
Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: May 11, 2018
Panel Date: June 4-5, 2018

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

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 11, 2018
Subject: Draft Tentative Report on Vinylpyrrolidone Polymers

A Scientific Literature Review (SLR) on 30 Vinylpyrrolidone Polymers was issued on April 13, 2018. The following data (attached and included in the draft report) were received from the Personal Care Products Council (Council) either prior to or after issuance of the SLR: use concentration data (*vinylp062018data1* and *vinylp062018data2*), a human controlled use test of an eye shadow containing 12.22% VP/Hexadecene Copolymer (*vinylp062018data3*), and a human 48-h patch test of a cosmetic base containing 14.95% VP/Hexadecene Copolymer (*vinylp062018data3*). Comments on the SLR that were received from the Council (*vinylp062018pcpc*), also attached, have been addressed.

The draft report also contains use concentration data on the Vinylpyrrolidone Polymers, a controlled use test of an eye shadow containing 12.22% VP/Hexadecene Copolymer, and a human patch test of a cosmetic base containing 14.95% VP/Hexadecene Copolymer that were received from the Council.

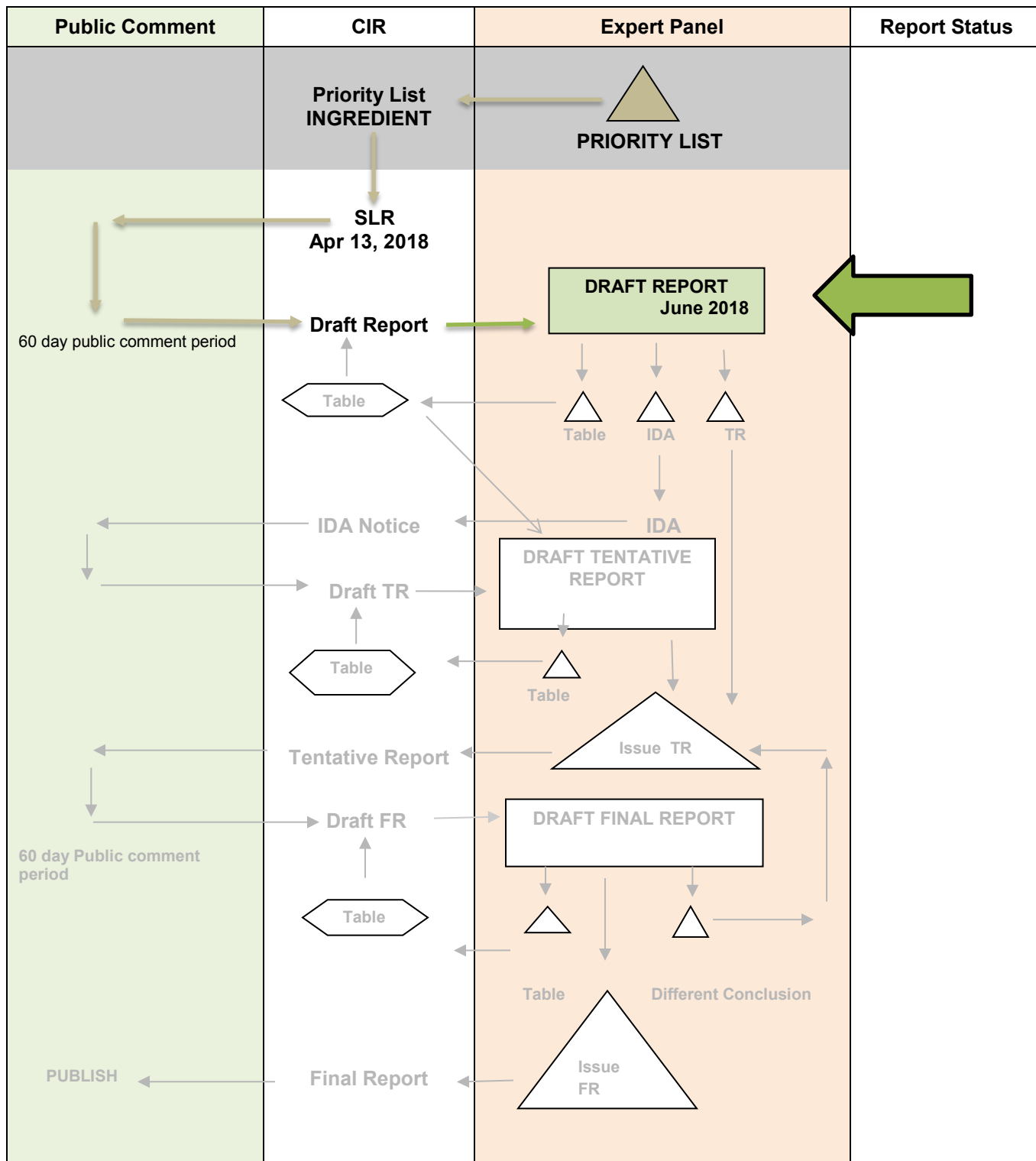
Also included in this package for your review are the Draft Report (*vinylp062018rep*), CIR report history (*vinylp062018hist*), flow chart (*vinylp062018flow*), literature search strategy (*vinylp062018strat*), ingredient data profile (*vinylp062018prof*), 2018 FDA VCRP data (*vinylp062018FDA*), Final Report on acrylates copolymer and 33 related ingredients (*vinylp062018final1*), Final Report on acryloyldimethyltaurate polymers (*vinylp062018final2*), Final Report on styrene and vinyl-type styrene copolymers (*vinylp062018final3*), Final Report on polyvinylpyrrolidone (*vinylp062018final4*), and Final Report on polyvinylpyrrolidone/vinyl acetate copolymer (*vinylp062018final5*).

It should be noted that the Panel has evaluated the safety of, and issued conclusions (in published reports) on, 8 ingredients/ingredient groups that are similar to the 22 ingredients that are being reviewed for the first time in this safety assessment. Collectively, the Final Reports (mentioned above) that are included in this package correspond to the 8 ingredients/ingredient groups that have been reviewed by the Panel. Furthermore, data from these reports are summarized in this Draft Tentative Report, where appropriate.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY	Vinylpyrrolidone Polymers
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MEETING June 2018

CIR History of:

Vinylpyrrolidone Polymers

A Scientific Literature Review (SLR) on Vinylpyrrolidone Polymers was issued on April 13, 2018.

Draft Report, Teams/Panel: June 4-5, 2018

The draft report also contains use concentration data on the Vinylpyrrolidone Polymers, a human controlled use test of an eye shadow containing 12.22% VP/Hexadecene Copolymer, and a human 48-h patch test of a cosmetic base containing 14.95% VP/Hexadecene Copolymer that were received from the Council. These data, received either before or after issuance of the SLR, are included in the draft report. Comments on the SLR that were received from the Council will be addressed.

Triaccontanyl PVP																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
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X = data

[Vinylpyrrolidone Polymers – 2/6-16/2018]

[illegible]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECET-OC	Web
Styrene/VP Copolymer	25086-29-7	Yes	427/2	3/0	7/0	No	No	No	No	No	No	No	No	No	No	No	No	
Triacontanl PVP	157148-07-7 136445-69-7	Yes	101/0	0/0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	
Triacotene/VP Copolymer		Yes	0/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer		Yes	0/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Acrylates/Lauryl Methacrylate Copolymer	83120-95-0	Yes	85/2	2/1	2/2	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester		Yes	1/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Dimethylaminoethylmethacrylate Copolymer	30581-59-0	Yes	612/0	0/0	2/1	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester		Yes	1/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
VP/DMAA Acrylates Copolymer	175893-71-7	Yes	8/0	0/0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Polycarbamyl Polyglycol Ester		Yes	2/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
VP/VA Copolymer	25086-89-9	Yes	113/6	4/0	10/1	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Vinyl Alcohol Copolymer	26008-54-8	Yes	292/1	4/0	4/1	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Vinyl Caprolactam/DMAA Acrylates Copolymer		Yes	0/0	0/0	2/0	No	No	No	No	No	No	No	No	No	No	No	No	

Search Strategy

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

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

LINKS

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

FDA databases – <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm> (CFR); then, list of all databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>; then, <http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true> (EAFUS); <http://www.fda.gov/food/ingredientpackaginglabeling/gras/default.htm> (GRAS); <http://www.fda.gov/food/ingredientpackaginglabeling/gras/scogs/ucm2006852.htm> (SCOGS database); <http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives> (indirect food additives list); <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm> (drug approvals and database); <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf> (OTC ingredient list); <http://www.accessdata.fda.gov/scripts/cder/iig/> (inactive ingredients approved for drugs)

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

Botanical Websites, if applicable

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

Fragrance Websites, if applicable

IFRA (International Fragrance Association) – <http://www.ifraorg.org/>

RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers

Absorption

Acute

Allergy

Allergic

Allergenic

Cancer

Carcinogen

Chronic

Development

Developmental

Excretion

Genotoxic

Irritation

Metabolism

Mutagen

Mutagenic

Penetration

Percutaneous

Pharmacokinetic

Repeated dose

Reproduction

Reproductive

Sensitization

Skin

Subchronic

Teratogen

Teratogenic

Toxic

Toxicity

Toxicokinetic

Toxicology

Tumor

Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics

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INTRODUCTION

The safety of the following 30 ingredients, as used in cosmetics, is being reviewed in this safety assessment:

VP/Hexadecene Copolymer	VP/Acrylates/Lauryl Methacrylate Copolymer
VP/Eicosene Copolymer	VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester
Acrylates/Stearyl Methacrylate/VP Copolymer	VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester
Acrylic Acid/VP Crosspolymer	VP/DMAA Acrylates Copolymer
Butylated PVP	VP/Polycarbamyl Polyglycol Ester
Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer	VP/Vinyl Alcohol Copolymer
Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer	VP/Vinyl Caprolactam/DMAA Acrylates Copolymer
Hydrolyzed Wheat Protein/PVP Crosspolymer	Acrylates/VP Copolymer*
Maltodextrin/VP Copolymer	Ammonium Acryloyldimethyltaurate/VP Copolymer*
PVP/Decene Copolymer	Methacrylic Acid/Styrene/VP Copolymer*
PVP/VA/Itaconic Acid Copolymer	PVP*
PVP/VA/Vinyl Propionate Copolymer	Sodium Acryloyldimethyltaurate/VP Crosspolymer*
Triaccontanyl PVP	Styrene/VP Copolymer*
Triaccontene/VP Copolymer	VP/Dimethylaminoethylmethacrylate Copolymer*
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer	VP/VA Copolymer*

*Previously reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel)

Most of these ingredients have the film former function in cosmetics in common (see Table 1).¹ Viscosity increasing agent and binder are two other functions that are frequently being reported.

It should be noted that the Panel has evaluated the safety of, and issued conclusions (in published reports) on, 8 ingredients/ingredient groups (identified with an asterisk above) that are similar to the 22 ingredients that are being reviewed for the first time in this safety assessment. The Panel's published conclusions on the 8 ingredients/ingredient groups previously reviewed are stated in Table 2, and the published reports may be found at <https://www.cir-safety.org/ingredients>. Data on other polymers that were reviewed in these published safety assessments that may have been used to evaluate safety in the absence of data on the polymers that were being evaluated are not included in this safety assessment. The published reports may be consulted for safety test data on those polymers, as well as the available data on monomers. Safety test data on vinylpyrrolidone polymers (i.e., polymers that are the subject of this review) that are included or referenced in the published reports (italicized within the text of this safety assessment) and ingredient use frequency/use concentration data (both current data and data from a published CIR report) are included in this safety assessment. Data on vinylpyrrolidone polymers that were published since the most recent published CIR safety assessment on any of these ingredients are also included. Information relating to the CIR review status of the monomer components of vinylpyrrolidone polymers is presented in Table 3.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (<http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <http://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition and General Characterization

The definitions, structures, and functions of the vinylpyrrolidone copolymers that are reviewed in this safety assessment are presented in Table 1. These polymeric ingredients share in common a vinylpyrrolidone monomer (Figure 1).

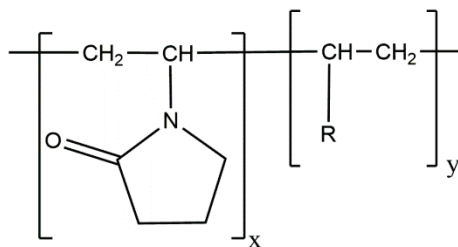


Figure 1. Polyvinylpyrrolidone ingredients (wherein $-\text{C}(\text{R})\text{HCH}_2-$ represents at least one co-monomer residue).

Chemical and Physical Properties

The physical properties of 5 vinylpyrrolidone polymers are presented in Table 4. Maltodextrin/VP Copolymer has an average molecular weight of 132,999 Da.² According to one supplier, Triacontanyl PVP is another high molecular weight polymer, and is insoluble in water, acid, or base solution.³ VP/Acrylates/Lauryl Methacrylate Copolymer is expected to have low water solubility based on its mostly hydrophobic structure.⁴ Sodium Acryloyldimethyltaurate/VP Crosspolymer is miscible with water and VP/Dimethylaminoethylmethacrylate Copolymer has a density of 1.047 g/cm³.^{5,6} Additionally, the molecular weight of PVP can range from 10,000 to 700,000 Da, and PVP with an average molecular weight of 40,000 Da is commonly used in cosmetic formulations.⁷

VP/VA Copolymer

*VP/VA Copolymer does not absorb energy over the UVA, UVB, or visible light spectrum.*⁸

Method of Manufacture

VP/VA Copolymer

*VP/VA Copolymer is prepared by free radical polymerization in ethyl alcohol.*⁸

VP/VA copolymer is produced by free radical copolymerization of *N*-vinyl-2-pyrrolidone (NVP) and vinyl acetate (VA) in solution in isopropanol, in the presence of initiators.⁹ The process is continuous and temperature controlled. Hydrazine is formed from amines present in this reaction mixture. Sodium bisulfite is added to the batch for color stability. Isopropanol is exchanged for deionized water by adding deionized water to the reactor and performing a solvent exchange via vacuum distillation. Sodium acetate (for pH stabilization) and a microbiological preservative (identity not specified) are added. The batch is then heated, sampled, and adjusted for solids content. The product is isolated as an aqueous solution/emulsion, or as a spray-dried solid.

Composition/Impurities

Acrylates/VP Copolymer and VP/Dimethylaminoethylmethacrylate Copolymer

*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.*¹⁰

Ammonium Acryloyldimethyltaurate/VP Copolymer and Sodium Acryloyldimethyltaurate/VP Crosspolymer

*Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer was reported to be >90% pure. Sodium Polyacryloyldimethyl Taurate is reported to contain <2000 ppm AMPS and <10 ppm acrylamide.*¹¹

Australia's National Industrial Chemical Notification and Assessment Scheme (NICNAS) has noted that Sodium Acryloyldimethyltaurate/VP Crosspolymer contains residual monomers and/or impurities (identities and concentrations not stated) that are classified as hazardous according to the *Globally Harmonized System of Classification and Labeling of Chemicals (GHS)*, as adopted for industrial chemicals in Australia.⁵

Maltodextrin/VP Copolymer

Maltodextrin/VP Copolymer, a high molecular weight polymer (132,999 Da), contains an unnamed low molecular weight species that is < 1000 Da (0.8% of composition) and an unnamed low molecular weight species that is < 500 Da (0.1% of composition).²

Methacrylic Acid/Styrene/VP Copolymer

*Data provided by industry indicate that styrene and vinyl-type styrene copolymer trade name materials contain styrene monomer at levels of < 100 ppm or less.*¹²

PVP

*The [United States Pharmacopeia] USP specifies that pharmaceutical grade PVP cannot contain more than 1 ppm hydrazine.*⁷

PVP, an NVP-containing polymer, is imported into Australia for industrial uses, and the residual NVP monomer levels in PVP were obtained from a few (number not stated) major importers of PVP.¹³ It was noted that it appears that there are different grades of PVP imported into Australia, depending on the end use (i.e., pharmaceutical, cosmetic, or industrial grade). The residual NVP monomer content in the PVP imported into Australia varies and ranges from 10 ppm to 2000 ppm. In Europe (countries not specified), NVP residues in PVP are generally below 100 ppm.

Triaccontanyl PVP

According to one source, Triaccontanyl PVP has a purity of > 97% and consists of < 2% water.³

VP/VA Copolymer

*VP/VA Copolymer is supplied either in 100% concentration as a powder or as a 50% solution in alcohol.*⁸ *VP/VA Copolymers may contain the residual monomers, vinyl acetate at 1.0%, and vinyl pyrrolidone at 0.5%.*

*For VP/VA copolymers with molecular weights of approximately 12,000 and greater, the level of vinyl acetate is smaller than or equal to 300 ppm as measured using HPLC.*¹⁴ *Another source reported vinyl acetate levels of less than 100 ppm for copolymers of molecular weights of 12,700 to approximately 30,000, and levels of less than 1000 ppm for a copolymer of a molecular weight of approximately 51,000.*

Specifications for VP/VA Copolymer that were submitted to the European Food Safety Authority (EFSA) are presented in Table 5. Some of the specifications relate to monomer content and impurities.⁹

USE

Cosmetic

The safety of vinylpyrrolidone polymers is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.¹⁵ Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Council, of maximum reported use concentrations by product.¹⁶

According to 2018 VCRP data, the greatest use frequency is being reported for PVP, which is being used in 900 cosmetic products (798 leave-on products + 101 rinse-off products + 1 product diluted for bath use).¹⁵ The second highest use frequency (597 cosmetic products: 525 leave-on products + 62 rinse-off products) is being reported for Ammonium Acryloyldimethyltaurate/VP Copolymer. In general, the differences in current use frequencies of vinylpyrrolidone polymers in cosmetics versus those reported in previous years are unremarkable. The results of a concentration of use survey conducted in 2017 indicate that VP/VA Copolymer is being used at concentrations up to 44% in rinse-off products (paste masks and mud packs), which is the highest maximum ingredient use concentration that is being reported for vinylpyrrolidone polymers.¹⁶ Notably, in 2003, the highest maximum use concentration of VP/VA Copolymer in rinse-off products was 10%, which is 4-fold lower than the current highest maximum use concentration in rinse-off products.¹⁴ The highest maximum ingredient use concentration of vinylpyrrolidone polymers in leave-on products is being reported for PVP, which is being used at concentrations up to 35% in leg and body paints. Notably, in 2013, the highest maximum use

concentration of PVP in leave-on products was lower, 12%. Thus, the highest maximum use concentration of PVP in leave-on products is approximately 3-fold greater than the highest maximum use concentration of this ingredient in leave-on products that was reported in 2013. Current and historical use frequency and concentration of use data are presented in Table 6.

According to VCRP and Council survey data, the following 9 vinylpyrrolidone polymers are not being used in cosmetic products:

Acrylates/Stearyl Methacrylate/VP Copolymer
 Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer
 Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer
 Methacrylic Acid/Styrene/VP Copolymer
 PVP/Decene Copolymer
 PVP/VA/Itaconic Acid Copolymer
 PVP/VA/Vinyl Propionate Copolymer
 Triacontene/VP Copolymer
 VP/Vinyl Alcohol Copolymer

Cosmetic products containing vinylpyrrolidone polymers may be applied to the skin and hair or, incidentally, may come in contact with the eyes (e.g., at maximum use concentrations up to 17.2% VP/Hexadecene Copolymer [in eye shadows]) and mucous membranes (e.g., at maximum use concentrations up to 24.1% VP/Hexadecene Copolymer [in lipstick]). The incidental ingestion of ingredients may result from the use of lipstick products. Products containing vinylpyrrolidone polymers 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.

VP/VA Copolymer is being used in both pump hair sprays (maximum use concentrations up to 9%) and aerosol hair sprays (maximum use concentrations up to 10%), which may result in incidental inhalation exposure. These 2 concentrations are the highest maximum cosmetic use concentrations that are being reported for vinylpyrrolidone polymers in cosmetic products that are sprayed. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters $> 10 \mu\text{m}$, with propellant sprays yielding a greater fraction of droplets/particles below $10 \mu\text{m}$, compared with pump sprays.^{17,18,19,20} 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.^{17,18}

VP/Eicosene Copolymer is being used in face powders at concentrations up to 0.5% (highest maximum use concentration). Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.^{21,22,23}

The ingredients reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.²⁴

Noncosmetic

PVP

PVP is cleared for the following uses: as a clarifying agent in beverages and vinegar; as a tableting adjuvant; and as a stabilizer, bodying agent, and dispersant in nonnutritive sweeteners in concentrated liquid form, and vitamin and mineral concentrates. It is also cleared for use in packaging that comes in contact with various foods. PVP K-30 (average MW 40,000) is used as a food additive.

PVP is used widely in industries such as pharmaceuticals, adhesives, agriculture, and surface coating.¹³ It is used in medicine and in the pharmaceutical industry as a blood plasma expander, and it is a common ingredient in drug manufacture.²⁵

VP/VA Copolymer

The European Food Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources added to Food has provided a scientific opinion on the use of VP/VA Copolymer in food supplements.⁹ This opinion addresses the safety of VP/VA Copolymer for use in food supplements, in tablet form as a binding/coating agent in an amount of up to 10% of

weight per tablet, for a tablet weight of 1000 mg. Overall, the EFSA Panel concluded that the use of VP/VA copolymer in solid food supplements as a binding/coating agent is unlikely to be a safety concern at the proposed uses and use levels provided. The EFSA Panel also concluded that the residual level of hydrazine, proposed at a maximum of 1.0 mg/kg in the final product, is unlikely to be of safety concern. However, the EFSA Panel noted that it would be prudent to lower the level of hydrazine as far as reasonably achievable.

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

PVP

The absorption, distribution, metabolism, and excretion of PVP is dependent on molecular weight, amount and frequency of dosing, and route of administration.⁷ Polymers with a weight < 25,000 are eliminated through the kidneys. An oral dosing study using 0.9 mg per rat of a PVP trade name material found no significant absorption.

New data on the absorption, distribution, metabolism and excretion of PVP or other vinylpyrrolidone polymers were not found in the published literature.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Animal

Dermal

Triacontanyl PVP

A single dose of a Triacontanyl PVP trade name material (moistened with water, dose = 2 g/kg) was applied, under an occlusive wrap, for 24 h to the backs of 10 New Zealand white rabbits.³ The animals were observed for up to 14 days after test substance application, and all gained weight during the study. None of the animals died, and no abnormal clinical signs were observed. The acute dermal LD₅₀ was > 2 g/kg.

Oral

Ammonium Acryloyldimethyltaurate/VP Copolymer

The acute oral LD₅₀ for Ammonium Acryloyldimethyltaurate/VP Copolymer was reported to be >2000 mg/kg in rats.¹¹

PVP

The oral LD₅₀ of PVP (avg. MW of 40,000) is > 100 g/kg body weight for both rats and guinea pigs.⁷

Triacontanyl PVP

The acute oral toxicity of a Triacontanyl PVP trade name material was evaluated using 10 Sprague-Dawley rats (5 males, 5 females).³ A single 5 g/kg oral dose of the test substance (ground into a powder and mixed with peanut butter and honey) was fed to the animals. The test substance was consumed within 18 h to 24 h. Dosing was followed by a 14-day observation period. None of the animals died and no gross organ changes were observed at necropsy. The LD₅₀ was > 5 g/kg.

VP/Acrylates/Lauryl Methacrylate Copolymer

An LD₅₀ of > 5 g/kg (rats) has been reported for undiluted VP/Acrylates/Lauryl Methacrylate Copolymer.⁴ Dyspnea was observed in 1 animal. The number of animals tested and details relating to the test protocol and study results were not specified.

VP/VA Copolymer

Acute oral toxicity studies were performed with VP/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 surviving animals showed, at most, decreased activity and ataxia at maximum doses of 5 g/kg of a solution containing 12.5% VP/VA Copolymer.⁸

Short-Term Toxicity Studies

Dermal

VP/VA Copolymer

A hair product containing 1% VP/VA Copolymer was tested in a six-week 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.⁸

Oral

VP/VA Copolymer

VP/VA Copolymer was administered in the diet of 3 groups of male and female Sprague-Dawley rats (5 animals/sex/group; control group: 5 animals/sex) for 28 days at doses of 0 (control), 100, 300, and 1000 mg/kg/day, respectively.⁹ The control group was fed the basal diet only. All animals survived to the scheduled necropsy. There were no clinical signs of toxicity, and there were no effects on the following: body weight gain, feed consumption, hematology parameters, serum chemistry, and urinalyses. There also were no test substance-related effects on organ weights, macroscopic and microscopic evaluations. The authors concluded that the no-observed-adverse-effect level (NOAEL) was 1000 mg/kg/day.

PVP

In two short-term inhalation studies using rats, PVP was detected in lung samples but no inflammatory response was noted. Mild lymphoid hyperplasia and fibroplasia were noted in the subpleural, perivascular, and peribronchial lymphatics.⁷

The short-term oral toxicity of a PVP tradename material (5% w/v in water) was evaluated using 2 groups of 6 HanWistar rats (RccHan:WIST; 3 males, 3 females/group).²⁶ The test animals received oral doses (dose volume of 10 ml/kg, by gavage) daily for 28 consecutive days. The control group received water. At day 1 after the final dose, the animals were killed and scheduled for necropsy. The following tissues were examined microscopically: eyes, liver, kidneys, urinary bladder, lungs, heart, thymus, sternum, upper jaw (with nares and nasal turbinates), lower jaw with skin, stomach/duodenum, intestine (jejunum, ileum, cecum, and rectum), mesenteric lymph node, and the tongue. All hematology findings were within the normal background range for the rat strain that was tested, and there was no induction of cytochrome P450 protein (CYP1A1/2, CYP2B1, CYP3A, and CYP4A) levels. There were no toxicologically relevant effects on body weight gain, food consumption, or water consumption, and there were no treatment-related microscopic changes.

Subchronic Toxicity Studies

Oral

VP/VA Copolymer

VP/VA Copolymer was administered in the diet of 3 groups of male and female Sprague-Dawley rats (10 animals/sex/group; control group 10 animals/sex) for 90 days at doses of 0 (control), 100, 300, and 1000 mg/kg/day, respectively.⁹ The control group was fed the basal diet only. All animals survived to the scheduled necropsy. There were no

clinical signs of toxicity, and there were no effects on the following: body weight gain, feed consumption, functional observational battery, and locomotor activity evaluations. Furthermore, there were no ophthalmic lesions indicative of toxicity, and no test-substance-related effects on hematology parameters, serum chemistries, and urinalyses. No test substance-related effects on organ weights, macroscopic, and microscopic evaluations were observed. The authors concluded that the NOAEL was 1000 mg/kg/day.

Inhalation

VP/VA Copolymer

Rats and hamsters were exposed for 13 weeks to a spray containing 4.0% VP/VA Copolymer.⁸ 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/m³ (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. Subchronic inhalation of a spray formulation containing 1.72% VP/VA Copolymer for 90 days produced no effects in rabbits.

Chronic Toxicity Studies

Animal

Oral

PVP

Neither toxic effects nor gross lesions attributable to PVP were found in rats maintained for 2 years on a diet containing up to 10% of a PVP trade name material. A similar 2-year feeding study in dogs found swollen phagocytic cells in the lymph nodes.⁷

VP/VA Copolymer

Chronic (1 year) oral ingestion of a solution containing 10.2 mg/l of VP/VA Copolymer produced no effects in mice or rats.⁸

In a 52-week oral feeding (diet) study, the chronic oral toxicity of VP/VA Copolymer was evaluated using the following groups of male and female pure-bred beagle dogs: group 1 (4 males, 4 females: 510 mg/kg/day), group 2 (4 males, 4 females: 1518 mg/kg/day), and group 3 (6 males, 6 females: 2522 mg/kg/day).²⁷ The control group was fed a diet without the test substance. All animals were killed at the end of the dosing period, and both gross and histopathologic examinations were performed. None of the animals died during the study and no treatment-related clinical signs were observed. Furthermore, the following parameters were unaffected by treatment: food consumption, ophthalmoscopic examinations, hearing tests, electrocardiograms, and blood pressure. There were no treatment-related body weight losses during the study. Hematology, clinical biochemistry, and urinalysis parameters were unaffected by feeding with the test substance; sporadic statistically significant intergroup differences were observed, but these findings were not dose-related. Therefore, differences in these parameters were considered to represent the expected spontaneous variations that occur in dogs of the age and strain that are being used in this study.

There were no treatment-related or dose-related changes in organ weights or organ-to-body weight ratios. At gross examination, the type and incidence of findings were comparable between test and control groups. At microscopic examination, the incidence and severity of findings were comparable between test and control groups and were considered commonly observed changes in dogs of the age and strain used in this study. No inflammatory and/or degenerative changes (i.e., necrosis, granulomas, etc.) were associated with vacuolated histiocytes that were diagnosed in the sinusoids and trabeculae of some mesenteric lymph nodes. The NOAEL was determined to be the target dose of 2500 mg/kg/day (target dose for highest dose group).²⁷

The chronic oral toxicity of VP/VA Copolymer was evaluated using 3 groups of male and female Wistar rats of the Chbb:THOM (SPF) strain (50 males, 50 females/group).²⁷ The 3 groups were fed the test substance (in the diet) at the following doses for 24 months: group 1 (high dose: 686 mg/kg/day [males] and 691 mg/kg/day [females]), group 2 (mid dose: 1374 mg/kg/day [males] and 1378 mg/kg/day [females]), and group 3 (low dose: 2625 mg/kg/day [males] and 2759 mg/kg/day [females]). A fourth group (control) was fed a diet without the test substance for the same duration. The test substance (same doses) was also fed to 4 satellite groups (4 test and 1 control) for 18 months. These 4 groups were included for hematological evaluation. For all groups in the study, the animals were killed after a 16-h to 20-h fasting period that

began after the end of the dosing period. Numerous tissues were submitted for histopathological examination. The mortality rates ranged from 14% in the high-dose males to 36% in the control males, and 26% in the high-dose females to 30% in the control females. Data were comparable in the satellite groups. Food consumption was described as normal. Due to the absence of a dose-response relationship, and a higher mortality rate in control rats of both sexes, it was concluded that the test substance did not affect survival. No remarkable test substance-related clinical signs were observed in the study. Body weight and body weight change were statistically significantly reduced in high-dose males at most time points throughout most of the study. Marginal differences in hematological parameters (within historical control ranges) were observed, but there was no dose-response relationship and the differences were not considered treatment-related. The vast majority of the gross lesions in the main groups in the study were comparable to the incidence in controls, and there was no clear dose-response relationship. The NOAEL was determined to be the target dose of 2800 mg/kg/day (target dose for highest dose group). Results relating to tumor formation are included in the Carcinogenicity section of this report.

A 2-year feeding study on VP/VA Copolymer (60% VP and 40% VA) was performed using 2 groups of Sprague-Dawley rats (51 males and 51 females/group, test and control groups).⁹ Test animals were given feed containing 5% VP/VA Copolymer, and control animals were given feed containing 5% cellulose. Based on the consumption of the entire diet, test animals were fed ~0.67 g VP/VA Copolymer (equivalent to ~450 mg/kg/day) for the duration of the study. Hemoglobin content and leukocyte count were determined in 5 rats per sex (test and control groups) for up to 364 days of the study. Hematology, blood chemistry, and urinalysis parameters were evaluated after ~500 days of the study. These 3 parameters were evaluated using 10 test and control rats of each sex, as well as in all test (20 rats) and control (11 rats) animals that remained alive after 675 days. Survival in both the control and test groups was described as poor (8% to 14%), due to inflammatory diseases of the respiratory tract. There were no signs of toxicity in test or control rats, and no treatment-related clinical chemistry changes. At histopathological examination of organs (liver, kidneys, and other organs [not stated]), an increased incidence of liver congestion and fatty degeneration in the test group, compared to the control group, was reported. No gross pathologically detectable lesions were observed. Results relating to carcinogenic potential are included in the Carcinogenicity section of this report.

Inhalation

VP/VA Copolymer

Chronic (2 years) inhalation exposure to hair spray aerosols containing 0.08 ± 0.08 mg/l and 0.35 ± 0.09 mg/l for 2 years produced no effects in hamsters.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

PVP

No teratogenic effects were observed when up to 500 µg of PVP (MW 11,500) was injected into the yolk sac of rabbit embryos.⁷

GENOTOXICITY STUDIES

In Vitro

Ammonium Acryloyldimethyltaurate/VP Copolymer

Ammonium Acryloyldimethyltaurate/VP Copolymer was not mutagenic in bacterial reverse mutation assays.¹¹

PVP

PVP was negative in the majority of mutagenicity studies conducted.⁷ The in vitro assays that were performed in these studies included Ames, mouse lymphoma, and Balb/c 3T3 tests.

Three formulations containing PVP-iodine were not genotoxic in a comet assay or a chromosome aberration test, with or without metabolic activation.²⁸ The solutions contained 3% or 10% PVP-iodine. In both tests, [Chinese hamster ovary] CHO-K1 cells were exposed for 4 h to the test solutions. Expected results were observed with positive and negative controls.

The genotoxicity of PVP was evaluated in the Ames test using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, and TA1537.^{29,30} Each strain was tested with 10% PVP (in water) with and without metabolic activation. The results were classified as negative in all bacterial strains, with and without metabolic activation.

Sodium Acryloyldimethyltaurate/VP Crosspolymer

The genotoxicity of Sodium Acryloyldimethyltaurate/VP Crosspolymer was evaluated in the Ames test (bacterial strains and doses not stated) (Organization for Economic Co-operation and Development (OECD) Test Guideline (TG) 471).⁵ The test substance was classified as non-genotoxic.

Triaccontanyl PVP

The genotoxicity of a Triaccontanyl PVP trade name material was evaluated in the Ames test using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538.³ The test substance was evaluated (with and without metabolic activation) at doses up to 2500 µg/plate. 2-Aminoanthracene, 2-nitrofluorene, sodium azide, and ICR-191 served as positive controls. The test substance was not genotoxic in any of the *Salmonella typhimurium* strains tested. Marked increases in the number of revertant colonies were observed in positive control cultures.

In Vivo

PVP

PVP was negative in the majority of the in vivo mutagenicity studies conducted.⁷ The assays that were performed were dominant lethal, micronucleus, and Chinese hamster bone marrow tests.

CARCINOGENICITY STUDIES

Animal

Oral

VP/VA Copolymer

The carcinogenicity of VP/VA Copolymer was evaluated using 3 groups of male and female Wistar rats of the Chbb:THOM (SPF) strain (50 males, 50 females/group).²⁷ The 3 groups were fed the test substance (in the diet) at the following doses for 24 months: group 1 (low dose: 2625 mg/kg/day [males] and 2759 mg/kg/day [females]), group 2 (mid dose: 1374 mg/kg/day [males] and 1378 mg/kg/day [females]), and group 3 (high dose: 686 mg/kg/day [males] and 691 mg/kg/day [females]). A fourth group (control) was fed a diet without the test substance for the same duration. At histopathological examination, there was no treatment-related increase in the number of animals with the following: neoplasms (primary neoplasm or benign, malignant, systemic and metastasized neoplasms). There also was no treatment-related increase in the total number of primary neoplasms, or benign, malignant, systemic, or metastasized neoplasms. Additionally, there was no indication that the test substance caused any non-neoplastic alteration of organs or organ systems, when comparing the incidence and graded severity of microscopic findings of treated animals with the corresponding observations in control animals. All neoplastic and non-neoplastic microscopic findings were considered to have developed spontaneously and were not related to treatment.

A 24-month feeding study on VP/VA Copolymer (60% VP and 40% VA) was performed using 2 groups of Sprague-Dawley rats (51 males and 51 females/group, test and control groups).⁹ Test animals were given feed containing 5% VP/VA Copolymer, and control animals were given feed containing 5% cellulose. Based on the consumption of the entire diet, test animals were fed ~0.67 g VP/VA Copolymer (equivalent to ~450 mg/kg/day) for the duration of the study. No treatment-related tumors or other gross pathologically detectable lesions were induced.

Implantation

PVP

Implantation of PVP sponges into mice and rats resulted in development of local sarcomas, but without metastases.⁷

ANTICARCINOGENICITY STUDY

PVP

Orally administered PVP significantly decreased the rate of bladder tumors in mice exposed to bracken fern. IARC classified PVP as a "group 3" agent, "not classifiable as to its carcinogenicity in humans."⁷

OTHER RELEVANT STUDIES

Cytotoxicity

PVP

A study was performed to evaluate the effects of PVP amphiphilic polymers and polymeric nanoparticles on MCF-7 cell (human cancer cell line) growth and viability, using the MTT (thiazoyl blue tetrazolium bromide) cell viability assay.³¹ The PVP amphiphilic polymers that were used to prepare the nanoparticles were defined as follows: PVP-OD4000 (amphiphilic *N*-vinylpyrrolidone polymer with molecular weight of hydrophilic polymer fragment of 4000 Da and 1 hydrophobic octadecyl group), PVP-OD8000 (amphiphilic *N*-vinylpyrrolidone polymer with molecular weight of hydrophilic polymer fragment of 8000 Da and 1 hydrophobic octadecyl group), and PVP-DD₂4000 (amphiphilic *N*-vinylpyrrolidone polymer with molecular weight of hydrophilic polymer fragment of 4000 Da and 1 hydrophobic di(dodecyl) group). Amphiphilic PVP polymeric nanoparticles were prepared using an emulsification and solvent evaporation technique. The particle sizes of the PVP-OD4000, PVP-OD8000, and PVP-DD₂4000 nano-aggregates were 32 nm, 47 nm, and 86 nm, respectively. MCF-7 cells were incubated with each type of unassociated polymer (PVP-OD4000, PVP-OD8000 and PVP-DD₂4000) or nanoparticles for 24, 48 or 72 h before MTT assays were performed. Polymer concentrations ranged from 0.05% to 0.5%, and nanoparticle concentrations ranged from 0.5% to 5%. Additionally, the critical aggregation concentration (CAC) of amphiphilic PVP polymers was determined using pyrene fluorescence probe spectrometry. The CACs of all 3 polymers were in the micromolar range (6.2 to 14.6 $\mu\text{mol/l}$).

Polymers with an *n*-alkyl octadecyl hydrophobic group demonstrated low cytotoxic effects against MCF-7 cells (compared to untreated control cells) ($P < 0.05$). PVPDD₂4000 nanoparticles were slightly more cytotoxic due to the presence of more branched hydrophobic groups. All polymers demonstrated no cytotoxicity both at concentrations less than the critical aggregation concentration (simple polymer solution) and at higher concentrations, when amphiphilic macromolecules are self-assembled in nanoparticles ($P < 0.05$). For example, incubation with PVP-OD4000 and PVP-OD8000 at concentrations as high as 5% resulted in cell viabilities of 99%. Furthermore, the corresponding nanoparticles did not cause marked cell death ($P < 0.05$).³¹

The effect of PVP on the ultrastructure of spermatozoa from 12 fertile patients was evaluated.³² A sperm suspension (0.1 ml) from each patient was added to a 10% PVP solution (0.5 ml) and incubated for 30 minutes. An aliquot of the sperm suspension without PVP served as the control. The samples were analyzed by transmission electron microscopy. Results indicated that the untreated sperm fractions and the PVP-treated fractions were significantly different. The means of the percentages of spermatozoa devoid of defects in untreated sperm fractions versus PVP-treated fractions were 4.2808% and 0.5490%, respectively ($P = 0.001$). The sperm organelles that were deteriorated by PVP treatment were as follows: swollen, reacted or absent acrosomes, the granular and decondensed chromatin, and swollen and badly shaped mitochondria. The most affected organelle was the plasma membrane, which appeared broken in a high percentage of the cells. In cross sections of sperm tails after PVP treatment, the plasma membrane was broken, the mitochondria were swollen, and the axoneme was disassembled. Thus, PVP strongly affected the fine structure of spermatozoa. The authors concluded that PVP exerted a disintegrating effect on the various kinds of sperm membranes, and, as a secondary consequence of the eventual necrotic process, alteration of chromatin and cytoskeletal components.

The effect of a PVP tradename material on cultured HeLa cells (human cervical carcinoma cells) was evaluated.³³ HeLa cells were incubated for 24 h at concentrations of 5%, 10%, and 20%. Treatment with the test substance produced a dose- and time-dependent toxicity (i.e., inhibitory effect on cell proliferation) to HeLa cells. The hallmarks of apoptosis, such as chromatin condensation, DNA fragmentation, and formation of apoptotic bodies, were observed. Other results indicated that the apoptosis induced by the test substance may have been via cell cycle arrest at the G2/M phase.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

Animal

Ammonium Acryloyldimethyltaurate/VP Copolymer

Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed applied neat, not specified) was nonirritating to rabbit skin.¹¹

PVP

A 10% PVP-iodine solution did not cause neither dermal irritation in rabbits.⁷

Triaccontanyl PVP

The skin irritation potential of a Triaccontanyl PVP trade name material (moistened with saline) was evaluated using 6 new Zealand white rabbits.³ The test substance (0.5 g) was applied, under an occlusive wrap, for 24 h to both an abraded and intact site on each animal. The area (cm²) of the application site was not stated. Very slight erythema was observed at 2 intact sites and 4 abraded sites (at 24 h) and at 1 intact site and 2 abraded sites (at 72 h). Slight edema was observed at 1 intact site and 2 abraded sites, only at 24 h. The test substance was classified as a slight skin irritant.

VP/VA Copolymer

Acute skin irritation studies of VP/VA Copolymer were conducted on the abraded and intact skin of rabbits. Formulations containing 0.25%-4.0% VP/VA Copolymer produced mild irritation. Solutions of 50% VP/VA in alcohol produced mild irritation, and one sample of the 100% powder moistened in water produced no irritation.⁸

Human

PVP

In 48-h and 96-h Shelanski patch tests, both involving 200 subjects, undiluted PVP-iodine (10% PVP and 2% iodine) was not a skin irritant.⁷ In 3 studies, groups of 20 subjects were patch tested with a foundation containing 2% PVP. One to 2 subjects in each group had minimal faint, uniform or spotty erythema.

The irritation and sensitization potential of different preparations that contain iodine, including PVP-iodine, was investigated in 24 fair-skinned, healthy subjects without a history of iodine allergy.³⁴ PVP-iodine was tested at concentrations of 1%, 5%, 7.5%, and 10% on the intrascapular area on the back or on the volar forearm (2-day application) with Finn Chambers on Scanpor tape. Only 1 subject reacted to PVP-iodine, at concentrations of 7.5% (vesiculation on day 4) and 10% (definite erythema on day 4).

VP/VA Copolymer

VP/VA Copolymer (50% in alcohol solution, 5 g dose) was mildly irritating to the skin in 24-h patch tests involving groups of 6 rabbits, whereas the undiluted ingredient was nonirritating to the skin of 6 rabbits.⁸ In 24-h skin irritation tests, using groups of 3 to 9 rabbits, on product formulations containing various concentrations of VP/VA Copolymer, concentrations of 0.5%, 1.50% and 4% were nonirritating and a test concentration of 1.75% had the potential for minimal irritation.

Sensitization

Animal

Ammonium Acryloyldimethyltaurate/VP Copolymer

Ammonium Acryloyldimethyltaurate/VP Copolymer (neat) was not sensitizing to guinea pigs.¹¹

PVP

A 10% PVP-iodine solution did not cause dermal sensitization in rabbits.⁷

Sodium Acryloyldimethyltaurate/VP Crosspolymer

The skin sensitization potential of Sodium Acryloyldimethyltaurate/VP Crosspolymer was evaluated in the LLNA (OECD TG 429).⁵ There was no evidence of sensitization.

VP/VA Copolymer

VP/VA Copolymer was not a sensitizer to guinea pigs after repeated intracutaneous injections.⁸ The skin was inspected 24 h after each injection.

Human

PVP

Undiluted PVP-iodine (10% PVP, 2% iodine) did not induce sensitization in an HRIPT involving 100 subjects.⁷ In an exaggerated use study (Draize-Shelanski patch test technique) on a PVP trade name material (PVP concentration not stated) involving 150 subjects, results were negative for skin sensitization. Results were also negative in an HRIPT (27 subjects) on a PVP trade name material (10% aqueous solution). In a maximization test involving 25 subjects, 2% PVP did not induce contact allergy.

Triacontanyl PVP

The skin sensitization potential of a Triacontanyl PVP trade name material was evaluated in an HRIPT involving 102 subjects (21 males, 81 females).³ Nine 24-h induction patches (type not stated), each containing ~200 mg of the test substance, were applied to the left upper back of each subject over a 3-week period. The area of application (cm²) was not stated. A 24-h challenge patch was applied 2 weeks after removal of the last induction patch. Reactions were scored at 48 h and 72 h post-application. A minimal reaction (not defined) was observed in 6 subjects during the induction phase. Reactions were not observed during the challenge phase. The test substance was a non-sensitizer.

VP/Acrylates/Lauryl Methacrylate Copolymer

In an HRIPT involving 105 subjects, VP/Acrylates/Lauryl Methacrylate Copolymer (96%) induced minimal erythema in 6 and 2 subjects during the induction and challenge phases, respectively.⁴ These results were not considered positive by the authors of this study. Details relating to the test protocol were not included.

VP/VA Copolymer

Repeated insult patch tests of a 5.0% formulation of VP/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.⁸

Photosensitization/Phototoxicity

Animal

VP/VA Copolymer

No photosensitization data on VP/VA Copolymer were available for review, but the UV absorption characteristics suggest that photosensitization is unlikely.⁸

Human

PVP

A PVP trade name material (10% aqueous solution) did not induce a phototoxic response in a study involving 10 human subjects.⁷

Triacontanyl PVP

The phototoxicity of a Triaccontanyl PVP trade name material was evaluated using 10 subjects (1 male, 9 females). The test substance (~200 mg) was applied, under an occlusive wrap, for 24 h to both forearms of each subject.³ The area of application (cm²) was not stated. After removal of the occlusive wrap, 1 forearm of each subject was irradiated with UVA light. Both arms of each subject were evaluated for reactions on days 2, 3, and 4, and reactions were not observed. The test substance did not induce a contact dermal phototoxic response.

During the induction phase of a photoallergenicity study, a Triaccontanyl PVP trade name material (200 mg) was applied, under an occlusive wrap, for 24 h to both forearms of 28 subjects.³ The area of application (cm²) was not stated. The study involved a 3-week induction phase, 2-week non-treatment period, and then a challenge phase. After 24 h, the occlusive wraps were removed and 1 forearm of each subject was irradiated for 15 minutes with UVA light (3.3 joules) and UVB light (108 to 144 m Joules). Induction was repeated 6 times during a 3-week period. The challenge phase began 2 weeks after the last induction (followed by irradiation). The test substance was applied (under an occlusive wrap) for 24 h to a new site on the forearm. After removal of the occlusive wrap, 1 forearm was irradiated with UVA light. Test sites were evaluated immediately after irradiation and at 48 h and 72 h post-application. A challenge reaction (minimal reaction) was observed in 1 subject, only at the site that was irradiated after test substance application. The test substance did not induce contact photoallergy.

OCULAR IRRITATION STUDIES

In Vitro

PVP

PVP-iodine was severely toxic to corneal endothelium at concentrations of 5% and 10% in a rabbit eye model.³⁴ An in vitro study of cultured bovine corneal endothelial cells with PVP-iodine concentrations up to 0.1% found that concentrations of 0.05% or less did not induce endothelial cell damage.³⁴

Animal

Ammonium Acryloyldimethyltaurate/VP Copolymer

In an ocular irritation assay, Ammonium Acryloyldimethyltaurate/VP Copolymer was nonirritating to the eyes of rabbits.³⁵

PVP

In ocular irritation studies using rabbits, a 10% PVP-iodine solution (without detergent) was minimally toxic, whereas repeated instillations of 0.5% PVP-iodine did not cause ocular irritation.⁷

An in vivo study on rabbits with PVP-iodine up to 1% found concentrations of 0.1% or less did not damage the corneal endothelium.³⁴

Sodium Acryloyldimethyltaurate/VP Crosspolymer

The ocular irritation potential of Sodium Acryloyldimethyltaurate/VP Crosspolymer (test concentration unknown) was evaluated using rabbits in accordance with OECD TG 405.⁵ Slight conjunctival effects were observed and had resolved by 24 h. The test substance was classified as slightly irritating.

VP/Acrylates/Lauryl Methacrylate Copolymer

Undiluted VP/Acrylates/Lauryl Methacrylate Copolymer was slightly irritating to the eyes of rabbits.⁴ The number of animals tested and details relating to the test protocol and study results are not included.

VP/VA Copolymer

The acute ocular irritation of VP/VA Copolymer, as supplied, and in formulation, was tested on albino rabbits. Solutions of 25%-50% VP/VA in alcohol produced no reaction to severe irritation. Formulations containing 2.5%-24% VP/VA Copolymer also produced no reaction or moderate irritation.⁸

Triacantanil PVP

In a study involving 6 New Zealand white rabbits, a Triacantanil PVP (unknown concentration) trade name material was instilled (50 mg) into the conjunctival sac (1 eye) of each animal.³ Untreated eyes served as controls. The eyes of 3 rabbits were rinsed after instillation. Reactions were scored for up to 7 days post-instillation according to the Draize scale. In all treated eyes, slight erythema, edema, and discharge were observed at 1 h post-instillation. Conjunctival irritation persisted for 4 days in 1 eye (unrinsed) and, for 1 day, in 1 rinsed eye. The test substance was classified as a slight ocular irritant.

Human

VP/Hexadecene Copolymer

A controlled user test of an eye shadow containing 12.22% VP/Hexadecene Copolymer was performed using 10 healthy female subjects, 5 of whom wore contact lenses.³⁶ The product was applied to the face (eye region) daily for 2 weeks, and the subjects were examined by an ophthalmologist. No subject had subjective or objective eye irritation in the form of tears or pain, and there was no evidence of eyelid irritation or incompatibility (redness, itching). Furthermore, examination of the eye with a slit-lamp microscope did not reveal any evidence of irritant contact conjunctivitis with chemosis. The authors concluded that the product should be classified as harmless regarding the possibility of eye or eyelid irritation.

CLINICAL STUDIES

Case Reports

PVP

A woman with pollinosis developed anaphylaxis after vaginal application of a PVP-iodine solution for disinfection during a medical examination.³⁴ Wheal and flare responses (3+) to the PVP-iodine solution (10% aq.), PVP-iodine (0.1% aq.) and PVP (0.001% aq.) were observed following prick tests. In another case study, a man had an anaphylactic reaction minutes after oral ingestion of acetaminophen-containing tablets.³⁴ A positive test reaction to PVP (5% in water), one of the drug's components, was reported.

A case of a boy with a history of anaphylactic reactions following treatment for impetigo contagiosum was reported.³⁴ Skin prick tests with PVP-iodine solution (0.1-100 mg/dl in water) and PVP (K30; 0.1-10 mg/ml in water) were negative. However, in a histamine release test (using peripheral blood basophils), histamine release was observed in a dose-dependent manner after stimulation with PVP in the presence of autologous serum. A rare case of iododerma was reported in a man with a history of diabetes, hypertension, asthma, and gout.³⁴ Treatment with a 10% topical solution of PVP-iodine resulted in multiple pinpoint pustules (consistent with iododerma) on both lower extremities.

Four days following surgery to treat carpal tunnel syndrome, a woman presented with an acute vesicular dermatitis on her left hand, palm and dorsal surface, and interdigital spaces.³⁴ These reactions were observed after application of a 10% PVP-iodine solution to the surgical site. Patch testing with PVP-iodine solution (1% diluted in water) caused a positive (4+) reaction. A positive reaction (++) was also observed in the repeated open application test (ROAT).

Severe irritant contact dermatitis resulting in necrosis of the skin occurred in a woman following surgical preparation of her chest and upper abdomen with 10% PVP-iodine solution.³⁴ A woman with no significant medical history developed transient hypotension, anuric renal failure, hemolysis, coagulopathy, and uterine infarction following intra-uterine injection of 2% PVP-iodine solution as a dye in a hydrotubation procedure.³⁴ In another report, PVP-iodine-induced irritant contact dermatitis was diagnosed in a woman following antiseptic preparation of a spinal anesthesia site for an emergency Caesarean section.³⁴

Other Clinical Reports

PVP

In the patch testing of 500 consecutive patients with 10% PVP-iodine solution (diluted 10 times in water), 14 patients (2.8%) had a positive reaction to the test material.³⁴ These patients then underwent ROATs with a PVP-iodine solution and only 2 of the 14 patients tested positive.

Patch testing was performed on 10 patients with a history of contact dermatitis following application of PVP-iodine preparations and positive patch test reactions to the preparations.³⁴ On days 3 and 5, “+” reactions or stronger were observed in 10/10 patients with 10% PVP-iodine, in 9/9 patients with 5% PVP-iodine, and in 5/9 patients with 2% PVP-iodine. All patients (10/10) had positive reactions to the PVP-iodine preparation tested neat. In the control group, “+” reactions were observed in 3/10 to 5% and 10% PVP-iodine and to the PVP-iodine preparation. No reactions were observed to lower test concentrations or to any of the other components tested. The strong reactions were classified as allergic sensitization.

In a survey of physicians in Japan for occupational allergy, 17 out of 307 reported contact allergy to PVP-iodine.³⁴ Nineteen patients (12 men and 7 women) developed extensive patchy or linear erythema, sometimes accompanied by bullae and erosion, on both sides of the buttocks, the back and posterior areas of the thighs a few days after operations or cardioangiography. The patients were patch tested with 10% PVP-iodine solution and had strongly positive results (irritant contact dermatitis).

VP/Eicosene Copolymer

An atopic male with a history of xerosis and pruritus of the hands, lower arms, and legs applied a prescribed emollient cream containing VP/Eicosene Copolymer (concentration not stated) daily.³⁷ Within a month, the patient developed an itchy, vesicular dermatitis of the limbs. Patch testing of the cream was performed, and reactions were scored on days 2 and 3. A mild erythematous-edematous (+) reaction to the cream was observed on both days. In a repeated open application test in which the cream was applied to the antecubital fossa, a positive reaction was observed within 3 days. At 6 months after resolution of the dermatitis, the patient was patch tested with the cream and its ingredients. Reactions were scored on days 2, 3, and 4. A delayed, but clearly positive, erythematous-edematous reaction (+ reaction) to 10% VP/Eicosene Copolymer in petrolatum was observed on day 4. A positive reaction to the cream (+/+) was observed on days 3 and 4. The patch test reaction to VP/Eicosene Copolymer was considered allergic and clinically relevant. Positive reactions were not observed in the 15 control subjects patch tested with VP/Eicosene Copolymer.

Acute facial eczema was observed in a female patient after application of a sunscreen containing VP/Eicosene Copolymer (concentration not stated) and 23 other ingredients.³⁸ Product application was followed by moderate sun exposure. The patient had a childhood history of eczema. One month later, patch testing (Finn chambers, applied to back) of the ingredient and product was performed. Reactions were scored after days 2 and 3, and a positive reaction (+/+) to the sunscreen was observed. In a second patch test on the sunscreen, the test site was irradiated with UVA (10 J/cm²) on day 2. A positive reaction was observed on days 2 and 3 (+/+). Patch testing of the individual ingredients was also performed, and test results indicated that VP/Eicosene Copolymer was the only ingredient that caused a positive reaction. A positive reaction to this ingredient (1% in petrolatum) was observed on days 2 and 3 (+/+).

VP/Hexadecene Copolymer

The skin irritation potential of a cosmetic base containing 14.95% VP/Hexadecene Copolymer (undiluted) was evaluated in an occlusive patch test involving 50 subjects, identified as follows: 27 subjects (normal, healthy), 6 (with eczema), 3 (with allergy), and 14 (with sensitive skin).³⁹ The product was applied to the back (dose per cm² not stated) for 48 h using clear, square patch test chambers. Reactions were scored at 48 h (30 minutes after patch removal) and 72 h post-application. Sodium dodecyl sulfate (1% in water) and water served as positive and negative controls, respectively. There were no reactions to the product in any of the subjects tested. The positive control caused reactions in 21 subjects. Reactions to the negative control were not observed.

SUMMARY

The safety of 30 vinylpyrrolidone polymers as used in cosmetics is being reviewed in this safety assessment. Most of these ingredients have the film former function in cosmetics in common. Viscosity increasing agent and binder are 2 other functions that are frequently being reported.

VP/VA Copolymer is produced by free radical copolymerization of NVP and VA in solution in isopropanol, in the presence of initiators. The process is continuous and temperature-controlled. Hydrazine is formed from amines present in this reaction mixture. Some of the proposed specifications for VP/VA Copolymer, as a food ingredient, in a petitioner's submission to the EFSA are: vinylpyrrolidone (5 mg/kg maximum), vinyl acetate (5 mg/kg maximum), and hydrazine (1 mg/kg maximum).

One supplier reports that Maltodextrin/VP Copolymer contains an unnamed low molecular weight species that is <1000 Da (0.8% of composition) and an unnamed low molecular weight species that is < 500 Da (0.1% of composition). The residual NVP monomer content in the PVP imported into Australia varies and ranges from 10 ppm to 2000 ppm. In Europe (countries not specified), NVP residues in PVP are generally below 100 ppm.

According to 2018 VCRP data, the greatest use frequency is being reported for PVP, which is being used in 900 cosmetic products (798 leave-on products + 101 rinse-off products + 1 product diluted for bath use). The second highest use frequency (597 cosmetic products: 525 leave-on products + 62 rinse-off products) is being reported for Ammonium Acryloyldimethyltaurate/VP Copolymer. Some of the ingredients in this safety assessment were reviewed previously by the Panel. In general, the differences in current use frequencies of vinylpyrrolidone polymers in cosmetics versus those reported in previous years are unremarkable.

The results of a concentration of use survey conducted in 2017 indicate that VP/VA Copolymer is being used at concentrations up to 44% in rinse-off products (paste masks and mud packs), which is the highest maximum ingredient use concentration that is being reported for vinylpyrrolidone polymers. Notably, in 2003, the highest maximum use concentration of VP/VA Copolymer in rinse-off products was 10%, which is 4-fold lower than the current highest maximum use concentration in rinse-off products. The highest maximum ingredient use concentration of vinylpyrrolidone polymers in leave-on products is being reported for PVP, which is being used at concentrations up to 35% in leg and body paints. Notably, in 2013, the highest maximum use concentration of PVP in leave-on products was lower, 12%. Thus, the highest maximum use concentration of PVP in leave-on products is approximately 3-fold greater than the highest maximum use concentration of this ingredient in leave-on products that was reported in 2013.

The absorption, distribution, metabolism, and excretion of PVP are dependent on molecular weight, amount and frequency of dosing, and route of administration. Polymers with a weight < 25,000 Da are eliminated through the kidneys. An oral dosing study using 0.9 mg per rat of a PVP (unknown concentration) trade name material found no significant absorption. After subcutaneous injection, VP/VA Copolymer was stored in the spleen, the liver, kidneys, lung, and bone marrow. Some of the copolymer was excreted in the urine.

A single dose of a Triacetyl PVP (unknown concentration) trade name material was applied, under an occlusive wrap, for 24 h to the backs of 10 New Zealand white rabbits. None of the animals died, no abnormal clinical signs were observed, and the acute dermal LD₅₀ was > 2 g/kg. An oral LD₅₀ of > 5 g/kg (rats) has been reported for undiluted VP/Acrylates/Lauryl Methacrylate Copolymer. Dyspnea was observed in 1 animal.

The acute i.p. toxicity of PVP amphiphilic polymers and polymeric nanoparticles was evaluated using groups of 8 BALB/C mice and groups of 6 Wistar rats. Unassociated polymer solutions or polymer nanoparticles preparations were administered at doses 1 mg/kg to 50 mg/kg body weight (for polymers) and 500 mg/kg to 6000 mg/kg (for nanoparticles). For rats and mice, dosing with the 3 PVP polymers did not result in death, toxicity, or other negative symptoms. For the 3 types of PVP nanoparticles, LD₅₀ values for rats and mice were in the 3000 to 5500 mg/kg range (practically nontoxic substances).

VP/VA Copolymer was administered in the diet of 3 groups of male and female Sprague-Dawley rats (5 animals/sex/group) for 28 days at doses up to 1000 mg/kg/day. There were no clinical signs of toxicity or test substance-related macroscopic or microscopic tissue changes. The short-term (28 days) oral toxicity of a PVP trade name material (5% w/v in water) was evaluated using 2 groups of 6 HanWistar rats (RccHan:WIST strain). There were no toxicologically relevant effects on body weight gain, food consumption, or water consumption, and there were no treatment-related microscopic changes.

In a 90-day study, VP/VA Copolymer was also administered in the diet of 3 groups of male and female Sprague-Dawley rats (10 animals/sex/group) for at doses up to 1000 mg/kg/day, respectively. There were no clinical signs of toxicity or test substance-related macroscopic or microscopic tissue changes.

The chronic oral toxicity of VP/VA Copolymer was evaluated using groups of 100 male and female Wistar rats of the Chbb:THOM (SPF) strain. The groups were fed the test substance (in the diet) for 2 years, and 2759 mg/kg/day was the highest dose that was administered. There were no effects on survival and no remarkable test substance-related clinical signs in any of the dose groups. The vast majority of the gross lesions were comparable to the incidence in controls, and there was no clear dose-response relationship. A 2-year feeding study on VP/VA Copolymer (5% in diet) was also performed using groups of 102 Sprague-Dawley rats. Survival in both the control and test groups was described as poor (8% to 14%), due to inflammatory diseases of the respiratory tract. There were no signs of toxicity in test or control rats, and no treatment-related

clinical chemistry changes. No gross pathologically detectable lesions were observed. However, at microscopic examination, an increased incidence of liver congestion and fatty degeneration was observed.

In a chronic (52 weeks) feeding study, groups of 8 to 12 dogs were fed VP/VA Copolymer in the diet, and 2522 mg/kg/day was the highest dose that was administered. None of the animals died and no treatment-related clinical signs were observed. At gross and microscopic examinations, the type and incidence of findings were comparable between test and control groups.

The genotoxicity of 10% aqueous PVP was evaluated in the Ames test (with and without metabolic activation) using the *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537. Results were negative. Sodium Acryloyldimethyltaurate/VP Crosspolymer was also non-genotoxic (doses not stated) in the Ames test, and the same was true for a Triacantanlyl PVP trade name material (doses up to 2500 µg/plate, with and without metabolic activation).

The carcinogenicity of VP/VA Copolymer was evaluated using groups of 100 male and female Wistar rats of the Chbb:THOM (SPF) strain. The groups were fed the test substance (in the diet) for 2 years, and 2759 mg/kg/day was the highest dose that was administered. All neoplastic and non-neoplastic microscopic findings were considered to have developed spontaneously and were not related to treatment. A 2-year feeding study on VP/VA Copolymer (5% in diet) was also performed using groups of 102 Sprague-Dawley rats. No treatment-related tumors or other gross pathologically detectable lesions were induced.

A Triacantanlyl PVP trade name material (0.5 g, moistened with saline) was slightly irritating to the skin of 6 New Zealand white rabbits. Formulations containing 1.75%, 4%, and 5% VP/VA Copolymer produced no irritation in 24-hour patch tests. The skin irritation potential of a cosmetic base containing 14.95% VP/Hexadecene Copolymer (undiluted) was evaluated in an occlusive patch test involving 50 subjects (27 with normal skin; remainder with eczema, allergy, or sensitive skin). Skin irritation was not observed.

Results for Sodium Acryloyldimethyltaurate/VP Crosspolymer were negative in a LLNA. The skin sensitization potential of a Triacantanlyl PVP (unknown concentration) trade name material (~200 mg) was evaluated in an HRIPT involving 102 subjects, and results were negative. In an HRIPT involving 105 subjects, VP/Acrylates/Lauryl Methacrylate Copolymer (96%) induced minimal erythema in 6 and 2 subjects during the induction and challenge phases, respectively. These reactions were not considered positive.

In a study involving 10 subjects, a Triacantanlyl PVP (unknown concentration) trade name material (~200 mg) did not induce a contact dermal phototoxic response in the presence of UVA light. During the induction phase of a photoallergenicity study, a Triacantanlyl PVP (unknown concentration) trade name material (200 mg) was applied to the forearms of 28 subjects. A challenge reaction (minimal reaction) was observed in 1 subject, only at the site that was irradiated after test substance application. It was concluded that the trade name material did not induce contact photoallergy.

An unknown concentration of Sodium Acryloyldimethyltaurate/VP Crosspolymer was classified as slightly irritating to the eyes of rabbits. Undiluted VP/Acrylates/Lauryl Methacrylate Copolymer was also slightly irritating to the eyes of rabbits. In a study involving 6 New Zealand white rabbits, a Triacantanlyl PVP (unknown concentration) trade name material (50 mg) was classified as slightly irritating. A controlled user test of an eye shadow containing 12.22% VP/Hexadecene Copolymer was performed using 10 healthy female subjects. The product was applied to the face (eye region) daily for 2 weeks, and neither ocular or eyelid irritation was observed in any of the subjects.

An allergic (erythematous-edematous) reaction was observed in an atopic patient patch-tested with 10% VP/Eicosene Copolymer in petrolatum, but not in 15 control subjects. Acute facial eczema was observed in a female patient after application of a sunscreen containing VP/Eicosene Copolymer (concentration not stated). When the patient was patch-tested with the ingredient (1% in petrolatum), a positive reaction was observed.

TABLES**Table 1.** Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^{(1; CIR Staff) *}

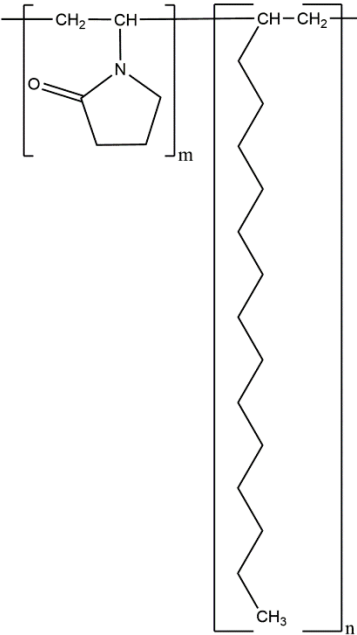
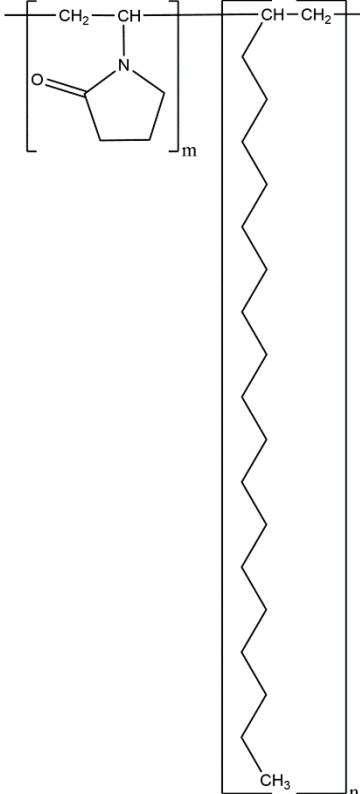
Ingredient CAS No.	Definition & Structures	Function(s)
VP/Hexadecene Copolymer 32440-50-9 63231-81-2	VP/Hexadecene Copolymer is a polymer of hexadecene and vinylpyrrolidone monomers 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Hair Fixatives; Viscosity Increasing Agents - Nonaqueous
VP/Eicosene Copolymer 28211-18-9 77035-98-4	VP/Eicosene Copolymer is a polymer of vinylpyrrolidone and eicosene monomers. It conforms generally to the formula: 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Viscosity Increasing Agents - Nonaqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^{(1; CIR Staff) *}

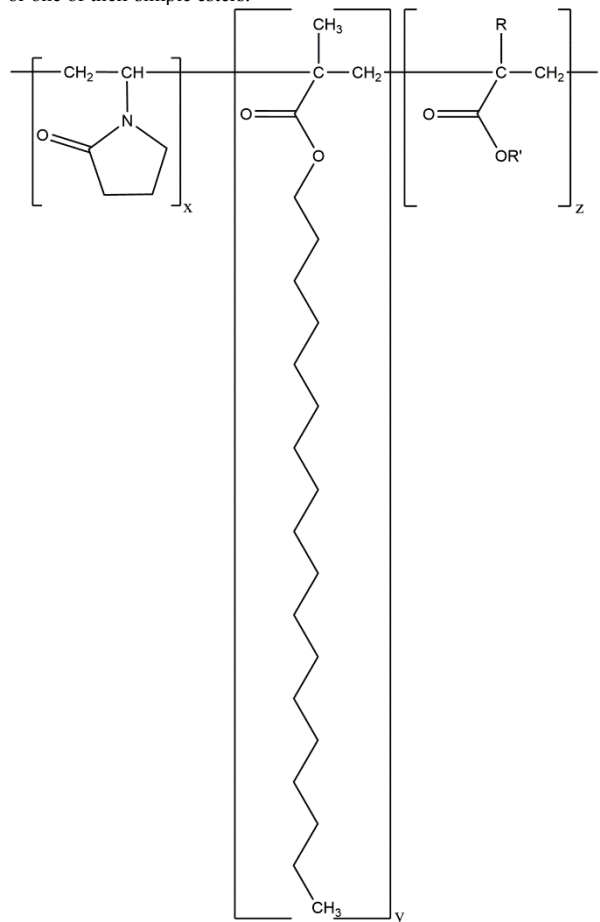
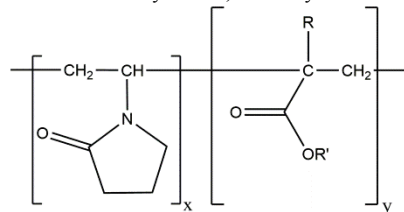
Ingredient CAS No.	Definition & Structures	Function(s)
Acrylates/Stearyl Methacrylate/VP Copolymer	Acrylates/Stearyl Methacrylate/VP Copolymer is a copolymer of vinylpyrrolidone, stearyl methacrylate, and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters.  [wherein R is methyl or hydrogen and R' is hydrogen, methyl, ethyl, propyl, or butyl]	Emulsion Stabilizers; Film Formers; Hair Fixatives; Viscosity Increasing Agents - Aqueous
Acrylates/VP Copolymer 26589-26-4	Acrylates/VP Copolymer is a copolymer of <i>N</i>-vinyl pyrrolidone and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters.  [wherein R is methyl or hydrogen and R' is hydrogen, methyl, ethyl, propyl, or butyl]	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Hair Fixatives

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^{(1; CIR Staff) *}

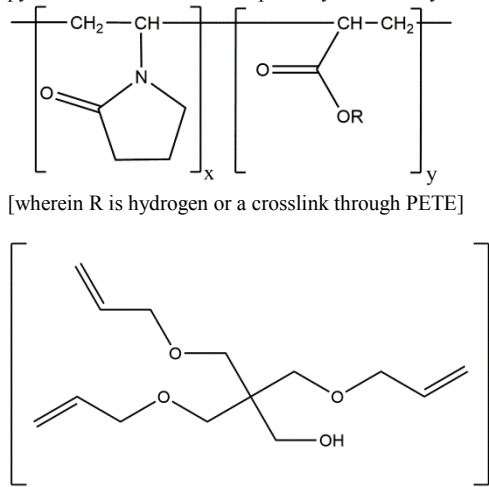
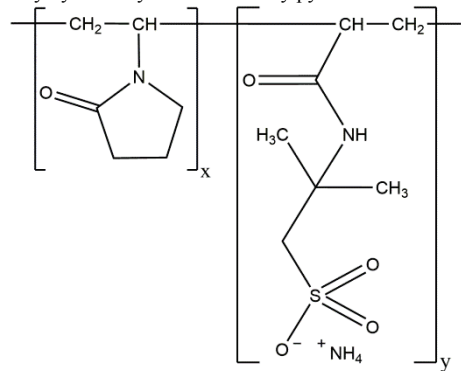
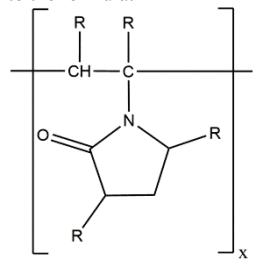
Ingredient CAS No.	Definition & Structures	Function(s)
Acrylic Acid/VP Crosspolymer 527685-31-0	Acrylic Acid/VP Crosspolymer is a copolymer of acrylic acid and <i>N</i>-vinyl pyrrolidone crosslinked with pentaerythritol triallyl ether (PETE).  [wherein R is hydrogen or a crosslink through PETE] pentaerythritol triallyl ether	Dispersing Agents - Nonsurfactant; Slip Modifiers; Surface Modifiers
Ammonium Acryloyldimethyltaurate/VP Copolymer	Ammonium Acryloyldimethyltaurate/VP Copolymer is a copolymer of ammonium acryloyldimethyltaurate and vinylpyrrolidone monomers. 	Viscosity Increasing Agents - Aqueous
Butylated PVP	Butylated PVP is a polymer of butylated vinylpyrrolidone that conforms generally to the formula:  where R represents either a butyl group or hydrogen.	Binders; Film Formers; Hair Fixatives

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^(1: CIR Staff) *

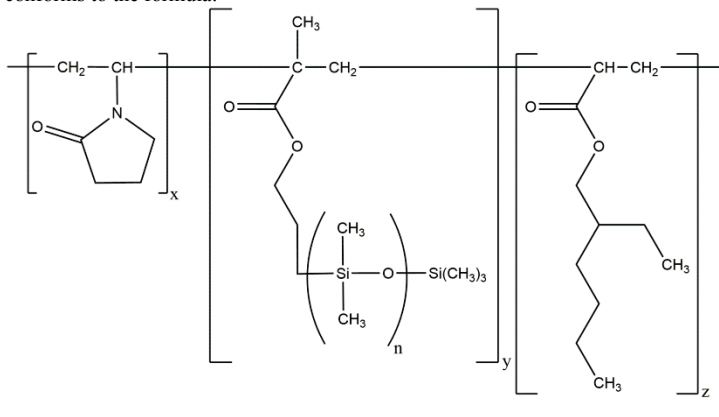
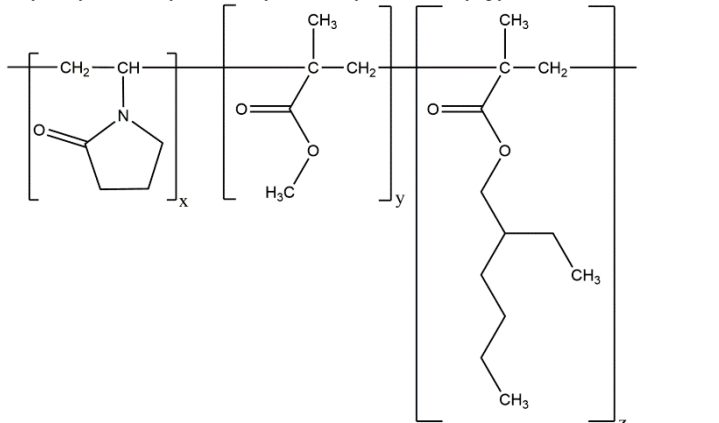
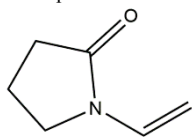
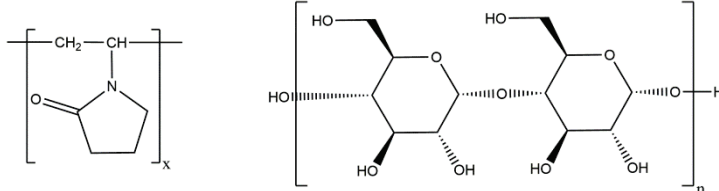
Ingredient CAS No.	Definition & Structures	Function(s)
Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer Methacrylate Copolymer	Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer is a copolymer of vinylpyrrolidone, 2-ethylhexyl acrylate, and dimethicone propylmethacrylate. It conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Nonaqueous
Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer 155532-97-1	Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer is the copolymer of ethylhexyl methacrylate, methyl methacrylate and vinyl pyrrolidone monomers. 	Film Formers
Hydrolyzed Wheat Protein/PVP Crosspolymer Crosspolymer	Hydrolyzed Wheat Protein/PVP Crosspolymer is a crosslinked copolymer of hydrolyzed wheat protein and PVP.  [Monomer:] vinylpyrrolidone [The monomer, hydrolyzed wheat protein, is the partial hydrolysate of wheat protein derived by acid, enzyme or other method of hydrolysis.]	Film Formers; Hair Conditioning Agents; Hair Fixatives; Skin-Conditioning Agents - Miscellaneous
Maltodextrin/VP Copolymer 1323833-56-2	Maltodextrin/VP Copolymer is a copolymer of Maltodextrin and vinyl pyrrolidone. 	Film Formers

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^{(1; CIR Staff) *}

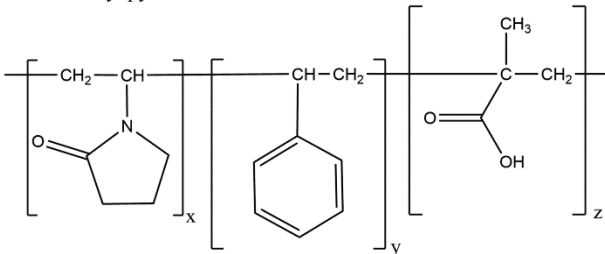
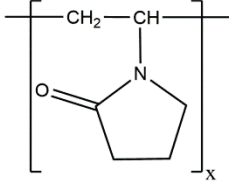
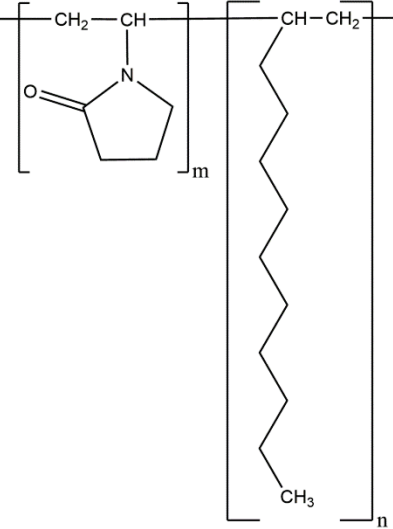
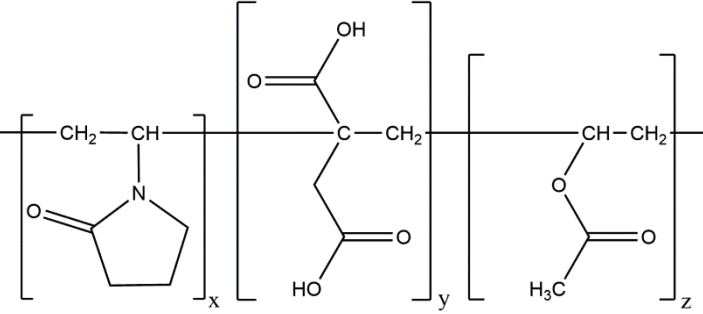
Ingredient CAS No.	Definition & Structures	Function(s)
Methacrylic Acid/Styrene/VP Copolymer 27554-92-3	Methacrylic Acid/Styrene/VP Copolymer is a copolymer of styrene, methacrylic acid and vinyl pyrrolidone. 	Opacifying Agents
PVP 9003-39-8	PVP is the linear polymer that consists of 1-vinyl-2-pyrrolidone monomers conforming generally to the formula: 	Binders; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Film Formers; Hair Fixatives
PVP/Decene Copolymer	PVP/Decene Copolymer is a polymer of vinylpyrrolidone and decene monomers. It conforms generally to the formula: 	Binders; Emulsion Stabilizers; Viscosity Increasing Agents - Aqueous; Viscosity Increasing Agents - Nonaqueous
PVP/VA/Itaconic Acid Copolymer 68928-72-3	PVP/VA/Itaconic Acid Copolymer is a polymer formed from vinylpyrrolidone, vinyl acetate and itaconic acid monomers. 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Hair Fixatives

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^{(1; CIR Staff) *}

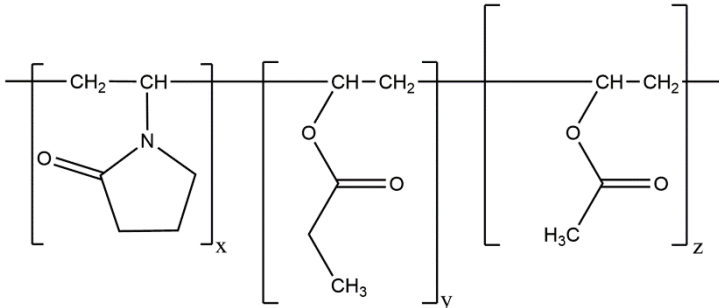
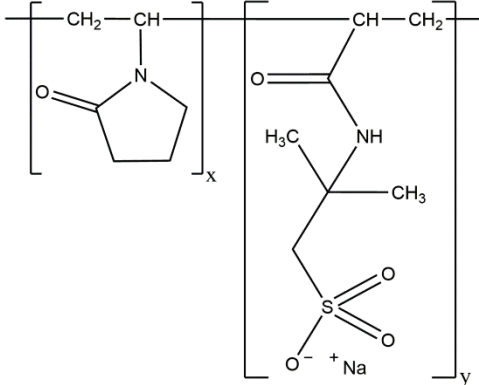
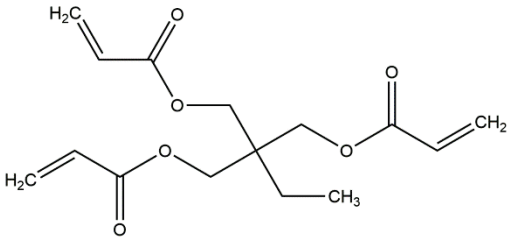
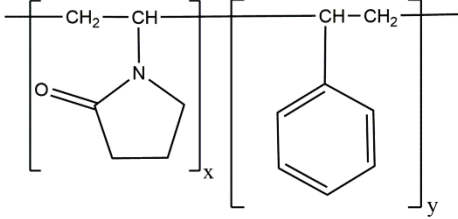
Ingredient CAS No.	Definition & Structures	Function(s)
PVP/VA/Vinyl Propionate Copolymer	PVP/VA/Vinyl Propionate Copolymer is a polymer of vinylpyrrolidone, vinyl acetate and vinyl propionate monomers.	Film Formers; Hair Fixatives
		
Sodium Acryloyldimethyltaurate/VP Crosspolymer	Sodium Acryloyldimethyltaurate/VP Crosspolymer is a copolymer of sodium acryloyldimethyltaurate and vinylpyrrolidone crosslinked by 1,1,1-trimethylolpropane triacrylate.	Emulsion Stabilizers
		
	[crosslinked with]	
		
Styrene/VP Copolymer 25086-29-7	Styrene/VP Copolymer is a copolymer prepared from vinylpyrrolidone and styrene monomers.	Film Formers
		

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^{(1; CIR Staff) *}

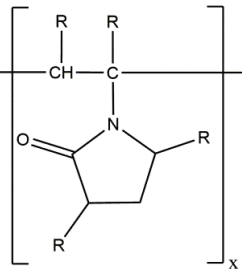
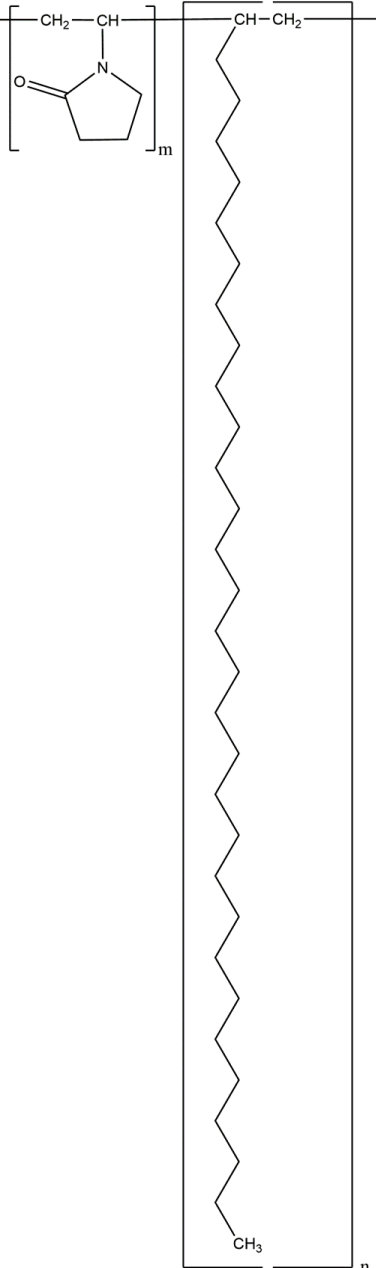
Ingredient CAS No.	Definition & Structures	Function(s)
Triacontanyl PVP 157148-07-7 136445-69-7	Triacontanyl PVP is a polymer of vinyl pyrrolidone and 1-triacontene. It conforms to the formula:  where R represents the triacontene moiety [a 30 carbon, straight alkyl chain] or hydrogen.	Film Formers; Viscosity Increasing Agents - Nonaqueous
Triacontene/VP Copolymer	Triacontene/VP Copolymer is a copolymer of triacontene and vinylpyrrolidone monomers. 	Emulsion Stabilizers; Film Formers

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^(1; CIR Staff) *

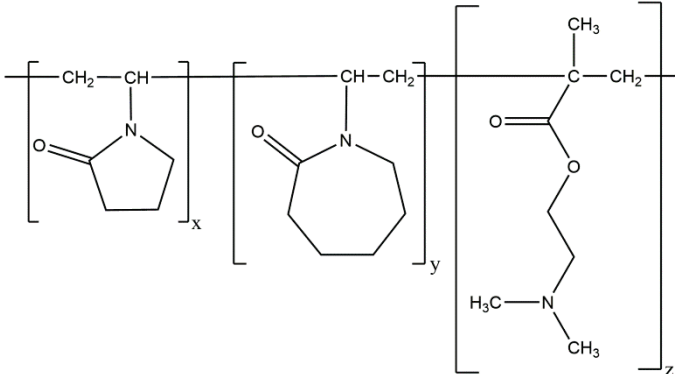
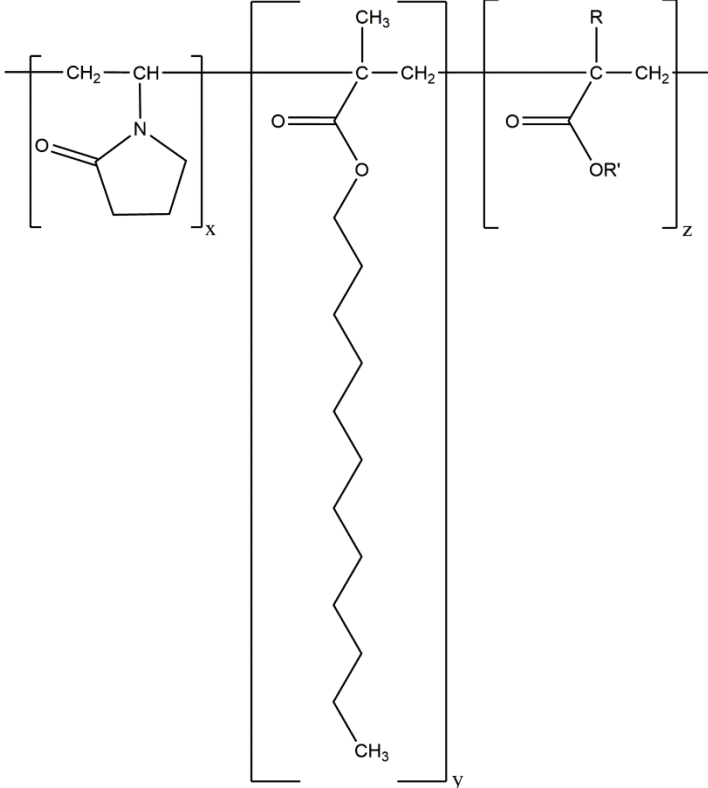
Ingredient CAS No.	Definition & Structures	Function(s)
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer	Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer is a copolymer of vinylcaprolactam, vinylpyrrolidone, and dimethylaminoethyl methacrylate monomers. 	Film Formers; Hair Fixatives
VP/Acrylates/Lauryl Methacrylate Copolymer 83120-95-0	VP/Acrylates/Lauryl Methacrylate Copolymer is a copolymer of vinylpyrrolidone, lauryl methacrylate, and one or more monomers of acrylic acid, methacrylic acid or one of its simple esters.  [wherein R is methyl or hydrogen and R' is hydrogen, methyl, ethyl, propyl, or butyl]	Hair Fixatives
VP/Dimethiconylacrylate/ Polycarbamyl/Polyglycol Ester	VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester is a copolymer of vinylpyrrolidone, acrylated dimethiconol and polyurethane. [More information needed to depict structure.]	Film Formers

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment. ^(1; CIR Staff) *

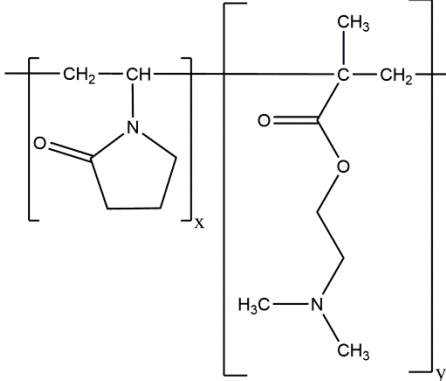
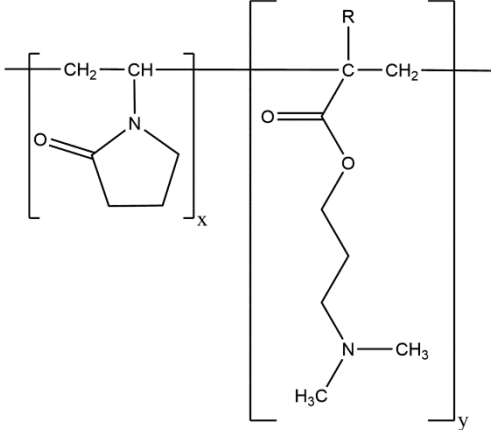
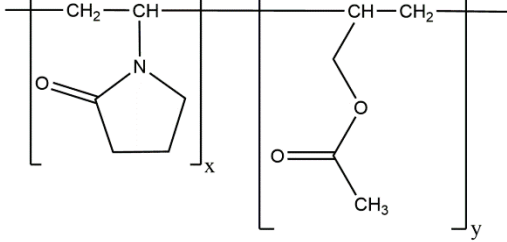
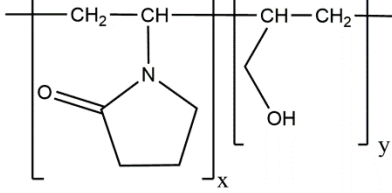
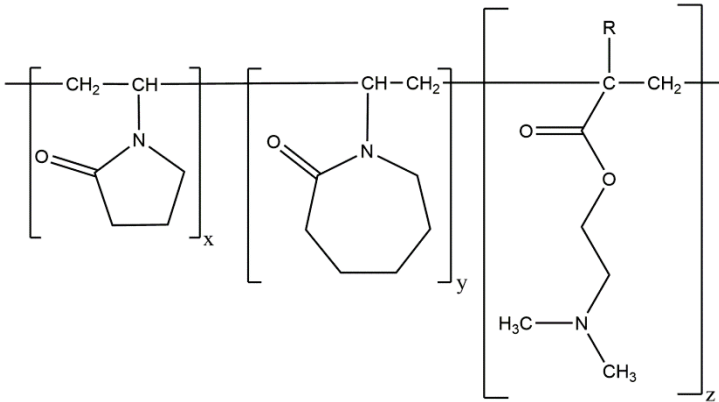
Ingredient CAS No.	Definition & Structures	Function(s)
VP/Dimethylaminoethylmethacrylate Copolymer 30581-59-0	VP/Dimethylaminoethylmethacrylate Copolymer is a polymer prepared from vinylpyrrolidone and dimethylaminoethylmethacrylate monomers. 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Hair Fixatives
VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester	VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester is a copolymer of vinylpyrrolidone, dimethylaminoethylmethacrylate and polyurethane. [More information needed to depict structure.]	Film Formers
VP/DMAA Acrylates Copolymer 175893-71-7	VP/DMAA Acrylates Copolymer is a copolymer of vinylpyrrolidone and dimethylaminopropylacrylamide or methacrylamide.  [wherein R is hydrogen or methyl]	Hair Fixatives
VP/Polycarbamyl Polyglycol Ester	VP/Polycarbamyl Polyglycol Ester is a copolymer of vinylpyrrolidone and polyurethane. [More information needed to depict structure.]	Film Formers
VP/VA Copolymer 25086-89-9	VP/VA Copolymer is a copolymer of vinyl acetate and vinylpyrrolidone monomers. 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Hair Fixatives
VP/Vinyl Alcohol Copolymer 26008-54-8	VP/Vinyl Alcohol Copolymer is the product formed by the polymerization and subsequent hydrolysis of vinylpyrrolidone and vinyl acetate. 	Film Formers; Hair Fixatives; Humectants; Viscosity Increasing Agents - Aqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.^{(1; CIR Staff) *}

Ingredient CAS No.	Definition & Structures	Function(s)
VP/Vinyl Caprolactam/DMAA Acrylates Copolymer	VP/Vinyl Caprolactam/DMAA Acrylates Copolymer is a copolymer of vinylpyrrolidone, vinyl caprolactam, dimethylaminopropylacrylamide, and one or more monomers of acrylic acid or one of their simple esters.  [wherein R is hydrogen or methyl]	Hair Fixatives

*Please note: For the sake of simplicity, these ingredients have only been drawn as simple block co-polymers. The periodicity and pattern of interconnectivity between each monomer may vary significantly per ingredient, or even per supplier of the same ingredient.

Table 2. Published Reports on Similar Ingredients Reviewed by CIR

Ingredients	CIR Review Status
Acrylates/VP Copolymer and VP/Dimethylaminoethylmethacrylate Copolymer	Published Final Report (2002) - Conclusion: Safe for use in cosmetics when formulated to avoid skin irritation. ¹⁰ A rereview of this safety assessment is in progress.
Ammonium Acryloyldimethyltaurate/VP Copolymer and Sodium Acryloyldimethyltaurate/VP Crosspolymer	Final Report (issued in 2017) - Conclusion: Safe in cosmetics in the present practices of use and concentration described in this safety assessment. ¹¹
Methacrylic Acid/Styrene/VP Copolymer and Styrene/VP Copolymer	Final Report (issued in 2014) - Conclusion: Safe in the present practices of use and concentration in cosmetics, as described in this safety assessment. ¹²
PVP	Published Final Report (2017) - Conclusion: Safe as used in cosmetics. ⁷
	Published Rereview (2018) - Conclusion: Panel reaffirmed the original conclusion ³⁴
VP/VA Copolymer	Published Final Report (1983) - Conclusion: Safe as a cosmetic ingredient under present conditions of concentration and use. ⁸
	Published Rereview (2006) - Conclusion: The Panel reaffirmed the original conclusion ¹⁴

Table 3. Monomer Components of Vinylpyrrolidone Polymers

Monomer	CIR Review Status
Acrylated Dimethiconol	Not reviewed
Acrylic Acid	Not reviewed. However, data on this monomer are summarized in the published (2002) CIR final report on Acrylates Copolymer. ¹⁰
Ammonium Acryloyldimethyltaurate	Not reviewed
Butylated Vinylpyrrolidone	Not reviewed
Decene	Not reviewed
Dimethicone Propylmethacrylate	Not reviewed
Dimethylaminoethyl Methacrylate	Not reviewed
Dimethylaminopropylacrylamide	Not reviewed
Eicosene	Not reviewed
Ethylhexyl Methacrylate	Not reviewed
Hexadecene	Not reviewed
Hydrolyzed Wheat Protein	Final Report - Conclusion: Safe for use in cosmetics when formulated to restrict peptides to a weight-average MW of 3500 Da or less. ⁴⁰
Itaconic Acid	Not Reviewed
Lauryl Methacrylate	Published Final Report - Conclusion: Safe as used in nail enhancement products when skin contact is avoided. Products containing these ingredients should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates. ⁴¹
Maltodextrin	Final Report - Conclusion: Safe in the present practices of use and concentration in cosmetics, as described in this safety assessment. ⁴²
Methacrylamide	Not Reviewed
Methacrylic Acid	Published Final Report - Conclusion: Safe as used as a nail primer by trained professionals, but there are insufficient data for retail use by consumers. ⁴³
Methyl Methacrylate	Scientific Literature Review (SLR) was issued in 2003, but the report was terminated
Polyurethane	Final Report - Conclusion: Safe as used in the present practices of use and concentration described in this safety assessment. ⁴⁴
Sodium Acryloyldimethyltaurate	Not Reviewed
Stearyl Methacrylate	Not Reviewed
Styrene	Not Reviewed
Triacotene	Not Reviewed
Vinyl Acetate	Not Reviewed
Vinyl Caprolactam	Not Reviewed
Vinyl Propionate	Not Reviewed
Vinylpyrrolidone	Not Reviewed

Table 4. Chemical and Physical Properties of Vinylpyrrolidone Polymers

Property	Value/Results	Reference
Maltodextrin/VP Copolymer		
Weight average molecular weight (Da)	132,999	2
Number average molecular weight (Da)	21,499	2
Sodium Acryloyldimethyltaurate/VP Crosspolymer		
Form (at 20 °C and 101.3 kPa)	White powder	5
Particle size (µm)	< 10 (65.4%); < 100 (86.8%)	5
Formula Weight (Da)	>10,000	5
Melting Point (°C)	Not determined. Decomposes prior to melting	5
Water solubility (mg/l)	Miscible, gel forming. When gel was diluted by further addition of water, low viscosity solution was formed	5
Triaccontanyl PVP (trade name mixture)		
Form	White to off-white solid flakes	3
Particle size distribution (cm ²)	0.25 to 1	3
Molecular weight (Da)	Approximately 70 to 80% of the polymer has a molecular weight of > 1000	3
Maximum percentage of low molecular weight species (molecular weight <1000 Da) (%)	20 to 30	3
Density (kg/m ³)	947	3
Solubility	Insoluble in water, acid or base solutions	3
Partition coefficient	Not applicable, as the polymer is insoluble in water	3
VP/Acrylates/Lauryl Methacrylate Copolymer		
Form	White powder	4
Particle size (µm)	< 10	4
Number average molecular weight (Da)	> 10,000	4
Density (kg/m ³)	1000	4
Solubility	Expected to have low water solubility based on high molecular weight and predominantly hydrophobic structure	4
VP/Dimethylaminoethylmethacrylate Copolymer		
Density (g/cm ³)	1.047	6

Table 5. Specifications for VP/VA Copolymer.⁹

Characteristics	Proposed Specifications
K-value (1% solids in aqueous solution)	25.2 to 30.8
pH-value (10% w/w in distilled water)	3 to 7
Vinyl acetate component in copolymer (%)	Maximum: 35.3 to 42.0
Nitrogen content (%)	7 to 8
Loss on drying (%)	Maximum: 5
Residuals	
Aldehydes (as acetaldehyde) (%)	0.2
Vinyl acetate (mg/kg)	Maximum: 5
Vinylpyrrolidone (mg/kg)	Maximum: 5
Hydrazine (mg/kg)	Maximum: 1
Peroxide content (mg/kg)	Maximum: 400
Isopropanol (mg/kg)	Maximum: 150
Arsenic	Maximum: 3
Lead	Maximum: 2
Mercury	Maximum: 1
Cadmium	Maximum: 1
Ash (residue on ignition/sulfated) (%)	0.1

Table 6. Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure.

Table 6: Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure.								
	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	VP/Hexadecene Copolymer				VP/Eicosene Copolymer			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵		2017 ¹⁶	
Totals*	443		0.036-24.1		378		0.11-8	
Duration of Use								
Leave-On	442		0.036-24.1		377		0.11-8	
Rinse-Off	1		2		1		NR	
Diluted for (Bath) Use	NR		NR		NR		NR	
Exposure Type								
Eye Area	87		0.25-17.2		239		0.44-8	
Incidental Ingestion	268		0.7-24.1		101		0.96-5.6	
Incidental Inhalation-Spray	6;5 ^a		NR		NR;6 ^a		4.3	
Incidental Inhalation-Powder	3		NR		NR		0.3-0.5	
Dermal Contact	144		0.036-17.2		92		0.11-8	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	NR		NR		1		NR	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		10.3		NR		NR	
Mucous Membrane	268		0.7-24.1		101		0.96-5.6	
Baby Products	NR		NR		NR		2	
	Acrylic Acid/VP Crosspolymer				Ammonium Acryloyldimethyltaurate/VP Copolymer			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵	2017 ¹¹	2017 ¹⁶	2016 ¹¹
Totals*	20		0.3-1		597	584	0.096-2	0.016-3
Duration of Use								
Leave-On	20		0.3-1		535	524	0.096-2	0.016-3
Rinse-Off	NR		0.5		62	60	0.2-2	0.3-1.8
Diluted for (Bath) Use	NR		NR		NR	NR	NR	NR
Exposure Type								
Eye Area	3		1		60	66	0.5-3	1.4-3
Incidental Ingestion	NR		NR		2	2	1.5	1.5
Incidental Inhalation-Spray	NR;14 ^a		0.3-1 ^a		1;197 ^a	1;199 ^a , 205 ^b	0.096-1;1.5 ^a	0.096-1;0.4 ^a
Incidental Inhalation-Powder	NR		NR		3	1;1 ^c , 205 ^b	NR	0.18-2 ^c
Dermal Contact	10		0.5-1		591	579	0.096-3	0.016-3
Deodorant (underarm)	NR		NR		NR	NR	NR	NR
Hair - Non-Coloring	8		0.3-1		NR	NR	0.8	0.4
Hair-Coloring	NR		NR		NR	NR	NR	NR
Nail	1		NR		NR	NR	NR	NR
Mucous Membrane	NR		0.5		7	5	0.25-1.5	1.5
Baby Products	NR		NR		2	1	0.5	NR
	Butylated PVP				Hydrolyzed Wheat Protein/PVP Crosspolymer			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵		2017 ¹⁶	
Totals*	4		NR		48		0.017-0.45	
Duration of Use								
Leave-On	3		NR		34		0.017-0.45	
Rinse-Off	1		NR		14		NR	
Diluted for (Bath) Use	NR		NR		NR		NR	
Exposure Type								
Eye Area	NR		NR		23		0.18-0.4	
Incidental Ingestion	NR		NR		NR		NR	
Incidental Inhalation-Spray	NR;2 ^a		NR		NR;8 ^a		0.017-0.055; 0.088-0.24 ^a	
Incidental Inhalation-Powder	NR		NR		NR		NR	
Dermal Contact	NR		NR		7		0.038-0.45	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	4		NR		18		0.017-0.24	
Hair-Coloring	NR		NR		1		NR	
Nail	NR		NR		NR		NR	
Mucous Membrane	NR		NR		NR		NR	
Baby Products	NR		NR		NR		NR	

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

^a It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^c It is possible that these products may be powders, but it is not specified whether the reported uses are powders

NR - no reported use

Table 6. Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure.

Table 6: Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure.								
	# of Uses				# of Uses		Max Conc of Use (%)	
	Maltodextrin/VP Copolymer				PVP			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵	2013	2017 ¹⁶	2013
Totals*	3		0.35-3		900	799	0.000003-35	0.0005-12
Duration of Use								
Leave-On	3		0.35-3		798	675	0.005-35	0.002-12
Rinse-Off	NR		NR		101	123	0.000003-13.3	0.0005-10.5
Diluted for (Bath) Use	NR		NR		1	1	0.016-3	NR
Exposure Type								
Eye Area	NR		NR		292	222	0.005-12	0.05-12
Incidental Ingestion	NR		NR		43	35	0.065-13.3	0.1-10.5
Incidental Inhalation-Spray	NR;3 ^a		0.35		31;283 ^a	22	0.6-5;0.5-9 ^a	0.002-5
Incidental Inhalation-Powder	NR		NR		NR	NR	0.1	NR
Dermal Contact	NR		0.35		299	186	0.000003-35	0.0005-12
Deodorant (underarm)	NR		NR		NR	NR	0.66	0.5
Hair - Non-Coloring	3		3		378	423	0.0005-9	0.0005-10.5
Hair-Coloring	NR		NR		11	7	1.4-10	1.6-3.3
Nail	NR		NR		NR	1	0.5-5	0.3-5
Mucous Membrane	NR		NR		44	37	0.065-13.3	0.1-10.5
Baby Products	NR		NR		2	1	4.4	NR
	Sodium Acryloyldimethyltaurate/VP Crosspolymer				Styrene/VP Copolymer			
	2018 ¹⁵	2017 ¹¹	2017 ¹⁶	2016 ¹¹	2018 ¹⁵	2013 ¹²	2017 ¹⁶	2013-2014 ¹²
Totals*	9	8	0.5-1	NR	70	82	0.007-0.8	0.000038-1
Duration of Use								
Leave-On	9	8	0.5-1	NR	17	30	0.012-0.62	0.000038-0.4
Rinse-Off	NR	NR	NR	NR	53	52	0.007-0.8	0.02-1
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	1	1	NR	NR	1	NR	0.038-0.4	0.2-0.4
Incidental Ingestion	NR	NR	NR	NR	NR	1	NR	NR
Incidental Inhalation-Spray	NR;5 ^a	4 ^a ;3 ^b	NR;0.89-1 ^a	NR	3;8 ^a	22	NR;0.016-0.2 ^a	0.12
Incidental Inhalation-Powder	NR	3 ^b	NR	NR	NR	6	NR	0.12-0.2 ^c
Dermal Contact	9	8	0.5-1	NR	15	18	0.012-0.62	0.000038-0.4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	19	36	0.08-0.2	0.032-1
Hair-Coloring	NR	NR	NR	NR	33	25	0.007-0.8	0.04-0.7
Nail	NR	NR	NR	NR	2	2	0.29	NR
Mucous Membrane	NR	NR	NR	NR	3	6	NR	0.057
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Triacetyl PVP				Vinyl Caprolactam/ VP/Dimethylaminoethyl Methacrylate Copolymer			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵		2017 ¹⁶	
Totals*	72		0.66-7.3		70		0.3-5	
Duration of Use								
Leave-On	72		0.66-7.3		65		0.3-5	
Rinse-Off	NR		NR		5		1.2	
Diluted for (Bath) Use	NR		NR		NR		NR	
Exposure Type								
Eye Area	23		0.66-3.2		1		NR	
Incidental Ingestion	31		3-7.3		NR		NR	
Incidental Inhalation-Spray	NR;1 ^a		6.3;1.5-4.5 ^a		21;35 ^a		1;1.2-5 ^a	
Incidental Inhalation-Powder	3		NR		NR		NR	
Dermal Contact	24		0.66-2		3		0.3	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	1		1.5-6.3		49		1.2-5	
Hair-Coloring	NR		NR		17		1-1.2	
Nail	NR		NR		NR		NR	
Mucous Membrane	31		3-7.3		NR		NR	
Baby Products	NR		NR		NR		NR	

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

^a It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^c It is possible that these products may be powders, but it is not specified whether the reported uses are powders

NR - no reported use

Table 6. Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure.

Table 6: Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure					# of Uses		Max Conc of Use (%)	
	VP/Acrylates/Lauryl Methacrylate Copolymer				VP/Dimethiconylacrylate/ Polycarbamyl/ Polyglycol Ester			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵		2017 ¹⁶	
Totals*	15		0.0097-3.5		3		0.04-2.5	
Duration of Use								
Leave-On	15		0.0097-3.5		3		0.1-2.5	
Rinse-Off	NR		NR		NR		0.04	
Diluted for (Bath) Use	NR		NR		NR		NR	
Exposure Type								
Eye Area	NR		0.0097		NR		0.3-2.5	
Incidental Ingestion	NR		NR		NR		NR	
Incidental Inhalation-Spray	1;4 ^a		NR;3.5 ^a		NR;1 ^a		NR; 0.2-0.6 ^a	
Incidental Inhalation-Powder	NR		NR		NR		NR	
Dermal Contact	NR		0.0097-3.5		2		0.04-2.5	
Deodorant (underarm)	NR		NR		NR		NR	
Hair - Non-Coloring	15		NR		NR		NR	
Hair-Coloring	NR		NR		NR		NR	
Nail	NR		NR		NR		NR	
Mucous Membrane	NR		NR		NR		NR	
Baby Products	NR		NR		NR		NR	
	VP/Dimethylaminoethylmethacrylate Copolymer				VP/DMAPA Acrylates Copolymer			
	2018 ¹⁵	1998 ¹⁰	2017 ¹⁶	1984 ¹⁰	2018 ¹⁵		2017 ¹⁶	
Totals*	72	43	0.04-6	5-10	31		0.08-7.5	
Duration of Use								
Leave-On	65	37	0.2-6	NR	23		1-7.5	
Rinse-Off	7	6	0.04	NR	8		0.08	
Diluted for (Bath) Use	NR	NR	NR	NR	NR		NR	
Exposure Type								
Eye Area	4	3	0.2-1	NR	NR		NR	
Incidental Ingestion	NR	NR	NR	NR	NR		NR	
Incidental Inhalation-Spray	1;45 ^a	NR;21 ^a	NR	NR	1;21 ^a		NR;1-7.5 ^a	
Incidental Inhalation-Powder	NR	NR	NR	NR	NR		NR	
Dermal Contact	6	NR	0.04-1.2	NR	NR		NR	
Deodorant (underarm)	NR	NR	NR	NR	NR		NR	
Hair - Non-Coloring	63	40	0.5-6	NR	27		0.08-7.5	
Hair-Coloring	1	NR	NR	NR	4		NR	
Nail	NR	NR	NR	NR	NR		NR	
Mucous Membrane	NR	NR	NR	NR	NR		NR	
Baby Products	NR	NR	NR	NR	NR		NR	
	VP/Polycarbamyl Polyglycol Ester				VP/VA Copolymer			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵	2002 ¹⁴	2017 ¹⁶	2003 ¹⁴
Totals*	6		0.036		480	210	0.001-44	0.3-12
Duration of Use								
Leave-On	6		0.036		442	181	0.001-10	0.3-12
Rinse-Off	NR		NR		37	29	0.07-44	3-10
Diluted for (Bath) Use	NR		NR		1	NR	NR	NR
Exposure Type								
Eye Area	3		0.036		46	10	0.5-10	0.3-9
Incidental Ingestion	NR		NR		NR	NR	0.07-4	NR
Incidental Inhalation-Spray	NR		NR		35;236 ^a	27;87 ^a	1-10;0.07-9.9 ^a	0.5-4;4-12 ^a
Incidental Inhalation-Powder	NR		NR		5	NR	NR	NR
Dermal Contact	5		NR		93	15	0.0075-44	0.3-10
Deodorant (underarm)	NR		NR		NR	NR	NR	NR
Hair - Non-Coloring	NR		NR		330	190	1-10	2-12
Hair-Coloring	NR		NR		33	3	0.29-1.5	0.5
Nail	NR		NR		1	NR	0.001	NR
Mucous Membrane	NR		NR		1	NR	0.07-4	NR
Baby Products	NR		NR		NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

^a It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^c It is possible that these products may be powders, but it is not specified whether the reported uses are powders

NR - no reported use

Table 6. Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure.

Table 6: Frequency and Concentration of Vinylpyrrolidone Polymers According to Duration and Exposure.								
	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer				Acrylates/VP Copolymer			
	2018 ¹⁵		2017 ¹⁶		2018 ¹⁵	1998 ¹⁰	2017 ¹⁶	1997 ¹⁰
Totals*	19		0.5-1.4		9	4	0.67-1.5	NR
Duration of Use								
Leave-On	19		0.5-1.4		4	2	0.67-1.5	NR
Rinse-Off	NR		1.4		5	2	0.81	NR
Diluted for (Bath) Use	NR		NR		NR	NR	NR	NR
Exposure Type								
Eye Area	NR		NR		3	NR	NR	NR
Incidental Ingestion	NR		NR		NR	NR	NR	NR
Incidental Inhalation-Spray	19		0.5-1.4		NR	NR; ^{2a}	0.67-0.95 ^a	NR
Incidental Inhalation-Powder	NR		NR		NR	NR	NR	NR
Dermal Contact	NR		NR		2	NR	0.67 -1.5	NR
Deodorant (underarm)	NR		NR		NR	NR	NR	NR
Hair - Non-Coloring	6		1.4		3	4	0.95	NR
Hair-Coloring	13		0.5		1	NR	NR	NR
Nail	NR		NR		NR	NR	NR	NR
Mucous Membrane	NR		NR		NR	NR	NR	NR
Baby Products	NR		NR		NR	NR	NR	NR
	VP/Dimethylaminoethylmethacrylate/ Polycarbamyl/Polyglycol Ester							
	2018 ¹⁵		2017 ¹⁶					
Totals*	NR		5.6					
Duration of Use								
Leave-On	NR		5.6					
Rinse-Off	NR		NR					
Diluted for (Bath) Use	NR		NR					
Exposure Type								
Eye Area	NR		NR					
Incidental Ingestion	NR		NR					
Incidental Inhalation-Spray	NR		5.6					
Incidental Inhalation-Powder	NR		NR					
Dermal Contact	NR		NR					
Deodorant (underarm)	NR		NR					
Hair - Non-Coloring	NR		5.6					
Hair-Coloring	NR		NR					
Nail	NR		NR					
Mucous Membrane	NR		NR					
Baby Products	NR		NR					

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

^a It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

^b Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^c It is possible that these products may be powders, but it is not specified whether the reported uses are powders

NR - no reported use

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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 car-

cinogenic 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.

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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²Related 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.

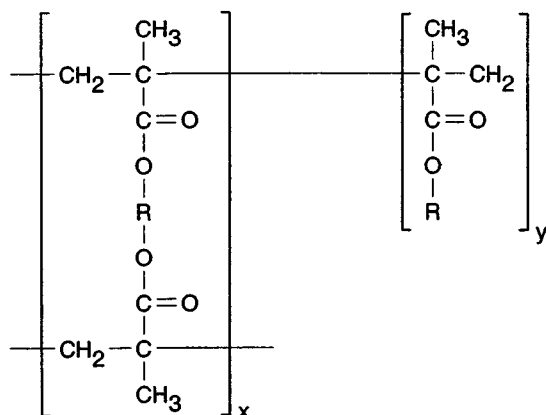
TABLE 1
 Ingredients descriptions (Wenninger, Canterbury, and McEwen 2000)

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 of 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, Canterbury, 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 $<1 \mu$ 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, Canterbury, 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, Canterbury, 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, Canterbury, 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, Canterbury, 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, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid with Ethene (Wenninger, Canterbury, 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 $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xCa$ (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Calcium Salt (Wenninger, Canterbury, 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 $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xMg$ (Wenninger, Canterbury, 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 $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xNa$ (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Sodium Salt (Wenninger, Canterbury, 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 $(C_3H_4O_2 \cdot C_2H_4)_x \cdot xZn$ (Wenninger, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene, Zinc Salt (Wenninger, Canterbury, 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, Canterbury, and McEwen 2000). It is also known as 2-Propenoic Acid, Polymer with Ethene and Ethenyl Acetate (Wenninger, Canterbury, 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, Canterbury, 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, Canterbury, 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, Canterbury, 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, Canterbury, 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, Canterbury, 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 of their simple esters (Wenninger, Canterbury, 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, Canterbury, 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, Canterbury, 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, Canterbury, 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, Canterbury, and McEwen 2000).

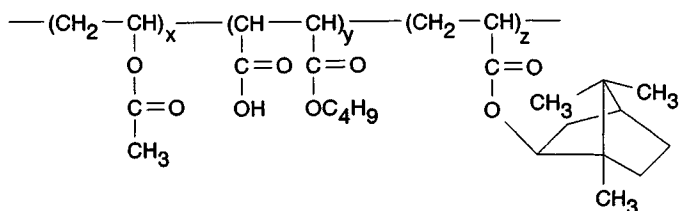
Sodium Styrene/Acrylates Copolymer. Sodium Styrene/Acrylates Copolymer (CAS No. 9010-92-8) is the sodium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid, or one of their simple esters (Wenninger, Canterbury, and McEwen 2000).

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, Canterbury, 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, Canterbury, 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, Canterbury, and McEwen 2000).

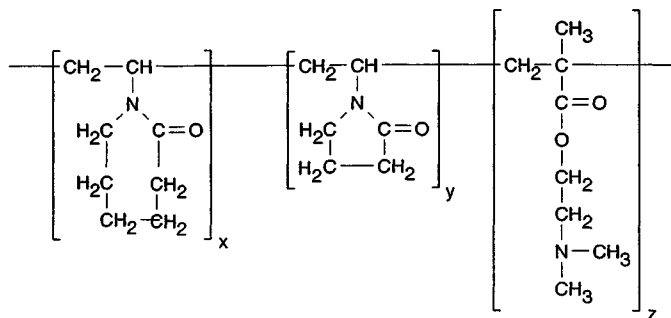
VA/Butyl Maleate/Isobornyl Acrylate Copolymer. VA/Butyl Maleate/Isobornyl Acrylate Copolymer is a copolymer of vinyl acetate, butyl maleate, and isobornyl acrylate monomers (Wenninger, Canterbury, and McEwen 2000) and has the following structure (Patel and Petter 1992):



VA/Butyl Maleate/Isobornyl Acrylate Copolymer

Ethylene/Methacrylate Copolymer. Ethylene/Methacrylate Copolymer is a copolymer of ethylene and methyl methacrylate monomers (Wenninger, Canterbury, 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, Canterbury, and McEwen 2000) and has the following chemical structure (Patel and Petter 1992):



Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer

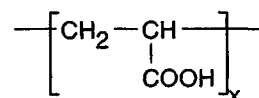
Sodium Acrylates/Acrolein Copolymer. Sodium Acrylates/Acrolein Copolymer is a polymer consisting of sodium acrylate and acrolein monomers (Wenninger, Canterbury, and McEwen 2000).

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

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



Polyacrylic Acid

Polyacrylic Acid is also known as 2-Propenoic Acid, Homopolymer (International Agency for Research on Cancer [IARC] 1979; Wenninger, Canterbury, 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 Carboxypolyethylene (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, Canterbury, and McEwen 2000). It is also known as Poly(Acrylic Acid), Ammonium Salt; 2-Propenoic Acid, Homopolymer, Ammonium Salt (Wenninger, Canterbury, 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, Canterbury, 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, Canterbury, and McEwen 2000). It is also known as Polyacrylic Acid, Potassium Salt (Wenninger, Canterbury, 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, Canterbury, and McEwen 2000). It is also known as Polyacrylic Acid, Sodium Salt; 2-Propenoic Acid, Homopolymer, Sodium Salt (Wenninger,

Canterbury, 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/cm³ (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/cm³ (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 ≤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, Canterbury, 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, Canterbury, 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
<i>Acrylates Copolymer</i>		
Eyebrow pencil	91	1
Eyeliners	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
<i>Ammonium Acrylates Copolymer</i>		
Eyeliners	514	3
Mascara	167	18
1998 total Ammonium Acrylates Copolymer		21
<i>Sodium Acrylates Copolymer</i>		
Hair dyes and color	1572	5
1998 total Sodium Acrylates Copolymer		5
<i>Ethylene/Acrylic Acid Copolymer</i>		
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
<i>Ethylene/Sodium Acrylate Copolymer</i>		
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
<i>Acrylates/PVP Copolymer</i>		
Tonics, dressings, and other hair-grooming aids	549	2
Wave sets	5555	2
1998 total Acrylates/PVP Copolymer		4
<i>Steareth-10 Allyl Ether/Acrylates Copolymer</i>		
Hair dyes and color	1572	6
1998 total Steareth-10 Allyl Ether/Acrylates Copolymer		6
<i>Acrylates/Steareth-20 Methacrylate Copolymer</i>		
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
<i>Acrylates/Ammonium Methacrylate Copolymer</i>		
Mascara	167	1
1998 total Acrylates/Ammonium Methacrylate Copolymer		1
<i>Styrene/Acrylates Copolymer</i>		
Eyeliners	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
<i>Styrene/Acrylates/Ammonium Methacrylate Copolymer</i>		
Eyeliners	514	1
1998 total Styrene/Acrylates/Ammonium Methacrylate Copolymer		1
<i>Sodium Styrene/Acrylates Copolymer</i>		
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
<i>VA/Butyl Maleate/Isobornyl Acrylate Copolymer</i>		
Other hair preparations	276	5
1998 total VA/Butyl Maleate/Isobornyl Acrylate Copolymer		5
<i>Ethylene/Methacrylate Copolymer</i>		
Blushers (all types)	238	1
Foundations	287	1
Makeup bases	132	1
Other makeup preparations	135	2
1998 total Ethylene/Methacrylate Copolymer		5
<i>Vinyl Caprolactam/PVP/Dimethylaminoethyl Methacrylate Copolymer</i>		
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
<i>PVP/Dimethylaminoethylmethacrylate Copolymer</i>		
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
<i>Polyacrylic Acid</i>		
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
<i>Sodium Polyacrylate</i>		
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 formu-

lation" 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^{25} 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 $1\text{-}^{14}\text{C}$ -acrylic acid in acetone (approximately $30\text{ }\mu\text{Ci/kg}$, $501\text{ }\mu\text{g/cm}^2$) 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/HeNCrIBR 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 $10\text{ }\mu\text{Ci/animal}$, respectively) and the mice were dosed with 10 or 40 mg/kg (5 or $20\text{ }\mu\text{Ci/animal}$, 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

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

Location	Rats		Mice	
	10 mg/kg	40 mg/kg	10 mg/kg	40 mg/kg
$^{14}\text{CO}_2$	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

a $1.0 \times 2.5\text{-cm}$ (low-dose rats), $2.5 \times 4.0\text{-cm}$ (high-dose rats), or $1.0 \times 1.0\text{-cm}$ (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 $^{14}\text{CO}_2$ were collected at various intervals. The animals were killed after 1, 8, or 72 hours.

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 $[2,3\text{-}^{14}\text{C}]$ 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 $[2,3\text{-}^{14}\text{C}]$ -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 $[^{14}\text{C}]$ -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 $[^{14}\text{C}]$ -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. $^{11}\text{CO}_2$ 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 $\mu\text{Ci/kg}$) 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- $^{13}\text{C}_3$]-acrylic acid coadministered with [2,3- ^{14}C]-acrylic

acid (40 to 46 $\mu\text{Ci/kg}$) 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 $\mu\text{Ci/kg}$) 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/HeNCrIBR 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 $\mu\text{Ci/animal}$) and the mice were with 40 or 150 mg/kg (20 or 10 $\mu\text{Ci/animal}$, 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 $^{14}\text{CO}_2$ 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)

Location	Rats		Mice	
	40 mg/kg	150 mg/kg	40 mg/kg	150 mg/kg
Exhaled $^{14}\text{CO}_2$	90.3 $\pm$ 1.0	81.6 $\pm$ 1.8	76.8 $\pm$ 2.8	80.0 $\pm$ 4.1
Exhaled volatiles	0.1 $\pm$ 0.2	0.2 $\pm$ 0.4	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0
Urine	2.9 $\pm$ 0.2	4.2 $\pm$ 1.0	3.0 $\pm$ 1.4	3.4 $\pm$ 1.3
Feces	0.7 $\pm$ 0.0	0.6 $\pm$ 0.1	1.2 $\pm$ 0.4	1.2 $\pm$ 1.2
Tissues	0.3 $\pm$ 0.2	0.3 $\pm$ 0.1	0.3 $\pm$ 0.0	0.1 $\pm$ 0.1
Carcass	0.8 $\pm$ 0.1	1.0 $\pm$ 0.2	0.8 $\pm$ 0.1	0.3 $\pm$ 0.1
Total recovery	95.2 $\pm$ 0.9	88.1 $\pm$ 2.0	82.5 $\pm$ 2.1	86.9 $\pm$ 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 $\mu\text{Ci/kg}$; 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 $^{14}\text{CO}_2$ 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 $\mu\text{Ci/kg}$, 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 $\mu\text{g/kg}$ [^{14}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 [^{14}C]-acrylic acid. For the animals killed after 65 minutes, approximately 25% of the administered ^{14}C was retained and 8.1% of the activity was associated with the snout. Approximately 65% of the radioactivity had been expired as $^{14}\text{CO}_2$, 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 $^{14}\text{CO}_2$ 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 $\mu\text{Ci/kg}$) 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 $\mu\text{g/g}$ 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 $\mu\text{g/g}$, respectively, after 45 minutes; 53.5, 33.7, and 18.5 $\mu\text{g/g}$, respectively, after 2 hours; and 45.0, 23.0, and 19.8 $\mu\text{g/g}$, 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 $\mu\text{g/g}$, 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 (Nadzhitmidinov 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 $\mu\text{g/ml}$ PAIGP; the hemolytic activity of the complement was almost completely lost at concentrations of 50 $\mu\text{g/ml}$ 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; Cos-

metic, 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 LD₅₀ of Acrylates Copolymer using rats was >2 g/kg.

The oral LD₅₀ 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 LD₅₀ was >5 g/kg.

The oral LD₅₀ 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 LD₅₀ of Acrylates Copolymer using rats was >9 g/kg.

The oral LD₅₀ 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 LD₅₀ of Acrylates Copolymer using rats was >7.5 g/kg.

The oral LD₅₀ 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 LD₅₀ 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 LD₅₀ for rats was >4 g/kg.

In a similar study, the oral LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ of Vinyl Acetate/Maleate/Acrylate Copolymer solution using rats was >5 g/kg.

Polyacrylic Acid. The oral LD₅₀ 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 × 10⁶ 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 LD₅₀ 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 LD₅₀ of acrylic acid for rats was 2100 to 3200 mg/kg (IARC 1979). The oral LD₅₀ of glacial acrylic acid for rats was 193 to 350 mg/kg. Dow Chemical Co. (1998) reported the oral LD₅₀ of glacial acrylic acid for rats was 0.34 ml/kg.

The oral LD₅₀ of undiluted acrylic acid was 0.34 ml/kg for male rats (DePass et al. 1983). The oral LD₅₀ 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 vesicles), 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 LC₅₀ 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 μ m. The animals appeared normal throughout the study, and lesions were not found during gross examination. The LC₅₀ 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 LC₅₀ for rats exposed to acrylic acid vapors for 4 hours was 3600 mg/m³ (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 LD₅₀ 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 LD₅₀ values of 120 and 100 mg/kg, respectively. The copolymers containing 69% and 70% acrylic acid were slightly toxic, with LD₅₀ values of 350 and 225 mg/kg, respectively. The copolymers containing 25% and 45% acrylic acid were non-toxic, with LD₅₀ 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 pre-treated 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 LD₅₀ 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

CrI: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 $\mu\text{g/l}$ 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 ($\leq 5 \mu$) dust (Rohm and Haas Co. 1984a). Groups of 8 male and 8 female rats were exposed to 4.9, 47.8, or 258.6 $\mu\text{g/l}$ and a group of 16 male and 16 female rats was exposed to 949.6 $\mu\text{g/l}$ 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 949.6- $\mu\text{g/l}$ groups had dry corneas, chromorhinorrhea, a "thrifless 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- $\mu\text{g/l}$ 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- $\mu\text{g/l}$ group were extensive, with mean severity scores of 2.4 for males and females and a diffuse distribution. The lesions in the 258.6- $\mu\text{g/l}$ 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- $\mu\text{g/l}$ 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 $\mu\text{g/l}$ of the acrylic polymer, and none of the control animals had pneumonitis. The minimum observed effect concentration was 258.6 $\mu\text{g/l}$ and the maximum no-observed-effect concentration was 47.8 $\mu\text{g/l}$.

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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ mice were treated dermally three times per week for up to 13 weeks with 100 μ l 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 B6C3F₁ mice, tolerated the dose. The majority of the animals (14 of 30 ICR mice, 21 of 30 C3H mice, and 21 of 30 B6C3F₁ 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 B6C3F₁ 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, dystelektases, 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, ≤ 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 CrI: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/m³ of the Acrylates Copolymer formulation. (Particle size was 2.4, 2.4, and 2.5 μ m, 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/m³, 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/m³ (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/m³ 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, basophilic 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/m³ 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/m³ (corresponding to 4.94 mg/m³ 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/m³ (corresponding to 1.67 mg/m³ 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/m³ for groups 2 to 5, respectively, with MMD ranging from 4.4 to 5.4 μ m and GSD from 2.6 to 2.7. The 13-week mean dust concentrations were 6.1, 22.1, and 52.4 mg/m³ for groups 2 to 4, respectively, with MMD ranging from 4.8 to 5.2 μ m 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/m³ 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/m³ as compared to the target concentrations of 0.05, 0.2, 1, and 10 mg/m³.

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/m³ and female rats exposed to 10 mg/m³ 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/m³, respectively, female rats of necropsy group 3 that were exposed to 10 mg/m³, and female rats of necropsy group 5 that were exposed to 0.05 and 1 mg/m³ 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/m³ 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/m³ 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/m³, females of necropsy groups 1 and 5 that were exposed to 0.2 mg/m³, and males and females of all necropsy groups except 4 and 2, respectively, that were exposed to 10 mg/m³ had a significant increase in the number or segmented neutrophils. With the exception of the changes in the animals of the 0.2-mg/m³ group, the changes were considered

treatment-related. For the animals of the 10-mg/m³ 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/m³. 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/m³. 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/m³. In the 10-mg/m³ 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/m³ 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/m³, and in all animals exposed to 10 mg/m³. 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/m³ groups. For the animals of the 1-mg/m³ 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/m³ acrylic acid polymer had collagen associated with the few foci of inflammation; this collagen formation was minimal. For the animals of the 10 mg/m³ 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/m³ 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/m³; 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/m³ [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 B6C3F₁ 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 mea-

sured 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/m³ 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 semioclusive 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 semioclusive 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 PII 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 semioclusive 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 semioclusive 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 semioclusive 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 semioclusive 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 semioclusive 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 semioclusive 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 B6C3F₁ 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 hour and 1, 2, 3, and 7 days after dosing. Corneal opacity, seen in four animals, and iritis, seen in three animals, cleared by day 7. Conjunctival irritation, which was observed in all animals, cleared in all but one animal by day 7. The researchers stated that Acrylates Copolymer was "an eye irritant but not corrosive."

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

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

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

The ocular irritation potential of Acrylates Copolymer (containing 1500 and 200 ppm stearyl acrylate and methacrylic acid, respectively; CTFA 1999b) was determined using New Zealand white rabbits (MB Research Laboratories 1999d). Initially, 0.1 ml Acrylates Copolymer was instilled into the conjunctival

sac of one male animal, and the eye was graded 1, 24, 48, and 72 hours after dosing. Subsequently, 0.1 ml was instilled into the eyes of four males and one female. Again, the eyes were evaluated 1, 24, 48, and 72 hours after dosing. No corneal opacity or iritis was observed. Conjunctival irritation, which was observed in all animals, cleared by 48 hours. The researchers stated that according to OECD guidelines, "the test article is an ocular irritant but not corrosive." According to the methods of Kay and Calandra, "the test article is minimally irritating."

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

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

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

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

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

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

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

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

In Vitro

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

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

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

In the low-molecular-weight Sodium Polyacrylate study, two animals of the mid-dose group and one of the high-dose group died accidentally during the study. Significant differences in body weight gains and feed consumption were not observed.

Dams of the high-dose group had soft or liquid stools. Effects on embryo viability and fetal growth were not observed, and significant differences in soft-tissue or skeletal abnormalities and variations were not seen between the treated and control groups.

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

Acrylic Acid. Groups of 10 male and 20 female Fischer 344 rats were given 83, 250, or 750 mg/kg acrylic acid in the drinking water daily, and the animals were mated after 13 weeks of dosing (DePass et al. 1983). The neonates, culled to litter size of 10 on day 5 of lactation, were weighed as litters on day 7 and individually on day 21. After weaning, five males and five females randomly selected from each group of the F₀ and F₁ generations were killed and necropsied.

For the F₀ 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 F₁ 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 202.9 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 μ m; 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 LD₅₀ (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 μ g/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 μ g/fetus, but 78% of the fetuses were resorbed with a dose of 1000 μ g/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 μ g/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 μ l/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 μ l/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 μ g/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 μ g/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 μ g/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 $\mu\text{g/ml}$ in the monolayer assay and of 14 to 26 $\mu\text{g/ml}$ 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 $\mu\text{l/plate}$ of 2000-Da molecular weight Sodium Polyacrylate (54% polymer prior to neutralization; 10% [w/v] sodium following neutralization) and 0.2 to 20 $\mu\text{l/plate}$ 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 $\mu\text{l/ml}$ of the 2000-Da molecular weight Sodium Polyacrylate without and with metabolic activation, respectively, and 7.5 to 75 and 3.2 to 32 $\mu\text{l/ml}$ 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 $\mu\text{l/ml}$ 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 $\mu\text{l/ml}$ of 2000-Da molecular weight Sodium Polyacrylate and 0.2 to 20.0 $\mu\text{l/ml}$ 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 non-toxic 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 $\mu\text{g}/\text{plate}$ 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, ≤ 5000 $\mu\text{g}/\text{plate}$, 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 $\mu\text{g}/\text{plate}$ in water and DMSO, respectively, and methacrylic acid, tested at concentrations of 33 to 4000 $\mu\text{g}/\text{plate}$ 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 Bensink 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 $\mu\text{g}/\text{plate}$, 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 $\mu\text{g}/2$ 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 $\mu\text{mol}/\text{plate}$ 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 $\mu\text{g}/\text{ml}$ methyl acrylate (highest ineffective dose [HID]) was not mutagenic without or with metabolic activation.

Ethyl acrylate, 0.001 to 5.0 $\mu\text{l}/\text{plate}$, 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 $\mu\text{g}/\text{ml}$, 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 $\mu\text{g}/\text{ml}$, methyl acrylate was tested at concentrations of 16 to 24 $\mu\text{g}/\text{ml}$, and ethyl acrylate was tested at concentrations of 20 to 37.5 $\mu\text{g}/\text{ml}$. 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 μ g/ml were tested, and positive and negative controls were used. Ethyl acrylate induced significant increases in mutant fraction at doses of 20 μ g/ml in one experiment and 40 μ g/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 μ g/ml. For methyl acrylate, survival was 100%, 34%, 23%, and 16% with 0.0, 16.0, 22.0, and 24.0 μ g/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 μ g/ml, respectively. For 0.0, 16.0, 22.0, and 24.0 μ g/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 μ g/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 μ g/ml methyl acrylate, respectively, and 148/37, 430/45, and 680/58 $\times 10^{-6}$ for 20.0, 30.0, and 37.5 μ g/ml ethyl acrylate, respectively. With 0.0 and 25.0 μ g/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 μ g/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 μ g/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 pulsed-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 ≥ 20 μ g/ml ethyl acrylate within 30 minutes, and at 4 hours, the cellular concentrations were reduced 70% to 90% with 10 to 40 μ g/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 μ g/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 μ g/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 μ g/ml ethyl acrylate, but not 10 or 20 μ g/ml. With PFGE detection of DNA double-strand breaks, 50 μ g/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 K₁-BH₄ cells at concentrations of ≤ 1.9 and ≤ 2.8 μ l/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 *hgp* locus without metabolic activation (Moore et al. 1989). Doses of 14.0 to 18.0 and 21 to 24 μ g/ml methyl and ethyl acrylate, respectively, were used. Total mutant frequencies were 17, 6, and 20 $\times 10^{-6}$ with 14, 16, and 18 μ g/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 μ g/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 μ g/ml, respectively, in the monolayer assay and methyl acrylate was tested at concentrations of 10 to 20.5 μ g/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 μ g/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 μ g/ml ethyl acrylate in DMSO. In order to expose blast-transformed (cycling) cells, the cultures were exposed to 1 to 20 μ g/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 ≥ 30 μ g/ml. After blast transformation (G_1 -S), exposure of splenocytes to 2 or 5 μ g/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 μ g/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) μ g/ml were used in the UDS assay, 0.5 to 10 μ g/ml were used in the micronucleus assay, and 5 to 50 (acrylic acid) and 5 to 15 (*n*-butyl acrylate) μ g/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 μ g/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 ≤ 0.6 μ l/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 μ l of 60, 300, or 600 μ M 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), N⁶-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 μ l 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 μ g 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 le-

sions 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 μ l 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-methylcholanthrene) 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 of the 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 μ l 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 B6C3F₁ 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 B6C3F₁ 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/m³, respectively) or *n*-butyl acrylate (86, 258, or 773 mg/m³, 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 B6C3F₁ 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 B6C3F₁ 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 μ mol (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). Semioclusive 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/m³ in air (IARC 1999). The recommended TLVs for occupational exposure to methyl and ethyl acrylate in workplace air are 7 and 20 mg/m³, respectively. The 8-hour TLV-TWA for occupational exposure to *n*-butyl acrylate in workplace air is 52 mg/m³. Rohm and Haas Co. (1985) reported a TWA of 2 mg/m³ 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 ≤ 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 LD₅₀ 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 LD₅₀ was > 5 g/kg. The oral LD₅₀ 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 LD₅₀ for rats of the emulsion was 8.57 ml/kg. The dermal LD₅₀ for rabbits and the oral LD₅₀ for rats of Vinyl Acetate/Maleate/Acrylate Copolymer solution was > 5 g/kg. For rats, the oral LD₅₀ 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/m³. 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 LD₅₀ of acrylic acid was 295 to 950 mg/kg for rabbits. The oral LD₅₀ was 2100 to 3200 mg/kg for rabbits and for rats and 0.34 ml/kg for male rats. The oral LD₅₀ 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 LC₅₀ of acrylic acid was 3600 mg/m³ 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, ≤750 mg/kg, also produced toxic effects, and ≤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 mal-segregation 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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Safety Assessment of Acryloyldimethyltaurate Polymers as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 21 acryloyldimethyltaurate polymers as used in cosmetics. The reported functions of these ingredients include dispersing agent – nonsurfactant, emulsion stabilizers, opacifying agent, and viscosity increasing agent – aqueous. The Panel expressed concern about residual monomers and impurities including acrylamide, vinyl formamide, and methacrylamidolauric acid monomers. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities. The Panel concluded that acryloyldimethyltaurate polymers are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a review of published scientific literature and unpublished data provided by Industry relevant to assessing the safety of 21 acryloyldimethyltaurate polymers as used in cosmetics. This group of ingredients comprises homopolymers, copolymers, and crosslinked polymers, the monomers of which are at least partially composed of acryloyldimethyltaurate. According to the *International Cosmetic Ingredient Dictionary and Handbook*, the functions of these ingredients include dispersing agent – nonsurfactant, emulsion stabilizer, opacifying agent, and viscosity increasing agent – aqueous (Table 1).¹ The ingredients in this safety assessment are:

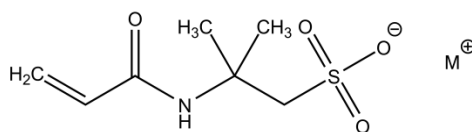
Acrylamide/Sodium Acryloyldimethyltaurate Copolymer	HEA/Sodium Acryloyldimethyltaurate/Steareth-20
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer	Methacrylate Copolymer
Ammonium Acryloyldimethyltaurate/Beheneth-25	Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer
Methacrylate Crosspolymer	Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer	Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer
Ammonium Acryloyldimethyltaurate/Laureth-7	Sodium Acrylate/Sodium Acryloyldimethyl Taurate/Acrylamide Copolymer
Methacrylate Copolymer	Sodium Acryloyl Dimethyl Taurate/PEG-8 Diacrylate Crosspolymer
Ammonium Acryloyldimethyltaurate/Steareth-25	Sodium Acryloyldimethyl Taurate/Acrylamide/VP Copolymer
Methacrylate Crosspolymer	Sodium Acryloyldimethyltaurate/Methacrylamidolauric Acid Copolymer
Ammonium Acryloyldimethyltaurate/Steareth-8	Sodium Acryloyldimethyltaurate/VP Crosspolymer
Methacrylate Copolymer	Sodium Polyacryloyldimethyl Taurate
Ammonium Acryloyldimethyltaurate/Vinyl Formamide Copolymer	
Ammonium Acryloyldimethyltaurate/VP Copolymer	
Ammonium Polyacryloyldimethyl Taurate	
Dimethylacrylamide/Sodium Acryloyldimethyltaurate Crosspolymer	

The Panel has previously reviewed polymers that are similar to the acryloyldimethyltaurate polymers (Table 2). Some of the ingredients in this report are copolymers with acrylate monomers; the Panel has reviewed the polyacrylates, and other acrylate copolymers, and concluded that they are safe as used when formulated to be non-irritating.² Some other ingredients in this report are copolymers with acrylamide monomers; polyacrylamides were found to be safe as used if the concentration of residual acrylamide monomers in formulation is not greater than 5 ppm, and Polyvinylpyrrolidone (PVP; another polymer with vinyl-type amide monomers) was found to be safe as used.^{3,4} The Panel has also previously reviewed components/monomers of the acryloyldimethyltaurate polymers. The alkyl taurate amides and taurate salts were found to be safe when formulated to be non-irritating.⁵

CHEMISTRY

Definition and Structure

The acryloyldimethyltaurate polymers are composed of homopolymers, copolymers and crosslinked polymers, the monomers of which are at least partially composed of acryloyldimethyltaurate.



acryloyldimethyltaurate

Figure 1. This monomer is common to all acryloyldimethyltaurate polymers, where M is a sodium cation or ammonium.

The definitions and structures of these acryloyldimethyltaurate polymers ingredients are presented in Table 1.

Physical and Chemical Properties

The characteristics of acryloyldimethyltaurate polymers may vary greatly with manufacturing methods. For instance, the fluidity, solubility, and swelling capacity of these polymers can be determined by the degree of polymerization and crosslinking. In other words, altering manufacturing conditions, such as temperature, reaction time, and/or stoichiometric ratios, may result in significantly different physical forms even when the same monomers are used (i.e., even included under one ingredient name). It is also possible that these polymers are manufactured *in situ* to produce hydrogels. Accordingly, only cosmetic ingredient-specific data on the chemical and physical properties (including the molecular weight) of these ingredients are useful, and the data cannot be assumed.

Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer and Ammonium Acryloyldimethyltaurate/VP Copolymer are reported to be white powders (Table 3).^{6,7}

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer is reported to be provided in water, at up to 27%.⁸

Acryloyldimethyltaurate polymers are large (2000 μm ; >1000 to >1,000,000 g/mol) molecules. None of the particle diameters of Ammonium Acryloyldimethyltaurate/VP Copolymer were >2000 μm , 97.2% were <2000 μm , 81.3% were <1000 μm , 11.8% were <200 μm , and 0.5% were <100 μm .⁶ For Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer, 90.8% of the particles were <100 μm and 84.5% were <10 μm , and had an overall median diameter of 2.8 μm .⁷ Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer is reported have a molecular weight of approximately 250,000 g/mol.⁸ The molecular weight of Sodium Polyacryloyldimethyl Taurate was reported to be >1,000,000 g/mol.⁹

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer, Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer, and a Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer mixture were reported to be stable under normal environmental conditions.¹⁰⁻¹² Under normal conditions of use in personal care products, Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer is not expected to degrade; however, it does have functional groups that can be hydrolyzed in the pH range of 4-9.¹⁰ Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer and Ammonium Acryloyldimethyltaurate/VP Copolymer were also reported to be stable under normal conditions, but may release ammonia under alkaline conditions.^{6,7}

Method of Manufacture

Information on the methods of manufacture of these ingredients was not found in the published literature and no unpublished data were submitted. However, it is likely that radical type polymerization is commonly used, as it is for polyacrylamide and other vinyl-type polymers. This type of synthesis begins with formaldehyde and acetylene, and proceeds through 2-butyne-1,4-diol and γ -butyrolactone to α -pyrrolidone and *N*-vinyl-2-pyrrolidone (the monomer), which is then polymerized to form the polymer. Usually, the monomer is polymerized in water; however, commercial polymerization may be carried out in isopropyl alcohol. The alcoholic solution is subsequently wetted to an aqueous solution by steam distillation and then either spray or drum dried.^{4,13,14}

Composition/Impurities

One supplier reported that Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer is supplied as an aqueous solution containing 25% to 27% of the polymer and the preservative sodium methylparaben (0.2%).⁸ This polymer is also reported to be supplied as an aqueous solution at 24%.¹²

Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer is reported to be supplied in a trade name mixture at <60%; the lowest concentration is not specified.¹¹

Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer is reported to be supplied in a trade name mixture at <45%; the lowest concentration is not specified.¹⁰

Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer was reported to be >90% pure; data on the remaining <10% was not provided.⁷

Sodium Polyacryloyldimethyl Taurate is reported to contain <2000 ppm 2-acrylamido-2-methylpropane sulfonic acid (AMPS) and <10 ppm (detection limit) acrylamide.⁹

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on the data the Panel receives from the U.S. Food and Drug Administration (FDA) and the cosmetics Industry on the expected cosmetic use of ingredients. The FDA collects data from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). Those data received from the cosmetic Industry are submitted in response to a survey conducted by the Personal Care Products Council (Council) of the maximum reported use concentrations by category.

According to VCRP data received from the FDA in 2017, Ammonium Acryloyldimethyltaurate/VP Copolymer was reported to be used in 584 formulations, including use in 524 leave-on products and 60 rinse-off products (Table 4).¹⁵ Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer was reported to be used in 541 formulations, including use in 516 leave-on products, 22 rinse-off products, and 3 products used in the bath. Ingredients with the next highest reported frequency of use are Acrylamide/Sodium Acryloyldimethyltaurate Copolymer, with 227 uses (220 leave-on and 7 rinse-off products), Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer with 197 uses (190 leave-on and 7 rinse-off products), and Ammonium Polyacryloyldimethyl Taurate, with 187 uses (178 leave-on and 9 rinse-off products). All other ingredients are reported to be used in 56 or fewer cosmetic products.

The results of a concentration of use survey conducted by the Council in 2015 indicate Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer has the highest reported maximum concentration of use; it is reported to be used at up to 4.3% in depilatories (rinse-off products) and up to 3.6% in eyeliner and eye shadow (leave-on products).^{16,17}

In some cases, reports of uses were received from the VCRP, but concentration of use data were not reported in the use concentration survey.¹⁵⁻¹⁷ For example, Sodium Acryloyldimethyltaurate/VP Crosspolymer is reported to be used in 8 cosmetic formulations, but no use concentrations were reported. In other cases, no uses were reported to the VCRP, but concentration of use data were reported by Industry; for example, Sodium Acryloyldimethyltaurate/Methacrylamidolauric Acid Copolymer had no reported uses in the VCRP, but concentrations of use (0.28%-0.35%) in product categories that result in dermal exposure were provided in the Industry survey. Therefore, it is assumed that there is at least one use in every cosmetic product category for which a concentration was reported.

The ingredients not in use, based on the data from both the VCRP and the Industry survey, are listed in Table 5.

Several of these ingredients were reported to be used in products that are used around the eye (the highest maximum reported concentration is 3.6% for Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer in eyeliners and eye shadow) and in products that come in contact with mucus membranes (the highest maximum reported concentration 2.4% Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer in the use category of other personal cleanliness products). Ammonium Acryloyldimethyltaurate/VP Copolymer and Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer were each reported to be used in 1 baby product (no concentration of use was reported for either).

Acrylamide/Sodium Acryloyldimethyltaurate Copolymer, Ammonium Polyacryloyldimethyl Taurate, Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer, and Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer are reported to be used in powder products, in which the highest reported concentration of use was 0.7% Acrylamide/Sodium Acryloyldimethyltaurate Copolymer in face powders. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.^{18,19} Additionally, some of the acryloyldimethyltaurate polymers are used in cosmetic sprays and could possibly be inhaled; for example, Dimethylacrylamide/Sodium Acryloyldimethyltaurate Crosspolymer is reported to be used at up to 3% in perfume. 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 <10 µm compared with pump sprays.^{20,21} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{22,23}

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) of Australia concluded that there is low concern to public health when Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer is used in rinse-off cosmetics at ≤2% and when Ammonium Acryloyldimethyltaurate/VP Copolymer is used in cosmetics at 0.5% to 1.2% (the concentrations requested to be reviewed by the suppliers) based on toxicity and environmental data.^{6,7} NICNAS also concluded that Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer is safe in cosmetics at <3% and that Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer is safe in cosmetics when used as a component of hair styling products for salon and home use at 1% to 2% (the concentrations requested by the suppliers) based on toxicity and environmental data.^{11,12}

Acrylamide/Sodium Acryloyldimethyltaurate Copolymer, Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer, Sodium Acrylate/Sodium Acryloyldimethyl Taurate/Acrylamide Copolymer, and Sodium Acryloyldimethyl Taurate/Acrylamide/VP Copolymer are restricted in Europe according to the European Union (EU) Annex III/66.²⁴ The amount of residual acrylamide content is limited to 0.1 mg/kg in leave-on cosmetics used on the body and 0.5 mg/kg in other cosmetic products that are used on specific body parts (e.g., eye, face, and hand).

Non-Cosmetic

Acrylamide/Sodium Acryloyldimethyltaurate Copolymer may be used as a component of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding dry food not to exceed 0.015 weight percent of dry fiber. [21CFR176.180]

According to the EU regulations on labelling and packaging of substances and mixtures, if Ammonium Acryloyldimethyltaurate/Beheneth-25 Methacrylate Crosspolymer is present in a product in a non-stabilized form, the name of the substance is to be followed by the words "non-stabilized" on the label.²⁵

TOXICOKINETICS

Toxicokinetic data were not found in the published literature and no unpublished data were submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity

Acute dermal and oral toxicity studies are summarized in Table 6.

Dermal

The acute dermal LD₅₀ for a solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (24% in water) was reported to be >5000 mg/kg (1200 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) in rats.¹² The acute dermal LD₅₀ for Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% solids in water) was reported to be >5000 mg/kg (1250 to 1350 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) in rats.²⁶

Oral

The acute oral LD₅₀ for a solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (24% in water) was reported to be >5000 mg/kg (>1200 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) in rats.¹² The acute oral LD₅₀ for Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer and Ammonium Acryloyldimethyltaurate/VP Copolymer was reported to be >2000 mg/kg in rats; the oral LD₅₀ for Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (<60%) in a trade name mixture was reported to be >1200 mg/kg.^{6,7,11} The acute oral LD₅₀ of Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% solids in water) was reported to be >5000 mg/kg (>1250 to >1350 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) in rats.²⁶

Short-Term to Chronic Toxicity

Short-term, subchronic, and chronic toxicity data were not found in the published literature and no unpublished data were submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Developmental and reproductive toxicity data were not found in the published literature and no unpublished data were submitted.

GENOTOXICITY STUDIES

In Vitro

In vitro genotoxicity studies are summarized in Table 7.

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer, Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer, Ammonium Acryloyldimethyltaurate/VP Copolymer, Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer, and Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer were not mutagenic in bacterial reverse mutation assays using *Salmonella typhimurium* and *Escherichia coli*.^{6,7,10-12} Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% solids in water) was not mutagenic in an Ames test at up to 5000 µg/plate (1250 to 1350 µg/plate).²⁶

CARCINOGENICITY STUDIES

Carcinogenicity data were not found in the published literature and no unpublished data were submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

Dermal irritation studies in rabbits are summarized in Table 8.

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (24%), Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer (100%), and Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed applied neat; concentration not specified) were slightly or not irritating to rabbit skin.^{6,7,12} A solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% in water; applied neat) was not irritating to rabbit skin.²⁶ An solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% in water; applied neat) was not irritating to rat skin after 24 h of exposure.²⁶

Human

Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer was reported to be non-irritating in a human irritation assay.¹¹ No further details were provided.

Sensitization

Animal and human sensitization studies are summarized in Table 9.

Animal

Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer (25%) and Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed applied neat, not specified) were not sensitizing to guinea pigs.^{6,7}

Human

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (24%), Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (<2.25%), and Sodium Polyacryloyldimethyl Taurate (30% to 40%) were not sensitizing in human repeated insult patch tests (HRIPT).^{9,10,12} An aqueous solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% solids in water; applied neat) was not sensitizing in an HRIPT.²⁶

A trade name mixture containing Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (<60%; assumed administered neat, not specified) was not sensitizing in a human sensitization assay.¹¹

OCULAR IRRITATION STUDIES

In vitro and animal ocular irritation studies are summarized in Table 10.

In Vitro

Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer was not an ocular irritant in an unspecified *in vitro* assay.¹¹ Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (<2.25%) was not considered an eye irritant in a Hens Eggs Test-Chorioallantoic Membrane (HET-CAM) assay.¹⁰

Animal

In ocular irritation assays, Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer, Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer, and Ammonium Acryloyldimethyltaurate/VP Copolymer were not irritating or slightly irritating in rabbit eyes.^{6,7,12} A solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% in water; applied neat) was not irritating, according to Organization for Economic Co-operation and Development Test Guideline (OECD TG) criteria,¹¹ or minimally irritating, according to US EPA criteria, to rabbit eyes.²⁶

SUMMARY

This is a review of published scientific literature and unpublished data provided by Industry for assessing the safety of 21 acryloyldimethyltaurate polymers as used in cosmetics. This group of ingredients is composed of homopolymers, copolymers, and crosslinked polymers, the monomers of which are at least partially composed of acryloyldimethyltaurate. The reported functions of these ingredients include dispersing agent – nonsurfactant, emulsion stabilizer, opacifying agent, and viscosity increasing agent – aqueous.

In a safety assessment of polyacrylamides, these ingredients were found to be safe as used if the concentration of residual acrylamide monomers in formulation is not greater than 5 ppm

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer is reported have a molecular weight of approximately 250,000 Da. None of the particles of Ammonium Acryloyldimethyltaurate/VP Copolymer were >2000 µm, 97.2% were <2000 µm, 81.3% were <1000 µm, 11.8% were <200 µm, and 0.5% were <100 µm. For Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer, 90.8% of the particles of were <100 µm and 84.5% were <10 µm, and had a median diameter of 2.8 µm. The molecular weight of Sodium Polyacryloyldimethyl Taurate was reported to be >1,000,000.

Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer was reported to be >90% pure. Sodium Polyacryloyldimethyl Taurate is reported to contain <2000 ppm AMPS and <10 ppm acrylamide.

According to VCRP data received from the FDA in 2017, Ammonium Acryloyldimethyltaurate/VP Copolymer was reported to be used in 584 formulations, including use in 524 leave-on products and 60 rinse-off products. Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer was reported to be used in 541 formulations, including use in 516 leave-on products, 22 rinse-off products, and 3 products used in the bath. Ingredients with the next highest reported frequency of use are Acrylamide/Sodium Acryloyldimethyltaurate Copolymer, with 227 uses (220 leave-on and 7 rinse-off products), Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer with 197 uses (190 leave-on and 7 rinse-off products), and Ammonium Polyacryloyldimethyl Taurate, with 187 uses (178 leave-on and 9 rinse-off products). All other ingredients are reported to be used in 56 or fewer cosmetic products.

The results of a concentration of use survey conducted by the Council in 2015 indicate Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer has the highest reported maximum concentration of use; it is reported to be used at up to 4.3% in depilatories (a rinse-off product) and up to 3.6% in eyeliner and eye shadow (leave-on products).

The acute dermal LD₅₀ for Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer was reported to

be >5000 mg/kg in rats. The acute dermal LD₅₀ for a product containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27%) was >5000 mg/kg (>1250 to >1350 mg/kg) in rats.

The acute dermal LD₅₀ for a solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (24% in water) was reported to be >5000 mg/kg (>1200 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) in rats. The acute oral LD₅₀ for a solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27%) was reported to be >5000 mg/kg (>1250 to >1350 mg/kg) in rats.

The acute oral LD₅₀ for a solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (24% in water) was reported to be >5000 mg/kg (>1200 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) in rats. The acute oral LD₅₀ for Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer and Ammonium Acryloyldimethyltaurate/VP Copolymer was reported to be >2000 mg/kg in rats; the oral LD₅₀ for Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (<60%) in a trade name mixture was reported to be >1200 mg/kg. The acute oral LD₅₀ for a solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% in water) was reported to be >5000 mg/kg (>1250 to >1350 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) in rats.

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer, Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer, Ammonium Acryloyldimethyltaurate/VP Copolymer, Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer, and Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer were not mutagenic in bacterial reverse mutation assays. A product containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27%) was not mutagenic in an Ames test.

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (up to 27%), Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer (100%), and Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed applied neat, not specified) were slightly or not irritating to rabbit skin. A solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% in water; applied neat) was not irritating to rat skin.

Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer was not irritating in a human assay.

In a Buehler test, Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer was not sensitizing to guinea pigs at 25%. Ammonium Acryloyldimethyltaurate/VP Copolymer (neat) was not sensitizing to guinea pigs.

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25%-27%), Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (<2.25%), and Sodium Polyacryloyldimethyl Taurate (30% to 40%) were not sensitizing in human repeated insult patch tests HRIPTs. Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer was not sensitizing in a human sensitization assay. A product containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27%) was not sensitizing in an HRIPT.

Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (up to 27%), Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (<2.25%), and Sodium Polyacryloyldimethyl Taurate (30% to 40%) were not sensitizing in HRIPTs. A trade name mixture containing Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (<60%; assumed administered neat, not specified) was not sensitizing in a human sensitization assay.

Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer was not an ocular irritant in an unspecified *in vitro* assay. Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (<2.25%) was not considered an eye irritant in a HET-CAM assay.

In ocular irritation assays Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer, Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer, and Ammonium Acryloyldimethyltaurate/VP Copolymer were not irritating or slightly irritating to rabbit eyes. A solution containing Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% in water) was not irritating, according to OECD TG criteria, or minimally irritating, according to US EPA criteria, to rabbit eyes.

DISCUSSION

The Panel examined data on dermal and oral acute toxicity, genotoxicity, dermal and ocular irritation, and sensitization for the acryloyldimethyltaurate polymers. There were no studies that elicited concern. The Panel also considered composition and the physical and chemical properties of these polymers.

These ingredients are large molecules (2000 µm; >1000 to >1,000,000 g/mol) and should not be absorbed through the skin. This is consistent with the favorable safety profile in dermal and oral toxicity studies.

The Panel expressed concern about impurities, including residual monomers, because of potential sensitization or other deleterious effects that may occur due to exposure. Monomers of concern include acrylamide (in Sodium Acryloyldimethyl Taurate/Acrylamide/VP Copolymer), vinyl formamide (in Ammonium Acryloyldimethyltaurate/Vinyl Formamide Copolymer), and methacrylamidolauric acid (in Sodium Acryloyldimethyltaurate/Methacrylamidolauric Acid Copolymer). The Panel agreed that it is appropriate to apply the limit of 5 ppm acrylamide imposed by the Panel in the safety assessment of Polyacrylamide to finished products containing the ingredients in this safety assessment. They stressed that the cosmetics industry should continue to use cGMPs to limit impurities.

The Panel discussed the issue of incidental inhalation exposure from perfumes; tonics, dressings and other hair grooming aids; body and hand products; and face powders. There were no inhalation toxicity data available. These

ingredients are reportedly used at concentrations up to 3% in cosmetic products that may be aerosolized and up to 0.7% in loose powder products that may become airborne. The Panel noted that droplets/particles from cosmetic products would not be respirable to any appreciable amount. Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the acryloyldimethyltaurate polymers and on data that shows that these ingredients are not irritants. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. They noted the lack of irritation or sensitization in tests of dermal exposure, no systemic toxicity at 5000 mg/kg, the absence of genotoxicity in Ames tests, and the fact that these ingredients are large molecules, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

CONCLUSION

The CIR Expert Panel concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Acrylamide/Sodium Acryloyldimethyltaurate Copolymer	HEA/Sodium Acryloyldimethyltaurate/Steareth-20
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic	Methacrylate Copolymer
Acid Copolymer*	Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate
Ammonium Acryloyldimethyltaurate/Beheneth-25	Copolymer
Methacrylate Crosspolymer	Sodium Acrylate/Acryloyldimethyltaurate/
Ammonium Acryloyldimethyltaurate/Carboxyethyl	Dimethylacrylamide Crosspolymer
Acrylate Crosspolymer	Sodium Acrylate/Sodium Acryloyldimethyl Taurate
Ammonium Acryloyldimethyltaurate/Laureth-7	Copolymer
Methacrylate Copolymer*	Sodium Acrylate/Sodium Acryloyldimethyl
Ammonium Acryloyldimethyltaurate/Steareth-25	Taurate/Acrylamide Copolymer
Methacrylate Crosspolymer	Sodium Acryloyl Dimethyl Taurate/PEG-8 Diacrylate
Ammonium Acryloyldimethyltaurate/Steareth-8	Crosspolymer*
Methacrylate Copolymer	Sodium Acryloyldimethyl Taurate/Acrylamide/VP
Ammonium Acryloyldimethyltaurate/Vinyl Formamide	Copolymer
Copolymer*	Sodium Acryloyldimethyltaurate/Methacrylamidolauric
Ammonium Acryloyldimethyltaurate/VP Copolymer	Acid Copolymer
Ammonium Polyacryloyldimethyl Taurate	Sodium Acryloyldimethyltaurate/VP Crosspolymer
Dimethylacrylamide/Sodium Acryloyldimethyltaurate	Sodium Polyacryloyldimethyl Taurate
Crosspolymer	

* Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

TABLES

Table 1. Definitions, idealized structures, and functions of acryloyldimethyltaurate polymers in this safety assessment.^{1; CIR Staff}

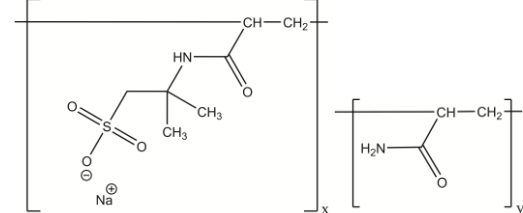
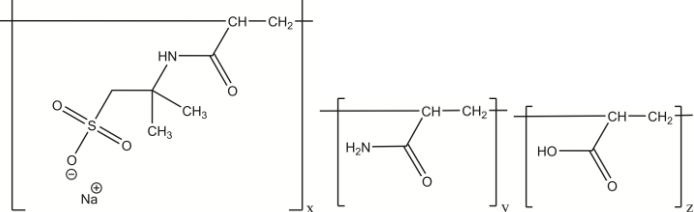
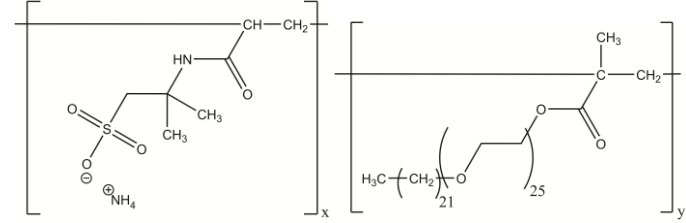
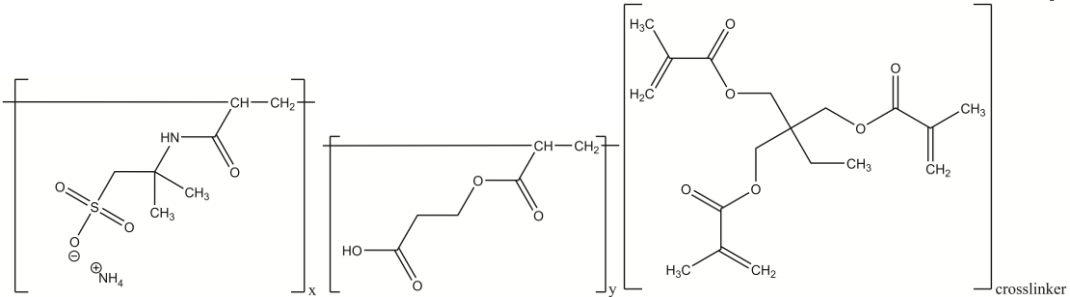
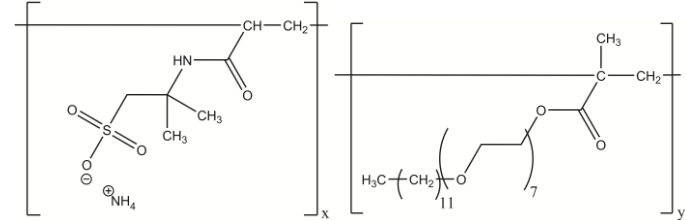
Ingredient CAS No.	Definition & Monomer Residue Structures	Function(s)
Acrylamide/Sodium Acryloyldimethyltaurate Copolymer 38193-60-1 [1258874-55-3; 159157-50-3]	Acrylamide/Sodium Acryloyldimethyltaurate Copolymer is a copolymer of acrylamide and sodium acryloyldimethyltaurate monomers. 	Emulsion stabilizer; viscosity increasing agent - aqueous
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer [1453194-38-1; 1417986-34-5]	Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer is a copolymer of acrylamide, sodium acryloyldimethyltaurate and acrylic acid monomers. 	Film former; hair fixative
Ammonium Acryloyldimethyltaurate/ Beheneth-25 Methacrylate Crosspolymer	Ammonium Acryloyldimethyltaurate/Beheneth-25 Methacrylate Crosspolymer is a copolymer of ammonium acryloyldimethyltaurate and beheneth-25 methacrylate monomers. 	Emulsion stabilizer
Ammonium Acryloyldimethyltaurate/ Carboxyethyl Acrylate Crosspolymer	Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer is a copolymer of ammonium acryloyl dimethyltaurate and carboxyethyl acrylate crosslinked with trimethylolpropane trimethacrylate. 	Dispersing agent – nonsurfactant; viscosity increasing agent - aqueous
Ammonium Acryloyldimethyltaurate/ Laureth-7 Methacrylate Copolymer 683748-07-4	Ammonium Acryloyldimethyltaurate/Laureth-7 Methacrylate Copolymer is a copolymer of ammonium acryloyldimethyltaurate and laureth-7 methacrylate monomers. 	Abrasive

Table 1. Definitions, idealized structures, and functions of acryloyldimethyltaurate polymers
in this safety assessment.^{1; CIR Staff}

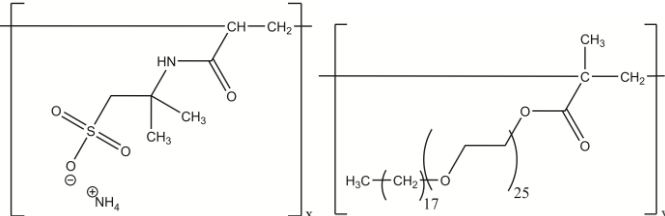
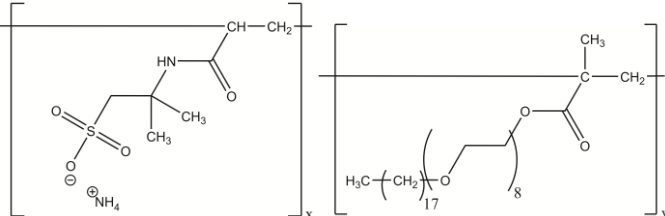
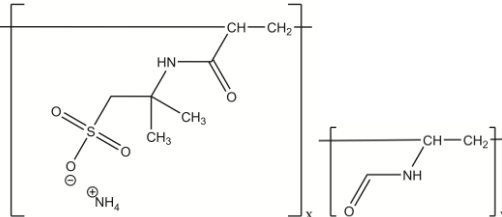
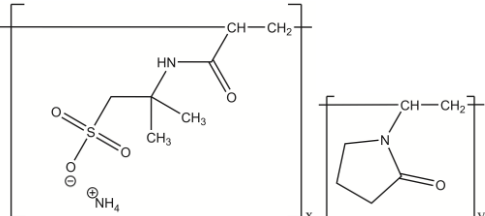
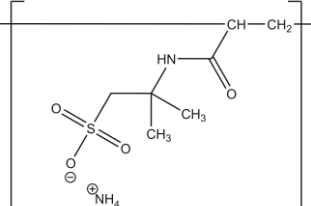
Ingredient CAS No.	Definition & Monomer Residue Structures	Function(s)
Ammonium Acryloyldimethyltaurate/ Steareth-25 Methacrylate Crosspolymer	Ammonium Acryloyldimethyltaurate/Steareth-25 Methacrylate Crosspolymer is a copolymer of ammonium acryloyldimethyltaurate and steareth-25 methacrylate monomers. 	Emulsion stabilizer
Ammonium Acryloyldimethyltaurate/ Steareth-8 Methacrylate Copolymer	Ammonium Acryloyldimethyltaurate/Steareth-8 Methacrylate Copolymer is a copolymer of ammonium acryloyldimethyltaurate and steareth-8 methacrylate monomers. 	Emulsion stabilizer; viscosity increasing agent - aqueous
Ammonium Acryloyldimethyltaurate/ Vinyl Formamide Copolymer [600172-76-7]	Ammonium Acryloyldimethyltaurate/Vinyl Formamide Copolymer is a copolymer of ammonium acryloyldimethyltaurate and vinyl formamide monomers. 	Emulsion stabilizer; viscosity increasing agent - aqueous
Ammonium Acryloyldimethyltaurate/ VP Copolymer [1509895-12-8; 53845-64-0]	Ammonium Acryloyldimethyltaurate/VP Copolymer is a copolymer of ammonium acryloyldimethyltaurate and vinylpyrrolidone monomers. 	Viscosity increasing agent - aqueous
Ammonium Polyacryloyldimethyl Taurate [62152-14-1]	Ammonium Polyacryloyldimethyl Taurate is the polymer that conforms generally to the formula. [Ammonium Polyacryloyldimethyl Taurate is the homopolymer of ammonium acryloyldimethyltaurate.] 	Emulsion stabilizer; viscosity increasing agent - aqueous

Table 1. Definitions, idealized structures, and functions of acryloyldimethyltaurate polymers
in this safety assessment.^{1: CIR Staff}

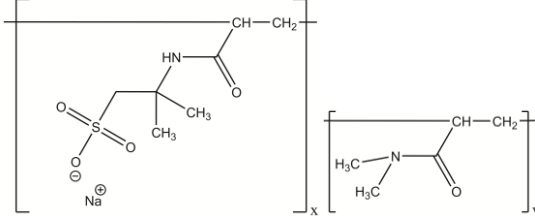
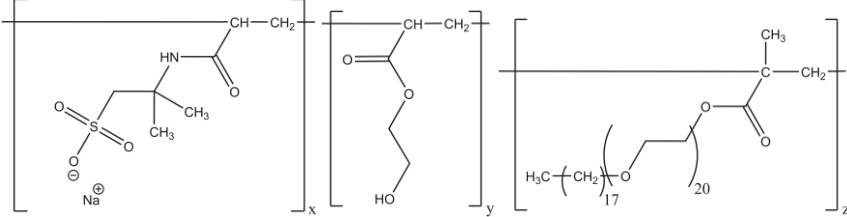
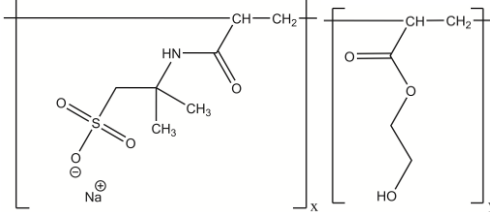
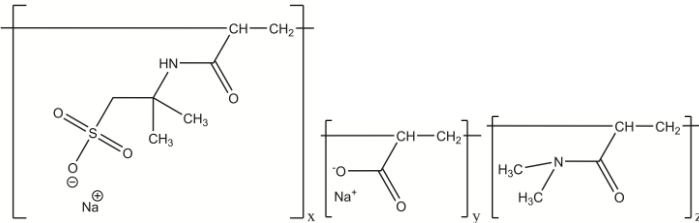
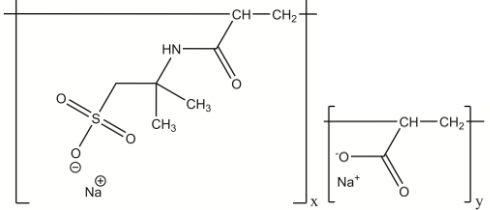
Ingredient CAS No.	Definition & Monomer Residue Structures	Function(s)
Dimethylacrylamide/Sodium Acryloyldimethyltaurate Crosspolymer [869772-40-7; 92815-96-8]	Dimethylacrylamide/Sodium Acryloyldimethyltaurate Crosspolymer is a copolymer of dimethylacrylamide and sodium acryloyldimethyltaurate crosslinked with methylene bis-acrylamide. 	Viscosity increasing agent – aqueous
HEA/Sodium Acryloyldimethyltaurate/ Steareth-20 Methacrylate Copolymer 1562414-82-7	HEA/Sodium Acryloyldimethyltaurate/Stearth-20 Methacrylate Copolymer is a copolymer of 2-hydroxyethylacrylate (HEA), sodium acryloyldimethyltaurate and steareth-20 methacrylate monomers. 	Dispersing agent – nonsurfactant; emulsion stabilizer; viscosity increasing agent – aqueous
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer 111286-86-3	Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer is a copolymer of sodium hydroxyethyl acrylate and acryloyldimethyl taurate monomers. 	Dispersing agent – nonsurfactant; emulsion stabilizer; opacifying agent; viscosity increasing agent – aqueous
Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer 187725-30-0	Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer is a crosslinked copolymer of sodium acrylate, acryloyldimethyltaurate and dimethylacrylamide. 	Dispersing agent – nonsurfactant; emulsion stabilizer; film former; viscosity increasing agent – aqueous
Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer 77019-71-7	Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer is a copolymer of sodium acrylate and sodium acryloyldimethyl taurate monomers. 	Dispersing agent – nonsurfactant; emulsion stabilizer; opacifying agent; viscosity increasing agent – aqueous

Table 1. Definitions, idealized structures, and functions of acryloyldimethyltaurate polymers in this safety assessment.¹; CIR Staff

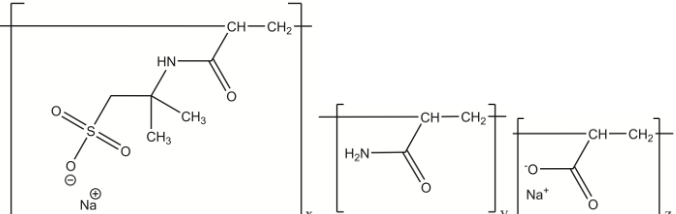
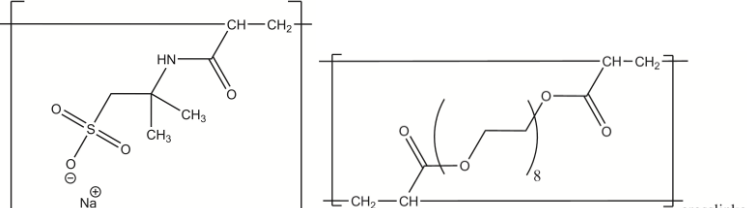
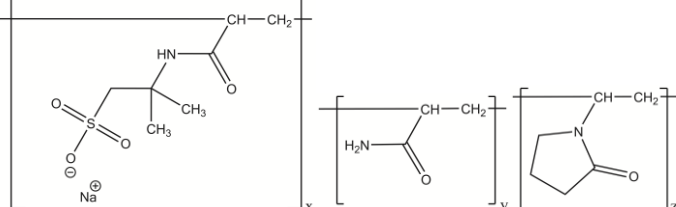
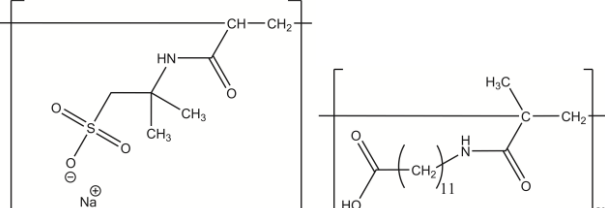
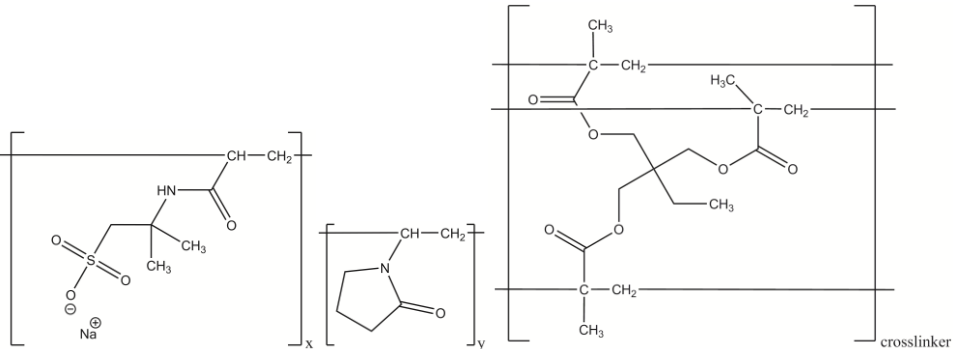
Ingredient CAS No.	Definition & Monomer Residue Structures	Function(s)
Sodium Acrylate/Sodium Acryloyldimethyl Taurate/Acrylamide Copolymer [1453194-38-1; 1417986-34-5]	Sodium Acrylate/Sodium Acryloyldimethyl Taurate/Acrylamide Copolymer is a copolymer of sodium acrylate, sodium acryloyldimethyltaurate and acrylamide monomers. 	Dispersing agent – nonsurfactant; emulsion stabilizer; opacifying agent; viscosity increasing agent – aqueous
Sodium Acryloyl Dimethyl Taurate/PEG-8 Diacrylate Crosspolymer	Sodium Acryloyl Dimethyl Taurate/PEG-8 Diacrylate Crosspolymer is a polymer of sodium acryloyl dimethyl taurate crosslinked by PEG-8 diacrylate. 	Skin-conditioning agent – miscellaneous
Sodium Acryloyldimethyl Taurate/Acrylamide/VP Copolymer [92815-97-9]	Sodium Acryloyldimethyl Taurate/Acrylamide/VP Copolymer is a copolymer of sodium acryloyldimethyltaurate, acrylamide and vinylpyrrolidone monomers. 	Dispersing agent – nonsurfactant; emulsion stabilizer; opacifying agent; viscosity increasing agent – aqueous
Sodium Acryloyldimethyltaurate/Methacrylamidolauric Acid Copolymer [882176-38-7]	Sodium Acryloyldimethyltaurate/Methacrylamidolauric Acid Copolymer is a copolymer of sodium acryloyldimethyltaurate and methacrylamidolauric acid monomers. 	Opacifying agent
Sodium Acryloyldimethyltaurate/VP Crosspolymer	Sodium Acryloyldimethyltaurate/VP Crosspolymer is a copolymer of sodium acryloyldimethyltaurate and vinylpyrrolidone crosslinked by 1,1,1-trimethylolpropane triacrylate. 	Emulsion stabilizer

Table 1. Definitions, idealized structures, and functions of acryloyldimethyltaurate polymers in this safety assessment.^{1; CIR Staff}

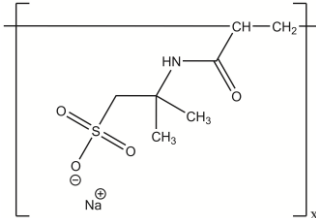
Ingredient CAS No.	Definition & Monomer Residue Structures	Function(s)
Sodium Polyacryloyldimethyl Taurate [35641-59-9]	Sodium Polyacryloyldimethyl Taurate is the polymer that conforms generally to the formula. [Sodium Polyacryloyldimethyl Taurate is the homopolymer of sodium acryloyldimethyltaurate.] 	Emulsion stabilizer; viscosity increasing agent-aqueous

Table 2. Previous safety assessments of similar ingredients and components/monomers of acryloyldimethyltaurate polymers in this safety assessment.

Constituent and ingredient group report	Conclusion	Maximum reported concentration of use reported for ingredients in the safety assessment	Reference
Alkyl Taurate Amides And Taurate Salts	Safe when formulated to be non-irritating	28% Sodium Methyl Oleoyl Taurate in bath products; 11% Calcium Lauroyl Taurate in leave-on products; 13% Sodium Methyl Cocoyl Taurate in rinse-off products	5
Acrylates Copolymers	Safe when formulated to be non-irritating	40% Acrylates Copolymer ^a	2
Polyacrylamide And Acrylamide Residues	Safe as used if the level of acrylamide monomer in formulation is not greater than 5 ppm	2.8% Polyacrylamide in leave-on formulations	3
Polyvinylpyrrolidone (PVP)	Safe as used	>5%-10% in leave-on eye products	4

^a Not known if leave-on or rinse-off product(s)**Table 3.** Chemical and physical properties of acryloyldimethyltaurate polymers.

Property	Value	Reference
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer		
Molecular Weight g/mol	~250,000	8
Water Solubility	Forms an aqueous clear colorless liquid at 25% to 27%	8
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer		
Physical Form	Powder	7
Color	White	7
Molecular Weight g/mol	>10,000	7
Bulk Density kg/m ³ @ 25 °C	237	7
Melting Point °C	>250 (decomposition)	7
Water Solubility g/L @ 20°C	200	7
Ammonium Acryloyldimethyltaurate/VP Copolymer		
Physical Form	Powder	6
Color	White	6
Molecular Weight g/mol	>1000	6
Bulk Density kg/m ³	230	6
Water Solubility g/L @ 20°C	>5	6

Table 3. Chemical and physical properties of acryloyldimethyltaurate polymers.

Property	Value	Reference
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer		
Physical Form	Viscous liquid	11
Color	White	11
Odor	Characteristic	11
Molecular Weight g/mol	>10,000	11
Bulk Density g/kg @ 25°C	1100	11
Melting Point °C	6	11
Water Solubility	Dispersible	11
Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer		
Molecular Weight g/mol	>10,000	10
Density/Specific Gravity kg/m ³ @ 25°C	1100	10
Melting Point °C	>200	10
Sodium Polyacryloyldimethyl Taurate		
Molecular Weight g/mol	>1,000,000	9

Table 4. Frequency of use according to duration and exposure of acryloyldimethyltaurate polymers.¹⁵⁻¹⁷

Use type	Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)	
Uses			Uses			Uses		
	Acrylamide/Sodium Acryloyldimethyltaurate Copolymer		Ammonium Acryloyldimethyltaurate /Beheneth-25 Methacrylate Crosspolymer		Ammonium Acryloyldimethyltaurate /Carboxyethyl Acrylate Crosspolymer		Ammonium Acryloyldimethyltaurate/ Steareth-25 Methacrylate Crosspolymer	
Total/range	227	0.34-3.2	56	0.1-2.5	1	NR	2	0.6-1.3
<i>Duration of use^a</i>								
Leave-on	220	0.34-3.2	54	0.1-2.5	NR	NR	2	0.6-1.3
Rinse-off	7	0.38-1.6	2	0.2-0.75	1	NR	NR	1
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
<i>Exposure type</i>								
Eye area	41	0.71-1.8	13	0.4-0.66	NR	NR	NR	0.8-0.94
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	1; 104 ^b ; 38 ^c	0.47-1.5 ^b	13 ^b ; 23 ^c	0.2; 0.1-0.5 ^b	NR	NR	2 ^b	NR
Incidental inhalation-powders	4; 38 ^c	0.7; 0.54-1.8 ^d	23 ^c	0.3-2.5 ^d	NR	NR	NR	0.6 ^d
Dermal contact	219	0.34-3.2	50	0.1-2.5	1	NR	2	0.6-1.3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	6	0.47-1.7	NR	0.5-0.8	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	0.2	NR	NR	NR	1
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

Table 4. Frequency of use according to duration and exposure of acryloyldimethyltaurate polymers.¹⁵⁻¹⁷

Use type	Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)	
	Uses		Uses		Uses		Uses	
	Ammonium Acryloyldimethyltaurate/ Steareth-8 Methacrylate Copolymer		Ammonium Acryloyldimethyltaurate /VP Copolymer		Ammonium Polyacryloyldimethyl Taurate		Dimethylacrylamide/ Sodium Acryloyldimethyltaurate Crosspolymer	
Total/range	1	0.42-0.65	584	0.016-3	187	0.015-2.3	10	0.06-3
<i>Duration of use</i>								
Leave-on	1	0.42-0.65	524	0.016-3	178	0.015-2.3	9	0.06-3
Rinse-off	NR	NR	60	0.3-1.8	9	0.078-1.5	1	3
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
<i>Exposure type</i>								
Eye area	NR	0.42	66	1.4-3	22	0.025-2	4	1-2
Incidental ingestion	NR	NR	2	1.5	NR	NR	NR	NR
Incidental Inhalation-sprays	1 ^b	NR	1; 199 ^b ; 205 ^c	0.096-1; 0.4 ^b	64 ^b ; 57 ^c	1.2 ^b	2 ^b ; 3 ^c	0.35-3; 0.72 ^b
Incidental inhalation-powders	NR	0.65 ^d	1; 1 ^d ; 205 ^c	0.18-2 ^d	1; 57 ^c	0.024-2 ^d	3 ^c	0.65-3 ^d
Dermal contact	1	0.42-0.65	579	0.016-3	187	0.015-2.3	10	0.06-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.6 ^e
Hair-noncoloring	NR	NR	NR	0.4	NR	1.2	NR	0.72
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	5	1.5	2	1.2	NR	NR
Baby	NR	NR	1	NR	NR	NR	NR	NR

	HEA/Sodium Acryloyldimethyltaurate/ Steareth-20 Methacrylate Copolymer		Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer		Sodium Acrylate/ Acryloyldimethyltaurate /Dimethylacrylamide Crosspolymer		Sodium Acrylate/Sodium Acryloyldimethyl Taurate Copolymer	
Total/range	NR	0.18	541	0.15-4.3	3	1.6	197	0.023-3.2
<i>Duration of use</i>								
Leave-on	NR	0.18	516	0.15-3.6	3	1.6	190	0.023-2.4
Rinse-off	NR	NR	22	0.2-4.3	NR	NR	7	0.6-3.2
Diluted for (bath) use	NR	NR	3	NR	NR	NR	NR	NR
<i>Exposure type</i>								
Eye area	NR	NR	37	0.15-3.6	NR	NR	22	0.18-1.2
Incidental ingestion	NR	NR	11	1.4	NR	NR	1	NR
Incidental Inhalation-sprays	NR	NR	1; 238 ^b ; 153 ^c	0.38-1 ^b	3 ^b	NR	47 ^b ; 86 ^c	0.45-0.6 ^b
Incidental inhalation-powders	NR	NR	3; 153 ^c	0.19-2.9 ^d	NR	NR	5; 1 ^d ; 86 ^c	0.088-1.1 ^d
Dermal contact	NR	NR	514	0.15-4.3	2	NR	188	0.023-2.4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	0.18	11	0.74	1	1.6	6	0.6-3.2
Hair-coloring	NR	NR	NR	0.94-1.4	NR	NR	NR	2.3
Nail	NR	NR	3	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	19	0.2-1.4	NR	NR	1	2.4
Baby	NR	NR	NR	NR	NR	NR	1	NR

Table 4. Frequency of use according to duration and exposure of acryloyldimethyltaurate polymers.¹⁵⁻¹⁷

Use type	Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)	
	Uses		Uses		Uses		Uses	
	Sodium Acrylate/Sodium Acryloyldimethyl Taurate/Acrylamide Copolymer		Sodium Acryloyldimethyl Taurate/Acrylamide/VP Copolymer		Sodium Acryloyldimethyltaurate /Methacrylamidolauric Acid Copolymer		Sodium Acryloyldimethyltaurate/ VP Crosspolymer	
Total/range	6	0.3-1.5	NR	0.65	NR	0.28-0.35	8	NR
<i>Duration of use</i>								
Leave-on	6	0.3-1.5	NR	0.65	NR	0.28-0.35	8	NR
Rinse-off	NR	0.3	NR	NR	NR	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
<i>Exposure type</i>								
Eye area	NR	0.58-0.75	NR	NR	NR	NR	1	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	1 ^b , 1 ^c	NR	NR	0.65 ^b	NR	NR	4 ^b , 3 ^c	NR
Incidental inhalation-powders	1 ^c	0.3-1.5 ^d	NR	NR	NR	0.28-0.35 ^d	3 ^c	NR
Dermal contact	6	0.3-1.5	NR	0.65	NR	0.28-0.35	8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	1.2	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

	Sodium Polyacryloyldimethyl Taurate	
Total/range	55	1.4
<i>Duration of use</i>		
Leave-on	49	1.4
Rinse-off	6	NR
Diluted for (bath) use	NR	NR
<i>Exposure type</i>		
Eye area	NR	NR
Incidental ingestion	NR	NR
Incidental Inhalation-sprays	40 ^b , 6 ^c	NR
Incidental inhalation-powders	6 ^c	1.4 ^d
Dermal contact	55	1.4
Deodorant (underarm)	NR	NR
Hair-noncoloring	NR	NR
Hair-coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
^a Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
^b It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
^c Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
^d It is possible these products may be powders, but it is not specified whether the reported uses are powders.
^e Not sprays.

Table 5. Acryloyldimethyltaurate polymers with no reported uses.¹⁵⁻¹⁷

Acrylamide/Sodium Acryloyldimethyltaurate/ Acrylic Acid Copolymer	Ammonium Acryloyldimethyltaurate/Laureth-7 Methacrylate Copolymer
Ammonium Acryloyldimethyltaurate/Vinyl Formamide Copolymer	Sodium Acryloyl Dimethyl Taurate/PEG-8 Diacrylate Crosspolymer

Table 6. Acute toxicity data on acryloyldimethyltaurate polymers.

Ingredient	Animal; Methods	Results	Reference
Dermal			
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 24%)	Rats (strain and n not specified); OECD TG 402	LD ₅₀ >5000 mg/kg (>1200 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer)	12
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 25% to 27%).	Rats (strain and n not specified); 24 h exposure under patch.)	No deaths. All rats gained weight and there were no clinical signs (gross toxicity, dermal irritation, adverse pharmacologic effects, or abnormal behavior). Necropsy was unremarkable. LD ₅₀ >5000 mg/kg (>1250 to >1350 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer)	26
Oral			
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 24%)	Rats (strain and n not specified); OECD TG 425	LD ₅₀ >5000 mg/kg (>1200 mg/kg polymer)	12
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 25% to 27%)	Rats (strain and n not specified); method not specified	LD ₅₀ >5000 mg/kg (>1250 to >1350 mg/kg Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer)	26
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer	HanRcc:WIST (SPF) Rats (n=3); OECD TG 423	LD ₅₀ >2000 mg/kg; 5 h after treatment, 3 rats showed slight ruffled fur; no other clinical signs were observed and no macroscopic findings were observed at necropsy. Body weight of the rats was within range commonly recorded for this strain and age.	7
Ammonium Acryloyldimethyltaurate/VP Copolymer	Rats; OECD TG 401	LD ₅₀ >2000 mg/kg	6
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (trade name mixture containing ingredient at <60%)	Rats (strain and n not specified); method not specified	LD ₅₀ >2000 mg/kg (>1200 mg/kg)	11

OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 7. In vitro genotoxicity assays of acryloyldimethyltaurate polymers.

Ingredient	Assay/Method	Results	Reference
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 24%; assumed applied neat, not specified)	Bacterial reverse mutation assay (OECD TG 471)	Not mutagenic	12
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 25% to 27%; applied at 2.5, 7.5, 25, 75, 200, 600, 1800, and 5000 µg/plate and at 75, 200, 600, 1800, and 5000 µg/plate)	Ames test. <i>S. typhimurium</i> (TA98, TA100, TA1535, and TA1537) and <i>E. coli</i> (WP2uvrA)	Not mutagenic up to 5000 µg/plate (1250 to 1350 µg/plate Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer) with and without metabolic activation	26
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer (concentration not provided)	Bacterial reverse mutation assay (OECD TG 471) <i>S. typhimurium</i> (TA98, TA100, TA1535, and TA1537) and <i>E. coli</i> (WP2uvrA)	Not mutagenic up to 2000 µg/plate with and without metabolic activation	7
Ammonium Acryloyldimethyltaurate/VP Copolymer (concentration not provided)	Bacterial reverse mutation assay (OECD TG 471)	Not mutagenic	6
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (trade name mixture at <60%; concentration not provided)	Bacterial reverse mutation assay;	Not mutagenic	11
Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (trade name mixture at <45%; assumed applied neat, not specified)	Bacterial reverse mutation assay (OECD TG 471)	Not mutagenic or cytotoxic up to 5000 µg/plate (<2250 µg/plate Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer)	10

OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 8. Dermal irritation studies of acryloyldimethyltaurate polymers in rabbits.

Ingredient (concentration)	Animal; method	Results	Reference
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 24%; assumed applied neat, not specified)	Rabbits (n and strain not specified); primary skin irritation test	Exhibited very slight to well-defined erythema and very slight edema 1 h after patch removal. All signs of dermal irritation were resolved at 48 h after patch removal. The PII according to Draize score was 1.2.	12
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution at 25% to 27%)	Rabbits (n and strain not specified); method not specified	US EPA: minimal irritant; OECD TG: Nonirritant	26
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer (100% moistened with water when administered)	New Zealand White rabbit (n=3); OECD TG 404	Mild signs of irritation (erythema formation) observed in all rabbits; no longer evident at day 7 after treatment.	7
Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed neat, not specified)	Rabbit (n and strain not specified); OECD TG 404	Not irritating	6

OECD TG = Organization for Economic Co-operation and Development Test Guideline

PII = Primary Irritation Index

Table 9. Sensitization studies of acryloyldimethyltaurate polymers.

Ingredient (concentration)	Assay; n	Results	Reference
Animal			
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer (25% in petrolatum)	Buehler Test OECD TG 406 in Pirbright-White guinea pigs/HsdPoc:DH; n=19; control=10	Not sensitizing	7
Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed neat, not specified)	OECD TG 406 in guinea pigs; n and strain not specified	No signs of irritation or sensitization	6
Human			
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 24%; assumed applied neat, not specified)	HRIPT; n not specified	No evidence of sensitization.	12
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (25% to 27% in water)	HRIPT; n=102	Not sensitizing	26
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (in a trade name mixture at <60%; assumed administered neat, not specified)	Not specified; not specified	Not sensitizing	11
Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (<2.25%; in a trade name mixture at <45%; tested at 5% in water)	HRIPT; n=50	One reaction of erythema/edema was observed in 1 subject on Day 40.	10
Sodium Polyacryloyldimethyl Taurate (30% to 40%)	HRIPT; n=100	No adverse reactions were observed during the study. Not irritating or sensitizing.	9

HRIPT = Human repeated insult patch test.

Table 10. *In vitro* and animal ocular irritation assays.

Ingredient (concentration)	Animal; method	Results	Reference
<i>In vitro</i>			
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer (trade name mixture <60%; assumed applied neat, not specified)	Not specified	Not an ocular irritant	11
Sodium Acrylate/Acryloyldimethyltaurate/Dimethylacrylamide Crosspolymer (<2.25%; in a trade name mixture at <45%; tested at 5% in water)	HET-CAM	No signs of hyperemia, hemorrhage, or coagulation were observed in any of the membranes tested. The test substance was not considered an eye irritant.	10
<i>Animal</i>			
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (aqueous solution containing ingredient at 24%; assumed tested neat, not specified)	Rabbit eyes (n and strain not specified); OECD TG 405	Not irritating	12
Acrylamide/Sodium Acryloyldimethyltaurate/Acrylic Acid Copolymer (solution containing 25% to 27% in water)	Rabbit eyes (n and strain not specified); primary eye irritation test	After a single instillation, no corneal opacity or iritis was noted for any treated eye during the study. ~1 h after instillation, conjunctivitis was observed in all treated eyes. All signs of ocular irritation were resolved by 48 h. US EPA scoring: Minimal irritant; OECD TG scoring: nonirritant.	26
Ammonium Acryloyldimethyltaurate/Carboxyethyl Acrylate Crosspolymer (assumed tested neat, not specified)	New Zealand White rabbit eyes (n=3); OECD TG 405	Slight to moderate reddening and slight swelling of the conjunctivae in all rabbits at 1 h; resolved 72 h after treatment. It was concluded that this polymer is slightly irritating to the eye.	7
Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed tested neat, not specified)	Rabbit eyes (n and strain not specified); OECD TG 405	Not irritating	6

HET-CAM = Hens Eggs test-Chorio-Allantoic Membrane

OECD TG = Organization for Economic Co-operation and Development Test Guideline

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

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Release Date: October 2, 2014
Panel Date: September 8-9, 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.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR 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.

ABSTRACT: These styrene and vinyl-type styrene copolymers function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products. After considering the large sizes of these molecules, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of toxicity tests provided the Panel with a sufficient basis to assess the safety of these polymers as used in cosmetics. The Panel concluded that the 35 styrene and vinyl-type styrene copolymers are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment.

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 include opacifying agent and viscosity increasing agent. Given the toxicity of two of the component monomers present in styrene and vinyl-type styrene copolymers, styrene and 1,3-butadiene, carcinogenicity data on these monomers are included. Styrene is a component of all of the copolymers reviewed in this safety assessment; however, butadiene monomer is a component of only three copolymers included in this review.

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.¹ 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.

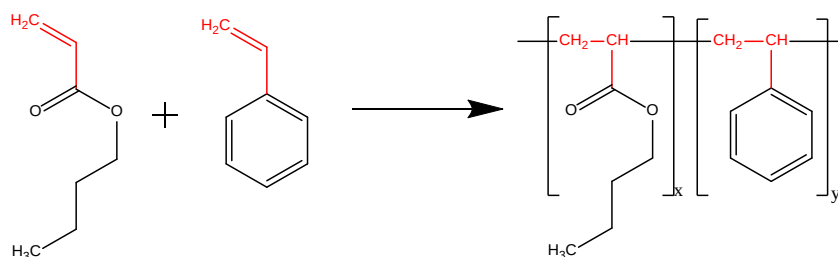


Figure 1. Butylacrylate/Styrene Copolymer

These ingredients are high molecular weight, large molecular volume, and 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 1.²

Physical and Chemical Properties

Polystyrene

Properties of polystyrene are presented in Table 2.^{3,4,5} 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.⁶ Reportedly, the principal limitations of polystyrene in industry are brittleness, inability to withstand the temperature of boiling water, and poor oil resistance.⁷ 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 copolymer.

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.⁸ 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-*t*-butylcatechol). Additionally, upon exposure to light and air, styrene undergoes polymerization and oxidation, with the formation of peroxides.⁴ Additional properties of styrene are presented in Table 3.⁴

Styrene-Butadiene Copolymer

Properties of styrene-butadiene copolymer are presented in Table 4.⁵

1,3-Butadiene

Properties of 1,3-butadiene are presented in Table 5.⁹

Composition/Impurities

Polystyrene

Polystyrene is available in the United States in a variety of grades, and the following are considered major grades:⁵ (1) 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%.¹⁰ Composition/impurities data from a 2013 safety dossier on a polystyrene trade name material summarized in Table 6 indicates that the residual monomer content of polystyrene is < 5 ppm. Furthermore, data summarized in Table 6 indicate that other styrene and vinyl-type styrene copolymer trade name materials contain styrene monomer at levels of < 100 ppm or less.

Styrene-Butadiene Copolymer

The following styrene-butadiene copolymers are available in the United States:⁵ (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.

Trade Name Materials

Composition/impurities data on styrene and vinyl-type styrene copolymer trade name materials included in this safety assessment are presented in Table 6. Data on properties of these trade name materials are also included.

Methods of Production

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer

The ethylene/propylene/styrene copolymer and butylene/ethylene/styrene copolymer used as thickeners are made by anionic polymerization, which results in little or no residual monomer in the polymer.¹¹

Polystyrene

Polystyrene is produced from styrene by mass, solution, suspension, or emulsion polymerization processes.⁷ Polystyrene resins are typically produced by a modified mass polymerization process in a continuous manner.⁵ 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.⁵ 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:⁵ butadiene (70), styrene (30), water (180), fatty acid soap (2.25), disproportioned rosin soap (2.25), potassium chloride (0.3), potassium hydroxide (0.3), *t*-dodecyl mercaptan (0.23), sodium formaldehyde β -naphthalene sulfonate (0.04), sodium formaldehyde sulfoxylate (0.04), *p*-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:⁵ 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.⁵ 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.⁵ 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.²

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).¹² 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, in skin care preparations) to 36.5% (polystyrene, in skin cleansing products) were reported.¹³ The highest maximum reported use concentrations for rinse-off and leave on products were 36.5% (polystyrene) and 35% (styrene/acrylates copolymer, in basecoats and undercoats), respectively. Ingredient frequency of use and concentration data are presented in Table 7.

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 these ingredients 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.^{14,15,14,16} 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.^{14,15}

Noncosmetic

Polystyrene

Polystyrene is used as a plasticizer in the bottled water industry, and studies have shown that styrene leaches continuously from polystyrene bottles.¹⁷ The skin adhesive layer of a pressure ulcer preventive dressing may contain styrene block copolymer as an adhesive compound.¹⁸ Polystyrene foam is widely used for thermal insulation.⁷

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.¹⁹ 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.²⁰ 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.²¹

TOXICOKINETICS

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 $1 \pm 0.5 \mu\text{g}/\text{cm}^2/\text{minute}$.^{22,23}

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.²² 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.²² However, based on the measurement of urinary metabolites, there was no styrene accumulation in workers exposed to 37 ppm (160 mg/m³) styrene in air during the work week.

Styrene is primarily metabolized to styrene 7,8-oxide by cytochrome P450 (CYP) enzymes.²² 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, phenylacetic acid, and hippuric acid. Styrene 7,8-oxide may also be metabolized by conjugation with glutathione to form mercapturic acids. The conversion of styrene to mercapturic acids, considered a minor pathway in humans, is < 1% of the absorbed dose of styrene.²⁴

Small amounts of styrene (0.7% to 4.4%) are exhaled unchanged.²² This finding has been confirmed in additional studies 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/m³) 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/m³]) was studied using 4 volunteers.^{22,25} 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 half-life of blood styrene was 3.9 h at 16 h after the end of the workshift.

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.²⁶

Mice and rats were exposed (dynamic flow exposure: 2 h [mice] and 4 h [rats]) to butadiene or styrene vapors at the following concentrations: 270 mg/liter (butadiene [mice]), 285 mg/liter (butadiene [rats]), 21 mg/liter (styrene [mice]), and 11.8 mg/liter (styrene [rats]).^{26,27} The number, strain, and sex of the animals tested were not specified. Following exposure, the concentrations of butadiene and styrene in tissues 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:^{26,27}

- 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.⁹ 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 (EH). 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

Composition data on copolymer trade name mixtures evaluated in toxicity tests are included in Table 6.

Acute Inhalation Toxicity

Styrene/Acrylates Copolymer

In an acute inhalation toxicity study on SunspheresTM Powder, an LC₅₀ of > 5.3 mg/L was reported. The test protocol was not provided.²⁸

An acute inhalation LC₅₀ (4 h) value of > 5.11 mg/L air was reported for ACUDYNETM Shine Polymer and ACUDYNETM Bold Polymer.^{29,30} The test protocol was not described. The animal species was not stated, but it was noted that no clinical signs or mortalities were observed.

1,3-Butadiene and Styrene

Mice and rats were exposed (dynamic flow exposure: 2 h [mice] and 4 h [rats]) to butadiene or styrene vapors.^{26,27} The number, strain, and sex of the animals tested were not specified. LC₅₀ values were: 270 mg/liter (butadiene [mice]), 285 mg/liter (butadiene [rats]), 21 mg/liter (styrene [mice]), and 11.8 mg/liter (styrene [rats]).

Acute Oral Toxicity

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A trade name mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in an acute oral toxicity study.³¹ The mixture was fed in large doses to male and female rats (number of animals not stated). Details relating to the test protocol were not included. The estimated acute oral LD₅₀ was > 5,050 mg/kg (nontoxic). It was noted that this finding was expected because the primary ingredient of the trade name mixture is white mineral oil.

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was evaluated in an acute oral toxicity study involving rats, and an LD₅₀ of > 5 ml/kg was reported. The test protocol was not stated.³²

An oral LD₅₀ of > 2,000 mg/kg body weight (rats) for Syntran® 5903 was reported in a study performed according to OECD guideline n°423.³³ There were no effects on body weight change, and no clinical and behavioral signs or mortalities were observed after dosing. In a toxicological assessment certificate on Syntran® 5907 (another styrene acrylates copolymer trade name material), it was noted that the acute oral toxicity data on Syntran® 5903 can be extrapolated to Syntran® 5907.³⁴ Similarly, in toxicological assessment reports on Syntran® 5904 and Syntran® 5905 it was determined that the acute oral toxicity study results for Syntran® 5903 are applicable to Syntran® 5904 and Syntran® 5905.^{35,36}

Acute Dermal Toxicity

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was evaluated in an acute dermal toxicity study involving rats, and an LD₅₀ of > 5 g/kg was reported. The test protocol was not stated.³²

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).³⁷ 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/m³, 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/m³. Mild to moderate pulmonary inflammation, which resolved during the recovery period, was observed in the 1.0 mg/m³ exposure group. Exposure to 10 mg/m³ (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/m³ 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/m³, respectively.³⁸

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/m³. Lung nodules were observed in 1 male and 3 females exposed to 0.2 mg/m³. The numbers of pulmonary nodules were even higher in the 0.8 mg/m³ 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.^{29,30} 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/m³, based on slight irritant effects in the lungs at a concentration of 100 mg/m³.

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/m³.^{29,30}

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 of dogs.³⁹ 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. The principal study that served as the basis for the oral RfD is summarized below.

Four beagle dogs/sex were gavaged with doses of 0, 200, 400, or 600 mg styrene/kg bw/day in peanut oil for 560 days.⁴⁰ No adverse effects were observed for dogs administered styrene at 200 mg/kg-day. In the higher dose groups, increased numbers of Heinz bodies in the RBCs, decreased packed cell volume, and sporadic decreases in hemoglobin and RBC counts were observed. Additionally, increased iron deposits and elevated numbers of Heinz bodies were found in the livers. Marked individual variations in blood cell parameters were noted for animals at the same dose. Other parameters examined were body weight, organ weights, urinalyses, and clinical chemistry. The NOAEL in this study was 200 mg/kg-day and the LOAEL was 400 mg/kg-day.

Ocular Irritation

Non-Human

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in an ocular irritation study involving albino rabbits (number of animals not stated).⁴¹ Details relating to the test protocol were not included. The mixture was not a primary ocular irritant in this study. It was noted that, under EPA Guideline No. 81-4, this mixture was “minimally irritating” in rinsed and unrinsed eyes. Additionally, the minimal irritation observed was reversible and the material was assigned to Category IV, EPA’s lowest toxicity category for ocular irritation.

Styrene/Acrylates Copolymer

In the embryonic hen’s egg chorioallantoic membrane (HET-CAM) assay, a 5% dilution of Syntran® 5903 in distilled water was classified as a weak irritant.^{42,33} In this test system, the hen’s egg chorioallantoic membrane

was treated with the test material for 20 seconds and the following endpoints were evaluated: hyperemia, hemorrhage, and coagulation (including opacity and thrombosis).

Sunspheres™ Powder was classified as minimally irritating to the eyes of rabbits.²⁸ The test protocol was not stated.

In an ocular irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-irritant. The test protocol was not stated.³²

Human

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.⁴³

In Vitro

Polyacrylate-15, Polyacrylate-18, Polyacrylate-19, and Polyacrylate-21

In the *in vitro* EpiOcular™ ocular irritation screening assay, the following copolymers were classified as non-irritating to the eye: polyacrylate-15 (Syntran® PC 5208),⁴⁴ polyacrylate-18 and polyacrylate-19 mixtures (Syntran® PC 5117 and Syntran® PC 5107),^{45,46} and a product (100.58BM) closely related to polyacrylate-21 (Syntran® PC 5100CG).⁴⁷

Styrene/Acrylates Copolymer

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.²⁹

ACUDYNE™ Bold Polymer was classified as a non-irritant in the bovine corneal opacity and permeability test *in vitro*.³⁰ The test protocol was not stated.

Skin Irritation and Sensitization

Non-Human

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in a skin irritation study involving albino rabbits (number of animals not stated).⁴⁸ Details relating to the test protocol were not included. The material was not a primary skin irritant in this study. It was noted that the descriptive rating (under EPA Guideline No. 81-5) for this mixture was “slightly irritating”, the lowest descriptive rating possible. Additionally, because this slight irritation was reversible, the trade name material was assigned to the EPA’s lowest toxicity category (Category IV) for dermal irritation.

Styrene/Acrylates Copolymer

In a skin irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-irritant. The test protocol was not stated.³²

The skin irritation potential of ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer was evaluated in the EpiDermal *in vitro* assay.^{29,30} The test protocol was not stated. Results were negative.

Styrene/Acrylates Copolymer and Polystyrene

Syntran® 5903 (undiluted) was classified as a non-sensitizer in a guinea pig sensitization test, performed according to OECD guideline n°406.^{42,33} Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-sensitizers.^{42,35,34,36}

ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were classified as non-sensitizers in the mouse local lymph node assay.^{29,30} The test protocol was not stated.

Styrene and Methylstyrene

The skin sensitization potential of styrene was evaluated in the guinea pig maximization test (15 guinea pigs).⁴⁹ 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 and Polystyrene

Syntran® 5903 (5% in distilled water) was classified as having good skin compatibility in 10 volunteers patch tested (single application patch test). Study details were not provided.^{42,33} No signs of irritation were recorded, and observations throughout the test interval were within normal limits. Based on these results for Syntran® 5903, Syntran® 5904 (another styrene acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-irritants.^{42,35,34,36}

Styrene/Acrylates Copolymer

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.³²

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.⁵⁰

Styrene and Methylstyrene

Styrene (5% w/v in petrolatum) was evaluated in a skin sensitization study involving 303 patients (diagnoses not stated).⁴⁹ 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.

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in a human repeated insult patch test involving 117 subjects.⁵¹ Details relating to the test protocol were not included. The subjects were evaluated for redness, swelling, “flares” and itching. The mixture did not induce allergic contact dermatitis in any of the subjects. It was noted that this conclusion was confirmed by a board-certified dermatologist.

In Vitro

Styrene/Acrylates Copolymer and Polystyrene

In the embryonic hen's egg chorioallantoic membrane (HET-CAM) assay, a 5% dilution of Syntran® 5903 in distilled water was classified as a weak irritant.^{42,33} In this test system, the hen's egg chorioallantoic membrane was treated with the test material for 20 seconds and the following endpoints were evaluated: hyperemia, hemorrhage, and coagulation (including opacity and thrombosis). Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were also classified as weakly irritating to the chorioallantoic membrane.^{42,35,34,36} Based on the minimal irritation potential of Syntran® 5903 in the HET-CAM assay (generally used to evaluate ocular irritation potential), it was concluded that it is not likely that this trade name material, or the other trade name materials, would produce dermal irritation.

Polyacrylate-15, Polyacrylate-18, Polyacrylate-19, and Polyacrylate-21

Based on negative results in the *in vitro* EpiOcular™ ocular irritation screening assay (see Ocular Irritation section), it is expected that the following copolymers would not produce dermal irritation: polyacrylate-15 (Syntran® PC 5208),⁴⁴ polyacrylate-18 and polyacrylate-19 mixtures (Syntran® PC 5117 and Syntran® PC 5107),^{45,46} and a product (100.58BM) closely related to polyacrylate-21 (Syntran® PC 5100CG).⁴⁷

Polyacrylate-15

In a cosmetic ingredient safety dossier on Syntran® PC 5208, skin irritation data on this trade name material were not included.⁴⁴ However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on Syntran® PC 5208 indicates that this trade name material is not likely to produce skin sensitization, since skin is less susceptible to irritation than eye tissue.

Polyacrylate-18 and Polyacrylate-19 (mixture)

Skin irritation data were not included in a cosmetic ingredient safety dossier on polyacrylate-18 and polyacrylate-19 (Syntran® PC 5117).⁴⁵ However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on a closely related product (Syntran® 5100, composition not stated) indicates that Syntran® PC 5117 is not likely to produce dermal sensitization, since skin is less susceptible to irritation than eye tissue. These statements are also applicable to Syntran® PC 5107 (polyacrylate-18 and polyacrylate-19).⁴⁶

Polyacrylate-21

In a cosmetic ingredient safety dossier on polyacrylate-21 (Syntran® PC 5100CG), skin irritation data on this trade name material were not included.⁴⁷ However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on a closely related product (100.58BM, composition data not provided) indicates that Syntran® PC 5100CG is not likely to produce dermal sensitization, since skin is less susceptible to irritation than eye tissue.

Case Reports

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).⁴⁹ 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 methyl 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).⁵² 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.⁵³ In developmental toxicity studies in rats and rabbits, the highest exposure concentration/dose on gestation days 6-15 (600 ppm by inhalation or 300 mg/kg body weight/day by oral dosing) did not have any observable adverse effects on fetuses. Rats and rabbits were used in inhalation studies, and rats only were involved in the oral dosing study. 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 from 70 days prior to mating through gestation day 20. 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, a subset of animals (COBS (SD) BR rats) from a 2-year chronic toxicity study in which 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) were used. The parental generations were cohabited after 90 days on study. 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.⁵³

1,3-Butadiene

The following reproductive toxicity study summaries are included in the 1984 NTP report on the toxicology and carcinogenesis of 1,3-butadiene.²⁶ The fertility of rats was not severely impaired when they were exposed (via 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 (via inhalation) to 1,3-butadiene for 4 months at 45 ppm, increased embryonic mortality and teratogenesis were reported.

Pregnant female Sprague-Dawley rats exposed (via inhalation) to 1,3-butadiene at concentrations of 0, 200, 1,000, or 8,000 ppm for 6 hours per day during days 6-15 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.²⁶

GENOTOXICITY

Styrene/Acrylates Copolymer and Polystyrene

In the Ames test (OECD guideline n°471), Syntran® 5903 (doses up to 5,000 µg/plate) was non-genotoxic with and without metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and in *Escherichia coli* strains WP2, pKM101, and uvr A^{42,33}. Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-genotoxic.^{42,35,34,36}

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 TA1535.⁵⁴ 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.

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was not genotoxic in the Ames test, with or without metabolic activation. The test protocol was not stated.³² This trade name material also was not genotoxic in the *in vitro* cytogenetic assay, with or without metabolic activation (test protocol not stated).

In the Ames test, ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were not genotoxic.^{29,30} Negative results were also reported for these 2 trade name materials in the chromosomal aberrations test *in vitro* (test protocol not stated).

OPULYN™ 301 Opacifier was not genotoxic in the Ames test, with or without metabolic activation.⁵⁰ This trade name material also was not genotoxic in the *in vitro* cytogenetic assay, with or without metabolic activation (test protocol was not stated.).

Polyacrylate-18 and Polyacrylate-19 (mixture)

Syntran® PC 5117 (polyacrylate-18 and polyacrylate-19) was evaluated for genotoxicity in the Ames test at doses up to 5,000 µg/plate using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2 uvrA. Results were negative with and without metabolic activation.⁴⁵ These statements are also applicable to Syntran® PC 5107 (polyacrylate-18 and polyacrylate-19).⁴⁶

Polyacrylate-21

Syntran® PC 5100 (mixture of polyacrylate-21 and acrylates/dimethylaminoethyl methacrylate copolymer)² was evaluated for genotoxicity in the Ames test at doses up to 5,000 µg/plate using the following bacterial strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2 uvrA. Results were negative with and without metabolic activation.⁴⁷ Genotoxicity data on polyacrylate-21 (Syntran® 5100CG) were not provided, and data on a closely related product (Syntran® PC 5100) were used to evaluate the genotoxicity of Syntran® 5100CG. It was noted that negative results would be expected for Syntran® 5100CG.

Polyacrylate

The genotoxicity of polyacrylate (polymer of acrylic acid and sodium acrylate) was evaluated in the following assays:³⁷ 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.

CARCINOGENICITY

Information relating to the carcinogenicity of styrene and vinyl-type styrene copolymers and component monomers is presented in Table 8. Particularly, 1,3-butadiene and styrene monomer components have been classified as carcinogenic. In addition to the information presented in Table 8, a committee of the National Research Council (NRC) conducted a scientific peer review of the styrene assessment presented in the *12th Report on Carcinogens* (RoC). The committee found that the overall conclusion reached by the NTP in 2011, that styrene is “reasonably anticipated to be a human carcinogen”, is appropriate.⁵⁵

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

OTHER EFFECTS

Hormonal Activity

Polystyrene

The estrogenic (uterotrophic) activity of low molecular weight polystyrene (identified as F2L5250) was studied in the Tiecco test using groups of 10 weanling female Wistar outbred rats (HsdCpb:WU strain).⁵⁷ The test substance was fed to 5 groups at the following dietary concentrations, respectively, during a 4-day period: 10 ppm, 20 ppm, 40 ppm, 80 ppm, and 160 ppm. The control group was fed standard diet only. Diethylstilbesterol (DES) served as the positive control. The mean absolute and relative uterine weights of the treatment groups were used for qualitative and quantitative assessment of possible uterotrophic activity. There were no significant differences in mean absolute and relative uterus weights between the control group and the 10 ppm, 20 ppm, 40 ppm, or 80 ppm group. However, significant and dose-related increases in mean absolute and relative uterus weights were observed in the 160 ppm group and in groups fed 5 ppb, 10 ppb, and 20 ppb DES, respectively. The results of this study indicated that the highest no-effect-level for estrogenic activity was 80 ppm polystyrene in the diet, which corresponded to a daily intake of 13.3 mg polystyrene/kg body weight. It was noted that 100 ppm polystyrene induced the same level of estrogenic activity as 5 ppb DES. It was concluded that the potency (estrogenic activity) of low molecular weight polystyrene (F2L5250) was a factor of 20,000 less than that of DES.

SUMMARY

The safety of 35 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 obtained from FDA’s VCRP in 2014. 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.

Data provided by industry indicate that styrene and vinyl-type styrene copolymer trade name materials contain styrene monomer at levels of < 100 ppm or less.

The absorption of styrene was low (averaging 1 $\mu\text{g}/\text{cm}^2/\text{minute}$) 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 the percutaneous absorption of styrene was not an important contribution to the body burden. 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 oxidation 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. The particle size (MMAD) used in this study was 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.

The 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. Polyacrylates were 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 carcinogenicity 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 EPA and IARC have also classified styrene as possibly carcinogenic to

humans. A committee of the NRC conducted a scientific peer review of the styrene assessment presented in the NTP 12th Report on Carcinogens, and concluded that the overall conclusion reached by the NTP is appropriate.

In NTP inhalation carcinogenicity studies, 1,3-butadiene was carcinogenic in B6C3F₁ mice at concentrations ≥ 20 ppm (male mice) and ≥ 6.25 ppm (female mice). 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 EPA and IARC have concluded that 1,3-butadiene is carcinogenic in humans by inhalation exposure.

The IARC 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 NTP's *Report on Carcinogens*, but have not yet been approved for formal review.

With certain exceptions, results were negative in the following toxicity tests on styrene and vinyl-type styrene copolymers reviewed in this safety assessment: acute inhalation, acute oral, acute dermal, ocular irritation, skin irritation, skin sensitization, and genotoxicity. The exceptions include: In an *in vitro* skin irritation test, styrene/ acrylates copolymer (Syntran® PC5903) was classified as a weak irritant. Styrene/acrylates copolymer (Sunspheres™ powder) was minimally irritating to the eyes of rabbits. In a 2-week aerosol (nose-only) study on 2 styrene/acrylates copolymer trade name materials (Acudyne™ Bold Polymer and Acudyne™ Shine Polymer), a slight irritant effect on the lungs was noted at a concentration of 100 mg/m³. In light of these findings, it should be noted that a 13-week aerosol (nose-only) study on these 2 trade name materials yielded an NOAEL of 8.3 mg/m³.

Low molecular weight polystyrene was found to have estrogenic (uterotrophic) activity in rats fed a dietary concentration of 160 ppm during a 4-day period.

DISCUSSION

After considering the large sizes of these molecules, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of toxicity tests provided the Panel with a sufficient basis to assess the safety of these polymers as used in cosmetics. Styrene monomer, a component of all of the copolymers reviewed in this safety assessment, and 1,3-butadiene monomer are classified as carcinogenic in animals and in humans. Taking into consideration ingredient use concentrations and the data on residual monomer content, the Panel agreed that levels of residual styrene or 1,3-butadiene in cosmetic products would be substantially below levels of concern.

The Panel also discussed the potential for incidental inhalation exposures to these ingredients in products that are sprayed or in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone, ingredient use concentrations, and negative results in toxicity tests, incidental inhalation would not lead to local respiratory effects or systemic effects.

CONCLUSION

The CIR Expert Panel concluded that the following 35 ingredients are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment.

Ethylene/Propylene/Styrene Copolymer	Sodium Styrene/Acrylates Copolymer
Butylene/Ethylene/Styrene Copolymer	Sodium Styrene/Acrylates/Ethylhexyl
Acrylates/Ethylhexyl Acrylate/Styrene Copolymer*	Acrylate/Lauryl Acrylate Copolymer*
Butyl Acrylate/Styrene Copolymer	Styrene/Acrylates Copolymer
C4-6 Olefin/Styrene Copolymer*	Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl
C5-6 Olefin/Styrene Copolymer*	Acrylate Copolymer*
Hydrogenated Butadiene/Isoprene/Styrene	Styrene/Butadiene Copolymer
Copolymer*	Styrene/Isoprene Copolymer*
Hydrogenated Butylene/Ethylene/Styrene Copolymer	Styrene/Methylstyrene Copolymer*
Hydrogenated Ethylene/ Propylene/Styrene	Styrene/Stearyl Methacrylate Crosspolymer*
Copolymer	Styrene/VA Copolymer*
Hydrogenated Styrene/Butadiene Copolymer	Styrene/VP Copolymer
Hydrogenated Styrene/Isoprene Copolymer	Polyacrylate-2*
Isobutylene/Styrene Copolymer	Polyacrylate-5
Methacrylic Acid/Styrene/VP Copolymer*	Polyacrylate-12*
Methylstyrene/Vinyltoluene Copolymer	Polyacrylate-15
Polystyrene	Polyacrylate-16
Polystyrene/Hydrogenated Polyisopentene	Polyacrylate-18*
Copolymer	Polyacrylate-21
Sodium Methacrylate/Styrene Copolymer*	Polyacrylate-30*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

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.²

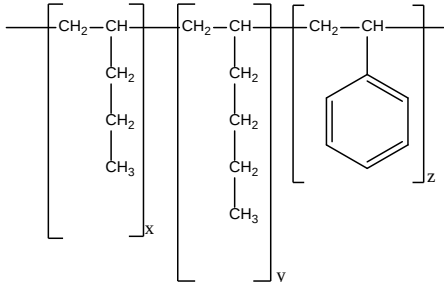
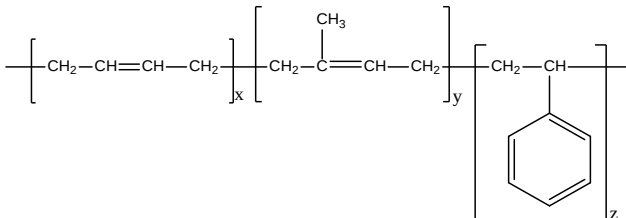
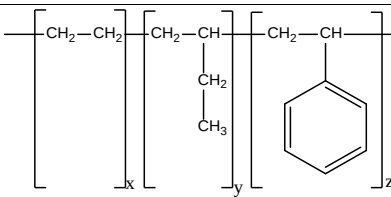
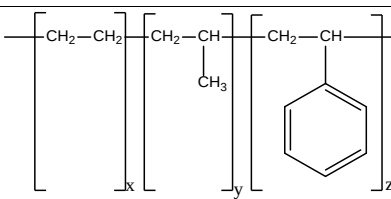
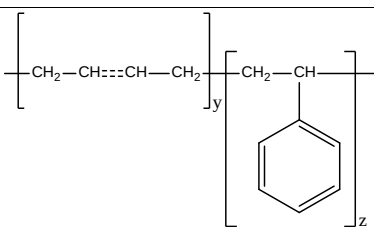
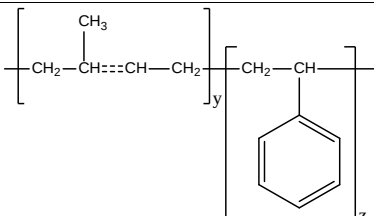
Ingredient CAS No.	Definition	Function(s)
C5-6 Olefin/Styrene Copolymer	C5-6 Olefin/Styrene Copolymer is the copolymer of C5-6 olefins and styrene monomers.	Epilating agents
		
Hydrogenated Butadiene/Isoprene/Styrene Copolymer 132778-07-5	Hydrogenated Butadiene/Isoprene/Styrene Copolymer is the end-product 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.²

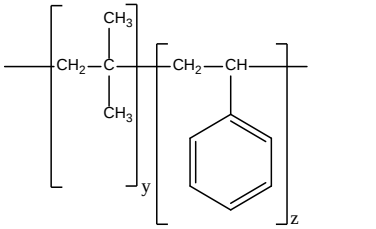
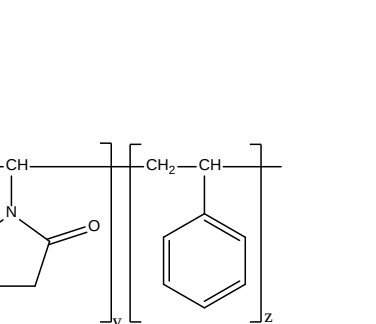
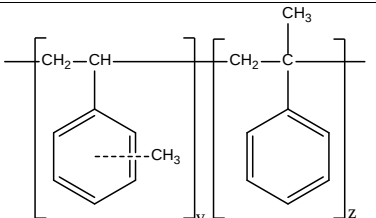
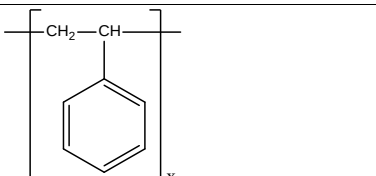
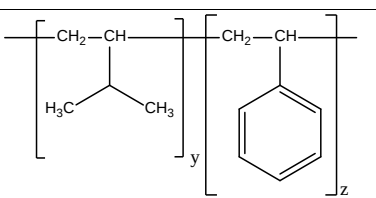
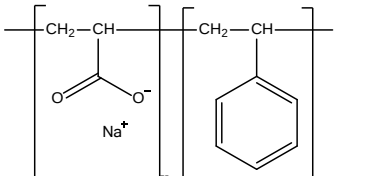
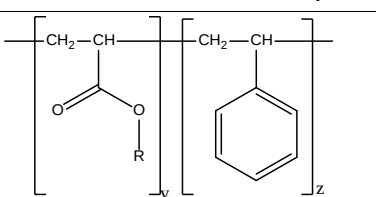
Ingredient CAS No.	Definition		Function(s)
Isobutylene/Styrene Copolymer 9011-12-5	Isobutylene/Styrene Copolymer is a copolymer of isobutylene and styrene monomers.		Film formers
Methacrylic Acid/Styrene/VP Copolymer 27554-92-3	Methacrylic Acid/Styrene/VP Copolymer is a copolymer of styrene, methacrylic 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. <i>Polystyrene is the homo-polymer formed from the polymerization of vinylbenzene.</i>		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.²

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 copolymer 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; epilating agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

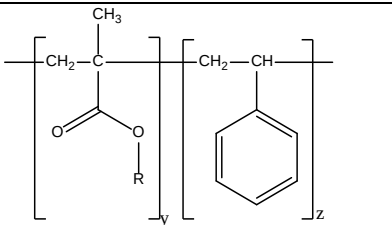
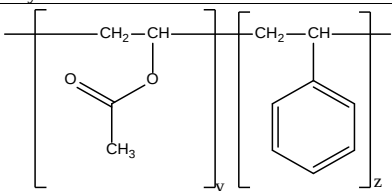
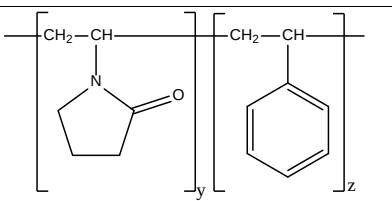
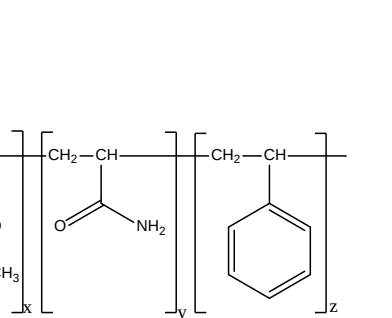
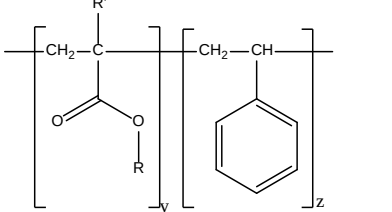
Ingredient CAS No.	Definition		Function(s)
Styrene/Stearyl Methacrylate Crosspolymer 91838-84-5	Styrene/Stearyl Methacrylate Crosspolymer is a copolymer of styrene and stearyl methacrylate monomers crosslinked with divinylbenzene.	 wherein R is an eighteen carbon, saturated alkyl chain	Absorbents; skin-conditioning 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 be methyl.	Film formers

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.²

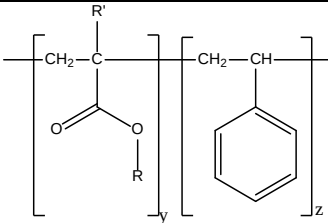
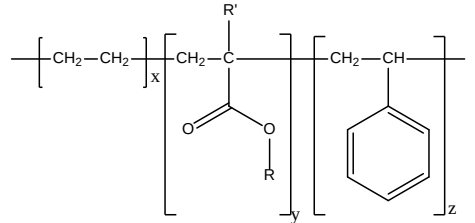
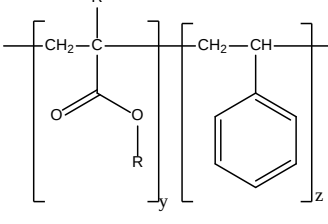
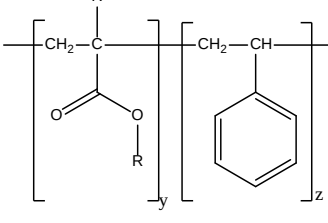
Ingredient CAS No.	Definition	Chemical Structure	Function(s)
Polyacrylate-12	Polyacrylate-12 is a copolymer of C3-11 acrylate, styrene, methacrylic Acid and acetoacetoxyethyl methacrylate monomers.	 wherein R is a hydrogen, methyl, an alkyl chain from 3 to 11 carbons in length methyl, or acetoacetoxyethyl 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.²

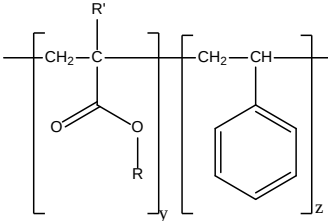
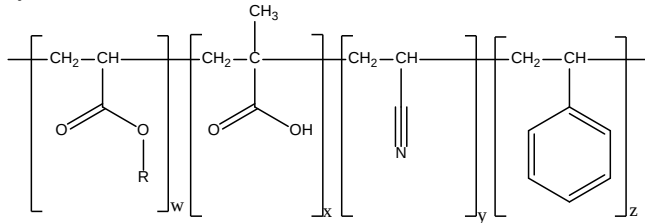
Ingredient CAS No.	Definition		Function(s)
Polyacrylate-21	Polyacrylate-21 is a copolymer of 2-ethylhexyl acrylate, butyl methacrylate, methacrylic acid, methyl methacrylate, hydroxypropyl methacrylate and styrene.		Binders; film formers; hair fixatives
Polyacrylate-30	Polyacrylate-30 is a copolymer 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.^{58,4,5}

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 $\approx 85^{\circ}\text{C}$
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 and 80 nm

Table 3. Properties of Styrene.⁴

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.⁵

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

Table 5. Properties of 1,3-Butadiene.⁹

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. Composition and Properties of Trade Name Materials

Ingredient Name and Trade Name	Composition/Impurities	Properties
Styrene/Acrylates Copolymer (Sunspheres™ LCG Polymer)	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). Impurity: copper (0.7 ppm). ⁵⁹	pH: 6.50-7.5. ⁵⁹
Styrene/Acrylates Copolymer (Sunspheres™ Powder)	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%). Byproducts and impurities: 1,4-dioxane (1.23 ppm), toluene (< 0.05 ppm), 2-methyl-4-isothiazolin-3-one (5 ppm), and diethylene glycol (64 ppm), and iron (2 ppm). ²⁸	
Styrene/Acrylates Copolymer (OPULYN™ 302B Opacifier)	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%). Impurities: iron (2,153 ppb) and magnesium (1,735 ppb). ³²	molecular weight: > 1,000,000. ³²
Styrene/Acrylates Copolymer (ACUDYNE™ Shine Polymer)	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%). Impurities: chromium (70 ppb), iron (333-1996 ppb), and nickel (92 ppb). ²⁹	pH: 3-5. ²⁹
Styrene/Acrylates Copolymer (SunSpheres™ PGL Polymer)	styrene/acrylates copolymer (up to 26%), residual monomers (< 100 ppm; for styrene, butyl methacrylate, and methyl methacrylate), aqua ammonia (up to 0.1%), pentyleneglycol (up to 6%), and water (up to 69%). Impurity: iron (1 ppm). ⁶⁰	pH: 6.5-7.5. ⁶⁰
Styrene/Acrylates Copolymer (OPULYN™ 301 Opacifier)	styrene/acrylic copolymer (up to 41%), water (up to 61%), residual monomers (< 500 ppm), and styrene (≤ 20 ppm). Impurities: heavy metals not detected. ⁵⁰	molecular weight: > 1,000,000; pH: 2.05-2.50. ⁵⁰
Styrene/Acrylates Copolymer (ACUDYNE™ Bold Polymer)	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%). Impurities: chromium (82 ppb), iron (2,270 ppb), and nickel (173 ppb). ³⁰	pH: 3-5. ³⁰
Styrene/Acrylates Copolymer (Syntran® 5903; corresponds to CAS Nos. 9011-14-7 and 9010-92-8)	dry extract of 35% styrene/acrylates copolymer + 65% water. ³³	white, milky dispersion (pH 7). ³³
Styrene/Acrylates Copolymer (Syntran® 5904; (corresponds to CAS Nos. 9011-14-7 and 9010-92-8)	dry extract of 40% styrene/acrylates copolymer + 60% water. ³⁵	white, milky dispersion (pH 2.5). ³⁵
Styrene/Acrylates Copolymer (Syntran® 5905; (corresponds to CAS Nos. 9011-14-7 and 9010-92-8)	dry extract of 40% styrene/acrylates copolymer + 60% water. ³⁶	white, milky dispersion (pH 2.5). ³⁶
Styrene/Acrylates Copolymer (Syntran® 5907; (corresponds to CAS Nos. 9003-63-8 and 9010-92-8)	dry extract of 40% styrene/acrylates copolymer + 60% water. ³⁴	white, milky dispersion (pH 2.5). ³⁴

Table 6. Composition and Properties of Trade Name Materials

Ingredient Name and Trade Name	Composition/Impurities	Properties
Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer	Both are used in ingredient mixtures in which the total polymer content is usually in the range of 5 to 20 weight % and the main component may be either of the following: mineral oil, isohexadecane, isododecane, hydrogenated polyisobutene, isopropyl palmitate, isononyl isononanoate, and residual monomer (below limit of detection [100 ppb]) ¹¹	
Polyacrylate-15 (Syntran® PC 5208; corresponds to CAS No. 67892-91-5)	contains the following: olefin-acrylic graft polymer (37%), ethoxylated secondary alcohol (3%), 1,3-butanediol (2%), 0.20% methylparaben, 0.15% propylparaben, residual monomer (< 5 ppm), and water (58%). ⁴⁴	molecular weight reported as $m + n > 100$. ⁴⁴
Polyacrylate-18 and Polyacrylate-19 (Syntran® PC 5117; corresponds to CAS No. 848236-12-4)	contains the following: acrylate copolymer (35%), 1,3-butanediol (4%), methylparaben (0.20%), propylparaben (0.15%), residual monomer (< 5 ppm), and water (60%). ⁴⁵	molecular weight reported as $n > 50$. ⁴⁵
Polyacrylate-18 and Polyacrylate-19 (Syntran® PC 5107; corresponds to CAS No. 848236-12-4)	contains the following: acrylate copolymer (30%), 1,3-butanediol (4%), methylparaben (0.20%), propylparaben (0.15%), residual monomer (< 5 ppm), and water (65%). ⁴⁶	molecular weight reported as $n > 50$. ⁴⁶
Polyacrylate-21 (Syntran® PC 5100 CG (corresponds to CAS Nos. 68541-61-7 and 26316-50-7)	acrylate copolymers in an aqueous phase. dry extract of 25% non-volatiles. ⁴⁷	typical pH: 8.0. ⁴⁷
Polystyrene (Syntran® 5900)	contains the following: polystyrene (31% to 33%), surfactants (2% to 3%), residual monomer (< 5 ppm), and balance is water. ⁴²	molecular weight of $\sim 50,000$ daltons. ⁴²

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.^{12,13}

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

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.^{12,13}

	Polystyrene		Polystyrene/Hydrogenated Polyisopentene Copolymer		Sodium Styrene/Acrylates Copolymer	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	19	0.08-36.5	16	0.0002-1.2	25	0.49
Duration of Use						
<i>Leave-On</i>	16	0.08-0.4	13	0.015-1.2	19	0.49
<i>Rinse off</i>	3	36.5	3	0.0002	4	NR
<i>Diluted for (bath) Use</i>	NR	NR	NR	NR	2	NR
Exposure Type						
<i>Eye Area</i>	2	NR	7	0.15-1.2	NR	NR
<i>Incidental Ingestion</i>	NR	NR	NR	0.05	NR	NR
<i>Incidental Inhalation- Sprays</i>	5	0.4**	2**	NR	4**	NR
<i>Incidental Inhalation- Powders</i>	4	0.2*	2**	NR	4*	NR
<i>Dermal Contact</i>	10	0.08-36.5	16	0.0002-1.2	22	NR
<i>Deodorant (underarm)</i>	NR	NR	NR	NR	13	NR
<i>Hair - Non-Coloring</i>	9	0.4	NR	NR	3	NR
<i>Hair-Coloring</i>	NR	NR	NR	NR	NR	NR
<i>Nail</i>	NR	NR	NR	NR	NR	0.49
<i>Mucous Membrane</i>	2	NR	NR	0.05	2	NR
<i>Baby Products</i>	NR	NR	NR	NR	NR	NR
	Styrene/Acrylates Copolymer		Styrene/Butadiene Copolymer		Styrene/VP Copolymer	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	272	0.028-35	9	NR	82	0.000038-1
Duration of Use						
<i>Leave-On</i>	121	0.028-35	NR	NR	30	0.000038-0.4
<i>Rinse off</i>	135	0.04-12	9	NR	52	0.021-1
<i>Diluted for (bath) Use</i>	16	0.2-0.4	NR	NR	NR	NR
Exposure Type						
<i>Eye Area</i>	11	0.36-15	NR	NR	NR	0.2-0.4
<i>Incidental Ingestion</i>	3	0.13	NR	NR	1	NR
<i>Incidental Inhalation- Sprays</i>	34	0.35-3.5	NR	NR	22	0.12
<i>Incidental Inhalation- Powders</i>	21	0.028-2.7*	NR	NR	6	0.12-0.2*
<i>Dermal Contact</i>	201	0.028-17.7	8	NR	18	0.000038-0.4
<i>Deodorant (underarm)</i>	2	0.4	NR	NR	NR	NR
<i>Hair - Non-Coloring</i>	8	0.2-1	1	NR	36	0.032-1
<i>Hair-Coloring</i>	NR	0.04-12	NR	NR	25	0.04-0.7
<i>Nail</i>	57	0.52-35	NR	NR	2	NR
<i>Mucous Membrane</i>	133	0.04-7.7	8	NR	6	0.057
<i>Baby Products</i>	2	0.2	NR	NR	NR	NR
	Polyacrylate-5		Polyacrylate-15		Polyacrylate-16	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	3	NR	22	0.38	4	1-11.3
Duration of Use						
<i>Leave-On</i>	3	NR	NR	0.38	4	1-11.3
<i>Rinse off</i>	NR	NR	22	NR	NR	NR
<i>Diluted for (bath) Use</i>	NR	NR	NR	NR	NR	NR
Exposure Type						
<i>Eye Area</i>	NR	NR	NR	NR	4	1-4.5
<i>Incidental Ingestion</i>	2	NR	NR	NR	NR	11.3
<i>Incidental Inhalation- Sprays</i>	NR	NR	NR	NR	NR	NR
<i>Incidental Inhalation- Powders</i>	NR	NR	NR	0.38*	NR	NR
<i>Dermal Contact</i>	NR	NR	NR	0.38	4	1-4.5
<i>Deodorant (underarm)</i>	NR	NR	NR	NR	NR	NR
<i>Hair - Non-Coloring</i>	NR	NR	NR	NR	NR	NR
<i>Hair-Coloring</i>	NR	NR	22	NR	NR	NR
<i>Nail</i>	1	NR	NR	NR	NR	NR
<i>Mucous Membrane</i>	2	NR	NR	NR	NR	11.3
<i>Baby Products</i>	NR	NR	NR	NR	NR	NR

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.^{12,13}

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

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.

***Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation

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.

Table 8. Carcinogenicity Studies/Reviews of Carcinogenic Potential on Copolymers/Monomers

Copolymer/Monomer	Test Protocol/Basis for Conclusion	Results/Conclusion
Polystyrene	Groups of Wistar rats. Subcutaneous implantation of various forms of polystyrene: smooth discs (47 rats); perforated discs (51 rats); rods, spheres, and fibers (40 rats); and powder (number of rats not stated).	Sarcoma incidences: 37 of 47 rats (78.7%), 25 of 51 rats (49%), and 15 of 40 rats (37.5%). Powder did not induce sarcomas. ^{5,61}
Polystyrene	Wistar rats (from 3 different laboratory sources; number not stated).	Differences in incidence of local sarcomas (8% to 40%) found, depending on the animal strain. ^{5,62}
Styrene	Groups of Fischer 344 rats and B6C3F ₁ mice (50 males, 50 females/species) in NTP oral carcinogenicity bioassay. Styrene (in corn oil, by gavage) 5 days per week at doses up to 2,000 mg/kg/day (rats) and 300 mg/kg/day (mice). Dosing for 78 weeks (rats: 1,000 and 2,000 mg/kg/day dose groups; mice: 150 and 300 mg/kg/day dose groups) and 103 weeks (rats: 500 mg/kg/day dose group)	No convincing evidence for carcinogenicity of styrene found in rats or mice of either sex. ⁶³
1,3-Butadiene	Groups of 50 male and 50 female B6C3F ₁ mice in NTP inhalation carcinogenicity study. Exposure to air containing 625 ppm or 1,250 ppm 1,3-butadiene 5 days per week (6 h/day) for 60 or 61 weeks.	Clear evidence of carcinogenicity in male and female mice. ²⁶
1,3-Butadiene	Groups of 70 male and 70 female B6C3F ₁ mice in NTP inhalation carcinogenicity study. Exposure to air containing 6.25, 20, 62.5, or 200 ppm 1,3-butadiene 5 days/week (6 h/day) for up to 2 years	Clear evidence of carcinogenicity in male and female mice. ⁶⁴
1,3-Butadiene	Groups of 90 male and 90 female B6C3F ₁ mice in NTP inhalation carcinogenicity study. Exposure to 625 ppm 1,3-butadiene 5 days/week (6 h/day) for up to 2 years	Clear evidence of carcinogenicity in male and female mice. ⁶⁴
Styrene	Sufficient evidence of carcinogenicity from studies involving experimental animals. Limited evidence of carcinogenicity of styrene in humans 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	According to the NTP, styrene reasonably anticipated to be a human carcinogen. ⁶⁵
Styrene	Limited evidence of carcinogenicity of styrene in humans and in experimental animals	According to IARC, styrene possibly carcinogenic to humans. ²²
Styrene		According to the the United States EPA, styrene possibly carcinogenic to humans. ⁶⁶
1,3-Butadiene	Unit cancer risk estimate of 0.08/ppm, based on linear modeling and extrapolation of human data	According to the United States EPA, 1,3-butadiene carcinogenic to humans by inhalation exposure. ⁶⁷
1,3-Butadiene	1,3-Butadiene causes cancer of the hematolymphatic organs. There is strong evidence that 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.	According to IARC, sufficient evidence for carcinogenicity of 1,3-butadiene in humans and in experimental animals. ⁶⁸

Table 8. Carcinogenicity Studies/Reviews of Carcinogenic Potential on Copolymers/Monomers

Copolymer/Monomer	Test Protocol/Basis for Conclusion	Results/Conclusion
Styrene/Butadiene Copolymer	Multi-plant cohort studies of male styrene/butadiene rubber workers	Significantly increased cancer risks, including risks of non-Hodgkin's lymphoma (NHL), NHL-chronic lymphocytic leukemia, and leukemia. ^{69,70}
Styrene/Butadiene Copolymer	Epidemiological information on styrene/butadiene copolymer workers	According to IARC, this epidemiological information suggests elevated risk for lymphato-hematopoietic malignancies. ⁵
Polyacrylate	Cross-sectional respiratory survey of 164 workers exposed to polyacrylate dust for average of 20.7 years	No evidence of excess risk of lung cancer. ⁷¹

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FINAL REPORT ON THE SAFETY ASSESSMENT OF POLYVINYLPIRROLIDONE (PVP)¹

Polyvinylpyrrolidone (PVP) is a linear polymer of 1-vinyl-2-pyrrolidone monomers used as a binder, emulsion stabilizer, film former, hair fixative, and suspending agent-nonsurfactant. The molecular weight of the polymer ranges from 10,000 to 700,000. PVP K-30, with an average molecular weight of 40,000, is typically used in cosmetic formulations. The highest concentration reported to be used is 35%. There was no significant absorption of PVP K-30 given orally to rats, and the acute oral LD₅₀ was >100 g/kg for rats and guinea pigs. Neither toxic effects nor gross lesions were found in rats maintained for two years on a diet containing 10% PVP K-30. Short-term PVP inhalation studies produced mild lymphoid hyperplasia and fibroplasia in rats, but no inflammatory response. In animal studies, no evidence of significant ocular irritation, skin irritation, or skin sensitization was found at PVP-iodine solution concentrations of 10%. While PVP-iodine is not a cosmetic ingredient, these negative findings were considered to support the safety of the PVP component. Undiluted PVP K-30 was not a dermal irritant or sensitizer in clinical tests. No developmental toxicity was seen in vehicle controls where PVP was used as a vehicle for another agent. In certain assay systems, PVP was genotoxic, but was negative in the majority of studies. Orally administered PVP significantly decreased the rate of bladder tumors in mice exposed to bracken fern. Several studies tested the carcinogenicity of subcutaneous implants of particulate PVP in rats, mice, and rabbits. Although the majority of these studies conducted in rats were positive, tumors (sarcomas) were localized to the site of implantation. Based on the available data, it was concluded that PVP is safe as used in cosmetics.

DEFINITION AND STRUCTURE

Polyvinylpyrrolidone (PVP) (CAS No. 9003-39-8) is a linear polymer consisting of 1-vinyl-2-pyrrolidone monomers conforming to the formula shown in Figure 1 (Wenninger and McEwen 1997). The monomer has a molecular weight (MW) of 111.1; the molecular weight of the polymer can range from 10,000 to 700,000 (IARC 1979). Synonyms include: polyvinylpyrrolidone; 1-Ethenyl-2-Pyrrolidone, Homopolymer; Povidone (Wenninger and McEwen 1997); polyvidone; polyvidon; polyvidonum;

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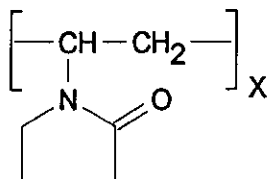


Figure 1. Chemical formula for polyvinylpyrrolidone.

poly(*N*-vinyl-2-pyrrolidone); poly(*N*-vinyl-butylrolactam); poly(1-vinyl-2-pyrrolidone); 1-vinyl-2-pyrrolidinone polymer and poly[1-(2-oxo-1-pyrrolidinyl)ethylene] (Robinson et al. 1990). A water insoluble crosslinked homopolymer of PVP is called polyvinylpolypyrrolidone or PVPP, crosspovidone (Robinson et al. 1990).

PHYSICAL AND CHEMICAL PROPERTIES

PVP is a faintly yellow solid resembling albumin (Budavari 1989). It is soluble in water, ethanol, and chloroform and is insoluble in ether (USP 1975; Budavari 1989). PVP is defined by its viscosity in aqueous solution, relative to that of water. This viscosity is expressed as a K-value which ranges from 10 to 95 (USP 1990). A solution of PVP K-30 typically has an average MW of 40,000, though the MW range and distribution can vary among batches with the same nominal K-value (Robinson et al. 1990).

UV Absorption

The amide region of the pyrrolidone substituent absorbs in the UV region at wavelengths below ~235 nm (International Specialty Products [ISP] 1995).

Method of Manufacture

The synthesis of PVP is shown in Figure 2. It begins with formaldehyde and acetylene and proceeds through 2-butyne-1,4-diol and γ -butyrolactone to α -pyrrolidone and *N*-vinyl-2-pyrrolidone (the monomer), which is then polymerized to form PVP (Robinson et al. 1990). Usually, the monomer is polymerized in water using the method described by Reppe (1949). According to Robinson et al. (1990), commercial polymerization is carried out in isopropyl alcohol. The alcoholic solution is subsequently converted to an aqueous solution by steam distillation and then either spray or drum dried.

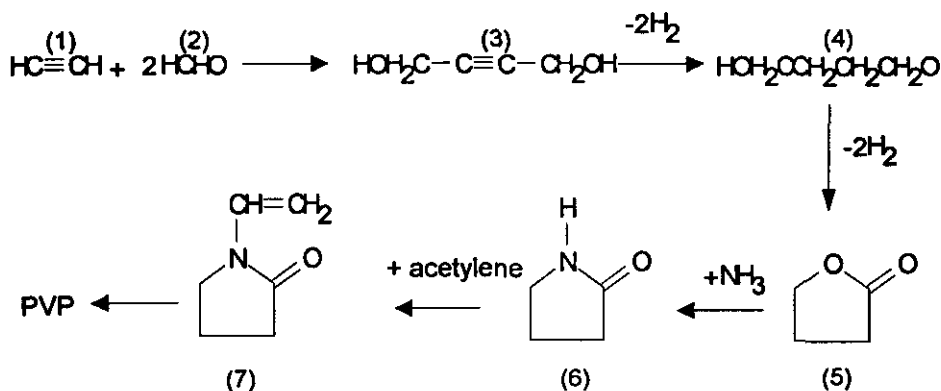


Figure 2. Steps in the chemical synthesis of PVP. Intermediates are (1) acetylene; (2) formaldehyde; (3) 2-butyne-1,4-diol; (4) 1,4-butanediol; (5) gamma-butyrolactone; (6) alpha-pyrrolidone; and (7) *N*-vinyl-2-pyrrolidone.

Impurities

The following specifications are defined for cosmetic grade PVP: 95.0% minimum PVP (as vinylpyrrolidone); 0.5% maximum aldehyde (as acetaldehyde); 1.0% maximum vinylpyrrolidone; 0.05% maximum sulfated ash; 5.0% maximum water; 2 ppm maximum arsenic (as elemental As); and 10 ppm maximum lead (as elemental Pb) [Nikitakis and McEwen 1990]. For pharmaceutical grade PVP, the United States Pharmacopeia (USP) (1990) placed limits of 1 ppm hydrazine, 0.2% aldehydes as acetaldehyde, and <0.2% *N*-vinyl-2-pyrrolidone monomer. ISP (1995) stated that typical PVP preparations have hydrazine contamination of 200 ppb.

USE

Cosmetic

PVP functions in cosmetic formulations as a binder, emulsion stabilizer, film former, hair fixative, and suspending agent—nonsurfactant (Wenninger and McEwen 1997). According to Robinson et al. (1990), PVP can be combined with cationic substances, such as disinfectants or basic dyes; therefore, care is needed as it does have a marked affinity for dyes.

In January of 1996, PVP was reported to the Food and Drug Administration (FDA) to be used in 395 cosmetic formulations (Table 1). Concentrations of use are no longer required to be reported to the FDA (FDA 1992). Data submitted directly to Cosmetic Ingredient Review (CIR) by the cosmetics industry indicated that PVP is used at a variety of concentrations (see Table 1.) In addition to the values listed in Table 1, the cosmetics industry reported that PVP is used at 1–5% in hair

Table 1. Cosmetic product use of PVP

Product category	Formulations in category	No. containing PVP	Concentration of use (%)
Baby shampoos	23	1	0.5
Eye brow pencil	99	2	5
Eyeliner	533	23	5.23
Mascara	218	96	8
Other eye makeup preparations	136	8	2; > 5-10
Cologne and toilet waters	834	1	1
Other fragrance preparations	195	1	
Hair conditioner	715	37	1
Hair spray (aerosol fixatives)	334	21	0.25; PVP K90 < 0.15
Hair straighteners	50	1	
Permanent waves	434	2	
Rinses (noncoloring)	60	3	
Shampoos (noncoloring)	972	15	2
Tonics, dressings, and other hair grooming aids	604	76	4
Wave sets	95	21	2
Other hair preparations	395	28	2
Hair rinses (coloring)	50	4	
Hair bleaches	113	1	
Foundations	355	4	1.5
Lipstick	997	1	0.5
Other oral hygiene products	3	1	
Bath soaps and detergents	372	3	
Other personal cleanliness products	339	2	
Preshave lotions (all types)	20	2	
Shaving creams	158	4	
Other shaving preparation products	63	1	
Cleansing	820	6	
Face and neck	300	5	
Body and hand	1012	4	
Moisturizing	942	5	
Night	226	1	
Paste masks	300	8	
Skin fresheners	244	1	
Other skin care preparations	810	6	
1996 total		395	

Source. FDA, 1996; CTFA, 1995.

fixatives, at 8% in blushers, at 7.5% in lip products, and up to 35% in makeup fixatives (CTFA 1995).

Robinson et al. (1990) reported that PVP K-25 and K-30 (average MW 40,000) are commonly used in cosmetic formulations. PVP K-90 may be used in aerosol hair sprays (CTFA 1995). Most hair fixative dispensers emit a spray with a mass median aerodynamic diameter of ~60 microns, with usually less than 0.5% of the particles being smaller than 10 microns (ISP 1995).

International

PVP is listed in the Comprehensive Licensing Standards (CLS) of Cosmetics by Category and must conform to the specifications of the Japanese Standards of Cosmetic Ingredients (Yakuji Nippo, Ltd. 1994). It can be used without restrictions in all CLS categories.

Noncosmetic

Food

PVP is cleared for the following uses: as a clarifying agent in beverages and vinegar; as a tableting adjuvant; and as a stabilizer, bodying agent, and dispersant in nonnutritive sweeteners in concentrated liquid form, and vitamin and mineral concentrates. It is also cleared for use in packaging that comes in contact with various foods (Rothschild 1991). Robinson et al. (1990) reported that PVP K-30 (average MW 40,000) is used as a food additive. In 1986, the 30th Joint Expert Committee on Food Additives (JECFA) set an acceptable daily intake (ADI) level for PVP of 0–50 mg/kg (World Health Organization 1986b). At the 29th meeting, the committee had acknowledged the possibility of a hydrazine contaminant in PVP K-30 (a possible by-product of the polymerization process). In a 1987 report on hydrazine, the IARC working group declared that although there was “inadequate” evidence of carcinogenicity in humans, there was “sufficient” evidence of carcinogenicity in animals, citing studies in which rodents were exposed via inhalation and the oral route. However, the 29th JECFA stated, “the probability of carcinogenic effects arising from such low levels of hydrazine seems remote in view of the large amount of data that indicate that polyvinylpyrrolidone itself is not a carcinogen” (World Health Organization 1986a).

OTC Drugs

The FDA has approved PVP as safe and effective for use as a demulcent (FDA 1991). FDA has proposed that PVP is not recognized as safe and effective against poison ivy, oak, and sumac (FDA 1991). In the medical setting, PVP was used during World War II as a blood plasma

extender. This practice eventually lost favor as PVP was not easily broken down by the body and settled in the monocyte/macrophage system (MMS), which is referred to as the reticuloendothelial system (RES) in some early literature (Wessel, Schoog, and Winkler 1971). As reported by Robinson et al. (1990), the German drug regulatory body (Bundesgesundheitsamt) issued the following recommendations concerning parenteral use of drugs containing PVP: (1) For intravenous use, drugs may contain an unrestricted (but identified) amount of PVP up to K-18 (average MW 9,000); (2) for i.m. use, each dose should not contain more than 50 mg PVP with an upper limit of K-18; (3) care should be used with repeated dosing on patients with renal function complications; (4) care should also be taken to avoid repeated injection into either the same site or sites with reduced perfusion; and (5) observations should be made for accumulation of PVP in the MMS and the production of foreign body granulomas (see Clinical Assessment—General Biology section for more historic details). PVP is an ingredient in some commercially available artificial tear preparations (York et al. 1988).

PVP has been associated with iodine (I_2) to form the antiseptic Betadine (Pietsch and Meakins 1976). The structure of the resulting tri-iodide is shown in Figure 3 (Schenck et al. 1980). The tri-iodide is in rapid equilibrium with iodine and iodide (the iodine reacts with water and is reduced to iodide). The equilibrium is a function of pH (at lower pH the iodine is released from the complex), concentration, solvent, and temperature. The toxicity of iodine is reduced because most of it remains as a reserve in the complex whereas the small amount of free iodine that is present retains antimicrobial properties (York et al. 1988). PVP, which has a high membrane affinity, serves as the carrier polymer delivering the free iodine directly to the bacterial cell surface (Zamora 1986). There is discrepancy in the published literature as to the iodine content of a PVP-iodine formulation. According to Zamora (1986), a 10% solution of PVP-iodine is comprised of 90% water, 8.5% PVP, and 1% available iodine and iodide. He reported a free iodine concentration of 0.0001% (1 ppm). However, Tosti et al. (1990) reported a free iodine level of 0.001%

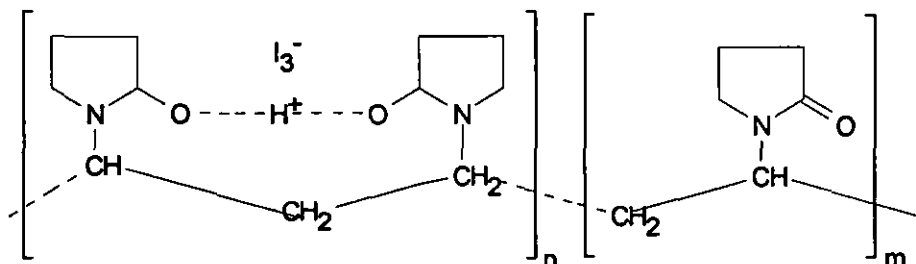


Figure 3. Chemical formula for PVP-iodine antiseptic ($m \cong 18n$)

and still others referred to a free iodine content of 1% (Ancona 1985; van Ketel and van den Berg 1990). FDA has proposed that PVP-iodine is safe and effective as an antifungal agent and first-aid antiseptic (FDA 1991).

GENERAL BIOLOGY

Absorption, Metabolism, Distribution, Excretion

In a study of the permeability of the capillaries in normal kidneys reviewed by Wessel, Schoog, and Winkler (1971), PVP of varying MWs was injected into rats and rabbits. It was determined that the capillaries of the glomeruli allow only PVP molecules of a MW of $< 25,000$ to pass through the ultrafilter. However, the postglomerular capillaries have pores of three different sizes, allowing PVP with MWs of 11,500, 110,000, and 650,000 to pass through. Thus, the permeability for macromolecules is greater in the postglomerular capillaries than in the glomerulus. The researchers considered that most higher molecular weight PVP (up to MW 650,000) goes directly from the postglomerular capillaries into the interstice or lymphatic channels without passing the ultrafiltrate.

In a review of early literature, Wessel, Schoog, and Winkler (1971) reported that PVP elimination was inversely related to MW. They noted discrepancies among the published literature concerning the renal threshold for PVP (reports of limits have ranged from 25,000 to 60,000). However, it was generally agreed that polymers with a MW $< 20,000$ were completely eliminated through healthy kidneys. In their review, Robinson et al. (1990) cited studies, which provided evidence that PVP was taken into the monocyte/macrophage system via low affinity pinocytosis, though phagocytes may also play a role.

Ravin, Seligman, and Fine (1952) conducted an excretion study in which 300 mg ^{131}I -PVP (of K values between 25 and 50) were rapidly infused into groups of dogs (50,000 to 500,000 counts per minute). Blood samples were taken at 5, 15, and 30 minutes, and 1, 2, 6, and 12 hours after the PVP injection. Urine samples were taken at 3, 6 and 12 hours. The plasma level of radioactivity declined rapidly during the first two hours following infusion. A short inflection phase followed during which the rate of PVP disappearance from the plasma changed rapidly. Finally, a straight-line decay curve was reached. In a complement experiment, ^{131}I -PVP was administered by rapid injection to dogs which had thoracic-duct fistulas. Analysis of lymph samples established that the initial rapid fall of serum radioactivity was matched by a rapid rise in extracellular-fluid radioactivity. The inflection point in the blood-disappearance curve coincided with a peak concentration of PVP in the lymph; the levels in the serum and lymph approached one another at a rate that was related to the K-value of the solution. For example, it was

determined that PVP with a MW of < 20,000 (the lower half of the K-25 sample) established an equilibrium within an hour. Within 48 hours, 40–80% of the infused dose of ^{131}I -PVP was recovered in the urine.

In a metabolism study, ^{14}C -PVP (K-33) was rapidly infused via the i.v. route into rats and dogs. Radioactive PVP was also infused in a 45-minute timespan into humans (rapid infusion was not conducted in order to avoid rapid expansion of the circulating blood volume). Blood and urine samples were taken at the same intervals as in the above-described excretion study. The blood-disappearance and urinary excretion curves were similar to those noted in dogs infused with ^{131}I -PVP. Approximately 0.3–0.5% of the administered dose appeared in the stool of both man and dog within 24 hours of infusion. Fecal excretion declined thereafter to an average of 0.001%/day. Between 0.15–0.20% of the administered dose was found in the expired air during the first 12 hours after infusion in man; the value fell to 0.01% in subsequent 12-hour periods. After 36 hours, no radioactivity was detected in the respired air. The researchers concluded that there was no metabolic degradation of PVP and no significant route of excretion except by the kidneys (Ravin, Seligman, and Fine 1952).

Distribution was determined by injecting six rats with 350 mg of ^{14}C -PVP (K-33) via the i.v. route (Ravin, Seligman, and Fine 1952). Pairs of rats were killed at 2, 4, and 7 hours after infusion. In a similar experiment, rabbits were given 8–9 g of the same preparation daily in seven divided doses. The rabbits were killed at 1, 2, and 6 months after infusion. Five moribund human patients received the same preparation of PVP. A similar distribution pattern was observed in all three species. The skeletal muscle, skin, and subcutaneous tissue contained the largest fraction but lowest concentration of PVP; the organs of the MMS had the highest concentration. Samples were taken at different times following infusion; the amount and concentration of PVP retained in the skin and subcutaneous tissue and in skeletal muscle decreased progressively, whereas the values remained constant for organs with large populations of monocytes/macrophages.

The effect of MW on retention was examined by separating a sample of K-30.2, C^{14} -PVP into K-37 and K-27 fractions. (Analysis determined that 23% of the K-30.2 sample had a mean MW of 117,000.) Groups of rats were infused with 35 mg of either fraction or the original unfractionated solution. Two animals from each group were killed after 2 weeks. Overall retention was greater with increasing K-value. Most significant was the finding that retention by the spleen (representative of the MMS) increased with increasing K-value disproportionately to retention by other organs. An estimated 10% of the unfractionated PVP was retained by the MMS. It was therefore concluded that the MMS retained molecules with a MW > 117,000 (Ravin, Seligman, and Fine 1952).

In humans, it was determined that the K-value of PVP excreted within the first 6 hours following infusion was lower than the K-33 of the infused preparation. The K-value of urinary PVP rose 48–96 hours following infusion to a peak corresponding to a MW of 40,000. PVP continued to be excreted at the rate of 25 mg/day (0.06% of a clinical dose of 17.5 g) for as long as one year. The excreted dose was of MW between 40,000–120,000 as smaller particles passed rapidly through the glomerulus and larger particles were retained in the MMS (Ravin, Seligman, and Fine 1952).

In a study by Hespe, Blankwater, and Wieriks (1975), male Wistar rats were dosed (via the i.v. route) with 500 mg/kg PVP along with the antibiotic oxytetracycline (OTC). Of the PVP administered, 50 mg/kg was radioactive. Although there were some particles with MWs of 190,000, 94% of the PVP had MW of $\leq 20,000$. The researchers noted a slight, reversible disturbance in respiration 15 minutes after injection. One animal was killed at each time of 15, 30 minutes, 1, 2, 4, 8, 24, and 72 hours postdosing, and a whole-body autoradiography was performed. (A fluorograph was also performed to detect the presence of the antibiotic.) At 15 and 30 minutes postdosing, a high level of radioactivity was detected in the blood, kidneys, urinary bladder, lungs, skin and hair follicles, sclera, connective tissue, interstitial tissue, and tissue spaces. Particularly at 15 minutes, the stomach wall and portions of the intestinal wall had high activity. (No levels were reported.) With time, greater activity was detected in the gastrointestinal lumen. A slight uptake was noted in the liver with the maximum activity being attained at 30 minutes. Elimination was rapid. By 8 hours, only the kidneys, areas of the lungs, and intestinal contents had high levels of activity. By 72 hours, the kidneys, as well as localized areas of the lungs and skin, still had high radioactivity; residual levels were noted in the liver, connective tissue, and spleen. No radioactivity was detected at any time in the central nervous system; radioactivity was not detected in the bulk of skeletal muscle and fatty tissue. By comparing the autoradiographs to the fluorographs of the same animals as well as to the fluorographs of rats treated only with the antibiotic, the researchers considered a PVP-OTC complex to have formed in solution, which remained in equilibrium with free PVP and OTC. The complex allowed for penetration of the antibiotic into various organs that were inaccessible by free OTC alone. PVP had no effect on the activity of the antibiotic.

Hespe, Meier, and Blankwater (1977) used male Wistar rats to determine the effects on distribution and excretion of two radioactive PVP (3.2 mCi/g) preparations both with a low mean MW but differing MW distributions. Ninety-five percent of the particles in sample A were below a MW of 25,000. In contrast, 99.5% of the particles in sample B had a MW below 25,000. Each of the samples were administered intravenously at

doses of 50 and 200 mg/kg. Bile was continually collected over a 5-hour period from animals dosed with 50 mg/kg. Excretion products were collected and analyzed by liquid scintillation. Animals were sacrificed at 4, 6, 8, 12, or 24 days after dosing and whole-body autoradiography was performed. During the 72-hour period following administration of the 50 mg/kg dose, radioactivity was detected in the following distribution. For sample A, 92.6 ($\pm$ 11.3)% of the administered dose was detected in the urine, 7.0 ($\pm$ 6.3)% in the feces, and 0.43 ($\pm$ 0.04)% as respired CO₂. For sample B, 93.1 ($\pm$ 4.6)% of the administered dose was detected in the urine, 4.4 ($\pm$ 3.4)% in the feces, and 0.47 ($\pm$ 0.01)% as respired CO₂. The researchers considered the data to indicate good recovery; however, they noted that the standard deviation values indicated large individual differences. In the period 0–1 day following dosing, 84.5% of the administered 200 mg/kg dose of sample A was recovered as compared to 91.0% of sample B. By day 22, 86% of the administered amount of sample A and 92.2% of sample B had been recovered. The differences were not statistically significant. Analysis of the bile collected for 5 hours after dosing with 50 mg/kg indicated that within the first hour postdosing, 61.1 μ g of sample A had been recovered compared to 123.2 μ g of sample B. The bulk of the administered dose of both samples was eliminated by 24 hours. Radioactivity continued to be detected in the bile samples. By 5 h, 94.5 μ g of sample A and 176.0 μ g of sample B had been recovered, which represented 1.2 and 1.9% of the administered dose, respectively. In autoradiographs taken 6 days postadministration of the 200 mg/kg dose, the kidneys and gastrointestinal tract of animals dosed with either sample had high levels of radioactivity. However, high levels were also detected in the urinary bladder, liver, spleen, pancreas, skin, sclera, connective tissue, bone marrow, and joints of animals treated with sample A, whereas levels in these same areas were difficult to detect in sample B-treated animals. The researchers considered that sample B was retained in the body to a lesser extent. They attributed the difference in elimination to sample B having 0.5% of its molecules with a MW > 25,000, "which is regarded as the limit for rapid glomerular filtration", whereas sample A had 5% of its molecules with a MW >25,000.

Digenis et al. (1987) performed a single-dose oral study using groups of five male Sprague-Dawley rats. Radioactive PVP (0.9 mg/rat, 10.6 μ Ci/dose) with an average MW of 40,000 was administered by gavage. Animals were killed at 6, 12, 24, and 48 hours postdosing, and major organs and blood samples were collected. Samples were weighed and then combusted and analyzed by a liquid scintillation counter. The feces was the major pathway of elimination; 90.8% of the dose was recovered after 12 h (five animals) and 98.4% after 48 hours (three animals). After 6 hours, approximately 0.04% of the administered dose was detected in the urine. The researchers reported that radioactivity detected

in major tissues and in the blood was not significantly different from untreated controls (data not provided). Dialysis studies suggested that the absorbed oligomer (referring to the small amount detected in the blood and subsequently in the urine during the first 6 hours) was of $MW < 3500$. It was estimated that perhaps 4% of the total sample was of such size. The researchers considered that an oral dose of PVP was not significantly absorbed in the rat.

Oral Drug Absorption

Stupak and Bates (1973), using groups of 15 Sprague-Dawley rats, found that oral administration of a coprecipitate of digitoxin-PVP had a higher solubility and dissolution rate than did either a physical mixture of digitoxin and PVP or digitoxin alone. The PVP used in both the physical mixture and the coprecipitate had a MW of 40,000. The drug-PVP physical mixture (1:9) was administered at drug doses of 50 and 75 mg/kg body weight (hence, PVP doses of 450–675 mg/kg); the coprecipitate (1:9) was administered at doses of 6–10 mg digitoxin/kg body weight (54–90 mg/kg of PVP). Animals were observed for 72 hours postdosing. Drug absorption was measured indirectly by determining oral toxicity. The coprecipitate had markedly lower LD_{50} values than did digitoxin alone (7.80 mg/kg for the coprecipitate versus 88 mg/kg for digitoxin alone). Pure PVP had no untoward effects when administered at doses up to 100 g/kg and thus, the increased toxicity of the coprecipitate was due to “an increase in the amount of drug in the body produced by a marked enhancement in the rate at which drug absorption occurs.”

Immunologic Effects

In their review, Robinson et al. (1990) cited studies which indicate that PVP functions as a thymus-independent antigen that produced a primary 19S immune response. (The reviewers noted that linear molecules with repeating antigenic determinants are typically expected to incite a T cells-dependent immunologic response.)

Lymphocyte Transformation

Robinson et al. (1990) described a study in which three beagle dogs were inoculated subcutaneously with 50 mg PVP in phosphate-buffered saline into the front and rear right feet on each of days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, and 31. The MW of the PVP was not reported. On day 16, the treated dogs, as well as an additional three dogs, were inoculated with 50 μ g of turkey gamma-globulin (TGG) in

Freund's adjuvant. The right and left popliteal lymph nodes were removed on days 32 and 33. Lymph node cells were used in *in vitro* assays where the response to various stimuli was measured by incorporation of tritiated thymidine (thus indicating lymphocyte transformation). The researchers found variable responses among the animals. However, no difference was observed in lymphocyte transformation in cells from the right node (PVP inoculated) versus those cells from the left node (control). It was considered that the effect of the nonspecific T-cell mitogens, concanavalin A, and phytohemagglutinin (PHA), was not inhibited by previous inoculation with PVP. Further, PVP inoculation did not alter the proliferative response of lymph node cells to specific antigen challenge with PVP. A slight (not statistically significant) increase in mitogen response was observed in control dogs which received TGG alone.

Hoshi et al. (1986) reported that PVP (MW 500,000) did not induce a recognized plasma cell reaction, germinal cell development, or formation of new lymph follicles in mice following injection into the rear foot pad. PVP was not considered very immunogenic.

ANIMAL TOXICOLOGY

Oral Toxicity

Acute

The oral LD₅₀ for PVP with an average MW of 40,000 was > 100 g/kg body weight in both rats and guinea pigs (Burnette 1962).

Chronic

For two years, groups of Sherman Wistar albino rats (50 males and females per group) received feed containing the following: 1% PVP (group I), 10% PVP (group II), or unmodified diet (group III, control) (Antara Chemicals, unknown date a). PVP K-30 (average MW 40,000) was used. Ten animals from each group were necropsied at the end of the study. The animals in all groups gained weight. For the last 12 months of the study, the pattern of growth was identical between groups I and III. Body weight gain was depressed by 10% in animals of group II as compared to controls. All hematologic parameters were comparable. For 15 months of the study, urinalysis results were similar among the groups. By 18 months, albumin was noted in the urine of animals from group II. By 21 months, albumin was detected in the urine from all animals. The animals of group II had more frequent and more fluid stools. No toxic effects or gross lesions attributable to PVP consumption were noted.

Antara Chemicals (unknown date b) also conducted a 2-year feeding study using beagle dogs. Groups of four dogs received feed containing either 10% cellulose (group 1, control), 2% PVP K-30 plus 8% cellulose

(group 2), 5% PVP K-30 plus 5% cellulose (group 3), or 10% PVP K-30 (group 4). Findings at microscopic examination were generally unremarkable among the groups. Of note, swollen monocytes/macrophages in the lymph nodes were found in group 4 dogs. To a lesser extent, this observation was also noted in dogs of groups 2 and 3. The researchers suggested that the effect appeared reversible and was perhaps a transient stage in the elimination of the PVP. Growth curves were within the normal range, as were results from periodic blood and urine analysis. Organ weights and other gross observations were normal.

Inhalation Toxicity

Short-Term

Four Sprague-Dawley rats were exposed 8 h/day, 5 days/week (30 exposures) to an aerosol of PVP K-30 dissolved in water at an average concentration of 118 mg/m^3 (MW 40,000; 99.3% of the particles had a mean particle diameter $< 4 \mu$, and 87.6% were $< 2 \mu$). Animals were killed 4 days following the last exposure. Lungs were removed and stained with hematoxylin and eosin. Macrophages were filled with a granular material that, when stained with iodide-iodate solution, was compatible with PVP, though the material did not stain with periodic acid-Schiff (PAS), congo red, and chlorazol fast pink. No evidence of inflammation was found in the lungs (Lowsma et al. 1966).

Lowsma et al. (1966) also reported a study in which eight rats were exposed to aerosolized PVP-water solution at an average concentration of 146 mg/m^3 . Exposure conditions and duration were the same as in the above described study. Two animals were killed at 1, 3, 4, and 6 months after exposure. Lungs were removed for analysis. Lungs from animals killed at 1 month were identical to those from the first experiment where animals had been killed days after exposure. Lungs from animals killed at 3 months had mild lymphoid hyperplasia in the peribronchial, perivascular, and subpleural lymphoid tissue. A few giant cells with vacuoles and free particles were seen in these areas. The PAS, congo red, and chlorazol fast pink stains were negative. Lungs of animals killed at 4 months had areas in peribronchial and perivascular regions containing particles which were positive in the PAS and congo red stains. Giant cells were observed, which were negative when stained. Lungs from animals killed after 6 months were microscopically similar to those from animals killed at 3 and 4 months. Particles staining with PAS, congo red, and chlorazol fast pink were noted in the peribronchial lymphoid tissue. No PVP was seen in sections of the liver, spleen, and hilar lymph nodes until the sixth month at which time, small PVP particles were noted within the lymph nodes. The particles were stained

by PAS, congo red, and chlorazol fast pink stains. Particles were also noted in the macrophages of the lymph nodes. In one lung from each test animal, the PVP concentration was 7.6–26.5 mg/g wet weight versus a PVP concentration of 1 mg/g wet weight in nonexposed controls. The researchers considered PVP to be inert in that it did not cause an inflammatory response.

Chronic

Groups of 20 Sprague-Dawley rats were exposed to 5, 15, 45, or 120 ppm of *N*-vinylpyrrolidone-2 (NVP, the component monomer of PVP) in the air for 6 hours a day for 3 months (BASF 1985). Two control groups were exposed to fresh air. Sixteen of 20 animals of the 120-ppm group died by the fifth exposure. Another four animals of this group were moribund after the fifth exposure and were killed. Signs of toxicity observed in rats of the highest-dosing group included irritation of the mucous membranes, apathy, atony, and cyanosis. Generalized hemorrhagic diathesis, especially of the mucous membrane of the stomach, was noted. At necropsy, most of the animals were cachectic and had fatty degeneration of the liver with transitions to toxic dystrophy and necrosis of the olfactory epithelium of the nasal cavity. None of the animals of the control or other treatment groups died during the study and no clinical signs were observed. However, changes were noted in the liver of animals of the 15- and 45-ppm groups and changes in the nasal mucosa were noted in all treated animals. Some changes in hematologic and biochemical parameters were indicative of liver damage. A dose-related decrease in total protein, albumin, and α_1 -globulin was more pronounced in female rats than in males, especially in samples taken during the testing period rather than at termination. Female rats also had noticeably lower values for creatinine (significantly), urea (significantly), and potassium. (Values not reported). The changes were dose-dependent. Increases in the total bilirubin content and alkaline phosphatase activity and a decrease in the cholesterol level were pronounced in males. Rats of both sexes of the 15- and 45-ppm groups had slight decreases in values for hemoglobin, hematocrit, and erythrocytes, a reduction in the mean cell volume, and a slightly increased platelet count. With the exception of males of the 15-ppm group, the absolute and relative liver weights were increased in both sexes of the 15- and 45-ppm groups. The animals of these two groups had "centro-acinar enlargement of hepatocytes (hypertrophy) together with foci, with distinct boundaries, of atypical hepatocytes." Atrophy of the olfactory epithelium and hyperplasia of the respiratory epithelium were noted. NVP was considered hepatotoxic in rats when inhaled at concentrations ≥ 15 ppm. The no-adverse-effect level was < 5 ppm; earlier studies had found no effects at 1 ppm (BASF 1985).

A review, supported by the GAF Corporation, of the above study provided more detail. A follow-up study had been conducted in which female rats were exposed to 45 ppm NVP in the air for 3 months; animals were killed at 7 weeks (*during treatment*), 3 months (*at the end of treatment*), 12 months, or 24 months. At the end of the study, 4 control and 6 treated rats of the 15 animals designated to be killed at 24 months had survived. Hepatic toxicity was noted at 7 weeks and was more severe at 3 months. Recovery from toxicity was noted in the livers of animals killed at 12 months. A variety of lesions was noted in both groups including foci of altered cells. A hepatocarcinoma was noted in a treated animal; however, the GAF reviewers dismissed it as not significant, citing the 45-ppm dosage exceeded the maximum tolerated dose for a carcinogenicity study, the small number of survivors in both the control and dosed groups, the absence of hepatic neoplasms in animals which died before the end of the study, and the historical 1/30 incidence of liver tumors in the particular rat strain (Anonymous 1985).

Dermal Toxicity

Short-Term

A 13-week dermal toxicity study was conducted using groups of albino rats (10 of each sex). The test material, a shampoo containing 2.0% PVP, was applied to a shaved anterior dorsal site, once a day, 5 days a week, for 66 to 67 days. One group was dosed with 240 mg/kg of a 2.5% (w/v) dilution of the test material. Another three groups received 2400 mg/kg of a 25% dilution of the test material; one of these groups was rinsed with tap water 15 minutes after dosing. (It is unclear why there were two high-dose leave-on groups.) The doses were based on multiples of observed human use levels of the product calculated from a product use of 240 mg/kg (for a hypothetical 50–70 kg person). The control groups consisted of an untreated group and a rinse-off with water only group. Blood and urine samples were obtained after weeks 7 and 13; at the termination of the study animals were necropsied. Dermal irritation was noted in rats of the high-dose group, irrespective of rinse-off or leave-on protocol. All animals survived the full term of the study. Body weight gains for rats of the 2400 mg/kg group were significantly depressed as compared to controls. This depression was more noted in rats of the leave-on groups. Body weight gains for the low-dose group were comparable to control values. Glucose values were significantly depressed for male rats in both high-dose leave-on groups; blood urea nitrogen (BUN) values were elevated in both male and female rats of one high-dose leave-on group and in males of the second high-dose leave-on group. The researchers considered these discrepancies “may be related to a proposed decrease

in food intake in these animals causing increased protein catabolism which elevates BUN in circulating blood." Other blood parameters, as well as urine analysis and organ weight values were within normal range (CTFA 1978).

Ocular Toxicity/Irritation

MacRae et al. (1984) used rabbits to compare various presurgical skin antiseptics including a 7.5% PVP-iodine solution (with detergent) and 10% PVP-iodine solution (without detergent). The test substance was applied topically to one eye of each of six animals. The animals were examined by slit-lamp and corneal thick measurements made 5, 10, 30, 90, and 180 minutes after application. The tests were repeated on days 1, 3, and 7 after application. Five minutes after application, moderate corneal epithelial edema was noted in all groups except the saline control. After 3 hours, marked corneal deepithelialization, conjunctival chemosis, and anterior stromal edema were noted in all treated groups except for the 10% PVP-iodine (without detergent) and the control. After 1 week, all corneas had returned to normal appearance. The 10% PVP-iodine solution without detergent caused minimal corneal toxicity in rabbits whereas the other antiseptics tested, including the 7.5% PVP-iodine with detergent, were toxic to the cornea.

York et al. (1988) studied the effects of frequent dosing with PVP-iodine by evaluating ocular irritation in 18 rabbits according to the McDonald-Shadduck method. The right eye of each animal was dosed once each hour for 8 hours, on each of three consecutive days. Concentrations of 0.5% PVP-iodine or less were practically nonirritating when administered six times a day. Corneal epithelial wound healing was studied in 16 rabbits with superficially abraded corneas. The right eye was dosed four times daily for 7 days; eyes were examined for wound closure and the corneas stained with fluorescein. Eyes treated with 0.33% PVP-iodine had epithelial healing comparable to 0.3% gentamicin treated eyes. PVP-iodine, at concentrations of 0.5%, delayed healing by one day. Mild conjunctival congestion and swelling were noted in all eyes.

Dermal Irritation and Sensitization

Shelanski and Shelanski (1956) applied a PVP-iodine solution (10% PVP) to the hairless backs of 25 rabbits. The sites were occluded for 96 hours of contact. After 2-weeks of nontreatment, a second patch was applied in the same manner for 48 hours of contact. No dermal reactions were noted after either exposure.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Claussen and Breuer (1975) employed the yolk-sac method to determine the teratogenic effects, if any, of tetracyclines administered in a PVP vehicle. On the ninth day of gestation, New Zealand White rabbits were laparotomized. The baseline control had physiologic saline injected into both horns of each yolk sac. The vehicle control had 500 μg PVP (average MW 11,500), dissolved in saline and distilled water, injected into one horn of each sac; the other horn was injected with a saline/water solution. The yolk sacs of the experimental group were injected with a solution containing 50 μg doxycycline, and 500 μg PVP (6.07 μg magnesium was also added as a stabilizing agent). The rabbits were killed and examined on the 28th day of gestation. Results from females with lesions were omitted, thus leaving 20 control animals, 17 PVP-treated animals, and 13 doxycycline and PVP-treated animals. Resorptions and living and dead fetuses were counted. Each fetus was weighed and macroscopically examined. The skeletons were stained with alizarin blue and the crown-rump length was measured. Results were statistically evaluated with the Wilcoxon test at the 5% significance level. In the group treated with PVP alone, no difference was observed in any of the parameters measured as compared to the saline control. Adverse effects/malformations noted in fetuses treated with doxycycline and PVP were attributed to the antibiotic. PVP alone had no teratogenic effects.

MUTAGENICITY

Bacterial

The studies detailed in this section are summarized in Table 2.

Wlodkowski, Speck, and Rosenkranz (1975) tested the mutagenic potential of the PVP-iodine complex following the Ames protocol and using *Salmonella typhimurium* strains TA1530 and TA1538. Concentrations of the complex up to 20 μl did not induce a significant amount of histidine revertants when compared to positive controls capable of inducing either base substitutions (ethyl methanesulfonate, methyl methanesulfonate, and β -propiolactone) or frameshift mutations (2-nitrofluorene). The researchers also tested the in vivo mutagenic potential of the complex in *Escherichia coli* (pol A₁ -). These cells are deficient in an enzyme needed in the DNA-repair process and are unable to recover from the actions of a DNA-modifying agent. Thus, the growth of these bacteria would be inhibited by a test substance that alters the wild type genotype (pol A+). (Substances which interfere with structures other than DNA would inhibit the two strains to the same extent.) In this assay, concentrations of PVP-Iodine greater than 2 μl produced positive results.

Table 2. Mutagenicity studies on polyvinylpyrrolidone

Assay/strain	Concentration/procedure	Results/comments	Reference
Bacterial			
Ames Assay/ <i>Salmonella typhimurium</i> TA1530 and TA1538	PVP-iodine up to 20 μ l	Not mutagenic; PVP-I in contact with bacteria for 48 h	Wlodkowski et al. 1975
<i>Escherichia coli</i> (pol A-)	PVP-iodine at various amounts	Mutagenic at concentrations > 2 μ l	Wlodkowski et al. 1975
<i>Salmonella typhimurium</i> TA1530 and 1538	Not stated	Mutagenic in TA 1530; capable of base-substitution mutations; test conducted at 4°C as opposed to 37°C	Rosenkranz et al. 1976
Modified Ames/tested ability of PVP to inhibit the mutagenicity of benzo(a)pyrene (BP) in <i>S. typhimurium</i> TA98	10 and 50 times the concentration of BP	Weak inhibitor of BP mutagenicity	Calle and Sullivan 1982
Mammalian			
In vitro mouse (TK +/-) lymphoma assay	PVP up to 100 mg/ml PVP-I up to 10 mg/ml with and without activation	Not mutagenic without activation; with activation, aberrant non-dose related mutations observed with PVP-I; PVP alone not mutagenic	Kessler et al. 1980

Balb/c 3T3 transformation assay	48-h incubation of cells with up to 100 mg/ml PVP; number of transformed foci counted	Not mutagenic (non-dose- related transformations observed)	Kessler et al. 1980
In vivo Dominant lethal assay/20 male NMRI mice	Intraperitoneal injection of 72 mg PVP-I/kg (11.2% available iodine); males then mated with untreated females	Not mutagenic; initial decrease in conception rate in females mated with treated males; average number of implantations not affected	Merkle and Zeller 1979
Micronucleus test/10 NMRI mice	Intraperitoneal injection of 36 mg PVP-I/kg (11.2% available iodine); animals killed 6h after dosing; bone marrow smears prepared	Not mutagenic	Merkle and Zeller 1979
Chinese Hamster bone marrow test	Single dose: three groups of 12 mice received 38.3 mg PVP-I/kg; another three groups received 82.5 mg PVP-I/kg; animals killed at various times, metaphases evaluated Repeated dosing: five application of 38.3 mg PVP-I/kg; killed 6 h after application; metaphases examined	Not mutagenic after either single or repeated application	Merkle and Zeller 1979

In response to the above described results of Wlodkowski, Speck, and Rosenkranz, Rosenkranz, Gutter, and Speck (1976) demonstrated the mutagenic ability of PVP-iodine in *Salmonella typhimurium* TA1530, but not TA1538, when the bacteria were exposed to the test substance in suspension at 4°C (as opposed to the 37°C of most assays). The researchers concluded that the PVP-iodine complex was capable of inducing base-substitution mutations in *Salmonella*. They considered the studies of Wlodkowski, Speck, and Rosenkranz (1975) to have obscured these findings by counting mutants per plate as opposed to mutants per survivors, which was important, considering the bactericidal action of the complex. Further, the assay by Wlodkowski, Speck, and Rosenkranz (1975) allowed for 48 hours contact between the bacteria and the complex that may have resulted in toxic conditions, although those authors did not report cytotoxicity.

Calle and Sullivan (1982) used the Ames test to determine the effectiveness of several compounds, including PVP, as inhibitors of benzo(a)pyrene (BP) mutagenicity for *Salmonella typhimurium* strain TA98. For the initial screening, the test substances (dissolved in dimethylsulfoxide) were used at 10 and 50 times the concentration of BP. Plates containing 8.2 nmoles of a BP solution were incubated with 50 μ l of a test substance and the bacterial strain. The cultures also contained biotin and histidine and an S-9 activation fraction obtained from liver homogenates of β -naphtholflavone-induced rats. A BP blank, consisting of five plates, was run with each batch and served as the control. In the assay with PVP, the BP control had 270 ± 46 His revertants per plate, the plates containing 10 times as much PVP as BP had 219 ± 30 revertants per plate, and the batch containing 50 times as much PVP as BP had 141 ± 22 revertants per plate. PVP was defined as a weak inhibitor of BP mutagenicity as it produced greater than 25% inhibition at concentrations no more than 50 times the concentration of BP.

Mammalian

In Vitro

Kessler et al. (1980) used two assays to test the mutagenic potential of various chemicals including PVP and the PVP-iodine complex. In the L5178 mouse (TK+/-) lymphoma assay, concentrations of PVP up to 100 mg/ml and concentrations of the PVP-iodine complex up to 10 mg/ml did not significantly alter the mutation frequency (MF) as compared to established positive controls. The researchers considered the 100 mg/ml PVP-iodine exposure similar to typical human exposure; higher concentrations of PVP-iodine could not be tested due to cytotoxicity. In order to determine whether metabolic activation was a necessary condition for

mutagenic ability, the compounds were also tested in the presence of an S-9 fraction of liver microsomes. At a concentration of 5 mg/ml, the PVP-iodine complex produced an MF score of 4.7; this value was significant ($p < .01$). However, the MF value of 3.2 at a dose of 10 mg/ml was not significantly different from controls (high incidence of cytotoxicity was observed at this dose). PVP alone at concentrations up to 100 mg/ml was inactive in the presence of S-9. The positive controls dimethylnitrosamine (DMN) and *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) had MF scores of 25 and 4, respectively, and were classified as potent mutagens.

The second assay used by Kessler et al. (1980) was the Balb/c 3T3 transformation assay. Ten thousand 3T3 cells were incubated with the test agents for 48 hours after which the cell sheets were rinsed and cultured for 21 days. Cells were then stained and the number of transformed foci were counted. Values of 2.5 times greater than those observed in the negative control were considered to be positive transformational events. The media alone culture (negative control) had 1.22 transformed foci. In comparison, concentrations of PVP up to 100 mg/ml were inactive in this assay. PVP-iodine at a concentration of 5 mg/ml had a significant number (3.67) of transformed foci ($p < .01$); however, the results at 10 mg/ml were not significant (.67). Similarly, iodine alone produced significant results at 170 μ g/ml (3.67 transformed foci), but not at 340 μ g/ml (2.33 transformations). Thus, no dose-response relationship was established. The positive control, MNNG, produced 7.50 transformed foci. The authors concluded PVP and PVP-iodine were nonmutagenic.

In Vivo

Merkle and Zeller (1979) tested the mutagenicity of the PVP-iodine complex in mice using either the micronucleus test or the dominant lethal assay and in Chinese hamsters using the bone marrow test. All three assays used a PVP-iodine complex (11.2% available iodine) dissolved in distilled water and administered intraperitoneally. Feed and water were provided ad libitum. The significance of results were determined using the X^2 test or *U* test. In the dominant lethal assay, germ cell mutations in treated male animals are indirectly indicated by changes in the reproductive capacity of untreated females following mating. One group of 20 male NMRI mice received 72 mg of PVP-iodine/kg. A second group, the vehicle control, received one dose of 10 ml distilled water/kg. A third group was left untreated. Each male was mated with three females for 8 weeks. The animals tolerated a single dosing without incidence. The conception rate in the treated animals decreased significantly in the first week, but the average number of implantations (and resultingly, the mutagenicity index) was not affected. In the remaining weeks, all parameters remained similar between control and treated groups.

The micronucleus test screens for structural and numeric chromosome aberrations in somatic cells. An increase in micronuclei in the erythrocytes indirectly indicates mutations and spindle poisons. Groups of 10 NMRI mice (five each sex) received two intraperitoneal injections of either 36 mg of PVP-iodine/kg, or 10 ml distilled water/kg within a 24-hour period. A third group was left untreated. Six hours after the final dose, the animals were killed and bone marrow smears were prepared; 4000 normochromatic and 2000 polychromatic erythrocytes were examined per animal. The parameters evaluated in the normochromatic erythrocytes were comparable between treated and nontreated groups. In the polychromatic erythrocytes examined, micronuclei were detected in 4.3% of the cells from the treated group as compared to rates of 2.9% in the vehicle control and 3.7% in the untreated control. While the increase was of significance in comparison to control values ($p < .05$), the researchers stated that the value was within normal range (Merkle and Zeller 1979).

The bone marrow assay was conducted using groups of twelve (six of each sex) Chinese hamsters. Three groups received a single i.p. injection of 38.3 mg PVP-iodine/kg, another three received 82.5 mg PVP-iodine/kg. Three groups remained untreated and served as controls. Animals were killed 6, 24, or 48 hours after the application; 100 metaphases were evaluated. In the repeated application assay, a group received injections of 38.3 mg PVP-iodine/kg on five successive days. A vehicle control received five injections of saline solution and another group of animals remained untreated. Animals were killed 6 hours after the fifth dose; 100 metaphases were examined. The animals tolerated the single exposure without incidence; repeated injections caused signs of pain in the animals which lasted ~ 1 minute. No increases were observed in the rates of aberrant metaphases after the single or repeated dosings as compared to controls (Merkle and Zeller 1979).

CARCINOGENICITY

Pamukcu, Yalciner, and Bryan (1977) studied the ability of several compounds to inhibit the carcinogenic effects of bracken fern (BF) in albino rats. According to the researchers, BF is "strongly carcinogenic for rat bladder and intestine." The rats received a weekly s.c. injection of thiamine hydrochloride in order to maximize tumor formation. One group of 28 rats received feed containing 0.33 g BF/g of diet and 50 mg PVP/g of diet for 12 months. Another group of 20 rats received 50 mg PVP/g of diet without BF. The positive-control group (30 rats) received 0.33 g BF/g of diet; the negative-control (20 rats) group remained untreated. Intestinal tumors were found in 100% and tumors of the urinary bladder were

detected in 73% of the positive control. No such tumors were detected in the untreated control group. Rats which received a diet of both BF and PVP had a 93% incidence of intestinal tumors and an 18% incidence of urinary bladder tumors. This decrease in the incidence of bladder tumors was significant ($p < .001$). As with the untreated control, neither intestinal nor urinary bladder tumors developed in animals which received feed supplemented only with PVP.

In 1979, the International Agency for Research on Cancer (IARC) issued a monograph which evaluated the carcinogenic risk of PVP (IARC 1979). The cancer studies cited in the monograph are summarized in Table 3. Based on these studies, the IARC working group concluded "the available data do not permit an evaluation of the carcinogenicity of ... Polyvinyl Pyrrolidone to humans. The *limited evidence* of the carcinogenicity of PVP in experimental animals, together with the widespread human exposure to both compounds, suggest the need for epidemiological studies and for animal studies using the dermal, inhalational, and oral routes." In a 1987 update of the earlier monograph, PVP was classified as a "group 3" agent (IARC 1987). That is, "not classifiable as to its carcinogenicity to humans." A review by Robinson et al. (1990) of these same studies as well as of others conducted earlier concluded "the local administration of PVP results in the development of sarcomas (a 'foreign body' type reaction) but no metastases."

CLINICAL ASSESSMENT OF SAFETY

Intravenous Toxicity

In their review, Robinson et al. (1990) summarized the findings of early literature concerning human exposure to PVP via the intravenous route. These publications reported "storage disease" in humans who had received > 70 g of PVP (when it was used as a plasma expander). "Foam cells and/or deposits of vacuolar amorphous clumps" were observed in spleen, bone marrow, kidneys, and liver. The storage observations were related to dose and MW. Robinson et al. (1990) noted that the same effects were observed following administration of dextran, sucrose, and gelatin. Prolonged high-dose administration of PVP has been associated with "marginal alterations" of liver function. Robinson et al. (1990) also cited studies in which PVP storage and foreign body reactions were mistakenly diagnosed as malignant tumors.

In early studies, terms such as Dupont-Lachapelle disease, cutaneous storage syndrome, or cutaneous thesaurismosis were used to describe storage following s.c. or i.m. administration of at least 200 g of PVP. Again, storage was dependent on MW and dosing conditions (frequency, site of injection). Storage was noted in lymph nodes, kidneys, liver,

Table 3. Carcinogenicity Studies on polyvinylpyrrolidone cited in IARC monograph (1979)

Animal (no. and strain)	Dosage/route	Results	Comments	Reference
Subcutaneous				
S50 C57BL mice	Implant of 200 mg of powder of PVPs I, II, III, IV ^a surviving animals were killed after 23 months	PVP IV: 1/50 reticulum-cell sarcoma. PVP II: 3/50 lymphosarcomas. None noted among 75 untreated controls		Hueper 1957
30 C57BL mice	Implant of 200 mg of powder, MW of 10,000	No tumors detected during 2 years of observation		Hueper 1959
30 female Bethesda black rats	500 mg of powder, implanted of PVPs I, II, III, and IV	PVP IV: 1/30 squamous-cell carcinoma of skin at site of implantation. 14 benign and 24 malignant neoplasms were observed in treated animals after 26 months (see comments). Of 23 controls (observed for 13 months), 1 developed reticulum-cell sarcoma ^b	Tumors observed in treated animals were mainly RES sarcomas ^b , adenocarcinomas or squamous-cell carcinomas of the uterus and adenocarcinomas of the ovary. These were similarly distributed among groups I, III, and IV (none were found in those treated with PVP II)	Hueper 1957

20 female Bethesda Black rats	Implant of 500 mg of powder, MW of 10,000	4 reticulum-cell sarcomas		Hueper 1959
30 female Bethesda black rats	1-3 implants of 300 mg of powder, MW of 50,000	Reticulum-cell sarcomas developed in 5/30 receiving a single implant and 2/30 receiving repeated implants	Malignant tumors reticulum-cell sarcomas and carcinomas of the uterus were found in 17/200 untreated controls	Hueper 1959
20 Osborne- Mendel rats and 10 male Bethesda black rats	1 ml s.c. injections of 6% PVP in water weekly for 73 weeks	Injection site sarcomas in 13/30; none observed in rats given 0.9% saline solutions		Lusky and Nelson 1957
Intraperitoneal Groups of 50 C57BL mice	i.p. implants of 200 mg of powder of PVPs I, II, III, and IV	In 23 months: PVP II: 1 lymphosarcoma. PVP III: 2 lymphosarcomas, 1 reticulum-cell sarcoma	None seen 75 controls	Hueper 1957
PV30 C57BL mice	200 mg implant, MW of 10,000	1 lymphoma and 1 mesothelioma of the pericardium		Hueper 1959

(Table continued on next page.)

Table 3. Carcinogenicity Studies on polyvinylpyrrolidone cited in IARC monograph (1979) (*continued*)

Animal (no. and strain)	Dosage/route	Results	Comments	Reference
30 Bethesda black rats	i.p. implant of 500 mg of powder of PVPs I, II, III, and IV	PVP I: 1 squamous-cell carcinoma at incision site. A total of 13 benign and 29 malignant neoplasms were found in treated animals (see Comments). One reticulum-cell sarcoma noted among 23 controls observed for 13 months ^b	Tumors seen in treated animals were mainly RES sarcomas, adenocarcinomas and squamous-cell carcinomas of the uterus	Hueper 1957
20 female Bethesda black rats	Injection of 10,000 MW PVP	3 reticulum-cell sarcomas in treated rats	Malignant tumors, mostly reticulum- cell sarcomas and carcinomas of the uterus were found in 17/200 untreated controls	Hueper 1959
Groups of 20-35 female NIH black rats	(A) 2 g PVP average MW 10,000 (max MW: 38,000). (B) 2 g PVP average MW 18,000 (max MW: 80,000). (C) and (D) 15 g of 2 types of PVP (each of MW of 50,000) [Note: IARC described dose as 9 g]	Cancers observed in treated animals were identical or very close in number, location and structure to those seen in untreated controls.		Hueper 1961

Intra venous

15 female rats	8 injections of 2.5 ml of a 7% solution of PVPs I, II, III, and IV (weekly intervals)	2 benign and 14 malignant tumors (10 were RES sarcomas) occurred at different sites.	1 reticulum-cell sarcoma noted among 23 untreated controls in 13 month observation period ^c	Hueper 1957
27 Dutch rabbits	PVPs I, II, III, IV, and the two PVPs of MW 50,000 were injected as 7% saline solutions for a total dose of between 22,000–56,000 mg in the different groups	No tumors seen within 4 years.		Hueper 1961

^aPVP I, average MW 20,000; PVP II, average MW 22,000; PVP III, average MW 50,000; PVP IV, average MW 300,000

^bRES sarcomas: lymphosarcomas, reticulum-cell sarcomas, Kupffer cell sarcomas

^cIARC working group noted the short observation period for controls

spleen, bone, and bone marrow (Robinson et al. 1990). Parenterally administered PVP accumulated in neoplastic tissue. In discussion of these studies, Robinson et al. (1990) considered selective concentration of PVP by monocytes/macrophages to occur when the renal excretory system was overwhelmed by injections of very large amounts of material.

Inhalation Toxicity

In the early literature, several reports asserted a relation between use of hair sprays and pulmonary toxicity. Bergmann, Flance, and Blumenthal (1958) reported that women who used hair spray daily for 2 to 3 years had x-ray abnormalities which disappeared after discontinuation of hair spray use. Later, Bergmann et al. (1962) reported observations varying from slight hyperplasia to marked granuloma formation resembling sarcoidosis in lymph node biopsies of six of twelve patients who had used hair sprays. Robinson et al. (1990) reported on literature from 1958–1972 including eleven epidemiologic studies of hair dressers, totaling 2155 individuals. Twelve cases of tissue storage were recorded, eleven of which were in a single study. They state that identifiable material should be detected in the lungs or lymph nodes before a diagnosis of storage disease can be made. In their review, Robinson et al. (1990) did not consider any of these studies to report “unique pulmonary effects following the inhalation of PVP sprays.”

Ocular Toxicity

The anterior chamber was reformed with 25% PVP K-60 (MW 160,000) in salt solution after 124 cataract extractions. No postoperative infections occurred and no evidence of corneal edema was observed. Twelve patients developed small hyphemas within the first 10 postoperative days which cleared quickly and without sequellae. After slit-lamp examination, it was found that in all but one case, the PVP had disappeared from the anterior chamber 1 day after surgery; in the one exception, it disappeared after the third day. Further, in the six cases where the vitreous had been lost during the cataract extractions, no complications were noted with the mixing of vitreous and PVP. Follow-up examinations done from 1 month to 2 years postsurgery found no evidence of PVP-related complications. The investigators also reported no PVP-related complications in 25 cases of penetrating keratoplasties and eight cases of open angle glaucoma where the 25% PVP K60-balanced salt solution was used to restore the anterior chamber (King and McTigue 1964) Similar findings were reported by Sarda, Makhija, and Sharma (1969).

Dermal Irritation and Sensitization

Shelanski and Shelanski (1956) reported no dermal irritation in 200 panelists after 96 hours of contact with a patch containing PVP-iodine (10% PVP and 2% iodine). After 2 weeks, the patches were reapplied for 48 hours. No reactions were noted.

In three studies, groups of 20 panelists received a single occlusive patch of a foundation containing 2.0% PVP. One to two panelists in each group had minimal faint uniform or spotty erythema. The Primary Irritation Indexes for the three studies were 0.03, 0.03, and 0.05, respectively (CTFA 1993).

There are various published case reports of contact dermatitic reactions to the PVP-iodine antiseptic. In those cases in which patch testing of the individual components was performed, iodine was determined to be the sensitizer (Ancona 1985; Lachapelle 1984; Marks 1982; Torinuki 1990; Tosti et al. 1990). However, a different conclusion was reported by van Ketel and van den Berg (1990) who patch tested eight individuals with contact eczema to PVP-iodine. Positive reactions were noted to 5 or 10% PVP-iodine in petrolatum or to the commercial PVP-iodine solution, ointment, or scrub, but negative reactions were noted in 5 of 8 individuals also tested with 5–20% potassium iodide in petrolatum. Further, no positive reactions were observed in three of the eight who were open tested with iodine tincture. The researchers ruled out iodine as the cause of sensitization.

Repeat Insult Patch Test

A human Repeat Insult Patch Test (RIPT) was conducted by Shelanski and Shelanski (1956) using 100 panelists. During induction, patches containing PVP-iodine (10% PVP, 2% iodine) were applied for 24-hour contact, every other day for 15 applications. No reactions were noted during induction. After a 3-week nontreatment period, a 48-hour challenge patch was applied. PVP-iodine "elicited no subjective complaints and no visible reactions." Although details were not provided, the investigators reported that the study was also conducted on human skin which had been purposely abraded with coarse sandpaper. The findings were similar to those observed in intact skin with no development of infection (the abrasions were healed or healing when the patches were removed).

In an exaggerated-use study, the Draize-Shelanski patch technique was used to test powder PVP K-30 on 150 panelists. Within the 21-day induction period, nine moistened occlusive patches containing PVP were applied to the same site (usually the upper back) on panelists. Patches were removed after 24 hours, and the site was graded for irritation. A 10-day nontreatment period followed induction. At challenge, a single 24-hour occlusive patch was applied to an area adjacent to, but not in

contact with, the induction area. The challenge site was evaluated at the time of patch removal and after an additional 24 and 48 hours. During induction, "slight" reactions (graded as 2, maximum score 8) were noted at one isolated observation in five panelists (0.35% incidence). No reactions were noted at challenge (Toxigenics Inc. 1981).

PVP K-30 was tested as a 10% aqueous solution in anRIPT on 27 panelists (5 male and 22 female; age range 20–59). During the 3-week induction period, nine 24-hour occlusive patches were applied to an area of the arm. Patches were applied every other day and the site was evaluated prior to application of successive patches. Following a 2-week nontreatment period, panelists were challenged at a previously unexposed site with a 24-hour occlusive patch of the test material. The challenge site was evaluated at the time of patch removal and after an additional 24 and 48 hours. No reactions were noted during induction or challenge (Harrison Research Laboratories, Inc. 1983b).

Maximization Test

A clinical maximization assay tested a foundation containing 2.0% PVP on 25 healthy panelists (Ivy Laboratories 1993). The test consisted of three phases: pretesting, induction, and challenge. During pretesting, an occlusive patch containing the test material (0.1 ml) was applied for 48 hours of skin contact. As no irritation was noted in any of the panelists at the time of patch removal, sodium lauryl sulfate (SLS) was used in the induction phase. During induction, 1% of SLS (0.1 ml) was applied under an occlusive patch for 24 hours. The patch was then removed and replaced with a 48-hour patch containing the test substance. If no irritation was observed at the time of patch removal, the same protocol was repeated for a total of five induction exposures. Following a 10-day nontreatment period, panelists were challenged with a single 48-hour patch of the test substance placed on previously unexposed skin site (pretreatment with a 10.0% SLS patch applied for 1 hour was done prior to challenge). The challenge site was evaluated at 1 and 24 hour after patch removal. No instances of contact allergy were observed.

Phototoxicity

A 24-hour patch containing a 10% aqueous solution of PVP K-30 was applied to both volar forearms of ten panelists (2 male and 8 female; age range 18–50). One arm was irradiated with UVA light from four F40 BL Fluorescent tubes (source emits $\sim 3.3 \text{ J/cm}^2$ at a distance of 10 cm). Care was taken to avoid irradiating the other arm during the study, and panelists were cautioned against sunlight exposure during the test period. Arms were scored immediately after irradiation and after an additional 24 and 48 hours. No reactions were noted (Harrison Research Laboratories, Inc. 1983a).

Photoallergenicity

A 10% aqueous solution of PVP K-30 was tested for induction of photo-sensitivity by immunologic pathways (in such cases, the absorption of ultraviolet energy is required for the formation of the hapten or complete antigen). During the 3-week induction period, nine 24-hour occlusive patches containing 0.2 ml of the test material were applied to both forearms of 31 panelists (3 male and 28 female; age range 24–63). One arm of each panelist was irradiated with UVA and UVB light following each patch removal. Arms were irradiated for 15 minutes with UVA light emitted from four F40 BL Fluorescent tubes (source emits $\sim 3.3 \text{ J/cm}^2$ at a distance of 10 cm). Length of exposure to UVB light (from a Solarium 300 lamp which emits $1.4 \text{ mJ/cm}^2/\text{sec}$ at a distance of 20 cm) was dependent on skin type and varied from 75–105 seconds. Both arms were scored immediately before and after irradiation of the designated arm. A 2-week nontreatment period followed induction. At challenge, 24-hour patches were applied to a previously untreated site on each forearm. The challenge site of the designated arm was irradiated at the time of patch removal. Challenge sites on both arms were evaluated after patch removal, after irradiation, and at 48 and 72 hours postpatching. During induction, all panelists had slight reactions (graded as minimal erythema or erythema and/or slight edema) at the irradiated (test material applied) site. Similar reactions were noted at the control (no test material applied) irradiated site. Tanning of the irradiated arm was noted. At one induction observation, minimal erythema was noted in one panelist at the nonirradiated (test material) site. No reactions were noted at challenge. PVP K-30 did not induce contact dermal photoallergy or contact dermatitis sensitization (Harrison Research Laboratories, Inc. 1983c).

SUMMARY

PVP is a linear polymer consisting of 1-vinyl-2-pyrrolidone monomers. The monomer has a MW of 111.1; the polymer can range from 10,000–700,000. The viscosity of PVP solutions, expressed as a K-value, gives an indication of the average MW of polymers present. Typically, PVP K-30 (average MW 40,000) is used in cosmetic formulations, food additives, and pharmaceuticals.

The World Health Organization (WHO) set an ADI for PVP of 0–25 mg/kg. The USP specifies that pharmaceutical grade PVP cannot contain more than 1 ppm hydrazine. PVP has been associated with iodine to form the antiseptic Betadine.

PVP is used in cosmetic formulations as a binder, emulsion stabilizer, film former, hair fixative, and suspending agent–nonsurfactant. In January 1996, there were 395 reported cosmetic uses. PVP is used in cosmetic formulations up to 35%.

PVP induces a thymus-independent immune response, but local injection does not transform lymphocytes.

The absorption, distribution, metabolism, and excretion of PVP is dependent on MW, amount and frequency of dosing, and route of administration. PVP is taken up by cells of the monocyte/macrophage system via either pinocytosis or phagocytosis. Polymers with a weight < 25,000 are eliminated through the kidneys. An oral dosing study using 0.9 mg per rat of PVP K-30 found no significant absorption.

The oral LD₅₀ of PVP K-30 is > 100 g/kg body weight for both rats and guinea pigs. Neither toxic effects nor gross lesions attributable to PVP were found in rats maintained for 2 years on a diet containing up to 10% PVP K-30. A similar 2-year feeding study in dogs found swollen phagocytic cells in the lymph nodes. In two short-term inhalation studies using rats, PVP was detected in lung samples but no inflammatory response was noted. Mild lymphoid hyperplasia and fibroplasia were noted in the subpleural, perivascular, and peribronchial lymphatics. A 3-month inhalation study using rats and testing the PVP monomer determined a no observable adverse effect level of < 5 ppm.

In ocular studies using rabbits, a 10% PVP-iodine solution (without detergent) was minimally toxic, whereas repeated dosing with 0.5% PVP-iodine was nonirritating. A 10% PVP-iodine solution caused neither dermal irritation nor sensitization in rabbits.

No teratogenic effects were observed when up to 500 µg of PVP (MW 11,500) was injected into the yolk sac of rabbits. PVP was negative in the majority of mutagenicity studies conducted. Orally administered PVP significantly decreased the rate of bladder tumors in mice exposed to bracken fern. IARC classified PVP as a "group 3" agent, "not classifiable as to its carcinogenicity in humans." Implantation of PVP sponges into mice and rats resulted in development of local sarcomas, but without metastases.

Early literature reported "storage disease" in humans given large doses of PVP via the i.v., i.m., or s.c. routes. There also existed an unproven hypothesis relating hair spray use with pulmonary thesaurosis. In clinical studies, PVP K-30 did not induce either sensitization or a phototoxic response.

DISCUSSION

In reviewing the available data, the CIR Expert Panel elected not to delete studies on the PVP-iodine complex. The Panel acknowledged that although the complex is a separate entity from the polymer, the majority of studies done on the complex demonstrated its safety. Because fewer adverse effects would be expected from PVP compared to the PVP-iodine

complex, the Panel was confident that studies conducted on the PVP-iodine complex supported the safety of PVP.

Animal toxicity studies conducted on PVP supported its safety. Further, in a clinical sensitization study, PVP K-30 powder did not induce sensitization in any of 150 panelists. The Panel decided that PVP is safe for use in cosmetics.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that PVP (polyvinyl pyrrolidone) is safe as used in cosmetics.

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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

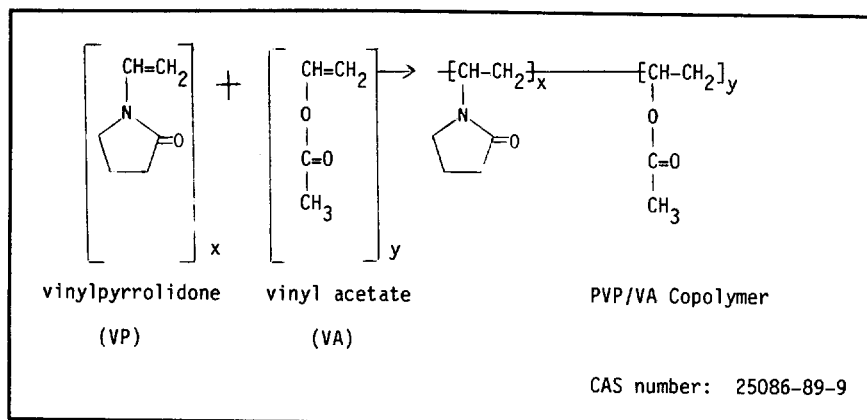
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (PVP/VA Copolymer) is the copolymer of vinyl pyrrolidone (VP) and vinyl acetate (VA) monomers.⁽¹⁾ The copolymers vary in their ratio of VP to VA and range from 70:30 to 30:70 VP to VA.⁽²⁾

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 $50 \pm 2\%$ 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

<i>Properties</i>	<i>Values</i>
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 $\pm$ 0.01 (solid) 0.955 $\pm$ 0.01 (alcohol solution)
Soluble in:	Alcohols Ether alcohols Ketone alcohols Butyrolactone Triethanolamine Aromatic hydrocarbons Esters Water (partially)
Odor	Slight and characteristic

^aData 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

^aData from Ref. 14.^bPreset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).^cData 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 observation 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)		No. dead	Days of observation	Comments	Ref.
				Formulation or solution	Ingredient (as PVP/VA)				
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.

<i>Ingredient conc. (%)</i>	<i>Dose (ml)</i>	<i>Tested in</i>	<i>Number of albino rabbits</i>	<i>Days of observation</i>	<i>Greatest irritation score/110 (max)</i>	<i>Comments</i>	<i>Ref.</i>
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) W 29(max)	Severely irritating. Some lasted through day 7. Moderately irritating. Some effects lasted through day 7.	31
50	0.1	alcohol solution	9	7	NW 16(max) W 10(max) (2 sec) W 10(max) (4 sec)	Corneal and conjunctival involvement. No reaction to conjunctival involvement. Clear by day 3. No reaction to conjunctival involvement. Clear by day 3.	32
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

^aNo wash.^bWash.

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.

<i>Ingredient conc. (%)</i>	<i>Dose</i>	<i>Tested in</i>	<i>Number of albino rabbits</i>	<i>Hours of observation time</i>	<i>Irritation score/8.0 (max)</i>	<i>Comments</i>	<i>Ref.</i>
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 cm² 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/m³ (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 $\mu\text{l/ml}$ 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 $\mu\text{l/ml}$. 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 detectable UDS in primary rat hepatocytes over an applied concentration range of 0.284–9.09 $\mu\text{l/ml}$. This concentration range produced a cell survival rate of 84.5%–6.2% 24 hours after treatment; whereas, exposure to 18.2 $\mu\text{l/ml}$ 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 semioclusion. 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⁾

Thesauriosis and Epidemiological Studies

PVP/VA Copolymer is one of several resins used in hair spray formulations.⁽²⁾ Whether these hair spray polymers cause "thesauriosis," 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 thesauriosis 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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2018 FDA VCRP Data**VP/Hexadecene Copolymer**

03A - Eyebrow Pencil	3
03B - Eyeliner	18
03C - Eye Shadow	28
03E - Eye Makeup Remover	1
03F - Mascara	31
03G - Other Eye Makeup Preparations	6
04B - Perfumes	2
04E - Other Fragrance Preparation	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07A - Blushers (all types)	8
07B - Face Powders	3
07C - Foundations	19
07D - Leg and Body Paints	3
07E - Lipstick	268
07F - Makeup Bases	3
07G - Rouges	3
07I - Other Makeup Preparations	33
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	1
12F - Moisturizing	2
12J - Other Skin Care Preps	2
13A - Suntan Gels, Creams, and Liquids	2
Total	443

VP/Eicosene Copolymer

03A - Eyebrow Pencil	12
03B - Eyeliner	12
03C - Eye Shadow	15
03D - Eye Lotion	3
03E - Eye Makeup Remover	1
03F - Mascara	185
03G - Other Eye Makeup Preparations	11
05I - Other Hair Preparations	1
07A - Blushers (all types)	2
07C - Foundations	8
07E - Lipstick	101
07G - Rouges	2
07I - Other Makeup Preparations	3
12C - Face and Neck (exc shave)	4
12D - Body and Hand (exc shave)	5
12F - Moisturizing	6
12J - Other Skin Care Preps	1
13A - Suntan Gels, Creams, and Liquids	6
Total	378

Acrylates/Stearyl Methacrylate/VP Copolymer**No Uses in FDA Database****Acrylates/VP Copolymer**

03F - Mascara	3
05H - Wave Sets	2
05I - Other Hair Preparations	1
06B - Hair Tints	1
12A - Cleansing	2
Total	9

Acrylic Acid/VP Crosspolymer

03D - Eye Lotion	1
03F - Mascara	1
03G - Other Eye Makeup Preparations	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	7
05I - Other Hair Preparations	1
08E - Nail Polish and Enamel	1
12C - Face and Neck (exc shave)	1
12F - Moisturizing	3
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	1
13C - Other Suntan Preparations	2
Total	20

Ammonium Acryloyldimethyltaurate/VP Copolymer

01B - Baby Lotions, Oils, Powders, and Creams	2
03B - Eyeliner	12
03D - Eye Lotion	28
03E - Eye Makeup Remover	2
03F - Mascara	4
03G - Other Eye Makeup Preparations	14
04E - Other Fragrance Preparation	1
07B - Face Powders	1
07C - Foundations	2
07D - Leg and Body Paints	2
07E - Lipstick	2
07I - Other Makeup Preparations	7
10E - Other Personal Cleanliness Products	5
11A - Aftershave Lotion	6
11D - Preshave Lotions (all types)	2
11G - Other Shaving Preparation Products	4
12A - Cleansing	14
12C - Face and Neck (exc shave)	185
12D - Body and Hand (exc shave)	35
12F - Moisturizing	138
12G - Night	44

12H - Paste Masks (mud packs)	35
12I - Skin Fresheners	4
12J - Other Skin Care Preps	37
13B - Indoor Tanning Preparations	10
13C - Other Suntan Preparations	1
Total	597

Butylated PVP

05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
05I - Other Hair Preparations	1
Total	4

Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer**No uses in FDA Database****Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer****No uses in FDA Database****Hydrolyzed Wheat Protein/PVP Crosspolymer**

03F - Mascara	22
03G - Other Eye Makeup Preparations	1
05A - Hair Conditioner	5
05F - Shampoos (non-coloring)	7
05G - Tonics, Dressings, and Other Hair Grooming Aids	6
06D - Hair Shampoos (coloring)	1
07C - Foundations	2
12C - Face and Neck (exc shave)	1
12F - Moisturizing	2
12H - Paste Masks (mud packs)	1
Total	48

Maltodextrin/VP Copolymer

05G - Tonics, Dressings, and Other Hair Grooming Aids	3
Total	3

Methacrylic Acid/Styrene/VP Copolymer**No uses in FDA Database****PVP**

01A - Baby Shampoos	1
02A - Bath Oils, Tablets, and Salts	1
03A - Eyebrow Pencil	9
03B - Eyeliner	61
03C - Eye Shadow	15

03D - Eye Lotion	7
03E - Eye Makeup Remover	1
03F - Mascara	169
03G - Other Eye Makeup Preparations	30
04E - Other Fragrance Preparation	16
05A - Hair Conditioner	18
05B - Hair Spray (aerosol fixatives)	15
05F - Shampoos (non-coloring)	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	260
05H - Wave Sets	13
05I - Other Hair Preparations	67
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	1
06B - Hair Tints	8
06C - Hair Rinses (coloring)	1
06H - Other Hair Coloring Preparation	1
07A - Blushers (all types)	1
07C - Foundations	12
07D - Leg and Body Paints	3
07E - Lipstick	20
07F - Makeup Bases	5
07H - Makeup Fixatives	4
07I - Other Makeup Preparations	8
09C - Other Oral Hygiene Products	23
11E - Shaving Cream	4
12A - Cleansing	6
12B - Depilatories	1
12C - Face and Neck (exc shave)	44
12D - Body and Hand (exc shave)	14
12F - Moisturizing	17
12G - Night	1
12H - Paste Masks (mud packs)	19
12I - Skin Fresheners	1
12J - Other Skin Care Preps	15
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	2
13C - Other Suntan Preparations	1
Total	900

PVP/Decene Copolymer**No uses in FDA Database****PVP/VA/Itaconic Acid Copolymer****No uses in FDA Database****PVP/VA/Vinyl Propionate Copolymer****No uses in FDA Database**

Sodium Acryloyldimethyltaurate/VP Crosspolymer

03G - Other Eye Makeup Preparations	1
12C - Face and Neck (exc shave)	1
12D - Body and Hand (exc shave)	2
12F - Moisturizing	4
13B - Indoor Tanning Preparations	1
Total	9

Styrene/VP Copolymer

03F - Mascara	1
04A - Cologne and Toilet waters	1
04E - Other Fragrance Preparation	2
05D - Permanent Waves	4
05F - Shampoos (non-coloring)	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	6
05H - Wave Sets	2
05I - Other Hair Preparations	3
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	6
06H - Other Hair Coloring Preparation	27
08B - Cuticle Softeners	2
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	2
12A - Cleansing	1
12C - Face and Neck (exc shave)	4
12F - Moisturizing	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	2
Total	70

Triaccontanyl PVP

03B - Eyeliner	2
03C - Eye Shadow	2
03F - Mascara	17
03G - Other Eye Makeup Preparations	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07B - Face Powders	3
07C - Foundations	11
07E - Lipstick	31
07F - Makeup Bases	1
07I - Other Makeup Preparations	1
12C - Face and Neck (exc shave)	1
Total	72

Triaccontene/VP Copolymer

No uses in FDA Database

Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer

03F - Mascara	1
05B - Hair Spray (aerosol fixatives)	8
05C - Hair Straighteners	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	35
05I - Other Hair Preparations	5
06E - Hair Color Sprays (aerosol)	13
06H - Other Hair Coloring Preparation	4
12C - Face and Neck (exc shave)	3
Total	70

VP/Acrylates/Lauryl Methacrylate Copolymer

05B - Hair Spray (aerosol fixatives)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	4
05I - Other Hair Preparations	10
Total	15

VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester

03F - Mascara	1
11A - Aftershave Lotion	1
12G - Night	1
Total	3

**VP/Dimethylaminoethylmethacrylate/
Polycarbamyl/Polyglycol Ester****No uses in FDA Database****VP/Dimethylaminoethylmethacrylate Copolymer**

03D - Eye Lotion	1
03F - Mascara	2
03G - Other Eye Makeup Preparations	1
05A - Hair Conditioner	4
05B - Hair Spray (aerosol fixatives)	1
05C - Hair Straighteners	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	44
05H - Wave Sets	2
05I - Other Hair Preparations	11
06B - Hair Tints	1
12C - Face and Neck (exc shave)	1
12D - Body and Hand (exc shave)	1
12G - Night	1
12J - Other Skin Care Preps	1
Total	72

VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester

No uses in FDA Database

VP/DMAPA Acrylates Copolymer

05A - Hair Conditioner	2
05B - Hair Spray (aerosol fixatives)	1
05F - Shampoos (non-coloring)	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	21
05I - Other Hair Preparations	1
06H - Other Hair Coloring Preparation	4
Total	31

VP/Polycarbamyl Polyglycol Ester

03D - Eye Lotion	2
03F - Mascara	1
12C - Face and Neck (exc shave)	2
12J - Other Skin Care Preps	1
Total	6

VP/VA Copolymer

02A - Bath Oils, Tablets, and Salts	1
03A - Eyebrow Pencil	2
03B - Eyeliner	13
03C - Eye Shadow	1
03D - Eye Lotion	1
03F - Mascara	23
03G - Other Eye Makeup Preparations	6
05A - Hair Conditioner	5
05B - Hair Spray (aerosol fixatives)	17
05C - Hair Straighteners	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	234
05H - Wave Sets	12
05I - Other Hair Preparations	61
06B - Hair Tints	2
06E - Hair Color Sprays (aerosol)	18
06G - Hair Bleaches	8
06H - Other Hair Coloring Preparation	5
07A - Blushers (all types)	10
07B - Face Powders	5
07C - Foundations	19
07D - Leg and Body Paints	2
07F - Makeup Bases	2
07I - Other Makeup Preparations	18
08A - Basecoats and Undercoats	1
12B - Depilatories	2
12C - Face and Neck (exc shave)	6

12D - Body and Hand (exc shave)	1
12F - Moisturizing	1
12H - Paste Masks (mud packs)	2
13B - Indoor Tanning Preparations	1
Total	480

VP/Vinyl Alcohol Copolymer

No uses in FDA Database

VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer

05B - Hair Spray (aerosol fixatives)	6
06E - Hair Color Sprays (aerosol)	13
Total	19

19 Ingredients Used



Memorandum

TO: Bart Heldreth, Ph.D., Executive Director
COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 2, 2017

SUBJECT: Concentration of Use by FDA Product Category: Vinylpyrrolidone Polymers

Concentration of Use by FDA Product Category – Vinylpyrrolidone Polymers*

VP/Hexadecene Copolymer
 VP/Eicosene Copolymer
 Acrylates/Stearyl Methacrylate/VP Copolymer
 Acrylates/VP Copolymer
 Acrylic Acid/VP Crosspolymer
 Ammonium Acryloyldimethyltaurate/VP Copolymer
 Butylated PVP
 Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer
 Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer
 Hydrolyzed Wheat Protein/PVP Crosspolymer
 Maltodextrin/VP Copolymer
 Methacrylic Acid/Styrene/VP Copolymer
 PVP
 PVP/Decene Copolymer
 PVP/VA/Itaconic Acid Copolymer
 PVP/VA/Vinyl Propionate Copolymer
 Sodium Acryloyldimethyltaurate/VP Crosspolymer
 Styrene/VP Copolymer
 Triacontanyl PVP
 Triacontene/VP Copolymer
 Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer
 VP/Acrylates/Lauryl Methacrylate Copolymer
 VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester
 VP/Dimethylaminoethylmethacrylate Copolymer
 VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester
 VP/DMAPA Acrylates Copolymer
 VP/Polycarbamyl Polyglycol Ester
 VP/VA Copolymer
 VP/Vinyl Alcohol Copolymer
 VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer

Ingredient	Product Category	Maximum Concentration of Use
VP/Hexadecene Copolymer	Eye brow pencils (3A)	0.4-12.2%
VP/Hexadecene Copolymer	Eyeliners (3B)	1.2-11.5%
VP/Hexadecene Copolymer	Eye shadows (3C)	2-17.2%
VP/Hexadecene Copolymer	Eye lotions (3D)	1.5%
VP/Hexadecene Copolymer	Mascara (3F)	0.25-4.1%
VP/Hexadecene Copolymer	Blushers (7A)	0.036-11.5%
VP/Hexadecene Copolymer	Foundations (7C)	1-9.6%

VP/Hexadecene Copolymer	Lipstick (7E)	0.7-24.1%
VP/Hexadecene Copolymer	Makeup bases (7F)	1.2-4.5%
VP/Hexadecene Copolymer	Other makeup preparations (7I)	3.7-8.9%
VP/Hexadecene Copolymer	Cuticle softeners (8B)	10.3%
VP/Hexadecene Copolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	3%
VP/Hexadecene Copolymer	Depilatories (12B)	2%
VP/Hexadecene Copolymer	Face and neck products Not spray (12C)	0.25-3%
VP/Hexadecene Copolymer	Body and hand products Not spray (12D)	2.5-3%
VP/Hexadecene Copolymer	Moisturizing products Not spray (12F)	0.5%
VP/Hexadecene Copolymer	Other skin care preparations (12J)	0.5%
VP/Hexadecene Copolymer	Suntan products Not spray (13A)	1-5%
VP/Eicosene Copolymer	Baby lotions, oils and creams Not powder (1B)	2%
VP/Eicosene Copolymer	Eyebrow pencils (3A)	0.44%
VP/Eicosene Copolymer	Eyeliners (3B)	2.3-8%
VP/Eicosene Copolymer	Eye shadows (3C)	2-3%
VP/Eicosene Copolymer	Eye lotions (3D)	2%
VP/Eicosene Copolymer	Mascara (3F)	2-5.5%
VP/Eicosene Copolymer	Other eye makeup preparations (3G)	1.5%
VP/Eicosene Copolymer	Other fragrance preparations (4E)	4.3%
VP/Eicosene Copolymer	Blushers (7A)	0.11-2%
VP/Eicosene Copolymer	Face powders (7B)	0.3-0.5%
VP/Eicosene Copolymer	Foundations (7C)	0.15-2%
VP/Eicosene Copolymer	Lipstick (7E)	0.96-5.6%
VP/Eicosene Copolymer	Makeup fixatives (7H)	1.5%
VP/Eicosene Copolymer	Other makeup preparations (7I)	0.2-6.9%
VP/Eicosene Copolymer	Face and neck products Not spray (12C) Spray (12C)	0.7-2% 3%
VP/Eicosene Copolymer	Body and hand products Not spray (12D)	0.4-2%
VP/Eicosene Copolymer	Moisturizing products Not spray (12F)	2.9%
VP/Eicosene Copolymer	Night products Not spray (12G)	0.7%
VP/Eicosene Copolymer	Other skin care preparations (12J)	0.5%
VP/Eicosene Copolymer	Suntan products Not spray (13A)	1-3%
Acrylates/VP Copolymer	Tonics, dressings and other hair	0.95%

	grooming aids (5G)	
Acrylates/VP Copolymer	Shaving cream (11E)	0.81%
Acrylates/VP Copolymer	Body and hand products Not spray (12D)	1.5%
Acrylates/VP Copolymer	Suntan products Not spray (13A)	0.67%
Acrylic Acid/VP Crosspolymer	Other eye makeup preparations (3G)	1%
Acrylic Acid/VP Crosspolymer	Tonics, dressings and other hair grooming aids (5G)	0.3-1%
Acrylic Acid/VP Crosspolymer	Bath soaps and detergents (10A)	0.5%
Acrylic Acid/VP Crosspolymer	Face and neck products Not spray (12C)	0.8%
Acrylic Acid/VP Crosspolymer	Suntan products Not spray (13A)	0.5%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Baby lotions, oils and creams Not powder (1B)	0.5%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Eye shadows (3C)	0.55%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Eye lotions (3D)	0.5-3%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Eye makeup removers (3E)	1.4%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Perfumes (4B)	1%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Other fragrance preparations (4E)	0.35%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Tonics, dressings and other hair grooming aids (5G)	0.8%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Foundations (7C)	1%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Lipstick (7E)	1.5%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Other personal cleanliness products (10E)	0.25%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Aftershave lotions (11A)	0.96-1%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.2-2%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Face and neck products Not spray (12C)	0.5-2%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Body and hand products Not spray (12D) Spray (12D)	0.33-1.7% 0.096%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Moisturizing products Not spray (12F)	1.4-2%

Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Night products Not spray (12G)	1.2%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Paste masks and mud packs (12H)	0.5-1.4%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Other skin care preparations (12J)	0.3-1.5%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Suntan products Not spray (13A)	1.2%
Ammonium Acryloyldimethyltaurate/VP Crosspolymer	Other suntan preparations (13C)	1.5%
Hydrolyzed Wheat Protein/PVP Crosspolymer	Other eye makeup preparations (3G)	0.18-0.4%
Hydrolyzed Wheat Protein/PVP Crosspolymer	Hair sprays Aerosol (5B) Pump spray (5B)	0.055% 0.017-0.04%
Hydrolyzed Wheat Protein/PVP Crosspolymer	Tonics, dressings and other hair grooming aids (5G)	0.088-0.24%
Hydrolyzed Wheat Protein/PVP Crosspolymer	Foundations (7C)	0.4-0.45%
Hydrolyzed Wheat Protein/PVP Crosspolymer	Face and neck products Not spray (12C)	0.4%
Hydrolyzed Wheat Protein/PVP Crosspolymer	Body and hand products Not spray (12D)	0.038%
Hydrolyzed Wheat Protein/PVP Crosspolymer	Suntan products Not spray (13A)	0.4%
Maltodextrin/VP Copolymer	Tonics, dressings and other hair grooming aids Not spray (5G)	3%
Maltodextrin/VP Copolymer	Body and hand products Spray (12D)	0.35%
PVP	Baby lotions, oils and creams Not powder (1B)	4.4%
PVP	Bath oils, tablets and salts (2A)	0.016-3%
PVP	Eyebrow pencils (3A)	2-9%
PVP	Eyeliners (3B)	0.66-12%
PVP	Eye shadows (3C)	0.78-8%
PVP	Eye lotions (3D)	0.005-1.5%
PVP	Mascara (3F)	0.34-5%
PVP	Other eye makeup preparations (3G)	1-5%
PVP	Hair conditioners (5A)	0.002-1.1%
PVP	Hair sprays Aerosol (5B) Pump spray (5B)	0.6-5% 0.6-3.6%
PVP	Shampoos (noncoloring) (5F)	0.0005-0.29%
PVP	Tonics, dressings and other hair grooming aids (5G)	0.5-9%

PVP	Other hair preparations (noncoloring) (5I)	0.8%
PVP	Hair dyes and colors (6A)	10%
PVP	Other hair coloring preparations (6H)	1.4%
PVP	Blushers (7A)	1.5-3%
PVP	Face powders (7B)	0.1%
PVP	Foundations (7C)	0.1-1%
PVP	Leg and body paints (7D)	35%
PVP	Lipstick (7E)	0.4-5%
PVP	Makeup bases (7F)	0.95%
PVP	Makeup fixatives (7H)	1-5%
PVP	Other makeup preparations (7I)	1-2%
PVP	Cuticle softeners (8B)	5%
PVP	Nail polish and enamel (8E)	0.5%
PVP	Other manicuring preparations (8G)	2%
PVP	Dentifrices (9A)	0.065-13.3%
PVP	Mouthwashes and breath fresheners (9B)	2.3%
PVP	Deodorants Not spray (10B)	0.66%
PVP	Aftershave lotions (11A)	0.005%
PVP	Beard softeners (11B)	2%
PVP	Shaving cream (11E)	0.1-0.45%
PVP	Other shaving preparations (11G)	10%
PVP	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.000003-0.38%
PVP	Face and neck products Not spray (12C)	0.1-10%
PVP	Body and hand products Not spray (12D)	0.2-3%
PVP	Moisturizing products Not spray (12F)	0.6%
PVP	Night products Not spray (12G)	0.1%
PVP	Paste masks and mud packs (12H)	0.1-1%
PVP	Other skin care preparations (12J)	0.19-4%
PVP	Suntan products Not spray (13A)	0.1%
Sodium Acryloyldimethyltaurate/VP Crosspolymer	Face and neck products Not spray (12C)	0.5%
Sodium Acryloyldimethyltaurate/VP Crosspolymer	Moisturizing products Not spray (12F)	1%
Sodium Acryloyldimethyltaurate/VP	Night products	

Crosspolymer	Not spray (12G)	0.89%
Sodium Acryloyldimethyltaurate/VP Crosspolymer	Suntan products Not spray (13A)	1%
Styrene/VP Copolymer	Eyeliner (3B)	0.4%
Styrene/VP Copolymer	Eye lotions (3D)	0.038%
Styrene/VP Copolymer	Mascara (3F)	0.4%
Styrene/VP Copolymer	Hair conditioners (5A)	0.15-0.2%
Styrene/VP Copolymer	Shampoos (noncoloring) (5F)	0.15%
Styrene/VP Copolymer	Tonics, dressing and other hair grooming aids (5G)	0.2%
Styrene/VP Copolymer	Other hair preparations (noncoloring) (5I)	0.08-0.2%
Styrene/VP Copolymer	Hair dyes and colors (6A)	0.8%
Styrene/VP Copolymer	Other hair coloring preparations (6H)	0.007%
Styrene/VP Copolymer	Other manicuring preparations (8G)	0.29%
Styrene/VP Copolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.021%
Styrene/VP Copolymer	Face and neck products Not spray (12C) Spray (12C)	0.012-0.4% 0.057%
Styrene/VP Copolymer	Moisturizing products Not spray (12F)	0.62%
Styrene/VP Copolymer	Skin fresheners (12I)	0.016-0.2%
Styrene/VP Copolymer	Other skin care preparations (12J)	0.012-0.2%
Triacetyl PVP	Eyeliner (3B)	0.66%
Triacetyl PVP	Mascara (3F)	3.2%
Triacetyl PVP	Hair sprays Aerosol (5B)	6.3%
Triacetyl PVP	Tonics, dressings and other hair grooming aids (5G)	1.5-4.5%
Triacetyl PVP	Lipstick (7E)	3-7.3%
Triacetyl PVP	Face and neck product Not spray (12C)	1.5%
Triacetyl PVP	Suntan products Not spray (13A)	2%
Triacetyl PVP	Other suntan preparations (13C)	2%
Vinyl Caprolactam/VP/ Dimethylaminoethyl Methacrylate Copolymer	Tonics, dressings and other hair grooming aids (5G)	1.2-5%
Vinyl Caprolactam/VP/ Dimethylaminoethyl Methacrylate Copolymer	Hair color sprays (6E)	1%
Vinyl Caprolactam/VP/	Hair bleaches (6G)	1.2%

Dimethylaminoethyl Methacrylate Copolymer		
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer	Face and neck products Not spray (12C)	0.3%
VP/Acrylates/Lauryl Methacrylate Copolymer	Eye lotions (3D)	0.0097%
VP/Acrylates/Lauryl Methacrylate Copolymer	Tonics, dressings and other hair grooming aids (5G)	3.5%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Eyeliners (3B)	2.5%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Eye shadows (3C)	1.2%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Mascara (3F)	0.3%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Foundations (7C)	0.1%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Makeup bases (7F)	0.1%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Face and neck creams Not spray (12C)	1%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Night creams Not spray (12G)	0.6%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Paste masks and mud packs (12H)	0.04%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Other skin care preparations (12J)	1%
VP/Dimethylconylacrylate/Polycarbamyl/Polyglycol Ester	Indoor tanning preparations (13B)	0.2%
VP/Dimethylaminoethylmethacrylate/Polycarbamyl/Polyglycol Ester	Hair sprays Aerosol (5B)	5.6%
VP/Dimethyaminoethylmethacrylate Copolymer	Mascara (3F)	0.2-1%
VP/Dimethyaminoethylmethacrylate Copolymer	Tonics, dressings and other hair grooming aids (5G)	0.5-6%
VP/Dimethyaminoethylmethacrylate Copolymer	Skin cleansing (cold creams, cleansing lotions, liquids and pads) (12A)	0.04%
VP/Dimethyaminoethylmethacrylate Copolymer	Face and neck products Not spray (12C)	0.6%
VP/Dimethyaminoethylmethacrylate Copolymer	Body and hand products Not spray (12D)	1.2%
VP/DMAA Acrylates Copolymer	Hair conditioners (5A)	0.08%
VP/DMAA Acrylates Copolymer	Tonics, dressings and other hair grooming aids (5G)	1-7.5%
VP/Polycarbamyl Polyglycol Esters	Mascara (3F)	0.036%

VP/VA Copolymer	Eye brow pencils (3A)	1.5-10%
VP/VA Copolymer	Eyeliners (3B)	0.5-3%
VP/VA Copolymer	Eye shadows (3C)	1.3-1.6
VP/VA Copolymer	Mascara (3F)	0.96-8.5%
VP/VA Copolymer	Other eye makeup preparations (3G)	10%
VP/VA Copolymer	Hair sprays Aerosol (5B) Pump spray (5B)	4.2-10% 4-9%
VP/VA Copolymer	Tonics, dressings and other hair grooming aids (5G)	1-9.9%
VP/VA Copolymer	Other hair preparations (noncoloring) (5I)	4.5%
VP/VA Copolymer	Hair dyes and colors (6A)	0.29-0.98%
VP/VA Copolymer	Hair color sprays (6E)	1-1.5%
VP/VA Copolymer	Hair lighteners with color (6F)	1.5%
VP/VA Copolymer	Blushers (all types) (7A)	0.5-1.5%
VP/VA Copolymer	Foundations (7C)	0.0075-4%
VP/VA Copolymer	Leg and body paints (7D)	1.5%
VP/VA Copolymer	Lipstick (7E)	4%
VP/VA Copolymer	Makeup bases (7F)	1.4%
VP/VA Copolymer	Other makeup preparations (7I)	1.5%
VP/VA Copolymer	Nail polish and enamel (8E)	0.001%
VP/VA Copolymer	Mouth washes and breath fresheners (9B)	0.07%
VP/VA Copolymer	Beard softeners (11B)	0.5%
VP/VA Copolymer	Depilatories (12B)	6.8%
VP/VA Copolymer	Body and hand products Not spray (12D)	6.3%
VP/VA Copolymer	Paste masks and mud packs (12H)	44%
VP/VA Copolymer	Indoor tanning preparations (13B)	0.5%
VP/Vinyl Caprolactam/DMAPA Acrylates	Hair conditioners (5A)	1.4%
VP/Vinyl Caprolactam/DMAPA Acrylates	Hair sprays Pump spray (5B)	1.4%
VP/Vinyl Caprolactam/DMAPA Acrylates	Hair color sprays (6E)	0.5%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2017
Table prepared: October 2, 2017



Memorandum

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

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

DATE: April 24, 2018

SUBJECT: Studies of Products Containing VP/Hexadecene Copolymer

Derma Consult GmbH. 2013. Controlled use test of the product eye shadow containing 12.22% VP/Hexadecene Copolymer.

Derma Consult GmbH. 2016. Human patch test of a cosmetic base containing 14.95% VP/Hexadecene Copolymer.

DC Brunnenstraße 61 53347 Alfter Germany

Phone: 0 22 22 / 91 08 - 10
FAX: 0 22 22 / 91 08 - 40
E-mail: info@dermaconsult.com
Web: www.dermaconsult.com
Date: 13.03.2013

Controlled User Test of the Product "Eyeshadow"

Ophthalmologic Test *containing 12.22 %
VP / Hexadecene Copolymer*

Summary

Study Sponsor.....

Performance of Test: Derma Consult GmbH
and Evaluation by Brunnenstr. 61
53347 Alfter
Germany

Supervisor of Study: Dr. med. H. O. Vielhaber ophthalmologist
Dr. H. P. Nissen Ph.D.

Order date.....: 05.02.2013

Test Product.....

A. Eyeshadow

Subjects: Number of individuals.: 10 (5 wearers of contact lenses)
Sex: female
Age range.....: 20 - 59 years (average 38,2)

Test Area: Face (eye region)

Application: Duration....: 2 weeks
Frequency.: once daily

Study period: February / March 2013

manager: Dr. Hans-Peter Nissen B. Nissen-Zoufal Dr. J. Nissen
VAT-REG.No. DE 123369725

district court Bonn HRB 5272
Tax No. 222/5703/0374

Performance of Test

Subjects were informed about importance and meaning of the study. Written informed consent was obtained from all the volunteers prior to entry into the trial. Subjects could withdraw from study at any time without giving any reason. The following criteria were used for selection of subjects:

for inclusion in study:

- female
- age >18 years
- clinically healthy
- informed volunteers
- 5 subjects wearing contact lenses (type not standardized) regularly (min. 5 days/week)

for exclusion from study:

- eye diseases
- known allergies to pollen / dust mites
- skin diseases
- pregnancy
- use of corticoids / antiallergics

Day 1:

- Distribution of the test product along with application instructions

Day 14:

- Examination of the eye and eye region by an ophthalmologist

Results

The product was assessed by the subjects very positively. The examination by an ophthalmologist showed, that no subject had subjective or objective eye irritation in form of tears or pain, nor had eyelid irritation been seen after the use of the product for two weeks. No incompatibility (redness, itching) was observed in or reported by any of the volunteers and also no discomfort was reported on.

The examination of the eye ground with the help of a slit-lamp microscope showed that no irritant contact conjunctivitis with chemosis could be observed after the use of the product.

On the basis of the test results and under the test conditions, the product

“Eyeshadow

is to be classified as “harmless” as regards the possibility of eye or eyelid irritation and is suitable for use by contact lens wearers.

Signature:



Dr. H.-O. Vielhaber
Ophthalmologist

Signature:



Dr. H.-P. Nissen
Chemist – Ph.D.

13.03.2013
PROTOCOL

Eyeshadow

Subject	Sex	Age	Contact Lenses	Inclusion Criteria	Objective evaluation				Subjective Evaluation					Comment
					Tearing	Reddening	Scaling	Eyeground	Tearing	Pain	Itching	Discomfort	Reddening	
1	F	20	X	OK	-	-	-	OK	-	-	-	-	-	
2	F	37	X	OK	-	-	-	OK	-	-	-	-	-	
3	F	32	X	OK	-	-	-	OK	-	-	-	-	-	
4	F	50	-	OK	-	-	-	OK	-	-	-	-	-	
5	F	48	-	OK	-	-	-	OK	-	-	-	-	-	
6	F	24	X	OK	-	-	-	OK	-	-	-	-	-	
7	F	56	-	OK	-	-	-	OK	-	-	-	-	-	
8	F	59	-	OK	-	-	-	OK	-	-	-	-	-	
9	F	25	-	OK	-	-	-	OK	-	-	-	-	-	
10	F	31	X	OK	-	-	-	OK	-	-	-	-	-	

DC Brunnenstraße 61 53347 Alfter Germany

Phone: +49 - (0)2222 / 9108 - 10
Fax: +49 - (0)2222 / 9108 - 40
E-mail: info@dermaconsult.com
Web: www.dermaconsult.com
Date: 05.02.2016

Concentration: undiluted
by Human Patch Test (Cosmetic Trial)

*cosmetic base
containing 14.95%*

Performing Laboratory
Derma Consult GmbH

Brunnenstr. 61
53347 Alfter
Germany

*VP/Hexadene
copolymer*

Study Details

Type of study.....: Determination of irritating effects to the skin with an occlusive patch test.
Study Period: February 2016
Study Director: Dr. med. H. Prieur
Test subjects: 50 (18-67 years; sex distribution non-standardized)
27 normal healthy, 6 eczema, 3 allergy and 14 subjects with sensitive skin
Test site.....: Back
Concentration.....: Undiluted
Controls.....: SDS (1% in water), water

Summary Results

All participants completed the study. Under the test conditions, SDS (1% in water) caused positive reactions in 21 subjects. The negative control water showed no reactions. None of the subjects showed any reaction to the test product. On the basis of the test results and under the test conditions, the product

is to be classified as 'harmless' as regards the possibility of skin irritation.

Signature:


Dr. med. H. Prieur
Dermatologist - Allergist

Signature:


Dr. J. Nissen
Pharmacist - M.D.R.A.

Methodology

Introduction

The epicutaneous patch test allows us to assess the primary skin irritation potential of cosmetic-finished products and raw materials.

Description

All the work described in this expertise was conducted considering the guidelines by COLIPA (Walker A.P. et al: Test Guidelines for Assessment of Skin Compatibility of Cosmetic Finished Products in Man. Food and Chemical Toxicology 34, 1996, 651-660; COSMETICS EUROPE: Product test guidelines for the assessment of human skin compatibility 1997).

Because it was a study with humans, it was carried out taking into account the principle requirements of the Declaration of Helsinki (1964) and subsequent revisions.

Experiments were carried out on 50 volunteers (27 normal healthy subjects, 6 eczema patients, 3 allergy patients, 14 subjects with sensitive skin) between the ages of 18 to 67. Sex distribution was not standardized. The volunteers were clearly informed, verbally and in writing, regarding the nature of the study, the timetable, constraints and possible risks. They gave their written informed consent before participating in the study.

Participants could withdraw from the study at any time without giving reason. During the test period, the subjects refrained from using other substances on the test areas.

Inclusion criteria

- informed volunteers
- age $\geq$ 18 years

Exclusion criteria

- pregnant or lactating women
- blemishes or marks (tattoos, sunburn) which interfere with scoring
- any skin disease that may interfere with the aim of the study

Procedure

The product was applied in a concentration as outlined above in square test-chambers (allergEAZE[®] clear Patch Test Chambers; SmartPractice[®], Phoenix, AZ) to the backs of the panellists for a period of 48 hours. Proper adherence of the test patches was assured by the inclusion of sodium dodecyl sulphate (SDS) in one concentration (1%) as positive control. Water was used as a negative control.

The treatment sites were assessed for the presence of irritation by a trained evaluator using a 5 point visual scoring scale at 48 h (30 min after patch removal) and 72 h after patch application.

Scoring scale

<u>Erythema</u>	0: no E., 1: slight E., 2: significant E., 3: pronounced E., 4: strong E.
<u>Fissure</u>	0: no F., 1: minimal F., 2: significantly perceptible F., 3: pronounced F., 4: ulceration
<u>Scaling</u>	0: no Sc., 1: minimal Sc., 2: moderate Sc., 3: significant Sc., 4: closed scale crust

Results

The test results outlining the data for erythema, scaling and fissure formation on a per subject base for the test product are attached in tabulated form.

Literature

Magnus Lindberg and Mihaly Matura:
"Patch Testing" in
J. D. Johansen, P.J. Frosch, J.-P. Lepoittevin (Eds.),
Contact Dermatitis 5th Edition
Springer-Verlag, Berlin Heidelberg, Germany (2011), pp. 439-464

J.-M. Lachapelle, H. I. Maibach:
"Patch Testing and Prick Testing - A practical Guide
Official Publication of the ICDRG"
Third Edition
Springer-Verlag, Berlin Heidelberg, Germany (2012)

Appendix: test protocol

04.02.2016 Product:
PROTOCOL

No.	Type	after 48 h			after 72 h		
		E	F	S	E	F	S
1	S	0	0	0	0	0	0
2		0	0	0	0	0	0
3	A	0	0	0	0	0	0
4		0	0	0	0	0	0
5		0	0	0	0	0	0
6	S	0	0	0	0	0	0
7		0	0	0	0	0	0
8		0	0	0	0	0	0
9	E	0	0	0	0	0	0
10	S	0	0	0	0	0	0
11	S	0	0	0	0	0	0
12		0	0	0	0	0	0
13		0	0	0	0	0	0
14	S	0	0	0	0	0	0
15		0	0	0	0	0	0
16		0	0	0	0	0	0
17	A	0	0	0	0	0	0
18		0	0	0	0	0	0
19	S	0	0	0	0	0	0
20		0	0	0	0	0	0
21	E	0	0	0	0	0	0
22		0	0	0	0	0	0
23	S	0	0	0	0	0	0
24	S	0	0	0	0	0	0
25		0	0	0	0	0	0
26		0	0	0	0	0	0
27	A	0	0	0	0	0	0
28		0	0	0	0	0	0
29		0	0	0	0	0	0
30	S	0	0	0	0	0	0
31		0	0	0	0	0	0
32		0	0	0	0	0	0
33	E	0	0	0	0	0	0
34		0	0	0	0	0	0
35		0	0	0	0	0	0
36		0	0	0	0	0	0
37	S	0	0	0	0	0	0
38	S	0	0	0	0	0	0
39		0	0	0	0	0	0
40		0	0	0	0	0	0
41	S	0	0	0	0	0	0
42	S	0	0	0	0	0	0
43		0	0	0	0	0	0
44		0	0	0	0	0	0
45		0	0	0	0	0	0
46		0	0	0	0	0	0
47	E	0	0	0	0	0	0
48	E	0	0	0	0	0	0
49	S	0	0	0	0	0	0
50	E	0	0	0	0	0	0
SUM		0,0	0,0	0,0	0,0	0,0	0,0

Erythema (E): no E.: 0, slight E.: 1, clear E.: 2, severe E.: 3, very severe E.: 4
 Fissures (F): no F.: 0, minimal F.: 1, clearly visible F.: 2, distinct F.: 3, ulceration: 4
 Scales (S): no S.: 0, minimal S.: 1, clearly visible S.: 2, moderate S.: 3, distinct S.: 4

S: subjects with sensitive skin
 E: patients with eczema
 A: patients with allergy



Memorandum

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

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: April 25, 2018

SUBJECT: Scientific Literature Review: Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics (release date: April 13, 2018)

The Council has no suppliers listed for the following ingredients included in the report on vinylpyrrolidone polymers:

- Acrylates/Stearyl Methacrylate/VP Copolymer
- PVP/Decene Copolymer
- PVP/VA/Itaconic Acid Copolymer
- PVP/VA/Vinyl Propionate Copolymer
- VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester

The Council respectfully submits the following comments on the Scientific Literature Review: Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics.

Key Issues

According to the March 2018 post-meeting announcement, Vinyl Caprolactum/VP/Dimethylaminoethyl Methacrylate Copolymer is also included in the Acrylates Copolymer re-review (it should have ** in the list of ingredients in the Introduction). Does the CIR Expert Panel really want to review three ingredients (Vinyl Caprolactum/VP/Dimethylaminoethyl Methacrylate Copolymer; Acrylates/VP Copolymer; VP/Dimethylaminoethylmethacrylate Copolymer) in two different reports at the same time?

In the Introduction, it would be helpful to identify the ingredients for which NICNAS reports are available. It should also be stated if NICNAS considers these polymers to be polymers of low concern (PLC). The criteria to be considered a polymer of low concern are at <https://www.nicnas.gov.au/reforms/consultation-paper-5/attachment-b-polymer-of-low-concern-criteria#22>.

Additional Considerations

Introduction - In the Introduction, it would be helpful to state why this report is being completed as a new report, rather than a re-review.

Please be more specific and state what is meant by “a rereview of this safety assessment”, e.g., re-review of the Acrylates Copolymer report.

The Introduction is not clear as to whether or not the 8 (should be 9) previously reviewed ingredients are being reviewed in this report, or if the data on these ingredients are being used to support the safety of the new ingredients in the report.

Composition/Impurities, Ammonium Acryloyldimethyltaurate/VP Copolymer and Sodium Acryloyldimethyltaurate/VP Crosspolymer - It is misleading to state that Sodium Acryloyldimethyltaurate/VP Crosspolymer contains residual monomers and/or impurities that are classified as hazardous, when the NICNAS report also states: “These [monomer and/or impurities] are not present in the notified polymer as introduced above the cut off concentration for classification [as a polymer of low concern].”

Cosmetic Use - As this report is being prepared because of the number of uses of VP/Hexadecene Copolymer and VP/Eicosene Copolymer reported to the VCRP, the text should also describe the uses of these two ingredients.

It should be noted that use concentrations of VP/VA Copolymer in the CIR original report in which it was found safe as used (report published in 1983) were up to 50% in rinse-off hair products. The 50% concentration is similar to concentrations in the 2017 survey. It should also be noted that when PVP was originally found safe for use (report published in 1998), the maximum leave-on concentration of use reported was 35% in makeup fixatives, which is the same maximum concentration reported in leave-on products in the 2017 survey.

Short-Term, Oral, VP/VA Copolymer, Subchronic, Oral, VP/VA Copolymer - Who are “The authors”? - the authors of the EFSA report or the authors of the 28-day study or 90-day study?

Chronic, Oral, VP/VA Copolymer - The description of the rat 24 month study is not correct. It currently says the high dose was 686 mg/kg/day and the low dose was 2625 mg/kg/day. It also says that there were “4 satellite groups (4 test and 1 control)” (it should be (3 test and 1 control)).

Chronic, Inhalation, VP/VA Copolymer, old report summary - It is not clear what the concentrations represent, the concentrations of the hair spray aerosols or the concentrations of the VP/VA Copolymer in the hair spray aerosols. How long each day and how many days each week were the hamsters exposed to the hair spray aerosols?

Carcinogenicity, Oral, VP/VA Copolymer - Please correct: low dose 2625 mg/kg/day; high dose 686 mg/kg/day

Anticarcinogenicity - The IARC conclusion for PVP does not belong in the Anticarcinogenicity section. The IARC conclusion should be cited to IARC (it is now in a 1999 IARC monograph), not the CIR report (correct date 1998).

Cytotoxicity, PVP - The material studied in reference 31 (n-alkyl terminated (octadecyl or di(dodecyl)) PVP) is not actually PVP and this study should not be included under the PVP subheading.

As only one concentration was studied, it should be made clear that the authors conclusion concerning the effect of PVP on sperm referred to a concentration of 10%.

Please clarify the following sentence: "He La cells were incubated for 24 h at concentrations of 5%, 10%, and 20%." Do the concentrations represent PVP or the He La cells?

Irritation, PVP, old report summary - Please correct: "A 10% PVP-iodine solution did not cause neither dermal irritation in rabbits."

Summary - The concentration of use information from the original reports, which is similar to the 2017 survey should also be mentioned in the Summary. Use information on VP/Hexadecene Copolymer and VP/Eicosene Copolymer should be included in the Summary.

Table 2 - As some of the CIR reports in this table are not yet "published", the title of the table needs to be changed. In addition, the ingredients in this table are not "Similar"; they are ingredients included in the old reports and this report. The date of the original published report on PVP is not correct; it should be 1998, not 2017. The date of the published re-review including PVP is not correct; it should be 2017 not 2018.

Reference 7 - Please correct the date of this reference (it should be 1998).

Reference 34 - Please correct the date of this reference (it should be 2017).