymer

02B - Bubble Baths	1
02D - Other Bath Preparations	1
05F - Shampoos (non-coloring)	2
05I - Other Hair Preparations	1
10B - Deodorants (underarm)	14
12A - Cleansing	2
Total	**21**

Styrene/Acrylates Copolymer

01A - Baby Shampoos	1
01C - Other Baby Products	1
02B - Bubble Baths	6
02D - Other Bath Preparations	10
03B - Eyeliner	5
03G - Other Eye Makeup Preparations	3
04A - Cologne and Toilet waters	1
04E - Other Fragrance Preparation	7
05B - Hair Spray (aerosol fixatives)	1

05F - Shampoos (non-coloring)	10
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07C - Foundations	5
07E - Lipstick	3
07I - Other Makeup Preparations	1
08A - Basecoats and Undercoats	4
08C - Nail Creams and Lotions	4
08E - Nail Polish and Enamel	125
08F - Nail Polish and Enamel Removers	1
08G - Other Manicuring Preparations	4
10A - Bath Soaps and Detergents	87
10B - Deodorants (underarm)	2
10E - Other Personal Cleanliness Products	38
12A - Cleansing	13
12C - Face and Neck (exc shave)	12
12D - Body and Hand (exc shave)	3
12F - Moisturizing	7
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	7
13A - Suntan Gels, Creams, and Liquids	3
13B - Indoor Tanning Preparations	1
Total	**368**

Styrene/Butadiene Copolymer

05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	1
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	15
Total	**18**

Styrene/VP Copolymer

04A - Cologne and Toilet waters	1
04E - Other Fragrance Preparation	2
05A - Hair Conditioner	2
05C - Hair Straighteners	1
05D - Permanent Waves	10
05F - Shampoos (non-coloring)	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	10
05H - Wave Sets	2
05I - Other Hair Preparations	2
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	6
06H - Other Hair Coloring Preparation	19
07E - Lipstick	1
08B - Cuticle Softeners	2
10A - Bath Soaps and Detergents	3

10E - Other Personal Cleanliness Products	2
12A - Cleansing	1
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	1
12F - Moisturizing	2
12I - Skin Fresheners	1
12J - Other Skin Care Preps	2
Total	**79**

Polyacrylate-15

06B - Hair Tints	22
Total	**22**

Polyacrylate-16

03B - Eyeliner	3
Total	**3**

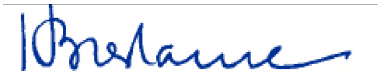
Polyacrylate-5

07E - Lipstick	2
08E - Nail Polish and Enamel	1
Total	**3**

Personal Care Products Council
Committed to Safety, Quality & Innovation

TO: Lillian Gill, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel



DATE: February 4, 2014

SUBJECT: Concentration of Use by FDA Product Category: Styrene and Vinyl-Type Styrene Copolymers

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 10, 2014

SUBJECT: Information on Trade Name Mixtures Containing Styrene/Acrylates Copolymer

The Dow Chemical Company. 2013. SunSpheres™ LCG Polymer (26-28% Styrene/Acrylates Copolymer) Global cosmetic dossier.

The Dow Chemical Company. 2013. SunSpheres™ Powder (86-90% Styrene/Acrylates Copolymer) Global cosmetic dossier.

The Dow Chemical Company. 2013. Opulyn™ 302B Opacifier (39-41% Styrene/Acrylates Copolymer) Global cosmetic dossier.

The Dow Chemical Company. 2012. Acudyne™ SHINE Polymer (39-41% Styrene/Acrylates Copolymer) Global cosmetic dossier.

The Dow Chemical Company. 2013. SunSpheres™ PGL Polymer (25-26% Styrene/Acrylates Copolymer) Global cosmetic dossier.

The Dow Chemical Company. 2012. Opulyn™ 301 Opacifier (39-41% Styrene/Acrylates Copolymer) Global cosmetic dossier.

The Dow Chemical Company. 2012. Opulyn™ PQG Opacifier (34-36% Styrene/Acrylates Copolymer) Global cosmetic dossier.

The Dow Chemical Company. 2012.Acudyne™ Bold Polymer (39-41% Styrene/Acrylates Copolymer) Global cosmetic dossier.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

SunSpheres™ LCG Polymer

Global Cosmetic Dossier

Version: 6

Date: 15 January 2013

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

Table of Contents

Contents

IDENTIFICATION

Trade Name: SunSpheres™ LCG Polymer

INCI Name: Styrene/Acrylates Copolymer

CAS Registry Number: Proprietary

Physical Form: Liquid

COMPOSITION

The composition shown below is representative of what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the "**Specifications**" section for the actual product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Function *	Feedstock Origin
Styrene/Acrylates Copolymer	Proprietary	26.0	28.0	Key Ingredient	Synthetic
Individual residual monomers			<100.0 ppm	Carryover	Synthetic
Aqua ammonia	1336-21-6		0.1		Synthetic
Water	7732-18-5	72.0	74.0	Solvent	Municipal
Mixture of: 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1)	55965-84-9		23 ppm	Preservative	Synthetic

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Complies[1]
Canada	Domestic Substances List (DSL)	Complies[1]
China	China Chemical Inventory	Does Not Comply[4]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Complies[1]
Japan	Ministry of International Trade and Industry (MITI)	Does Not Comply[4]
Korea	Korean Existing Chemical Substances (KECL)	Complies[1]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Complies[1]
United States	Toxic Substances Control Act Inventory (TSCA)	Exempt[2]

[1] Complies – All components of the product comply with the respective inventory.

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications. In Japan, this product is allowed in cosmetic applications only.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until some time in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory. Restrictions on volume limits may apply.

[5] We have reviewed the composition of product and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

[6] Complies by Polymer Exemption – The polymer component complies by valid polymer exemption. All other components of the product comply with the respective inventory.

Cosmetic Approvals

European Union
Complies with Council Directive 76/768/EEC and its 7th Amendment.

Japan, Korea, and Australia
Permitted for use in cosmetic applications.

United States
Allowed for use in cosmetic applications. SunSpheres™ LCG Polymer has been reviewed by the Cosmetic Ingredient Review Panel in the broad context of acrylate copolymers. An assessment of these Acrylates copolymers was published in a CIR Panel report on December 21,1999.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of SunSpheres™ LCG Polymer to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin. To the best of our knowledge, none of the raw materials used to produce SunSpheres™ LCG Polymer are derived from genetically modified organism sources.

Kosher/Halal Certification

With regards to Halal and Kosher status, SunSpheres™ LCG Polymer is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

SunSpheres™ LCG Polymer does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. SunSpheres™ LCG Polymer does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive (2003/15/EC). SunSpheres™ LCG Polymer is gluten-free.

CA Prop65 Certification

To the best of our knowledge, SunSpheres™ LCG Polymer does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act.

Residual Solvent Statement

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of SunSpheres™ LCG Polymer. Any available analyses of organic volatile impurities are listed in the ANALYTICAL section of this document.

Fragrance Materials Certification

SunSpheres™ LCG Polymer does not contain any fragrance materials.

Endocrine Disruptor Certification

To the best of our knowledge, SunSpheres™ LCG Polymer does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction, of category 1,2, and 3 under Annex I to Directive 67/548/EEC are intentionally used in the manufacture of SunSpheres™ LCG Polymer.

Impurities Statement

To the best of our knowledge, SunSpheres™ LCG Polymer does not contain dioxin, glycol ethers, asbestos, organotin compounds, phthalates, azo dyes, acrylamide, nonyl phenol ethoxylates, or alkyl phenol ethoxylates. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce SunSpheres™ LCG Polymer.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, SunSpheres™ LCG Polymer does not contain any components that are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), SunSpheres™ LCG Polymer does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, SunSpheres™ LCG Polymer does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

Irradiation Certification

SunSpheres™ LCG Polymer does not contain materials that have been irradiated nor are the polymers themselves irradiated at any stage in the manufacturing process.

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although SunSpheres™ LCG Polymer does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of SunSpheres™ LCG Polymer, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of SunSpheres™ LCG Polymer by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

Shelf Life Certification

The shelf life for SunSpheres™ LCG Polymer is 540 days (18 months) from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

SunSpheres™ LCG Polymer is manufactured by an emulsion polymerization process for the North American, Latin American, and Asian markets by Dow at 3100 State Rd, Croydon, PA USA 19021.

SPECIFICATIONS

Certificate of Analysis (COA) Specifications

Appearance, as-is visual	Milk-white fluid, free from gel or particles of visible impurity
Solids content, % by wt. *(Dry 0.6 gram at 150°C for 20 minutes in a forced draft oven.)*	26.00 – 28.00
pH	6.50 – 7.50
Viscosity, as is, cps *(Brookfield LV, spindle #2, 60 rpm, 25°C)*	100, maximum
Gel particles on 150 micron screen, ppm	50, maximum
Gel particles on 45 micron screen **After passing through 150 micron screen, ppm**	100, maximum
Residual Total Acrylates **Pass means ≤ 100 ppm.** **Fail means > 100 ppm.**	Pass/Fail
Residual Styrene **Pass means ≤ 35 ppm.** **Fail means > 35 ppm.**	Pass/Fail
FTIR identity	Conforms to reference

Microbiological Specifications on the COA

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass
Absence of *Candida albicans* in 1 g	Pass
Absence of Gram Negative Bacteria	Pass
Absence of *Staphylococcus aureus* in 1 g	Pass

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	≤ 35 ppm	
Butyl methacrylate	97-88-1	≤ 100 ppm	
Methyl methacrylate	80-62-6	≤ 100 ppm	

Heavy Metals

Metals were determined by Inductively Coupled Plasma Emission Spectroscopy.

Metal	CAS-No.	Results (ppm)	Limit of Detection (ppm)
Arsenic	7440-38-2	No detect	0.1
Cadmium	7440-43-9	No detect	0.1
Cobalt	7440-48-4	No detect	0.1
Chromium	7440-47-3	No detect	0.1
Copper	7440-50-8	0.7	0.1
Iron	7439-89-6	No detect	0.1
Mercury	7439-97-6	No detect	0.5
Nickel	7440-02-0	No detect	0.1
Lead	7439-92-1	No detect	0.1
Zinc	7440-66-6	No detect	0.1

TOXICOLOGY

Overall evaluation

The acrylic polymer, SunSpheres™ LCG Polymer was tested in number of non-clinical and clinical tests to evaluate potential hazards associated with handling and use of the material in personal care applications.

SunSpheres™ LCG Polymer produces no irritation to the eyes and skin, is non irritating and non sensitizing to humans, negative in the photoxicity and photoallergy assays, and non-mutagenic in the Ames assay. Based on compositionally similar materials, SunSpheres™ LCG Polymer would be expected to be non-toxic by single oral and dermal exposure, non-toxic to representative bacteria, activated sludge microorganisms, aquatic organisms, and has been shown to be not readily biodegraded via adsorptive processes. Several tests were conducted with materials that were nearly identical in monomer composition, however, there were no marked differences in these materials.

This material is safe and appropriate for use in a broad range of rinse-off and leave-on personal care applications.

Acute Toxicity Profile

Data for a compositionally similar product is below:

Test	Results	GLP
Oral LD50, rat	> 5.0 g/kg non-toxic	Yes
Dermal LD50, rabbit	> 5.0 g/kg non-toxic	Yes

Data for SunSpheres™:

Test/Species	Results	GLP
Eye irritation – rabbit	Non irritating (US, EEC)	Yes
Dermal irritation – rabbit	Non irritating (US, EEC)	Yes

Genetic Toxicity Profile

Data for SunSpheres™:

Test/Species	Results	GLP
Ames Test	Non mutagenic with and without metabolic activation	Yes

Human Toxicity Profile

Data for SunSpheres™:

Test	Results	GCP
Human Repeated Insult Patch Test (HRIPT)	Non-sensitizing and non-irritating	Yes
Phototoxicity	Not phototoxic	Yes
Photoallergy	No evidence of photosensitivity	Yes

Ecotoxicity Profile

Data for a compositionally similar product are below:

Test/Species	Results	GLP
Algae EC50 – 72 hr (Selenastrum capricornutum) Algae NOEC– 72 hr	>100 ppm – non toxic * 100 ppm	Yes
Daphnia magna LC50 – 48 hr Daphnia magna NOEC– 48 hr	>100 ppm – non toxic * 100 ppm	Yes
Rainbow Trout LC50 – 96 hr (Oncorhynchus mykiss) Rainbow trout NOEC – 96 hr	>100 ppm – non toxic * 100 ppm	Yes

* US EPA TSCA criteria

Environmental Fate Profile

Environmental fate data for a compositionally similar product are:

Test	Results	GLP
Biodegradation	<50% elimination, Not readily biodegraded	Yes
Activated sludge EC50	> 100 mg/L – non toxic	Yes
Microtox Assay EC50 – 15 minutes	> 300 ppm, non-toxic to bacteria	Yes

Animal Testing Statement

SunSpheres™ LCG Polymer was last tested in animals in August 2001.

Biodegradation

Acrylic polymers are generally stable materials and can almost be considered 'inert' in the environment. These materials do not readily decompose or biodegrade in the environment. While these polymers are non-biodegradable, they are bioeliminable. In other words, they are removed from environmental compartments where they could be available to aquatic organisms. The removal process is via rapid sorption to sediment, suspended solids and organic matter. This process makes the polymers less bioavailable thereby reducing toxicity further. Typically the molecular weight of these emulsion polymers is such that it precludes uptake by aquatic organisms and thus bioaccumulation is highly unlikely. The emulsion polymers are also generally non-toxic to activated sludge waste water systems and are considered bioeliminable in waste water treatment plants (via sorption to biosolids).

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

For additional information please contact:
Dow Customer Information Group
800-447-4369 - Toll free
989-832-1542 - Toll call
CUSTINFOGRP@dow.com - Email

15 January 2013

SunSpheres™ Powder

Global Cosmetic Dossier

Version: 13

Date: 10 January 2013

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

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IDENTIFICATION

Trade Name: SunSpheres™ Powder

INCI Name: Styrene/Acrylates Copolymer

CAS Registry Number: Proprietary

Physical Form: Powder

Function: SPF Booster

COMPOSITION

The composition shown below is representative of what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the "**Specifications**" section for the actual product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Feedstock Origin
Styrene/Acrylates Copolymer	Proprietary	86.0	90.0	Synthetic
Individual Residual Monomers			≤ 100.0 ppm	Synthetic
Fatty acid ethoxylate*	9004-81-3	9.0	11.0	Synthetic
Related reaction products		1.0	2.0	Synthetic
Water	7732-18-5		3.0	Municipal

INCI Name: PEG-8 Laurate

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Complies[1]
Canada	Domestic Substances List (DSL)	Complies[1]
China	China Chemical Inventory	Complies[7]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Exempt[2]
Japan	Ministry of International Trade and Industry (MITI)	Complies[7]
Korea	Korean Existing Chemical Substances (KECL)	Complies[1]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Complies[1]
United States	Toxic Substances Control Act Inventory (TSCA)	Exempt[2]
New Zealand	New Zealand Inventory of Chemicals (NZIoC)	Complies[6]

[1] Complies – All components of the product comply with the respective inventory.

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications. In Japan and Korea, the polymer is not on the respective country inventory, but this product is allowed to be used only in cosmetic applications.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until some time in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory. Restrictions on volume limits may apply.

[5] We have reviewed the composition of product and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

[6] There is no requirement to list components of this product on the New Zealand Inventory of Chemicals (NZIoC).

[7] Complies by Polymer Exemption/Notification where restrictions may apply – The polymer component complies by valid polymer exemption or notification where volume restrictions may apply. All other components of the product comply with the respective inventory.

Cosmetic Approvals

European Union
Complies with Council Directive 76/768/EEC and its 7th Amendment as well as Regulation (EC) No 1223/2009 on cosmetic products.

Japan
Permitted for use in cosmetic applications.

United States
Permitted for use in cosmetic applications, INCI name accepted.

SunSpheres™ Powder has been reviewed by the Cosmetic Ingredient Review Panel in the broad context of acrylate copolymers. An assessment of these Acrylates copolymers was published in a CIR Panel report on December 21,1999.

China
SunSpheres™ Powder's INCI Name is listed under the China Existing Cosmetic Ingredient List (2003) as an approved cosmetic ingredient.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of SunSpheres™ Powder to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin.

Kosher/Halal Certification

With regards to Halal and Kosher status, SunSpheres™ Powder is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

SunSpheres™ Powder does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. SunSpheres™ Powder does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive. SunSpheres™ Powder is gluten-free.

CA Prop65 Certification

To the best of our knowledge, SunSpheres™ Powder does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act.

Residual Solvent Statement

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of SunSpheres™ Powder.

Fragrance Materials Certification

SunSpheres™ Powder does not contain any fragrance materials.

Endocrine Disruptor Certification

To the best of our knowledge, SunSpheres™ Powder does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction, of category 1,2, and 3 under Annex I to Directive 67/548/EEC are intentionally used in the manufacture of SunSpheres™ Powder.

Impurities Statement

To the best of our knowledge, SunSpheres™ Powder does not contain dioxin, glycol ethers, asbestos, organotin compounds, phthalates, azo dyes, acrylamide, nonyl phenol ethoxylates, or alkyl phenol ethoxylates. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce SunSpheres™ Powder.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, SunSpheres™ Powder does not contain any components that are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), SunSpheres™ Powder does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, SunSpheres™ Powder does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although SunSpheres™ Powder does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of SunSpheres™ Powder, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of SunSpheres™ Powder by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

REACH SVHC Statement

SunSpheres™ Powder does not contain any of the substances on the Substances of Very High Concern (SVHC) list at ≥ 0.1% as currently (as of the date of this document) defined by the European Chemical Agency.

We also encourage you to visit our REACH website www.reach.dow.com where you will be able to find and download the most recent REACH related documents on our products.

Shelf Life Certification

The shelf life for SunSpheres™ Powder is 900 days (30 months) from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

The polymer in SunSpheres™ Powder is manufactured for the North American, European, Latin American, and Asian markets by The Dow Chemical Company at 3100 State Rd, Croydon, PA USA 19021. The powder form is manufactured by the American Custom Drying Company (ACD) at 109 Elbow Lane, Burlington, NJ 08016.

SPECIFICATIONS

Certificate of Analysis (COA) Specifications

Appearance, visual	White Powder
Moisture content, % by wt.	0.00 – 3.00
Bulk Density, Loose, g/cc	0.220 – 0.320
Particle Size	
% through 60 mesh	98.0, minimum
% through 100 mesh	85.0, minimum
Residual Total Acrylates **Pass means ≤ 100 ppm.** **Fail means > 100 ppm.**	Pass/Fail
Residual Styrene **Pass means ≤ 35 ppm.** **Fail means > 35 ppm.**	Pass/Fail
FTIR Identity	Conforms to reference

Microbiological Specifications on the COA

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass / Fail
Absence of *Candida albicans* in 1 g	Pass / Fail
Absence of Gram Negative Bacteria	Pass / Fail
Absence of *Staphylococcus aureus* in 1 g	Pass / Fail

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	≤ 35 ppm	
Butyl methacrylate	97-88-1	≤ 100 ppm	
Methyl methacrylate	80-62-6	≤ 100 ppm	

Heavy Metals

Metals were determined by Inductively Coupled Plasma Emission Spectroscopy.

Metal	CAS-No.	Results (ppm)	Limit of Detection (ppm)
Arsenic	7440-38-2	No detect	0.1
Cadmium	7440-43-9	No detect	0.1
Cobalt	7440-48-4	No detect	0.1
Chromium	7440-47-3	No detect	0.1
Copper	7440-50-8	No detect	0.1
Iron	7439-89-6	2.0	0.1
Mercury	7439-97-6	No detect	0.1
Nickel	7440-02-0	No detect	0.1
Lead	7439-92-1	No detect	0.1
Zinc	7440-66-6	No detect	0.1

By-Products and Impurities

Impurity	CAS-No.	Results (ppm)	Limit of Detection (ppm)
1,4-Dioxane*	123-91-1	1.23	0.1
Toluene	108-83-3	<0.05	-
2methyl-4-isothiazolin-3-one	2682-20-4	5.7	-
Diethylene Glycol	111-46-6	64 ppm	-

TOXICOLOGY

Overall evaluation

The acrylic co-polymer in SunSpheres™ Powder was tested in number of non-clinical and clinical tests to evaluate potential hazards associated with handling and use of the material. Some tests were conducted with a material that varied slightly in monomer composition and percent solids however; there are no marked differences in these materials.

Acute Toxicity Profile

Data for a compositionally similar product:

Test/Species	Results	GLP
Oral LD50 – rat	>5000 mg/kg – non toxic	Yes
Dermal LD50 – rabbit	>5000 mg/kg – non toxic	Yes
Eye irritation – rabbit	Non irritating (US, EEC)	Yes
Dermal irritation – rabbit	Non irritating (US, EEC)	Yes

Data for SunSpheres™ products:

Test/Species	Results	GLP
Eye irritation – rabbit	Minimally irritating (US); non-irritating (EEC)	Yes
Dermal irritation – rabbit	Non irritating (US, EEC)	Yes

Data for SunSpheres™ Powder:

Test/Species	Results	GLP
Eye irritation – rabbit	Minimally irritating (US); non-irritating (EEC)	Yes
Inhalation LC50 – rat	>5.3 mg/L	Yes

Genetic Toxicity Profile

Data for SunSpheres™ products:

Test/species	Results	GLP
Ames Test	Non mutagenic with and without metabolic activation	Yes

Animal Testing Statement

SunSpheres™ LCG and SunSpheres™ PGL were last tested in animals in August 2001.
SunSpheres™ Powder was last tested in animals in March 2004.

Human Toxicity Profile

Data for SunSpheres™ products:

Test/Species	Results	GCP
HRIPT	Non sensitizing and non irritating	Yes
Phototoxicity	Not phototoxic	Yes
Photoallergy	No evidence of photosensitivity	Yes

Environmental Fate

Data for a compositionally similar product:

Test	Results	GLP
Biodegradation	Not readily biodegraded	Yes
Bioelimination	37% adsorption	Yes
Activated sludge EC50	> 100 mg/L – non toxic	Yes
Microtox Assay EC50 – 15 minutes	> 300 ppm, non-toxic to bacteria	Yes

Ecotoxicity Profile

Data for a compositionally similar product:

Test/Species	Results	GLP
Algae EC50 – 72 hr (Selenastrum capricornutum) Algae NOEC– 72 hr	>100 ppm – non toxic * 100 ppm	Yes
Daphnia magna LC50 – 48 hr Daphnia magna NOEC– 48 hr	>100 ppm – non toxic * 100 ppm	Yes
Rainbow Trout LC50 – 96 hr (Oncorhynchus mykiss) Rainbow trout NOEC – 96 hr	>100 ppm – non toxic * 100 ppm	Yes

* US EPA TSCA criteria

Biodegradation

Acrylic polymers are generally stable materials and can almost be considered 'inert' in the environment. These materials do not readily decompose or biodegrade in the environment. While these polymers are non-biodegradable, they are bioeliminable. In other words, they are removed from environmental compartments where they could be available to aquatic organisms. The removal process is via rapid sorption to sediment, suspended solids and organic matter. This process makes the polymers less bioavailable thereby reducing toxicity further. Typically the molecular weight of these emulsion polymers is such that it precludes uptake by aquatic organisms and thus bioaccumulation is highly unlikely. The emulsion polymers are also generally non-toxic to activated sludge waste water systems and are considered bioeliminable in waste water treatment plants (via sorption to biosolids).

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

10 January 2013

OPULYN™ 302B Opacifier

Global Cosmetic Dossier

Version: 8

Date: 20 August 2013

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

Table of Contents

IDENTIFICATION

Trade Name: OPULYN™ 302B Opacifier

CSPA Dictionary Name: Styrene/Acrylates Copolymer

CAS Registry Number: 58353-15-4

Molecular Weight: >1,000,000

Physical Form: Liquid

Function: Opacifying Agent

COMPOSITION

The composition shown below represents what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the "Specifications" section for the product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Function *	Feedstock Origin
Styrene/acrylic copolymers	58353-15-4	39.0	41.0	Key Ingredient	Synthetic
Individual residual monomers			<500.0 ppm	Carryover	Synthetic
Water	7732-18-5	59.0	61.0	Solvent	Municipal
Benzoic Acid	65-85-0		0.5	Preservative	Synthetic

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Does Not Comply[4]
Canada	Domestic Substances List (DSL)	Complies[1]
China	China Chemical Inventory	Does Not Comply[4]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Exempt[2]
Japan	Ministry of International Trade and Industry (MITI)	Does Not Comply[4]
Korea	Korean Existing Chemical Substances (KECL)	Complies[1]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Complies[1]
United States	Toxic Substances Control Act Inventory (TSCA)	Exempt[2]

[1] Complies – All components of the product comply with the respective inventory..

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until some time in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory..

[5] We have reviewed the composition of OPULYN™ 302B Opacifier and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

Cosmetic Approvals

European Union
Complies with Council Directive 76/768/EEC and its 7th Amendment as well as Regulation (EC) No 1223/2009 on cosmetic products.

Japan
Permitted for use in cosmetic applications.

United States
Permitted for use in cosmetic applications, INCI name accepted.

OPULYN™ 302B Opacifier has been reviewed by the Cosmetic Ingredient Review Panel in the broad context of acrylate copolymers. An assessment of Acrylates copolymers was published in a CIR Panel report on December 21, 1999.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of OPULYN™ 302B Opacifier to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin.

Kosher/Halal Certification

With regards to Halal and Kosher status, OPULYN™ 302B Opacifier is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

OPULYN™ 302B Opacifier does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. OPULYN™ 302B Opacifier does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive. OPULYN™ 302B Opacifier is gluten-free.

CA Prop65 Certification

To the best of our knowledge, OPULYN™ 302B Opacifier does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act.

CA SB484 Cosmetic Act Certification

OPULYN™ 302B Opacifier does not contain any components that would qualify for reporting under the California Safe Cosmetics Act of 2005 (SB 484).

VOC Certification

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of OPULYN™ 302B Opacifier. Any available analyses of organic volatile impurities are listed in the ANALYTICAL section of this document.

Fragrance Materials Certification

OPULYN™ 302B Opacifier does not contain any fragrance materials.

Endocrine Disruptor Certification

To the best of our knowledge, OPULYN™ 302B Opacifier does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction, of category 1,2, and 3 under Annex I to Directive 67/548/EEC are intentionally used in the manufacture of OPULYN™ 302B Opacifier.

Impurities Statement

To the best of our knowledge, OPULYN™ 302B Opacifier does not contain dioxin, glycol ethers, asbestos, organotin compounds, phthalates, azo dyes, acrylamide, nonyl phenol ethoxylates, or alkyl phenol ethoxylates. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce OPULYN™ 302B Opacifier.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, OPULYN™ 302B Opacifier does not contain any components that are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), OPULYN™ 302B Opacifier does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, OPULYN™ 302B Opacifier does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although OPULYN™ 302B Opacifier does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of OPULYN™ 302B Opacifier, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of OPULYN™ 302B Opacifier by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

REACH SVHC Statement

OPULYN™ 302B Opacifier does not contain any of the substances on the Substances of Very High Concern (SVHC) list at ≥ 0.1% as currently (as of the date of this document) defined by the European Chemical Agency.

We also encourage you to visit our REACH website www.reach.dow.com where you will be able to find and download the most recent REACH related documents on our products.

Shelf Life Certification

The shelf life for OPULYN™ 302B Opacifier is 600 days (20 months) from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

OPULYN™ 302B Opacifier is manufactured by The Dow Chemical Company at 3100 State Rd, Croydon, PA USA 19021.

SPECIFICATIONS

COA Specifications

Appearance, as-is	Opaque, White to off-white liquid free of visible impurities
Solids content, % by wt. *(Dry 0.6 gram at 150°C for 20 minutes in a forced draft oven.)*	39.00 – 41.00
pH	2.05 – 3.00
Viscosity, as is, cps *(Brookfield LV, spindle #1, 60 rpm, 25°C)*	50, maximum
FTIR Identity	Conforms to reference

COA Microbiological Specifications

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass / Fail
Absence of *Candida albicans* in 1 g	Pass / Fail
Absence of Gram Negative Bacteria	Pass / Fail
Absence of *Staphylococcus aureus* in 1 g	Pass / Fail

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	≤ 50 ppm	

Heavy Metals

Metals were determined by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS). All values are in **parts per billion**.

Metal	Results (ppb)	Limit of Detection (ppb)
Antimony	No detect	50.0
Arsenic	No detect	50.0
Barium	No detect	50.0
Beryllium	No detect	50.0
Cadmium	No detect	50.0
Chromium	No detect	50.0
Cobalt	No detect	50.0
Copper	No detect	50.0
Iron	2153	50.0
Lead	No detect	50.0
Magnesium	1735	50.0
Manganese	No detect	50.0
Molybdenum	No detect	50.0
Mercury	No detect	50.0
Nickel	No detect	50.0
Selenium	No detect	50.0
Silver	No detect	50.0
Thallium	No detect	50.0
Vanadium	No detect	50.0
Zirconium	No detect	50.0
Zinc	222	50.0

TOXICOLOGY

Overall evaluation

The acrylic co-polymer in OPULYN™ 302B Opacifier was tested in number of non-clinical and clinical tests to evaluate potential hazards associated with handling and use of the material. Several tests were conducted with a material that varied slightly in monomer composition and percent solids however; there are no marked differences in these materials.

Data for compositionally similar acrylic co-polymers are below:

Acute Toxicity Profile

Test/Species	Results	GLP
Oral LD50 – rat	>5.0 ml/kg	Yes
Dermal LD50 – rat	>2.0 g/kg	Yes
Dermal irritation – rabbit	Not irritant (US, EEC)	Yes
Eye irritation - rabbit	Not irritant (US, EEC)	Yes

Genetic Toxicity Profile

Test/Species	Results	GLP
Ames Test	Not mutagenic with and without metabolic activation	Yes
In vitro cytogenetic	Not mutagenic with and without metabolic activation	Yes

Animal Testing Statement

OPULYN™ 302B Opacifier has not been tested in animals.

Human Toxicity Profile

Test/Species	Results	GCP
21-day cumulative irritation	Non sensitizing and non-irritating	Yes

Ecotoxicity Profile

Ecotoxicity data for a compositionally similar acrylic co-polymer are below:

Test/Species	Results	GLP
Algae EC50 – 72 hr NOEC – 72 hr	>100 ppm – low concern * 100 ppm	Yes
Daphnia magna LC50 – 48 hr NOEC 48 hr	>100 ppm – low concern * 100 ppm	Yes
Rainbow trout LC50 – 96 hr NOEC – 96 hr	>100 ppm – low concern * 100 ppm	Yes

* US EPA TSCA criteria

Environmental Fate Profile

Environmental fate data for a compositionally similar acrylic co-polymer are below:

Test/Species	Results	GLP
Inherent 25-day biodegradation	37% elimination (expressed as % DOC), not readily eliminable	Yes
Activated sludge respiratory inhibition	EC50 > 100 mg/L, non-inhibitory to bacteria	Yes
Microtox bacteria assay	EC50 (15 min) = 824 ppm, practically non-toxic	Yes

Biodegradation

Acrylic polymers are generally stable materials and can almost be considered 'inert' in the environment. These materials do not readily decompose or biodegrade in the environment. While these polymers are non-biodegradable, they are bioeliminable. In other words, they are removed from environmental compartments where they could be available to aquatic organisms. The removal process is via rapid sorption to sediment, suspended solids and organic matter. This process makes the polymers less bioavailable thereby reducing toxicity further. Typically the molecular weight of these emulsion polymers is such that it precludes uptake by aquatic organisms and thus bioaccumulation is highly unlikely. The emulsion polymers are also generally non-toxic to activated sludge waste water systems and are considered bioeliminable in waste water treatment plants (via sorption to biosolids).

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

20 August 2013

ACUDYNE™ SHINE Polymer

Global Cosmetic Dossier

Version: 1

Date: 23 August 2012

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

Table of Contents

IDENTIFICATION

Trade Name: ACUDYNE™ SHINE Polymer

INCI Name: Styrene/Acrylates Copolymer

CAS Registry Number: Proprietary

Physical Form: Liquid

Function: Hair Fixative

COMPOSITION

The composition shown below is representative of what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the "**Specifications**" section for the actual product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Function *	Feedstock Origin
Styrene/Acrylates Copolymer	Proprietary	39.0	41.0	Key Ingredient	Synthetic
Individual residual monomers			< 100 ppm	Carryover	Synthetic
Water	7732-18-5	59.0	61.0	Solvent	Municipal
Benzoic Acid	65-85-0		0.75	Preservative	Synthetic

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Does not comply[4]
Canada	Domestic Substances List (DSL)	Does not comply[4]
China	China Chemical Inventory	Complies[7]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Exempt[2]
Japan	Ministry of International Trade and Industry (MITI)	Exempt[2]
Korea	Korean Existing Chemical Substances (KECL)	Exempt[2]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Complies[1]
United States	Toxic Substances Control Act Inventory (TSCA)	Exempt[2]
New Zealand	New Zealand Inventory of Chemicals (NZIoC)	Complies[6]

[1] Complies – All components of the product comply with the respective inventory.

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications. In Japan and Korea, the polymer is not on the respective country inventory, but this product is allowed to be used only in cosmetic applications.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until some time in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory. Restrictions on volume limits may apply.

[5] We have reviewed the composition of product and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

[6] There is no requirement to list components of this product on the New Zealand Inventory of Chemicals (NZIoC).

[7] Complies by Polymer Exemption/Notification where restrictions may apply – The polymer component complies by valid polymer exemption or notification where volume restrictions may apply. All other components of the product comply with the respective inventory.

Cosmetic Approvals

United States

Permitted for use in cosmetic applications, INCI name accepted. This product has been reviewed by the Cosmetic Ingredient Review Panel in the broad context of Acrylates Copolymers. An assessment of these Acrylates Copolymer s was published in a CIR Panel report on December 21,1999.

European Union

Complies with Council Directive 76/768/EEC and its 7th Amendment as well as Regulation (EC) No 1223/2009 on cosmetic products.

Japan, Korea, and the Phillippines

Permitted for use in cosmetic applications.

China

ACUDYNE™ SHINE Polymer's INCI Name is listed under the China Existing Cosmetic Ingredient List (2003) as an approved cosmetic ingredient.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of ACUDYNE™ SHINE Polymer to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin.

Kosher/Halal Certification

With regards to Halal and Kosher status, ACUDYNE™ SHINE Polymer is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

ACUDYNE™ SHINE Polymer does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. ACUDYNE™ SHINE Polymer does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive. ACUDYNE™ SHINE Polymer is gluten-free.

CA Prop65 Certification

To the best of our knowledge, ACUDYNE™ SHINE Polymer does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act.

Residual Solvent Statement

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of ACUDYNE™ SHINE Polymer. Any available analyses of organic volatile impurities are listed in the ANALYTICAL section of this document.

Endocrine Disruptor Certification

To the best of our knowledge, ACUDYNE™ SHINE Polymer does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction (CMR), of Categories 1A, 1B, or 2 under Annex VI of Regulation (EC) No. 1272/2008 are intentionally used in the manufacture of ACUDYNE™ SHINE Polymer.

Nanomaterials Statement

ACUDYNE™ SHINE Polymer does not meet the definition of a nanomaterial as listed in Article 2(k) of the EU Cosmetic Regulation. ACUDYNE™ SHINE Polymer would not trigger the notification requirements of Article 16 or the need for any further safety assessment that is required for a cosmetic product due to the presence of nanomaterials.

Impurities Statement

To the best of our knowledge, ACUDYNE™ SHINE Polymer does not contain dioxin, glycol ethers, asbestos, organotin compounds, phthalates, azo dyes, acrylamide, nonyl phenol ethoxylates, or alkyl phenol ethoxylates. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce ACUDYNE™ SHINE Polymer.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, ACUDYNE™ SHINE Polymer does not contain any components that are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), ACUDYNE™ SHINE Polymer does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, ACUDYNE™ SHINE Polymer does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

Irradiation Certification

ACUDYNE™ SHINE Polymer does not contain materials that have been irradiated nor are the polymers themselves irradiated at any stage in the manufacturing process.

REACH SVHC Statement

ACUDYNE™ SHINE Polymer does not contain any of the substances on the Substances of Very High Concern (SVHC) list at ≥ 0.1% as currently (as of the date of this document) defined by the European Chemical Agency.

We also encourage you to visit our REACH website www.reach.dow.com where you will be able to find and download the most recent REACH related documents on our products.

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although ACUDYNE™ SHINE Polymer does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of ACUDYNE™ SHINE Polymer, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of ACUDYNE™ SHINE Polymer by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

Shelf Life Certification

The shelf life for ACUDYNE™ SHINE Polymer is 18 months from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

ACUDYNE™ SHINE Polymer is manufactured for the North American, European, Latin American, and Asian markets by The Dow Chemical Company at 3100 State Rd, Croydon, PA 19021, USA.

SPECIFICATIONS

Certificate of Analysis (COA) Specifications

Appearance, as-is visual	Milk-white fluid, free of visible impurities
Solids content, % by wt. *(Dry 0.6 gram at 150° C for 20 minutes in a forced draft oven.)*	39.00 – 41.00
pH	3.00 – 5.00
Viscosity, as is, cpo *(Brookfield LVt, spindle #2, 60 rpm, 25°C)*	100, maximum
Acid concentration, meq/g	2.70 – 3.00

Microbiological Specifications on the COA

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass
Absence of *Candida albicans* in 1 g	Pass
Absence of Gram Negative Bacteria in 1 g	Pass
Absence of *Staphylococcus aureus* in 1 g	Pass

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	< 10 ppm	
Butyl Acrylate	141-32-2	< 100 ppm	
2-Ethyl Hexyl Acrylate	103-11-7	< 50 ppm	
Total Residual Monomer		< 100 ppm	

Heavy Metals

Metals were determined by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS). All values are in **parts per billion**.

Metal	Results (ppb)	Limit of Detection (ppb)
Antimony	No detect	5.0
Arsenic	No detect	5.0
Cadmium	No detect	5.0
Chromium	LOD - 70	5.0
Cobalt	No detect	5.0
Iron	333 - 1996	5.0
Lead	No detect	5.0
Mercury	No detect	5.0
Nickel	LOD - 92	5.0

TOXICOLOGY

Overall evaluation

The polymer in ACUDYNE™ SHINE Polymer is a high molecular weight co-polymer. The polymer has been tested in a number of non-clinical tests to evaluate potential hazards associated with handling and use of the material. Also, where appropriate, toxicity data from structurally related polymers has been used to supplement the data set.

ACUDYNE™ SHINE Polymer is considered non-toxic by single oral, dermal and inhalation exposure, not irritating to the skin and eyes and not a sensitizer. Tests have shown that the co-polymer is not mutagenic when tested in two *in vitro* mutagenicity assays. Following inhalation exposure at high concentrations in sub-acute and sub-chronic studies, the polymer produced slight effects in the lungs, which were consistent with inflammatory effects observed for inert particles in general and other acrylate polymers in particular.

This material is safe and appropriate for use in a broad range of rinse-off and leave-on personal care applications.

Acute Toxicity Profile

Test/Species	Results	GLP
Oral LD_{50} *	> 5000 mg/kg – non toxic	Yes
Dermal LD_{50} *	> 5000 mg/kg – non toxic	Yes
Eye irritation – *in vitro* methods (BCOP)	Not irritating	Yes
Skin irritation – *in vitro* method (EpiDermal)	Not irritating	Yes
Inhalation LC_{50}, 4 hr	> 5.11 mg/L air - No clinical signs or mortality were observed.	Yes
Sensitization –LLNA, mice	Not a sensitizer	Yes

* based on data from studies on compositionally similar polymers

Subacute and Subchronic Inhalation

Test/Species	Results	GLP
Inhalation, 2-week study, nose only aerosol exposure in rat	No signs of clinical toxicity observed at any dose. No-Observed-Effect-Concentration (NOEC) was 10.8 mg polymer solids/M^3 based on slight irritant effects of the lungs at 100 mg/M^3.	Yes
Inhalation, 13-week study – nose only aerosol exposure In rat	No-Observable Adverse-Effect Level (NOAEL) for the changes in lung (and related lymph nodes) was 8.3 mg/M3	Yes

Genetic Toxicity Profile

Test/Species	Results	GLP
Bacterial Reverse Mutation Assay (Ames Test)	Not mutagenic	Yes
In vitro Chromosomal Aberration Test	Not mutagenic	Yes

Human Dermatological Studies

No dermatological studies (i.e., HRIPT, photo-toxicity or photo-allergy) have been conducted with ACUDYNE™ SHINE Polymer. However, previous studies with other acrylic polymers have produced no evidence of irritation or sensitization in human dermatological studies.

Ecotoxicity Profile

ACUDYNE™ SHINE Polymer was tested in a battery of aquatic studies and produced minimal to no toxicity.

Test/Species	Results	GLP
Fish LC_{50} -96 hr	LC_{50} > 1000 mg product/L	Yes
Daphnia magna EC_{50} – 48 hr	LC_{50} > 1000 mg product/L	Yes
Algal EC_{50} – 72 hr	LC_{50} > 1000 mg product/L	Yes

Biodegradation

The polymer would not be considered as readily biodegradable, but is likely bio-eliminable to some extent (removed via adsorption to sediment, suspended solids and organic matter wherein the polymer would more slowly degrade over time). ACUDYNE™ SHINE Polymer is not likely to bioconcentrate (accumulate in the food chain) because of its relatively high molecular weight.

Animal Testing Statement

Validated animal alternatives, where possible, were used to avoid testing in animals. In the case of some endpoints (e.g., delayed contact sensitization), validated alternatives to animal testing do not exist; and limited animal studies were performed to evaluate safe handling of ACUDYNE™ SHINE Polymer and/or to meet other non-EU regulatory requirements. The animal testing was not performed in order to fulfill the requirements of EU Cosmetics Regulation 1223/2009.

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

23 August 2012

SunSpheres™ PGL Polymer

Global Cosmetic Dossier

Version: 7

Date: 10 January 2013

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

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IDENTIFICATION

Trade Name: SunSpheres™ PGL Polymer

INCI Name: Styrene/Acrylates Copolymer

CAS Registry Number: Proprietary

Physical Form: Liquid

COMPOSITION

The composition shown below is representative of what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the "**Specifications**" section for the actual product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Function *	Feedstock Origin
Styrene/Acrylates Copolymer	Proprietary	25.0	26.0	Key Ingredient	Synthetic
Residual monomers			<100.0 ppm	Carryover	Synthetic
Aqua ammonia	1336-21-6	0.0	0.1		Synthetic
Pentylene Glycol	5343-92-0	5.0	6.0	Preservative	Synthetic
Water	1732-18-5	68.0	69.0	Solvent	Municipal

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Complies[1]
Canada	Domestic Substances List (DSL)	Does Not Comply[4]
China	China Chemical Inventory	Does Not Comply[4]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Complies[1]
Japan	Ministry of International Trade and Industry (MITI)	Does Not Comply[4]
Korea	Korean Existing Chemical Substances (KECL)	Complies[1]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Complies[1]
United States	Toxic Substances Control Act Inventory (TSCA)	Exempt[2]

[1] Complies – All components of the product comply with the respective inventory.

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications. In Japan, this product is allowed in cosmetic applications only.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until some time in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory. Restrictions on volume limits may apply.

[5] We have reviewed the composition of product and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

[6] Complies by Polymer Exemption – The polymer component complies by valid polymer exemption. All other components of the product comply with the respective inventory.

Cosmetic Approvals

European Union
Complies with Council Directive 76/768/EEC and its 7th Amendment.

Japan, Korea, and Australia
Permitted for use in cosmetic applications.

United States
Permitted for use in cosmetic applications. SunSpheres™ PGL Polymer has been reviewed by the Cosmetic Ingredient Review Panel in the broad context of acrylate copolymers. An assessment of these Acrylates copolymers was published in a CIR Panel report on December 21,1999.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of SunSpheres™ PGL Polymer to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin. To the best of our knowledge, none of the raw materials used to produce SunSpheres™ PGL Polymer are derived from genetically modified organism sources.

Kosher/Halal Certification

With regards to Halal and Kosher status, SunSpheres™ PGL Polymer is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

SunSpheres™ PGL Polymer does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. SunSpheres™ PGL Polymer does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive (2003/15/EC). SunSpheres™ PGL Polymer is gluten-free.

CA Prop65 Certification

To the best of our knowledge, SunSpheres™ PGL Polymer does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act.

Residual Solvent Statement

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of SunSpheres™ PGL Polymer. Any available analyses of organic volatile impurities are listed in the ANALYTICAL section of this document.

Fragrance Materials Certification

SunSpheres™ PGL Polymer does not contain any fragrance materials.

Endocrine Disruptor Certification

To the best of our knowledge, SunSpheres™ PGL Polymer does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction, of category 1,2, and 3 under Annex I to Directive 67/548/EEC are intentionally used in the manufacture of SunSpheres™ PGL Polymer.

Impurities Statement

To the best of our knowledge, SunSpheres™ PGL Polymer does not contain dioxin, glycol ethers, asbestos, organotin compounds, phthalates, azo dyes, acrylamide, nonyl phenol ethoxylates, or alkyl phenol ethoxylates. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce SunSpheres™ PGL Polymer.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, SunSpheres™ PGL Polymer does not contain any components that
are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), SunSpheres™ PGL Polymer does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, SunSpheres™ PGL Polymer does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

Irradiation Certification

SunSpheres™ PGL Polymer does not contain materials that have been irradiated nor are the polymers themselves irradiated at any stage in the manufacturing process.

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although SunSpheres™ PGL Polymer does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of SunSpheres™ PGL Polymer, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of SunSpheres™ PGL Polymer by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

Shelf Life Certification

The shelf life for SunSpheres™ PGL Polymer is 540 days (18 months) from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

SunSpheres™ PGL Polymer is manufactured by an emulsion polymerization process for the North American, European, Latin American, and Asian markets by Dow at 3100 State Rd, Croydon, PA USA 19021.

SPECIFICATIONS

Certificate of Analysis (COA) Specifications

Appearance, as-is visual	Milk-white fluid, free from gel or particles of visible impurities
Solids content, % by wt. *(Dry 0.6 gram at 150°C for 20 minutes in a forced draft oven.)*	24.50 – 26.50
pH	6.50 – 7.50
Viscosity, as is, cps *(Brookfield LV, spindle #2, 60 rpm, 25°C)*	100, maximum
Gel particles on 150 micron screen, ppm	50, maximum
Gel particles on 45 micron screen after passing through 150 micron screen, ppm	100, maximum
Residual Total Acrylates **Pass means ≤ 100 ppm.** **Fail means > 100 ppm.**	Pass/Fail
Residual Styrene **Pass means ≤ 35 ppm.** **Fail means > 35 ppm.**	Pass/Fail
FTIR Identity	Conforms to reference

Microbiological Specifications on the COA

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass
Absence of *Candida albicans* in 1 g	Pass
Absence of Gram Negative Bacteria	Pass
Absence of *Staphylococcus aureus* in 1 g	Pass

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	≤ 35 ppm	
Butyl methacrylate	97-88-1	≤ 100 ppm	
Methyl methacrylate	80-62-6	≤ 100 ppm	

Heavy Metals

Metals were determined by Inductively Coupled Plasma Emission Spectroscopy.

Metal	CAS-No.	Results (ppm)	Limit of Detection (ppm)
Arsenic	7440-38-2	No detect	0.1
Cadmium	7440-43-9	No detect	0.1
Cobalt	7440-48-4	No detect	0.1
Chromium	7440-47-3	No detect	0.1
Copper	7440-50-8	No detect	0.1
Iron	7439-89-6	1.0	0.1
Mercury	7439-97-6	No detect	0.1
Nickel	7440-02-0	No detect	0.1
Lead	7439-92-1	No detect	0.1
Zinc	7440-66-6	No detect	0.1

TOXICOLOGY

Overall evaluation

The acrylic polymer, SunSpheres™ PGL Polymer was tested in number of non-clinical and clinical tests to evaluate potential hazards associated with handling and use of the material in personal care applications.

SunSpheres™ PGL Polymer produces no irritation to the eyes and skin, is non irritating and non sensitizing to humans, negative in the photoxicity and photoallergy assays, and non-mutagenic in the Ames assay. Based on compositionally similar materials, SunSpheres™ PGL Polymer would be expected to be non-toxic by single oral and dermal exposure, non-toxic to representative bacteria, activated sludge microorganisms, aquatic organisms, and has been shown to be not readily biodegraded via adsorptive processes. Several tests were conducted with materials that were nearly identical in monomer composition, however, there were no marked differences in these materials.

This material is safe and appropriate for use in a broad range of rinse-off and leave-on personal care applications.

Acute Toxicity Profile

Data for a compositionally similar product is below:

Test	Results	GLP
Oral LD50, rat	> 5.0 g/kg non-toxic	Yes
Dermal LD50, rabbit	> 5.0 g/kg non-toxic	Yes

Data for SunSpheres™:

Test/Species	Results	GLP
Eye irritation – rabbit	Non irritating (US, EEC)	Yes
Dermal irritation – rabbit	Non irritating (US, EEC)	Yes

Genetic Toxicity Profile

Data for SunSpheres™:

Test/Species	Results	GLP
Ames Test	Non mutagenic with and without metabolic activation	Yes

Human Toxicity Profile

Data for SunSpheres™:

Test	Results	GCP
Human Repeated Insult Patch Test (HRIPT)	Non-sensitizing and non-irritating	Yes
Phototoxicity	Not phototoxic	Yes
Photoallergy	No evidence of photosensitivity	Yes

Environmental Fate Profile

Environmental fate data for a compositionally similar acrylic co-polymer are below:

Test	Results	GLP
Biodegradation	<50% elimination, Not readily biodegraded	Yes
Activated sludge EC50	> 100 mg/L – non toxic	Yes
Microtox Assay EC50 – 15 minutes	> 300 ppm, non-toxic to bacteria	Yes

Exotoxicity Profile

Data for a compositionally similar product are below:

Test/Species	Results	GLP
Algae EC50 – 72 hr (Selenastrum capricornutum) Algae NOEC– 72 hr	>100 ppm – non toxic * 100 ppm	Yes
Daphnia magna LC50 – 48 hr Daphnia magna NOEC– 48 hr	>100 ppm – non toxic * 100 ppm	Yes
Rainbow Trout LC50 – 96 hr (Oncorhynchus mykiss) Rainbow trout NOEC – 96 hr	>100 ppm – non toxic * 100 ppm	Yes

Animal Testing Statement

SunSpheres™ PGL Polymer was last tested in animals in August 2001.

Biodegradation

Acrylic polymers are generally stable materials and can almost be considered 'inert' in the environment. These materials do not readily decompose or biodegrade in the environment. While these polymers are non-biodegradable, they are bioeliminable. In other words, they are removed from environmental compartments where they could be available to aquatic organisms. The removal process is via rapid sorption to sediment, suspended solids and organic matter. This process makes the polymers less bioavailable thereby reducing toxicity further. Typically the molecular weight of these emulsion polymers is such that it precludes uptake by aquatic organisms and thus bioaccumulation is highly unlikely. The emulsion polymers are also generally non-toxic to activated sludge waste water systems and are considered bioeliminable in waste water treatment plants (via sorption to biosolids).

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

For additional information please contact:
Dow Customer Information Group
800-447-4369 - Toll free
989-832-1542 - Toll call
CUSTINFOGRP@dow.com - Email

10 January 2013

OPULYN™ 301 Opacifier

Global Cosmetic Dossier

Version: 8

Date: 28 August 2012

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

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IDENTIFICATION

Trade Name: OPULYN™ 301 Opacifier

INCI Name: Styrene/Acrylates Copolymer

CAS Registry Number: 9010-92-8

Molecular Weight: >1,000,000

Physical Form: Liquid

Function: Opacifying Agent

COMPOSITION

The composition shown below represents what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the "Specifications" section for the product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Function *	Feedstock Origin
Styrene/acrylic copolymer	9010-92-8	39.0	41.0	Key Ingredient	Synthetic
Water	7732-18-5	59.0	61.0	Solvent	Municipal
Residual monomers			< 500.0 ppm	Carryover	Synthetic

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Complies[1]
Canada	Domestic Substances List (DSL)	Complies[1]
China	China Chemical Inventory	Complies[1]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Exempt[2]
Japan	Ministry of International Trade and Industry (MITI)	Complies[1]
Korea	Korean Existing Chemical Substances (KECL)	Complies[1]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Complies[1]
United States	Toxic Substances Control Act Inventory (TSCA)	Exempt[2]

[1] Complies – All components of the product comply with the respective inventory.

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications. In Japan and Korea, the polymer is not on the respective country inventory, but this product is allowed to be used only in cosmetic applications.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until some time in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory. Restrictions on volume limits may apply.

[5] We have reviewed the composition of product and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

[6] There is no requirement to list components of this product on the New Zealand Inventory of Chemicals (NZIoC).

[7] Complies by Polymer Exemption/Notification where restrictions may apply – The polymer component complies by valid polymer exemption or notification where volume restrictions may apply. All other components of the product comply with the respective inventory.

Cosmetic Approvals

European Union
Complies with Council Directive 76/768/EEC and its 7th Amendment.

Japan
Permitted for use in cosmetic applications.

United States
Permitted for use in cosmetic applications, INCI name accepted.

OPULYN™ 301 Opacifier has been reviewed by the Cosmetic Ingredient Review Panel in the broad context of acrylate copolymers. An assessment of Acrylates copolymers was published in a CIR Panel report on December 21, 1999.

China
OPULYN™ 301 Opacifier 's INCI Name is listed under the China Existing Cosmetic Ingredient List (2003) as an approved cosmetic ingredient.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of OPULYN™ 301 Opacifier to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin.

Kosher/Halal Certification

With regards to Halal and Kosher status, OPULYN™ 301 Opacifier is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

OPULYN™ 301 Opacifier does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. OPULYN™ 301 Opacifier does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive. OPULYN™ 301 Opacifier is gluten-free and does not contain lanolin or its derivatives.

CA Prop65 Certification

To the best of our knowledge, OPULYN™ 301 Opacifier does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act.

CA SB484 Cosmetic Act Certification

To the best of our knowledge, OPULYN™ 301 Opacifier does not contain any components that would qualify for reporting under the California Safe Cosmetics Act of 2005 (SB 484).

VOC Certification

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of OPULYN™ 301 Opacifier. Any available analyses of organic volatile impurities are listed in the ANALYTICAL section of this document.

Fragrance Materials Certification

OPULYN™ 301 Opacifier does not contain any fragrance materials.

Endocrine Disruptor Certification

To the best of our knowledge, OPULYN™ 301 Opacifier does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction (CMR), of Categories 1A, 1B, or 2 under Annex VI of Regulation (EC) No. 1272/2008 are intentionally used in the manufacture of OPULYN™ 301 Opacifier.

Impurities Statement

To the best of our knowledge, OPULYN™ 301 Opacifier does not contain parabens, dioxin, glycol ethers, asbestos, organotin compounds, phthalates, azo dyes, acrylamide, nonyl phenol ethoxylates, or alkyl phenol ethoxylates. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce OPULYN™ 301 Opacifier.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, OPULYN™ 301 Opacifier does not contain any components that are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), OPULYN™ 301 Opacifier does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, OPULYN™ 301 Opacifier does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

REACH SVHC Statement

OPULYN™ 301 Opacifier does not contain any of the substances currently on the Substances of Very High Concern (SVHC) list at ≥ 0.1% (as currently defined in EU Regulation 1907/2006 and listed on the first candidate list published on October 28 2008 by the European Chemical Agency).

We also encourage you to visit our REACH website www.reach.dow.com where you will be able to find and download the most recent REACH related documents on our products.

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although OPULYN™ 301 Opacifier does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of OPULYN™ 301 Opacifier, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of OPULYN™ 301 Opacifier by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

Shelf Life Certification

The shelf life for OPULYN™ 301 Opacifier is 600 days (20 months) from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

OPULYN™ 301 Opacifier is manufactured for the North American, Latin American, and Asian markets by The Dow Chemical Company at 3100 State Rd, Croydon, PA USA 19021.
OPULYN™ 301 Opacifier is manufactured for the European market by The Dow Chemical Company at Ringvägen 163, SE-26122 Landskrona, Sweden.

SPECIFICATIONS

COA Specifications

Appearance, as-is	Milk-white fluid, free of coagulated gum and visible impurities
Solids content, % by wt. *(Dry 0.6 gram at 150°C for 20 minutes in a forced draft oven.)*	39.00 – 41.00
pH	2.05 – 2.50
Viscosity, as is, cps *(Brookfield LV, spindle #1, 60 rpm, 25°C)*	50, maximum
Gel particles on 150 micron screen, ppm	50, maximum
Gel particles on 45 micron screen, ppm after passing through 150 micron screen	100, maximum
FTIR Identity	Conforms to reference

COA Microbiological Specifications

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass / Fail
Absence of *Candida albicans* in 1 g	Pass / Fail
Absence of Gram Negative Bacteria	Pass / Fail
Absence of *Staphylococcus aureus* in 1 g	Pass / Fail

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	≤ 20 ppm	

Heavy Metals

Metals were determined by Inductively Coupled Plasma Emission Spectroscopy on representative batches.

Metal	CAS-No.	Results (ppm)	Limit of Detection (ppm)
Arsenic	7440-38-2	No detect	0.1
Cadmium	7440-43-9	No detect	0.1
Cobalt	7440-48-4	No detect	0.1
Chromium	7440-47-3	No detect	0.1
Copper	7440-50-8	No detect	0.1
Iron	7439-89-6	No detect	0.1
Mercury	7439-97-6	No detect	0.5
Nickel	7440-02-0	No detect	0.1
Lead	7439-92-1	No detect	0.1
Zinc	7440-66-6	No detect	0.1

TOXICOLOGY

Overall evaluation

The acrylic co-polymer in OPULYN™ 301 Opacifier was tested in number of non-clinical and clinical tests to evaluate potential hazards associated with handling and use of the material. Several tests were conducted with a material that varied slightly in monomer composition and percent solids however; there are no marked differences in these materials.

Acute Toxicity Profile

Toxicity data for compositionally similar acrylic co-polymers are below:

Test/Species	Results	GLP
Oral LD50 – rat	>5.0 g/kg	Yes
Dermal LD50 – rat	>2.0 g/kg	Yes
Skin irritation – rabbit	Not irritant (US, EEC)	Yes
Eye irritation – rabbit	Not irritant (US, EEC)	Yes

Genetic Toxicity Profile

Test/Species	Results	GLP
Ames Test	Not mutagenic with and without metabolic activation	Yes
In vitro cytogenetic	Not mutagenic with and without metabolic activation	Yes

Human Toxicity Profile

Test/Species	Results	GCP
21-day cumulative irritation	Non sensitizing and non-irritating	Yes

Animal Testing Statement

OPULYN™ 301 Opacifier was not tested in animals.

Ecotoxicity Profile

Ecotoxicity data for a compositionally similar acrylic co-polymer are below:

Test/Species	Results	GLP
Algae EC50 – 72 hr Algae NOEC– 72 hr	100 ppm, low concern * 100 ppm	Yes
Daphnia magna LC50 – 48 hr Daphnia magna NOEC– 48 hr	100 ppm, low concern * 100 ppm	Yes
Rainbow trout LC50 – 96 hr Rainbow trout NOEC – 96 hr	100 ppm, low concern * 100 ppm	Yes

* US EPA TSCA criteria

Environmental Fate Profile

Environmental fate data for a compositionally similar acrylic co-polymer are below:

Test/Species	Results	GLP
Inherent 25-day biodegradation	37% elimination (expressed as % DOC), bioeliminable via adsorptive processes	Yes
Activated sludge respiratory inhibition	EC50 > 100 mg/L, non-inhibitory to bacteria	Yes
Microtox bacteria assay	EC50 (15 min) = 824 ppm, practically non-toxic	Yes

Biodegradation

Acrylic polymers are generally stable materials and can almost be considered 'inert' in the environment. These materials do not readily decompose or biodegrade in the environment. While these polymers are non-biodegradable, they are bioeliminable. In other words, they are removed from environmental compartments where they could be available to aquatic organisms. The removal process is via rapid sorption to sediment, suspended solids and organic matter. This process makes the polymers less bioavailable thereby reducing toxicity further. Typically the molecular weight of these emulsion polymers is such that it precludes uptake by aquatic organisms and thus bioaccumulation is highly unlikely. The emulsion polymers are also generally non-toxic to activated sludge waste water systems and are considered bioeliminable in waste water treatment plants (via sorption to biosolids).

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

28 August 2012

OPULYN™ PQG Opacifier

Global Cosmetic Dossier

Version: 5

Date: 3 August 2012

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

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IDENTIFICATION

Trade Name: OPULYN™ PQG Opacifier

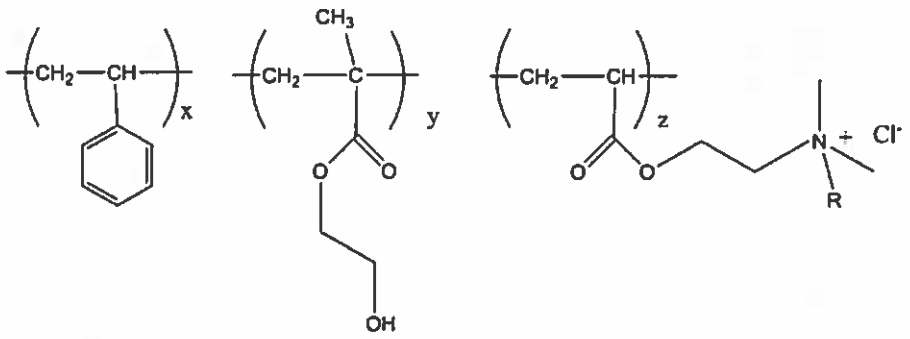
INCI Name: Ethalkonium Chloride Acrylate/HEMA/Styrene Copolymer

CAS Registry Number: 26010-51-5 P(HEMA/Styrene)

Physical Form: Liquid

Particle Size: 0.18 micron

Function: OPULYN™ PQG Opacifier is a novel opacifying polymer providing long-term stability in formulations containing cationic conditioning polymers as well as excellent compatibility in systems with a high level of amphoteric surfactants.



COMPOSITION

The composition shown below is representative of what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the SPECIFICATIONS section for the actual product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Function *	Feedstock Origin
Ethalkonium Chloride Acrylate/HEMA/Styrene Copolymer	26010-51-5	34.0	36.0	Key Ingredient	Synthetic
Residual monomers			< 500.0 ppm	Carryover	Synthetic
Water	7732-18-5	63.0	65.0	Solvent	Municipal
Ethoxylated alcohols		1.0	2.0	Process Aid	Synthetic
2-Methyl-4-isothiazolin-3-one	2682-20-4		82 ppm	Preservative	Synthetic
Phenoxyethanol	122-99-6		0.4	Preservative	Synthetic

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Complies[1]
Canada	Domestic Substances List (DSL)	Complies[1]
China	China Chemical Inventory	Complies[7]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Exempt[2]
Japan	Ministry of International Trade and Industry (MITI)	Exempt[2]
Korea	Korean Existing Chemical Substances (KECL)	Exempt[2]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Exempt[2]
United States	Toxic Substances Control Act Inventory (TSCA)	Complies[1]
New Zealand	New Zealand Inventory of Chemicals (NZIoC)	Complies[5]

[1] Complies – All components of the product comply with the respective inventory.

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications. In Japan, Korea, and the Philippines, the polymer is not on the respective country inventory, but this product is allowed to be used only in cosmetic applications.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until sometime in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory. Restrictions on volume limits may apply.

[5] We have reviewed the composition of product and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

[6] There is no requirement to list components of this product on the New Zealand Inventory of Chemicals (NZIoC).

[7] Complies by Polymer Exemption/Notification where restrictions may apply – The polymer component complies by valid polymer exemption or notification where volume restrictions may apply. All other components of the product comply with the respective inventory.

Cosmetic Approvals

European Union
Complies with Council Directive 76/768/EEC and its 7th Amendment.

Japan, Korea, and Australia
Permitted for use in cosmetic applications.

United States
Permitted for use in cosmetic applications, INCI name accepted.

China

Following the China SFDA's Application and Evaluation Guide for New Cosmetic Ingredients, effective July 1st, 2011, Dow will submit the registration application of OPULYN™ PQG Opacifier's INCI name to the Chinese Authority under the new requirements.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of OPULYN™ PQG Opacifier to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin. To the best of our knowledge, none of the raw materials used to produce OPULYN™ PQG Opacifier are derived from genetically modified organism sources.

Kosher/Halal Certification

With regards to Halal and Kosher status, OPULYN™ PQG Opacifier is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

OPULYN™ PQG Opacifier does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. OPULYN™ PQG Opacifier does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive (2003/15/EC). OPULYN™ PQG Opacifier is gluten-free.

CA Prop65 Certification

To the best of our knowledge, OPULYN™ PQG Opacifier does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act..

Residual Solvent Statement

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of OPULYN™ PQG Opacifier. Any available analyses of organic volatile impurities are listed in the ANALYTICAL section of this document.

Endocrine Disruptor Certification

To the best of our knowledge, OPULYN™ PQG Opacifier does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction (CMR), of Categories 1A, 1B, or 2 under Annex VI of Regulation (EC) No. 1272/2008 are intentionally used in the manufacture of OPULYN™ PQG Opacifier.

Impurities Statement

To the best of our knowledge, OPULYN™ PQG Opacifier does not contain dioxin, glycol ethers, asbestos, organotin compounds, phthalates, acrylamide, parabens, or formaldehyde-releasers. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce OPULYN™ PQG Opacifier. OPULYN™ PQG Opacifier may contain some ethoxylate derivatives.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, OPULYN™ PQG Opacifier does not contain any components that are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), OPULYN™ PQG Opacifier does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, OPULYN™ PQG Opacifier does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

Irradiation Certification

OPULYN™ PQG Opacifier does not contain materials that have been irradiated nor are the polymers themselves irradiated at any stage in the manufacturing process.

REACH SVHC Statement

OPULYN™ PQG Opacifier does not contain any of the substances currently on the Substances of Very High Concern (SVHC) list at ≥ 0.1% (as currently defined in EU Regulation 1907/2006 and listed on the first candidate list published on October 28 2008 by the European Chemical Agency).

We also encourage you to visit our REACH website www.reach.dow.com where you will be able to find and download the most recent REACH related documents on our products.

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although OPULYN™ PQG Opacifier does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of OPULYN™ PQG Opacifier, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of OPULYN™ PQG Opacifier by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

Shelf Life Certification

The shelf life for OPULYN™ PQG Opacifier is 18 months from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

OPULYN™ PQG Opacifier is manufactured in the United Kingdom by an emulsion polymerization process for the North American, European, Latin American, and Asian markets.

SPECIFICATIONS

Certificate of Analysis (COA) Specifications

Appearance, as-is	Pass
Solids content, % by wt. *(Dry 0.6 gram at 150°C for 20 minutes in a forced draft oven.)*	34.00 – 36.00
pH	2.05 – 3.30
Brookfield Viscosity, mPa.s *(Brookfield LV, spindle #2, 30 rpm, 25°C)*	100, maximum

Microbiological Specifications on the COA

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass
Absence of *Candida albicans* in 1 g	Pass
Absence of Gram Negative Bacteria	Pass
Absence of *Staphylococcus aureus* in 1 g	Pass

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	≤ 50 ppm	manufacturing specification
Hydroxyethyl methacrylate HEMA	868-77-9	< 50 ppm	not a manufacturing specification

Heavy Metals

Heavy metals analysis was conducted on a sample of OPULYN™ PQG Opacifier by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS). Results are reported in **parts per billion**.

Metal	Results (ppb)	Limit of Detection (ppb)
Arsenic	Not Detected	50.0
Barium	133	50.0
Beryllium	Not Detected	50.0
Cadmium	Not Detected	50.0
Chromium	Not Detected	50.0
Cobalt	Not Detected	50.0
Copper	264	50.0
Iron	831	50.0
Lead	Not Detected	50.0
Mercury	Not Detected	50.0
Nickel	Not Detected	50.0
Selenium	Not Detected	50.0
Silver	Not Detected	50.0
Thallium	Not Detected	50.0
Vanadium	Not Detected	50.0
Zinc	190	50.0

TOXICOLOGY

Overall evaluation

OPULYN™ PQG Opacifier is a high molecular weight co-polymer. The co-polymer has been tested in a number of non-clinical tests to evaluate potential hazards associated with handling and use of the material. Also, where appropriate, toxicity data from structurally related polymers has been used to supplement the data set.

OPULYN™ PQG Opacifier is considered non-toxic by single oral and dermal exposure, not irritating to the skin and eyes and not a sensitizer. Tests have shown that the co-polymer is not mutagenic when tested in two in vitro mutgenicity assays.

This material is safe and appropriate for use in a broad range of rinse-off and leave-on personal care applications.

Acute Toxicity Profile

Test/Species	Results	GLP
Acute oral toxicity [Information based on other polymers]	>2000 mg/kg non-toxic	----
Acute dermal toxicity [Information based on other polymers]	>2000 mg/kg non-toxic	----
Eye irritation – *in vitro* methods (BCOP, EpiOccular)	Not irritating	Yes
Skin irritation – in vitro method (EpiDermal)	Not irritating	Yes
Sensitization –LLNA, mice	Not a sensitizer	Yes

Genetic Toxicity Profile

Test/species	Results	GLP
Ames Test	Not mutagenic	Yes
In vitro Chromosomal Aberration Test	Not mutagenic	Yes

Human Toxicity Profile

No dermatological studies (i.e., HRIPT, photo-toxicity, or photo-allergy) have been conducted.

Animal Testing Statement

Validated animal alternatives, where possible, were used to avoid testing in animals. In the case of some endpoints (e.g., delayed contact sensitization), validated alternatives to animal testing do not exist; and limited animal studies were performed to evaluate safe handling of OPULYN™ PQG Opacifier and/or to meet other non-EU regulatory requirements. The animal testing was not performed in order to fulfill the requirements of EU Cosmetics Regulation 1223/2009.

Ecotoxicity Profile

Test/Species	Results	GLP
Daphnia magna	48-Hour EC_{50}: 31 mg/L No-Immobility Level: <6.3 mg/L No-Observed-Effect Level: <6.3 mg/L	Yes
Fish (FHM)	96-Hour LC_{50}: >100 mg/L No-Mortality Level: 13 mg/L No-Observed-Effect Level: 13 mg/L	Yes
Fresh Water Algae	96-Hour ErC_{50}: >25 mg/L (50% effect level not achieved at highest practical conc. tested, 25 mg/L) No-Observed-Effect Level (72 hr): 10 mg/L No-Observed-Effect Level (96 hr): 4.0 mg/L	Yes

Biodegradation

Acrylic polymers are generally stable materials and can almost be considered 'inert' in the environment. These materials do not readily decompose or biodegrade in the environment. While these polymers are non-biodegradable, they are bioeliminable. In other words, they are removed from environmental compartments where they could be available to aquatic organisms. The removal process is via rapid sorption to sediment, suspended solids and organic matter. This process makes the polymers less bioavailable thereby reducing toxicity further. Typically the molecular weight of these emulsion polymers is such that it precludes uptake by aquatic organisms and thus bioaccumulation is highly unlikely. The emulsion polymers are also generally non-toxic to activated sludge waste water systems and are considered bioeliminable in waste water treatment plants (via sorption to biosolids).

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

For additional information please contact:
The Dow Customer Information Group
800-447-4369 (Toll free)
989-832-1542 (Toll call)
CUSTINFOGRP@dow.com

3 August 2012

ACUDYNE™ BOLD Polymer

Global Cosmetic Dossier

Version: 1

Date: 1 June 2012

The Dow Chemical Company
Spring House Technical Center
727 Norristown Rd
PO Box 904
Spring House, PA 19477

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IDENTIFICATION

Trade Name: ACUDYNE™ BOLD Polymer

INCI Name: Styrene/Acrylates Copolymer

CAS Registry Number: Proprietary

Physical Form: Liquid

Function: Hair Fixative

COMPOSITION

The composition shown below is representative of what is listed in Section 2 of the US MSDS. The minimum and maximum values presented in this table do not necessarily represent product specifications. Please see the "**Specifications**" section for the actual product specifications.

CONSTITUENT	CAS#	Min. %	Max. %	Function *	Feedstock Origin
Styrene/Acrylates Copolymer	Proprietary	39.0	41.0	Key Ingredient	Synthetic
Individual residual monomers			< 100 ppm	Carryover	Synthetic
Water	7732-18-5	59.0	61.0	Solvent	Municipal
Benzoic Acid	65-85-0		0.75	Preservative	Synthetic

REGULATORY STATUS

Global Inventory Status

Country	Inventory / Registration	Status
Australia	Australian Inventory of Chemical Substances (AICS)	Does not comply[4]
Canada	Domestic Substances List (DSL)	Does not comply[4]
China	China Chemical Inventory	Complies[7]
European Union	European Inventory of Existing Chemical Substances (EINECS)	Exempt[2]
Japan	Ministry of International Trade and Industry (MITI)	Exempt[2]
Korea	Korean Existing Chemical Substances (KECL)	Exempt[2]
Philippines	Philippines Inventory of Chemicals and Chemical Substances (PICCS)	Complies[1]
United States	Toxic Substances Control Act Inventory (TSCA)	Exempt[2]
New Zealand	New Zealand Inventory of Chemicals (NZIoC)	Complies[6]

[1] Complies – All components of the product comply with the respective inventory.

[2] Exempt - In Europe, the polymer in this product meets the definition of a polymer and is exempt from listing on the EINECS inventory. All other components of this product comply. In the United States, this product is exempt from TSCA if used only in cosmetic applications. In Japan and Korea, the polymer is not on the respective country inventory, but this product is allowed to be used only in cosmetic applications.

[3] Delayed - Rohm and Haas Company, A Wholly Owned Subsidiary of The Dow Chemical Company, has submitted a notification on an intentional component in this product and has received permission to import or manufacture in the applicable country. However, this intentional component will not be added to the country's inventory until some time in the future.

[4] Does Not Comply – One or more components of the product do not comply with the respective inventory. Restrictions on volume limits may apply.

[5] We have reviewed the composition of product and conclude that none of the components, as described on our Material Safety Data Sheet (MSDS), are subject to any reporting requirements associated with rules or orders under Sections 4, 5, 6, 7, and 12b of TSCA.

[6] There is no requirement to list components of this product on the New Zealand Inventory of Chemicals (NZIoC).

[7] Complies by Polymer Exemption/Notifcation wher restrictions may apply – The polymer component complies by valid polymer exemption or notification where volume restrictions may apply. All other components of the product comply with the respective inventory.

Cosmetic Approvals

United States

Permitted for use in cosmetic applications, INCI name accepted. This product has been reviewed by the Cosmetic Ingredient Review Panel in the broad context of Acrylates Copolymers. An assessment of these Acrylates Copolymer s was published in a CIR Panel report on December 21,1999.

European Union

Complies with Council Directive 76/768/EEC and its 7th Amendment as well as Regulation (EC) No 1223/2009 on cosmetic products.

Japan, Korea, and the Phillippines

Permitted for use in cosmetic applications.

China

ACUDYNE™ BOLD Polymer's INCI Name is listed under the China Existing Cosmetic Ingredient List (2003) as an approved cosmetic ingredient.

CERTIFICATIONS

Raw Material Origin Certification

With regards to Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE), we do not intentionally add, nor would we expect any component of ACUDYNE™ BOLD Polymer to be derived from bovine, ovine, caprine, porcine or related ingredients of animal origin. This product is derived from materials of synthetic, petrochemical and/or mineral origins. The manufacturing equipment for the product is not used for the manufacture of products of animal origin or products containing ingredients of animal origin. This product is not stored with products of animal origin or products containing ingredients of animal origin.

Kosher/Halal Certification

With regards to Halal and Kosher status, ACUDYNE™ BOLD Polymer is free of wheat, oat, barley or rye derivatives. Although this product has not been officially certified by a Rabbinical or Islamic council, we believe this product is judged to be "pareve" within the framework of the Jewish definition and permitted under Muslim standards. We are disclosing above information, to the best of knowledge based upon data from our raw material suppliers and our manufacturing process. Please note that we do not test any of the raw materials used in the product for the presence of the above mentioned substances.

Allergens Certification

ACUDYNE™ BOLD Polymer does not contain any of the eight major food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and/or soybeans) or proteins as listed in the FALCPA of 2004 and in FDA Guidance Sec.550.250 and does not contact these food allergen during the manufacturing process. ACUDYNE™ BOLD Polymer does not contain any of the 26 allergen ingredients as defined in the 7th Amendment of the European Cosmetics Directive. ACUDYNE™ BOLD Polymer is gluten-free.

CA Prop65 Certification

To the best of our knowledge, ACUDYNE™ BOLD Polymer does not contain any contaminants or by products known to the State of California to cause cancer or reproductive toxicity as listed under the Proposition 65 State Drinking Water and Toxic Enforcement Act.

Residual Solvent Statement

None of the Class 1, Class 2, and Class 3 Residual Solvents specified in USP General Chapter <467> effective on 1 JUL 2008 are used in the manufacture of ACUDYNE™ BOLD Polymer. Any available analyses of organic volatile impurities are listed in the ANALYTICAL section of this document.

Endocrine Disruptor Certification

To the best of our knowledge, ACUDYNE™ BOLD Polymer does not contain any potential endocrine disruptors.

CMR Certification

No substances classified as Carcinogenic, Mutagenic or toxic for Reproduction (CMR), of Categories 1A, 1B, or 2 under Annex VI of Regulation (EC) No. 1272/2008 are intentionally used in the manufacture of ACUDYNE™ BOLD Polymer.

Nanomaterials Statement

ACUDYNE™ BOLD Polymer does not meet the definition of a nanomaterial as listed in Article 2(k) of the EU Cosmetic Regulation. ACUDYNE™ BOLD Polymer would not trigger the notification requirements of Article 16 or the need for any further safety assessment that is required for a cosmetic product due to the presence of nanomaterials.

Impurities Statement

To the best of our knowledge, ACUDYNE™ BOLD Polymer does not contain dioxin, glycol ethers, asbestos, organotin compounds, phthalates, azo dyes, acrylamide, nonyl phenol ethoxylates, or alkyl phenol ethoxylates. These substances are not intentionally added and are not expected to be generated during the manufacturing process. We do not expect these substances to be present in the raw materials used to produce ACUDYNE™ BOLD Polymer.

Clean Water Act Toxic Pollutant List Certification

To the best of our knowledge, ACUDYNE™ BOLD Polymer does not contain any components that are listed on the Clean Water Act Toxic Pollutant List in 40 CFR 401.15.

Clean Air Act Certification

To the best of our knowledge, with regards to the Clean Air Act, Section 112(b), ACUDYNE™ BOLD Polymer does not contain any Hazardous Air Pollutants (HAPs) at or above 0.1%.

To the best of our knowledge, ACUDYNE™ BOLD Polymer does not contain any components that are listed on the Clean Air Act Sec. 602 Class I and II Ozone Depleting Substances List (40 CFR 82).

Irradiation Certification

ACUDYNE™ BOLD Polymer does not contain materials that have been irradiated nor are the polymers themselves irradiated at any stage in the manufacturing process.

REACH SVHC Statement

ACUDYNE™ BOLD Polymer does not contain any of the substances on the Substances of Very High Concern (SVHC) list at ≥ 0.1% as currently (as of the date of this document) defined by the European Chemical Agency.

We also encourage you to visit our REACH website www.reach.dow.com where you will be able to find and download the most recent REACH related documents on our products.

RoHS Directive 2002/95/EC Certification

Directive 2002/95/EC on the restriction of the use of certain hazardous substances in electrical and electronic equipment requires that electrical and electronic equipment placed on the EU market does not contain lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyl, polybrominated biphenyl ether.

Although ACUDYNE™ BOLD Polymer does not fall in the scope of this directive, it can be used as a raw material in the manufacture of some components of electrical and electronic equipment.

We hereby confirm that in the manufacture of ACUDYNE™ BOLD Polymer, we do not intentionally use polybrominated biphenyl or polybrominated biphenyl ether. Based upon data from our raw material suppliers and knowledge of the manufacturing process, we have no reason to believe that these substances are present.

Heavy metals analyses of ACUDYNE™ BOLD Polymer by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS) showed that lead, mercury, and cadmium are not present with a Limit of Detection of less than 1 part per billion (ppb). Hexavalent chromium was not analyzed, but it is not expected to be found at greater than trace levels.

Shelf Life Certification

The shelf life for ACUDYNE™ BOLD Polymer is 18 months from the date of manufacture provided on the Certificate of Analysis (COA) for each batch lot.

Manufacturing Location Certification

ACUDYNE™ BOLD Polymer is manufactured for the North American, European, Latin American, and Asian markets by The Dow Chemical Company at 3100 State Rd, Croydon, PA 19021, USA.

SPECIFICATIONS

Certificate of Analysis (COA) Specifications

Appearance, as-is visual	Milk-white fluid, free of visible impurities
Solids content, % by wt.	39.00 – 41.00
(Dry 0.6 gram at 150° C for 20 minutes in a forced draft oven.)	
pH	3.00 – 5.00
Viscosity, as is, cpo	100, maximum
(Brookfield LVt, spindle #2, 60 rpm, 25°C)	
Acid concentration, meq/g	2.70 – 3.00

Microbiological Specifications on the COA

Method	Results
Aerobic Plate Count < 100 CFU/g	Pass
Absence of *Candida albicans* in 1 g	Pass
Absence of Gram Negative Bacteria in 1 g	Pass
Absence of *Staphylococcus aureus* in 1 g	Pass

ANALYTICAL

Residual Monomer

Monomer	CAS-No.	Concentration	Comment
Styrene	100-42-5	< 10 ppm	
Butyl Acrylate	141-32-2	< 100 ppm	
2-Ethyl Hexyl Acrylate	103-11-7	< 50 ppm	
Total Residual Monomer		< 100 ppm	

Heavy Metals

Metals were determined by Inductively Coupled Plasma Mass Spectroscopy (ICP/MS). All values are in **parts per billion**.

Metal	Results (ppb)	Limit of Detection (ppb)
Antimony	No detect	5.0
Arsenic	No detect	5.0
Cadmium	No detect	5.0
Chromium	82	5.8
Cobalt	No detect	5.0
Iron	2270	108.7
Lead	No detect	5.0
Mercury	No detect	18.4
Nickel	173	5.0

TOXICOLOGY

Overall evaluation

The polymer in ACUDYNE™ BOLD Polymer is a high molecular weight polymer. The polymer has been tested in a number of non-clinical tests to evaluate potential hazards associated with handling and use of the material. Also, where appropriate, toxicity data from structurally related polymers has been used to supplement the data set.

ACUDYNE™ BOLD Polymer is considered non-toxic by single oral, dermal and inhalation exposure, not irritating to the skin and eyes and not a sensitizer. Tests have shown that the co-polymer is not mutagenic when tested in two *in vitro* mutagenicity assays. Following inhalation exposure at high concentrations in sub-acute and sub-chronic studies, the polymer produced slight effects in the lungs, which were consistent with inflammatory effects observed for inert particles in general and other acrylate polymers in particular.

This material is safe and appropriate for use in a broad range of rinse-off and leave-on personal care applications.

Acute Toxicity Profile

Test/Species	Results	GLP
Oral LD_{50} *	> 5000 mg/kg – non toxic	Yes
Dermal LD_{50} *	> 5000 mg/kg – non toxic	Yes
Eye irritation – *in vitro* methods (BCOP)	Not irritating	Yes
Skin irritation – *in vitro* method (EpiDermal)	Not irritating	Yes
Inhalation LC_{50}, 4 hr	> 5.11 mg/L air - No clinical signs or mortality were observed.	Yes
Sensitization –LLNA, mice	Not a sensitizer	Yes

* based on data from studies on compositionally similar polymers

Subacute and Subchronic Inhalation

Test/Species	Results	GLP
Inhalation, 2-week study, nose only aerosol exposure in rat	No signs of clinical toxicity observed at any dose. No-Observed-Effect-Concentration (NOEC) was 10.8 mg polymer solids/M^3 based on slight irritant effects of the lungs at 100 mg/M^3.	Yes
Inhalation, 13-week study – nose only aerosol exposure In rat	No-Observable Adverse-Effect Level (NOAEL) for the changes in lung (and related lymph nodes) was 8.3 mg/M3	Yes

Genetic Toxicity Profile

Test/Species	Results	GLP
Bacterial Reverse Mutation Assay (Ames Test)	Not mutagenic	Yes
In vitro Chromosomal Aberration Test	Not mutagenic	Yes

Human Dermatological Studies

No dermatological studies (i.e., HRIPT, photo-toxicity or photo-allergy) have been conducted with ACUDYNE™ BOLD Polymer. However, previous studies with other acrylic polymers have produced no evidence of irritation or sensitization in human dermatological studies.

Ecotoxicity Profile

ACUDYNE™ BOLD Polymer was tested in a battery of aquatic studies and produced minimal to no toxicity.

Test/Species	Results	GLP
Fish LC_{50} -96 hr	LC_{50} > 1000 mg product/L	Yes
Daphnia magna EC_{50} – 48 hr	LC_{50} > 1000 mg product/L	Yes
Algal EC_{50} – 72 hr	LC_{50} > 1000 mg product/L	Yes

Biodegradation

The co-polymer would not be considered as readily biodegradable, but is likely bio-eliminable to some extent (removed via adsorption to sediment, suspended solids and organic matter wherein the polymer would more slowly degrade over time). ACUDYNE™ BOLD Polymer is not likely to bioconcentrate (accumulate in the food chain) because of its relatively high molecular weight.

Animal Testing Statement

Validated animal alternatives, where possible, were used to avoid testing in animals. In the case of some endpoints (e.g., delayed contact sensitization), validated alternatives to animal testing do not exist; and limited animal studies were performed to evaluate safe handling of ACUDYNE™ BOLD Polymer and/or to meet other non-EU regulatory requirements. The animal testing was not performed in order to fulfill the requirements of EU Cosmetics Regulation 1223/2009.

David J. Randazzo
Product Steward
Home and Personal Care
The Dow Chemical Company
Tel: 215-641-7265
Fax: 215-619-1654
E-mail: DRandazzo@dow.com

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7

Final Report on the Safety Assessment of Polyvinylpyrrolidone/ Vinyl Acetate Copolymer

Polyvinylpyrrolidone/Vinyl Acetate Copolymer (PVP/VA Copolymer) is the copolymer of vinyl pyrrolidone (VP) and vinyl acetate (VA) monomers. The ingredient is used primarily in hair care products and secondly in skin and nail products.

Acute oral toxicity studies on mice and rats showed low to no toxicity. Chronic oral and inhalation studies produced no effects. The acute ocular irritation of PVP/VA Copolymer at concentrations ranging from 25% to 50% in alcohol produced no reaction to severe irritation. Acute skin irritation studies of 50% PVP/VA Copolymer in alcohol on abraded and intact skin produced mild skin irritation. PVP/VA Copolymer was not a sensitizer to guinea pigs after intracutaneous injections. Formulations containing 1.75%, 4.0%, and 5.0% PVP/VA Copolymer produced no irritation in 24-hour clinical patch tests nor any evidence of sensitization in a repeated insult patch test at a concentration of 5.0%.

On the basis of the available information, it is concluded that Polyvinylpyrrolidone/Vinyl Acetate Copolymer is safe as a cosmetic ingredient under present conditions of concentration and use.

CHEMICAL AND PHYSICAL PROPERTIES

Structure/Composition

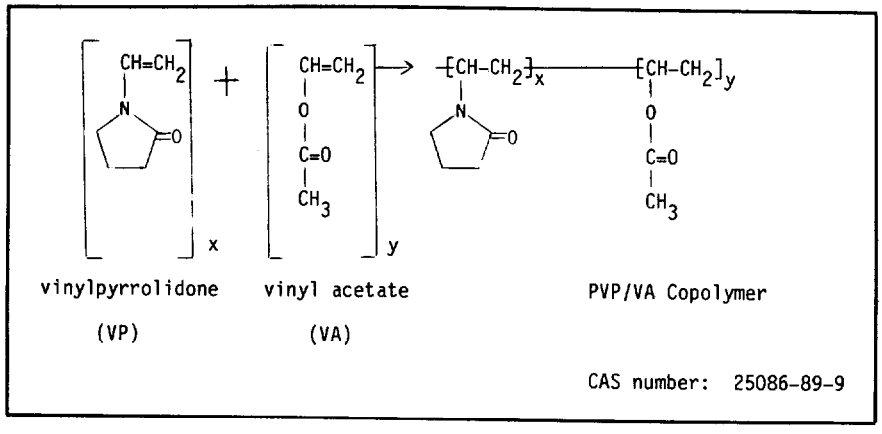
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (PVP/VA Copolymer) is the copolymer of vinyl pyrrolidone (VP) and vinyl acetate (VA) monomers.[1] The copolymers vary in their ratio of VP to VA and range from 70:30 to 30:70 VP to VA.[2]

Production

PVP/VA Copolymer can be prepared by free radical polymerization in ethyl alcohol: some monomer(s) is added to the ethyl alcohol solvent, a free-radical initiator (an azo or peroxide compound) is added to catalyze the formation of the additional polymer, and the remaining monomer(s) is added at a rate to control

the polymerization and to obtain the desired end product.[3] Emulsion polymerization using various catalysts is an additional method of preparation.[4] Another, but commercially unimportant, production method combines solutions of vinyl acetate and vinyl pyrrolidone varying between 0.1 and 0.9 *M*. These solutions are irradiated with a Cobalt-60 source at dose rates of 1,965 and 35,600 rads/min., and copolymerization occurs at a constant temperature of 5°C.[5]

The equation for the production of PVP/VA Copolymer is as follows:[2,3]



Properties

PVP/VA Copolymer has properties similar to those of the PVP monomer. It is a white, free-flowing amorphous powder, dispersible in water and soluble in organic solvents.[3,6,7] PVP/VA Copolymers are supplied in 100% concentration as a powder and diluted to 50 ± 2% in either 95% ethanol or isopropanol. The specific gravity at 25°C is 1.27 ± 0.01 for the powder and 0.955 ± 0.01 for the alcohol solutions. These copolymers are stable for at least one year under normal conditions of storage but readily absorb atmospheric moisture. Films of the copolymers are permeable to air. Photospectroanalysis revealed that PVP/VA Copolymers do not absorb energy in the UVA, UVB, or visible light spectrum.[2,3,7-9] See Table 1.

Analytical Methods

Trace amounts of PVP/VA Copolymers can be determined with colorimetric-chromatographic methods. Samples are treated with various dyes that complex with the PVP and are then passed through a chromatographic column; PVP is absorbed at the top as a colored band. This method can determine as little as 0.1 ppm copolymer.[10]

The impurities in PVP/VA Copolymer may be determined with the following methods: Kjeldahl or Dumas method for nitrogen; USP method for arsenic; Fischer method for moisture content of solid copolymers; Cenco moisture balance method for moisture content in solutions; Standard Iodometric titration for determination of residual monomers, and spectrographic emission for heavy metal determination.[3,4]

TABLE 1. Chemical and Physical Properties of PVP/VA Copolymer.[a]

Properties	*Values*
Physical form	White powder; clear liquid in solution
Vehicles	Ethanol; isopropanol
Residual vinyl pyrrolidone	0.5% max
Residual vinyl acetate	1.0% max
Specific gravity	1.27 ± 0.01 (solid) 0.955 ± 0.01 (alcohol solution)
Soluble in:	Alcohols Ether alcohols Ketone alcohols Butyrolactone Triethanolamine Aromatic hydrocarbons Esters Water (partially)
Odor	Slight and characteristic

[a]Data from Ref. 7.

Impurities

The impurities in PVP/VA Copolymer are the residual, uncombined monomers, vinyl acetate (1.0% max), vinyl pyrrolidone (0.5% max), and moisture (0.5% max).[2,3,7]

USE

Noncosmetic Uses

PVP/VA Copolymer is used in tablet coating, spray bandages, protective masks, spray or rub-on gloves, plant leaf sprays, shoe polishes, and film production; it is also used as a dye medium in adhesive sticks and in the synthesis of peptides.[3,7,10-13]

Cosmetic Uses

Industry's voluntary submission of cosmetic product formulation data to the Food and Drug Administration (FDA) lists PVP/VA Copolymer in 114 formulations.[14] The 1979 FDA list includes PVP/VA Copolymer in 133 formulations.[15]

The cosmetic product formulation computer printout which is made available by the FDA is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[16] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value 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 submitted only 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 tenfold error in the assumed ingredient concentration.

Purpose in Cosmetics

PVP/VA Copolymer is the hair-holding ingredient in hair sprays, hairsets and conditioners, hair dressings, and wave lotions.[4,6]

PVP/VA Copolymer is used in eye and facial makeup preparations in concentrations of >0.1% to 5%. In manicuring and skin care preparations, it is used from >1% to 5%, and in hair care preparations, from >0.1% to 50%.[14] See Table 2.

PVP/VA Copolymer may be applied several times a day in facial makeup or a few times yearly as in permanent wave products. The material may stay in contact with the body from minutes, as in shampoos, to several days, as in hair sprays and grooming aids.[14]

PVP/VA Copolymer may come in contact with the eyes, the skin of the hands and face, the scalp, the hair, and the nails. Since it can be dispersed in aerosols, PVP/VA Copolymer may also come in contact with the respiratory mucosa.

Potential Interactions with Other Ingredients

PVP/VA Copolymers are compatible with water, common propellants, and with many plasticizers and polymers.[7] No information was available on interactions of the copolymer with other cosmetic ingredients.

BIOLOGICAL PROPERTIES

General Studies

Storage and Excretion

PVP/VA Copolymer storage in the body was studied in 30 female Wistar rats by injecting it under the skin of the back. Up to seven daily 2 ml doses of solution containing 10 g of solid copolymer in 15 ml of physiological saline were given. Animals were sacrificed between 1 and 365 days later, and tissues were examined. Most of the copolymer was found in the spleen, and repeated injections caused up to an 80% increase in splenic weight. Two to three days after treatment, large reticular cells were found in the spleen; later, similar but vacuolated cells were found. There were macrophages in the follicular germinal center. After one to six months, copolymer-containing macrophages decreased in size and number and often showed an iron-positive reaction. Large vacuolated cells were also present in the portal regions of the liver lobes. The podocytes of the kidney

TABLE 2. Product Formulation Data.[a]

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]							
		Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Mascara	2	–	–	–	–	–	2	–	–
Hair conditioners	17	–	–	1	1	7	8	–	–
Hair sprays (aerosol fixatives)	27	–	–	–	–	2	19	6	–
Permanent waves	1	–	–	–	–	–	–	1	–
Hair shampoos (noncoloring)	2	–	–	1	–	–	–	1	–
Tonics, dressings, and other hair grooming aids	6	–	–	–	1	1	2	2	–
Wave sets	50	–	2	4	2	12	16	14	–
Other hair preparations (noncoloring)	4	–	–	–	3	1	–	–	–
Hair bleaches	1	–	–	–	–	–	1	–	–
Makeup fixatives	1	–	–	–	–	–	–	1	–
Other makeup preparations (not eye)	1	–	–	–	–	–	–	1	–
Cuticle softeners	1	–	–	–	–	–	1	–	–
Skin care preparations	1	–	–	–	–	–	1	–	–
1976 TOTALS	114	0	2	6	7	23	50	26	0
1979 TOTALS[c]	133	48	1	5	2	19	38	19	1

[a]Data from Ref. 14.
[b]Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).
[c]Data from Ref. 15.

glomeruli contained PVP/VA, and some kidney specimens showed large aggregates of foam cells. Some PVP/VA seemed to be stored in epithelial cells and lymphatics of the testes. There were no inflammatory changes in any of the tissues. Some reticular cells in bone marrow and lymph nodes showed PVP/VA Copolymer storage, and large macrophages were found in the interstitial tissue of the lungs. After 12 months, there was no evidence of tumors or systemic disease related to administration of the compound. The author reported that one-half hour after a single subcutaneous 2 ml dose was administered, a color reaction was induced in the urine by a KJ_3-solution; this indicated that PVP/VA was in the urine. Maximum excretion occurred one and one-half hours after injection.[17]

Animal Toxicology

Acute

Oral

The acute oral toxicity of PVP/VA Copolymer in aqueous alcohol solutions and in formulations has been studied. The results are tabulated in Table 3 and summarized as follows:

Five lots of 50% PVP/VA Copolymer in alcohol were tested in albino rats. One sample was tested at the 50% concentration and four at 25% (w/v) aqueous suspensions (final concentrations were 12.5%). In these four tests on the 12.5% copolymer, 5 g/kg of the material were administered by gastric intubation into ten young, fasted albino rats per solution. During the following 14 days, the animals showed decreased activity and ataxia for an unspecified length of time, but none died. These results show that the test solutions are slightly toxic according to the classification of Hodge and Sterner.[18-22] A dose of 5 ml/kg (4.78 g/kg) of the 50% solution administered orally by stomach tube caused piloerection in some of the six rats. None of the animals died, and necropsy examinations showed no pathology. This solution is also practically nontoxic.[23] See Table 3.

Five product formulations containing actual concentrations of 0.25% (setting lotion), 0.5% (setting lotion), 1.75% (mascara), 4.0% (setting lotion), and 24% (setting lotion) PVP/VA Copolymer in doses of 5.0–15 g/kg were administered orally by stomach tube to groups of Sherman–Wistar and Sprague–Dawley albino rats. Two out of five animals died after administration of the hair setting formulation containing 4.0% PVP/VA Copolymer in a 15 g/kg dose; none of the surviving rats showed signs of toxicity during the 7- to 13-day observations periods. None of the other formulations produced toxicity.[24-28] See Table 3.

Ocular

Formulations and solutions containing PVP/VA Copolymer were studied for acute ocular toxicity. These studies are detailed below and summarized in Table 4.

A Draize eye irritation test of a 50% alcohol solution of PVP/VA Copolymer was conducted on six rabbits. This same solution was then diluted in petrolatum to 75% and 50% of its original concentration (actual concentration of copolymer was 37.5% and 25%) and tested on rabbits. A 0.1 ml volume of each solution was instilled into one eye of each of six animals with no rinse. Observations, made for

TABLE 3. Acute Oral Toxicity PVP/VA Copolymer.

Ingredient conc. (%)	Dose/kg	Tested in	Species and number of animals	LD50 (g/kg) Formulation or solution	LD50 (g/kg) Ingredient (as PVP/VA)	No. dead	Days of observation	Comments	Ref.
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	19
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	20
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	21
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	22
50	5 ml 4.78 g)	50% alcohol solution	Albino rats–6	>5 ml	>2.5 ml	0	–	Piloerection; necropsy not remarkable	23
0.25	5 g	formulation –setting lotion	Sherman-Wistar albino rats–10	–	–	0	14	No signs of toxicity.	24
0.5	5 g	formulation –setting lotion	Sherman-Wistar albino rats–10	–	–	0	14	No signs of toxicity.	25
1.75	15 g	formulation –mascara	Albino rats–5	–	–	0	7	No signs of toxicity.	26
4.0	15 g	formulation –setting lotion	Albino rats–5	–	–	2	7	2 deaths. All other animals appeared normal with no signs of toxicity.	27
24	15 g	formulation –setting lotion	Sprague-Dawley rats 5–10	–	–	–	–	LD50 not reached.	28

TABLE 4. Eye Irritation PVP/VA Copolymer.

Ingredient conc. (%)	*Dose (ml)*	*Tested in*	*Number of albino rabbits*	*Days of observation*	*Greatest irritation score/110 (max)*	*Comments*	*Ref.*
25	0.1	solution of alcohol and petrolatum	6	7	14(max)	Minimal irritation at day 1; effect disappeared by day 7.	23
37.5	0.1	solution of alcohol and petrolatum	6	7	23(max)	Mildly irritating on day 1; effect disappeared by day 7.	23
50	0.1	solution of alcohol	6	7	30(max)	Moderate irritation on day 1; Minimal irritation by day 7.	23
50	0.1	alcohol solution	9	7	NW[a] 43(max) W[b] 33(max)	Moderately irritating with and without wash. Some irritation lasted through 7 days.	29
50	0.1	alcohol solution	9	7	NW 43(max) W 26(max)	Moderately irritating with and without wash. Some irritation lasted through 7 days.	30
50	0.1	alcohol solution	9	7	NW 63(max)	Severely irritating. Some lasted through day 7.	31
					W 29(max)	Moderately irritating. Some effects lasted through day 7.	
50	0.1	alcohol solution	9	7	NW 16(max)	Corneal and conjunctival involvement.	
					W 10(max) (2 sec)	No reaction to conjunctival involvement. Clear by day 3.	32
					W 10(max) (4 sec)	No reaction to conjunctival involvement. Clear by day 3.	
0.25	0.1	formulation setting lotion	6	7	0	No irritation.	33
0.5	0.1	formulation setting lotion	6	7	0	No irritation.	34
1.75	0.1	formulation mascara	6	7	1	Practically nonirritating.	35
4.0	0.1	formulation setting lotion	6	7	W 3 NW 26	Minimally irritating. Moderately irritating.	27
2.4	–	formulation setting lotion	3	2	–	Conjunctival irritation which cleared by day 2.	28
24	–	formulation setting lotion	3	2	–	Conjunctival irritation which cleared by day 2.	28

[a]No wash.
[b]Wash.

seven days, were scored according to the Draize method (maximum irritation score = 110). The 25% solution of PVP/VA in petrolatum was minimally irritating on the first observation day, and irritation disappeared by day 7. The 37.5% solution was mildly irritating on day 1 and practically nonirritating on day 7. The 50% solution in alcohol produced moderate irritation on day 1 and minimal irritation on day 7.[23]

A 50% solution of PVP/VA Copolymer in alcohol was tested for ocular irritation by the Draize method in three different studies. One eye of each of nine rabbits was instilled with 0.1 ml of solution; the other eye was used as control. In three out of nine animals, the eye was washed four seconds after instillation, and observations were made for seven days. Moderate irritation occurred in unwashed eyes instilled with two of the 50% test solutions, and severe irritation was produced by the third solution when not washed out. Eyes irrigated after four seconds were moderately irritated. In most animals, irritation persisted throughout the seven days.[29-31]

Another test of 50% PVP/VA Copolymer in alcohol was performed on nine rabbits. One eye of each animal was instilled with 0.1 ml of solution. The eyes of three were washed two seconds after instillation, and a second group of three underwent a washout after four seconds. Observations were made for seven days. The three eyes that remained unwashed had some conjunctivitis for a maximum of six days. Eyes washed after two and four seconds showed some conjunctivitis for three days.[32]

Five product formulations containing PVP/VA Copolymer were tested for acute ocular irritation in rabbits. One setting lotion product containing 0.25% and another containing 0.5% PVP/VA were tested according to 16 CFR 1500.42. A 0.1 g sample of each solution was instilled into the right eye of each of six albino rabbits without rinse. No irritation occurred from either product at 1, 24, 48, and 72 hours and five and seven days after instillation.[33,34] One mascara formulation with 1.75% PVP/VA Copolymer and a setting lotion with 4.0% of the copolymer were tested according to a modified Draize method on six albino rabbits. A 0.1 ml volume of each full strength formulation was instilled into one eye of each rabbit per formulation. The eyes receiving the 1.75% concentration were not washed, and those of three rabbits instilled with the 4.0% concentration were rinsed four seconds after instillation. The 1.75% formulation was practically nonirritating.[35] The setting lotion containing 4.0% PVP/VA Copolymer, when washed, was minimally irritating on the first observation day, and the irritation cleared thereafter; the unwashed eyes had mild to moderate irritation on the first three observation days. The product was practically nonirritating on the fourth and seventh day.[27] A hair setting formulation containing 24% PVP/VA Copolymer was tested at full strength and at 10% concentration (2.4% of the Copolymer), on three New Zealand rabbits per concentration. One eye of each rabbit was instilled with 0.1 ml of solution. Both concentrations caused conjunctival irritation; the full strength product caused more severe irritation. There was no irritation by the second observation day.[28]

Skin Irritation

PVP/VA Copolymer, in alcohol solution and in formulation, was tested for

acute skin irritation. In general, the tests produced minimal to no irritation; the studies are detailed below and summarized in Table 5.

Four 50% solutions of PVP/VA Copolymer in alcohol and one solid 100% concentration were each applied to the backs of six albino rabbits. In one test, three repeated applications of the 50% solution caused definite erythema in five of six animals.[23] The remaining three 50% solutions were each applied in 0.5 ml (approximately 0.5 g) volumes under occlusive patching to the clipped abraded and intact skin of the rabbits. The patches were removed after 24 hours and the sites graded according to the Draize method, 24 and 72 hours after application. The solutions were mildly to moderately irritating.[36-38]

A primary dermal irritation test of solid, 100% PVP/VA Copolymer on six albino rabbits produced no irritation.[39]

Five formulations containing varying concentrations of PVP/VA Copolymer were tested for primary skin irritation on rabbits. Of these, one hair setting lotion containing 0.25% PVP/VA Copolymer and another setting lotion having 0.50% copolymer were each applied in 0.5 g amounts under occlusive dressing to the clipped intact and abraded skin of six albino rabbits and allowed to remain for 24 hours. The sites were scored 24 and 72 hours after application. According to the Draize method, neither product produced irritation.[40,41]

A hair conditioner formulation containing 1.5% PVP/VA Copolymer was tested on the abraded and intact skin of three rabbits. The 0.5 ml volume of test

TABLE 5. PVP/VA Copolymer Skin Irritation.

Ingredient conc. (%)	*Dose*	*Tested in*	*Number of albino rabbits*	*Hours of observation time*	*Irritation score/8.0 (max)*	*Comments*	*Ref.*
50	–	alcohol solution	6	72	–	5 of 6 animals showed definite erythema.	23
50	0.5 g	alcohol solution	6	72	1.71	Mildly irritating	36
50	0.5 g	alcohol solution	6	72	2.5	Mildly irritating	37
50	0.5 g	alcohol solution	6	72	2.54	Mildly irritating	38
100	0.5 g	solid	6	72	0.0	No irritation	39
0.25	0.5 g	formulation setting lotion	6	72	0.0	No irritation	40
0.50	0.5 g	formulation setting lotion	6	72	0.0	No irritation	41
1.50	0.5 ml	formulation hair conditioner	3	72	0.0	No irritation	42
1.75	0.5 ml	formulation mascara	9	48	0.61	Potential for minimal irritation	43
4.0	0.5 ml	formulation setting lotion	9	48	0.0	No irritation	44

material was applied under occlusion, and readings were taken 24 and 72 hours after application. The product caused no irritation.[42]

A mascara and a hair setting formulation containing 1.75% and 4.0% PVP/VA Copolymer, respectively, were tested by a modified Draize method. A 0.1 ml volume of each formulation was applied under occlusion to the shaved skin of nine albino rabbits for 24 hours. Sites were read 2 and 24 hours after patch removal. The mascara caused minimal irritation,[43] and the hair setting lotion caused no irritation.[44]

Sensitization Reaction

The skin sensitization potential of PVP/VA Copolymer in a product formulation was studied. A hair conditioner containing 1.5% PVP/VA Copolymer was diluted in physiological saline to make the actual copolymer concentration 0.015%; this was injected intradermally into eight guinea pigs. A 4 cm^2 area of skin was clipped, and injections were given every other day, the first at a dose of 0.05 ml and the nine subsequently at 0.2 ml each. A 0.05 ml injection was administered two weeks after the last injection, and the skin was inspected 24 hours after each injection. The material was nonsensitizing to the guinea pigs.[45]

Endotracheal Injection

The storage of PVP/VA Copolymer in the lungs and other body organs was studied in 20 female Wistar rats. The animals were given single or an unspecified number of repeated endotracheal applications of 0.5 ml of a solution containing 10 g polymer in 15 ml of physiological saline solution. Fifteen control animals received physiological saline in similar doses. The animals were sacrificed between 1 and 365 days later, and tissues were examined. There were no signs of pneumonia, bronchitis, or bronchiolitis one or two days after injection. All pulmonary alveoli were closely packed with macrophages. After six days there were numerous large macrophages in the pulmonary interstitial tissues and particularly in the peribronchial and perivascular lymphatics. Macrophages were found in the lymph nodes of the hilar and tracheal regions. Four to six months after the last injection, lungs still contained PVP/VA Copolymer, predominantly in the macrophages in the alveoli near the bronchi and vessels and in the fibrous septae. Animals sacrificed one year after administration did not show further accumulation of storage cells in the lung. No copolymer was found in the liver, kidneys, and bone marrow of animals that had been treated repeatedly, but some was found in solitary or grouped storage cells in the spleen. There was no acute inflammatory reaction, and control animals showed no abnormalities.[17]

Inhalation

In an acute inhalation study, Draize et al.[46] exposed five rabbits to 30-second spray releases of an aerosol product containing 1.72% PVP/VA Copolymer. The sprayings were released every half hour until the contents of the container were exhausted, but the investigators did not report the duration of the exposure. Each 30-second spray released approximately 30 g of material. The animals were inspected during exposure and during the next four days; they were then sacrificed for gross and histopathological examination. The tissues and behavior of the animals during and after inhalation were normal.

Subchronic

Dermal Toxicity

A hair product containing 1% PVP/VA Copolymer was tested in a six-week subchronic dermal toxicity study on 50 albino rats. Volumes of 2.0 ml/kg of the product were applied five days a week for six weeks for a total of 30 applications to the clipped skin of the animals. All rats survived, and their body weight, physical appearance, behavior, and gross and microscopic anatomy were normal. No systemic toxic effects could be attributed to the test material.[47]

Inhalation Toxicity

Rats and hamsters were exposed for 13 weeks to a spray containing 4.0% PVP/VA Copolymer. Each of three groups comprised of 12 rats and 12 hamsters per group inhaled the spray for four hours per day, five days per week for 13 weeks in doses of 5.4 mg/m^3 (calculated to be the equivalent of one hundred times the normal human use level of the product). No gross or microscopic changes occurred that could be attributed to the test material. Lungs and other tissues were similar in control and tested animals.[48]

Chronic

Oral

White mice and rats were given daily in their drinking water an aqueous 10.2 mg/l solution of PVP/VA Copolymer for one year. Each mouse ingested an average of 2–3 ml per day and 650 ml for the duration of the experiment, and each rat ingested 15–20 ml per 24 hours and 4140 ml for the year. There were no changes attributable to the copolymer in either mice or rats. Furthermore, there were no histological changes in the internal organs.[49]

Inhalation

Mokler et al.[50] conducted a chronic study of hair spray aerosols containing high and low concentrations of PVP/VA Copolymer. Thirty-six male and 36 female Syrian hamsters were exposed to the low concentration of 0.08 ± 0.08 mg/l PVP/VA in air, 4–32 minutes a day, once a week for up to two years. The high-level group consisted of 36 male and 36 female hamsters exposed to 0.35 ± 0.09 mg/l, 9–35 minutes a day, once a week for up to two years. A similar group of 36 males and 36 females was exposed to air as a control. All animals were repeatedly exposed by inhalation until they were sacrificed. Six males and six females from each group were sacrificed at three, six, and nine months. This assured that at least 12 animals (six male, six female) were available for study at each time period and that 36 animals were available for long-term (2-year) study. Necropsies were performed on all that were sacrificed or that died spontaneously. Survival time, body weight, and weight and appearance of lungs were similar in control and aerosol-exposed animals.

Draize et al.[46] exposed five rabbits to a spray formulation containing 1.72% PVP/VA Copolymer. During the 90-day test, the animals received one 30-second exposure each morning and afternoon and were left in the spray atmosphere for 15 minutes. The animals remained normal during the entire study; radiographs of the chest and upper body and hematological tests remained normal.

Special Studies

Mutagenicity

The residual monomers of PVP/VA Copolymer, vinyl acetate and vinyl pyrrolidone, found at 1.0% and 0.5%, respectively, have been tested for their mutagenic potential. *Salmonella typhimurium* strains TA100, TA98, TA1530, TA1535, and TA1537 were exposed to vinyl acetate. No mutagenic effects were detected when the organisms were exposed to the chemical with and without the addition of rat liver metabolic activation preparation.[51-55]

Vinyl pyrrolidone was tested for mutagenicity in three different assays. In the Mouse Lymphoma Assay, concentrations of up to 5.0 μl/ml vinyl pyrrolidone did not induce a significant change in mutant frequency at the TK locus in L5178Y cells in the presence or absence of rat liver S-9 microsomal activation.[56] In the Balb/3T3 in vitro transformation assay, vinyl pyrrolidone did not induce a significant increase in transformed foci over the applied concentration range of 0.1–0.5 μl/ml. This concentration range produced 83%–52.3% survival in the cytotoxicity test, and the material was considered to be mutagenically inactive.[57] In the primary rat hepatocyte unscheduled DNA synthesis (UDS) assay, vinyl pyrrolidone did not induce detectible UDS in primary rat hepatocytes over an applied concentration range of 0.284–9.09 μl/ml. This concentration range produced a cell survival rate of 84.5%–6.2% 24 hours after treatment; whereas, exposure to 18.2 μl/ml was completely lethal. The material was considered to be inactive in producing UDS in this assay.[58]

Polyvinyl pyrrolidone polymers including PVP/VA Copolymers have been deleted from the list of 39 priority chemicals selected for testing by the National Toxicology Program (NTP) in June 1980. According to NTP, adequate screening toxicity testing data have been reported in the literature.[59]

Carcinogenicity

No carcinogenicity studies have been reported on PVP/VA Copolymer. IARC has noted the subcutaneous tumorigenic activity of PVP in animals. Despite this fact, NTP has deleted it from its list of chemicals selected for testing.[59,60] Vinyl Acetate, a residual monomer impurity in PVP/VA Copolymer, was used as a comparative compound in a carcinogenicity assay of vinyl chloride. Ninety-six Sprague–Dawley rats were exposed four hours per day, five days per week, for 52 weeks to vapor concentrations of 8.8 g/m^3 (2500 ppm) vinyl acetate in air. No tumors occurred after 135 weeks; however, only 49 animals survived longer than 26 weeks.[55,60-64]

Clinical Assessment of Safety

The human clinical studies of PVP/VA Copolymer are summarized in Table 6.

Patch Testing

A dose of 0.1 ml of 5.0% solution of PVP/VA Copolymer in alcohol was applied in a single occlusive 24-hour patch to either the forearms or upper arms of 20 individuals without causing a reaction.[65]

A dose of 0.1 ml of mascara containing 1.75% PVP/VA Copolymer was applied in a single, full strength occlusive 24-hour patch to either the forearms or

TABLE 6. PVP/VA Copolymer Human Clinical Data.

Test							
Ingred. conc. (%)	*Dose/ml*	*Tested in*	*No. of subjects*	*No. of test days*	*Irritation max*	*Comments*	*Ref.*
24-Hour occlusive patch							
5.0	–	solution	20	1	0.0	No irritation	65
1.75	0.1	mascara formulation	18	1	0.0	No irritation	66
4.0	0.1	setting lotion formulation	20	1	0.0	No irritation	67
Repeated insult patch test							
50	–	solution	50	15	0.0	No reactions on abraded or intact skin	68
50	0.15	solution	150	34	–	No irritation or sensitization	69
50	0.15	solution	150	34	–	No irritation or sensitization	
5	0.4	hair spray formulation	51	24	0.0	No irritation	70

the upper arms of 18 subjects. No irritation occurred.[66] Similar patch tests of hair setting lotion containing 4.0% PVP/VA on 20 individuals caused no irritation.[67]

Repeated Insult Patch Test

A 50% solution of PVP/VA Copolymer in alcohol was tested in a repeated insult patch test on 50 subjects. Abraded and intact sites were used on each person for a total of 15 patches per person according to the procedure of Shelanski and Shelanski.[71] No irritation occurred in either intact or abraded skin, and the investigators concluded that the compound is neither a primary irritant nor a sensitizer and is not a fatiguing agent.[68]

Two samples of 50% PVP/VA Copolymer in alcohol were each tested on 150 subjects according to the Draize–Shelanski patch technique under semiocclusion. Volumes of 0.15 ml were applied to the upper backs for nine induction patches within a period of 21 days. Patches were removed after 24 hours and sites scored. After a ten-day rest period, a challenge patch was applied for 24 hours to an adjacent site and scored immediately after patch removal and again after two and three days. The first of the two samples produced moderate irritation in five subjects and mild irritation in two subjects during induction. The second sample produced slight irritation in three subjects. These reactions were categorized as singular, random occurrences, and there was no evidence of skin irritation or sensitization following the challenge application.[69]

A hair spray formulation containing approximately 5% PVP/VA Copolymer was tested on 51 black people. The material was applied to the upper arms under occlusion, each Monday, Wednesday, and Friday for 9–24 hours. Patch sites were scored immediately after each patch removal. The product was found to be essentially nonirritating.[70]

Thesaurosis and Epidemiological Studies

PVP/VA Copolymer is one of several resins used in hair spray formulations.[2] Whether these hair spray polymers cause "thesaurosis," a unique pulmonary disorder caused by the accumulation and storage of polymers on the pulmonary epithelium, has been disputed for over 20 years. The potential occurrence of thesaurosis owing to such storage was considered and discounted in a previous literature review prepared by the Cosmetic Ingredient Review.[72]

DISCUSSION

The animal toxicity studies on PVP/VA Copolymer alone and in cosmetic formulations are adequate; the ingredient causes little to no irritation. Studies on the ingredient in alcohol solution have shown slight oral toxicity, substantial eye irritation, and mild skin irritation. However, since assays with powdered 100% PVP/VA Copolymer elicit no deleterious dermatological effects, the irritation caused by the solution is due to the alcohol. Although data are not available on animal and human phototoxicity and photoallergenicity, photoabsorption curves show that PVP/VA Copolymer does not absorb radiant energy in the UVA, UVB, or visible light spectra. Absence of absorption in these ranges makes it unlikely that the ingredient has photosensitivity potential. Furthermore, there are no reports in the literature of photodermatological disorders from the use of this copolymer.

Epidemiological surveys of cosmetologists who routinely work in an environment containing high concentrations of respirable copolymers have shown no adverse effects from exposure to these ingredients. It appears that when properly used, the copolymer in these products should be of minimal risk to the general public.

SUMMARY

Polyvinylpyrrolidone/Vinyl Acetate Copolymer (PVP/VA Copolymer) is the copolymer of vinyl pyrrolidone (VP) and vinyl acetate (VA) monomers; it is prepared by free radical polymerization in ethyl alcohol. The molecular weight of the copolymer varies directly with both the ratio of VP to VA in the molecule and with the length of the polymer chain. PVP/VA Copolymer is supplied either in 100% concentration as a powder, which is partially soluble in water and soluble in organic solvents, or as a 50% solution in alcohol. This copolymer does not absorb energy over the UVA, UVB, or visible light spectrum. In cosmetics, PVP/VA Copolymer is used primarily in hair sprays and other hair products and

secondarily in skin and nail products. Noncosmetic uses include applications in adhesives and films.

Acute oral toxicity studies were performed with PVP/VA Copolymer in formulation and in solutions of the raw ingredient. Tests on mice and rats showed low to no toxicity on more than 76 animals. Two animals died from administration of a formulation containing other, unidentified ingredients. The survivors showed, at most, decreased activity and ataxia at maximum doses of 5 g/kg of a solution containing 12.5% PVP/VA Copolymer.

The acute ocular irritation of PVP/VA Copolymer, as supplied, and in formulation, was tested on albino rabbits. Solutions of 25%–50% PVP/VA in alcohol produced no reaction to severe irritation. Formulations containing 2.5%–24% PVP/VA also produced no reaction or moderate irritation.

Acute skin irritation studies of PVP/VA Copolymer were conducted on the abraded and intact skin of rabbits. Formulations containing 0.25%–4.0% PVP/VA Copolymer produced mild irritation. Solutions of 50% PVP/VA in alcohol produced mild irritation, and one sample of the 100% powder moistened in water produced no irritation.

PVP/VA (10 g in 15 ml of saline) was administered repeatedly in 0.5 ml doses to rats by endotracheal injection. The animals were sacrificed at different times for up to one year later. PVP/VA Copolymer was found in the lung, primarily in alveoli and in the spleen, although no inflammation was found.

After subcutaneous injection, PVP/VA Copolymer was stored in the spleen, the liver, kidneys, lung, and bone marrow. Some of the copolymer was excreted in the urine.

PVP/VA Copolymer was not a sensitizer to guinea pigs after intracutaneous injection. No irritation or systemic effects occurred when 30 subchronic dermal applications of 1% PVP/VA Copolymer in formulation were given to rats. Subchronic inhalation of 4.0% PVP/VA in a spray by rats and hamsters caused no abnormalities.

Chronic oral ingestion of a solution containing 10.2 mg/l of PVP/VA Copolymer produced no effects in mice or rats. Likewise, chronic inhalation of aerosols containing 1.72%, 0.08 ± 0.08 mg/l, and 0.35 ± 0.09 mg/l for three months to two years produced no effects in rabbits and hamsters.

Polyvinyl Pyrrolidone polymers were deleted from the list of 39 priority chemicals selected for testing by NTP in 1980 because "adequate toxicity data exist in the literature." PVP/VA Copolymers may contain the residual monomers, vinyl acetate at 1.0%, and vinyl pyrrolidone at 0.5%. In a test using *S. typhimurium,* with and without metabolic activation, vinyl acetate was nonmutagenic. Vinyl pyrrolidone was nonmutagenic in the Mouse Lymphoma assay, the Balb/3T3 in vitro transformation assay, and in the primary rat hepatocyte unscheduled DNA synthesis assay.

Vinyl acetate was not carcinogenic to rats when they were exposed to its vapor for one year.

PVP/VA Copolymer was tested in human clinical studies. Formulations containing 1.75%, 4.0%, and 5.0% PVP/VA Copolymer produced no irritation in 24-hour patch tests. Repeated insult patch tests of a 5.0% formulation of PVP/VA Copolymer caused no irritation or sensitization in 50 subjects. Likewise, three

solutions of 50% PVP/VA Copolymer in alcohol caused no irritation in 150 subjects. No photosensitization data were available for review, but the UV absorption characteristics suggest that photosensitization is unlikely.

CONCLUSION

On the basis of the available information presented in this document, the Panel concludes that Polyvinylpyrrolidone/Vinyl Acetate Copolymer is safe as a cosmetic ingredient under present conditions of concentration and use.

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Annual Review of Cosmetic Ingredient Safety Assessments—2004/2005[1]

The Cosmetic Ingredient Review (CIR) program Expert Panel has assessed the safety of almost 1300 cosmetic ingredients since its inception in 1976 These safety assessments were published in the *Journal of Environmental Pathology and Toxicology* in 1980, the *Journal of the American College of Toxicology*, from 1982 to 1996, and since then in the *International Journal of Toxicology*

Because information relevant to the safety of ingredients may have become available since early safety assessments were published, the CIR Expert Panel has initiated a re-review process If new information is thought to be available or if a long period of time has passed, the CIR Expert Panel may initiate a search for relevant new data

In some cases, newly available data are largely redundant with the data available in the original safety assessment In other cases, there are new safety data If the CIR Expert Panel decides to not reopen a safety assessment, this finding is summarized and announced publicly To assure that the scientific community is aware of any new information and the decision to not reopen, this *Annual Review of Cosmetic Ingredient Safety Assessments* is prepared

A reference list is provided that updates the available published literature and includes any unpublished data made available since the original safety assessment The re-review also captures information on the industry's current practices of ingredient use, updating the data available in the earlier report Although this material provides the opinion of the CIR Expert Panel regarding the new data described, it does not constitute a full safety review

The ingredients the CIR Expert Panel reconsidered in 2004/2005, and decided not to reopen are

Benzethonium Chloride and Methylbenzethonium Chloride
2-Bromo-2-Nitropropane-1,3-Diol
Butylated Hydroxyanisole (BHA)
Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol
Cetearyl Octanoate (Ceteraryl Ethylhexanoate)
Cholesterol
Chloroxylenol
Diisopropanolamine, Isopropanolamine, Triisopropanolamine, and Mixed Isopropanolamines
Dioctyl Adipate and Diisopropyl Adipate
Formaldehyde
Hydrolyzed Collagen
p-Hydroxyanisole
Isostearyl Neopentanoate
2-Nitro-*p*-Phenylenediamine and 4-Nitro-*o*-Phenylenediamine
Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, Stearic Acid
Panthenol and Pantothenic Acid
p-Phenylenediamine
Phenyl Trimethicone
Propylene Carbonate
Propyl Gallate
Polyvinylpyrrolidone/Vinyl Acetate Copolymer
Safflower Oil
Sodium Borate and Boric Acid
Sodium Dehydroacetate and Dehydroacetic Acid
Sodium Lauryl Sulfoacetate
Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate
Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol
Toluene
Toluenesulfonamide/Formaldehyde Resin
Tragacanth Gum
Vinyl Acetate/Crotonic Acid Copolymer
Zinc Phenolsulfonate

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA

BENZETHONIUM CHLORIDE AND METHYLBENZETHONIUM CHLORIDE

A safety assessment of Benzethonium Chloride and Methylbenzethonium Chloride was published in 1985 with the conclusion that these ingredients are safe at concentrations of 0 5% in cosmetics applied to the skin, and up to 0 02% for cosmetics used in the eye area (Elder 1985). New studies, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

Benzethonium Chloride is a quaternary ammonium salt used as an antimicrobial agent, cosmetic biocide, deodorant

TABLE 1

Historical and current cosmetic product uses and concentrations for Benzethonium Chloride and historical uses of Methylbenzethonium Chloride

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
	Benzethonium Chloride			
Baby care*	1	—	>0 1–1	—
Bath*	1	—	≤0 1	—
Eye makeup				
Eyeliners	2	—	>0 1–1	—
Fragrances				
Colognes and toilet waters	6	—	>0 1–1	—
Perfumes	3	—	>0 1–1	—
Powders	1	—	>0 1–1	—
Noncoloring hair care				
Conditioners	2	—	>0 1–1	—
Sprays/aerosol fixatives	1	—	≤ 0 1	—
Rinses	3	—	≤0 1	—
Shampoos	1	—	>0 1–1	—
Tonics, dressings, etc	1	2	≤0 1	—
Wave sets	1	—	≤0 1	—
Other noncoloring hair care	2	3	≤0 1	—
Makeup				
Other makeup	—	—	—	0 03
Personal hygiene				
Underarm deodorants	11	6	≤0 1	0 05
Douches	7	1	>0 1–5	—
Feminine deodorants	3	1	≤0 1	—
Other personal hygiene	7	5	≤1	0 1–0 3
Shaving				
Aftershave lotions	2	3	≤0 1	—
Mens talcum	2	—	≤1	0 1
Preshave lotions	1	—	>0 1–1	—
Other	—	1	—	—
Skin care				
Cleansing creams, lotions, etc	5	2	≤1	0 2%
Face and neck skin care	7**	1	≤1**	—
Body and hand skin care		5		—
Foot powders and sprays	—	2	—	0 1
Moisturizers	2	1	≤0 1	≤0 1
Paste masks/mud packs	2	—	≤0 1	—
Skin fresheners	13	—	≤1	—
Other skin care	3	4	≤0 1	—
Suntan products				
Suntan gels, creams, liquids and sprays	2	2	≤0 1	—
Indoor tanning preparations	1	—	≤0 1	—
Total uses/ranges for Benzethonium Chloride	**93**	**39**	**≤5**	**0 03–0 3**
	Methylbenzethonium Chloride			
Baby Care				
Lotions, oils, powders, and creams	2	—	≤1	—

TABLE 1

Historical and current cosmetic product uses and concentrations for Benzethonium Chloride and historical uses of Methylbenzethonium Chloride *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Fragrances				
Colognes and toilet waters	1	—	≤0.1	—
Noncoloring hair care				
Conditioners	1	—	≤0.1	—
Sprays/aerosol fixatives	6	—	≤0.1	—
Personal hygiene				
Underarm deodorants	5	—	≤1	—
Douches	1	—	>0.1–1	—
Feminine deodorants	2	—	≤0.1	—
Other personal hygiene	1	—	≤0.1	—
Shaving				
Aftershave lotions	4	—	≤1	—
Other shaving	1	—	≤0.1	—
Skin care				
Cleansing creams, lotions, etc	1	—	≤0.1	—
Face and neck creams, lotions, powder and sprays	1	—	≤0.1	—
Moisturizers	1	—	≤0.1	—
Skin fresheners	3	—	≤0.1	—
Suntan				
Suntan gels, creams, liquids and sprays	2	—	≤0.1	—
Other suntan	1	—	≤0.1	—
Total uses/ranges for Methylbenzethonium Chloride	**33**	—	**≤1.0**	—

*No details were provided describing specific product categories
**These categories were combined and have since been separated

agent, or surfactant—suspending agent in cosmetics In voluntary reports provided by industry to the Food and Drug Administration (FDA) in 1981, Benzethonium Chloride was used in 93 cosmetic products, with a maximum concentration up to 5% (Elder 1985) In 2002, information provided by industry to FDA indicated that Benzethonium Chloride was used in 39 cosmetic products (FDA 2002) A survey conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) found that the maximum use concentration for Benzethonium Chloride was 5% in douches (CTFA 2003) The current and historical data on use as a function of product category are given in Table 1 The most recent information now constitutes the present use of this ingredient

Newly available unpublished toxicology data were considered supportive of the original conclusion The CIR Expert Panel did consider an analysis by Blumenthal et al (1995), in which a margin of safety was calculated for Benzethonium Chloride as an antibacterial agent in consumer handsoaps as follows

- Soap usage of 15 g/day (90th percentile of human use = 10 × 1.5 g)
- Maximum use concentration of 5%
- 1% of soap remaining on human skin after washing
- human dermal absorption of Benzethonium Chloride from hand soap formulations = 50%
- Average body weight 40 kg
- No observable effect level (NOEL) of 12.5 mg/kg day^{-1} for systemic toxicity from an NTP 13-week dermal study

Exposure calculation

1.5 g/day × 5% × 1% × 50% = 3.75 mg/day

3.75 mg/day/40 kg = 0.09375 mg/kgday^{-1} maximum possible exposure

The NOEL value divided by the maximum possible exposure yielded a margin of safety of 113 for Benzethonium Chloride

Methylbenzethonium Chloride is also a quaternary ammonium salt with functions in cosmetics that include antimicrobial agent, antistatic agent, cosmetic biocide, and deodorant agent In the earlier safety assessment, Methylbenzethonium Chloride was used in 33 cosmetic products, at a maximum concentration up to 1% in baby lotions, oils, powders, and creams, and

in underarm deodorants, douches, and aftershave lotions (Elder 1985) Industry reported no uses to the FDA in 2002 (FDA 2002) and CTFA found no uses in its survey (CTFA 2003)

The historical data on use of Methylbenzethonium Chloride as a function of product category are given in Table 1 Were this ingredient to be used in the future, the CIR Expert Panel expects that it would be used at concentrations and in product types similar to those in the original safety assessment

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[2]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA

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2-BROMO-2-NITROPROPANE-1,3-DIOL (BRONOPOL)

A safety assessment of 2-Bromo-2-Nitropropane-1,3-Diol was published in 1980 with the conclusion that this preservative is safe as a cosmetic ingredient at concentrations up to and including 0 1% except under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides (Elder 1980)

In 1984, a report addendum considered newly available data that use concentrations were reported at levels up to 1% In addition, the action of 2-Bromo-2-Nitropropane-1,3-Diol as a nitrosating agent was emphasized and data provided demonstrating that it was present in formulations with amines such as Triethanolamine The CIR Expert Panel reaffirmed the concentration limitation at 0 1% and the need to avoid use where nitrosamines or nitrosamides could be formed (Elder 1984)

Studies available since the addendum was completed, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

2-Bromo-2-Nitropropane-1,3-Diol was used in 323 products in 1976 (Elder 1980), with the largest single use in makeup fixatives at concentrations of $\leq$0 1% Frequency of use data provided by industry to FDA in 2002 indicated that 2-Bromo-2-Nitropropane-1,3-Diol was used in only one noncoloring hair preparation (FDA 2002) Use concentration data provided from an industry survey in 2003 indicated use in several other product categories (CTFA 2003) The current maximum use concentration was 0 1% Complete information is included in Table 2

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[3] Available for review Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA

TABLE 2

Historical and current cosmetic product uses and concentrations for 2-Bromo-2-Nitropropane-1,3-Diol

Product category	1976 use (Elder 1980)	2002 use (FDA 2002)	1976 concentrations (Elder 1980) %	2003 concentrations (CTFA 2003) %
Bath				
Bath oils, tablets, and salts	1	—	≤0 1	—
Bubble baths	4	—	≤0 1	—
Bath soaps and detergents	1	—	≤0 1	—
Other bath	5	—	≤0 1	—
Eye makeup				
Eyebrow pencil	14	—	≤0 1	—
Eyeliner	11	—	≤0 1	—
Eye shadow	3	—	≤0 1	0 1
Eye makeup remover	—	—	—	0 05
Mascara	6	—	≤0 1	—
Other eye makeup	2	—	≤0 1	—
Fragrances				
Colognes and toilet waters	—	—	—	0 03
Perfumes	—	—	—	0 1
Other fragrances	2	—	>0 1–1	—
Noncoloring hair care				
Hair conditioners	22	—	≤0 1–1	—
Rinses	6	—	≤0 1–1	—
Shampoos	9	—	≤0 1	—
Hair tonics dressings, etc	3	—	≤0 1–1	—
Wave sets	1	—	≤0 1	—
Other noncoloring hair care	1	1	≤0 1	—
Hair coloring				
Hair dyes and colors	3	—	>0 1–1	—
Shampoos	6	—	≤0 1	—
Makeup				
Blushers	20	—	≤0 1	0 1
Foundations	6	—	≤0 1	—
Leg and body paints	2	—	≤0 1	—
Lipstick	—	—	—	0 1
Makeup bases	3	—	≤0 1	—
Makeup fixatives	134	—	≤0.1	—
Other makeup	1	—	≤0 1	—
Personal hygiene				
Underarm deodorants	2	—	≤0 1	—
Shaving				
Aftershave lotion	1	—	≤0 1	0 03
Skin care				
Cleansing creams, lotions, etc	17	—	≤0 1	0 02
Depilatories				
Face and neck skin care preparations	3*	—	>0 1–1*	—
Body and hand skin care preparations		—		—
Moisturizers	9	—	≤0 1	—
Night skin care preparations	3	—	≤0 1	—
Paste masks/mud packs	8	—	≤0 1	—
Skin fresheners	3	—	≤0 1	0 01
Other skin care	6	—	≤0 1	0 009
Suntan preparations				
Suntan gels, creams, and liquids	3	—	≤0 1–1	0 05
Indoor tanning preparations	1	—	≤0 1	—
Other suntan	1	—	≤0 1	—
Total uses/ranges for 2-Bromo 2-Nitropropane-1,3-Diol	**323**	**1**	**≤0 1–1**	**≤0 1**

*These categories were originally combined, but are now separate

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BUTYLATED HYDROXYANISOLE (BHA)

A safety assessment of Butylated Hydroxyanisole was published in 1984 with the conclusion that this ingredient is safe as a cosmetic ingredient in the practices of use (Elder 1984) New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

The name of Butylated Hydroxyanisole as listed in the *International Cosmetic Ingredient Dictionary and Handbook* has been changed to BHA (Pepe et al 2002)

BHA functions in cosmetics include antioxidant and fragrance ingredient It was used in 3217 cosmetic products in 1981, with the largest use occurring in lipstick at concentrations of $\leq$10% (Elder 1984) In 2002, BHA was used in 1224 cosmetic products (FDA 2002), at a maximum use concentration of 0 2% in colognes, toilet waters, and perfumes (CTFA 2003) Table 3 presents the available use information for BHA The most recent information now constitutes the present use of this ingredient

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TABLE 3
Historical and current cosmetic product uses and concentrations for BHA

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
Baby care				
Lotions, oils, powders, and creams	1	1	>0 1–1	0 0001
Bath				
Oils, tablets, and salts	20	4	≤0 1	0 0004
Bubble baths	7	—	≤0 1	0 00001
Bath soaps and detergents	2	5	≤0 1	0 000004
Other bath	10	3	≤1	0 0001
Eye makeup				
Eyebrow pencil	33	51	≤1	0 0001
Eyeliner	75	399	≤1	0 1
Eye shadow	410	38	≤5	0 002
Eye lotion	2	2	≤0 1	—
Eye makeup remover	11	6	≤0 1	0 02
Mascara	65	18	≤1	0 1
Other eye makeup	39	10	≤1	0 001
Fragrances				
Colognes and toilet waters	97	18	≤1	0 2
Perfumes	62	6	≤1	0 2
Powders	12	2	≤0 1	0 0002
Sachets	21	—	≤0 1	—
Other fragrances	24	10	≤1	0 004
Noncoloring hair care				
Conditioners	8	5	≤0 1	0 0002
Sprays	1	—	—	0 0001
Shampoos	6	—	≤0 1	0 0005
Tonics, dressings, etc	10	8	≤1	0 02
Wave sets	1	—	—	—
Other noncoloring hair care	—	—	—	0 05
Hair coloring				
Other hair coloring	5	1	≤0 1	—
Makeup				
Blushers	176	26	≤5	0 2
Face powders	98	11	≤1	0 005
Makeup foundations	119	30	≤0 1	0 05
Lipstick	1256	279	≤25	0 2
Makeup bases	64	4	≤1	0 005
Rouges	48	1	≤1	0 04
Makeup fixatives	10	—	≤0 1	—
Other makeup	106	23	≤5	0 05
Nail care				
Basecoats and undercoats	1	3	≤0 1	—
Cuticle softeners	2	2	≤0 1	0 001
Creams and lotions	4	1	≤0 1	—
Polish and enamel	—	—	—	0 06
Polish and enamel remover	1	—	≤0 1	—
Other nail care	2	4	≤0 1	0 004

TABLE 3

Historical and current cosmetic product uses and concentrations for BHA *(Continued)*

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
Oral hygiene				
Dentifrices	—	—	—	0 01
Personal hygiene				
Underarm deodorants	1	1	≤0 1	0 002
Other personal hygiene	2	4	≤1	0 002
Shaving				
Aftershave lotions	11	2	≤1	0 006
Preshave lotions	3	—	—	—
Shaving cream	8	10	≤0 1	0 0003
Shaving soap	1	—	>0 1–1	—
Other shaving	3	—	≤1	0 0003
Skin care				
Cleansing creams, lotions, etc	51	23	≤1	0 05
Face and neck skin care	77*	15	≤1*	0 1
Body and hand skin care		72		0 1
Hormone skin care**	1	**	—	**
Foot powders and sprays	—	1	—	0 004
Moisturizers	111	51	≤1	0 06
Night skin care	30	26	≤1	0 04
Paste masks/mud packs	6	3	≤1	0 004
Skin lighteners**	11	**	≤0 1	**
Skin fresheners	6	2	≤0 1	—
Wrinkle smoothers**	6	**	≤0 1	**
Other skin care	42	30	≤1	0 03
Suntan				
Suntan gels, creams, and liquids	27	7	≤1	0 1
Indoor tanning	2	1	≤0 1	—
Other suntan	9	5	≤0 1	—
Total uses/ranges for BHA	**3217**	**1224**	**≤0 1–25**	**0 000004-0 2**

*These categories were combined, but now are listed separately

**No longer listed as product categories

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BUTYLENE GLYCOL, HEXYLENE GLYCOL, ETHOXYDIGLYCOL, AND DIPROPYLENE GLYCOL

A safety assessment was published in 1985 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1985) New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

Butylene Glycol was reported to be used in 165 cosmetic preparations in 1981, with the greatest use occurring in mascara, and at concentrations that ranged from less than 0 14% to greater than 50% (Elder 1985) In 2002, industry reports to FDA indicated that Butylene Glycol was used in 813 preparations (FDA 2002) An industry survey of use concentrations in

TABLE 4

Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
		Butylene Glycol		
Baby care				
Lotions, oils, powders, and creams	—	2	—	13
Other baby care	—	—	—	3–4
Bath				
Oils, tablets, and salts	1	3	5–10	0 08
Soaps and detergents	1	10	5–10	0 02–1
Other bath	4	20	5–>50	1
Eye makeup				
Eyebrow pencils	—	1	—	0 007
Eyeliners	3	12	1–5	3–12
Eye shadow	13	3	5–25	2
Eye lotions	—	5	—	3–8
Eye makeup remover	4	16	1–5	5
Mascara	34	14	1–10	0 00007–3
Other eye makeup	1	19	1–5	7
Fragrances				
Colognes and toilet waters	3	5	0 1–25	4
Perfumes	2	4	1–5	—
Powders	—	4	—	—
Other fragrances	1	18	5–10	2
Noncoloring hair care				
Conditioners	5	10	≤1–10	<1–3
Sprays/aerosol fixatives	—	—	—	3
Permanent waves	—	2	—	1
Shampoos	1	9	≤0 1	1–4
Tonics, dressings, etc	1	11	1–5	0 02–5
Other noncoloring hair care	—	12	—	<1–6
Makeup				
Blushers	7	—	1–25	—
Face powders	1	2	1–5	2
Foundations	19	66	5–25	6–9
Lipsticks	—	4	—	0 2–3
Makeup bases	1	12	5–10	6
Rouges	2	—	5–>50	—
Makeup fixatives	—	3	—	6
Other makeup	2	15	5–25	3–4
Nail care				
Cuticle softeners	1	3	5–10	—
Creams and lotions	—	2	—	—
Nail polishes and enamels	—	5	—	—
Other nail care	—	2	—	—
Oral hygiene				
Other oral hygiene	—	—	—	0 01
Personal hygiene				
Underarm deodorants	1	14	10–25	20–30
Other personal hygiene	1	1	1–5	—

(Continued on next page)

TABLE 4

Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Shaving				
Aftershave lotions	4	8	0.1–5	0.05–7
Shaving cream	—	5	—	1
Other shaving	—	5	—	—
Skin care				
Cleansing creams, lotions, etc	13	66	≤0.1–10	0.05–20
Depilatories	—	—	—	4
Face and neck skin care	8*	30	≤ 0.1–>50*	3–7
Body and hand skin care		43		0.01–14
Foot powders and sprays	—	4	—	
Moisturizers	13	171	≤0.1–>50	0.02–13
Night skin care	1	23	≤0.1	3–8
Paste masks/mud packs	3	27	0.1–10	3–12
Skin fresheners	6	16	≤0.1–5	2–6
Other skin care	7	78	≤0.1–10	4–89
Suntan products				
Suntan gels, creams, liquids, and sprays	1	7	1–5	2–5
Indoor tanning	—	18	—	0.5–20
Other suntan	—	3	—	5
Total uses/ranges for Butylene Glycol	**165**	**813**	**≤0.1–>50**	**0.00007–89**
		Hexylene Glycol		
Baby care				
Other baby care	—	—	—	1
Bath				
Oils, tablets, and salts	4	1	5–25	—
Soaps and detergents	3	3	1–5	—
Bubble baths	3	2	0.1–5	—
Other bath	—	2	—	—
Eye makeup				
Eye lotions	—	2	—	2
Eye makeup remover	1	20	0.1–1	2
Mascara	—	1	—	0.1
Other eye makeup	—	3	—	0.8
Fragrances				
Colognes and toilet waters	—	—	—	0.03
Other	—	1	—	—
Noncoloring hair care				
Conditioners	7	3	0.1–10	4
Permanent waves	1	2	10–25	—
Rinses	1	—	10–25	—
Shampoos	29	12	≤0.1–10	—
Tonics, dressings, etc	—	2	—	4
Wave sets	—	1	—	—
Other noncoloring hair care	—	2	—	—
Hair coloring				
Dyes and colors	20	179	1–25	—

TABLE 4

Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Rinses	—	2	—	—
Bleaches	1	1	1–5	—
Makeup				
Foundations	—	4	—	0 3
Lipsticks				0 003
Makeup bases	—	1	—	
Makeup fixatives	—	—	—	1
Nail care				
Nail polish and enamel removers	—	1	—	—
Personal hygiene				
Underarm deodorants	2	—	0 1–1	0 002
Other personal hygiene	—	1	—	0 0009
Shaving				
Aftershave lotions	—	—	—	0 1–2
Shaving cream	—	1	—	—
Other shaving	—	—	—	2
Skin care				
Cleansing creams, lotions, etc	4	22	0 1–5	0 005–6
Face and neck skin care	1*	5	1–5*	0 001–4
Body and hand skin care		1		0 0009–1
Moisturizers	3	7	0 1–5	1
Night skin care	—	2	—	1–4
Paste masks/mud packs	1	6	5–10	0 3
Skin fresheners	3	2	0 1–5	—
Other skin care	1	6	1–5	3
Suntan				
Suntan gels, creams, liquids, and sprays	—	6	—	0 01
Other suntan	—	2	—	—
Total uses/ranges for Hexylene Glycol	**85**	**306**	**≤0 1–25**	**0 0009–6**
		Ethoxydiglycol		
Baby care				
Shampoos	—	—	—	<1
Lotions, oils, powders, and creams	—	—	—	<0 5
Bath				
Oils, tablets, and salts	—	3	—	—
Soaps and detergents	—	—	—	0 6
Bubble baths	—	2	—	0 006
Eye makeup				
Eye lotions	—	—	—	0 0001–2
Eye makeup remover	—	1	—	—
Mascara	1	7	0 1–1	—
Other eye makeup	—	1	—	—
Fragrances				
Colognes and toilet waters	3	—	0 1–10	1
Perfumes	—	—	—	1

TABLE 4

Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Other fragrances	—	2	—	—
Noncoloring hair care				
Conditioners	4	11	0 1–5	0 04
Sprays/aerosol fixatives	—	4	—	0 00008
Rinses	—	1	—	—
Shampoos	1	15	0 1–1	0 02–1
Tonics, dressings, etc	—	4	—	0 03
Wave sets	1	1	1–5	—
Other noncoloring hair care	—	4	—	0 4
Hair coloring				
Dyes and colors	14	495	1–10	—
Tints	13	—	1–5	—
Bleaches	5	6	1–5	—
Other hair coloring	1	2	1–5	—
Makeup				
Blushers	—	—	—	0 0006
Face powders	—	—	—	0 0008
Foundations	—	1	—	0 005
Lipsticks	—	—	—	0 00004
Makeup bases	—	—	—	0 008
Rouges	—	—	—	0 05
Other	—	—	—	0 04
Nail care				
Basecoats and undercoats	—	1	—	—
Nail polish and enamel removers	1	—	5–10	—
Other nail care	—	—	—	42
Personal hygiene				
Underarm deodorants	—	—	—	0 2
Douches	—	—	—	0 1
Other personal hygiene	—	—	—	0 3
Shaving				
Aftershave lotions	2	2	0 1–1	0 6
Preshave lotions	—	—	—	0 0005
Shaving cream	—	2	—	5
Other shaving	—	2	—	—
Skin care				
Cleansing creams, lotions, etc	14	10	≤0 1–> 50	0 02–80
Depilatories	—	—	—	2
Face and neck skin care	3*	5	≤0 1–1*	0 2–15
Body and hand skin care		6		0 1–0 5
Moisturizers	3	3	1–10	0 04–3
Night skin care	2	—	≤0 1–5	0 09–10
Paste masks/mud packs	3	2	0 1–25	0 002–8
Skin fresheners	3	—	1–5	5–8
Other skin care	5	14	0 1–10	0 05–53
Skin lighteners**	1	—*	—	

TABLE 4
Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Suntan				
Suntan gels, creams, liquids, and sprays	—	5	—	—
Indoor tanning	—	10	—	1–5
Other suntan	—	—	—	0.2–9
Total uses/ranges for Ethoxydiglycol	**80**	**622**	**≤0.1–> 50**	**0.00004–80**
		Dipropylene Glycol		
Baby care				
Lotions, oils, powders, and creams	—	1	—	—
Bath				
Oils, tablets, and salts	1	3	>50	—
Soaps and detergents	—	4	—	0.8
Bubble baths	—	1	—	0.03
Eye makeup				
Eye lotions	—	2	—	0.1–4
Eye makeup remover	—	1	—	—
Mascara	—	7	—	—
Fragrances				
Colognes and toilet waters	2	—	5–10	7–9
Perfumes	12	4	0.1–>50	0.01–20
Powders	—	5	—	—
Sachets	1	—	>50	—
Other fragrances	1	5	>50	4
Noncoloring hair care				
Conditioners	—	8	—	0.2
Sprays/aerosol fixatives	1	—	≤0.1	0.6
Rinses	—	—	—	0.004
Shampoos	1	6	5–10	0.4
Tonics, dressings, etc	1	3	10–25	0.4
Wave sets	4	4	5–10	—
Hair coloring				
Dyes and colors	—	10	—	—
Other hair coloring	—	2	—	—
Makeup				
Blushers	—	1	—	0.08
Foundations	—	5	—	0.2
Lipsticks	4	15	≤0.1–10	0.03
Makeup bases	1	4	1–5	0.05
Rouges	—	—	—	0.08
Other makeup	—	2	—	0.2–7
Nail care				
Nail polish and enamel removers	—	—	—	0.004
Personal hygiene				
Underarm deodorants	4	25	1–5	8–50
Other personal hygiene	—	13	—	1

(Continued on next page)

TABLE 4

Historical and current cosmetic product uses and concentrations for Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Shaving				
Aftershave lotions	2	2	0 1–5	3–5
Preshave lotions	—	—	—	0 6
Shaving cream	—	—	—	0 07
Skin care				
Cleansing creams, lotions, etc	4	38	≤0 1	0 01–12
Face and neck skin care	3*	24	1–5*	2
Body and hand skin care		19		0 1–9
Foot powders and sprays	1	—	0 1–1	—
Moisturizers	4	39	1–10	7
Night creams, lotions, powder, and sprays	—	4	—	2–3
Paste masks/mud packs	—	14	—	0 02–0 03
Skin fresheners	2	3	0 1–25	2
Other skin care	1	18	5–10	1–2
Suntan				
Suntan gels, creams, liquids and sprays	—	5	—	—
Indoor tanning	—	4	—	1
Other suntan	—	3	—	—
Total uses/ranges for Dipropylene Glycol	**50**	**304**	**≤0 1–>50**	**0 004–50**

*This category was combined when the original safety assessment was performed and is now two separate categories

**No longer included as a cosmetic product category

2003 found concentrations of use ranging from 0 00007% to 89% (CTFA 2003)

Hexylene Glycol was reported to be used in 85 preparations in 1981, with the largest use in shampoos, and at concentrations ranging from less than 0 1% to 25% (Elder 1985) In 2002, Hexylene Glycol was reported to be used in 306 preparations, with the greatest use in hair dyes and colors (FDA 2002) Concentrations of use in 2003 ranged from 0 0005% to 6% (CTFA 2003)

Ethoxydiglycol was reported to be used in 80 preparations in 1981, with the largest uses in hair dyes and colors as well as skin cleansing creams, lotions, liquids, and pads The concentration of use ranged from less than 0 1% to greater than 50% (Elder 1985) In 2002, Ethoxydiglycol was used in 622 preparations (FDA 2002) and at concentrations ranging from 0 0004% to 80% (CTFA 2003)

Dipropylene Glycol was reported to be used in 50 preparations in 1981, with the largest single use occurring in perfumes, and at concentrations ranging from less than 0 1% to greater than 50% (Elder 1985) In 2002, Dipropylene Glycol was reported to be used in 304 preparations (FDA 2002) at concentrations ranging from 0 004% to 50% (CTFA 2003)

Table 4 presents the available use and concentration information The most recent information now constitutes the present practices of use

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CETEARYL OCTANOATE (CETEARYL ETHYLHEXANOATE)

A safety assessment of Cetearyl Octanoate was published in 1982 with the conclusion that this ingredient is safe as a cosmetic ingredient in the present practices of use (Elder 1982) Studies available since that safety assessment was completed have been considered by the CIR Expert Panel, along with updated information regarding uses and use concentrations The Panel determined to not reopen this safety assessment

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed—Ceteraryl Ethylhexanoate is the current terminology (Pepe et al 2002)

Significant among the new data were data on 2-ethylhexanoic acid (2-EHA), which has been shown to be a liver and developmental toxicant in animal studies at high dose levels 2-EHA is a possible metabolite of Cetearyl Ethylhexanoate

In developmental toxicity studies, it has been postulated that 2-EHA maternal liver toxicity begins a cascade of effects that includes metallothionein (MT) induction, zinc accumulation in the liver due to MT binding, and a resulting zinc deficiency in the developing embryo In this model, it is the zinc deficiency in the developing embryo that causes developmental toxicity Support for this mechanism of action come from several sources Animal studies have demonstrated that dietary zinc supplementation reduces this toxic effect and that further zinc deficiency makes 2-EHA more toxic In vitro studies using embryo cultures have demonstrated that either zinc-deficient or 2-EHA–treated sera produced developmental toxicity Zinc supplementation of either/both sera eliminated the effect

To further examine this question, di-2-ethylhexyl terephthalate (DEHT), a 2-EHA precursor, was chosen as a model that would result in 2-EHA exposures without liver toxicity, MT induction, etc DEHT is metabolized in the gut and liver to 2-ethylhexanol (2-EH) and terephthalate Two moles of 2-EH are produced per mole of DEHT Subsequent hydrolysis of 2-EH produces 2-EHA It can be hypothesized that this pathway to 2-EHA production from a precursor would not give rise to acute liver toxicity, MT induction, zinc sequestration, and developmental toxicity

In a reproductive and developmental toxicity study, 0%, 0 3%, 0 6%, and 1% DEHT was provided in the feed of rats The doses were calculated to be 614 to 823 mg/kg day^{-1} for males and 783 to 1021 mg/kg day^{-1} for females Neither reproductive toxicity or developmental toxicity were seen at any dose level These findings suggest that the process of metabolic conversion of DEHT to 2-EH, and subsequent hydrolysis to 2-EHA results in a time course of 2-EHA appearance that allows clearance before sufficient levels can arise to produce acute liver toxicity

Although this study was undertaken to understand 2-EHA developmental toxicity, the Panel considered that it is relevant to the assessment of Cetearyl Ethylhexanoate Like DEHT, Cetearyl Ethylhexanoate must undergo conversion in order to produce 2-EHA In addition, Cetearyl Ethylhexanoate, as used in cosmetics, would have to pass through the stratum corneum and the epidermis before entering the blood stream, further moderating the time course of 2-EHA appearing in the liver The Panel recognized that Cetearyl Ethylhexanoate is used in lipsticks and that ingestion is possible from that use It was the view of the CIR Expert Panel that these considerations would preclude any possibility that Cetearyl Ethylhexanoate in cosmetics could present a risk of developmental toxicity

Cetearyl Ethylhexanoate was used in 243 cosmetic products in 1976 (Elder 1982) The highest concentrations were in eye makeup, makeup, and skin care preparations Currently there are 229 reported uses of Cetearyl Ethylhexanoate reported to FDA (FDA 2002), with the highest concentrations (up to 35%) in makeup (CTFA 2002) Although current use concentrations have increased compared to those reported in 1976, available skin irritation data show no irritation at concentrations up to 30%

Table 5 presents the available use and concentraton information The most recent information now constitutes the present practices of use

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TABLE 5

Historical and current cosmetic product uses and concentrations for Cetearyl Ethylhexanoate

Product category	1976 uses (Elder 1982)	2002 uses (FDA 2002)	1976 concentrations (Elder 1982) %	2002 concentrations (CTFA 2002a) %
Baby care				
Lotions, oils, powders, and creams	—	1	—	—
Bath				
Oils, tablets, and salts	1	—	Unknown	—
Capsules	—	—	—	9
Other bath	2	—	1–10	—
Eye makeup				
Eyeliners	1	—	0 1–1	—
Eye shadows	22	4	0–25	26–28
Mascara	6	—	0 1–1	0 07
Other eye makeup	2	3	0 1–5	3–5
Fragrances				
Powders	—	2	—	—
Other fragrances	—	12	—	—
Noncoloring hair care				
Conditioners	5	—	0–5	—
Sprays (aerosol fixatives)	5	5	0–5	—
Straighteners	1	—	0 1–1	—
Rinses	1	—	0 1–1	—
Shampoos	—	—	—	0 2
Tonics, dressings, etc	1	32	0 1–1	0 1
Wave sets	1	—	1–5	—
Other noncoloring hair	3	2	0–5	—
Makeup				
Blushers	19	3	1–25	3
Face powders	10	6	0 1–1	1–4
Foundations	—	5	—	0 1–34
Lipstick	—	4	—	0 1–8
Makeup bases	25	—	0 1–5	—
Rouges	2	—	5–25	—
Makeup fixatives	1	—	5–10	—
Other makeup	10	—	0 1–5	35
Nail care				
Nail creams and lotions	1	—	10–25	—
Personal hygiene				
Underarm deodorants	—	—	—	3
Feminine deodorants	1	—	1–5	—
Shaving				
Aftershave lotion	—	2	—	—
Mens talcum	—	1	—	—
Preshave lotions	1	—	1–5	—
Other shaving	1	—	1–5	—
Skin care				
Cleansing creams, lotions, etc	15	7	>0–10	13
Face and neck skin care	35*	21	>0–25*	3
Body and hand skin care		38		3–10
Moisturizers	39	23	0 1–25	2–34
Night skin care	16	13	0 1–10	2–7
Paste masks/mud packs	3	8	0 1–5	—
Skin fresheners	1	2	0 1–1	—
Other skin care	4	21	1–25	6
Suntan				
Suntan gels, creams, and liquids	7	9	0-5	0 5–9
Indoor tanning	—	2	—	3
Other suntan	1	3	5–10	—
Total uses/ranges for Cetearyl Ethylhexanoate	**243**	**229**	**0–25**	**0 07–35**

*This category was combined when the original safety assessment was performed and is now two separate categories

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CHOLESTEROL

A safety assessment of Cholesterol was published in 1986 with the conclusion that this ingredient is safe as presently used in cosmetic products (Elder 1986) The CIR Expert Panel reviewed new studies available since that time, along with updated information regarding types and concentrations of use, and determined to not reopen this safety assessment

According to the entry in the *International Cosmetic Ingredient Dictionary and Handbook*, Cholesterol functions as an emulsion stabilizer, miscellaneous skin-conditioning agent, and nonaqueous viscocity-increasing agent in cosmetic products (Gottschalck and McEwen 2004)

Frequency of use data provided by industry to FDA for 2002 show that cholesterol is used in 258 cosmetic products (FDA 2002), an increase compared to 145 uses reported in 1981 (Elder 1986) In 1981, Cholesterol use concentrations (again, as reported by industry to FDA) ranged from ≤0 1% to 5% (Elder 1986) A survey by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in 2004 found the range of use concentrations to be 0 002% to 3%, with majority of products around 0 1%

Historical and current cosmetic product uses and concentrations for Cholesterol are given in Table 6 The most recent information now constitutes the present practices of use

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CHLOROXYLENOL

A safety assessment of Chloroxylenol was published in 1985 with the conclusion that this ingredient was safe as a cosmetic ingredient in the practices of use at that time (Elder 1985) New studies, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined not to reopen this safety assessment

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, the functions of Chloroxylenol in cosmetic products are now described as a cosmetic biocide, deodorant agent, and preservative (Gottschalck and McEwen 2006)

[7]Available for review: Director, Cosmetic Ingredient Review (CIR), 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA

TABLE 6

Historical and current cosmetic product uses and concentrations for Cholesterol

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2004 concentrations (CTFA 2004) %
Bath				
Soaps and detergents	—	2	—	—
Eye makeup				
Eyeliners	6	1	>0 1–1	—
Eye shadow	15	—	<0 1–1	0 01
Eye lotions	—	1	—	0 04–0 3
Eye makeup remover	—	—	—	0 002
Mascara	16	2	>0 1–5	—
Other eye makeup	3	4	>0 1–5	—
Fragrances				
Other fragrances	1	2	>0 1–1	—
Noncoloring hair care				
Conditioners	7	13	≤0 1–1	0 3
Straighteners	—	—	—	0 003
Rinses	—	1	—	—
Shampoos	1	5	>0 1–1	—
Tonics, dressings, etc	—	3	—	2
Other noncoloring hair care	—	4	—	0 2
Hair coloring				
Dyes and colors	—	27	—	—
Makeup				
Face powders	—	3	—	—
Foundations	7	7	≤0 1–1	3
Lipsticks	—	5	—	0 1
Makeup bases	12	3	≤0 1–1	0 02
Rouges	—	1	—	—
Makeup fixatives	—	2	—	—
Other makeup	14	4	≤0 1–1	—
Nail care				
Cuticle softeners	—	1	—	0 1
Nail polish and enamel removers	—	1	—	—
Shaving				
Aftershave lotions	1	3	>0 1–1	0 1
Shaving cream	—	—	—	0 1
Other shaving	1	—	>0 1–1	—
Skin care				
Cleansing creams, lotions, etc	5	11	≤0 1–1	1
Face and neck skin care	11*	22	≤0 1–5*	0 3–2
Body and hand skin care		19		0 01–0 5
Foot powders and sprays	—	3	—	0 5
Moisturizers	19	61	≤0 1–5	0 005–1
Night skin care	15	24	≤0 1–5	0 1–1
Wrinkle smoothers**	2	—	≤0 1–5	—
Paste masks/mud packs	—	4	—	0 5
Skin fresheners	—	3	—	—
Other skin care	8	13	≤0 1–5	—
Suntan				
Suntan gels, creams, liquids, and sprays	1	1	>0 1–1	0 02–0 4
Indoor tanning	—	—	—	0 005
Other suntan	—	2	—	—
Total uses/ranges for Cholesterol	**145**	**258**	**≤0 1–5**	**0 002–3**

*This category was combined when the original safety assessment was performed and is now two separate categories

**No longer listed as product categories

In 1984, Chloroxylenol was used as an antimicrobial compound in 93 cosmetic products, with the maximum concentrations at up to 5% in fragrance powders, noncoloring shampoos, and other hair preparations (Elder 1985) In 2002, industry reports of Chloroxylenol use to the FDA included 43 cosmetic products (FDA 2002) Based on an industry survey, CTFA (2002) reported that Chloroxylenol was used in cosmetic products at a maximum concentration of use of 0 5% in skin cleansing products

Table 7 summarizes these data The most recent information now constitutes the present practices of use

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[8]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW Suite 412, Washington, DC 20036-4702, USA

DIISOPROPANOLAMINE, ISOPROPANOLAMINE, TRIISOPROPANOLAMINE, AND MIXED ISOPROPANOLAMINES

A safety assessment of Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed Isopropanolamines was published in 1987 with the conclusion that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration, if not used in products containing N-nitrosating agents (Elder 1987) The CIR Expert Panel considered new studies, along with updated information regarding types and concentrations of use The Panel determined not to reopen this safety assessment

No uses of Mixed Isopropanolamines were reported in the original safety assessment, in frequency of use data collected by FDA in 2002 (FDA 2002) or in a recent industry survey (CTFA 2004)

Diisopropanolamine reportedly was used in 66 products in 1981, at concentrations of $\leq$10%, and in 33 products in 2002, at concentrations of up to 0 7% (from the 2004 survey)

Isopropanolamine was used in 11 cosmetic products in 1981, at concentrations of $\leq$1%, and in 27 products in 2002, at the same concentrations (from the 2004 survey)

Triisopropanolamine had 36 cosmetic uses in 1981, at concentrations of $\leq$ 5%, and 25 uses in 2002, at concentrations up to 1% (from the 2004 survey)

Table 8 summarizes the historical and recent uses of Diisopropanolamine, Isopropanolamine, and Triisopropanolamine in

TABLE 7
Historical and current cosmetic product uses and concentrations for Chloroxylenol

Product category	1979 uses (Elder 1985)	2002 uses (FDA 2002)	1979 concentrations (Elder 1985) %	2003 concentrations (CTFA 2004) %
Baby care				
Lotions, oils, powders, and creams	—	—	—	0.1
Bath				
Soaps and detergents	2	1	>0.1–1	—
Eye makeup				
Eye shadow	—	1	—	—
Eye makeup remover	2	—	≤1	—
Fragrances				
Powders	2	—	>1–5	—
Noncoloring hair care				
Conditioners	8	3	≤1	—
Straighteners	4	—	>0.1–1	—
Shampoos	29	3	≤5	—
Tonics, dressings, etc	3	6	>0.1–1	—
Wave sets	1	—	≤0.1	—
Other noncoloring hair care	3	—	≤5	—
Hair coloring				
Dyes and colors	1	—	≤1	—
Rinses	2	—	>0.1–1	—
Makeup				
Blushers	1	—	>0.1–1	—
Rouges	—	1	—	—
Makeup fixatives	1	—	>0.1–1	—
Other makeup	—	5	—	—
Nail care				
Basecoats and undercoats	1	—	≤1	—
Cuticle softeners	1	—	>0.1–1	—
Oral hygiene				
Other oral hygiene	—	—	—	0.4
Personal hygiene				
Underarm deodorants	1	1	>0.1–1	—
Feminine deodorants	1	—	≤0.1	—
Other personal hygiene	8	11	≤1	—
Shaving				
Shaving cream	—	1	—	—
Skin care				
Cleansing creams, lotions, etc	5	4	≤1	0.5
Depilatories	1	—	>0.1–1	—
Face and neck skin care	7*	—	≤1*	0.2
Body and hand skin care		2		—
Moisturizers	—	1	—	0.1
Paste masks/mud packs	2	—	≤1	—
Skin fresheners	1	—	≤1	—
Other skin care	5	3	≤1	—
Suntan products				
Suntan gels, creams, liquids and sprays	1	—	0.1–1	—
Total uses/ranges for Chloroxylenol	**93**	**43**	**≤5**	**0.1–0.5**

*This category was combined when the original safety assessment was performed and is now two separate categories

TABLE 8

Historical and current uses and use concentrations for Diisopropanolamine, Isopropanolamine, and Triisopropanolamine in cosmetic products

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2004) %
	Diisopropanolamine			
Fragrances				
Colognes and toilet waters	2	1	≤0.1	—
Other fragrances	13	10	≤1	—
Noncoloring hair care				
Conditioners	1	1	>0.1–1	—
Sprays	1	—	>1–5	—
Permanent waves	7	3	>0.1–10	—
Tonics, dressings, etc	2	5	≤1	0.7
Wave sets	1	1	>0.1–1	—
Other noncoloring hair care	2	1	>1–5	—
Hair coloring				
Hair dyes and colors	—	3	—	—
Makeup				
Makeup foundations	2	—	>1–5	—
Other makeup	5	—	>0.1–5	—
Shaving				
Aftershave lotion	4	2	≤1	—
Other shaving	2	3	≤1	—
Skin care preparations				
Cleansing creams, lotions, etc	—	—	—	<0.01
Face, body, and hand skin care	10	—	>0.1–1	—
Moisturizers	4	—	≤5	—
Night skin care	1	—	>0.1–1	—
Paste masks/mud packs	2	1	>0.1–5	—
Skin fresheners	2	1	≤1	—
Wrinkle smoothers**	1	—**	>0.1–1	—**
Other skin care	1	1	>0.1–1	—
Suntan preparations				
Suntan gels, creams, and liquids	2	—	>0.1–1	—
Indoor tanning	1	—	>0.1–1	—
Total uses/ranges for Diisopropanolamine	**66**	**33**	**≤10**	**<0.01–0.7**
	Isopropanolamine			
Eye makeup				
Eyeliner	—	1	—	—
Mascara	3	22	≤1	—
Noncoloring hair care				
Tonics, dressings, etc	1	1	≤0.1	—
Hair coloring				
Hair dyes and colors	—	—	—	1
Shaving				
Aftershave lotions	2	—	>0.1–1	—
Skin care				
Depilatories	1	—	≤0.1	—
Body and hand skin care	—	1	—	—
Moisturizers	3	1	≤1	—

(Continued on next page)

TABLE 8

Historical and current uses and use concentrations for Diisopropanolamine, Isopropanolamine, and Triisopropanolamine in cosmetic products *(Continued)*

Product category	1981 uses (Elder, 1985)	2002 uses (FDA, 2002)	1981 concentrations (Elder, 1985) %	2004 concentrations (CTFA, 2004) %
Suntan				
Suntan gels, creams, and lotions	1	1	≤0.1	—
Total uses/ranges for Isopropanolamine	**11**	**27**	**≤1**	**1**
	Triisopropanolamine			
Baby care				
Lotions, oils, powders, and sprays	1	—	>0.1–1	—
Noncoloring hair care				
Conditioners	4	—	>0.1–5	—
Sprays	9	9	≤1	0.4
Tonics, dressings, etc	13	12	≤5	0.7
Wave sets	2	3	>0.1–1	—
Other hair care	2	1	>0.1–1	1*
Skin care				
Cleansing creams, lotions, etc	1	—	>1–5	—
Face and neck skin care preparations	1***	—	>0.1–1***	—
Body and hand skin care preparations		—		—
Moisturizers	3	—	>0.1–1	—
Total uses/ranges for Triisopropanolamine	**36**	**25**	**≤5**	**0.4–1**

*Nonaerosol pump spray

**No longer a cosmetic product category

***This category was combined when the original safety assessment was performed and is now two separate categories

cosmetic products The most recent information now constitutes the present practices of use

The CIR Expert Panel did note that Diisopropanolamine has a structure that is related to diethanolamine (DEA), which has been implicated as an animal carcinogen Data were provided suggesting a mechanism for DEA carcinogenicity in animals is related to choline metabolism Data also were provided demonstrating that Diisopropanolamine does not act by the same mechanism It was suggested, therefore, that Diisopropanolamine is unlikely to present any risk of carcinogenicity

The Panel acknowledged the use of Diisopropanolamine in hair sprays The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition (Jensen and O'Brien 1993) within the respiratory system Particle size is the most important factor affecting the location of depostion The mean aerodynamic diameter of pump hair spray particles is approximately 80 μm, and diameter of anhydrous hair spray particles is 60 to 80 μm Typically, less than 1% are below 10 μm, which is the upper limit for respirable particles (Bowen 1999) Based on the particle size, Diisopropanolamine would not be respirable in formulation Therefore, exposure of the lung by inhalation was not considered likely

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TABLE 9
Historical and current uses and use concentrations for Diethylhexyl Adipate and Diisopropyl Adipate

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
	Diethylhexyl Adipate			
Bath				
Oils, tablets, salts	4	—	>10–25	—
Eye makeup				
Lotion	—	—	—	0.6
Other eye makeup	—	2	—	0.4–2
Fragrances				
Colognes and toilet waters	6	—	>1–5	—
Other fragrance	—	5	—	—
Makeup				
Blushers	1	3	≥ 0.1	13
Foundations	4	2	>0.1–10	16
Makeup bases	—	6	—	6
Lipsticks	5	1	>1–5	—
Other makeup	1	2	>1–5	—
Nail care				
Nail polish & enamel remover	2	—	>1–5	—
Nail creams and lotions	—	1	—	—
Cuticle softeners	—	1	—	—
Personal hygiene				
Underarm deodorants	1	—	>0.1–1	8
Other personal hygiene	—	4	—	—
Shaving				
Aftershave lotions	1	—	>1–5	1
Shaving cream	—	5	—	—
Skin care				
Face and neck skin care	1*	2	>1–5*	—
Body and hand skin care		2		—
Moisturizers	—	4	—	—
Other skin care	—	5	—	—
Suntan				
Suntan gels, creams, and liquids	—	1	—	38
Indoor tanning	—	2	—	12
Other suntan	1	1	—	—
Total uses/ranges for Diethylhexyl Adipate	**27**	**49**	**≥0.1–25**	**0.4–38**
	Diisopropyl Adipate			
Bath				
Oils, tablets, and salts	7	5	>1–25	5
Bubble baths	1	—	>1–5	—
Other bath	—	1	—	8
Eye makeup				
Eyeliner	1	—	>1–5	—
Eye shadow	1	—	>10–25	—
Fragrances				
Colognes and toilet waters	15	16	>0.1–5	8
Perfumes	20	14	>1–10	8

(Continued on next page)

TABLE 9

Historical and current uses and use concentrations for Diethylhexyl Adipate and Diisopropyl Adipate *(Continued)*

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
Sachets	1	—	>10–25	—
Other fragrances	9	2	>0 1–25	15
Noncoloring hair care				
Conditioners	3	—	≥0 1–1	0 1
Sprays	1	1	>1–5	3
Tonics, dressings, etc	4	2	>1–5	—
Wave sets	2	—	>0 1–5	—
Makeup				
Blushers	1	—	>1–5	—
Face powders	1	—	>1–5	—
Foundations	1	—	>0 1–1	5
Nail care				
Nail polish and enamel removers	—	1	—	3
Personal hygiene				
Underarm deodorants	—	—	—	0 01
Other personal hygiene	1	—	>0 1–1	—
Shaving				
Aftershave lotions	16	10	>1–5	1
Preshave lotions	1	—	>5–10	5
Skin care				
Cleansing creams, lotions, etc	5	1	>0 1–1	—
Face and neck skin care	—*	1	—*	—
Body and hand skin care		1		2–3
Foot powders and sprays	1	—	>0 1–1	—
Moisturizers	2	5	>0 1–5	0 2
Night skin care	1	—	>5–10	—
Skin fresheners	11	2	—	—
Other skin care	2	—	>1–10	4
Suntan				
Suntan gels, creams, and liquids	2	3	>5–10	4
Indoor tanning	2	—	>1–5	—
Other suntan	—	1	—	—
Total uses/ranges for Diisopropyl Adipate	**112**	**66**	**≥0 1–25**	**0 1–15**

*This category was combined when the original safety assessment was performed and is now two separate categories

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DIOCTYL ADIPATE AND DIISOPROPYL ADIPATE

A safety assessment of Dioctyl Adipate and Diisopropyl Adipate was published in 1984 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1984) New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

The name of Dioctyl Adipate as listed in the *International Cosmetic Ingredient Dictionary and Handbook* has been changed to Diethylhexyl Adipate (Pepe et al 2002)

Diethylhexyl Adipate, according to information provided by industry to FDA under a voluntary reporting program, was used in 27 cosmetic products in 1981, with the maximum use concentration at 25% Use increased in 2002 to 49 cosmetic products As reported in an industry survey, the maximum use concentration increased to 38% in 2003

Diisopropyl Adipate was used in 112 cosmetic products in 1981, with the maximum use concentration in the 10% to 25% range Use decreased to 66 reported uses in 2002 The maximum use concentration was 15% in 2003, consistent with that reported in 1981

Table 9 gives the available use and concentration data for Dioctyl Adipate and Diisopropyl Adipate The most recent data now constitute the present practices of use

The CIR Expert Panel noted that Dioctyl Adipate and Diisopropyl Adipate are used in cosmetic products that may be incidentally inhaled during use (e g , hair sprays) The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition (Jensen and O'Brien 1993) within the respiratory system Particle size is the most important factor affecting the location of depostion

The mean aerodynamic diameter of pump hair spray particles is approximately 80 μm, and diameter of anhydrous hair spray particles is 60 to 80 μm Typically, less than 1% are below 10 μm, which is the upper limit for respirable particles (Bowen 1999) Based on the particle size, these ingredients would not be respirable in formulation Therefore, exposure of the lung by inhalation was not considered likely

The increase in the maximum concentration of use to 38% (in suntan lotion) was considered in the context of newly available reproductive and developmental toxicity data suggesting that Diethylhexyl Adipate can be fetotoxic in animal studies This was a threshold effect and the systemic dose at which no adverse effects were seen (NOAEL) was 200 mg/kg day^{-1} Using an estimated use of 40 g per day of suntan lotion containing Diethylhexyl Adipate at 38%, a 60-kg person would receive a dermal dose of 250 mg/kg day^{-1} Given that Diethylhexyl Adipate is soluble in organic solvents, but not in water, dermal penetration of Diethyhexyl Adipate is likely to be less than 1%, yielding a maximum possible systemic dose of <2 5 mg/kg day^{-1}, well below the level demonstrated to have no fetotoxic effect

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FORMALDEHYDE

A safety assessment of Formaldehyde was published in 1984 (Elder 1984) with the conclusion that this ingredient is safe in cosmetic products to the great majority of consumers, however, because of skin sensitivity of some individuals to this agent, the formulation and manufacture of a cosmetic product should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0 2% measured as free formaldehyde Furthermore, it cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized An extensive number of new studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

Data reported to the FDA by industry in 1981 indicated that Formaldehyde was used in a total of 805 cosmetic products, but that figure decreased to 120 reported uses in 2002 The maximum use concentration reported to FDA in 1981 was in the ≤0 1% to 10% range Data from an industry use concentration survey in 2003 indicate a maximum use concentration of 0 08%

Table 10 presents the recent and historical frequency of use and concentration of use data as a function of product category

The discussion section in the original safety assessment acknowledged that Formaldehyde can be a skin irritant and sensitizer in clinical tests, and a developmental toxin, a genotoxin, and a neoplastic agent in experimental animal studies The new clinical studies confirmed that Formaldehyde can be a skin irritant and sensitizer, but at levels higher than the 0 2% free Formaldehyde upper limit established by the CIR Expert Panel

The developmental toxicity, genotoxicity, and carcinogenicity of high doses of Formaldehyde was also confirmed in the new studies These studies demonstrate that there is a threshold effect, that is, high doses are required before any effect is seen Again, the limit on the amount of free Formaldehyde established by the CIR Expert Panel precludes any risk as a result of use of cosmetic products containing Formaldehyde

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TABLE 10
Historical and recent uses and use concentrations of Formaldehyde in cosmetic products

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
Baby care				
Shampoos	7	—	≤ 0 1–1	—
Lotions, oils, powders and creams	1	—	>0 1–1	—
Bath				
Soaps and detergents	5	5	≤0 1–1	<0 002–0 08
Oils, tablets and salts	10	6	≤0 1–1	0 08
Bubble baths	109	4	≤0 1–1	0 08
Other bath	24	1	≤0 1–5	0 08
Eye makeup				
Mascara	1	—	≤0 1	0 0002
Other eye makeup	3	—	≤0 1–1	—
Fragrance				
Sachets	2	—	≤0 1–1	—
Other fragrance	—	—	—	0 02
Noncoloring hair care				
Conditioners	95	11	≤0 1–5	—
Permanent waves	11	2	≤0 1–1	—
Rinses	32	2	≤0 1–1	—
Shampoos	316	59	≤0 1–5	<0 005–0 08
Tonics, dressings, etc	21	9	≤0 1–10	<0 005
Wave sets	37	8	≤0 1–10	—
Other hair	13	3	≤0 1–5	—
Hair coloring				
Dyes and colors	5	—	≤0 1	—
Shampoos	3	2	≤0 1–1	—
Makeup				
Face powders	1	—	>0 1–1	—
Foundations	2	—	≤0 1–1	—
Leg and body paints	—	—	—	0 02
Makeup bases	3	—	≤0 1–1	—
Other makeup	—	—	—	0 01
Nail care				
Cuticle softeners	1	—	≤0 1	—
Nail creams and lotions	1	1	≤0 1	—
Other manicuring	—	1	—	2*
Oral hygiene				
Dentifrices	—	—	—	0 04
Mouthwashes and breath fresheners	2	—	≤0 1–1	—
Personal hygiene				
Underarm deodorants	7	—	>0 1–1	—
Feminine hygiene deodorants	1	—	>1–5	—
Other personal cleanliness	1	1	≤0 1	0 07–0 08
Shaving				
Aftershave lotions	1	—	>0 1–1	—
Shaving creams	2	1	≤0 1	—
Other shaving	1	—	>1–5	—

(Continued on next page)

TABLE 10

Historical and recent uses and use concentrations of Formaldehyde in cosmetic products *(Continued)*

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
Skin care				
Cleansing creams, lotions, etc	13	1	≤0 1–1	<0 0001–0 002
Face and neck skin care	47**	—	≤0 1–1**	—
Body and hand skin care		2		<0 0001
Foot powders and sprays	1	—	>0 1–1	—
Moisturizers	11	1	≤0 1–1	—
Night skin care	5	—	≤0 1–1	—
Paste masks/mud packs	3	—	≤0 1–1	—
Skin fresheners	1	—	>0 1–1	—
Other skin care	4	—	>0 1–1	0 06
Suntan				
Suntan gels, creams, and liquids	2	—	≤0 1–1	—
Total uses/ranges for Formaldehyde	**805**	**120**	**≤0 1–10**	**<0 0001–0 08**

*This product was sold only in Europe and no longer marketed

**This category was combined when the original safety assessment was performed and is now two separate categories

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HYDROLYZED COLLAGEN

A safety assessment of Hydrolyzed Collagen concluded that this ingredient is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1985) New studies, along with the updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined not to reopen this safety assessment

Data reported to the FDA by industry in 1981 indicated that Hydrolyzed Collagen was used in 936 cosmetic products at concentrations ranging from $\leq$0 1% to >50% (Elder 1985) Uses reported to FDA in 2002 (Hydrolyzed Animal Protein and Hydrolyzed Animal Collagen were listed in this FDA database) decreased to 569 (FDA 2002) and an industry survey of use concentrations yielded a maximum use concentration of 1% (CTFA 2004)

Table 11 presents the historical and recent uses and concentrations of Hydrolyzed Collagen in cosmetic products The most recent data now constitute the present practices of use and concentration

The CIR Expert Panel did note that the description of Hydrolyzed Collagen has been expanded recently to include specific mention of animal and fish collagen as the source material (Hydrolyzed Collagen is the hydrosylate of animal or fish collagen derived by acid, enzyme, or other method of hydrolysis) (Gottschalck and McEwen 2004)

The CIR Expert Panel is aware of the concerns about infectious prions in products obtained from mammalian tissues As with all animal-derived ingredients, the use of Hydrolyzed Collagen should comply with FDA regulations to ensure that this ingredient is free of infectious agents, including bovine spongiform encephalopathy

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ISOSTEARYL NEOPENTANOATE

A safety assessment of Isostearyl Neopentanoate concluded that this ingredient is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1985) One new study, along with the updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined not to reopen this safety assessment

Data reported to the FDA by industry in 1981 indicated that Isostearyl Neopentanoate was used in 208 cosmetic products at concentrations >1% to 50% (Elder 1985) Uses reported to FDA in 2002 decreased to 71 (FDA 2002) and an industry survey of use concentrations yielded a use concentration range from 0 2% to 14% (CTFA 2003)

Table 12 presents the historical and recent uses of Hydrolyzed Collagen in cosmetic products The most current data are now considered the present practices of use

The CIR Expert Panel did note a new use in lipsticks at concentrations of use of 9% to 14% Oral toxicity studies in the original report suggest no concerns relating to this new use

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[13]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA

TABLE 11

Historical and recent uses and use concentrations of Hydrolyzed Collagen in cosmetic products

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2004) %
Baby care				
Shampoos	1	—	≤0 1	—
Bath				
Oils, tablets and salts	2	—	>1–5	—
Bubble baths	2	2[a]	>0 1–1	—
Soaps and detergents	3	13[a]	>0 1–5	0 1
Other bath	2	2[a]	>0 1–1	—
Eye makeup				
Eyebrow pencils	—	1[a], 1	—	—
Eyeliners	1	1[a]	≤0 1	1
Eye shadow	6	7[a]	≤1	—
Eye lotion	—	—	—	3
Eye makeup remover	—	1[a]	—	—
Mascara	28	9[a]	≤1	0 02–1
Other eye makeup	5	1[a]	≤5	0 000004
Noncoloring hair				
Hair conditioners	174	126[a]	>50	—
Hair sprays/aerosol fixatives	7	3[a]	≤1	—
Hair Straighteners	7	7[a]	>0 1–1	—
Permanent waves	70	13[a]	≤25	0 05
Rinses	34	7[a]	≤10	—
Shampoos	224	116[a]	≤10	0 02
Hair tonics, dressings, etc	35	40[a]	>50	—
Wave sets	39	4[a]	≤25	—
Other noncoloring hair	18	15[a]	≤10	0 03–0 2
Hair coloring				
Tints	14	2[a]	≤5	—
Rinses	24	—	≤0 1	—
Shampoos	—	2[a]	—	—
Bleaches	7	—	≤5	—
Other hair coloring	1	—	>0 1–1	—
Makeup				
Blushers	5	2[a]	>0 1–1	0 5
Face powders	5	4[a]	≤1	0 5
Foundations	10	7[a]	≤1	0 5–4
Lipsticks	15	7[a]	≤1	1
Makeup bases	15	4[a]	≤1	—
Other makeup	—	—	—	0 2
Nail care				
Basecoats	—	1[a]	—	—
Cuticle softeners	3	2[a]	≤1	—
Creams and lotions	6	5[a]	≤50	—
Polishes and enamels	1	—	>1–5	—
Polish and enamel removers	2	—	≤0 1	—
Other nail care	6	1[a]	≤5	—
Personal hygiene				
Other personal hygiene	—	4[a]	—	—

TABLE 11
Historical and recent uses and use concentrations of Hydrolyzed Collagen in cosmetic products *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2004) %
Shaving				
Aftershave lotions	3	1[a]	>0 1–1	0 007
Other shaving	—	1[a]	—	0 007
Skin Care				
Cleansing creams, lotions, etc	27	17[a]	≤5	—
Face and neck skin care	46[c]	18[a]	≤10[c]	0 06–6
Body and hand skin care		20[a]		1
Moisturizers	43	36[a]	≤25	1
Night skin care	11	15[a]	>0 1–25	0 02
Paste masks/mud packs	6	8[a]	≤5	0 008
Skin fresheners	7	8[a]	≤5	—
Wrinkle smoothers[d]	1	—[d]	>1–5	—[d]
Other skin care preparations	7	27[a]	≤0 1–5	0 5
Suntan Preparations				
Suntan gels, creams and liquids	—	7[a]	—	0 000004
Other suntan preparations	—	2[a]	—	0 05
Total uses/ranges for Hydrolyzed Collagen	**923**	**569[a], 1[b]**	**≤0 1– >50**	**000004–6**

[a]Ingredient identified as "Hydrolyzed Animal Protein" in the FDA database
[b]Ingredient identified as "Hydrolyzed Animal Collagen" in the FDA database
[c]This category was combined when the original safety assessment was performed and is now two separate categories
[d]No longer a cosmetic product category

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2-NITRO-*p*-PHENYLENEDIAMINE AND 4-NITRO-*o*-PHENYLENEDIAMINE

A safety assessment of 2-Nitro-*p*-Phenylenediamine and 4-Nitro-*o*-Phenylenediamine was published in 1985 with the conclusion "for those persons not sensitized, the Expert Panel concludes that 2-Nitro-*p*-Phenylenediamine and 4-Nitro-*o*-Phenylenediamine are safe as hair dye ingredients at the current concentration of use" (Elder 1985) Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

2-Nitro-*p*-Phenylenediamine was reported to be used in 28 hair dyes and colors in 1981 at concentrations from ≤0 1% to 1% (Elder 1985) In 2002, voluntary reports provided by industry to FDA indicated that 2-Nitro-*p*-Phenylenediamine was used in 113 hair dyes and colors (FDA 2002) Use concentration data from a survey of industry practices by the Cosmetic, Toiletry, and Fragrance Association (CTFA) indicated use at concentrations from 0 1% to 1% in cosmetic products (CTFA 2003)

4-Nitro-*o*-Phenylenediamine was reported to be used in 26 hair dyes and colors in 1981, at concentrations of ≤ 0 1% to 1% (Elder 1985) Industry reports to FDA in 2002 included 22 uses as hair dyes and colors Use concentration data from an industry survey in 2003 indicated use at concentrations of 0 1% to 0 2% (CTFA 2003)

The available use and concentration as a function of product type is given in Table 13 The most recent information now constitutes the current practices of use and concentration

In 2003, an updated review of the available hair dye epidemiology literature was prepared (Helzlsouer et al 2003) The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers The review highlighted well-designed studies with an exposure assessment that included hair dye type, color, and frequency or duration of use, which found associations between personal hair dye use and development of bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma These findings, however, were not consistently observed across studies

In considering all these data, the CIR Expert Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints The Panel stated that use of direct

TABLE 12

Historical and recent uses and use concentrations of Isostearyl Neopentaoate in cosmetic products

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Eye makeup				
Eyeliner	5	—	>5–10	8–13
Eye shadow	135	5	>1–10	1–13
Eye makeup remover	1	1	>10–25	—
Eye lotion	—	—	—	2
Other eye makeup preparations	3	1	>1–10	13
Fragrances				
Perfumes	—	1	—	—
Powders	—	1	—	—
Other fragrances	—	4	—	—
Makeup				
Blushers	20	8	>1–50	2–10
Foundations	10	9	>1–10	—
Face powders	—	2	—	3–6
Lipstick	—	3	—	9–14
Foundations	—	—	—	1–10
Makeup bases	16	9	>1–50	1–2
Rouges	2	—	>1–5	—
Other makeup	1	4	>10–25	0 2–12
Skin care				
Cleansing creams, lotions, etc	1	2	>5–10	3–8
Face and neck skin care	1*	1	>1–5*	4
Body and hand skin care		1		2–5
Body and hand sprays	—	—	—	6
Moisturizers	8	11	>0 1–10	—
Night skin care	1	1	>1–5	—
Paste masks/mud packs	—	1	—	4
Other skin care	1	5	>1–5	1–7
Suntan				
Suntan gels, creams, and liquids	2	—	>1–5	2–4
Indoor tanning	—	1	—	—
Other suntan	1	—	>1–5	—
Total uses/ranges for Isostearyl Neopentaoate	**208**	**71**	**>0 1–50**	**0 2–14**

*This category was combined when the original safety assessment was performed and is now two separate categories

TABLE 13

Historical and current uses and use concentrations for 2-Nitro-*p*-phenylenediamine and 4-Nitro-*o*-phenylenediamine

Product category	1981 use (Elder 1980)	2002 use (FDA 2002)	1981 concentrations (Elder 1980) %	2003 concentrations (CTFA 2003) %
	2-Nitro-*p*-phenylenediamine			
Hair dyes and colors	28	113	≤0 1–1	0 1–1
Total uses/ranges for 2-Nitro-*p*-phenylenediamine	**28**	**113**	**≤0 1–1**	**0 1–1**
	4-Nitro-*o*-phenylenediamine			
Hair dyes and colors	26	22	≤0 1–1	0 1–0 2
Total uses/ranges 4-Nitro-*o*-phenylenediamine	**26**	**22**	**≤0 1–1**	**0 1–0 2**

hair dyes, although not the focus in all investigations, appears to have little evidence of an association with adverse events as reported in epidemiology studies However, direct hair dyes are a diverse group of chemicals and the determination of safety may hinge on other safety test data

Discussion of the most recent available hair dye epidemiology data is available at http //www cir-safety org/findings shtml

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OLEIC ACID, LAURIC ACID, PALMITIC ACID, MYRISTIC ACID, AND STEARIC ACID

A safety assessment of the Oleic Acid group was published in 1987 with a conclusion that these ingredients are safe in present practices of use and concentration in cosmetics New studies regarding these fatty acids available since then, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

Oleic Acid usage increased from 424 in 1981 to 1131 in 2002, based on industry voluntary reports provided to FDA (Elder 1987, FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00004% to 20%, within the range reported in 1981 (Elder 1987)

Lauric Acid usage increased from 22 in 1981 to 121 in 2002, based on industry voluntary reports provided to FDA (Elder 1987, FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00003% to 11%, within the range reported in 1981 (Elder 1987)

Palmitic Acid usage increased from 29 in 1981 to 132 in 2002, based on industry voluntary reports provided to FDA (Elder 1987, FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00006% to 20%, within the range reported in 1981 (Elder 1987)

Myristic Acid usage increased from 36 in 1981 to 73 in 2002, based on industry voluntary reports provided to FDA (Elder 1987, FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00001% to 38%, within the range reported in 1981 (Elder 1987)

Stearic Acid usage decreased from 2465 in 1981 to 2133 in 2002, based on industry voluntary reports provided to FDA (Elder 1987, FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 000002% to 43%, within the range reported in 1981 (Elder 1987)

The available use and concentration data are given in Table 14 The most recent information now constitutes the present practices of use and concentration

The newly available studies reported findings consistent with the data in the original safety assessment One area not covered in the original report was reproductive and developmental toxicity One new study was available that demonstrated little or no toxicity to sperm cells by Oleic Acid, Palmitic Acid, and Stearic Acid

These fatty acids may be plant derived In such cases, established limits for pesticide and heavy metal residues should not be exceeded (lead $\leq$10 ppm, arsenic $\leq$3 ppm, mercury $\leq$1 ppm, total PCB/pesticide $\leq$40 ppm, with $\leq$10 ppm for any specific pesticide residue)

These fatty acids may also be derived from animal sources, including beef The Panel agrees with the Food and Drug Administration's position that tallow derivatives, including these fatty acids, would not present any risk of transmissible encephalopathies

TABLE 14
Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) %	2004 concentrations (CTFA 2005) %
		Oleic Acid		
Baby care				
Shampoos	1	1	>10–25	—
Lotions, oils, powders, and creams	1	1	>1–5	1
Other baby care	2	4	>1–25	2
Bath				
Oils, tablets, and salts	1	1	>5–10	—
Soaps and detergents	5	20	>1–10	0 000004–15
Other bath	—	10	—	—
Eye makeup				
Eyeliners	16	10	>0 1–25	0 1–3
Eye shadow	5	—	>0 1–5	0 4
Eye makeup remover	2	—	>1–5	—
Mascara	41	38	>0 1–10	1–4
Other eye makeup	1	1	>1–5	2–5 [a]
Fragrances				
Colognes and toilet waters	—	—	—	0 001
Sachets	4	2	>0 1–1	—
Other fragrances	8	5	>0 1–5	—
Noncoloring hair care				
Conditioners	1	—	>25–50	—
Permanent waves	1	2	≤0 1	—
Rinses	—	1	—	—
Shampoos	9	5	>1–25	0 000007
Tonics, dressings, etc	1	1	>0 1–1	0 6
Other noncoloring hair care	—	—	—	20 [b]
Hair coloring				
Dyes and colors	205	946	≤0 1–25	19
Tints	14	9	>1–25	—
Shampoos	7	—	>0 1–5	—
Color sprays	—	1	—	—
Lighteners with color	1	1	>1–5	—
Bleaches	8	17	>1–50	—
Makeup				
Blushers	10	2	>1–5	0 4
Face powders	1	—	>0 1–1	0 0001
Foundations	20	9	>0 1–5	0 4–2
Lipsticks	1	5	>5–10	16
Makeup bases	5	3	≤0 1–5	0 4
Rouges	—	1	—	0 00005
Other makeup	4	3	>0 1–25	2
Nail care				
Basecoats and undercoats	1	1	>10–25	—
Nail polish and enamels	—	—	—	0 0008
Other nail care	—	1	—	—

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TABLE 14

Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2005) %
Personal hygiene				
Underarm deodorants	—	—	—	0 0007–0 6
Other personal hygiene	3	4	>1–10	6[e]
Shaving				
Aftershave lotions	3	—	≤0 1–1	0 00008
Shaving cream	2	3	>1–5	0 7–4
Skin care				
Cleansing creams, lotions, etc	10	5	>0 1–5	0 00002–9
Face and neck skin care	11[c]	—	>0 1–25[c]	2
Body and hand skin care		2		0 2–0 4
Moisturizers	14	7	>0 1–5	0 2–0 4
Night skin care	—	—	—	0 5
Other skin care	2	3	>0 1–5	—
Hormone preparations[d]	1	NA[d]	>1–5	NA[d]
Suntan products				
Suntan gels, creams, liquids, and sprays	2	5	>1–5	0 02
Indoor tanning preparations	—	1	—	—
Total uses/ranges for Oleic Acid	**424**	**1131**	**≤0 1–50**	**0 000004–20**
		Lauric Acid		
Bath				
Soaps and detergents	—	16	—	0 1–8
Other bath	—	20	—	2–11
Noncoloring hair care				
Conditioners	—	1	—	0 000004–4
Sprays	—	—	—	0 00002
Shampoos	3	1	>1–25	0 2–0 5
Tonics, dressings, etc	3	5	>0 1–1	0.00003
Fragrances				
Colognes and toilet waters	—	—	—	0 001
Perfumes	—	—	—	0 00002
Hair coloring				
Dyes and colors	—	43	—	—
Makeup				
Foundations	—	—	—	1
Lipsticks	—	1	—	0 00003
Personal hygiene				
Underarm deodorants	5	3	≤0 1–1	0 3
Other personal hygiene	4	3	≤0 1–10	5[e]
Shaving				
Aftershave lotions	—	—	—	0 0003
Shaving cream	3	1	>1–10	0 003
Other shaving	—	—	—	0 2[g]
Skin care				
Cleansing creams, lotions, etc	3	25	>1–5	—
Face and neck skin care	—[c]	—	—[c]	—
Body and hand skin care		—		0 00006
Moisturizers	1	2	>0 1–1	—

TABLE 14

Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2005) %
Night skin care	—	—	—	0 00003–0 5
Other skin care	—	—	—	2–3
Suntan				
Suntan gels, creams and liquids	—	—	—	1
Total uses/ranges for Lauric Acid	**22**	**121**	**≤0 1–25**	**0 000004–11**
		Palmitic Acid		
Bath				
Soaps and detergents	1	10	>5–10	0 3–10
Other	—	11	—	0 000006–2
Eye makeup				
Eyeliners	—	—	—	0 1–0 7
Eye shadow	1	—	>5–10	0 006–0 3
Eye lotion	—	—	—	0 05
Mascara	—	1	—	0 02–4
Other eye makeup	—	2	—	0 003
Fragrance				
Colognes and toilet waters	—	—	—	0 01–0 8
Other fragrances	—	1	—	3
Noncoloring hair care				
Conditioners	—	1	—	0 00002–0 4
Shampoos	2	26	>1–5	0 001–3
Tonics, dressings, etc	—	—	—	0 00003–2
Other noncoloring hair care	—	3	—	—
Hair coloring				
Other hair coloring	—	1	—	—
Makeup				
Blushers	—	—	—	0 008–0 2
Face powders	—	1	—	0 01–1
Foundations	2	10	>0 1–5	0 3–2
Lipsticks	—	1	—	0 2–16
Rouges	—	1	—	0 00005
Makeup fixatives	—	1	—	—
Other makeup	—	—	—	0 01–2
Nail care				
Nail polishes and enamels	—	—	—	0 02–0 03
Personal hygiene				
Underarm deodorants	—	1	—	0 09–3
Other personal hygiene	—	—	—	0 3–4
Shaving				
Aftershave lotions	—	—	—	0 006
Shaving cream	4	11	>0 1–10	2–20
Shaving soap	—	—	—	0 4–8
Other shaving	—	17	—	10
Skin care				
Cleansing creams, lotions, etc	8	8	>1–25	0 03–7
Depilatories	—	—	—	4

(Continued on next page)

TABLE 14

Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2005) %
Face and neck skin care	3[c]	1	>0 1–5[c]	0 2–3
Body and hand skin care		3		0 05–7
Foot powders and sprays	—	1	—	—
Moisturizers	3	8	>0 1–5	0 2–2
Night skin care	3	—	>1–25	0 05–1
Paste masks/mud packs	—	—	—	0 02
Skin fresheners	—	1	—	—
Other skin care	1	4	>1–5	0 2–2
Suntan				
Suntan gels, creams, liquids, and sprays	1	5	>10–25	0 0009–3
Indoor tanning	—	1	—	—
Other suntan	—	1	—	—
Total uses/ranges for Palmitic Acid	**29**	**132**	**>0 1–25**	**0 000006–20**
		Myristic Acid		
Bath				
Soaps and detergents	3	7	>5–25	0 005-19
Other bath	—	11	—	0 00001–14
Eye makeup				
Mascara	2	—	>0 1–1	0 005–0 8
Fragrances				
Colognes and toilet waters	—	—	—	0 001
Other fragrances	—	1	—	—
Noncoloring hair care				
Conditioners	—	1	—	—
Shampoos	2	3	>1–5	0 00006–0 2
Tonics, dressings, etc	—	—	—	0 00002–0 08
Makeup				
Face powders	—	—	—	0 05
Foundations	—	2	—	0 4
Lipsticks	—	1	—	—
Rouges	—	—	—	0 00005
Other makeup	—	—	—	0 00004
Oral hygiene				
Dentifrices	—	—	—	0 0003
Personal hygiene				
Underarm deodorants	—	1	—	—
Other personal hygiene	2	1	>10–25	1–38[f]
Shaving				
Aftershave lotions	—	—	—	0 00008
Beard softeners	2	—	>25–50	—
Shaving cream	16	13	>1–10	3–33
Shaving soap	—	—	—	2
Other shaving	1	3	>0 1–1	—
Skin care				
Cleansing creams, lotions, etc	5	26	1–25	0 0005–12
Depilatories	—	—	—	12
Face and neck skin care	2[c]	—	>0 1–5[c]	14
Body and hand skin care		1		0 5–10
Moisturizers	1	1	>0 1–1	0 0002–1

TABLE 14

Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2005) %
Night skin care	—	—	—	0 0003
Other skin care	—	1	—	0 003–15
Total uses/ranges for Myristic Acid	**36**	**73**	**>0 1–50**	**0 00001–38**
		Stearic Acid		
Baby care				
Shampoos	—	—	—	2
Lotions, oils, powders, and creams	9	11	>0 1–10	2–3
Other baby care	1	7	>10–25	0 1–2
Bath				
Soaps and detergents	13	41	>1–25	0 2–19
Bubble baths	—	1	—	1–2
Other bath	3	13	>0 1–5	0 000007–7[h]
Eye makeup				
Eyebrow pencils	9	12	>5–25	0 009–15
Eyeliners	55	74	>0 1–50	0 7–22
Eye shadow	128	4	>0 1–5	0 3–16
Eye lotions	1	4	>1–5	0 05–3
Eye makeup remover	1	3	>0 1–1	0 1–0 5
Mascara	139	95	>0 1–50	1–21
Other eye makeup	26	32	>0 1–10	1–14
Fragrances				
Colognes and toilet waters	3	—	>1–5	1
Perfumes	3	—	>0 1–10	—
Sachets	32	4	>0 1–10	—
Other fragrances	34	31	>0 1–10	16
Noncoloring hair care				
Conditioners	18	7	≤0 1–5	0 000002–0 5
Sprays/aerosol fixatives	1	—	>1–5	—
Straighteners	6	8	>0 1–10	—
Shampoos	17	10	>0 1–25	0 000007–7
Tonics, dressings, etc	18	4	≤0 1–>50	0 01–2
Hair coloring				
Dyes and colors	76	132	>1–5	—
Tints	—	1	—	—
Rinses	—	1	—	—
Color sprays	—	1	—	—
Bleaches	4	—	>0 1–5	—
Other hair coloring	8	2	>10–25	—
Makeup				
Blushers	47	4	>0 1–10	0 8–3
Face powders	2	6	>0 1–1	0 1–1
Foundations	190	119	>0 1–25	1–5
Lipsticks	27	40	>0 1–25	0 02–9
Makeup bases	263	35	>0 1–25	2–3
Rouges	9	—	>0 1–10	0 00005–0 1
Makeup fixatives	1	4	>1–5	—
Other makeup	20	22	>0 1–25	0 01–6

(Continued on next page)

TABLE 14

Historical and current cosmetic product uses and concentrations for Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985)%	2004 concentrations (CTFA 2005)%
Nail care				
Cuticle softeners	10	8	>0 1–25	1–4
Creams and lotions	6	5	>1–5	3–5
Nail polishes and enamels	—	—	—	0 04
Other nail care	2	—	>1–10	0 05–4
Personal hygiene				
Underarm deodorants	8	21	>1–25	0 2–9
Other personal hygiene	8	6	>1–25	5–6[e]
Shaving				
Aftershave lotions	5	9	>0 1–5	0 5–2
Shaving cream	100	100	>0 1–50	1–43
Shaving soap	1	1	>25–50	0 4–2
Other shaving	6	4	>1–25	0 5–8
Skin care				
Cleansing creams, lotions, etc	173	168	≤0 1–25	1–25
Depilatories	—	—	—	7
Face and neck skin care		84		3–7
Body and hand skin care	432[c]	320	>0 1–50[c]	0 1–16
Foot powders and sprays	—	5	—	4
Moisturizers	327	356	≤1–50	0 3–10
Night skin care	67	62	≤0 1–25	0 4–2
Paste masks/mud packs	15	55	>1–25	0 4–8
Skin fresheners	4	4	>10–25	—
Skin lighteners[d]	11	—[d]	>1–25	—[d]
Hormone preparations[d]	3	—[d]	>1–25	—[d]
Wrinkle smoothers[d]	4	—[d]	>1–5	—[d]
Other skin care	55	133	>0 1–25	0 0005–5
Suntan				
Suntan gels, creams, liquids, and sprays	48	42	>0 1–25	—
Indoor tanning	3	9	>0 1–1	0 3–2
Other suntan	13	13	>0 1–5	—
Total uses/ranges for Stearic Acid	**2465**	**2133**	**≤0 1–>50**	**0 000007–43**

[a]The 5% concentration was for a definer

[b]A hair care protective oil

[c]These categories were combined in 1981, but are now separate

[d]No longer considered as a cosmetic ingredient category

[e]A hand wash product

[f]The highest concentration was for a hand wash product

[g]The 0 2% concentration was specifically reported in a shave lubricant product

[h]The 7% concentration was for a body scrub product

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PANTHENOL AND PANTOTHENIC ACID

A safety assessment of Panthenol and Pantothenic Acid was published in 1987 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1987) Studies published since the last assessment, along with updated information concerning frequency of use and use concentrations, were considered by the CIR Expert Panel The Panel determined to not reopen the safety assessment

The safety assessment applies to Panthenol in both the D and the DL form

The available use and concentration information is provided in Table 15 The most recent information now constitutes the present use of these ingredients

Panthenol reported usage increased from 284 in 1981 to 1538 in 2002, based on industry voluntary reports provided to FDA (Elder 1987, FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00005% to 6%, which is lower than the maximum use concentration range reported in 1981 (Elder 1987)

Pantothenic Acid was not reportedly used in cosmetics in 1981 (Elder 1987), but industry voluntary reports provided to FDA in 2002 included three uses in eye makeup and skin care products (FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00001% to 0 01% in those product categories and in makeup and shaving preparations (categories in which no uses were reported to FDA)

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TABLE 15

Historical and current cosmetic product uses and concentrations for Panthenol and Pantothenic Acid

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) %	2004 concentrations (CTFA 2004) %
		Panthenol		
Baby care				
Lotions, oils, powders, and creams	—	3	—	—
Bath				
Oils, tablets and salts	—	—	—	2
Soaps and detergents	—	15	—	0 05–4
Bubble baths	—	3	—	0 01–2
Capsules	—	1	—	—
Other bath	—	11	—	0 3–2
Eye makeup				
Eyebrow pencils	—	3	—	0 01–2
Eyeliners	5	—	>0 1–1	0 01–0 05
Eye shadow	23	—	>0 1–1	0.5–1
Eye lotions	—	5	—	0 01–0 6
Eye makeup remover	2	8	>0 1–1	0 001–1
Mascara	10	70	>0 1–5	0 1–2
Other eye makeup	2	14	>0 1–1	0 3–0 5
Fragrances				
Colognes and toilet waters	1	5	>0 1–1	0 003–0 1
Perfumes	—	—	—	1
Powders	—	3	—	—
Other fragrances	—	11	—	1
Noncoloring hair care				
Conditioners	33	264	≤0 1–5	0 09–6
Sprays/aerosol fixatives	17	82	≤0 1–1	0 01–5
Straighteners	—	1	—	—
Permanent waves	2	6	>0 1–1	5
Rinses	1	6	>0 1–1	0 1–0 5
Shampoos	25	206	≤0 1–5	0 01–5
Tonics, dressings, etc	11	187	≤0 1–1	0 01–5
Wave sets	31	12	≤0 1–5	0 9–1
Other noncoloring hair care	6	93	≤0 1–1	0 01–1*
Hair coloring				
Dyes and colors	—	52	—	0 01–0 1
Tints	—	1	—	—
Color sprays	—	2	—	—
Bleaches	—	1	—	0 5
Other hair coloring	—	6	—	0 00005–1
Makeup				
Blushers	3	2	>0 1–1 >10–25	0 2–1
Face powders	1	1	>0 1–1	0 02–1
Foundations	8	45	≤0 1–1	0 2–1
Lipsticks	27	6	≤0 1–5	0 01–2
Makeup bases	1	8	≤0 1	0 5
Rouges	1	—	>0 1–1	—
Other makeup	2	4	>0 1–1	<1–6

TABLE 15

Historical and current cosmetic product uses and concentrations for Panthenol and Pantothenic Acid *(Continued)*

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) %	2004 concentrations (CTFA 2004) %
Nail care				
Basecoats and undercoats	—	9	—	0.03–0.2
Cuticle softeners	1	4	>0.1–1	0.1–0.2
Creams and lotions	1	1	>0.1–1	0.05–0.5
Polishes and enamels	—	10	—	0.2–1
Polish and enamel removers	—	5	—	0.03–0.5
Other nail care	—	11	—	0.1–0.2
Personal hygiene				
Underarm deodorants	1	3	>0.1–1	0.05–0.5
Douches	—	—	—	0.1–0.8
Other personal hygiene	—	8	—	0.1
Shaving				
Aftershave lotions	3	14	≤0.1–1	0.03–3
Preshave lotions	1	—	>0.1–1	—
Shaving cream	—	1	—	0.1–0.3
Other shaving	1	2	>0.1–1	0.4–1
Skin care				
Cleansing creams, lotions, etc	5	38	>0.1–1	0.05–3
Depilatories	—	—	—	1
Face and neck skin care	8**	29	≤0.1–1**	0.001–6
Body and hand skin care		32		0.1–5
Body and hand sprays	—	—	—	2
Foot powders and sprays	—	—	—	0.5
Moisturizers	22	98	≤0.1–5	0.1–3
Night skin care	14	29	>0.1–1	0.08–2
Paste masks/mud packs	1	24	≤0.1	0.1–5
Skin fresheners	2	15	>0.1–1	0.01–3
Other skin care	5	46	≤0.1–1	0.1–5
Suntan				
Suntan gels, creams, liquids, and sprays	5	10	>0.1–1	0.1–2
Indoor tanning	—	2	—	0.1–2
Other suntan	2	10	>0.1–1	0.5
Total uses/ranges for Panthenol	**284**	**1538**	**≤0.1–25**	**0.00005–6**
	Pantothenic Acid			
Eye makeup				
Mascara	—	—	—	0.001–0.01
Other eye makeup	—	1	—	—
Makeup				
Face powders	—	—	—	0.001
Foundations	—	—	—	0.002
Shaving				
Aftershave lotions	—	—	—	0.001
Shaving cream	—	—	—	0.00001
Skin Care				
Moisturizers	—	1	—	0.003
Other skin care	—	1	—	0.001
Total uses/ranges for Pantothenic Acid	**—**	**3**	**—**	**0.00001–0.01**

*Includes two non-aerosol hair sprays

**These categories were combined originally, but are now separate

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p-PHENYLENEDIAMINE

A safety assessment on *p*-Phenylenediamine was published in 1985 in which the CIR Expert Panel acknowledged that *p*-Phenylenediamine is a known sensitizer and some persons may be sensitized under intended conditions of use For those persons not sensitized, the Expert Panel concluded that *p*-Phenylenediamine is safe as a hair dye ingredient at the current concentrations of use (Elder 1985) Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel The Panel determined to not reopen the safety assessment

Although the safety of *p*-Phenylenediamine as a hair dye ingredient was reaffirmed, the Panel did agree with FDA that other uses of this dye are unapproved The Panel expressed particular concern over the practice of combining *p*-Phenylenediamine with henna (so-called dark henna) for use in temporary tattoos—*p*-Phenylenediamine is a known sensitizer, highly inappropriate for such use as evidenced by reports of severe adverse skin reactions to dark henna temporary tattoos The Panel urged users to report adverse reactions to the FDA (for more information see the FDA website at http //www cfsan fda gov/~dms/costatt html) The Panel also will work with the Consumer Federation of America to help the public understand the need to avoid using such unapproved and potentially dangerous products

The CIR Expert Panel also reviewed hair dye epidemiology data In 1993, an International Agency for Research on Cancer (IARC) working group evaluated 78 epidemiology literature citations and concluded that "personal use of hair colourants cannot be evaluated as to its carcinogenicity" and that occupation as a hairdresser or barber entails exposures that are probably carcinogenic" (IARC 1993) The IARC report did not distinguish between personal use of oxidative/permanent versus direct hair dyes, or distinguish among the multiple chemical exposures in addition to hair dyes to which a hairdresser or barber might be exposed

In 2003, an updated review of the available epidemiology literature was prepared (Helzlsouer et al 2003) This review considered 83 literature citations available since the IARC review The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers

In considering this information, the CIR Expert Panel agrees that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other end points described in the Helzlsouer et al (2003) review

The Panel also stated that use of direct hair dyes, although not the focus in all investigations, appear to have little evidence of an association with adverse events as reported in epidemiology studies However, direct hair dyes are a diverse group of chemicals and the determination of safety may hinge on other safety test data

p-Phenylenediamine was used in 500 hair-coloring products in 1981, at concentrations of ≤0 1% to 5% In 2002, *p*-Phenylenediamine was used in 1178 hair-coloring products and in 2 nail care products Use concentration data provided in 2002 indicated use at concentrations of ≤0014% to ≤4% in hair coloring products The 2004 use concentration data were provided by CTFA (CTFA 2004)

Available use and concentration information is shown in Table 16 The most recent information now constitutes the present practices of use

TABLE 16

Historical and current cosmetic product uses and concentrations for *p*-Phenylenediamine

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2004 concentrations (CTFA 2005) %
Hair coloring				
Dyes and colors	493	1167	≤0 1–5	≤4
Tints	7	9	≤0 1	—
Rinses	—	—	—	≤0 0014
Color sprays	—	1	—	—
Lighteners with color	—	1	—	—
Nail care				
Basecoats and undercoats	—	2	—	—
Total uses/ranges for *p*-Phenylenediamine	**500**	**1180**	**≤0 1–5**	**≤0 0014–≤4**

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PHENYL TRIMETHICONE

In 1986, the CIR Expert Panel found that Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1986) A review of the recent literature uncovered no new studies regarding Phenyl Trimethicone

but the Panel did consider updated information regarding uses and use concentrations The Panel determined to not reopen the safety assessment

Phenyl Trimethicone uses have increased from 169 in 1981 to 279 in 2002, based on industry voluntary reports provided to FDA (Elder 1986, FDA 2002) An industry survey in 2003 indicated that use concentrations range from 0 0075% to 36% (CTFA 2004) The maximum value in that range is higher than the maximum use concentration of 5% reported in 1981 (Elder 1986) Table 17 presents the available use and concentration information for Phenyltrimethicone The most recent information now represents the present practice of use and concentration

The Panel considered the increased use concentrations in the context of the reproductive and developmental toxicity data in the original safety assessment Phenyl Trimethicone was not teratogenic at 500 mg/kg/day in rats and rabbits For a 70-kg person, this dose corresponds to 35 g/day At the current maximum use in lipsticks and the amount of lipstick used in a typical day, a dose of Phenyl Trimethicone was estimated to be 10 mg/day This dose was 3500× lower than the observable effect level

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PROPYLENE CARBONATE

A safety assessment of Propylene Carbonate was published in 1987 with the conclusion that it is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1987) Studies published since the last assessment were reviewed along with updated information concerning frequency of use and use concentrations The CIR Expert Panel determined to not reopen the safety assessment

Based on voluntary reports provided by industry to FDA, there were 295 reported uses in 1981 (Elder 1987) and 178 reported uses in 2002 (FDA 2002) Use concentrations from an industry survey (CTFA 2003) ranged from 0 003% to 6%, not very different from the use concentration range reported in 1981 of ≤0 1% to >5% (Elder 1987)

Table 18 presents the available use and concentration information for Propylene Carbonate The most recent information constitutes present practices of use and concentration

[18]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW Suite 412, Washington, DC 20036-4702, USA

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POLYVINYLPYRROLIDONE/VINYL ACETATE COPOLYMER

In 1983, the CIR Expert Panel concluded that this ingredient is safe as a cosmetic ingredient under the present practices of product and concentration use (Elder 1983) New studies available since that review have been considered by the Expert Panel,

[19]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA

TABLE 17

Historical and current cosmetic product uses and concentrations for Phenyl Trimethicone

Product category	1981 uses (Elder 1986)	2002 uses (FDA 2002)	1986 concentrations (Elder 1986) %	2003 concentrations (CTFA 2004) %
Baby Care	1*	—	>0 1–1*	—
Bath				
Oils, tablets and salts	1	1	>0 1–1	—
Other bath	2	—	>1–5	—
Eye Makeup				
Eyeliners	—	1	—	2–6
Eye shadow	1	77	≤0 1–5	4–13
Eye lotions	—	—	—	0 008–1
Mascara	1	1	>0 1–1	0 1–0 4
Other eye makeup	1	4	>0 1–1	6–15
Fragrances				
Colognes and toilet waters	—	—	—	0 5
Perfumes	—	1	—	—
Powders	—	1	—	—
Other fragrances	—	—	—	0 5
Noncoloring hair care				
Conditioners	10	8	≤0 1–5	0 3–2
Sprays	25	23	≤0 1–1	0 1–18
Straighteners	1	—	>1–5	—
Rinses	1	—	>0 1–1	—
Shampoos	—	—	—	1
Tonics, dressings, etc	9	31	≤0 1–5	5–11
Wave sets	2	—	>0 1–5	—
Other noncoloring hair care	1	7	>0 1–1	0 5–2
Makeup				
Blushers	11	1	>1–5	2–15
Face powders	2	9	>0 1–1	0 1–8
Foundations	2	17	>1–5	2–22
Leg and body paints	—	—	—	2
Lipsticks	2	34	>1–5	0 08–36
Makeup bases	2	8	≤0 1–5	—
Rouges	—	2	—	—
Other makeup	—	13	—	0 0075–22
Nail care				
Creams and lotions	—	—	—	0 5
Polishes and enamels	7	—	>0 1–1	—
Personal hygiene				
Underarm deodorants	—	1	—	—
Other personal hygiene	—	1	—	—
Shaving				
Aftershave lotions	—	1	—	0 5–2
Preshave lotions	6	1	>0 1–5	2
Other shaving	—	—	—	0 5
Skin care				
Cleansing creams lotions, etc	—	4	—	2–4
Face and neck skin care	8**	3	≤0 1–1**	4–6
Body and hand skin care		4		0 2–18
Moisturizers	7	15	≤0 1–5	0 8–3
Night skin care	1		≤0 1	2
Other skin care	1		>1–5	2
Suntan				
Suntan gels creams, liquids and sprays	6	2	—	0 5–9
Indoor tanning	1	8	—	0 2–5
Other suntan	1		>1–5	2
Total uses/ranges for Phenyl Trimethicone	**113**	**279**	**≤0 1–5**	**0 0075–36**

*Product categories within the group not given

**These categories were combined originally, but are now separate

TABLE 18
Current and historical uses and concentrations of Propylene Carbonate in cosmetics

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) %	2003 concentrations (CTFA 2003) %
Bath				
Oils, tablets and salts	1	1	>1–5	—
Eye makeup				
Eyebrow pencils	6	6	>1–5	0 3
Eyeliners	17	15	>1–5	0 2–0 6
Eye shadow	42	10	>0 1–5	0 4–1
Eye lotions	1	—	>1–5	—
Eye makeup remover	—	3	—	—
Mascara	34	22	>0 1–5	2–4
Other eye makeup	9	12	>0 1–5	0 5
Fragrances				
Colognes and toilet waters	5	—	>1–5	—
Perfumes	4	—	>1–5	—
Noncoloring hair care				
Conditioners	1	—	>1–5	—
Tonics, dressings, etc	—	1	—	—
Hair Coloring				
Other hair coloring	3	1	>1–5	—
Makeup				
Blushers	13	1	≤0 1–>5	1–2
Face powders	1	—	>1–5	0 4
Foundations	11	3	>0 1–5	0 6–2
Rouges	—	—	—	0 1
Lipsticks	95	35	≤0 1–>5	0 03–2
Makeup bases	13	4	>0 1–1	—
Makeup fixatives	1	2	>1–5	—
Other makeup	9	20	>0 1–5	1
Nail care				
Creams and lotions	1	—	>1–5	—
Polish and enamel	—	—	—	0 003
Polish and enamel removers	—	6	—	1
Other nail care	—	—	—	4
Personal hygiene				
Underarm deodorants	—	2	—	0 2–5
Other personal hygiene	4	26	≤0 1–>5	—
Skin care				
Cleansing creams, lotions, etc	9	1	>1–5	0 1
Face and neck skin care	1*	—	>0 1–1*	—
Body and hand skin care		—		—
Moisturizers	2	4	>1–5	0 02–0 2
Night skin care	4	1	>1–5	—
Paste masks/mud packs	—	1	—	0 3–2
Skin fresheners	1	—	>0 1–1	—
Suntan preparations				
Suntan gels, creams, and liquids	6	1	>1–5	0 08–0 2
Other suntan preparations	1	—	>1–5	—
Total uses/ranges for Propylene Carbonate	**295**	**178**	**≤0 1–>5**	**0 003–5**

*These categories were combined originally, but are now separate

along with the most current information available on use and concentration The Panel noted that most of the newly available data concern Vinyl Acetate The Panel determined to not reopen this safety assessment

As given in the 9th edition of the *International Cosmetic Ingredient Dictionary and Handbook*, the name of this ingredient has been changed to VP/VA Copolymer (Pepe et al 2002)

Based on voluntary reports provided by industry to FDA, there were 114 reported uses of this ingredient in 1976 (Elder 1983) and 210 reported uses in 2002 (FDA 2002) Use concentrations from an industry survey (CTFA 2003) ranged from 0 3% to 68%, but these data were clarified to note that the product reported to contain 68% is no longer on the market The actual current use concentration range is 0 3% to 12%, which is in the range of >0 1% to >50% reported in 1976 (Elder 1983)

Table 19 presents the available use and use concentration information The most current data now represent the present practices of use

The Panel acknowledged that inhalation of Vinyl Acetate is associated with nasopharyngeal carcinoma The mechanism of action appears to be an irritant-hyperproliferative type which requires a threshold dose Two factors suggest that threshold doses could not be achieved from inhalation of cosmetics First, the VP/VA Copolymer is stable, even under adverse environmental conditions, so that there will be little, if any, Vinyl Acetate actually present, especially since the maximum use concentration is 12% Second, the effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition (Jensen and O'Brien 1993) within the respiratory system Particle size is the most important factor affecting the location of deposition The mean aerodynamic diameter of pump hair spray particles is approximately 80 μm, and diameter of anhydrous hair spray particles is 60 to 80 μm Typically, less than 1% are below 10 μm, which is the upper limit for respirable particles (Bowen 1999) Based on the particle size, VP/VA Copolymers would not be respirable in formulation

TABLE 19
Historical and current uses and use concentrations for VP/VA Copolymer

Product category	1976 uses (Elder 1983)	2002 uses (FDA 2002)	1976 use concentrations (Elder 1983) %	2003 use concentrations (CTFA 2003) %
Eye makeup				
Eyeliner	—	—	—	0 3
Eye shadow	—	—	—	2
Mascara	2	2	>1–5	6–9
Other eye makeup	—	8	—	—
Noncoloring hair care				
Hair conditioners	17	12	>1–50	0 3
Hair sprays	27	26	>0 1–10	2–4
Permanent waves	1	—	>0 1–1	—
Shampoos	2	1	>0 1–50	7
Tonics, dressings, etc	6	87	>0 1–25	4–12
Wave sets	50	12	>0 1–>50	7
Other noncoloring hair care	4	52	>5–25	8
Hair coloring				
Color sprays	—	1	—	0 5
Bleaches	1	2	>1–5	—
Makeup				
Foundations	—	—	—	0 5
Makeup fixatives	1	—	>0 1–1	4
Other makeup	1	4	>0 1–1	2
Nail care				
Cuticle softeners	1	—	>1–5	—
Skin care				
Body and hand skin care	—	1	—	—
Paste masks/mud packs	—	2	—	10
Other skin care preparations	1	—	>1–5	68*
Total uses/ranges of VP/VA Copolymer	**114**	**210**	**>0 1–>50**	**0 3–12**

*This product no longer is marketed, so this use concentration is not included in the total range

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[20]Available for review: Director Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA

SAFFLOWER OIL

In 1985 the CIR Expert Panel concluded that this ingredient is safe as a cosmetic ingredient in the present practices of use (Elder 1985) Studies available since that safety assessment was completed, along with the updated information regarding uses and use concentrations were considered by the CIR Expert Panel The Panel determined not to reopen this safety assessment

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottshcalck and McEwen 2004) has changed Safflower Oil is currently Carthamus Tinctorius (Safflower) Seed Oil

Carthamus Tinctorius (Safflower) Seed Oil was used in 94 products in 1981, based on voluntary reports provided to FDA by industry, and use concentrations ranged from less than 0 1% to greater than 50% (Elder 1985) In 2002 there were 142 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0 00005% to 84% (CTFA 2004)

Table 20 presents the available use information The most recent information is now considered to be the present practices of use and concentration

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SODIUM BORATE AND BORIC ACID

In 1983, the CIR Expert Panel concluded that Sodium Borate and Boric Acid, at concentrations ≤5%, are safe as cosmetic ingredients when used as currently recommended, but that cosmetic formulations containing free Sodium Borate or Boric Acid should not be used on infant or injured skin (Elder 1983) Studies available since that safety assessment was completed, along

[21]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA

TABLE 20

Historical and current cosmetic product uses and concentrations for Carthamus Tinctorius (Safflower) Seed Oil

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2004) %
Baby care				
Lotions, oils, powders, and creams	—	—	—	10
Bath				
Oils, tablets, and salts	1	—	>0 1–1	7
Other bath	2	1	>0 1–1	—
Eye makeup				
Eye makeup remover	1	—	>10–25	2
Mascara	—	—	—	1
Other eye makeup	1	5	>0 1–1	6
Fragrances				
Other fragrances	—	1	—	5
Noncoloring hair care				
Conditioners	—	15	—	—
Sprays/aerosol fixatives	1	2	>5–10	—
Rinses	—	1	—	—
Shampoos	—	5	—	—
Tonics, dressings, etc	—	5	—	0 00005–27
Hair coloring				
Other hair coloring	—	—	—	1
Makeup				
Blushers	—	—	—	2
Foundations	6	2	>0 1–5	0 02–27
Lipsticks	4	18	≤0 1–5	0 1–60
Makeup bases	5	3	—	—
Other makeup	3	1	>1–5	—
Nail care				
Creams and lotions	—	1	—	—
Other nail care	—	—	—	84
Shaving				
Shaving cream	—	—	—	0 01
Skin Care				
Cleansing creams, lotions, etc	7	3	≤0 1–10	0 001–5
Face and neck skin care	15*	4	≤0 1–50*	0 5–8
Body and hand skin care		16		0 3–4
Foot powders and sprays	—	—	—	—
Moisturizers	28	17	≤0 1– >50	0 2–20
Night skin care	3	5	>1–50	—
Paste masks/mud packs	1	3	>5–10	72
Skin fresheners	1	1	>0 1–1	—
Wrinkle smoothers**	1	—	>25–50	—
Other	7	16	≤0 1– >50	0 03
Suntan products				
Suntan gels, creams, liquids and sprays	7	16	>0 1–>50	0 1
Indoor tanning preparations	—	1	—	—
Total uses/ranges for Carthamus Tinctorius (Safflower) Oil	**94**	**142**	**≤0 1–>50**	**0 00005–84**

*These categories were combined in 1981, but since have been separated

**No longer a cosmetic product category

with the updated information regarding uses and use concentrations were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

Sodium Borate was used in 488 products in 1981, based on voluntary reports provided to FDA by industry, use concentrations ranged from less than 0 1% to greater than 50% (Elder 1983) In 2002 there were 280 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0 1% to 3% (CTFA 2002)

Boric Acid was used in 142 ingredients in 1981, based on voluntary reports provided to FDA by industry, and use concentrations ranged from less than 0 1% to greater than 50% (Elder 1985) In 2002 there were 77 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0 1% to 2% (CTFA 2002)

Table 21 presents the available usage and use concentration information as a function of cosmetic product category for both ingredients

Significant among the new studies considered by the CIR Expert Panel are those on the reproductive and developmental toxicity of Boric Acid Under the auspices of the National Toxicology Program, Fail et al (1991) reported results of a reproductive assessment by continuous breeding protocol in which Boric Acid administered to rats in their feed was determined to be a reproductive toxicant The NOAEL was suggested to be 110 mg/kg day^{-1} and the LOAEL was 598 mg/kg day^{-1} Price et al (1997) reported results of another rat feeding study with a NOEAL of 10 mg/kg day^{-1} and a LOEAL of 13 mg/kg day^{-1} for decreased fetal body weight per litter Yoshizaki et al (1999) reported that an oral study using rats resulted in a NOAEL of 50 mg/kg day^{-1} and a LOAEL of 150 mg/kg day^{-1} for reduced sperm counts and the same NOAEL and LOAEL values for reduced implants and viable embryos

The CIR Expert Panel considered that these findings do not suggest any reason for concern in the context of current use concentrations and the low dermal absorption through intact skin These findings reinforce the Panel's prior determination that these ingredients should not be used on damaged skin, i e , skin in which the barrier function has been compromised by disease or injury

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TABLE 21
Historical and current uses and use concentrations for Sodium Borate and Boric Acid

Product category	1981 uses (Elder 1983)	2002 uses (FDA 2002)	1981 use concentrations (Elder 1983) %	2002 use concentrations (CTFA 2002) %
		Sodium Borate		
Baby care				
Lotions, oils, powders, creams	1	—	0.1–1	—
Bath				
Soaps and detergents	1	1	>0–0.1	20[a]
Bath oils, tablets, salts	3	—	1–50	—
Bubble baths	10	—	10–50	—
Eye makeup				
Eyeliner	14	1	0.1–5	—
Eye shadow	—	—	—	0.2
Eye lotion	2	—	0.1–1	—
Eye makeup remover	5	2	>0–5	—
Mascara	24	12	0.1–10	0.6
Other eye makeup	4	1	0.1–1	2
Fragrances				
Other fragrances	4	1	>0–1	—
Noncoloring Hair Care				
Conditioners	3	2	0.1–1	0.6
Sprays	1	—	1–5	—
Straighteners	2	—	1–5	—
Permanent waves	16	5	0.1–10	—
Shampoos	2	1	0.1–1	—
Tonics, dressings, etc	13	7	>0–5	—
Wave sets	3	—	>0–1	—
Other hair care	3	1	0.1–10	—
Hair coloring				
Other hair coloring	3	—	0.1–1	—
Makeup				
Blushers	2	2	0.1–1	0.2
Face powders	—	1	—	—
Foundations	4	3	0.1–1	0.2–0.5
Lipstick	1	—	0.1–1	—
Makeup bases	19	15	0.1–5	—
Other makeup	1	—	0.1–1	1
Nail care				
Cuticle softeners	—	1	—	—
Nail creams and lotions	2	—	0.1–1	—
Oral hygiene				
Dentifrices	—	3	—	—
Mouthwashes and breath fresheners	—	1	—	—
Personal hygiene				
Underarm deodorants	2	—	>0–1	—
Other personal hygiene	8	6	5–>50	0.1
Shaving				
Aftershave lotions	2	—	>0–0.1	—
Shaving cream	4	8	0.1–5	—
Other shaving	1	1	0.1–1	—

TABLE 21
Historical and current uses and use concentrations for Sodium Borate and Boric Acid *(Continued)*

Product category	1981 uses (Elder 1983)	2002 uses (FDA 2002)	1981 use concentrations (Elder 1983) %	2002 use concentrations (CTFA 2002) %
Skin care				
Cleansing creams, lotions, etc	144	68	>0–5	0.4–1
Depilatories	1	—	0.1–1	—
Face and neck skin care	71[b]	11	>0–5[b]	—
Body and hand skin care		32		0.4–0.8
Moisturizers	47	31	>0–5	0.3–1
Night skin care	37	22	>0–1	0.4–0.9
Paste masks/mud packs	3	6	1–5	0.2–3
Fresheners	12	4	>0–1	0.3
Other skin care	1	23	>0–>50	0.6–0.8
Skin lighteners[c]	1	NA[c]	0.1–1	NA[c]
Hormone products[c]	2	NA[c]	0.1–5	NA[c]
Wrinkle smoothing[c]	4	NA[c]	0.1–5	NA[c]
Suntan				
Suntan gels, creams, liquids	5	5	0.1–1	0.4
Other suntan	—	3	—	—
Total uses/ranges for Sodium Borate	**488**	**280**	**>0–>50**	**0.1–3**
		Boric Acid		
Baby Care				
Baby shampoos	1	—	0.1–1	—
Bath				
Soaps and detergents	1	—	1–5	
Oils, tablets, and salts	1	1	0.1–1	—
Bubble baths	—	1	—	—
Eye makeup				
Eye lotion	1	—	1–5	—
Eye makeup remover	3	4	0.1–5	—
Fragrances				
Powders	13	7	0.1–5	—
Other fragrances	1	—	0.1–1	—
Noncoloring hair care				
Conditioners	—	1	—	2
Permanent waves	13	5	0.1–5	—
Rinses	1	—	1–5	—
Shampoos	13	8	0.1–5	—
Tonics, dressings, etc	3	1	>0–1	—
Wave sets	2	3	>0–5	—
Other hair care	3	—	0.1–5	—
Hair coloring				
Coloring rinses	14	—	1–10	—
Bleaches	—	3	—	—
Other hair coloring	3	—	0.1–5	—
Makeup				
Blushers	2	—	0.1–1	—
Face powders	1	1	0.1–1	—
Rouges	1	—	0.1–1	—
Makeup fixatives	2	2	1–5	—

(Continued on next page)

TABLE 21

Historical and current uses and use concentrations for Sodium Borate and Boric Acid *(Continued)*

Product category	1981 uses (Elder 1983)	2002 uses (FDA 2002)	1981 use concentrations (Elder 1983) %	2002 use concentrations (CTFA 2002) %
Oral hygiene				
Mouthwashes and breath fresheners	5	—	>0–5	—
Personal hygiene				
Underarm deodorants	5	2	1–10	—
Douches	5	1	>50	10[c]
Other personal hygiene	1	2	0 1–1	—
Shaving				
Aftershave lotions	5	5	>0–5	0 4
Preshave lotions	1	—	>0–0 1	—
Shaving cream	6	4	0 1–5	0 1–1
Other shaving	1	1	0 1–1	—
Skin care				
Cleansing creams, lotions, etc	4	2	0 1–5	—
Face and neck skin care	5[b]	—	0 1–5[b]	—
Body and hand skin care		9		—
Foot powders and sprays	—	1	—	—
Moisturizers	4	2	0 1–5	0 5
Night skin care	1	1	0 1–1	—
Paste masks/mud packs	3	3	0 1–5	—
Skin fresheners	17	6	>0–5	—
Other skin care	—	1	—	—
Total uses/ranges of Boric Acid	**142**	**77**	**>0–>50**	**0 1–2**

[a]Diluted to about 0 3% Sodium Borate during use

[b]These categories were combined in 1981 but are now separate

[c]No longer considered as cosmetic product categories

[d]Powder dissolved in water to produce a solution of about 0 1% Boric Acid before use

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SODIUM DEHYDROACETATE AND DEHYDROACETIC ACID

A safety assessment of Sodium Dehydroacetate and Dehydroacetic Acid was published in 1985 with the conclusion that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration (Elder 1985) Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

Sodium Dehydroacetate was used in 260 products in 1981, based on voluntary reports provided to FDA by industry, use concentrations ranged from less than 0 1% to 1% (Elder 1985) In 2002 there were 325 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0 00003% to 0 5% (CTFA 2002)

Dehydroacetic Acid was used in 139 products in 1981, based on voluntary reports provided to FDA by industry, use concentrations ranged from less than 0 1% to 1% (Elder 1985) In 2002 there were 88 uses (FDA 2002) and according to an industry survey the current range of use concentrations is 0 007% to 0 7% (CTFA 2002)

Table 22 presents the available use and concentration information The most recent information now constitutes the present practices of use

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SODIUM LAURYL SULFOACETATE

A safety assessment on Sodium Lauryl Sulfoacetate was published in 1987 with the conclusion "On the basis of the available data presented in this report, the Expert Panel concludes that Sodium Lauryl Sulfoacetate is safe as a cosmetic ingredient in the present practices of use and concentration" (Elder 1987) Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel After reviewing the available data, the Panel determined to not reopen this safety assessment

Sodium Lauryl Sulfoacetate was used in 93 products in 1981, based on voluntary reports provided to FDA by industry, use concentrations ranged from >0 1% to >50% (Elder 1985) In 2002 there were 68 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 0 6% to 21% (CTFA 2004)

Table 23 presents the available use and concentration information The most recent information now constitutes the present practices of use

The CIR Expert Panel did note that Stepan Company had submitted robust summaries and test plans on Sodium Lauryl Sulfoacetate as part of EPA's high production volume chemical testing program This submission argued that the only missing data were reproductive and developmental toxicity data The company proposed conducting such a study Though the Panel noted that there are no data in the published literature,

TABLE 22

Historical and current uses and use concentrations for Sodium Dehydroacetate and Dehydroacetic Acid

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
		Sodium Dehydroacetate		
Baby care				
Lotions, oils, powders & creams	—	—	—	0 6
Bath				
Soaps and detergents	—	2	—	0 0001
Oils, tablets, and salts	1	—	≤0 1	—
Eye makeup				
Eyebrow Pencil	—	—	—	0 2–0 3
Eyeliner	2	4	≤0 1–1	0 05–0 5
Eye shadow	56	74	≤0 1–1	0 05–0 3
Eye lotion	—	3	—	—
Eye makeup remover	—	1	—	0 05
Mascara	13	16	≤0 1–1	0 001–0 4
Other eye makeup	4	12	>0 1–1	0 0006–0 4
Fragrances				
Powders	1	3	>0 1–1	—
Colognes and toilet waters	—	—	—	0 001–0 5
Noncoloring hair care				
Conditioners	—	—	—	0 2
Shampoos	—	2	—	0 2
Tonics, dressings, etc	1	1	≤0 1	—
Other noncoloring hair care	—	4	—	—
Hair coloring				
Tints	—	1	—	—
Other hair coloring	—	2	—	—
Makeup				
Blushers	22	15	≤0 1–1	0 1–0 4
Face powders	23	31	≤0 1–1	0 05–0 4
Makeup foundations	8	10	≤0 1–1	0 0001–0 4
Makeup bases	14	6	>0 1–1	0 1
Leg and body paints	—	—	—	0 1
Lipstick	—	1	—	0 3
Rouges	2	—	≤0 1–1	—
Makeup fixatives	—	1	—	—
Other makeup	2	4	>0 1–1	0 0003–0 2
Nail care				
Basecoats and undercoats	—	—	—	0 02
Nail creams and lotions	—	3	—	—
Cuticle Softeners	4	2	>0 1–1	—
Creams and lotions	2	—	≤0 1–1	—
Polish and enamel	—	—	—	0 2
Other nail care	1	—	>0 1–1	0 2
Personal hygiene				
Underarm deodorants	—	2	—	—
Shaving				
Shaving cream	1	4	>0 1–1	—
Other shaving	1	1	>0 1–1	—
Aftershave lotions	1	1	≤0 1	0 0003

TABLE 22

Historical and current uses and use concentrations for Sodium Dehydroacetate and Dehydroacetic Acid *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) (%)	2003 concentrations (CTFA 2003) (%)
Skin care				
Skin-cleansing preparations	23	13	≤0.1–1	0.0003–0.3
Face and neck skin care	24*	4	≤0.1–1*	0.008–0.2
Body and hand skin care		20		0.00003–0.5
Moisturizers	27	39	≤0.1–1	0.001–0.3
Night skin care	7	5	≤0.1	0.003–0.2
Paste masks/mud packs	4	6	≤0.1–1	0.03–0.2
Fresheners	2	2	>0.1–1	—
Other skin care	—	25	—	0.00003–0.1
Skin lighteners**	2	—**	≤0.1–1	—**
Wrinkle smoothers**	1	—**	>0.1–1	—**
Suntan				
Suntan gels, creams, and liquids	5	1	>0.1–1	0.2
Indoor tanning preparations	3	2	≤0.1–1	0.4
Other suntan preparations	3	2	>0.1–1	0.1
Total uses/ranges for Sodium Dehydroacetate	**260**	**325**	**≤0.1–1**	**0.00003–0.6**
	Dehydroacetic Acid			
Bath				
Soaps and detergents	—	—	—	0.03
Oils, tablets and salts	1	—	≤0.1	—
Bubble baths	2	1	≤0.1	—
Eye makeup				
Eyeliner	1	—	>0.1–1	0.1
Eye shadow	11	4	≤0.1–1	0.3
Eye lotion	—	—	—	0.2
Eye makeup remover	8	5	≤0.1–1	0.1
Mascara	1	—	>0.1–1	0.2
Other eye makeup	9	—	≤0.1–1	—
Fragrances				
Colognes and toilet waters	4	—	≤0.1	—
Perfumes	4	—	≤0.1	—
Noncoloring hair care				
Shampoos	2	—	≤0.1	0.02–0.03
Tonics, dressings, etc	2	1	≤0.1–1	—
Makeup				
Blushers	5	1	≤0.1–1	0.05–0.2
Face powders	6	3	≤0.1–1	0.7
Makeup foundations	13	3	≤0.1–1	0.1
Makeup bases	1	—	≤0.1	—
Rouges	1	1	>0.1–1	—
Lipstick	1	—	≤0.1	—
Other makeup	1	—	≤0.1	0.07
Nail care				
Cuticle softeners	—	1	—	—
Polish and enamel	—	1	—	—
Personal hygiene				
Other personal hygiene	—	—	—	0.03

(Continued on next page)

TABLE 22

Historical and current uses and use concentrations for Sodium Dehydroacetate and Dehydroacetic Acid *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Skin care				
Cleansing creams, lotions, etc	15	8	≤0 1–1	0 007–0 02
Face and neck skin care	16*	11	≤0 1–1*	0 01–0 08
Body and hand skin care		9		0 03–0 05
Moisturizers	10	10	≤0 1–1	—
Night skin care	5	2	≤0 1–1	0 03
Paste masks/mud packs	3	6	≤0 1–1	—
Skin fresheners	2	—	≤0 1	—
Other skin care	9	16	≤0 1–1	0 03
Wrinkle smoothers**	2	—**	≤0 1	—**
Suntan				
Suntan gels, creams, and liquids	3	—	>0 1–1	0 2
Indoor tanning preparation	—	5	—	—
Other suntan preparations	1	—	>0 1–1	—
Total Uses/Ranges for Dehydroacetic Acid Totals	**139**	**88**	**≤0 1–1**	**0 007–0 7**

*These categories were combined in 1981 but are now separate

**No longer considered as cosmetic product categories

which suggest that the reproductive and developmental toxicity potential of Sodium Lauryl Sulfoacetate is an issue, it was agreed that the results of the proposed reproductive and developmental toxicity study would be considered when available

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SODIUM SESQUICARBONATE, SODIUM BICARBONATE, AND SODIUM CARBONATE

A safety assessment of Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate was published in 1987 with the conclusion that these ingredients are safe as presently used in cosmetic products (Elder 1987) Studies available since that safety assessment was completed, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel After reviewing the available data, the Panel determined to not reopen this safety assessment

Sodium Sesquicarbonate was used in 111 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from >1% to 50% (Elder 1985) In 2002 there were 24 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 2 0% to 90% (CTFA 2004)

Sodium Bicarbonate was used in 45 products in 1981, based on voluntary reports provided to FDA by industry, use concentrations ranged from less than 0 1% to 50% (Elder 1985) In 2002 there were 70 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 0 006% to 95% (CTFA 2004)

Sodium Carbonate was used in 25 products in 1981, based on voluntary reports provided to FDA by industry; use concentrations ranged from less than 0 1% to 25% (Elder 1985) In 2002 there were 21 uses (FDA 2002) and according to an industry survey in 2004 the current range of use concentrations is 0 000002% to 51% (CTFA 2004)

Table 24 presents the available use and concentration information The most recent information now constitutes the present practices of use

TABLE 23

Historical and current cosmetic product uses and concentrations for Sodium Lauryl Sulfoacetate

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) %	2004 concentrations (CTFA 2004) %
Baby care				
Lotions, oils, powders, and creams	—	—	—	1
Bath				
Oils, tablets and salts	1	13	>1–5	5–21
Soaps and detergents	—	—	—	0.6–4
Bubble baths	85	21	>1–>50	6–10
Other bath	—	27	—	6–10
Fragrances				
Other fragrances	—	1	—	2
Noncoloring hair care				
Shampoos	—	1	—	1–5
Hair coloring				
Bleaches	—	2	—	—
Nail care				
Other nail care	—	—	—	4
Oral hygiene				
Dentifrices	3	1	>0.1–5	—
Other oral hygiene	—	—	—	0.7*
Personal hygiene				
Douches	—	—	—	2
Other personal hygiene	1	—	>0.1–1	2
Shaving				
Shaving cream	—	—	—	2
Skin care products				
Cleansing creams, lotions, etc	2	2	>1–25	4
Body and hand skin care	—	—	—	2
Foot powders and sprays	—	—	—	3
Other skin care	1	—	>5–10	—
Total uses/ranges for Sodium Lauryl Sulfoacetate	**93**	**68**	**>0.1–>50**	**0.6–21**

*A denture cleanser

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TABLE 24

Historical and current uses and use concentrations for Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) (%)	2004 concentrations (CTFA 2004) (%)
	Sodium Sesquicarbonate			
Bath				
Oils, tablets, and salts	24	16	>1–50	2–90
Soaps and detergents	—	2	—	—
Bubble baths	68	2	>5–50	18
Capsules	2	—	>10–25	—
Other bath	11	2	>5–50	10–35
Fragrances				
Other fragrances	1	1	>5–10	—
Noncoloring hair care				
Straighteners	1	—	>50	—
Permanent waves	2	—	>1–10	—
Personal hygiene				
Other personal hygiene	2	1	>5–10	—
Skin care				
Foot powders and sprays	—	—	—	35–59
Total uses/ranges for Sodium Sesquicarbonate	**111**	**24**	**>1–50**	**2–90**
	Sodium Bicarbonate			
Baby care				
Lotions, oils, powders, and creams	—	1	—	5
Bath				
Oils, tablets, and salts	1	7	<5–10	30–64
Soaps and detergents	—	2	—	25–54
Bubble baths	4	—	>10–25	5–52
Capsules	—	—	—	49
Other bath	—	—	—	1–64
Eye makeup				
Eyebrow pencils	—	—	—	0 2
Eyeliners	2	1	≤0 1–1	0 04–0 1
Mascara	—	6	—	0 2
Other eye makeup		1		
Fragrance				
Powders	5	9	>0 1–10	20
Noncoloring hair care				
Conditioners	—	—	—	5
Straighteners	1	—	>0 1–1	—
Permanent waves	5	3	≤0 1–1	10
Shampoos	—	—	—	0 09
Other noncoloring hair care	1	—	>1–5	—
Hair-coloring products				
Dyes and colors	—	8	—	—
Bleaches	1	—	>25–50	0 1–10
Makeup				
Foundations	—	—	—	0 09
Lipsticks	—	—	—	0 03–1
Nail care				
Other	—	—	—	39

TABLE 24
Historical and current uses and use concentrations for Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate *(Continued)*

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) (%)	2004 concentrations (CTFA 2004) (%)
Oral hygiene				
Dentifrices	5	10	>1–50	3–95
Mouthwashes and breath fresheners	—	2	—	0.1
Other oral hygiene	—	1	—	0.5
Personal hygiene				
Underarm deodorants	2	—	>1–5	0.01–15
Douches	4	2	≤0.1–25	—
Feminine deodorants	—	2	—	—
Other personal hygiene	4	3	≤0.1–25	0.07–56
Shaving				
Shaving cream	—	—	—	0.006
Other shaving	1	1	≤0.1	—
Skin care				
Cleansing creams, lotions, etc	—	—	—	0.04–26
Face and neck skin care	—*	—	—*	0.01–7
Body and hand skin care		—		10
Foot powders and sprays	—	4	—	25–56
Moisturizers	—	—	—	0.4
Paste masks/mud packs	3	1	≤0.1–50	61
Skin fresheners	2	2	≤0.1–10	—
Other skin care	4	4	>10–25	2–5***
Suntan products				
Suntan gels, creams, liquids, and sprays	—	—	—	0.2
Total uses/ranges for Sodium Bicarbonate	**45**	**70**	**≤0.1–50**	**0.006–95**
	Sodium Carbonate			
Bath				
Oils, tablets, and salts	—	4	—	40–51
Soaps and detergents	2	1	>0.1–1	3–32
Bubble baths	4	—	>10–25	7–39
Other	—	—	—	0.009–39
Eye makeup				
Eyebrow pencils	—	—	—	0.2
Eye shadow	—	—	—	0.3
Eye lotions	—	—	—	0.004
Mascara	—	—	—	0.2
Fragrances				
Colognes and toilet waters	—	—	—	0.03
Noncoloring hair care				
Conditioners	1	2	>0.1–1	0.01
Straighteners	1	—	>1–5	—
Permanent waves	1	1	>1–5	—
Shampoos	2	1	>0.1–1	0.08
Tonics, dressings, etc	—	—	—	0.000002–0.01
Wave sets	—	—	—	1

(Continued on next page)

TABLE 24

Historical and current uses and use concentrations for Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate *(Continued)*

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) (%)	2004 concentrations (CTFA 2004) (%)
Hair coloring				
Dyes and colors	1	2	>1–5	0.1–0.6
Rinses	—	—	—	0.02
Bleaches	2	—	>0.1–10	25
Other hair coloring	—	—	—	1
Makeup				
Blushers	—	—	—	0.03
Foundations	1	1	≤0.1	0.3
Lipsticks	—	3	—	—
Nail care				
Other nail care	—	—	—	0.6
Oral hygiene				
Dentifrices	—	—	—	2
Other oral hygiene	—	—	—	22***
Personal hygiene				
Underarm deodorants	—	—	—	0.002
Douches	1		>5–10	—
Other	3	2	>1–5	—
Skin care				
Cleansing creams, lotions, etc	2	1	≤0.1	0.02–0.2
Face and neck skin care	—*	—	—*	0.008
Body and hand skin care		1		—
Moisturizers	2	2	≤0.1	—
Skin fresheners	1	—	≤0.1	—
Hormone preparations**	1	N/A**	≤0.1	N/A**
Total uses/ranges for Sodium Carbonate	**25**	**21**	**≤0.1–25**	**0.000002–51**

*This category was combined when the original safety assessment was performed and is now two separate categories

**No longer included as a cosmetic product category

***Denture cleanser

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STEARYL ALCOHOL, OLEYL ALCOHOL, AND OCTYLDODECANOL

A safety assessment of Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol was published in 1985 with the conclusion "safe as currently used in cosmetic products" (Elder 1985) New studies, along with the updated information in Table 25 regarding uses and used concentrations, were considered by the CIR Expert Panel The Panel determined not to reopen this safety assessment

Stearyl Alcohol was used in 425 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0 1% to 50% (Elder 1985) In 2002, Stearyl Alcohol was reportedly used in 1063 cosmetic products (FDA 2002) Concentration of use data from an industry survey in 2003 indicated that Stearyl Alcohol was used in a range from 0 002% to 56% (CTFA 2003)

The Panel noted that the Hannuksela (1988) report reviewed the previous literature which included a report of positive patch test reactions to Stearyl Alcohol as high as 44% Although this information raised some concern, Hannuksela (1988) did report current data with a frequency of 11 positive tests out of over 1000 patch tests performed, a low frequency consistent with current experience

Oleyl Alcohol was used in 1018 cosmetic products in 1981, with concentrations ranging from ≤0 1% to >50% (Elder 1985) In 2002, Oleyl Alcohol was used in 343 cosmetic products (FDA 2002) Concentration of use data from a 2003 survey indicated that Oleyl Alcohol was used in a range from 0 0002% to 18% (CTFA 2003)

Although Tosti et al (1996) reported a high proportion of 34 patients as positive to Oleyl Alcohol in a patch test, the Panel indicated that such reactions are not seen in their experience

Octyldodecanol was used in 371 cosmetic products in 1981, with concentrations ranging from ≤0 1% to >50% (Elder 1985) In 2002, Octyldodecanol was used in 814 cosmetic products (FDA 2002) Concentration use data from 2003 indicted that Octyldodecanol was used in a range from 0 006% to 85% (CTFA 2003)

Table 25 presents the available use information for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol The most current information now represents the present practices of use

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TOLUENE

A safety assessment of Toluene was published in 1987 with the conclusion that Toluene "is safe for cosmetic use at the present practices of use and concentration" despite limited skin exposure data (Elder 1987) Since then a large number of studies

TABLE 25

Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
		Stearyl Alcohol		
Baby care				
Lotions, oils, powders, and creams	2	9	>0 1–1	0 6–2
Other baby care	—	1	—	2
Bath				
Soaps and detergents	—	1	—	0 06
Bubble baths	—	—	—	2
Other bath	—	1	—	1–6
Eye makeup				
Eyebrow pencils	1	—	>1–5	3
Eyeliners	—	3	—	—
Eye shadow	24	6	≤0 1–1	8
Eye lotions	—	5	—	0 4–0 5
Eye makeup remover	—	—	—	0 9
Mascara	2	5	>0 1–1	0 2 - 2
Other eye makeup	2	9	≤0 1–1	5
Fragrances				
Perfumes	—	—	—	2
Powders	—	1	—	—
Sachets	26	1	>0 1–25	1
Other fragrances	—	8	—	2
Noncoloring hair care				
Conditioners	46	174	≤0 1–10	0 02–8
Straighteners	2	7	>0 1–1, >5–10	2
Permanent waves	5	4	≤0 1–1	3
Rinses	21	4	≤0 1–5	3–5
Shampoos	1	23	>0 1–1	0 1–5
Tonics, dressings, etc	—	9	—	1–5
Other noncoloring hair care	—	3	—	1–5
Hair coloring				
Dyes and colors	1	259	>0 1–1	—
Tints	—	—	—	4
Rinses	—	—	—	2–5
Lighteners with color	—	1	—	—
Bleaches	5	25	>0 1–5	—
Other hair coloring	2	1	>1–5	2
Makeup				
Blushers	15	—	≤0 1–1	2
Foundations	8	32	>0 1–1	0 8–3
Leg and body paints	3	—	>0 1–1	—
Lipsticks	3	2	≤0 1–1	0 2–3
Makeup bases	63	12	≤0 1–5	0 6
Rouges	1	1	≤0 1	—
Makeup fixatives	1	2	≤0 1	—
Other makeup	2	6	≤0 1–1	0 5–5
Nail care				
Cuticle softeners	2	1	>0 1–1	2

TABLE 25

Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Creams and lotions	1	2	>1–5	1
Other nail care	—	1	—	6
Personal hygiene				
Underarm deodorants	3	8	>25–50	13–25
Douches	—	—	—	0.1
Other personal hygiene	10	66	>1–5, >10–25	—
Shaving				
Aftershave lotions	—	5	—	0.2–3
Beard softeners	1	—	>5–10	—
Preshave lotions	—	—	—	1
Shaving cream	6	7	>0.1–5	0.2–3
Other shaving	2	—	≤0.1–1	2
Skin care				
Cleansing creams, lotions, etc	39	52	≤0.1–10	0.5–8
Depilatories	6	1	>1–5	1
Face and neck skin care	36*	19	≤0.1–10*	1–8
Body and hand skin care		96		0.002–9
Foot powders and sprays	—	3	—	2–17
Moisturizers	50	106	≤0.1–10	0.002–56
Night skin care	12	14	≤0.1–5	0.002–3
Paste masks/mud packs	2	11	>0.1–5	0.8–6
Skin fresheners	1	2	>0.1–1	—
Other skin care	9	31	≤0.1–10	0.02–12
Skin lighteners**	6	NA**	>0.1–10	NA**
Suntan products				
Suntan gels, creams, liquids, and sprays	2	3	>0.1–1, >5–10	1–4
Indoor tanning preparations	1	19	>1–5	2–3
Other	—	1	—	0.3
Total uses/ranges for Stearyl Alcohol	**425**	**1063**	**≤0.1–50**	**0.002–56**
		Oleyl Alcohol		
Bath				
Oils, tablets, and salts	17	1	≤0.1–25	—
Soaps and detergents	—	2	—	0.0003
Bubble baths	1	—	>1–5	—
Capsules	1	—	>5–10	1–5
Other bath	3	—	>1–5	—
Eye makeup				
Eyebrow pencils	1	—	>5–10	—
Eyeliners	15	5	>1–25	0.4–0.5
Eye shadow	124	5	≤0.1–25	1
Mascara	26	2	>1–5	—
Other eye makeup	8	2	>0.1–25	—
Fragrances				
Colognes and toilet waters	2	—	>0.1–1	—
Perfumes	5	1	≤0.1, >1–5, >10–25	5
Sachets	2	1	>1–5	—
Other fragrances	9	1	>0.1–5	1–5

(Continued on next page)

TABLE 25

Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Noncoloring hair care				
Conditioners	9	26	>0 1–5	0 3–3
Sprays/aerosol fixatives	—	3	—	—
Straighteners	4	9	>1–5	1
Permanent waves	—	—	—	3
Rinses	—	—	—	18
Tonics, dressings, etc	4	6	>0 1–5	0 3–4
Other noncoloring hair care	1	2	>1–5	—
Hair coloring				
Dyes and colors	63	143	>1–5, >10–25	6–8
Tints	13	—	>10–25	—
Bleaches	2	2	>1–5	—
Other hair coloring	—	1	—	—
Makeup				
Blushers	13	2	>1–>50	1–10
Face powders	1	—	>1–5	—
Foundations	5	5	>0 1–5	0 5–5
Lipsticks	633	82	≤0 1–> 50	—
Makeup bases	2	—	>1–5, >10–25	—
Rouges	3	—	>1–5, >10–25	—
Other makeup	10	5	>5–25	—
Nail care				
Basecoats and undercoats	—	1	—	—
Nail polish and enamel removers	1	—	>1–5	—
Personal hygiene				
Underarm deodorants	2	—	>1–5	0 0005
Feminine deodorants	1	1	>25–50	0 1
Other personal hygiene	2	2	>0 1–5	—
Shaving products				
Aftershave lotions	2	2	>1–5	0 05
Preshave lotions	1	1	>0 1–1	—
Skin care				
Cleansing creams, lotions, etc	2	1	>1–5	—
Face and neck skin care	6*	2	≤0 1–10*	0 0002–3
Body and hand skin care		6		0 05
Foot powders and sprays	—	—	—	2
Moisturizers	8	9	≤0 1–25	4
Night skin care	2	1	>1–25	3
Paste masks/mud packs	2	2	≤0 1–5	—
Skin fresheners	2	6	≤0 1–1	—
Other skin care	4	—	≤0 1–25	3
Hormone preparations**	1	NA**	>10–25	NA**
Suntan products				
Suntan gels, creams, liquids and sprays	5	3	>0 1–10	—
Total uses/ranges for Oleyl Alcohol	**1018**	**343**	**≤0 1–>50**	**0 0002–18**

TABLE 25

Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
		Octyldodecanol		
Bath				
Oils, tablets, and salts	4	8	>5–10	1–30
Soaps and detergents	1	—	≤0.1	—
Eye makeup				
Eyebrow pencils	1	10	>5–10	4
Eyeliners	14	202	>0.1–10	3–7
Eye shadow	82	17	>1–25	0.1–15
Eye lotions	1	—	>25–50	—
Eye makeup remover	3	3	>1–5, >10–25	5
Mascara	1	—	>1–5	1–3
Other eye makeup	4	20	>5–25	0.1
Fragrances				
Perfumes	3	—	>25–50	—
Powders	4	—	>0.1–1	0.3
Sachets	6	—	>25–50	—
Other fragrances	1	1	>5–10	—
Noncoloring hair care				
Conditioners	3	11	>0.1–5	3–15
Sprays/aerosol fixatives	2	2	>0.1–5	—
Straighteners	—	—	—	0.5
Rinses	2	3	>0.1–1	4–6
Tonics, dressings, etc	—	—	—	0.5–20
Other noncoloring hair care	—	—	—	3
Hair coloring				
Dyes and colors	41	84	>5–25	10
Rinses	—	—	—	1
Color sprays	—	1	—	—
Other hair coloring	—	1	—	—
Makeup				
Blushers	6	9	>1–25	15–23
Face powders	6	6	>0.1–10	8
Foundations	—	20	—	5–16
Lipsticks	112	182	>0.1–>50	3–82
Makeup bases	1	1	>0.1–1	—
Rouges	1	2	>10–25	10–20
Makeup fixatives	1	—	>5–10	—
Other	2	23	>1–10	3–17
Nail care				
Polishes and enamels	—	—	—	2
Other nail care	—	—	—	0.06
Personal hygiene				
Underarm deodorants	1	3	>10–25	2–17
Douches	—	—	—	0.4
Other personal hygiene	1	2	>1–5	1

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TABLE 25

Historical and current cosmetic product uses and concentrations for Stearyl Alcohol, Oleyl Alcohol, and Octyldodecanol *(Continued)*

Product category	1981 uses (Elder 1985)	2002 uses (FDA 2002)	1981 concentrations (Elder 1985) %	2003 concentrations (CTFA 2003) %
Shaving products				
Aftershave lotions	—	2	—	0.03–0.07
Preshave lotions	1	3	>0.1–1	—
Shaving cream	1	1	>0.1–1	0.4
Other	—	3	—	—
Skin care				
Cleansing creams, lotions, etc	9	22	≤0.1, >1–10	0.03–17
Face and neck skin care	23*	19	>0.1–50*	0.03–85
Body and hand skin care		59		0.006–6
Moisturizers	14	35	≤0.1–25	2–3
Night skin care	3	15	>1–5, >10–25	1
Paste masks/mud packs	—	7	—	
Other skin care	7	24	>1–25	0.03–14
Wrinkle smoothers**	1	NA**	>1–5	NA**
Skin lighteners**	4	NA**	>0.1–5	NA**
Suntan				
Suntan gels, creams, liquids, and sprays	3	9	>5–25	3–59
Other suntan	1	4	>1–5	
Total uses/ranges for Octyldodecanol	**371**	**814**	**≤ 0.1–>50**	**0.006–85**

*This category was combined when the original safety assessment was performed and is now two separate categories

**No longer included as a cosmetic product category

have appeared in the scientific literature These studies, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel Based on its consideration of the available data, the Panel decided to not reopen this safety assessment

Toluene was used in 555 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from >10%–50% (Elder 1987) In 2002, toluene was reportedly used in 59 cosmetic products (FDA 2002) Concentration of use data from an industry survey in 2003 indicated that Toluene was used in a range from 20% to 26% (CTFA 2004)

Table 26 provides the available data on usage and use concentration as a function of cosmetic product category The most current information now represents the present practices of use

Many of the newly available studies reported findings consistent with the data in the original safety assessment

New findings of adverse effects included the following effects Toluene was ototoxic for guinea pigs, interferes with performance and learning in neurotoxicity and behavior studies in animals, increased numbers of litters with low birth weights pups and adversely affected brain development, in cultured embryos exposed to Toluene, yolk sac diameter, crown-rump length, somite number, and protein concentration were significantly

TABLE 26

Historical and current cosmetic product uses and concentrations for Toluene

Product category	1984 uses (Elder 1987)	2002 uses (FDA 2002)	1984 concentrations (Elder 1987) %	2003 concentrations (CTFA 2004) %
Nail care				
Basecoats and undercoats	32	21	>10–50	—
Polishes and enamels	501	23	>10-50	20–25
Polish and enamel removers	—	2	—	—
Other nail care	22	13	>10–50	26
Total uses/ranges for Toluene	**555**	**59**	**>10–50**	**20–26**

reduced A National Toxicology Program study concluded that there was no evidence of carcinogenic activity for Toluene in F344/N rats and B6C3F$_1$ mice

The new adverse effects noted above appeared only at high exposures They were found only when animals were exposed to Toluene vapor at a level of 10^2 to 10^3 ppm Such exposures, however, were not attainable in an exposure study of human subjects using nail polish—those values ranged from 1–4 ppm

The Panel recognized that other data indicate adverse effects in the brain of Toluene abusers and in children born to mothers who inhaled Toluene during pregnancy Again, the nature of these studies suggests high exposures and are not relevant to the use of Toluene in cosmetic products

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TOLUENESULFONAMIDE/FORMALDEHYDE RESIN

A safety assessment of Toluenesulfonamide/Formaldehyde Resin (including Toluenesulfonamide/Formaldehyde Resin-80) was published in 1986 with the conclusion that these ingredients were safe as cosmetic ingredients in the present practices of use and concentration (Elder 1986) Studies available since that time, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel Based on its consideration of the available data, the Panel decided to not reopen this safety assessment

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed—Tosylamide/Formaldehyde Resin is the current terminology (Gottschalck and McEwen 2004)

TABLE 27
Historical and current cosmetic product uses and concentrations for Tosylamide/Formaldehyde Resin

Product category	1981 uses (Elder 1986)	2002 uses (FDA 2002)	1981 use concentrations (Elder 1986) %	2003 use concentrations (CTFA 2004) %
	Tosylamide/Formaldehyde Resin			
Nail care products				
Basecoats and undercoats	31	—	1–10	8–11
Nail polishes and enamels	172	29	≤0 1–25	7–13
Other	8	—	1–10	7–8
Total uses/ranges for Tosylamide/Formaldehyde Resin	**211**	**29**	**≤0 1–25**	**7–13**
	Tosylamide/Formaldehyde Resin-80			
Nail care products				
Basecoats and undercoats (44)	5	—	1–10	—
Nail polishes and enamels (767)	344	—	≤0 1–25	—
Other (50)	7	—	≤0 1–25	—
Total uses/ranges for Tosylamide/Formaldehyde Resin-80	**356**	**29**	**≤0 1–25**	—

Tosylamide/Formaldehyde Resin was used in 211 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0 1%–25% (Elder 1986) In 2002, stearyl alcohol was reportedly used in 29 cosmetic products (FDA 2002) Concentration of use data from an industry survey in 2003 indicated that Toluene was used in a range from 7%–13% (CTFA 2004)

Tosylamide/Formaldehyde Resin-80 was used in 356 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0 1%–25% (Elder 1986) In 2002, there were no reports of use (FDA 2002), nor did an industry survey in 2003 indicated any current use concentrations (CTFA 2004)

Table 27 provides the available data on usage and use concentration as a function of cosmetic product category The most current information now represents the present practices of use and concentration

Case reports of allergic reaction to nail care products containing Tosylamide/Formaldehyde Resin were consistent with the data in the original safety assessment

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TRAGACANTH GUM

A safety assessment of Tragacanth Gum was published in 1987 with the conclusion that these ingredients were safe as cosmetic ingredients in the present practices of use and concentration (Elder 1987) Studies available since that time, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel Based on its consideration of the available data, the Panel decided to not reopen this safety assessment

TABLE 28

Historical and current cosmetic product uses and concentrations for Astragalus Gummifer Gum

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) %	2004 concentrations (CTFA 2004) %
Eye makeup				
Eye shadow	3	—	≤0.1	—
Noncoloring hair care				
Conditioners	—	1	≤0.1	—
Tonics, dressings, etc	1	2	>0.1–1	≤0.01
Wave Sets	—	1		—
Hair coloring				
Hair Bleaches	2	1	>1–5	≤3
Makeup				
Blushers	2	—	>1–5	—
Face Powders	6	—	≤0.1–1	—
Foundations	1	—	>0.1–1	—
Rouges	1	—	>0.1–1	—
Oral hygiene				
Dentrifices	2	2	>0.1–5	—
Shaving				
Aftershave lotions	1	—	>0.1–1	—
Preshave lotions	1	—	>0.1–1	—
Skin care				
Cleansing creams, lotions, etc	1		>0.1–1	—
Face and neck skin care		—		—
Body and hand skin care	2*	—	>0.1–1*	—
Moisturizers	1	—	>0.1–1	—
Paste masks/mud packs	5	1	>0.1–10	—
Total uses/ranges for Astragalus Gummifer Gum	**29**	8	**≤0.1–10**	**≤0.01%–≤3**

*This category was combined when the original safety assessment was performed and is now two separate categories

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed—Astragalus Gummifer Gum is the current terminology (Gottschalck and McEwen 2004)

Astragalus Gummifer Gum was used in 29 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0.1% to 10% (Elder 1987) In 2002, stearyl alcohol was reportedly used in 8 cosmetic products (FDA 2002) Concentration of use data from an industry survey in 2004 indicated that Astragalus Gummifer Gum was used at concentrations from ≤0.01% to ≤3% (CTFA 2004)

Table 28 provides the available data on usage and use concentration as a function of cosmetic product category The most current information now represents the present practices of use and concentration

In the original safety assessment, this ingredient was described as derived from various Astragalus species, principally *Astragalus gummifer* More recent information suggests that *Astragalus microcephalus* may be another source of this gum The Panel suggested that the *International Cosmetic Ingredient Dictionary and Handbook* should be updated to include specific mention of Astragalus Microcephalus Gum, and a new name adopted, if needed

The Panel noted that pesticide impurities may form part of the composition of this plant-derived ingredient and has advised industry that the total (polychlorinated biphenyl) PCB/pesticide contamination should be limited to not more than 40 ppm, with not more than 10 ppm for any specific residue The following limitations for other impurities were also recommended arsenic (3 mg/kg max), heavy metals (0.002% max), and lead (5 mg/kg max)

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VINYL ACETATE/CROTONIC ACID COPOLYMER

A safety assessment of the Vinyl Acetate/Crotonic Acid Copolymer in 1983 concluded that this ingredient is considered safe as a cosmetic ingredient under present practices of product and concentration use (Elder 1983) New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

The terminology for this ingredient in the *International Cosmetic Ingredient Dictionary and Handbook* has changed—VA/Crotonates Copolymer is the current terminology (Gottschalck and McEwen 2004)

VA/Crotonates Copolymer was used in 55 cosmetic products in 1976, based on voluntary reports provided to FDA by industry with concentrations ranging from >0 01% to 25% (Elder 1986) In 2002, VA/Crotonates Copolymer was used in 38 cosmetic products (FDA 2002) Concentration of use data from an industry survey in 2003 indicated that this ingredient was used at concentrations from 0 05% to 11% (CTFA 2003)

Table 29 presents the available use information for VA/Crotonates Copolymer The most recent information now constitutes the present practice of use and concentration

The CIR Expert Panel acknowledged the use of Vinyl Acetate/Crotonic Acid Copolymer in aerosol hair sprays The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993) The mean aerodynamic diameter of pump hair spray particles is $\geq 80\ \mu$, and the diameter of anhydrous hair spray particles is 60 to 80 μ Typically less than 1% are below 10 μ, which is the upper limit for respirable particles (Bower 1999) Based on the particle size, Vinyl Acetate/Crotonic Acid Copolymer would not be respirable in formulation Therefore,

TABLE 29
Historical and current cosmetic product uses and concentrations for VA/Crotonates Copolymer

Product category	1976 uses (Elder 1983)	2002 uses (FDA 2002)	1976 use concentrations (Elder 1983, 1976) (%)	2002 use concentrations (CTFA 2002b) (%)
Bath capsules	—	—	—	9
Eye makeup remover	—	—	—	9
Mascara	—	5	—	—
Hair conditioners	4	1	>1–10	—
Hair sprays (aerosol fixatives)	30	9	> 01–25	2–11
Hair straighteners	—	1	—	—
Tonics, dressings, and other hair-grooming aids	2	10	>1–5	0 05–4
Wave sets	9	3	>1–5	2
Other hair preparations (noncoloring)	10	9	>1–10	2–3
Hair dyes and colors (all types requiring caution statement and patch testing)	—	—	—	5
Moisturizing creams, lotions, and powders	—	—	—	2
Total uses/ranges for VA/Crotonates Copolymer	**55**	**38**	**>0 01–25**	**0 05–11**

the Panel was not concerned about inhalation as a route of absorption

Although there were reports associating vinyl acetate with nasopharyngeal carcinoma in rat inhalation studies, the amount of residual vinyl acetate monomer in VA/Crotonates Copolymer was below the no observed effect level Additionally, studies show that the reported carcinogenicity of vinyl acetate in rats is through a nongenotoxic mechanism Occupational studies in which workers were exposure to vinyl acetate ranging from 5 to 10 ppm, with intermittent exposures near 50 ppm and acute exposures to 300 ppm, showed no long-term chronic effects These data support the CIR Expert Panel's confidence that vinyl acetate is not a concern in the safety of VA/Crotonates Copolymer

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TABLE 30
Historical and current cosmetic product uses and concentrations for Zinc Phenolsulfonate

Product category	1986 uses (CIR 1986)	2002 uses (FDA 2002)	1981 concentrations (CIR 1986) (%)	2004 concentrations (CTFA 2004) (%)
Fragrances				
Powders	5	1	>0 1–5	—
Personal hygiene				
Underarm deodorants	40	15	>0 1–5	4
Shaving				
Aftershave lotions	4	2	>0 1–5	—
Shaving cream	3	—	—	—
Skin care				
Skin cleansing creams, lotions, liquids, and pads	2		>0 1–5	—
Body and hand skin care preparations	—	2	—	—
Foot powders and sprays	—	1	—	3
Moisturizers	1	1	≤0 1	—
Paste masks/mud packs	1	—	>1–5	—
Skin fresheners	9	—	≤0 1–5	—
Other	2	1	1–5	—
Total uses/ranges for Zinc Phenolsulfonate	**67**	**23**	**≤0 1–5**	**3–4**

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ZINC PHENOLSULFONATE

A safety assessment of Zinc Phenolsulfonate published in 1986 concluded that this ingredient is considered safe as a cosmetic ingredient under present practices of product and concentration use (Elder 1986) New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel The Panel determined to not reopen this safety assessment

Zinc Phenolsulfonate was used in 67 cosmetic products in 1981, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0 1 to 5% (Elder 1986) In 2002, Zinc Phenolsulfonate was used in 23 cosmetic products (FDA 2002) Concentration of use data from an industry survey in 2004 indicated that this ingredient was used at concentrations from 3 to 4% (CTFA 2004)

Table 30 presents the available use information for Zinc Phenolsulfonate The most recent information now constitutes the present practice of use and concentration

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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.

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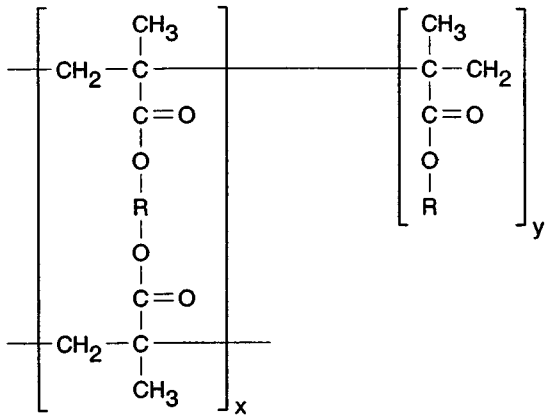
TABLE 1
Ingredients descriptions (Wenninger, Canterbery, and McEwen 2000)

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).

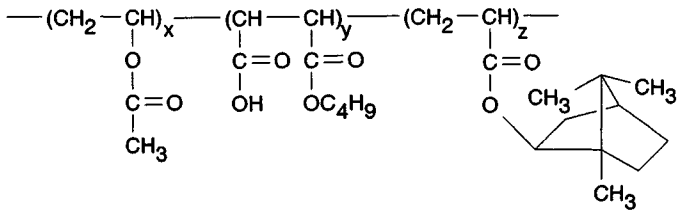
Sodium Styrene/Acrylates Copolymer. Sodium Styrene/Acrylates Copolymer (CAS No. 9010-92-8) is the sodium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbery, and McEwen 2000).

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).

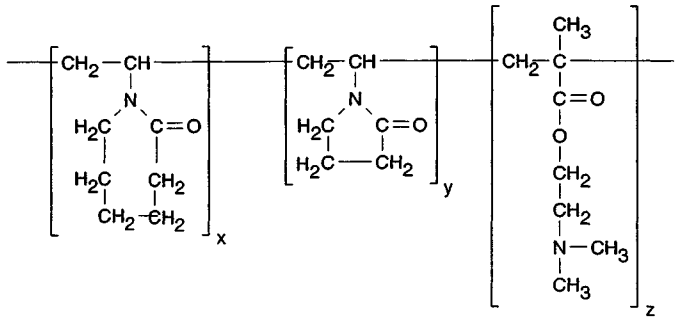
VA/Butyl Maleate/Isobornyl Acrylate Copolymer. VA/Butyl Maleate/Isobornyl Acrylate Copolymer is a copolymer of vinyl acetate, butyl maleate, and isobornyl acrylate monomers (Wenninger, Canterbery, and McEwen 2000) and has the following structure (Patel and Petter 1992):



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):



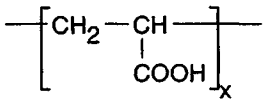
Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer

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% $\pm$ 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 ·e of the high-dose group died accidentally during the study. ·nificant differences in body weight gains and feed consu not o' erved. 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 carcinomas 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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Personal Care Products Council
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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 21, 2014

SUBJECT: Comments on the Scientific Literature Review: Safety Assessment of Styrene and Vinyl-type Styrene Copolymers as Used in Cosmetics

The Council has no suppliers listed for the following ingredients: Acrylates/Ethylhexyl Acrylate/Styrene Copolymer, Butyl Acrylate/Styrene Copolymer, Hydrogenated Butylene/Ethylene/Styrene Copolymer, Hydrogenated Ethylene/Propylene/Styrene Copolymer, Polystyrene/Hydrogenated Polyisopentene Copolymer, Sodium Methacrylate/Styrene Copolymer, Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer, Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer, Styrene/Stearyl Methacrylate Crosspolymer, Styrene/VA Copolymer, Polyacrylate-2, Polyacrylate-5 and Polyacrylate-30.

Key Issue

There is a second NTP inhalation study of 1,3-butadiene in mice that was published in 1994 that used exposure concentrations of 6.25, 20, 62.5, 200 and 625 ppm. This study needs to be added to this report.

Additional Comments

p.1, 3, 11 - Stating that ingredients function "mostly as" suggests that most of the ingredients in the report have the listed function. In this case, only 9/35 have viscosity increasing agent and 6/35 have opacifying agent listed as function. It would be more accurate to state that among the ingredients in the report, film former is the most frequent function reported (19/35). Other common functions include opacifying agent and viscosity increasing agent.

p.3, Cometic Use - It is misleading to state that information was provided to the FDA in 2013. The 2013 data is the information that was in the VCRP database in 2013. It was not provided to FDA by industry in 2013.

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p.4 - The description of the residual monomer permitted in food contact materials is not complete (see reference 20). For some uses (contact with fatty foods and in contact with ruber-modified polystyrene), the limit is "0.5 weight percent of total residual styrene monomer". For the use of styrene as a flavoring adjuvant (reference 21), it should also state that it should be "used in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice".

p.4 - How did they determine that the absorption of styrene was low in humans placing a hand in liquid styrene? Did they measure metabolites in urine?

p.5 - What were the concentrations of 1,3-butadiene in which organs of cats, rats and mice (perhaps some information could be presented in table)? To what concentrations were these animals exposed?

p.6 - On what data/endpoint is the EPA oral RfD based? It is not helpful to state an RfD without mentioning the basis for the value.

p.6, Skin Sensitization - As studies on methylstyrene are also included, methylstyrene needs to be added to some of the subheadings.

p.6-7 - The case report of a boy with a styrofoam bead stuck in his ear is not relevant to the cosmetic use of Polystyrene and should be deleted from this report.

p.5, Reproductive and Developmental Toxicity - The units ppm represent a concentration and should not be called "dose".

p.5 - How many hours/day, days/week were female rats exposed to 1,3-butadiene (4 month study)?

p.9 - The description of the NTP cacinogenicity study of 1,3-butadiene says: "mice were exposed to air containing 625 ppm or 1,250 ppm styrene".

p.11, Summary - As the VCRP and the Council use survey collects information by FDA cosmetic product category, please state the FDA product categories for which the maximum use concentrations were report.

Tables - Either the table numbers need to be corrected, or the report is missing tables 3-5. It is not clear why the use information for Polyacrylate-21 is in a table called Table 2, while the rest of the ingredients are in Table 6.