Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: August 29, 2018
Panel Date: September 24-25, 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.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: August 29, 2018
Subject: Draft Tentative Report on Vinylpyrrolidone Polymers

At the June 4-5, 2018 meeting, the Expert Panel issued an insufficient data announcement (IDA) on the 30 vinylpyrrolidone copolymers (21 ingredients reviewed for the first time + 9 ingredients previously reviewed) that are reviewed in this safety assessment. The data requests were as follows: (1) method of manufacture and (2) impurities. Therein, the Panel noted that data on a representative ingredient for each type of monomer composition would be sufficient for the group. It was also noted that it would be useful to know whether or not the product of each manufacturing process is an emulsion or solid, pure polymer. Furthermore, it would be useful to know the molecular weight % range for each ingredient.

The monomer composition groups were determined to be:

VP Copolymers
Acrylic Acid/VP Crosspolymer
Maltodextrin/VP Copolymer
PVP/Decene Copolymer
PVP/VA/Itaconic Acid Copolymer
PVP/VA/Vinyl Propionate Copolymer
Styrene/VP Copolymer
Triacontene/VP Copolymer
VP/Eicosene Copolymer
VP/Hexadecene Copolymer
VP/VA Copolymer
VP/Vinyl Alcohol Copolymer

VP Acrylate Copolymers
Acrylates/Stearyl Methacrylate/VP Copolymer
Acrylates/VP Copolymer
Ammonium Acryloyldimethyltaurate/VP Copolymer
Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer
Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer
Methacrylic Acid/Styrene/VP Copolymer
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer
VP/Acrylates/Lauryl Methacrylate Copolymer
VP/Dimethylaminoethylmethacrylate Copolymer
VP/DMAPA Acrylates Copolymer
VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer

Polyvinylpyrrolidone (PVP) and Modified PVP Polymers
Butylated PVP
PVP
Triacontanyl PVP

VP Crosspolymers
Hydrolyzed Wheat Protein/PVP Crosspolymer
Sodium Acryloyldimethyltaurate/VP Crosspolymer

Urethanes
VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester
VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester
VP/Polycarbamyl Polyglycol Ester

To date, the following data (highlighted in the report text) were received in response to this request:

- Method of manufacture and residual monomer data on VP/VA Copolymer (*vinylp092018data1*)
- Method of manufacture and impurities data on PVP (*vinylp092018data2*)
- A second statement on method of manufacture and impurities data on PVP (*vinylp092018data3*)

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Also included in this package for your review are the Draft Tentative Report (*vinylp092018rep)*, CIR report history (*vinylp092018hist*), flow chart (*vinylp092018flow*), literature search strategy (*vinylp092018strat*), ingredient data profile (*vinylp092018prof*), 2018 FDA VCRP data (*vinylp092018FDA*), and report comments on the draft report that were received from the Council just prior to the June meeting (*vinylp092018pcpc*). These comments have been addressed.

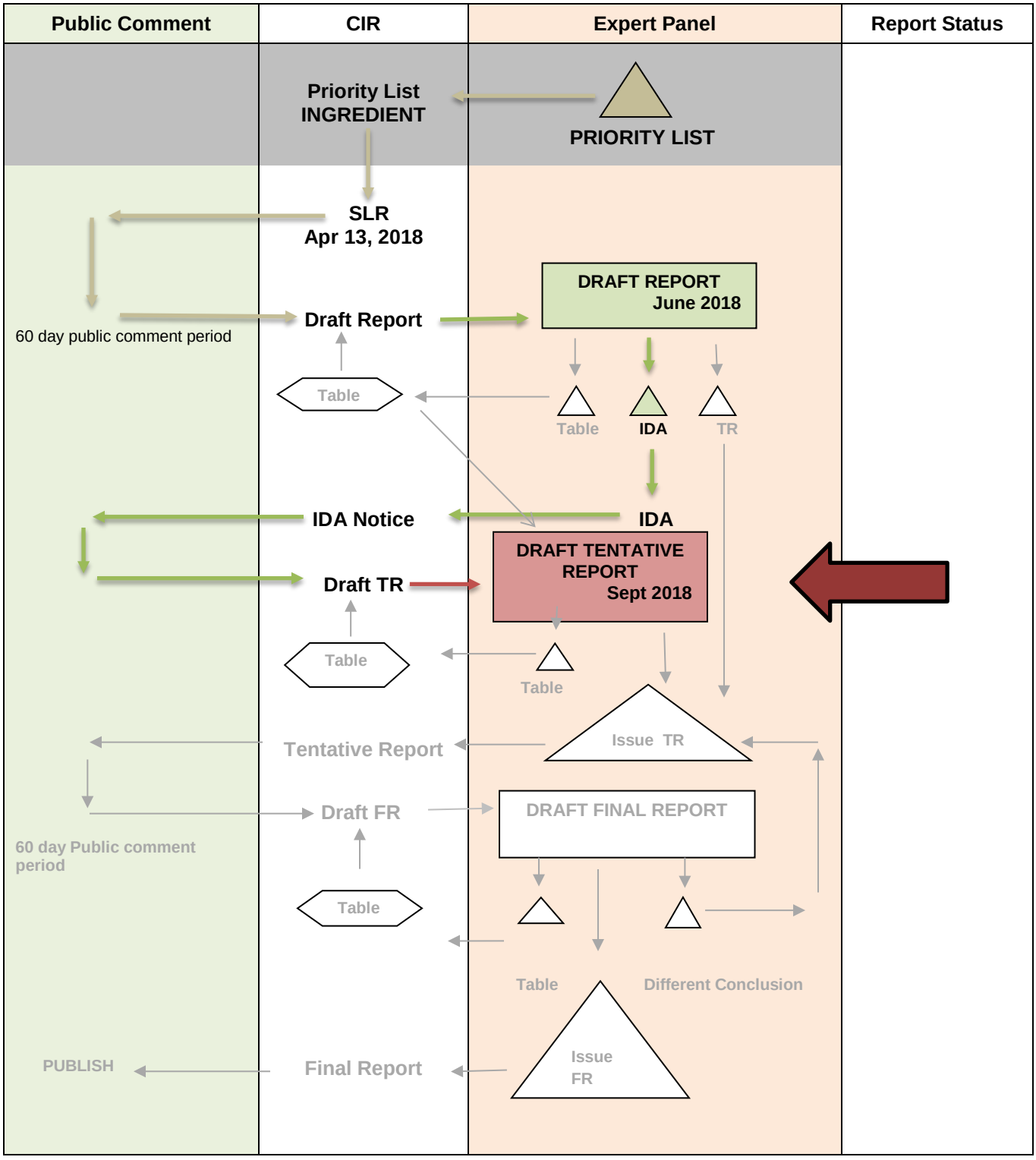
The Draft Tentative Report also contains a 2018 case report of anaphylaxis to PVP as an excipient in an ophthalmic preparation. A summary of this report is highlighted in the report text for the Panel's consideration.

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 still considered insufficient, the Panel should issue a Tentative Report with an insufficient data conclusion, specifying the data needs in the discussion section of the report. If the data are sufficient to determine safety for some ingredients, but insufficient for others, a split conclusion can be issued.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Vinylpyrrolidone Polymers

MEETING Sept 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.

The Panel issued an insufficient data announcement (IDA) on the 30 vinylpyrrolidone polymers that are being reviewed in this safety assessment. The data requests were as follows: (1) Method of manufacture and (2) Impurities.

Draft Tentative Report, Teams/Panel: September 24-25, 2018

The following data were received in response to the IDA that was issued at the June Panel meeting:

- Method of manufacture and residual monomer data on VP/VA Copolymer
- Method of manufacture and impurities data on PVP
- Method of manufacture and impurities data on PVP

Comments that were received from the Council prior to the June Panel meeting have been addressed.

Data Profile for September 24th-25th, 2018 Panel – Wilbur Johnson

	Dermal Penetration			Nail Penetration	Penetration Enhancement	ADME					Acute Toxicity			Short-Term Toxicity	Sub-Chronic Toxicity	Chronic Toxicity	DART		Genotoxicity	Carcinogenicity	Other Relevant Studies		Dermal Irritation*	Dermal Sensitization /Photosensitization		Ocular Irritation *		Clinical Studies	Case Reports		Epidemiology Studies
	In Vivo -Animal	In Vitro-Human	In Vivo-Human	In Vitro-Human	In Vitro-Animal	In Vitro-Human Dermal	Animal-Dermal	Animal-Oral	Animal-Inhalation	Human-Oral	Animal-Dermal	Animal-Oral	Animal-Inhalation	Animal	Animal	Animal	In Vitro	In Vivo	In Vitro/In Vivo	In Vivo	In Vitro	In Vivo-Animal	Animal/Human/In vitro	Animal	Human	In Vitro	Animal/Human	Human-MulticenterStudy	Human-Dermal	Human-Inhalation	Human
VP/Hexadecene Copolymer																							X				X				
VP/Eicosene Copolymer																													X		
Acrylates/Stearyl Methacrylate/VP Copolymer																															
Acrylates/VP Copolymer																															
Acrylic Acid/VP Crosspolymer																															
Ammonium Acryloyldimethyltaurate/VP Copolymer												X							X				X	X	X		X				
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								X				X		X		X	X		X	X	X		X	X	X	X	X		X		
PVP/Decene Copolymer																															
PVP/VA/Itaconic Acid Copolymer																															
PVP/VA/Vinyl Propionate Copolymer																															
Sodium Acryloyldimethyltaurate/VP Crosspolymer																			X					X			X				
Styrene/VP Copolymer																															

Triacontanyl PVP											X	X							X				X		X		X				
Triacontene/VP Copolymer																															
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer																															
VP/Acrylates/Lauryl Methacrylate Copolymer												X													X		X				
VP/Dimethiconylacrylate/ Polycarbamyl/Polyglycol Ester																															
VP/Dimethylaminoethylmethacrylate Copolymer																															
VP/Dimethylaminoethylmethacrylate/Poly-carbamyl Polyglycol Ester																															
VP/DMAPA Acrylates Copolymer																															
VP/Polycarbamyl Polyglycol Ester																															
VP/VA Copolymer												X		X	X	X				X			X	X	X		X				
VP/Vinyl Alcohol Copolymer																															
VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer																															

X = data

[Vinylpyrrolidone Polymers – 2/6-16/2018; 8/13/2018]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECET-OC	Web
VP/Hexadecene Copolymer	32440-50-9 63231-81-2	Yes	331/2	0/0	2/1	No	No	No	No	No	No	No	No	No	No	No	No	
VP/Eicosene Copolymer	28211-18-9 77035-98-4	Yes	436/3	4/2	3/1	No	No	No	No	No	No	No	No	No	No	No	No	
Acrylates/Stearyl Methacrylate/VP Copolymer		Yes	0/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
Acrylates/VP Copolymer	26589-26-4	Yes	28/1	28/1	3/1	No	No	No	No	No	No	No	No	No	No	No	No	
Acrylic Acid/VP Crosspolymer	527685-31-0	Yes	19/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
Ammonium Acryloyldimethyltaurate/VP Copolymer		Yes	35/0	3/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
Butylated PVP		Yes	2/0	4/0	5/1	No	No	No	No	No	No	No	No	No	No	No	No	
Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer		Yes	0/0	0/0	1/0	No	No	No	No	No	No	No	No	No	No	No	No	
Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer	155532-97-1	Yes	2/0	0/0	1/0	No	No	No	No	No	No	No	No	No	No	No	No	
Hydrolyzed Wheat Protein/PVP Crosspolymer		Yes	1/0	0/0	2/0	No	No	No	No	No	No	No	No	No	No	No	No	
Maltodextrin/VP Copolymer	1323833-56-2	Yes	3/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
Methacrylic Acid/Styrene/VP Copolymer	27554-92-3	Yes	4/0	0/0	3/0	No	No	No	No	No	No	No	No	No	No	No	No	
PVP	9003-39-8	Yes	1983/11	42/2	338/2	Yes	No	No	No	No	No	Yes	No	Yes	Yes	Yes	No	
PVP/Decene Copolymer		Yes	0/0	0/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	
PVP/VA/Itaconic Acid Copolymer	68928-72-3	Yes	15/0	0/0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	
PVP/VA/Vinyl Propionate Copolymer		Yes	0/0	0/0	1/0	No	No	No	No	No	No	No	No	No	No	No	No	
Sodium Acryloyldimethyltaurate/VP Crosspolymer		Yes	2/0	0/0	0/0	No	No	No	No	No	No	Yes	No	No	No	No	No	

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	
Triacontanyl 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	
Triacontene/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/DMAPA 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/DMAPA 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
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/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://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - 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

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

Vinylpyrrolidone Polymers

Okay, vinylpyrrolidone polymers. Gosh, Wilbur, you have a lot, here, don't you?

DR. SNYDER: The whole meeting is Wilbur.

DR. BELSITO: Okay. First of all, there's been an incredible increase in the use concentration of these materials.

DR. EISENMANN: Actually, if you compare it to the original report, there hasn't been. If you compare the concentrations to the original report, there has not been an increase, it's about the same.

DR. BELSITO: Okay.

DR. EISENMANN: He compared it to the re-review. And the re-review came in lower, for some reason. But the concentrations, now, are similar to what was reported in 1980 --

DR. BELSITO: Right. And I thought we had the safety to cover that. That was going to be my next point.

What I was unclear about was, are we being asked to roll everything into one here? Are we being asked to review not only the vinylpyrrolidone polymers, but are we being asked to roll in the acrylate copolymers; the acryloyldimethyltaurate polymers and the PVP report, into this, and making one gigantic report? And I'm okay with that combination if Dan is.

From the way this whole thing was phrased, I wasn't sure where we were going with this. Is this just a re-review of this?

DR. EISENMANN: It doesn't state it clearly; but I think this is a report because of two ingredients, eicosene and -- which two? VP/hexadecene copolymer and VP/eicosene copolymer has high levels of uses. You're going to do a new review and they were going to pull in some of the old ingredients. That was my understanding because it clearly states that in the beginning of this report.

DR. BELSITO: I was just confused because, at the end of the report, it sort of said, well maybe you can use some of the information from the acrylate copolymer, yada yada. But then it wasn't clear to me, are we being asked to combine all four of these reports into one. I mean, what are we being asked to look at here?

MS. FIUME: It's parts. There are a few of the acrylates copolymers that fit this report better than they did the acrylates copolymers report. Wilbur, do you have it broken out, where each of them come from? Is that in a table in the report?

DR. BELSITO: If it was, it wasn't clear to me what we're being asked to do here specifically. I ended up reading all of the reports.

DR. SNYDER: Well, I thought we were going to go to a report with 30 ingredients, bringing in eight previously reviewed ingredients.

MS. FIUME: Yes. The ones with the asterisks were previously reviewed, in a couple of different reports.

DR. BELSITO: Okay. Can you tell me what PDF you're on?

MS. FIUME: Page 13.

DR. BELSITO: Okay. Right.

DR. EISENMANN: And actually, there's one more that was previously reviewed, vinyl caprolactam/VP/dimethylaminoethyl methacrylate copolymer. It was called PVP in the original report instead of VP.

MR. JOHNSON: Monice, to answer your question; on PDF page 39, the published reports are in that Table 2, of all previously reviewed ingredients that are used in this safety test.

DR. BELSITO: Yeah, I understand. You're talking about Table 2.

MR. JOHNSON: Yeah.

DR. BELSITO: Yeah, but my question was, are we rolling all of those ingredients into one? That's what confused me. Or are we on whatever the PDF page before, and that's all we're looking at? I wasn't sure what we were being asked to include in this re-review.

MS. FIUME: So, it's 30 total; twenty-two are new. The eight came from those previous reports that you see in Table 2. The report was initiated based on VCRP data for the VP/hexadecene copolymer and VP/eicosene copolymer. So that's what started the report; and that's why it's a new report and not a re-review.

DR. BELSITO: Right. Okay. If I'm following you, what you're saying is, in looking at this there were eight ingredients previously reviewed in these other reports that we see in Page 2, that someone now thinks more appropriately belong in this group. And so, we're being asked do we want to move them into this group? Not merge all of the groups into one.

MS. FIUME: Correct. Because acrylates copolymer will come back to you, probably in September, as a re-review. When you see that group, there will be a few that had been pulled out and placed in this group, because they fit better.

DR. BELSITO: Okay. I now understand what we're being asked to do. Because when I was reviewing this, it wasn't clear to me whether you were asking me to just take all four groups and merge them into one. Dan, are you okay with moving those ingredients over, Red Rover?

DR. LIEBLER: Yes. Yes.

DR. BELSITO: Okay. Then I think we can move them over and go safe as used.

DR. LIEBLER: Agree. I think we need method of manufacture and impurities for most of the ingredients; and then they'll be safe as used.

DR. BELSITO: I think we have those in --

DR. SNYDER: We have lots of data. Actually, we have lots of impurity data.

DR. BELSITO: Do you want them for each of the ingredients?

DR. LIEBLER: One, two, three, four, five, six, seven. We got composition and impurities for seven. We got method of manufacture for one. And we've got 30 ingredients, right?

DR. KLAASSEN: Hell, that's close enough.

DR. LIEBLER: I think we're a little light.

DR. BELSITO: You want method of manufacture and impurities for all 30?

DR. LIEBLER: I think that's what we should ask for at this stage.

DR. KLAASSEN: Yeah.

DR. BELSITO: Okay.

DR. LIEBLER: I mean, these are really heterogeneous. If we had method of manufacture and impurities, not for everything but they covered the major sort of subgroupings here -- I'm wondering if we could think about putting these into any subgroups. We've got a lot of sort of orphans, I think, here. Like the wheat one, for example. And the VP/hexadecane, VP/eicosene, for example, they could go together, along with a couple of the others.

I hadn't thought until just now about trying to put these into any subgrouping, but it might be doable. And the reason I was even bringing that up, was that if we had representative data for members of the subgroupings, I think we would be okay. But I think we're pretty light right now on data for those.

DR. BELSITO: Do you want to propose some subgroups so that they have some direction as to exactly what bases need to be covered? So that we have our method of manufacture and impurities for one representative, at least, in each of those subgroups?

DR. LIEBLER: Yeah. I would be happy to work with Wilbur on that.

DR. BELSITO: Okay. We're moving the eight ingredients over. And we're going insufficient for method of manufacture and impurities on a representative for subgroups TBD by Dan and Wilbur. Is that what we're saying?

DR. LIEBLER: And maybe Ron Hill if he wants to collaborate on that.

DR. BELSITO: Okay.

DR. BERGFELD: I'm sorry, but you're not able to use some of the data from the other enclosed manuscripts, documents?

DR. LIEBLER: We might be able to.

DR. BERGFELD: Yeah.

DR. BELSITO: Well, but that data would be for method of manufacture and impurities on ingredients that we're not moving over.

DR. LIEBLER: Only if they're data from ingredients that got moved over.

DR. BERGFELD: Only if they in the eight.

DR. LIEBLER: Right. We don't have a limit of read across. Does the council consider any subgroupings here relevant? I mean, does industry have input that would be helpful to us, so we don't come up with some off-the-wall categories?

MS. KOWCZ: We can do that. We can do that as well.

DR. LIEBLER: Okay.

DR. BELSITO: Okay, so what I have is that we agree to move the eight over into this group

from others. And that having done that, we're going to go insufficient for manufacturing and impurities on subgroups, on at least one of the ingredients from a subgroup that are representative, that Wilbur, Dan, Council and other interested parties will form. Is that where we're at?

DR. LIEBLER: I have another question that could impact our use concentration significantly here. On PDF 14, under method of manufacture for the VP/VA copolymer, the last line of that paragraph says, "the product is isolated as aqueous solution/emulsion, or as a spray-dried solid." If it's a solid, like some kind of powder, I can see you can know how much is going in, what percent is used in a product. But if it's an emulsion, then you get into this sort of activity issue, what is the weight percent in the emulsion that goes into a product.

And is the percent that's represented in a product the total emulsion, or the solid material that's in the emulsion? And that can really impact the numbers for use concentration. I think we need some clarification on that.

Because I don't know if that's just as one ingredient; and if the other are all dried solids that are easy to calculate how much went into a product. Or if they're commonly supplied as aqueous emulsions. If it's the latter, then we need to check our numbers.

DR. EISENMANN: I can tell you, I asked for the concentration of the named ingredient. I mean, that's why sometimes things come in higher; but that's what I asked for, concentration of the named ingredient. That's what they're supposed to be giving me. I can never guarantee you what they're giving me.

DR. LIEBLER: If you know it's an emulsion --

DR. EISENMANN: I suspect most of these are mixtures.

DR. LIEBLER: Then this complication arises. And so, what would be useful to know, is are the emulsions -- approximately what is the solid weight percent range in the emulsion, for at least a representative number of these so we get some idea. Typical emulsion is probably in the neighborhood north of 50 percent.

MS. KOWCZ: I just know that normally you have emulsion, really, to ease in the batching process.

DR. LIEBLER: Right.

MS. KOWCZ: So many times, they'll use the emulsion versus powder. It's just a lot easier to incorporate, a lot easier to use, and it saves times and efficiency in the production process.

DR. LIEBLER: Right.

MS. KOWCZ: But we can find out.

DR. LIEBLER: But if it was like more than 90 percent, then it wouldn't be very useful as an emulsion, right?

MS. KOWCZ: Right.

DR. LIEBLER: And if it was less than 50 percent it would be too dilute; so, it's probably somewhere in the range. But that number -- you know, if something is said to be used at 10 percent, but it's actually at 50 percent emulsion, then it's actually a 5 percent concentration.

We just need to get some kind of idea of what the correction factor is. Because we may end up with a high use concentration that gives us a problem with sensitization, or something where we don't have data, and it turns out our estimate's too high.

DR. BELSITO: Okay, anything else? It is 12:01, I guess it's lunchtime and reconvene at 1:00.

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Marks'Team

Vinylpyrrolidone Polymers

DR. MARKS: Vinylpyrrolidone polymers. This is the first review of these 30 ingredients. Twenty-two of them are new ingredients, but they're similar to eight that have previously been reviewed.

So, Ron and Tom. And the ingredients are listed on page 5. And Wilbur, I don't know if you -- I guess I must have highlighted which ones were -- no. The ones that were previously reviewed, if you want to look at the introduction, Wilbur has those asterisked.

The first question is, do you like all these ingredients? Where's the introduction. That is page 13. And again, actually Wilbur, did you put those asterisks -- were they all at the end of this list?

MR. JOHNSON: Yes.

DR. MARKS: Yup. So, if you take a look at that list, you'll see the ones previously reviewed.

DR. HILL: Page 13 you said where that list is?

DR. MARKS: Yes.

DR. HILL: Okay.

DR. MARKS: It's right under the introduction, yeah.

DR. HILL: I got it.

DR. MARKS: This may be the best place to look at all of the ingredients. Make sure that we like all these 30 grouped together.

DR. HILL: I think what I saw was there are subgroups, but there's no reason to de-group them. That was just my take on it.

DR. MARKS: So, chemically you didn't have a problem?

DR. HILL: No. Just that there are obvious subgroups. There's a couple that have taurate in there. And there are a couple that have DMAPA in there as substructures.

DR. MARKS: And, Ron Shank, you're fine with all the ingredients, and Tom?

DR. SLAGA: I was.

DR. SHANK: I'd leave them in the report, but I'd separate them into two groups, because I'm going to split the conclusion.

DR. MARKS: Okay. And actually, Ron Hill suggested subgroups. So, which are the two subgroups you would suggest, Ron Shank?

DR. HILL: Did he say two?

DR. MARKS: Yes. He said two subgroups.

DR. HILL: Okay.

DR. SHANK: One group would be the polymers that have already been reviewed. And two that I would add, triacontanyl PVP, for which we have tox data, irritation sensitization; and those are safe.

DR. MARKS: So, the eight plus the tri --

DR. SHANK: Triacontanyl PVP.

DR. MARKS: Plus the eight? And they would be safe?

DR. SHANK: Yes.

DR. MARKS: And then the remainder?

DR. SHANK: Insufficient. And we need the amount of monomers in each polymer, the molecular weight range. If there's little monomer present, we could consider read across. But a significant amount of monomer is present, but those monomers have been reviewed, then we could use read across. So that's the split.

Then there are two ingredients where the monomers have been reviewed and considered safe only when exposure is limited to nails. So, we'll have to be careful not to extend that.

MR. JOHNSON: Repeat that, Dr. Shank, please.

DR. SHANK: Yes. There are two ingredients. One is methacrylic acid styrene VP copolymer and VP/acrylates/lauryl methacrylate copolymer. And these have been reviewed by the panel; and we said they were safe only when exposure is limited to the nails and there is no exposure to skin. So, we have to be careful how we handle those two. Maybe can be handled in the discussion.

DR. HILL: What was the second one? Because I thought you said lauryl and it's not starred as being reviewed before.

DR. MARKS: Exactly. It isn't. So, one is the VP acrylates/lauryl methacrylate copolymer. That's at the top of the second column. Which was the other one, Ron Shank?

DR. SHANK: Methacrylic acid/styrene/VP copolymer.

DR. MARKS: Oh, that's a previous review. So that's limited to the nail too.

DR. HILL: Oh, I see. Yeah.

DR. MARKS: Yeah, we've got to capture those nuances.

DR. SHANK: Yes. I have more comments, but --

DR. HELDRETH: You said the VP/acrylates/ lauryl methacrylate copolymer?

DR. MARKS: Yes.

DR. HELDRETH: It's a previously reviewed?

DR. SHANK: Well, that's what I had. No. The monomer has been reviewed.

DR. HELDRETH: Oh, okay. Lauryl methacrylate.

DR. SHANK: In both cases it was the monomer that was reviewed by the panel. And the panel said there can be no exposure to skin, limit only to nails.

DR. MARKS: So really what you're doing is say capture that either in the discussion or when you get the monomer concentration in it?

DR. SHANK: Yes.

DR. ANSELL: Was it polymethacrylate or the unreactive methacrylates that were limited?

DR. SHANK: No. It was the monomer.

DR. ANSELL: Yes. So, we want to see the monomer concentration.

DR. SHANK: Yes.

DR. MARKS: Right.

DR. ANSELL: It may not be relevant -- yeah, yeah. Okay.

DR. SHANK: That's right. If the monomer concentration is trivial, then no problem. If it's not, then we have to take heed to this caveat.

DR. ANSELL: Yeah.

DR. MARKS: Let me see what I had. One of my concerns was I was going to also suggest insufficient data announcement. But I had here that the concentrations in which PVP and VP/VA copolymer are being used now, we didn't have HRIPT to support for the PVP 35 percent use concentration. For the VP/VA copolymer 10 percent concentration. And it wasn't being used at those higher concentrations in the past.

Am I right on that? Yeah, patch evidence is saying repeat -- at 5 percent. That was the polyvinylpyrrolidone vinyl acetate, PVP.

So, we have a repeat insult patch at 5 percent. That's on page 194. It's being used now at 35 percent. To me if -- not if -- we're going to issue an insufficient data announcement. I'd like to see HRIPT for PVP at 35 percent, and VP/VA copolymer at 10 percent. That help cover the monomer issue, Ron Shank, as far as sensitization.

DR. SHANK: Okay.

DR. MARKS: Am I reading that correctly, that we don't have data that supports the safety of sensitivity at the present use for those two ingredients? And they're important ingredients in terms of use.

DR. ANSELL: We do have a two-year inhalation study on them.

DR. MARKS: Yeah. But inhalation, that's -- PVP 900 uses, up to 35 percent present use. That's from last year. And VP/VA 480 uses up to 10 percent. And what I see here is -- as I said the original report with PVP was 5 percent. And I didn't see anything on the VP/VA. Let me see here, where is that. So, I would include those.

DR. SHANK: These polymers are so large. Do you think they would cross stratum corneum?

DR. MARKS: Probably not.

DR. SHANK: And if they don't, is sensitization an issue?

DR. MARKS: I guess it's the monomers.

DR. SHANK: It's the monomers that we're worried about.

DR. MARKS: And actually -- let's go to 194. Actually, they should have put --

DR. HILL: That must be in Wave 2 -- no, not Wave 2.

DR. MARKS: No. That's in this original.

DR. HILL: The original, 194 is an old report.

DR. MARKS: Yeah. That's what I went back to look and see what the sensitization data and what the use data was there. But it's interesting because patch testing, repeat insult patch --

DR. ANSELL: Yeah, I don't think the data dye got up that high.

DR. MARKS: I would include those. And since we're going to send it out as insufficient, at this point, data announcement, presumably I'll be seconding that. And see what we get back for the HRIPT for those

two ingredients. So, split into two groups. Actually, with that in mind, even for the PVP and the VP/VA copolymers, I'd like to see HRIPT for those too. So even the previous reports -- at this point, I wouldn't say we had everything we need.

DR. SHANK: Okay.

DR. MARKS: And then for the others, other than the eight, we need to have the monomers and the molecular weight of those ingredients. And we need to be attune to the fact that previous reports with the monomer of the VP acrylate/lauryl methacrylate copolymer and the methacrylate acid styrene VP copolymer, there was a report on those monomers and nail use. Does that sound good for where we'll proceed tomorrow?

DR. HILL: I had some other things.

DR. MARKS: Oh, okay. Good. Do you like the idea of splitting them into two groups? Now that's based on what was reviewed and what wasn't. It's not so much, it sounds like, on chemistry or another reason.

DR. HILL: Are you talking about two groups in terms of two different reports?

DR. MARKS: No.

DR. HILL: Or just subgroups within the report?

DR. SHANK: Subgroups in one report.

DR. HILL: Okay, then I think I came up with four or five subgroups. But first thing was to find out some information that I didn't quite -- okay, maybe I'm seeing something now that I didn't see; on at least one of those I think I can scratch.

All right. Yeah. I don't remember seeing anything with the caprolactone. The caprolactone, that's a seven-membered ring, yeah. Before now. That's new. Caprolactam, that's what I'm trying to come up with. Caprolactam. I didn't see anything from before, previously reviewed and approved that had that monomer in there.

I also wanted to draw your attention, if you didn't catch it, this is one of the first reports where we have quite a bit of information about monomer concentrations, which was gratifying, on page 14 and 15.

This is Wilbur's, right? Yeah. So, in yellow highlights we have some information; ten companies representing the majority of the production of polymers sold. And they give some information about residual monomer levels.

We also have, in the next one down, something about low molecular weight distribution. In the next one down, which is the maltodextrin. In PVP down here we've got some information about monomer concentration.

So, we're seeing things in the range up to 1000 ppm, which is .1 percent, right? And that helps us to know that our interest in monomers is not just something dreamed out of thin air. But the amounts are modest.

DR. MARKS: Does it change anything from what Ron Shank wanted? Basically, the monomer concentrations in ingredients not previously reviewed.

I guess the question is if we get some sprinkling of monomers, I guess we'll have to go back and say can we cross read or not. The reason you've choose triacontanyl PVP, is that was close enough chemically to the ones already approved; you felt comfortable read across.

DR. SHANK: Yes.

DR. MARKS: Yeah. Okay. And in the other, of course, molecular weight ranges, that will give us an idea, you know, presumably what the lowest molecular weight is. Is there anything to be concerned with?

DR. HILL: Why do you say that the triacontanyl PVP is similar to the others? Because that has that triacontanyl moiety directly linked to the five-membered ring of the vinylpyrrolidone. So now you've got a completely different monomer than vinylpyrrolidone.

DR. SHANK: Okay. But we have tox data and we have the irritation.

DR. HILL: On what?

DR. SHANK: On triacontanyl PVP.

DR. HILL: Okay. Okay. All right. So, you say we have new data.

DR. SHANK: Which would cover us.

DR. HILL: Okay. All right. Okay, great. Because I didn't catch that.

DR. MARKS: Any other comments? Tom, do you have any? Ron? Yes, go ahead.

DR. SLAGA: No.

DR. SHANK: On page 14 under methods of manufacture, it says that VP/VA copolymers hydrazine is formed from the amines present. Hydrazine is a carcinogen --

DR. HILL: Correct.

DR. SHANK: -- so there should be no residual hydrazine in the finished polymer.

DR. HILL: Well no is no as in zero --

DR. SHANK: Well, no to a chemist. Right. Just a tiny bit.

DR. HILL: So actually, somewhere there is something written about that in terms of specification. And I can't remember where it is now.

DR. SLAGA: It's a carcinogen, but in a fairly large amount. I mean, you know, it takes a large concentration.

DR. SHANK: Probably more then you get from one of these polymers.

DR. SLAGA: Right.

DR. SHANK: On the other hand --

DR. SLAGA: No. We should deal with it and maybe --

DR. SHANK: We should recognize it.

DR. SLAGA: -- even in the discussion it could be dealt with.

DR. SHANK: Keep it to a minimum or only a teeny bit.

DR. SLAGA: Well, not a teeny bit. No one will keep it to a teeny bit, but a little bit.

DR. ANSELL: A skosh.

DR. SHANK: Oh, little bit's okay.

DR. HILL: A skosh.

DR. ANSELL: A skosh.

DR. HILL: I'll have to do a search for hydrazine, so I can remember where I read what I'm trying to find for you all.

DR. ANSELL: Yeah, I thought I saw something in here as well.

DR. SHANK: On hydrazine?

DR. HILL: Yes. Okay, so the United States -- the USP has a specification. The pharmaceutical grade PVP cannot contain more than one ppm of hydrazine. That's the USP.

DR. ANSELL: That's even less than a skosh.

DR. HILL: A little less than a skosh.

DR. MARKS: Well, that's important. And obviously, then the question is do you just mention that in the discussion. So, let's capture that in the discussion, that the panel's noted that hydrazine is formed from the means present in this reaction mixture; but per the limits that have been set, they should not exceed.

DR. SHANK: Just so we recognize it.

DR. MARKS: Yeah. No, thanks, Ron. Tomorrow do we need to mention that when we get in the initial discussion or we'll just capture that? Wilbur will capture it. What's your feeling? Wilbur can capture it.

DR. SHANK: Wilbur can just capture that in the discussion.

DR. MARKS: Yup. Okay.

MR. JOHNSON: So, that limit is acceptable in the one parts per million for hydrazine?

DR. SHANK: Is it acceptable?

MR. JOHNSON: Yes.

DR. SHANK: Depends on to whom you ask that question.

DR. MARKS: So, according to Tom, it's acceptable because it's just --

DR. SLAGA: It's below what -- I mean, the amount that you would get going through the skin and that being made, I think --

DR. MARKS: Yeah.

MR. JOHNSON: So how should the statement read in the discussion?

DR. ANSELL: People should be aware --

DR. SHANK: Aware of it.

MR. JOHNSON: Manufactures?

DR. ANSELL: -- that it may occur and USP has established a limit of one PPM in pharmaceutical grades.

DR. HILL: So, should keep it as low as reasonable achievable.

DR. SHANK: Yeah.

DR. HILL: Actually, the fact that -- when that popped up in here, because we didn't have that the last time -- as least I remember -- when we did the PVP polymers, that caused me to realize I didn't know what polymerization chemistry was being applied here. And also suggest there must be some -- well, it doesn't suggest, it mentioned free radical initiation without talking about what it is.

So, I wasn't sure if they were using hydrazine to do that initiation. It just as a means unspecified. So that caused me to wonder are there residual levels of whatever initiator they're using. Because typically, when

we did pre-radical chemistry in the lab, we would use something like t-butyl peroxide. That was our favorite one with some other possibilities.

DR. MARKS: Okay. Robust discussion. So tomorrow, presumably, I'm going to be seconding a motion that we put out an insufficient data announcement. And the needs our team wanted was HRIPT for PVP at use concentration 35 percent. VP/VA copolymer at 10 percent. We want the monomer concentration in the ingredients not previously reviewed, with the exception of the triacontanyl PVP. And also, the molecular weight range. Okay.

DR. SHANK: Good.

DR. MARKS: Okay. Let's move on to the next and last group of ingredients.

Day 2 of the June 4-5, 2018 CIR Expert Panel Meeting - Full Panel

Vinylpyrrolidone Polymers

DR. BELSITO: This Vinylpyrrolidone Polymers. This is the first time that we're looking at this report. The SLR was just released in April 2018, and we received a fair amount of data on it. Was noted that the panel has evaluated the safety of, and issued conclusions on, ingredients that are similar to the 22 ingredients that are being reviewed now here for the first time. And that information was also provided to us; and let me just find that report now.

And we thought that we could move eight of the ingredients from one of the reports, over to this report, and go with insufficient for manufacturing and impurities on representative subgroups. We felt we needed to subgroups these out; and Dan agreed to work with Wilbur, and any other interested parties, in determining the subgroups of the vinylpyrrolidones that are included in this reports. Is that correct Dan?

DR. LIEBLER: Great. Yes, actually Alex indicated that the council could work with us as well.

MS. KOWCZ: Definitely.

DR. LIEBLER: Give us some insight on the relevant groupings. And the point of that, is that if we don't get method of manufacture and impurity on every single last item, we could get enough representative data, I think, to give us confidence in going forward.

DR. MARKS: Second.

DR. BERGFELD: Second? Any other comments from any of the teams?

DR. SHANK: When you say impurities, would you include monomer in that? Because that would not be an impurity.

DR. LIEBLER: No, it is actually.

DR. SHANK: No.

DR. HILL: No, how is it not?

DR. LIEBLER: It is -- in the state of Tennessee, the monomers are an impurity.

DR. SHANK: It is. All right.

DR. HILL: I'm pretty sure that true in Louisiana, too.

DR. SHANK: But I'd make it very clear that we're very interested in the monomer concentration.

DR. LIEBLER: We are. I would normally look for monomer to be reported as the impurities, relative to the stated chemical substances -- residual monomer, right?

DR. MARKS: Ron Shank, you jumped in. Yeah, what Ron really -- yesterday -- mentioned, and it's in the minutes, is he wanted a monomer concentration ingredients, not previously reviewed. And he wanted monomer weight ranges, also, to get a sense of what the spread was. Is that correct Ron?

DR. SHANK: Yes, molecular weight.

DR. LIEBLER: Polymer weight ranges.

DR. HILL: Yes.

DR. LIEBLER: Got it.

DR. MARKS: And, if I understand correctly, and looking at the introduction, this is really 30 ingredients that's going to be in this report.

DR. BERGFELD: Thirty plus eight, isn't it?

DR. MARKS: No, it's 30, total; is that not correct?

MR. JOHNSON: That's correct.

DR. BERGFELD: Thirty total?

DR. MARKS: Yeah 30, total. Twenty-two new ingredients plus eight, previously reviewed, which are similar. And then in the discussion, Ron Shank pointed out that there's a nail use limit for the monomer, of VP, acrylates, lauryl methacrylate copolymer, and methacrylic acid/styrene/VP copolymer.

And so, in the discussion we should point out, that in the previous reports there was a monomer limitation on that, so that there's no concern about that when -- and the reader will be alerted to that. Again, Ron Shank, did I --

DR. SHANK: That's correct.

DR. MARKS: Yeah, okay.

DR. BERGFELD: So, it's been seconded. Marks seconded?

DR. MARKS: Yes.

DR. BERGFELD: And there's been discussion. Any further discussion? Because we're going to have to outline the needs, I think, on this one, again, to make sure they're clear.

DR. MARKS: I think Don did.

DR. BERGFELD: Don?

DR. BELSITO: The needs are -- first of all, we need to break these down into representative subgroups; and then obtain as much information, as we can, on manufacturing and impurities from those subgroups that we --

DR. BERGFELD: With the monomers?

DR. BELSITO: Well, that's part of the impurities, as we've just discussed, yes. And then we look at it.

DR. BERGFELD: Good. Any other discussion then? Seeing none, I'll call to question on this polymer. All those in favor of insufficient data report? Thank you. Unanimous. And then the next one is Dr. Marks with Hydrogen Peroxide.

Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
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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.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of vinylpyrrolidone polymers in cosmetic products; most of these ingredients have the reported film former function in common. The Panel reviewed data relevant to the safety of these ingredients under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of 21 of the following 30 vinylpyrrolidone (VP) polymer ingredients, as used in cosmetics, is being reviewed in this safety assessment:

VP Copolymers
Acrylic Acid/VP Crosspolymer
Maltodextrin/VP Copolymer
PVP/Decene Copolymer
PVP/VA/Itaconic Acid Copolymer
PVP/VA/Vinyl Propionate Copolymer
Styrene/VP Copolymer*
Triacontene/VP Copolymer
VP/Eicosene Copolymer
VP/Hexadecene Copolymer
VP/VA Copolymer*
VP/Vinyl Alcohol Copolymer

VP Acrylate Copolymers
Acrylates/Stearyl Methacrylate/VP Copolymer
Acrylates/VP Copolymer*
Ammonium Acryloyldimethyltaurate/VP Copolymer*
Ethylhexyl Acrylate/VP/Dimethicone Methacrylate Copolymer
Ethylhexyl Methacrylate/Methyl Methacrylate/VP Copolymer
Methacrylic Acid/Styrene/VP Copolymer*
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer*
VP/Acrylates/Lauryl Methacrylate Copolymer
VP/Dimethylaminoethylmethacrylate Copolymer*
VP/DMAPA Acrylates Copolymer
VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer

Polyvinylpyrrolidone (PVP) and Modified PVP Polymers
Butylated PVP
PVP*
Triacontanyl PVP

VP Crosspolymers
Hydrolyzed Wheat Protein/PVP Crosspolymer
Sodium Acryloyldimethyltaurate/VP Crosspolymer*

Urethanes
VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester
VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester
VP/Polycarbamyl Polyglycol Ester

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

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

It should be noted that of the 30 ingredients that are stated above, the Panel has previously evaluated the safety of 9 of these ingredients.[2,3,4,5,6,7,8] These 9 ingredients are included in this current assessment only because, in the absence of data, the available data on these ingredients may be useful in evaluating the safety of similar vinylpyrrolidone polymers that are the subject of this safety assessment (The Panel's published conclusions on the 9 ingredients that were previously reviewed are stated in Table 2, and the published reports may be found at https://www.cir-safety.org/ingredients.) The remaining 21 ingredients are being reviewed for the first time in this safety assessment. Thus, the total number of ingredients that is being reviewed in this safety assessment is 21, and not 30. Furthermore, a conclusion on ingredient safety will be determined for the 21 ingredients.

This report includes summaries of safety test data from the published reports of the previously-reviewed vinylpyrrolidone polymers, when available, and that information is identified using *italicized* text. The safety assessments of the previously-reviewed ingredients may have included data on other similar polymers when information on the named ingredient were lacking; however, those data are not included in this safety assessment. Furthermore, it should be noted that some monomers are toxic and that the residual monomer content of polymers should be taken into consideration. Information relating to the CIR review status of the monomer components of vinylpyrrolidone polymers is presented in Table 3. (The published reports that contain data on the related polymers, as well as on the monomers, can be accessed at the website identified above.)

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 polymers that are reviewed in this safety assessment are presented in Table 1. These polymeric ingredients share in common a vinylpyrrolidone monomer (Figure 1).

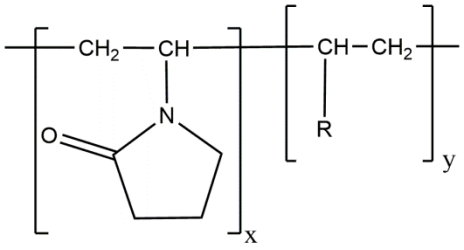


Figure 1. Vinylpyrrolidone polymer ingredients (wherein –C(R)HCH$_2$- represents at least one co-monomer residue).

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.[9] According to one supplier, Triacontanyl PVP is another high molecular weight polymer, and is insoluble in water, acid, or base solution.[10] VP/Acrylates/Lauryl Methacrylate Copolymer is expected to have low water solubility based on its mostly hydrophobic structure.[11] Sodium Acryloyldimethyltaurate/VP Crosspolymer is miscible with water and VP/Dimethylaminoethylmethacrylate Copolymer has a density of 1.047 g/cm^3.[12,13] 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.[8]

Australia's National Industrial Chemical Notification and Assessment Scheme (NICNAS) has issued reports on the following vinylpyrrolidone polymers: Maltodextrin/VP Copolymer, Triacontanyl PVP, VP/Acrylates/Lauryl Methacrylate Copolymer, and Sodium Acryloyldimethyltaurate/VP Crosspolymer. Of these, NICNAS has determined that Maltodextrin/VP Copolymer, VP/Acrylates/Lauryl Methacrylate Copolymer, and Sodium Acryloyldimethyltaurate/VP Crosspolymer are polymers of low concern (PLC).[12,9,11] The following statements relate to some of the NICNAS-established characteristics of a PLC: A polymer cannot be a PLC if it is designed to or can be expected to substantially degrade, decompose, or depolymerize, including polymers that substantially degrade, decompose or depolymerize after manufacture and end use, even though they are not intended to do so. Furthermore, a PLC does not contain a sequence of one or more fully fluorinated carbon atoms.[14]

VP Copolymers

VP/VA Copolymer

VP/VA Copolymer does not absorb energy over the UVA, UVB, or visible light spectrum.[2]

Method of Manufacture

VP Copolymers

VP/VA Copolymer

VP/VA Copolymer is prepared by free radical polymerization in ethyl alcohol.[2] Details about radical initiators, propagators, chain terminators, and solvent(s), were not provided.

VP/VA Copolymer is produced by free radical copolymerization of *N*-vinyl-2-pyrrolidone (NVP) and vinyl acetate (VA) in an isopropanol solution, in the presence of initiators.[15] The process is continuous and temperature controlled, and

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. The specification for the maximum concentration of hydrazine that is formed in the reaction mixture is included in the following section.

A cosmetic ingredient supplier reports that radical polymerization is used to make VP/VA Copolymer from vinylpyrrolidone and vinyl acetate. [16] Details about radical initiators, propagators, chain terminators, and solvent(s), were not provided.

PVP and Modified PVP Polymers

PVP

Two cosmetic ingredient suppliers report that radical polymerization is used to make PVP.[17,18] Details about radical initiators, propagators, chain terminators, and solvent(s), were not provided.

Composition/Impurities

VP Copolymers

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). [9]

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.[5]

VP/VA Copolymer

VP/VA Copolymer is supplied either in 100% concentration as a powder or as a 50% solution in alcohol.[2] *VP/VA Copolymers may contain the residual monomers, vinyl acetate at 1.0% (max), and vinyl pyrrolidone at 0.5% (max).*

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.[3,19] *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.[15]

Regarding the production process for VP/VA Copolymer, free radical copolymerization of NVP and vinyl acetate, specifications limit the concentration of hydrazine that is formed from amines present in the reaction mixture to a maximum of 0.1%.[15] Furthermore, due to the method of production (radical polymerization from vinylpyrrolidone and vinyl acetate) as described by a supplier, residual monomers may be present in VP/VA Copolymer at a maximum of 50 ppm vinylpyrrolidone and a maximum of 100 ppm vinyl acetate. [16]

PVP and Modified PVP Polymers

PVP

The United States Pharmacopeia (*USP) specifies that pharmaceutical grade PVP cannot contain more than 1 ppm hydrazine*. [8]

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.[20] 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.

As a result of the production method described by two cosmetic-ingredient suppliers of PVP, residual monomers may be present in PVP at a maximum of 100 ppm vinylpyrrolidone and a maximum of 100 ppm vinyl acetate. [17,18] Also, according to one of the suppliers, other impurities that may be present are acetaldehyde at a maximization concentration of 100 ppm and heavy metals in sum (as lead) at a maximum of 10 ppm.[18]

Triacontanyl PVP

According to one source, Triacontanyl PVP has a purity of > 97% and consists of < 2% water.[10]

VP Crosspolymers

Sodium Acryloyldimethyltaurate/VP Crosspolymer

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.[12] NICNAS has also noted that these residual monomers and/or impurities are not present in the notified polymer as introduced above the cut off concentration for classification. Sodium Polyacryloyldimethyl Taurate is reported to contain <2000 ppm AMPS and <10 ppm acrylamide.[6]

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.[21] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Council, of maximum reported use concentrations by product.[22]

According to 2018 VCRP data on the 9 ingredients previously reviewed by the CIR Panel, the greatest use frequency is 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).[21] Also, of the 9, the second highest use frequency is being reported for Ammonium Acryloyldimethyltaurate/VP Copolymer (597 cosmetic products: 525 leave-on products + 62 rinse-off products). Of ingredients with reported uses within the group of 21 vinylpyrrolidone polymers that is being reviewed for the first time, the greatest use frequency is reported for VP/Hexadecene Copolymer (443 cosmetic products: 442 leave-on products + 1 rinse-off product). The second highest use frequency is being reported for VP/Eicosene Copolymer (378 cosmetic products: 377 leave-on products + 1 rinse-off product). In general, the differences in current use frequencies of vinylpyrrolidone polymers in cosmetics versus those reported in previous years are unremarkable. [2,3,4,5,6,7,8,21]

Use concentration data relating to the 9 vinylpyrrolidone polymers previously reviewed by the CIR Panel are as follows: 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.[22] 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.[3] The highest maximum ingredient use concentration of vinylpyrrolidone polymers in leave-on products is being reported for PVP, which is 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%.[7] 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. It should also be noted that 35% was the maximum cosmetic use concentration that was reported in the original final report on PVP that was published in 1998.[8]

The following use concentration data relate to the 21 vinylpyrrolidone polymers that are being reviewed for the first time: The results of a concentration of use survey conducted in 2017 indicate that VP/Hexadecene Copolymer is being used at concentrations up to 24.1% in leave-on products (lipstick), which is the highest maximum ingredient use concentration that is being reported for the vinylyrrolidone polymers that are being reviewed.[22] 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 currentlyused 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]). 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 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[23,24,25,26] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[23,24]

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.[27,28,29]

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.[30]

Non-Cosmetic

VP Copolymers

VP/VA Copolymer

The 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.[15] 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.

PVP and Modified PVP Polymers

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.[8] *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.[20] It is used in medicine and in the pharmaceutical industry as a blood plasma expander, and it is a common ingredient in drug manufacture.[31]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion

PVP and Modified PVP Polymers

Animal

PVP

The absorption, distribution, metabolism, and excretion of PVP is dependent on molecular weight, amount and frequency of dosing, and route of administration. [8] *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 discovered in the published literature.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Animal

Dermal

PVP and Modified PVP Polymers

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.[10] 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 LD_{50} was > 2 g/kg.

Oral

VP Copolymers

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.[2]

VP Acrylate Copolymers

Ammonium Acryloyldimethyltaurate/VP Copolymer

The acute oral LD_{50} for Ammonium Acryloyldimethyltaurate/VP Copolymer was reported to be >2 g/kg in rats.[6]

VP/Acrylates/Lauryl Methacrylate Copolymer

An LD_{50} of > 5 g/kg (rats) has been reported for undiluted VP/Acrylates/Lauryl Methacrylate Copolymer.[11] Dyspnea was observed in 1 animal. The number of animals tested and details relating to the test protocol and study results were not specified.

PVP and Modified PVP Polymers

PVP

The oral LD_{50} of PVP (avg. MW of 40,000) is > 100 g/kg body weight for both rats and guinea pigs.[8]

Triacontanyl PVP

The acute oral toxicity of a Triacontanyl PVP trade name material was evaluated using 10 Sprague-Dawley rats (5 males, 5 females).[10] 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 LD_{50} was > 5 g/kg.

Short-Term Toxicity Studies

Dermal

VP Copolymers

VP/VA Copolymer

A hair product containing 1% VP/VA Copolymer was tested in a 6-week dermal toxicity study on 50 albino rats. Volumes of 2.0 ml/kg of the product were applied 5 days a week for 6 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.[2]

Oral

VP Copolymers

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.[15] 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 and Modified PVP Polymers

PVP

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).[32] The test animals received oral doses (dose volume of 10 ml/kg, by gavage) daily for 28 consecutive days. The control group received water. One day 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.

Inhalation

PVP and Modified PVP Polymers

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.[8] *The animals were exposed to an average PVP concentration of 118 or 146 mg/m*^{3} *5 days per week (8 hours per day) for a total of 30 exposures.*

Subchronic Toxicity Studies

Oral

VP Copolymers

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.[15] 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 Copolymers

VP/VA Copolymer

Rats and hamsters were exposed for 13 weeks to a spray containing 4.0% VP/VA Copolymer.[2] *Each of three groups comprised of 12 rats and 12 hamsters per group inhaled the spray for 4 hours per day, 5 days per week for 13 weeks in doses of 5.4 mg/m*^{3} *(calculated to be the equivalent of 100 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. On each day of this 90-day study, the animals received one 30-second exposure each morning and afternoon and were left in the spray atmosphere for 15 minutes.*

Chronic Toxicity Studies

Animal

Oral

VP Copolymers

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.[2]

In a 52-week dietary 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).[33] The control group (6 males, 6 females) 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.

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).[33]

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).[33] The 3 groups were fed the test substance (in the diet) at the following doses for 24 months: group 1 (low 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 (high dose: 2625 mg/kg/day [males] and 2759 mg/kg/day [females]). A fourth group (control group: 50 males, 50 females) was fed a diet without the test substance for the same duration. The test substance (same doses) was also fed to 4 satellite groups (3 -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 high 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).[15] 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.

PVP and Modified PVP Polymers

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. [8] *A similar 2-year feeding study in dogs found swollen phagocytic cells in the lymph nodes.*

Inhalation

VP Copolymers

VP/VA Copolymer

Thirty-six male and 36 female Syrian hamsters were exposed to the low concentration of 0.08 ± 0.08 mg/l VP/VA Copolymer in air, 4-32 minutes a day, once a week for up to 2 years.[2] *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. 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.*

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

PVP and Modified PVP Polymers

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.[8]

Additional DART data were not discovered in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

In Vitro

VP Acrylate Copolymers

Ammonium Acryloyldimethyltaurate/VP Copolymer

Ammonium Acryloyldimethyltaurate/VP Copolymer was not mutagenic (up to 5000 µg/plate) in bacterial reverse mutation assays.[6]

PVP and Modified PVP Polymers

PVP

The genotoxicity of PVP was evaluated in in vitro and in vivo mutagenicity assays.[8] *Bacterial assay results were as follows: PVP-iodine, up to 20 µl (non-mutagenic in Ames test), PVP-iodine, in various amounts (mutagenic at > 2 µl in Ames test), PVP-iodine, amount not stated (mutagenic to Salmonella typhimurium strain TA1530 in Ames test). In the in vitro mouse lymphoma assay, PVP (up to 100 mg/ml) was not mutagenic with or without metabolic activation. In the same assay, PVP-iodine (up to 10 mg/ml) caused aberrant non-dose-related mutations with, but not without, activation. In the in vitro BAlb/c 3T3 transformation assay, PVP (up to 100 mg/ml) was not mutagenic (non-dose-related transformations observed. In the in vivo dominant lethal assay (20 male NMRI mice), the intraperitoneal (i.p.) injection of 72 mg PVP-iondine/kg did not induce mutagenicity. The i.p. injection of 36 mg PVP-iodine into 10 NMRI mice in the in vivo micronucleus test also did not induce mutagenicity. In the Chinese hamster bone marrow test (groups of 12 hamsters), a single dose of 38.3 or 82.5 mg PVP-iodine/kg was not mutagenic. Also, in this test, repeated doses of 38.3 mg PVP-iodine/kg did not induce mutagenicity.*

Three formulations containing PVP-iodine were not genotoxic in a comet assay or a chromosome aberration test, with or without metabolic activation.[34] The solutions contained 3% or 10% PVP-iodine. In both tests, 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.[35] Each strain was tested with aqueous PVP (doses up to 10,000 µg/plate) with and without metabolic activation. The results were classified as negative in all bacterial strains, with and without metabolic activation.

Triacontanyl PVP

The genotoxicity of a Triacontanyl PVP trade name material was evaluated in the Ames test using the following *S. typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538.[10] 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 *S. typhimurium* strains tested. Marked increases in the number of revertant colonies were observed in positive control cultures.

VP Crosspolymers

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).[12] The test substance was classified as non-genotoxic.

In Vivo

PVP and Modified PVP Polymers

PVP

PVP-iodine complex (11.2% available iodine) was evaluated in the following 3 in vivo genotoxicity assays: dominant lethal assay (male NMRI mice dosed intraperitoneally (i.p.) with 72 mg of PVP-iodine/kg), micronucleus test (male and female NMRI mice dosed i.p. with 36 mg of PVP-iodine/kg), and a bone marrow assay (male and female Chinese hamsters dosed i.p. with up to 82.5 mg PVP-iodine/kg).[8] *In the dominant lethal assay, the conception rate decreased significantly during the first week, but the average number of implantations (and resultantly, the mutagenicity index) was not affected. In the remaining weeks, all parameters remained similar between control and treated groups. Micronucleus test results indicated a significant increase in the number of micronuclei when compared to controls, but the value was considered within normal range. In the bone marrow assay, there were no increases in the rates of aberrant metaphases.*

CARCINOGENICITY STUDIES

Animal

Oral

VP Polymers

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).[33] The 3 groups were fed the test substance (in the diet) at the following doses for 24 months: group 1 (high 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 (low 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. (Results relating to chronic toxicity were described earlier.)

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).[15] 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. (Results relating to chronic toxicity were described earlier.)

Implantation

PVP and Modified PVP Polymers

PVP

The implantation of PVP sponges into mice and rats resulted in development of local sarcomas, but without metastases.[8]

Human

PVP and Modified PVP Polymers

PVP

According to the International Agency for Research on Cancer , PVP is not classifiable as to its carcinogenicity to humans.[36]

ANTICARCINOGENICITY STUDY

PVP and Modified PVP Polymers
PVP

Orally administered PVP significantly decreased the rate of bladder tumors in mice exposed to bracken fern.[8]

OTHER RELEVANT STUDIES

Cytotoxicity

PVP and Modified PVP Polymers

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.[37] 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-$DD_2$4000 (amphiphilic *N*-vinylpyrrolidone polymer with molecular weight of hydrophilic polymer fragment of 4000 Da and 1 hydrophobic di(dodecyl) group). Amphiphilic PVP polymeric nanoparticles were prepared using an emulsification and solvent evaporation technique. The particle sizes of the PVP-OD4000, PVPOD8000, and PVP-$DD_2$4000 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 µmol/l).

Polymers with an *n*-alkyl octadecyl hydrophobic group demonstrated low cytotoxic effects against MCF-7 cells (compared to untreated control cells) ($P < 0.05$). PVP$DD_2$4000 nanoparticles were slightly more cytotoxic due to the presence of more branched hydrophobic groups. All polymers demonstrated no cytotoxicity both at concentrations less than the critical aggregation concentration (simple polymer solution) and at higher concentrations, when amphiphilic macromolecules are self-assembled in nanoparticles ($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$).[37]

The effect of PVP on the ultrastructure of spermatozoa from 12 fertile patients was evaluated.[38] 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, the 10% PVP solution strongly affected the fine structure of spermatozoa. The authors concluded that the 10% PVP solution 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 trade name material on cultured HeLa cells (human cervical carcinoma cells) was evaluated.[39] HeLa cells were incubated with the trade name material (at concentrations of 5%, 10%, and 20%) for 24 h. 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 SENSITZATION STUDIES

Irritation

Animal

VP Copolymers

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 non-irritating to the skin of 6 rabbits.[2] 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 non-irritating and a test concentration of 1.75% had the potential for minimal irritation.

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.[2]

VP Acrylate Copolymers

Ammonium Acryloyldimethyltaurate/VP Copolymer

In a study involving rabbits (number and strain not stated), Ammonium Acryloyldimethyltaurate/VP Copolymer (assumed applied neat, not specified) was applied for 4 h to a 6 cm^2 area of skin. The test substance was non-irritating to the skin of rabbits.[6]

PVP and Modified PVP Polymers

PVP

A 10% PVP-iodine solution was applied, under an occlusive patch, for 96 h to hairless dorsal skin of 25 rabbits.[8] *After a 2-week non-treatment period, another occlusive patch was similarly applied for 48 h. No dermal reactions were observed after either duration of patch application.*

Triacontanyl PVP

The skin irritation potential of a Triacontanyl PVP trade name material (moistened with saline) was evaluated using 6 new Zealand white rabbits.[10] 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 (cm^2) 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.

Human

VP Copolymers

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).[40] The product was applied to the back (dose per cm^2 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.

PVP and Modified PVP Polymers

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.[8] *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.[7] *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).*

Sensitization

Animal

VP Copolymers

VP/VA Copolymer

VP/VA Copolymer was not a sensitizer to guinea pigs after repeated intracutaneous injections.[2] *The skin was inspected 24 h after each injection.*

VP Acrylate Copolymers

Ammonium Acryloyldimethyltaurate/VP Copolymer

Ammonium Acryloyldimethyltaurate/VP Copolymer (neat) was not sensitizing to guinea pigs.[6]

PVP and Modified PVP Polymers

PVP

A 10% PVP-iodine solution did not cause dermal sensitization in rabbits.[8]

VP Crosspolymers

Sodium Acryloyldimethyltaurate/VP Crosspolymer

The skin sensitization potential of Sodium Acryloyldimethyltaurate/VP Crosspolymer (concentration not stated) was evaluated in the local lymph node assay (LLNA) (OECD TG 429).[12] There was no evidence of sensitization.

Human

VP Copolymers

VP/VA Copolymer

Repeated insult patch tests of a 5.0% formulation of VP/VA Copolymer caused no irritation or sensitization in 50 subjects..[2] *Likewise, three solutions of 50% VP/VA Copolymer in alcohol caused no irritation in 150 subjects*

VP Acrylates Copolymer

VP/Acrylates/Lauryl Methacrylate Copolymer

In a human repeated insult patch test (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.[11] These results were not considered positive by the authors of this study. Details relating to the test protocol were not included.

PVP and Modified PVP Polymers

PVP

Undiluted PVP-iodine (10% PVP, 2% iodine) did not induce sensitization in an HRIPT involving 100 subjects.[8] *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).[10] 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 (cm^2) 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.

Photosensitization/Phototoxicity

Animal

VP Copolymers

VP/VA Copolymer

No photosensitization data on VP/VA Copolymer were available for review, but the UV absorption characteristics suggest that photosensitization is unlikely.[2]

Human

PVP and Modified PVP Polymers

PVP

A PVP trade name material (10% aqueous solution) did not induce a phototoxic response in a study involving 10 human subjects.[8]

Triacontanyl PVP

The phototoxicity of a Triacontanyl 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.[10] The area of application (cm^2) 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 Triacontanyl PVP trade name material (200 mg) was applied, under an occlusive wrap, for 24 h to both forearms of 28 subjects.[10] The area of application (cm^2) 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 and Modified PVP Polymers

PVP

PVP-iodine was severely toxic to corneal endothelium at concentrations of 5% and 10% in a rabbit eye model.[7] *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.*[7]

Animal

VP Copolymers

VP/VA Copolymer

The acute ocular irritation potential of VP/VA Copolymer, as supplied and in formulation, was evaluated using albino rabbits.[2] *For the solutions that were tested, moderate to severe ocular irritation was observed at a concentration of 50% and mild irritation was observed at concentrations of 25% and 37.5% VP/VA Copolymer. For the product formulations that were tested, ocular irritation (degree not stated) was observed at concentrations of 2.4% and 24% VP/VA Copolymer, minimal to moderate ocular irritation was observed at a concentration of 4%, and concentrations of 0.25%, 0.5%, and 1.75% were non-irritating.*

VP Acrylate Copolymers

Ammonium Acryloyldimethyltaurate/VP Copolymer

In an ocular irritation assay, Ammonium Acryloyldimethyltaurate/VP Copolymer (undiluted, 0.1 ml) was non-irritating to the eyes of rabbits.[41]

VP/Acrylates/Lauryl Methacrylate Copolymer

Undiluted VP/Acrylates/Lauryl Methacrylate Copolymer was slightly irritating to the eyes of rabbits.[11] The number of animals tested and details relating to the test protocol and study results are not included.

PVP and Modified PVP Polymers

PVP

In ocular irritation studies using rabbits, a 10% PVP-iodine solution (without detergent) was minimally irritating, whereas repeated instillations of 0.5% PVP-iodine did not cause ocular irritation.[8]

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.[42]

Triacontanyl PVP

In a study involving 6 New Zealand white rabbits, a Triacontanyl PVP trade name material (unknown concentration; 50 mg was instilled into the conjunctival sac of 1 eye of each animal.[10] 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.

VP Crosspolymers

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.[12] Slight conjunctival effects were observed and had resolved by 24 h. The test substance was classified as slightly irritating.

Human

VP Copolymers

VP/Hexadecene Copolymer

A controlled use test of an eye shadow containing 12.22% VP/Hexadecene Copolymer was performed using 10 healthy female subjects, 5 of whom wore contact lenses.[43] 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 and Modified PVP Polymers

PVP

A woman with pollinosis developed anaphylaxis after vaginal application of a PVP-iodine solution for disinfection during a medical examination.[44] 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.[45] A positive test reaction to PVP (5% in water), one of the components of the drug, was reported.

A case of a boy with a history of anaphylactic reactions following treatment for impetigo contagiosum was reported.[46] 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.[47] 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.[48] 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.[49] 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.[50] 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.[51]

A case of a girl with an anaphylactic reaction to PVP has been reported. Prick-by-prick test results for a PVP-iodine 7.5% antiseptic solution were positive.[52]

Other Clinical Reports

VP Copolymers

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.[53] 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 erythemato-edematous (+) reaction to the cream was observed on both days. In a ROAT 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, erythemato-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.[54] 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/cm^2) 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 (+/+).

PVP and Modified PVP Polymers

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.[55] 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.[56] 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.[57] 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.[58] The patients were patch tested with 10% PVP-iodine solution and had strongly positive results (irritant contact dermatitis).

SUMMARY

The safety of 21 vinylpyrrolidone polymers as used in cosmetics is reviewed in this safety assessment. Most of these ingredients have the reported film former function in cosmetics in common. Viscosity increasing agent and binder are 2 other functions that are reported for many of these ingredients.

VP/VA Copolymer is produced by free radical copolymerization of NVP and VA in an isopropanol solution, in the presence of initiators. The process is continuous and temperature-controlled. Hydrazine is formed from amines present in this reaction mixture; but specifications limit the concentration to a maximum of 0.1%. 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).

Due to the method of production (radical polymerization) provided by one supplier, residual monomers may be present in VP/VA Copolymer at a maximum of 50 ppm vinylpyrrolidone and a maximum of 100 ppm vinyl acetate. Other suppliers reported that that radical polymerization is used to make PVP. Due to production via this method, residual monomers may be present at a maximum of 100 ppm vinylpyrrolidone and a maximum of 100 ppm vinyl acetate. Impurities that may be present are acetaldehyde at a maximization concentration of 100 ppm and heavy metals in sum (as lead) at a maximum of 10 ppm.

One supplier reported 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.

Of ingredients with reported uses within the group of 21 vinylpyrrolidone polymers that is being reviewed for the first time, the greatest use frequency is reported for VP/Hexadecene Copolymer (443 cosmetic products: 442 leave-on products + 1 rinse-off product). The second highest use frequency is being reported for VP/Eicosene Copolymer (378 cosmetic products: 377 leave-on products + 1 rinse-off product). The results of a concentration of use survey conducted in 2017 indicate that VP/Hexadecene Copolymer is being used at concentrations up to 24.1% in leave-on products (lipstick), which is the highest maximum ingredient use concentration that is being reported for the vinylyrrolidone polymers that are being reviewed.

The results of a concentration of use survey conducted in 2017 indicate that VP/VA Copolymer is 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 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 reported for PVP, which is 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, at just 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.

A single dose of a Triacontanyl PVP (unknown concentration) trade name material was applied, under an occlusive wrap, for 24 h to the backs of 10 New Zealand white rabbits; the acute dermal LD_{50} was > 2 g/kg. An oral LD_{50} of > 5 g/kg (rats) has been reported for undiluted VP/Acrylates/Lauryl Methacrylate Copolymer.

A single 5 g/kg oral dose of a Triacontanyl PVP trade name material (ground into a powder and mixed with peanut butter and honey) was fed to 10 Sprague-Dawley rats. None of the animals died and no gross organ changes were observed at necropsy. The LD_{50} was > 5 g/kg.

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 50 male and 50 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 Beagle 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 aqueous PVP (doses up to 10,000 µg/plate) was evaluated in the Ames test (with and without metabolic activation) using the *S. 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 Triacontanyl 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 Triacontanyl PVP trade name material (0.5 g, moistened with saline) was slightly irritating to the skin of 6 New Zealand white rabbits. 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 a LLNA of Sodium Acryloyldimethyltaurate/VP Crosspolymer (test concentration not stated) were negative. The skin sensitization potential of a Triacontanyl 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 Triacontanyl 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 Triacontanyl 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 Triacontanyl PVP (unknown concentration) trade name material (50 mg) was classified as slightly irritating. A controlled use 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 (erythemato-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.

DRAFT DISCUSSION

The Panel determined that method of manufacture and impurities data on all of the vinylpyrrolidone polymers that are being reviewed are needed for completion of this safety assessment. In response to this request for data, the following data were received: (1) Method of manufacture and residual monomer data on VP/VA Copolymer and (2) Method of manufacture and impurities data on PVP. The Panel had noted the possibility that data on all of the ingredients may not be provided, but anticipated that data applicable to the entire group would be received. Furthermore, the Panel agreed that the data received should be inclusive of residual monomer content.

The Panel also noted that CIR has published a safety assessment on methacrylate ester monomers (lauryl methacrylate included), with a conclusion stating that these monomers are safe as used in nail enhancement products when skin contact is avoided. Furthermore, the conclusion states that products containing these ingredients should be accompanied by directions to avoid skin contact because of the sensitizing potential of methacrylates. It was agreed that this conclusion should be considered in the current safety assessment because the residual monomer content of 2 of the ingredients that are being reviewed, VP/Acrylates/Lauryl Methacrylate Copolymer and VP/Acrylates/Lauryl Methacrylate Copolymer, may be a concern. Furthermore, the Panel noted that the production process for VP/VA Copolymer can yield hydrazine from amines that are present in the reaction mixture, and also considered that the USP specifies that pharmaceutical grade PVP cannot contain more than 1 ppm hydrazine. Thus, the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

CONCLUSION

To be determined.

TABLES

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

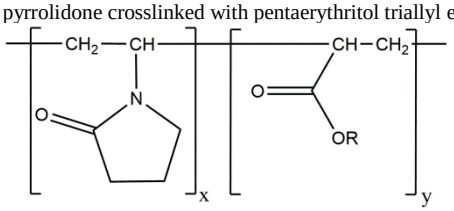
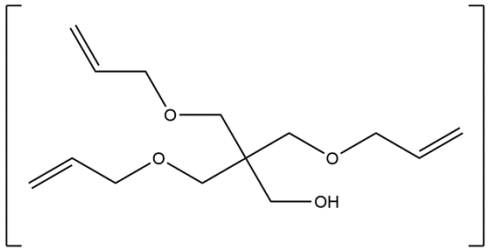
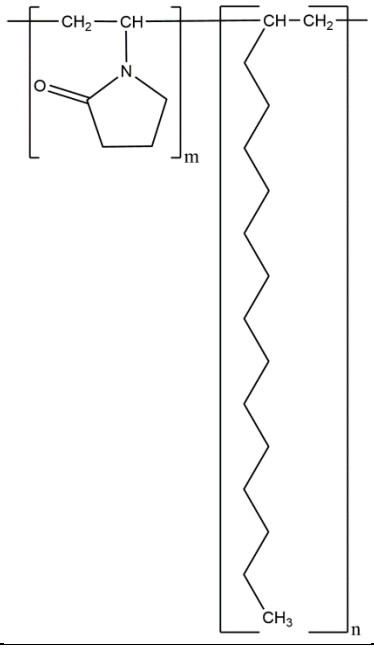
Ingredient CAS No.	Definition & Structures	Function(s)
VP Copolymers		
Acrylic Acid/VP Crosspolymer **527685-31-0**	Acrylic Acid/VP Crosspolymer is a copolymer of acrylic acid and *N*-vinyl pyrrolidone crosslinked with pentaerythritol triallyl ether (PETE).  [wherein R is hydrogen or a crosslink through PETE]  pentaerythritol triallyl ether	Dispersing Agents - Nonsurfactant; Slip Modifiers; Surface Modifiers
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

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

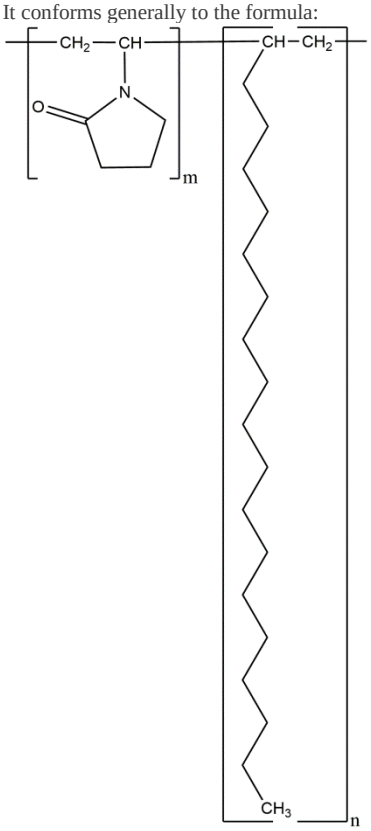
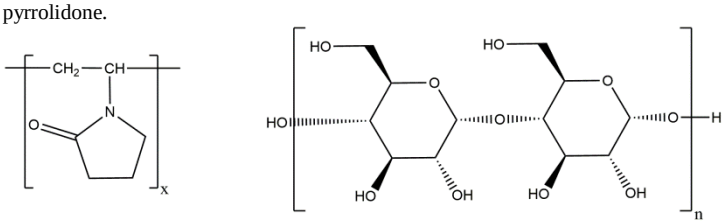
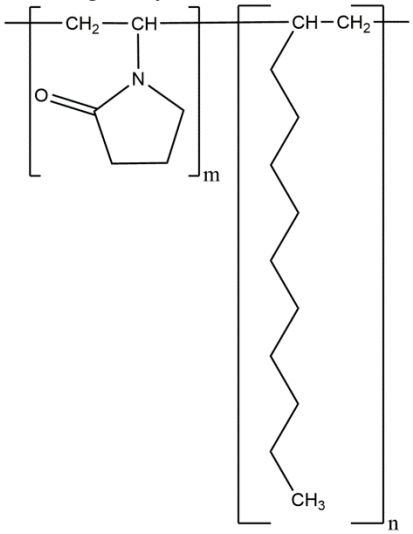
Ingredient CAS No.	Definition & Structures	Function(s)
VP/Eicosene Copolymer 28211-18-9 77035-98-4	VP/Eicosene Copolymer is a polymer of vinylpyrrolidone and eicosene monomers. It conforms generally to the formula: 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Viscosity Increasing Agents - Nonaqueous
Maltodextrin/VP Copolymer 1323833-56-2	Maltodextrin/VP Copolymer is a copolymer of Maltodextrin and vinyl pyrrolidone. 	Film Formers
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

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

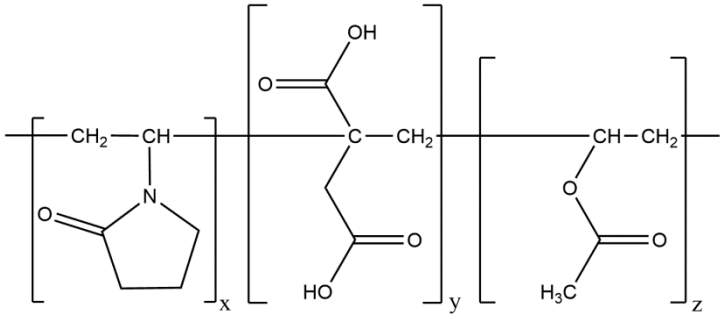
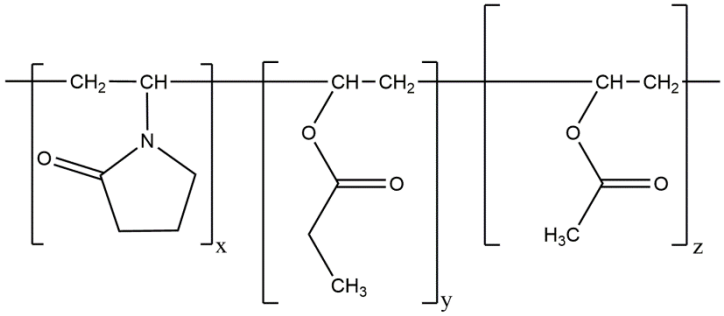
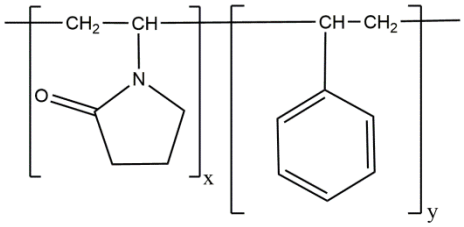
Ingredient CAS No.	Definition & Structures	Function(s)
PVP/VA/Itaconic Acid Copolymer 68928-72-3	PVP/VA/Itaconic Acid Copolymer is a polymer formed from vinylpyrrolidone, vinyl acetate and itaconic acid monomers. 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Hair Fixatives
PVP/VA/Vinyl Propionate Copolymer	PVP/VA/Vinyl Propionate Copolymer is a polymer of vinylpyrrolidone, vinyl acetate and vinyl propionate monomers. 	Film Formers; Hair Fixatives
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] *

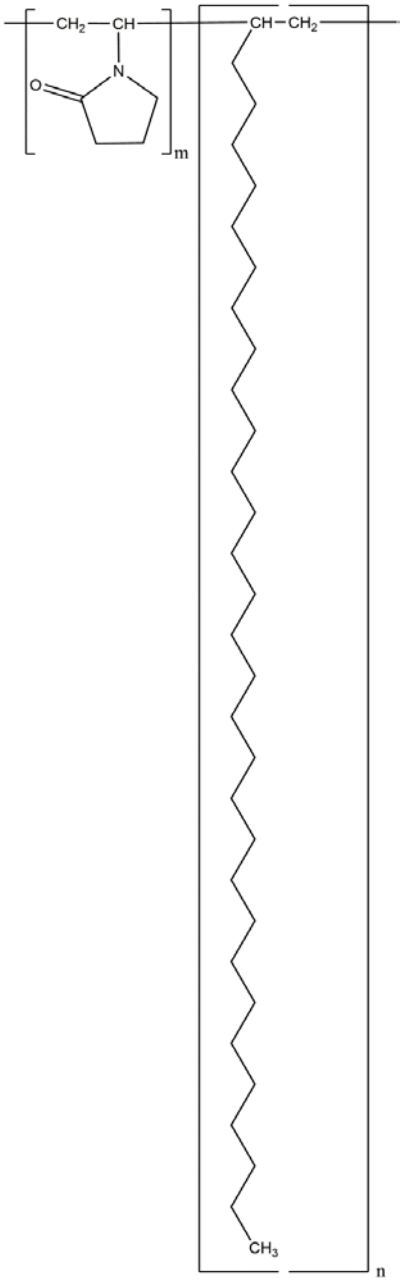
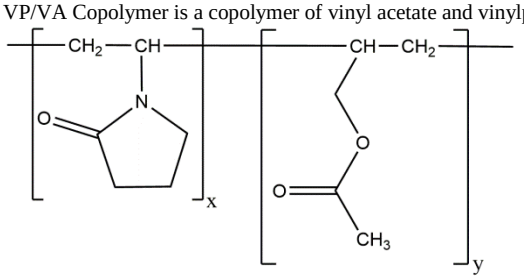
Ingredient CAS No.	Definition & Structures	Function(s)
Triacontene/VP Copolymer	Triacontene/VP Copolymer is a copolymer of triacontene and vinylpyrrolidone monomers. 	Emulsion Stabilizers; Film Formers
VP/VA Copolymer 25086-89-9	VP/VA Copolymer is a copolymer of vinyl acetate and vinylpyrrolidone monomers. 	Binders; Dispersing Agents - Nonsurfactant; Film Formers; Hair Fixatives

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

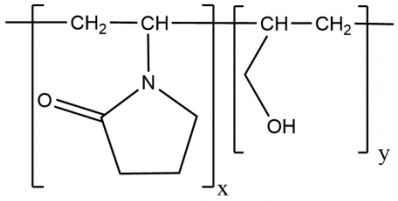
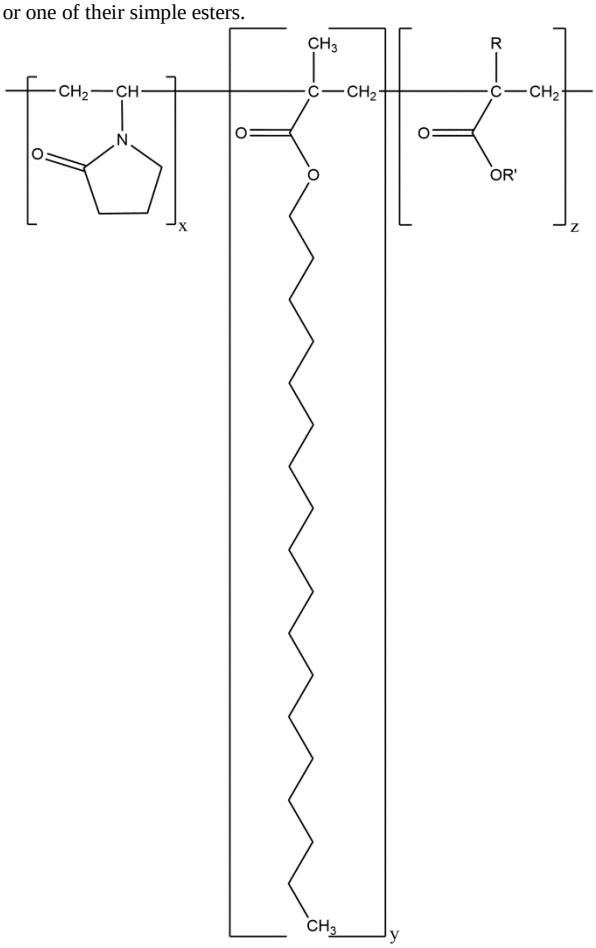
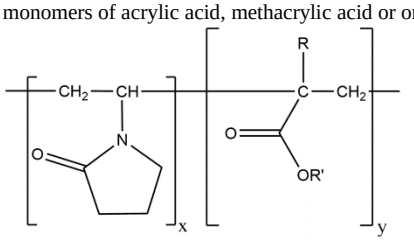
Ingredient CAS No.	Definition & Structures	Function(s)
VP/Vinyl Alcohol Copolymer 26008-54-8	VP/Vinyl Alcohol Copolymer is the product formed by the polymerization and subsequent hydrolysis of vinylpyrrolidone and vinyl acetate. 	Film Formers; Hair Fixatives; Humectants; Viscosity Increasing Agents - Aqueous
VP Acrylate Copolymers		
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 *N*-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] *

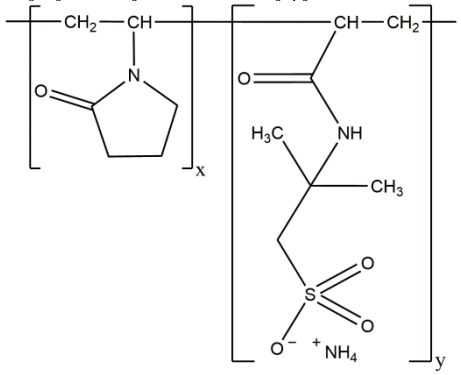
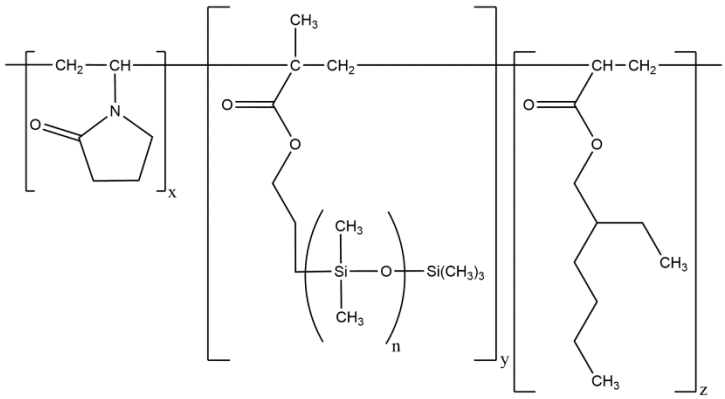
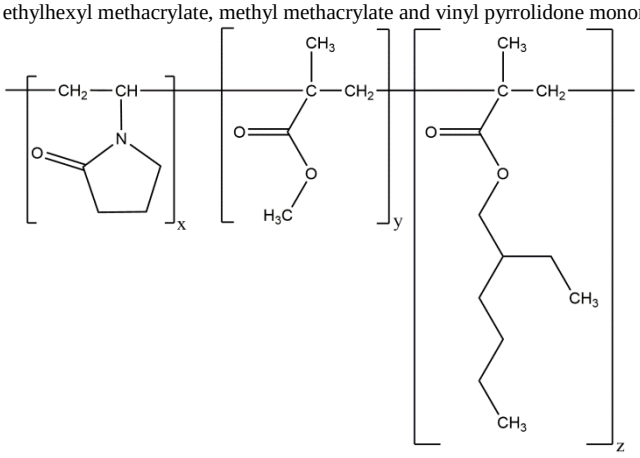
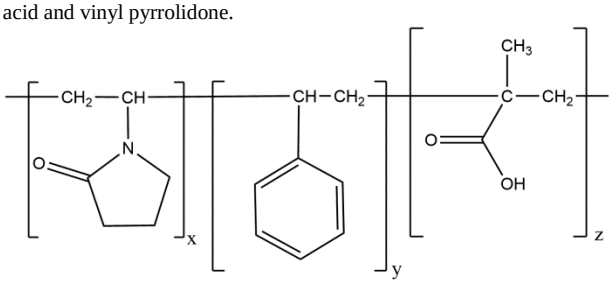
Ingredient CAS No.	Definition & Structures	Function(s)
Ammonium Acryloyldimethyltaurate/VP Copolymer	Ammonium Acryloyldimethyltaurate/VP Copolymer is a copolymer of ammonium acryloyldimethyltaurate and vinylpyrrolidone monomers. 	Viscosity Increasing Agents - Aqueous
Ethylhexyl Acrylate/VP/Dimethicone 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
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

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

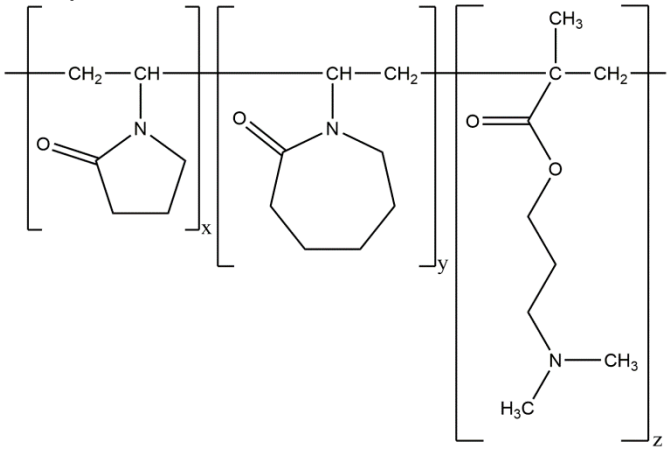
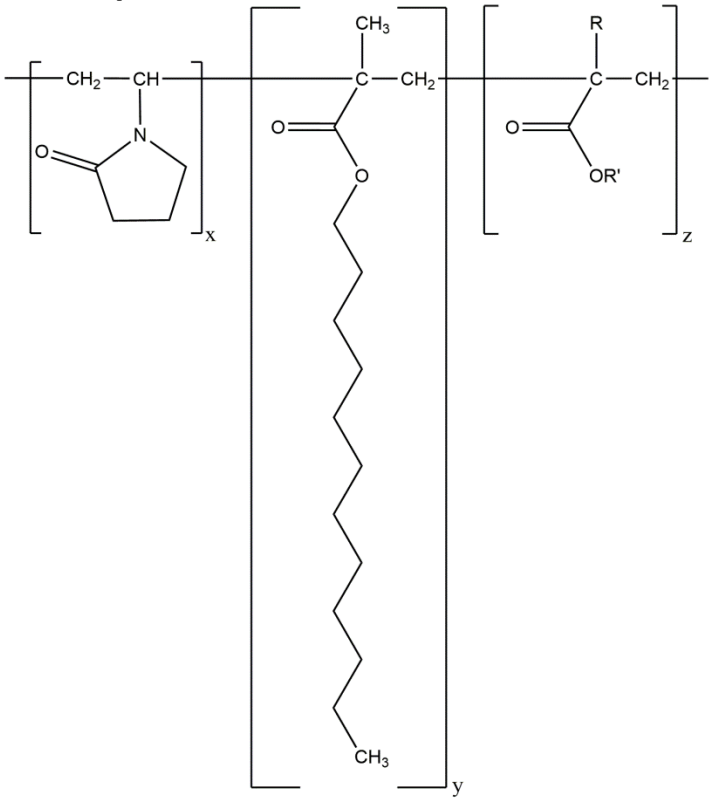
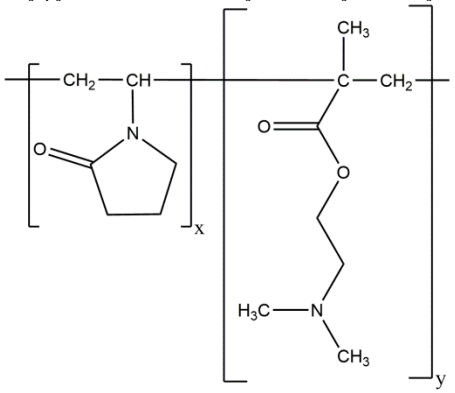
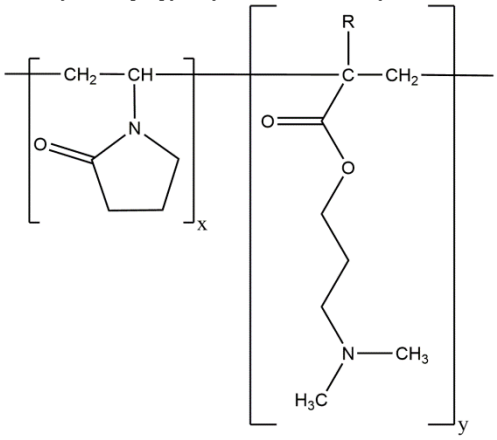
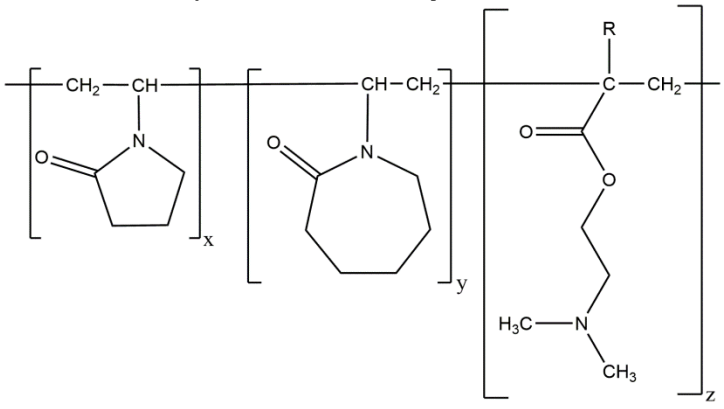
Ingredient CAS No.	Definition & Structures	Function(s)
Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer	Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer is a copolymer of vinylcaprolactam, vinylpyrrolidone, and dimethylaminoethyl methacrylate monomers. 	Film Formers; Hair 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

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/DMAPA Acrylates Copolymer 175893-71-7	VP/DMAPA Acrylates Copolymer is a copolymer of vinylpyrrolidone and dimethylaminopropylacrylamide or methacrylamide.  [wherein R is hydrogen or methyl]	Hair Fixatives
VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer	VP/Vinyl Caprolactam/DMAPA 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

PVP and Modified PVP Polymers

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

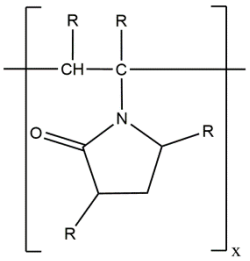
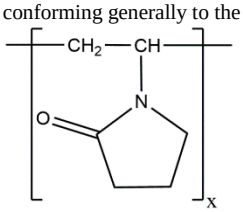
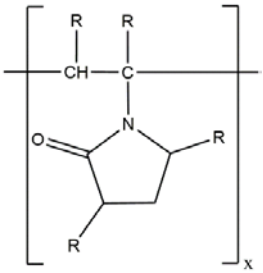
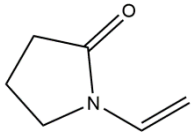
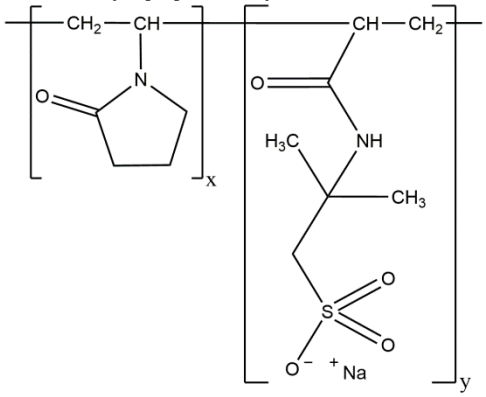
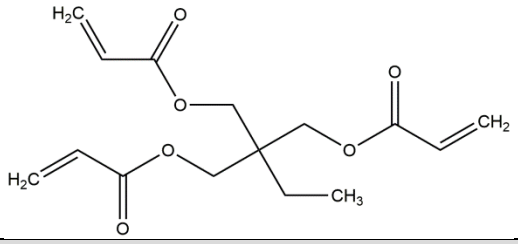
Ingredient CAS No.	Definition & Structures	Function(s)
Butylated PVP	Butylated PVP is a polymer of butylated vinylpyrrolidone that conforms generally to the formula:  where R represents either a butyl group or hydrogen.	Binders; Film Formers; Hair Fixatives
PVP 9003-39-8	PVP is the linear polymer that consists of 1-vinyl-2-pyrrolidone monomers conforming generally to the formula: 	Binders; Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Film Formers; Hair Fixatives
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
VP Crosspolymers		
Hydrolyzed Wheat Protein/PVP 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

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

Ingredient CAS No.	Definition & Structures	Function(s)
Sodium Acryloyldimethyltaurate/VP Crosspolymer	Sodium Acryloyldimethyltaurate/VP Crosspolymer is a copolymer of sodium acryloyldimethyltaurate and vinylpyrrolidone crosslinked by 1,1,1-trimethylolpropane triacrylate.  [crosslinked with] 	Emulsion Stabilizers
Urethanes		
VP/Dimethylaminoethylmethacrylate/Poly-carbamyl Polyglycol Ester	VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester is a copolymer of vinylpyrrolidone, dimethylaminoethylmethacrylate and polyurethane. [*More information needed to depict structure.*]	Film Formers
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
VP/Polycarbamyl Polyglycol Ester	VP/Polycarbamyl Polyglycol Ester is a copolymer of vinylpyrrolidone and polyurethane. [*More information needed to depict structure.*]	Film Formers

*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. Reports on Polymers Previously Reviewed by CIR

Ingredients	CIR Review Status
Acrylates/VP Copolymer, VP/Dimethylaminoethylmethacrylate Copolymer, and Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer	Published Final Report (2002) - Conclusion: Safe for use in cosmetics when formulated to avoid skin irritation.[4] 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.[6]
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.[5]
PVP	Published Final Report (1998) - Conclusion: Safe as used in cosmetics.[8] Published Rereview (2017) - Conclusion: Panel reaffirmed the original conclusion[7]
VP/VA Copolymer	Published Final Report (1983) - Conclusion: Safe as a cosmetic ingredient under present conditions of concentration and use.[2] Published Rereview (2006) - Conclusion: The Panel reaffirmed the original conclusion [3]

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.[4]
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.[59]
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.[60]
Maltodextrin	Final Report - Conclusion: Safe in the present practices of use and concentration in cosmetics, as described in this safety assessment.[61]
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.[62]
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.[63]
Sodium Acryloyldimethyltaurate	Not Reviewed
Stearyl Methacrylate	Not Reviewed
Styrene	Not Reviewed
Triacontene	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	9
Number average molecular weight (Da)	21,499	9
Sodium Acryloyldimethyltaurate/VP Crosspolymer		
Form (at 20 ºC and 101.3 kPa)	White powder	12
Particle size (µm)	< 10 (65.4%); < 100 (86.8%)	12
Formula Weight (Da)	> 10,000	12
Melting Point (ºC)	Not determined. Decomposes prior to melting	12
Water solubility (mg/l)	Miscible, gel forming. When gel was diluted by further addition of water, low viscosity solution was formed	12
Triacontanyl PVP (trade name mixture)		
Form	White to off-white solid flakes	10
Particle size distribution (cm^2)	0.25 to 1	10
Molecular weight (Da)	Approximately 70 to 80% of the polymer has a molecular weight of > 1000	10
Maximum percentage of low molecular weight species (molecular weight <1000 Da) (%)	20 to 30	10
Density (g/ml)	0.947	10
Solubility	Insoluble in water, acid or base solutions	10
Partition coefficient	Not applicable, as the polymer is insoluble in water	10
VP/Acrylates/Lauryl Methacrylate Copolymer		
Form	White powder	11
Particle size (µm)	< 10	11
Number average molecular weight (Da)	> 10,000	11
Density (g/ml)	1	11
Solubility	Expected to have low water solubility based on high molecular weight and predominantly hydrophobic structure	11
VP/Dimethylaminoethylmethacrylate Copolymer		
Density (g/ml)	1.047	13

Table 5. Specifications for VP/VA Copolymer.[15]

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.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	VP/Hexadecene Copolymer				**VP/Eicosene Copolymer**			
	2018[21]		**2017[22]**		**2018[21]**		**2017[22]**	
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[21]		**2017[22]**		**2018[21]**	**2017[6]**	**2017[22]**	**2016[6]**
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[21]		**2017[22]**		**2018[21]**		**2017[22]**	
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.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Maltodextrin/VP Copolymer				**PVP**			
	2018[21]		**2017[22]**		**2018[21]**	**2013[7]**	**2017[22]**	**2013[7]**
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[21]	**2017[6]**	**2017[22]**	**2016[6]**	**2018[21]**	**2013[5]**	**2017[22]**	**2013-2014[5]**
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
	Triacontanyl PVP				**Vinyl Caprolactam/ VP/Dimethylaminoethyl Methacrylate Copolymer**			
	2018[21]		**2017[22]**		**2018[21]**		**2017[22]**	
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.

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[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.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	VP/Acrylates/Lauryl Methacrylate Copolymer				**VP/Dimethiconylacrylate/ Polycarbamyl/ Polyglycol Ester**			
	2018[21]		**2017[22]**		**2018[21]**		**2017[22]**	
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[21]	**1998[4]**	**2017[22]**	**1984[4]**	**2018[21]**		**2017[22]**	
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[21]		**2017[22]**		**2018[21]**	**2002[3]**	**2017[22]**	**2003[3]**
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

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[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.

	# of Uses	*Max Conc of Use (%)*	*# of Uses*		*Max Conc of Use (%)*	
	VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer		**Acrylates/VP Copolymer**			
	2018[21]	**2017[22]**	**2018[21]**	**1998[4]**	**2017[22]**	**1997[4]**
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;2[a]	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[21]	**2017[22]**				
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				

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[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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2018 FDA VCRP Data

19 Ingredients Used

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

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

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

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

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

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

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

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

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

Maltodextrin/VP Copolymer	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	**3**
Total	

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

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

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

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

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

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

Triacontene/VP Copolymer

No uses in FDA Database

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

VP/Acrylates/Lauryl Methacrylate Copolymer	1
05B - Hair Spray (aerosol fixatives)	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	10
05I - Other Hair Preparations	**15**
Total	

VP/Dimethiconylacrylate/Polycarbamyl/Polyglycol Ester	1
03F - Mascara	1
11A - Aftershave Lotion	1
12G - Night	**3**
Total	

VP/Dimethylaminoethylmethacrylate/ Polycarbamyl/Polyglycol Ester

No uses in FDA Database

VP/Dimethylaminoethylmethacrylate Copolymer	1
03D - Eye Lotion	2
03F - Mascara	1
03G - Other Eye Makeup Preparations	4
05A - Hair Conditioner	1
05B - Hair Spray (aerosol fixatives)	1
05C - Hair Straighteners	44
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
05H - Wave Sets	11
05I - Other Hair Preparations	1
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	**72**
Total	

VP/Dimethylaminoethylmethacrylate/Polycarbamyl Polyglycol Ester

No uses in FDA Database

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

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

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

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

VP/Vinyl Alcohol Copolymer
No uses in FDA Database

VP/Vinyl Caprolactam/DMAPA Acrylates Copolymer	6
05B - Hair Spray (aerosol fixatives)	13
06E - Hair Color Sprays (aerosol)	**19**
Total	

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: June 18, 2018

SUBJECT: VP/VA Copolymer

Anonymous. 2018. Method of manufacture and residual monomers - VP/VA Copolymer.

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

June 2018

Method of Manufacture and Residual Monomers – VP/VA Copolymer

A cosmetic ingredient supplier reports that radical polymerization is used to make VP/VA Copolymer from vinylpyrrolidone and vinyl acetate. Residual monomers may be present at a maximum of 50 ppm vinylpyrrolidone and a maximum of 100 ppm vinyl acetate.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: June 20, 2018

SUBJECT: PVP

Anonymous. 2018. Method of manufacture and residual monomers - PVP.

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

June 2018

Method of Manufacture and Residual Monomers – PVP

A cosmetic ingredient supplier reports that radical polymerization is used to make PVP. Residual monomers may be present at a maximum of 100 ppm vinylpyrrolidone and a maximum of 100 ppm vinyl acetate.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: August 8, 2018

SUBJECT: PVP

Anonymous. 2018. Method of manufacture and impurities - PVP.

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

August 2018

Method of Manufacture and Impurities – PVP

A cosmetic ingredient supplier reports that radical polymerization is used to make PVP. Residual monomers may be present at a maximum of 100 ppm vinylpyrrolidone. Other impurities that may be present are acetaldehyde at a maximum concentration of 100 ppm and heavy metals in sum (as lead) maximum 10 ppm.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: May 30, 2018

SUBJECT: Draft Report: Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics (draft prepared for the June 4-5, 2018 CIR Expert Panel meeting)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics.

Comments on the SLR Not Yet Addressed

Key Issue

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 NICNAS 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.

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 [monomers

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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).

New Comments

Key Issue

Vinyl Caprolactam/VP/Dimethylaminoethyl Methacrylate Copolymer was previously reviewed in the acrylate copolymer report (published in 2002; currently being re-reviewed). In the original CIR report it was called Vinyl Caprolactam/PVP/Dimethyaminoethyl Methacrylate Copolymer. If this ingredient is left in this report, an asterisk needs to be added to this ingredient in the list of ingredients in the Introduction; the number of previously reviewed ingredients needs to be changed from 8 to 9; and the concentration of use information from the 2002 report needs to be added to Table 6.

Additional Considerations

Introduction - Table 22 needs to be corrected to Table 2, and Table 33 needs to be corrected to Table 3.

Short-Term, Oral, PVP - The information concerning short-term inhalation studies from the original report does not belong in the Oral subsection.

Subchronic, Inhalation, VP/VA Copolymer - How many hours/day, days/week were the rabbits exposed in the 90-day study of a formulation containing 1.72% VP/VA Copolymer?

Genotoxicity, In Vivo, PVP, old report summary - What was the maximum dose used in the *in vivo* mutagenicity studies of PVP? If the majority of the studies were negative, which studies had positive results?

Other Clinical Reports, VP/Hexadecene Copolymer - The single insult patch test on the cosmetic base containing 14.95% VP/Hexadecene Copolymer should be moved to the dermal irritation section.